MINITOPIC

New Treatments for Hepatitis B and C Viruses Show Promise

Several new drug combinations or other treatment strategies look promising for treating chronic infections with either the hepatitis B (HBV) or hepatitis C (HCV) viruses.

- Combining peginterferon with one of several nucleoside analogue antiviral agents appears superior to drug monotherapy in clearing HBV infections, according to Cihan Yurdaydin from the University of Ankara in Ankara, Turkey, who spoke last April during the International Liver Congress in London, England.
- A 12-week, dual-drug treatment course with ledipasvir and sofosbuvir is one of several new combinations that proved "highly effective" against chronic HCV infections, according to Nezam Afdhal at Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, Mass., and his collaborators. He spoke last April during the meeting of European Association for the Study of the Liver (EASL), held in London, England.
- A three-drug combination to treat HCV, consisting of the NS3/4A protease inhibitor ABT-450 dosed with ritonavir, the NS5A inhibitor ABT-267, and the NS5B RNA polymerase inhibitor ABT-333, yielded "consistently high cure rates across a number of patient types, including the more difficult-to-treat subtype GT1a," according to Alessio Aghemo of the University of Milan in Milan, Italy, who also spoke at the EASL meeting in April.
- Combining the NS3/4A protease inhibitor simeprevir with peginterferon and ribavirin proved effective and was well tolerated in genotype 4, HCV-infected patients, according to EASL Secretary General Markus Peck-Radosavljevic of the Medical University Vienna in Vienna, Austria.
- A once-daily combination of the nucleotide analogue polymerase inhibitor sofosbuvir and the NS5A inhibitor ledipasvir also "yields highly satisfactory cure rates" among patients infected with HCV, according to Peck-Radosavljevic.
- Germ-free mice being fed on an alcohol-only diet and then treated with gut microbiota from a human donor with alcohol abuse fared better than did comparable mice that received gut microbiota from an individual with alcoholic hepatitis—suggesting a role for the gut microbiota in alcohol-induced inflammation, according to Marta Llopis of INSERM in Clamart, France, and her collaborators.

living today than those living before the rise of oxygen. Thus, it appears also possible that thioredoxins were transferred into these methanogens after the rise of oxygen, but perhaps still long ago. The observations presented by [Mukhopadhyay and his collaborators] open up a new and interesting set of questions about when and how this chemistry appeared on Earth."

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RESEARCH ADVANCES

Phenazine-Detecting Chips Can Follow Bacterial Physiology in Biofilms

Carol Potera

Integrated circuits, designed to respond to specific metabolites, are now being used to detect signaling in microbial biofilms and someday might be used to disrupt those biofilms, according to Lars Dietrich and other biologists and electrical engineers at Columbia University in New York, N.Y. Details appeared February 11, 2014 in *Nature Communications* (doi:10.1038/ncomms4256).

Pseudomonas aeruginosa bacteria, including those within biofilms, produce redox-active phenazine metabolites that act as electron acceptors and help to control gene expression and colony morphology. For example, specific mutants that stop producing phenazines form wrinkled colonies with ruffled edges, whereas wild-type bacteria form smooth colonies. The researchers built a phenazine-responsive chip to probe how those metabolites contribute to colony morphology.

Images produced by the chip, which can track phenazines in space and time, show these metabolites diffusing and forming gradients, "which is likely to be of physiological significance and contribute to colony morphogenesis," Dietrich and his collaborators note. "Pairing genetic manipulation with direct detection of phenazines will allow us to dissect the organizational functions of phenazines further."

Since publishing their proof-of-concept results using a prototype chip with 60 electrodes, the team has built a new chip with 1,800 electrodes. "This allows us to image a complete colony with higher resolution," says Dietrich. The new chip shows that phenazines are not evenly released across a biofilm colony, and the ratio of different phenazines varies as well. The new chip will allow them to answer questions about when and where different phenazine species are produced, as well as how the redox state of phenazines controls colony development and spatial gene expression.

"This is a big step forward," Dietrich continues. "We describe using this chip to 'listen in' on conversations taking place in biofilms, but we are also proposing to use it to interrupt these conversations and thereby disrupt the biofilm. In addition to the pure science implications of these studies, a poten-

tial application of this would be to integrate such chips into medical devices that are common sites of biofilm formation, such as catheters, and then use the chips to limit bacterial colonization."

Like computers and cell phones, "the chip contains silicon transistors that actively interact with biofilms," says electrical engineer Ken Shepard, who is Dietrich's collaborator. The prototype device designed for these proof-of-principle experiments contained 60 electrodes, he notes. The latest version with 1,800 electrodes costs less than $1.00 to manufacture. In contrast, mass spectrometers that image biofilms cost $100,000 or more.

"Overall, the work is an outside-the-box marriage of microbiology with electronic, biomedical, and computer engineering. It will give insights not only into the physiological functions of phenazines in *P. aeruginosa,* but also could provide new perspectives on eukaryotic developmental processes," says research geneticist Linda Thomashow at Washington State University, Pullman.

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RESEARCH ADVANCES

Periodontal Pathogens from Medieval Teeth: Same Old, Same Old

John Otrompke

Analyses of DNA and proteins harvested from the dental calculus of four human skeletons in a 1,000-year-old graveyard and then subjected to protein and DNA sequencing as well as tandem mass spectrometry provide "a detailed picture of periodontal disease 1,000 years ago," says Christina Warinner of the University of Oklahoma in Norman. "Periodontal disease is caused by the same bacteria today as in the past, despite major changes in human diet and hygiene. This [disease] is not something that emerged in the last 1,000 years." Details appeared 23 February 2014 in *Nature Genetics* (doi:10.1038/ng.2906).

Periodontitis causes inflammation of the gums, and can lead to losses of bone as well as teeth. Although common among humans as well as pets, domesticated animals, and animals kept in zoos, this disease is considered rare in the wild.

The skeletons were buried between 950 and 1200 CE in a convent cemetery in Dalheim, Germany, according to Warinner and her collaborators. "The convent was sacked and burned to the ground around 1300 CE, but the site today has a monastery on it, with a big museum," she says. All four samples contain remnants of *Tannerella forsynhensis* as well as other known microbial pathogens of the oral cavity, including *Filifactor alocis*, a microbe that was recognized as a likely agent of periodontitis relatively recently.

Dental calculus "acts both as a long-term reservoir of the oral microbiome and as a trap for dietary and environmental debris," Warinner says. "These people all showed bone loss. Unlike bone, which rapidly loses much of its molecular information when buried, calculus grows slowly in the mouth and enters the soil in a much more stable state, helping it to preserve biomolecules. This allows us to investigate health and disease, as well as reconstruct aspects of an individual's life history and activities. Never before have we been able to retrieve so much information from one small sample.

"We don't know when periodontal disease first arose in humans, but analyzing the microbial communities of ancient dental calculus may help us understand how the human oral microbiome has changed through time and why periodontal disease has become so common," she continues. "I ultimately plan to analyze dental calculus samples from the Paleolithic to the present. We're still in the sample collection phase, so I'm not yet ready to reveal the populations we are targeting, but we are aiming for a broad survey of global ancient oral microbiome health."

"To reverse the calcification process, to completely dissolve that away and

MINITOPIC

FDA Says Industry Accepting Policy on Antibiotics in Animals

Officials of the Food and Drug Administration (FDA) in March said that they were "encouraged by the strong response" from industry to the agency's Guidance 213, issued in December 2013 (*Microbe*, February 2014, p. 48). That guidance seeks to curb development of antibiotic resistance by changing how those drugs are used in agriculture. "All but one animal drug company committed in writing to seek withdrawal of approvals," for antimicrobial agents whose nontherapeutic uses are to be phased out, FDA officials note.

Agency critics, however, claim that the guidance is too flawed to succeed. "There is still no evidence that the FDA's voluntary plan will do anything to limit the increase in the antibiotic-resistant bacteria," says health attorney Avinash Kar of the Natural Resources Defense Council in Washington, D.C. Adds the Washington-based coalition, Keep Antibiotics Working (KAW), the FDA policy "falls far short of what is required to protect public health." KAW urges the agency to "abandon this rule-making process, or significantly modify it."

In a related development this April, the Joint Programme on Antimicrobial Resistance in Europe issued its strategic research agenda outlining six broad steps to "minimize antimicrobial resistance." For details, see http://www.jpiamr.eu.