Current Topics

2014 ICAAC

Sometimes Baffling Tickborne Microbial Illnesses Continue To Emerge

Shannon Weiman

Genomic analyses are enabling investigators to uncover novel tickborne bacterial diseases that were previously of unknown origin or were misdiagnosed as Lyme, which is caused by *Borrelia burgdorferi*. These flu-like illnesses include symptoms such as fever, headache, and fatigue, but are transmitted by specific species of ticks, typically in particular geographic regions, according to several researchers who spoke during the symposium "Tick-borne Infectious Diseases" at the 2014 Interscience Conference on Antimicrobial Agents and Chemotherapy, held in Washington, D.C., last September.

A particularly gruesome tickborne illness, called scalp eschar and neck lymphadenopathy after tick bite, emerged recently in Europe, according to Arantza Portillo of the Center for Biomedical Research in Rioja, Spain. Infected individuals characteristically experience necrotic skin lesions and swollen lymph nodes but lack the telltale rash of other rickettsioses or of Lyme disease, she says. Nearly all lesions appear on the head of affected individuals because the tick vector, *Dermacentor marginatus,* climbs to 1.5 meters above the ground to await its prey. Nearly all these ticks in Europe carry one or more of the causative species *Rickettsia rioja*, *R. raoultii*, and *R. slovaca*. "These pathogens have probably been circulating in Europe for a long time," she says. A comparable disease, caused by *Rickettsia* spp. 364D, was recently reported in California.

Other gram-negative rickettsia species cause ehrlichiosis, another type of tick-borne disease. A new variety of ehrlichia was identified in 2009, and is found only in Minnesota and Wisconsin, according to Bobbi Pritt of Mayo Clinic in Rochester, Minn. That species is transmitted by *Ixodes scapularis* ticks, in contrast to other types of ehrlichia that are transmitted by *Amblyomma americanum* ticks, she says.

A Lyme-like disease, detected in the southern United States during the late 1980s, is called Southern-tick associated rash illness (STARI). Characterized by a more uniform rash than the bulls-eye rash that often occurs at the outset of Lyme disease, these early cases first appeared outside the geographic range of the primary tick vector of Lyme, *I. scapularis*. The Lyme spirochete "could not be isolated from human cases from the region, and the tick associated with the illness was *A. americanum*, which is not a vector for *B. burgdorferi*," says Adriana Marques of the National Institute for Allergy and Infectious Diseases in Bethesda, Md. While the causal agent for STARI remains unknown, this illness appears to be more prevalent than Lyme in some areas, she warns. "*A. americanum* are the most abundant biting ticks in the southern United States, and their range extends all the way up to Maine."

A tickborne agent, *Borrelia myamotoi*, found first in Japan in 1995, subsequently was found in several regions across Europe and North America, according to John Branda of Massachusetts General Hospital in Boston. This *Borrelia* species causes a severe acute illness that often requires infected individuals to be hospitalized, he says. It is transmitted by *Ixodes* ticks, and its

***Amblyomma americanum* tick. This wide-ranging tick rarely carries *Borrelia burgdorferi*, the causative agent of Lyme disease, but is a vector for Southern-tick associated rash illness (STARI), the causative agent of which is unknown (CDC photo.)**

prevalence may be about 10% that of Lyme disease.

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

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2014 ICAAC

Host Gene Changes Affect How Bacteria Colonize Those Hosts

Shannon Weiman

Single-nucleotide polymorphisms (SNPs) in genes encoding immune receptors, signaling molecules, and other molecules not classically associated with immune responses can affect how well some bacterial pathogens or commensal species colonize individual hosts, according to several researchers who spoke during the 2014 Interscience Conference on Antimicrobials and Chemotherapy (ICAAC), held in Washington, D.C., last September. Exploring these associations, researchers hope to reveal mechanisms underlying disease pathology and other host-microbe interactions.

Some individuals are particularly susceptible to invasive pneumococcal disease (IPD), according to Anna Sangil Betriu of the Hospital Universitari Mutua Terrassa in Catalonya, Spain. Some 43 SNPs in 10 immune genes are linked to rare cases occurring in otherwise healthy individuals, "which may explain their susceptibility," she says. Most prominent are minor alleles in the interleukin-1 receptor 1, which mediates innate inflammatory responses, and in two inhibitors of nuclear factor kB that regulate signaling of innate and adaptive responses. "If confirmed, these findings may help us to better understand the genesis of the illness, and to identify people at risk," she says.

A single SNP in the gene for the leptin receptor (LEPR) appears to confer a threefold-greater susceptibility to infections by *Clostridium difficile*, according to Rajat Madan of the University of Virginia in Charlottesville. This same Q233R mutation in LEPR is also linked to susceptibility to *Entamoeba histolytica* infections, he notes.

Leptin, better known for its role in appetite and obesity, also influences gut integrity, microbiome composition, and inflammatory responses, Madan says. "Leptin is pro-inflammatory and augments the host defense during infections, presumably by enhancing immune responses." The mutation impairs LEPR activation of signal transducer and activator of transcription 3 signaling, reducing mucosal chemokine production and neutrophil recruitment in mice, thus rendering them less able to clear *C. difficile* from the gut, he says. These findings "demonstrate a connection between metabolism and immunity."

In other cases SNPs in host genes may influence the gut microbiota, thereby indirectly affecting susceptibility to pathogens or the likelihood of developing still other types of diseases, according to Jose A. Oteo of the Centro de Investigación Biomédica de La Rioja in Rioja, Spain. "Changes in gut microbiota composition may be responsible for a plethora of pathologies, including inflammatory bowel diseases, colon cancer, and obesity," he says. For example, a SNP in the adrenomedullin gene (rs4910118), which decreases circulating levels of adrenomedullin, a peptide with antimicrobial properties, may dictate gut colonization by specific bacterial species. In female mice, knocking out this gene reduces the abundance of Bacteroidales and Clostridiales, while increasing Enterobacteriales, a bacterial order suggested to be implicated in high-fat-, diet-induced obesity, he says. He and his collaborators plan to examine whether humans with this SNP exhibit similar changes in microbiota and how this may influence their likelihood of developing various diseases. "This SNP is linked to cancer and high blood pressure," he notes.

MINITOPIC

White House Imposes Another Voluntary Halt to Gain-of-Function Research

The White House Office of Science and Technology Policy and Department of Health and Human Services announced in October that it was suspending funding for "gain-of-function" research, pending a "deliberative process" to assess its risks and benefits. Such gain-of-function studies typically try deliberately to enhance the pathogenicity or transmissibility of infectious agents such as the influenza and MERS viruses. The White House asked the National Science Advisory Board for Biosecurity (NSABB), which is a federal advisory board operating under the auspices of the National Institutes of Health, and the National Research Council of the National Academies to conduct this policy review. NSABB members were scheduled to confer late in November before issuing a statement on these issues. While this two-part review is under way, the government is asking researchers "to voluntarily pause their research, whether federally funded or not, while risks and benefits are being reassessed." An earlier voluntary moratorium on such research involving the H5N1 influenza virus ended in 2013 when several sets of researchers announced they would resume their investigations.

2014 ICAAC

Several Strategies in Search for Agents To Treat MERS-CoV

Shannon Weiman

Researchers are seeking to identify and develop agents that target the Middle East respiratory syndrome coronavirus

MINITOPIC

Progress in Developing Disparate Vaccines

Regulatory officials and researchers announced progress with the development of several different kinds of vaccines, including:

- Officials of the Food and Drug Administration (FDA) in October approved Trumenba, a vaccine to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age. The vaccine is made by Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., in Philadelphia, Pa.
- A tetravalent vaccine directed against the Dengue virus proved effective in protecting children against the virus, and use of the vaccine led to fewer hospitalizations during a phase 3 clinical trial in five Latin American countries where dengue is endemic, according to Gustavo Horacio Dayan of Sanofi Pasteur in Swiftwater, Pa., and his collaborators. Details appeared 3 November 2014 in the *New England Journal of Medicine* (doi:10.1056/NEJMoa1411037).
- An experimental nasal vaccine provides long-term protection for nonhuman primates against the deadly Ebola virus, according to Maria Croyle of the University of Texas at Austin and her collaborators. They reported recent findings during the annual meeting of the American Association of Pharmaceutical Scientists, held in San Diego, Calif., last November.
- A vaccine against the H1N1 influenza virus whose antigens were reformulated is "six times more active" than are conventional versions of the flu vaccine "in terms of hemagglutinin immunogenicity and in vivo protection," according to Manuel Rosa-Calatrava of VirPath and Emmanuel Dejean of Calixar, both in Lyon, France.

(MERS-CoV), which kills about 30% of individuals that it infects. Promising leads are arising from target-based drug development approaches and also from efforts to repurpose drugs that already are approved for treating other conditions, according to several researchers who summarized recent progress during the 2014 Interscience Conference on Antimicrobial Agents and Chemotherapy, held in Washington, D.C., last September.

Several inhibitors of viral helicase, spike protein, and RNA synthesis enzymes look promising when tested in vitro against MERS-CoV, according to Jasper Chan of the University of Hong Kong in China. Several of them are also active against the closely related severe acute respiratory syndrome coronavirus (SARS-CoV). Additionally, monoclonal antibodies and plasma from patients recovering from MERS-CoV infections neutralize that virus, he says, noting that convalescent plasma is being evaluated in clinical trials in the Middle East.

The papain-like protease (PLpro) of MERS-CoV, which is essential for its replication, is another target for candidate drugs, according to Hyuan Lee and Michael Johnson of the University of Illinois, Chicago. Although many inhibitors of the SARS-CoV PLpro proved to be ineffective against the MERS-CoV PLpro, she and her colleague Hao Lei recently identified an inhibitor of both viral enzymes. "High-throughput screening of 25,000 compounds produced a dual inhibitor that acts as an allosteric inhibitor against SARS-CoV PLpro and also acts as a competitive inhibitor against MERS-CoV PLpro," says Lee. The compound also works in synergy with other lead inhibitors against SARS-CoV PLpro.

However, this target-based approach is painstaking, and it could take years before any of these promising viral inhibitors are approved as drugs, Chan cautions. An alternate and perhaps faster strategy involves testing currently approved antiviral agents, in hopes of repurposing some of them to treat MERS-CoV infections. Broad-spectrum agents, such as type-I interferons, or those used to treat SARS such as ribavirin and lopinavir appear promising, he says. Moreover, interferons synergize with ribavirin in vitro and in rhesus macaques, he says.

Yet another strategy casts a wider net and seeks to repurpose other types of drugs. For example, several cancer drugs, antidepressants, and hormone receptor modulators show anti-MERS activity, according to Lisa Hensley of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md. She says that Chris Coleman of the University of Maryland in Baltimore, Lisa Johansen of Zalicus in Cambridge, Mass., and their collaborators identified 6 SARS-CoV-specific inhibitors, 33 MERS-CoV-specific inhibitors, and 27 inhibitors of both viruses while screening a set of 290 drugs that were approved by the Food and Drug Administration (FDA) for other purposes. For example, chlorpromazine HCl, a neurotransmitter antagonist used to treat patients with schizophrenia, synergizes with various other drugs, Hensley says. Chan finds that mycophenolic acid, an immunosuppressant used to prevent rejection of transplanted organs, has anti-MERS-CoV activity, particularly in combination with Interferon β1b.

Between 2012 when MERS-CoV emerged and July 2014, this virus infected at least 837 people across 20 countries with a fatality rate of about 30%, according the World Health Organization. SARS-CoV, which emerged in 2003, had a higher infectivity rate and caused about 8,000 cases worldwide that year and several dozen the next, but has not reappeared during the past decade. Its fatality rate was about 10%.

RESEARCH ADVANCES

Progress in Efforts To Harness Yeast for Making Opioid Drugs

Carol Potera

Saccharomyces cerevisiae, more commonly known as baker's yeast, is being developed as a means for producing opioid-based drugs, with the long-term goal of making those drugs from glucose instead of extracting them from poppy plants, according to Christina Smolke at Stanford University in Stanford, Calif., and her collaborators. They recently reported progress toward that goal after inserting genes from the poppy plant, *Papaver somniferum*, as well as other genes from *Pseudomonas putida* M10, which grows on poppy straw waste, into yeast cells—enabling them to produce opioids from intermediates that poppy plants make relatively early in that metabolic pathway and to do so with improved efficiency. Details appear October 2014 in *Nature Chemical Biology* (doi:10.1038/nchembio.1613).

Efforts to make such drugs in yeast prove to be painstaking, according to Smolke. In 2008, she and her collaborators engineered *S. cerevisiae* to produce salutaridine, a precursor of thebaine, a biochemical intermediate along the opioid biosynthetic pathway. "Salutaridine is just two enzymatic steps upstream of thebaine itself," she says. In this more recent work, her team introduced genes into yeast that convert thebaine into hydrocodone, oxycodone, and hydromorphone. These semisynthetic opioids are considered safer and more effective than natural opiates extracted from poppy plants. However, now they are produced commercially by chemical rather than biosynthetic means.

In three enzyme-catalyzed steps, poppy plants convert thebaine to morphine. Smolke and her collaborators took the genes that encode those three enzymes—thebaine 6-O-demethylase (T6ODM), codeine O-demethlyase (CODM), and codeinone reductase (COR)—and incorporated them into a yeast artificial chromosome (YAC). They also manipulated gene copy numbers and implemented other strategies to boost morphine yields. For example, they added two morphine dehydrogenase genes (*morA* and *morB*) from *P. putida* M10 onto the YAC to enhance the synthesis of both hydrocodone and hydromorphine. The modified yeast production strains churn out 51 milligrams/liter (mg/l) of hydrocodone, 70 mg/l oxycodone, and 1 mg/l of hydromorphone, she notes.

However, to be commercially competitive, these yields need to be improved by another 10- to 100-fold, according to Smolke. "We're optimizing the [strains] to produce an integrated production system," she says.

Efforts to develop a microbial fermentation system for making medically valuable opioids from glucose "moved one important step closer," says John Dueber, a bioengineer at the University of California, Berkeley, regarding the efforts of Smolke and her collaborators to make opioids in yeast. "Security measures will be required to prevent misuse," he cautions.

Nonetheless, the availability of such a means for producing opioids could reduce our current reliance on farmed poppies, which are subject not only to plant diseases and climate disruptions but also to illicit trade practices. Australia and Tasmania grow much of the poppies used for legalized opioid production. Having engineered yeast as an alternative means for making these drugs will help to make the supply chain more robust, Smolke says.

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Field of opium poppies. Opium poppies are the source of both licit and illicit opioid drugs. Researchers are working on developing ways to use the yeast *Saccharomyces cerevisisae* to manufacture both opioid compounds currently derived from the plants and and those currently produced by chemical synthesis.

F2

RESEARCH ADVANCES

Microorganisms in Oceans May Arise Faster than Currents Disperse Them

Barry E. DiGregorio

Marine microorganisms appear to be evolving faster than they can disperse, perhaps accounting for their distinctive geographic patterns across several oceans, according to microbial ecolo-

MINITOPIC

First Set of 2015 Gut Microbiota Studies

Efforts to understand how microorganisms in the gut affect the host continue to be part of the news. *Microbe*'s first set of examples for 2015 include:

- The microorganisms in the gastrointestinal tracts of humans are less diverse than those found in African apes, according to Andrew Moeller and Howard Ochman at the University of Texas at Austin and their collaborators. Details appeared 3 November 2014 in *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1419136111).
- Delivering fecal transplant material via capsules proves both effective and safe as a means for treating persistent infections with *Clostridium difficile*, according to Ilan Youngster at Massachusetts General Hospital and Boston Children's Hospital in Boston, Mass., and collaborators. Details appeared 5 November 2014 in the *Journal of the American Medical Association* (doi:10.1001/jama.2014.13875).
- Lipopolysaccharides and peptidoglycans from the gut microbiota stimulate specific inflammatory pathways in peripheral blood mononuclear cells that are correlated with alcohol craving, according to Philippe de Timary and Peter Stärkel of Université Catholique de Louvain in Belgium and their collaborators. Details appear November 1, 2014 in *Biological Psychiatry* (doi:10.1016/j.biopsych.2014.02.003).
- *Lactobacillus* species correlate, in the guts of mice, with mitigation of lupus symptoms, while Lachnospiraceae, a type of clostridium, correlate with worsening, according to Xin Luo of Virginia Tech in Blacksburg and collaborators. Details appeared 26 September 2014 in *Applied and Environmental Microbiology* (doi:10.1128/AEM.02676-14).
- Gut microorganisms produce γ-butyrobetaine from carnitine in red meat, giving rise to trimethylamine and trimethylamine-N-oxide, perhaps accounting for how meat accelerates atherosclerosis, according to Stanley Hazen, of Lerner Research Institute and the Miller Family Heart and Vascular Institute at Cleveland Clinic in Cleveland, Ohio, and his collaborators. Details appeared 4 November 2014 in *Cell Metabolism* (doi:10.1016/j.cmet.2014.10.006
- Disrupting the circadian clock in the host alters the rhythms and composition of the gut microbial community, helping to account for obesity and metabolic problems, according to Eran Elinav of the Weizmann Institute of Science in Rehovot, Israel. Details appeared 23 October 2014 in *Cell* (doi:10.1016/j.cell.2014.09.048).

gist Ferdi L. Hellweger from Northeastern University in Boston, Mass., and his collaborators there and at the University of New South Wales in Sydney, Australia. Their conclusions are based on simulations of marine microbial geography, emphasizing genomic mutations embedded in models of ocean currents. Details appear in the September 12, 2014 *Science* (**345:** 1346–1349).

"In a nutshell, microbes evolve faster than the ocean currents can disperse them," Hellweger says. "Even in an environment that is often considered to be well-mixed, dispersal limitation can be substantial. This [finding] is in contrast to the common notion that microbes are not dispersal limited, or that 'everything is everywhere.'"

For their simulations of how microorganisms move and evolve within ocean environments, Hellweger and his collaborators modeled about 100,000 individual cells that divide and die, each with a 1-million-base-pair genome subject to mutations. Because those mutations are set as neutral and do not affect the growth or death of the microbes, any patterns can be attributed solely to neutral evolution and limits on dispersal. They sampled the population of cells at different times and locations, and then compared their DNA sequences using alignment tools. This analysis revealed emerging patterns, with microbial populations congregating in "provinces," Hellweger says. Differences between those provinces grow gradually but then periodically collapse when populations coalesce.

"The evolution and distribution model [developed by] Hellweger and his collaborators is an excellent example of the growing use of simulation to explore potential hypotheses associated with biogeographic distribution of microbial assemblages," says Jack A. Gilbert from the Argonne National Laboratory in Argonne, Ill., who helps to coordinate the Earth Microbiome Project. "They identify that microbial genomic evolution driven by local processes outweighs potential global mixing.

"The Earth Microbiome Project is characterizing the distribution of phylogenetic units and functional genotypes across the world ecosystems, and sees the same principle of distribution," Gilbert continues. "Some . . . species, can be extremely well distributed, but strain-level variants of these species, some with extensive genotypic variance and, hence, functional ecology, are highly localized in time and space, exactly as predicted by this model."

"We hope to develop models with better predictive power and reconnect modeling with contemporary observa-

tions, like environmental metatranscriptomics," Hellweger says. One long-term goal is to model the transport of individual microbes in the oceans, taking into account their intracellular properties and behaviors, including genes, transcripts, proteins, and metabolism. "In this project," he adds, "we took a natural first step—modeling individuals with whole genomes. Future work on microbe biogeography will have to consider environmental selection and neutral evolution and dispersal limitation."

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NEW IN ASM JOURNALS

Engineered Chestnut Withstands Blight but Spares Fungi at Its Roots

David C. Holzman

Chestnut trees that are genetically engineered to resist the pathogenic fungus *Cryphonectria parasitica* remain good hosts for symbiotic fungi that grow along their roots, according to William A. Powell of the SUNY College of Environmental Science and Forestry (ESF) in Syracuse, N.Y., and his collaborators. This sparing of benign fungi helps in overcoming a potentially important regulatory concern, keeping this transgenic variety of chestnut, *Castanea dentate*, on track for eventual widespread planting, he says. Details appeared 17 October 2014 in *Applied and Environmental Microbiology* (doi: 10.1128/AEM.02169-14).

"Before these trees can be used for a restoration program, they must be tested and then reviewed by three federal agencies—the U.S. Department of Agriculture, the Environmental Protection Agency, and the U.S. Food and Drug Administration," Powell continues. "The American chestnut tree was one of the most abundant and important keystone tree species in the eastern forests of the U.S. Between three and four billion of these trees were lost to the exotic pathogen *C. parasitica* that was introduced into this country around 1900." The American chestnut was highly valued by the lumber industry for its fast growth and rot resistance. The wood was also used widely for making musical instruments and furniture because it is both strong and lightweight.

The transgenic variety that Powell and his collaborators are testing is the first American chestnut tree variety that is specifically engineered to withstand that fungal blight. Its transgene from wheat produces an oxalic acid-degrading enzyme, oxalate oxidase, that targets *C. parasitica*. One potential complication is that nonpathogenic mycorrhizal fungi that live in symbiosis with the roots of trees, including chestnuts, could be an unintended target of that enzyme. Indeed, one important task of such fungi is to produce oxalic acid, presumably to enhance the uptake of minerals by causing biogeochemical weathering of minerals from rock.

"We compared root colonization among the transgenic American chestnut trees, wild-type American chestnut trees, chestnut trees produced by traditional hybrid breeding, and other tree species typically found near chestnuts in the wild," Powell says. "The major relevant result from this work is that the Darling 4 transgenic American chestnut does not differ in ectomycorrhizal fungal associations from the wild-type chestnut." These results hold true for trees grown in both greenhouse and field settings.

These findings address important questions "that will be required for regulatory approval in order to release transgenic chestnut into the wild," says Ronald Sederoff of North Carolina State University in Raleigh. Unlike many other developments involving agricultural biotechnology, the "restoration of chestnut is not market driven," he adds. "It has a primary objective as a social benefit, particularly to the environment and to rural communities. This difference should make the acceptance of a [transgenic] chestnut different from most previous agricultural crops."

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

MINITOPIC

Viral and Fungal Pathogens Threatening Several Types of Amphibians

The fungal pathogen *Batrachochytrium salamandrivorans*, which led to a recent crash of wild fire salamanders in the Netherlands, will likely soon reach the United States unless steps are taken to halt its spread, according to An Martel and Frank Pasmans from Ghent University in Belgium and their collaborators. They find that the fungus probably originated in Southeast Asia and reached Europe through the international trade in Asian newts. Details appeared 31 October 2014 in *Science*, (doi:101126/science.1258268). Meanwhile, two closely related ranaviruses are causing havoc among three species of amphibians—the common midwife toad, the common toad, and the alpine newt—in the Picos de Europa National Park in Spain, according to Stephen Price of University College London in London, England, and his collaborators. Details appeared 3 November 2014 in *Current Biology* (http://dx.doi.org/10.1016/j.cub.2014.09.028).

Box4

NEW IN ASM JOURNALS

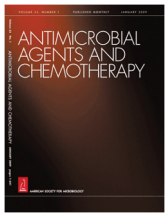
New Method Rapidly Determines Species and Susceptibility in Bacterial Infections

F3

Overprescription of antibiotics is selecting for antibiotic resistance, contributing to one of the great medical problems of our time. Diagnosis of bacterial infections, and determination of antibiotic susceptibility profiles are slow and tedious, and consequently, patients may frequently receive antibiotics to which their particular infection is resistant. Now Mats Nilsson and Dan I. Andersson of Uppsala University in Sweden and collaborators have developed a general method to rapidly identify culprit bacteria species and determine their antibiotic susceptibility profiles. An initial, short cultivation step to be conducted both in the absence, and in the presence of different antibiotics is combined with a sensitive species-specific padlock probe detection of the bacterial target DNA, to determine whether the bacteria are growing or not, to indicate resistance versus susceptibility. In a proof-of-concept for urinary tract infections, they applied the method to determine the susceptibility profile of *Escherichia coli* for two drugs. Accuracy was 100%; duration, just 3.5 hours. That, the investigators write, would minimize the need for prescribing broad-spectrum antibiotics due to unknown resistance profiles of the treated infection.

(A. Mezger, E. Gullberg, J. Göransson, A. Zorzet, D. Herthnek, E. Tano, M. Nilsson, and D. I. Andersson. 2014. A general method to rapidly determine antibiotic susceptibility and species in bacterial infections. J. Clin. Microbiol. Online ahead of print 19 November 2014; doi:10.1128/JCM.02434-14.)

Compounds Targeting DNA Packaging Enzymes Show Promise against Malaria Parasite



Malaria afflicts around 200 million people annually, killing more than 600,000, mostly in Africa, according to the Centers for Disease Control and Prevention. Now Nicholas A. Malmquist of the Pasteur Institute, Paris, France, et al. show that compounds derived from inhibitors of the histone-modifying methyltransferase enzymes kill malaria parasites in culture, as rapidly as the fastest-killing antimalarials available. They show further that these compounds are highly effective against multidrug resistant field isolates from Cambodia, and clinical isolates of the two most prevalent species of human malaria, *Plasmodium falciparum* and *P. vivax*. Furthermore, the compounds kill the malaria parasites specifically, that is, while remaining harmless to animal models and to their microbiomes. Additionally, they kill the parasites in both the form they takes in mosquitos, and in that in which they inhabit mammalian hosts. "All this suggests that this compound series can be developed into new antimalarials effective at both killing and reducing transmission of the relevant parasites currently threatening people in endemic regions," says Malmquist.

(N. A. Malmquist, S. Sundriyal, J. Caron, et al. 2014. Histone methyltransferase inhibitors: orally bioavailable, fast acting molecules with activity against different human malaria species. Antimicrob. Agents Chemother. Online ahead of print 24 November 2014; doi: 10.1128/AAC.04419-14.)

Some Flu Viruses Potentially More Dangerous Than Others

F5

F4

Certain subtypes of avian influenza viruses have the potential to cause more severe disease in humans than do others. Jeffery K. Taubenberger of the National Institute of Allergy and Infectious Disease et al. show that viruses expressing the avian H1, H6, H7, H10, or H15 hemagglutinins led to rapid weight loss and fatal pneumonia infections in mice and caused more cell damage in normal human lung cells than did avian influenza viruses with other hemagglutinin subtypes. Conversely, mice infected with H2, H3, H5, H9, H11, H13, H14, and H16-expressing viruses suffered only mild weight loss, with no significant disease. The team showed similar results using hemagglutinins from two 2013 H7N9 flu viruses from outbreaks in China. These results suggest that hemagglutinins may not require immune cells to trigger cell damage, but instead may cause apoptosis or other molecular processes that could lead to fatalities, says Taubenberger.

(L. Qi, L. M. Pujanauski, A. S. Davis, L. M. Schwartzman, D. S. Chertow, D. Baxter, K. Scherler, K. L. Hartshorn, R. D. Slemons, K.-A. Walters, J. C. Kash, and J. K. Taubenberger. 2014. Contemporary avian influenza A virus subtype H1, H6, H7, H10, and H15 hemagglutinin genes encode a mammalian virulence factor similar to the 1918 pandemic virus H1 hemagglutinin. mBio 5:6; Published 18 November 2014, doi: 10.1128/mBio.02116-14.)

Restrooms: Not as Unhealthy as You Might Think

F6

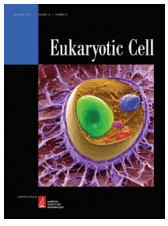
Microbial succession in a sterilized restroom begins with bacteria from the gut and the vagina, and is followed shortly by skin microbes. "We

hypothesized that while enteric bacteria would be dispersed rapidly due to toilet flushing, they would not survive long, as most are not good competitors in cold, dry, oxygen-rich environments," says coauthor Jack A. Gilbert of San Diego State University in California. Instead, as expected, skin microbes took over. Moreover, communities associated with each surface became increasingly similar in species and abundance within five hours of sterilization, and remaining stable for the remainder of eight weeks' sampling. Ultimately, skin and outdoor-associated taxa comprised 68–98% of cultured communities, with fecal taxa representing just 0–15% of these. Outdoor-associated taxa predominated prior to sterilization, and long-term poststerilization, suggesting that long-term, human bacteria must be dispersed in restrooms in order to be maintained. Pathogens were not abundant, and methicillin-resistant *Staphylococcus aureus* was "*Very* rare," says Gilbert.

Toilet seat samples, alone, clustered according to restroom gender, with *Lactobacillus* and *Anaerococcus*—vaginal flora—dominating women's-room toilet seats, while the gut-associated *Roseburia* and *Blautia* were more copious on toilet seats in men's rooms.

(S. M. Gibbons, T. Schwartz, J. Fouquier, M. Mitchell, N. Sangwan, J. A. Gilbert, and S. T. Kelley. 2014. Ecological succession and viability of human-associated microbiota on restroom surfaces. Appl. Environ. Microbiol. Online ahead of print 14 November 2014; doi: 10.1128/AEM.03117-14.)

Sleeping Sickness: Research Suggests Potential Novel Intervention Strategy



Approximately 60 million people live at risk for sleeping sickness, caused by trypanosomes, notably *T. brucei*, while livestock infections, which cause wasting disease, account for significant economic hardship in some of the most impoverished regions of the planet. Treatments are toxic, and increasingly ineffective. Thus, new perspectives are needed on trypanosome biology, transmission, and pathogenesis, in order to develop novel intervention strategies. Trypanosomes are capable of group-level behavior, but mechanisms governing *T. brucei* social motility have been unknown. Now Kent L. Hill and colleagues of the University of California, Los Angeles report that a subset of receptor-type adenylate cyclases in the trypanosome flagellum regulate social motility. RNAi-mediated knockdown of adenylate cyclase 6 (AC6) or dual knockdown of AC1 and AC2 causes a hypersocial phenotype but has no discernable effect on individual cells in suspension culture. Mutation of the AC6 catalytic domain phenocopies AC6 knockdown, demonstrating loss of adenylate cyclase activity is responsible for the phenotype. Notably, knockdown of other ACs did not affect social motility, indicating segregation of AC functions. "These studies reveal interesting parallels in systems that control social behavior in trypanosomes and bacteria, and provide insight into a feature of parasite biology that may be exploited for novel intervention strategies," the investigators write.

(M. A. Lopez, E. A. Saada, and Kent L. Hill. 2014. Insect stage-specific adenylate cyclases regulate social motility in African trypanosomes. Eukaryot. Cell. Online ahead of print 21 November 2014; doi:10.1128/EC.00217-14.)