engineered to produce inviable offspring or introducing mosquitoes infected with *Wolbachia* bacteria, which interfere with the capacity of the insects to produce and transmit CHIKV.

Ongoing phase 1 vaccine trials could lead eventually to preventive vaccine campaigns across the region. Infusion of anti-CHKV immunoglobulins for those at risk to develop severe disease is another potential option, and a clinical trial is under way, according to Marc Lecuit of the Institut Pasteur in Paris, France. Moreover, because type I interferon deficiency is linked to high viremia and severe disease in mice and humans, bolstering this host immune response may also be helpful for some such patients.

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

MINITOPIC

Microbiology Policy Bulletin Board

Recent developments involving microbiology and related science policy matters include:

- California Governor Edmund Brown, Jr., signed legislation in October that, beginning in 2018, will sharply limit antibiotic use in livestock—outright prohibiting use of medically important antimicrobial drugs for promoting weight gain in animals, while also restricting their use for treating sick animals to only those cases approved by licensed veterinarians.
- Federal regulations affecting scientific research at universities should be streamlined and made to be consistent across different agencies that fund such research, according to a report released in September by the National Academies of Sciences, Engineering, and Medicine in Washington, D.C. The report, "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century: Part One" is available at http://www.nap.edu.
- Officials of the U.S. Food and Drug Administration (FDA) in October approved the marketing of the first cerebrospinal fluid nucleic acid-based test for simultaneous detecting multiple pathogens that can cause central nervous system infections. The test battery, called the FilmArray Meningitis/Encephalitis Panel, is manufactured by BioFire Diagnostics of Salt Lake City, Utah.
- During the past 20 years, the number of drugs qualifying for expedited development and approval programs grew significantly at FDA, raising the question whether "this trend is being driven by drugs that are not first in class and thus potentially less innovative," according to Aaron S. Kesselheim of Harvard Medical School in Boston, Mass., and his collaborators. Details appeared 23 September 2015 in *BMJ* (doi.org/10.1136/bmj.h4633).
- Between 2008 and 2014, the United States invested approximately $820 million in synthetic biology research, with the Defense Department becoming a key funder and the Defense Advanced Research Projects Agency now outspending the National Science Foundation by threefold in this sector, according to a September 2015 report, "U.S. Trends in Synthetic Biology Research Funding," from the Woodrow Wilson International Center for Scholars in Washington, D.C. For details, see: http://www.synbioproject.org/.
- People who decide not to vaccinate themselves or their children fall into four main categories: complacency, inconvenience, a lack of confidence, and a rational calculation of pros and cons, according to Cornelia Betsch at the University of Erfurt in Erfurt, Germany, and collaborators in Germany and the United States. Details appeared in the October 2015 *Policy Insights from the Behavioral and Brain Sciences* (doi:10.1177/2372732215600716).

NEW FROM ASM

Chikungunya, Enterovirus D68 Cause Neurologic Symptoms in Children

Shannon Weiman

Recent outbreaks involving the chikungunya virus (CHIKV) and enterovirus D68 in the Americas led to rare but severe neurologic symptoms in infected children that, in some cases, gave rise to long-term neurologic deficits, according to several researchers who spoke during the 2015 Interscience Conference on Antimicrobial Agents and Chemotherapy, in partnership with the International Congress of Chemotherapy and convened in San Diego last September. Researchers continue to probe those rare neurotropisms, for which there are no treatment options, with an aim to develop deficit-sparing interventions.

CHIKV infections are known mainly for causing rheumatic symptoms. However, when transmitted from mother to infant at birth, severe neurologic manifestations afflict 50% of those newborns, while fatalities occur in nearly 17% of such patients, according to Marc Lecuit of the Institut Pasteur in Paris, France, who spoke in the session "Chikungunya: a Global Threat." With chikungunya's recent jump to the Americas, and outbreak numbers reaching 1.6 million within two years of its arrival, these severe cases are of growing concern.

"CHIKV infection acquired in the perinatal period can cause lifelong disability," says Patrick Gerardin of the French National Institute of Health and Medical Research (INSERM). "The neurological outcome of chikungunya encephalopathy . . . ranges from mild ocular, behavioral, or postural deficiency to severe cerebral palsy with

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Progress Notes for Novel Methods, Promising Diagnostics

Examples of recent progress toward developing useful methods for various purposes, such as genetic engineering of cells, genomic sequencing, and for diagnosing diseases include:

- A newly recognized CRISPR system, called Cpf1 and found in *Acidaminococcus* and *Lachnospiraceae* bacterial species, offers several advantages over the Cas9 system, including being simpler and smaller than Cas9, and also by introducing offset rather than blunt cuts into targeted DNA sites, according to Feng Zhang and his colleagues at the Broad Institute in Cambridge, Mass. Details appeared 25 September 2015 in *Cell* (doi:http://dx.doi.org/10.1016/j.cell.2015.09.038).
- The virome-capture-sequencing platform for vertebrate viruses uses some 2 million probes to test simultaneously for hundreds of different viruses, providing near-complete sequences of their genomes and is as sensitive as PCR, according to Ian Lipkin of the Columbia University Mailman School of Public Health in New York, N.Y., and his collaborators. Details appeared 22 September 2015 in *mBio* (doi:10.1128/mBio.01491–15).
- A new test, called ViroCap and based on targeted sequence capture to enrich for DNA and RNA viruses, detects "virtually any virus that infects people and animals," according to Gregory Storch at Washington University School of Medicine in St. Louis, Mo., and his collaborators. Details appeared 22 September 2015 in *Genome Research* (doi:10.1101/gr.191049.115).
- A rapid, DNA-based electrochemical test can be used to identify proteins or other biomarker molecules in the low nanomolar range in blood samples for diagnostic purposes, according to Alexis Vallée-Bélisle at Université de Montréal in Montreal, Quebec, Canada, and his collaborators. This testing device works on the basis of steric hindrance, they point out. Details appeared 24 September 2015 in the *Journal of the American Chemical Society* (doi:10.1021/jacs.5b04942).
- DNA sequencing of microbial pathogens in urine specimens using the MinION nanopore sequencing device yielded results four times more quickly than the traditional approach of culturing bacteria in such samples, according to Katarzyna Schmidt and Justin O'Grady of the University of East Anglia in the United Kingdom. They presented their findings during the 2015 Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) and International Society of Chemotherapy (ICC) meeting, held in San Diego last September.

extensive white matter damage." Deficits in language and coordination are most common, consistent with scans showing brain swelling in the frontal lobe. Developmental delays and persistent disability occurs in 30–40% of cases.

Unlike other neurotropic alphaviruses such as equine encephaloviruses, CHIKV does not infect the placenta. Instead it is transmitted from viremic mothers to babies during birth, says Lecuit. CHIKV then infects the brain through the choroid plexus, an epithelial barrier between the blood and cerebrospinal fluid (CSF). These cells are highly susceptible to CHIKV infection when tested in vitro and in mice, whereas endothelial cells along the blood-brain barrier, glial cells, and neurons are not. Within the CNS, CHIKV targets the leptomeninges, which envelop the brain and spinal cord, and cells that line cavities inside the central nervous system, replicating and amplifying virus in the CSF.

Enterovirus D68 (EV-D68), responsible for outbreaks of respiratory illnesses among children across the United States last year, also gives rise to rare polio-like neurologic manifestations, according to Aaron Milstone of Johns Hopkins University in Baltimore, Md., who spoke in the session "Enterovirus D68: What Is It and Where Did It Come From?" When mysterious cases of muscle weakness and paralysis emerged in Colorado and California in 2014, investigators from the Centers for Disease Control and Prevention (CDC) tested specimens suspecting that they would find polio or a similar virus but, instead, found EV-D68. As of July this year, the CDC reports 120 cumulative cases in 34 states.

Enteroviruses typically target the respiratory tract, causing cold-like symptoms, but neurotropic strains also exist. Sequencing of samples from the ongoing outbreak reveals mutations that could confer neurotropism in EV-D68, says Charles Chiu of the University of California, San Francisco. "Clade B1 strains have mutations that distinguish them from other enteroviruses by making them resemble polio virus," he reports. Chiu suspects a VP1 capsid polymorphism may be important for neuronal targeting. Neuroimaging reveals lesions in CNS grey matter and nerve dysfunction typical of neurotropic enteroviruses that target motor neurons, adds Kevin Messacar of Children's Hospital Colorado in Aurora.

NEW FROM ASM

Antibacterials: Siderophore Conjugates, Polymixins, and 2-Pyridones; Plus Antifungals

Jeffrey L. Fox

Several new antibacterial candidates shared the stage with some promising

antifungal candidate agents during the poster summary session "Early New Antimicrobial Agents" of the 2015 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), partnered with the International Congress of Chemotherapy, in San Diego, Calif., last September. The antibacterial agents include less-toxic versions of polymyxin, a 2-pyridone that is specific for *Neisseria*, and several siderophore conjugates with surprising types of antibacterial activities. The antifungal prospects include agents active against DNA but with unusual or, in another case, undisclosed mechanisms, as well as a stabilized echinocandin.

CA1051, a novel nonapeptide version of the antibiotic polymyxin, is "more potent than polymyxin itself, and it's less cytotoxic," says Mike Dawson of Cantab Antiinfectives in Welwyn Garden City, near London in the United Kingdom. This particular compound is one among several nonapeptide polymyxin variants, in which various sidechains are substituted for cyclic heptapeptides and a fatty acid that are part of this class of antimicrobial agents that target gram-negative bacteria. CA824, another candidate nonapeptide in this group, is 10-fold less cytotoxic than polymyxin, and its efficacy is equal to or better than polymyxin B when tested against infections in mice thighs or lungs, respectively, he says. Precisely why some of these new derivatives show such better efficacy in mouse lungs is not yet known but appears to be "quite consistent across various derivatives," he adds. "There's a whole range of these compounds that we're evaluating. We expect to see new compounds moving into clinical use within 5 to 10 years."

P300847, a 2-pyridone, is considered a "lead" antibacterial agent among a series of such compounds whose activity is directed against *Neisseria gonorrheae*, according to Melissa Dumble of PTC Therapeutics in South Plainfield, N.J. This particular derivative—specifically its S stereoisomer, is broadly active against many different isolates of this sexually transmitted bacterial pathogen, she says. Although also active against *N. meningitidis*, this and other similar 2-pyridones are not active against other gram-positive pathogens or microorganisms of the gut microbiome. These 2-pyridones are bactericidal inhibitors of DNA biosynthesis, with "novel mechanism of action," she notes. However, although the target of that activity was identified, she and her colleagues are not yet disclosing its nature.

"We are designing synthetic siderophores," says Marvin Miller of the University of Notre Dame in Notre Dame, Ind., and Hsiri Therapeutics in King of Prussia, Pa. Depending on the specifics of that design, some of these "sideromycins" are active against gram-negative bacterial pathogens such as *Pseudomonas aeruginosa*. For instance, ampicillin, which is not active alone against this pathogen, becomes active against *P. aeruginosa* once it is attached to an appropriate siderophore and, in that form, circumvents efflux mechanisms, he says. "If you want to use this concept, you need to use molecules that look like natural siderophores. We are beginning to test these compounds."

In another example, cephalosporin, which is not by itself active against *Acinetobacter baumannii*, "is very active" once connected to a siderophore against that pathogen when it infects mice, and it is "well tolerated" by those treated animals, Miller continues. "We are quite excited . . . *A. baumannii* is a very bad bug, but we get MICs in the nanomolar range with our conjugates." In another unusual twist, daptomycin, which typically is active against gram-positive bacterial pathogens, becomes active against gram-negative *A. baumannii* when conjugated to an appropriate siderophore, he adds. "This is pretty exciting—a game changer. There's still a lot to do, but we've dis-

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Tree of Life "First Draft" Maps 2.3 Million Species; Viruses Declared Living

A newly assembled "first draft" Tree of Life accounts for roughly 2.3 million species, including microbes, animals, and plants, according to Karen Cranston of Duke University in Durham, N.C., and collaborators from nearly a dozen institutions. This comprehensive tree was assembled by combining phylogenetic information already assembled from 484 other partial trees chosen from thousands of other such trees that are described in published reports. Although comprehensive as of the moment, the tree can be "easily updated" with newly published data, and some parts of it, particularly covering insects and microbes, remain "elusive," the researchers note. Details appeared 18 September 2015 in *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1423041112).

In a related development, viruses are released from their long-hazy status of being considered only quasi-living to be declared "living entities," after having been mapped onto a Tree of Life on the basis of protein "folds" encoded in their genomes and in those from cells of many other organisms, according to Gustavo Caetano-Anollés of the University of Illinois, Champaign, and his former graduate student Ashan Nasir. "Viruses now merit a place in the tree of life," says Caetano-Anollés, noting that 442 protein folds are shared between cells and viruses, whereas 66 appear unique to viruses. It appears likely, he adds, that viruses originated from multiple ancient cells, which may have contained segmented RNA genomes. Details appeared 25 September 2015 in *Science Advances* (doi:10.1126/sciadv.1500527).

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A Noteworthy Medley of Newly Identified Viruses or Viral Components

Recently identified viruses or virus components include:

- When expressed in mice, the envelope protein from one of the ordinarily latent human endogenous retroviruses (HERV), called HERV-K, which can be detected in the blood and cerebrospinal fluid of some patients with amyotropic lateral sclerosis (ALS), causes neurodegeneration in the motor cortex and disrupts motor neurons in the spines of such animals, according Avindra Nath of the National Institutes of Health in Bethesda, Md., and his collaborators. Details appeared 30 September 2015 *Science Translational Medicine* (doi:10.1126/scitranslmed.aac8201).
- *Mollivirus sibericum*, the fourth type of giant virus isolated from 30,000-year-old Siberian permafrost, is a spherical virion with a 0.6-μm diameter that encloses a 651-kb GC-rich DNA genome encoding 523 proteins, according to Jean-Michel Claverie of Aix-Marseille Université in Marseille, France, and his collaborators. One surprise is that the virus packages its *Acanthamoeba* host's ribosomal proteins. Details appeared 22 September 2015 in *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1510795112).
- The newly recognized human virus human hepegivirus 1 (HHpgV-1) shares features with hepatitis C virus and human pegivirus, was found in serum from blood transfusion recipients, and appears to be responsible for causing long-term viremia in at least two hemophilia patients, according to Amit Kapoor of Columbia University in New York, N.Y., and his collaborators. They call HHpgV-1 "unique" for sharing "genetic similarities with both highly pathogenic HCV and apparently nonpathogenic" viruses. Details appeared 22 September 2015 in *mBio* (doi:10.1128/mBio.01466–15).

pelled the myth that [sideromycins] will have no in vivo activity."

F901318, an orotomide molecule with novel activity against fungal pathogens, targets a key enzyme in the pyrimidine biosynthetic pathway, according to John Rex of Astra Zeneca, who is based in Waltham, Mass. Although humans depend on a similar enzyme for pyrimidines, this agent shows very little activity against the human version of that enzyme, he says. When tested in vitro, the minimal inhibitory concentrations (MICs) of F901318 are "very robust" against *Aspergillus fumigatus* and other filamentous fungi, but it is not active against *Candida* or *Cryptococcus* species. When administered in vitro to cells of *A. fumigatus*, it stops hyphae growth abruptly and appears to instigate membrane "perturbations." The compound distributes well in most tissues in mice, albeit poorly to the central nervous system, when administered either orally or intravenously, he adds. Further, it is well-tolerated in humans.

SCY-078, a novel triterpene compound that inhibits the β-1,3-glucan synthase enzyme that is critical for yeast cell-wall synthesis, is active against invasive fungal pathogens, according to Stephen Wring of Scynexis Inc. in Jersey City, N.J. Based on testing of tissue distributions in mice, rates, and dogs, it appears to be potentially useful for treating pulmonary infections, he says. Early this year, the Food and Drug Administration (FDA) granted this compound "fast-track" status as a potential orally available agent for treating invasive candidiasis and aspergillosis.

CD101, a novel antifungal agent from the echinocandin class, has "one key feature," according to Dirk Thye of Cidara Therapeutics in San Diego. A simple substitution stabilizes the echinocandin ring, thus extending the half-life of the candidate drug, making it "amenable to once-weekly dosing," he says. Moreover, the same chemical modification also reduces hepatotoxicity, suggesting clinicians could administer it in very high doses early during a therapeutic course. "Its potency is like other echinochandins," he adds. "It shows good activity against *Candida* strains, but also [against] *Aspergillus* and *Cryptococcus*. And, because it's fungicidal, the resistance potential is low." A phase 1 clinical study began several months ago, and results are expected by the end of this year.

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

NEW FROM ASM

Yeast-Breeding Efforts Augur a Fresh, Flavored Diversity for Lagers

David C. Holzman

By creating new genetic crosses among relevant brewing yeasts, lager beers can be made more variable in flavor—letting them compete more favorably perhaps with ales, long-known for their broader taste variability, according to Kevin Verstrepen and Stijn Mertens of the University of Leuven, Belgium, and their collaborators. Details appeared 25 September in *Applied and Environmental Microbiology* (doi:10.1128/AEM.02464–15/).

The relatively uniform flavor among lagers results largely from a lack of genetic diversity among the yeasts that are used to make them, Verstrepen says. The principal lager yeast used throughout the industry, *Saccharomyces pastorianus*, derived from a very few simple genetic crosses between two ancestral yeast species, *S. cerevisiae* and