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**QIIME: Better Described as EMSAP?**

The software described as QIIME (quantitative insights into microbial ecology) is being used widely for the analysis of molecular sequences recovered from microbial assemblages (http://qiime.org/). As an example of this wide use, there have been 144 citations including this term in ASM full-text articles (as of 24 November 2014) and approx. 93,000 hits in Google. This 16s rRNA-based approach (J. Caporaso et al., Nature Methods 7:335–336, 2010) “allows analysis of high-throughput community sequencing data,” including particularly the assessment of “diversity.”

Five critical words being used to describe this QIIME approach should be considered in relation to the molecular sequences that are being analyzed, particularly when using bulk extraction for recovery of nucleic acids.

(1) Quantitative. The word quantitative has several different implications for bulk extraction-based molecular microbial ecology. It is necessary to prove that some consistent percentage of the molecular sequences present in natural microbial assemblages are being recovered (ideally 100%). However, successive extractions of the same sample yield additional and possibly different nucleic acids (L. Feinstein et al., Appl. Environ. Microbiol. 75:5418–5433, 2009; M. Jones, et al., Appl. Environ. Microbiol. 77:2984–2991, 2011; F. Martin-Laurent et al., Appl. Environ. Microbiol. 67: 2354–2359, 2001). It would appear to be more appropriate to describe these raw sequences derived by bulk extraction. The 16s rRNA approach, in many respects, is problematic. There are concerns with PCR amplification, if used (I. Dahlöf, Curr. Opin. Biotech. 13:213–217, 2002), possible coamplification of eucaryotic DNA (G. Huys et al., Curr. Microbiol. 56:553–557, 2008), differing ecophysiological with identical 16S rRNA sequences (E. Jaspers and J. Overmann, Appl. Environ. Microbiol. 70:4831–4839, 2004), and in addition, intragenomic heterogeneity which can lead to overestimation of diversity (D. -L. Sun et al., Appl. Environ. Microbiol. 79:5962–5969, 2013). As an additional aspect of this word, important aspects of microbes and their ecology are not readily quantified. These would include the characteristics of indeterminate microbes, such as the filamentous fungi (D. Klein and M. Paschke, Microbial Ecol. 47:24–235, 2004) and pleomorphic microbes such as *Hyphomicrobiuim* (P. Hirsch, Ann. Rev. Microbiol. 28:391–440, 1974) and *Caulobacter* (V. Hughes et al., Current Biology 22:R507-R509, 2012) for which single value estimates such as biomass or biovolume (or an OTU) do not describe subtle aspects of morphological changes and their ecological implications. It would appear more appropriate to simply describe these raw sequences as having been derived from a microbial assemblage by the use of bulk extraction.

(2) Microbial. This word leads to the assumption that the full range of microbial entities is being studied, including the bacteria, archaea, fungi, protozoa, algae and the acellular entities, including viruses, prions, viroids and virusoids. With the 16s rRNA approach upon which QIIME is centered, bacteria, and possibly archaea are being studied. As discussed by T. White (Microbe 4;536, 2009) these studies might better be described as being predominantly bacteriocentric.

(3) Ecology. E. P. Odum (Fundamentals of Ecology. W.B.Saunders Company, Philadelphia, 3rd ed., 1971) defined ecology as: “the study of the relation of organisms or groups of organisms to their environment, or the science of the interrelations between living organisms and their environment.” Ecology, in a microbial context, can be defined as “The interactions of microorganisms with their abiotic and biotic environments.” Microbial ecology thus involves the study of in situ active microbes, usually a minor component of microbes in natural microbial assemblages. This point also was made by Baas Becking (Geobiologie of inleidende tot de milieukunde, W.P. Van Stockum & Zoon, The Hague, the Netherlands, 1934, page 13), who noted that most microbes in nature were present in a latent state, and by myself (Microbe 2:591–595, 2007) as well as many other workers. Microbial ecology, as its major task, is involved with the study of in situ active microbes. Without proof, bulk-extracted nucleic acids cannot be assumed to be derived exclusively from in situ active microbes, central to the study of microbial ecology.

(4) Community. The study of biological communities has its major emphasis on living, interacting, communicating organisms. In a macroecological context, E. Pielou (Ecological Diversity, John Wiley and Sons, Inc., New York, NY, 1975) provided the following definition: “Any assemblage of plants and animals living together in one place and to a greater or lesser degree, interacting with one another—in
a word, an ecological community—.” By replacing “plants and animals” with “microbes” this definition can be considered in a microbial context. It would not appear to be defensible to state that bulk-extracted nucleic acids represent the community, unless they are proven to be derived solely from in situ active microbes.

(5) Diversity. The QIIME approach is suggested to be able to provide information on diversity (J. Caporaso et al., Nature Methods 7:335–336, 2010). It is critical to state which specific aspect of diversity is being studied. In the context of molecular microbial ecology, “diversity” can be used to describe: (a) molecular sequence diversity, (b) cellular molecular diversity, (c) acellular molecular diversity, and (d) in situ active microbe molecular diversity. Without information concerning the more specific source of these raw sequences being provided, it would appear to be most appropriate to describe this as molecular sequence diversity.

The central problem is that bulk-extractable nucleic acids, used in most QIIME analyses, can be derived from microbes that are not active and interacting in situ due to abiotic or biotic limitations, or from extracellular DNA. These molecular sequence sources in microbial assemblages can include: (a) inactive microbes (abiotic-limited), (b) inactive microbes (abiotic permissive, biotic-limited), (c) dormant microbes (abiotic permissive, biotic-limited, but can become biotic permissive), (d) in situ active microbes (the microbial community), (e) viruses (virocells/virions/cryptic viral genomes), and (f) extracellular nucleic acids including extracellular DNA (eDNA), as discussed previously (D. Klein, Microbe, 2:591–595, 2007; 114th ASM General Meeting, abstract N-2753, 2014).

Based on these considerations, it is necessary to prove that molecular sequences are derived from in situ active microbes to be able to state that one is studying the ecology of microbes or the microbial community. I would suggest that this approach, described as QIIME, more properly should be described as EMSAP (environmental molecular sequence analysis program). This is based on my concern, expressed in a recent communication (D. Klein, Microbe, 6:377, 2011), that to be able to state the source of molecular sequences derived from microbial assemblages using bulk extraction, that it is necessary to provide proof of the source. In my view, such proof has not been provided in developing the entire “QIIME” approach.

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Carcinogenesis—Real Understanding at Last

Recent insights into cancer causation have revived memories of earlier disputes, and re-emphasized the significance of the oft-ridiculed Johannes Fibiger

Bernard Dixon

Not the least welcome implication of a recent paper by Cristian Tomasetti of Johns Hopkins Bloomberg School of Public Health and Bert Vogelstein at the Howard Hughes Medical Institute, both in Baltimore, Md., is that it appears to furnish a definitive resolution of longstanding disputes over the origin of cancer—whether primarily genetic or environmental. Writing in Science (347:78, 2015), they have shown that the lifetime risk of many cancers correlates strongly with the total number of divisions of the normal, self-renewing cells maintaining homeostasis in different tissues. Only a third of the variation in cancer risk among tissues can be attributed to either environmental factors or genetic predispositions.

A remarkable feature of past arguments over the etiology of cancer has been that not only have the scientific facts been polarized between researchers from differing perspectives, but so too have broader social deliberations. This was especially evident during the 1970s, a decade whose zeitgeist was characterized by the words environment and pollution. I recall one particular report, apparently erudite and scholarly, which was utterly irresponsible in its selection and use of information culled from the journals. The authors wanted to persuade the world that the real issues, upon which practical action could be taken, were carcinogens in food and in effluents discharged by the chemical industry. So they ignored or marginalized all evidence of genetic predispositions.

One instance of the determination of campaigners to emphasize the role of dietary factors in carcinogenesis was their dogged determination, until the very last, to resist the ending of the notorious Delaney clause. Named after Congressman James Delaney of New York and included in the Federal Food, Drugs and Cosmetic Act of 1958, it banned the use in food of any chemical “found to induce cancer in animals.” In reality this ruling was unworkable, though it did lead to the banning of several additives, used in foods in vanishingly tiny concentrations, that could cause malignancies in experimental animals when administered (often through unrealistic routes) at very high levels. The Delaney clause was finally abandoned only in 1996.

The Tomasetti/Vogelstein paper in January also brought back to mind the story of two scientists, one unfairly ridiculed and the other unfairly neglected, for their work on carcinogenesis. They were the Danish pathologist Johannes Fibiger and the Japanese pathologist Katsusaburo Yama
giwa. According to traditional ridicule, Fibiger received a Nobel Prize for the transparently barmy notion that nematodes caused malignant tumors in rats. Barmy, at least, it has seemed to several writers since that time who have been able to reflect with hindsight upon the false trails and frustrating mirages that have always accompanied cancer research.

William S. Beck, for example, in his otherwise splendid book Modern Science and the Nature of Life (Macmillan), records the event in these words, as part of a passage outlining wrong-headed speculations: “Many stories of this kind could be told. In 1926, the Nobel Prize was awarded to a man named Fibiger for ‘proving’ that cancer was caused by certain small worms.” Beck then leaves his readers to chuckle at the Dane’s naivety. Now it is true that by honoring Fibiger “for his discovery of the Spiroptera carcinoma,” the wise persons at the Caroline Institute in Stockholm implied that he had identified the specific agent of a form of cancer. He had not. But neither they nor Fibiger generalized his work to suggest that he had located the cause of the disease. Only later commentators have done that. More important, the meticulous Dane has rarely been credited for the considerable impact which...
his efforts had on the course of experimental on-

cology.

To appreciate Fibiger’s influence, we must re-
call that in 1907, when he began his studies in
Copenhagen, the field was in utter confusion. The
British surgeon Percival Pott had deduced that
chimney sweeps often succumbed to scrotal
cancer because they were exposed continually to
coal tars in soot. But repeated attempts in both
Europe and the United States to create tumors by
rubbing tar into animals’ skin had failed. Even
after months of application, the skin of rabbits,
rats, mice, and other recipients remained infuri-
atingly normal. So, despite Pott’s persuasive
work, the experimental study of cancer lan-
guished. Rival explanations for the origin of ma-
lignancy proliferated with corresponding vigor.
The theory that prolonged irritation was a con-
tributory factor emerged strongly from observa-
tions on occupational cancers. But far from there
being any proof, researchers were totally unable
to reproduce malignant tumors, by this or any
other means, in the laboratory.

Enter Johannes Fibiger. It was an accidental
observation that triggered his momentous con-
tribution. In the stomachs of some rats, he no-
ticed tumors which in turn contained a parasitic
worm, later called *Spiroptera neoplastica*. Neither
the cancer nor the nematode were known previ-
ously. Clarifying the relationship between the
two demanded a long, painstaking investigation
in which Fibiger’s scrupulous approach belies the
sarcasm of his later detractors.

First, Fibiger tried but failed to elicit tumors by
feeding rats with either the worms or their eggs.
Then he looked into the life cycle of *Spiroptera*
and realized that it passed part of its time in the
cockroach. The eggs produce larvae in the intest-
tines of this intermediary host, and these then
enter its striated muscles, where they become
encysted. Rats are not infected by consuming the
parasite directly, only by eating infected cock-
roaches. Sexually mature worms develop in the
rat stomach, in the forepart of which tumors may
then appear: The tumors are malignant, some-
times yielding metastases and being capable of
transplantation into healthy rats. By revealing
this sequence of events, Fibiger showed why the
tumors he had discovered were so rare: they ap-
peared only when rats ingested the parasite as
larvae—and even then not with predictable cer-
tainty.

Johannes Fibiger’s work had two conse-
quences for cancer research. First, it established
the experimental study of malignancy, by show-
ing for the first time that cancer could be induced
in laboratory animals. Well over half a century
later, as we turn increasingly towards epidemi-
ology and away from inordinate dependence
on bench work, the significance of this shift
may appear less than striking. In fact, it marked
a historic thrust in the advance of medical sci-
ence.

Fibiger’s other contribution was to convince
scientists that chronic irritation could indeed
trigger the appearance of cancer. It was probably
both mechanical and chemical irritation from the
*Spiroptera* parasites, rather than any specific on-
cogenicity, that precipitated the rat tumors. Al-
though the explanation of his work is uncertain to
this day (some investigators have suggested vita-


min A deficiency could have accounted for the
malignancy), its role as a stimulus to others is not
at issue. One direct result was that in 1915–16
Katsosaburo Yamagiwa succeeded, where others
had failed, in producing skin cancer by rubbing
coal tar repeatedly into rabbits’ ears. This, conse-
quent work by Ernest Kennaway at the Royal
Cancer Hospital, London, and the trail of re-
search leading to modern concepts of promoters
and inducers of malignancy, we can trace directly
to the Dane’s enthusiastic efforts.

So the 1926 Nobel Prize for Physiology and
Medicine went to Copenhagen. It did so not be-
cause anyone was convinced that Fibiger had pin-
pointed *the* agent of cancer, but because his work
had laid the foundations for a major forward
movement. According to the official record of
their deliberations, the mandarins of the Caroline
Institute adjudged that Yamagiwa’s work, al-
though apparently more spectacular, did not have “the same degree of originality.” The Nobel
authorities displayed rare discernment in select-
ing the scientist to receive their unique award.
Will Heat of Debate Thaw Latest Freeze on Gain-of-Function Viral Research?

Jeffrey L. Fox

Last October, the White House imposed a “pause” on gain-of-function (GoF) research involving the influenza and two coronaviruses, SARS and MERS, pending a two-part review of safety and security concerns that is aimed at developing a new policy for dealing with such research. One part of that review continues within the federal National Science Advisory Board for Biosecurity (NSABB), while the second part took place more publicly last December during the symposium “Potential Risks and Benefits of Gain-of-Function Research,” convened by the National Academy of Sciences in Washington, D.C. This latter phase apparently helped persuade officials late in December to exempt some MERS projects from the pause, which otherwise remains in effect.

During the symposium, differences between those who want to move ahead with such research and others who prefer its being restricted seemed palpable. The depth of those differences is no real surprise. Some insiders consider this moratorium to be the third time several research groups studying GoF influenza were stopped cold, albeit the first time for those studying MERS and SARS. Regardless of the validity of these shutdowns, they are intensely disruptive for those whose labs and lives are directly affected. Meanwhile, those favoring this pause in GoF research see the public health threat from making these already deadly viruses even more dangerous—more virulent or more readily transmissible—as too much to risk.

Proponents of this research are asking, why stop and start that influenza research, which already was subject to careful scrutiny? And why halt SARS and MERS studies at this juncture? The “pause” comes amid the ongoing Ebola outbreak in Africa and following disclosures in mid-2014 that several federal labs were found to be holding “improperly registered” cultures of select biological agents or toxins (Microbe, February 2015, p. 49). Although those recent mishaps may not account for the pause, surely they set a tone that was not helpful for the set of experts trying to persuade skeptics of the wisdom of resuming GoF research.

Another difficulty underlying this debate is the terminology itself, says influenza expert Robert Webster of St. Jude Children’s Research Hospital in Memphis, Tenn., among others. “It’s too associated with doomsday scenarios,” he says. “Is there another, better term?” Adds David Relman of Stanford University in Stanford, Calif., “The broad term GoF doesn’t capture what we’re most concerned over.” This quest, however, remains unmet.

A central argument invoked for resuming GoF research is that it provides insights needed to safeguard the public against natural pandemics. “For some questions, only GoF can provide accurate answers,” says Yoshihiro Kawaoka of the University of Wisconsin, Madi-
son, some of whose influenza research efforts are again on hold. Results from
his earlier GoF research on the H5N1 influenza virus led Japanese officials to
stockpile a vaccine to protect against the emergence of this strain, he says.

“But everything we saw about H5N1 prior to those experiments should have
led to vaccine stockpiling,” Relman says, cautioning against a hasty lifting of the
pause. “When we talk of benefits, they must be potent and immediately avail-
able to all. There are some experiments that should not be done at all, but we’re
talking of a very, very small set. We have to be good stewards of the ecosphere.”

The vehement opposition to some kinds of influenza research does not
seem to extend to GoF research involving MERS and SARS. “MERS is not as
high profile as flu,” says Mark Denison of Vanderbilt University in Nashville,
Tenn., who called for a more case-

based approach to imposing pauses. Unlike the influenza virus, “there is no
vaccine, therapeutics, or small-animal model” for MERS. The pause “endan-
gers the development of a vaccine for

MERS,” adds Ralph Baric of the Uni-

versity of North Carolina, Chapel Hill.
“Coronaviruses and flu are different,

and I hope regulators will recognize the
differences between them.”

Beyond this focused debate about
benefits from specific types of GoF re-
search are broader safety and security
concerns. What if GoF research pro-
duced a more dangerous flu or SARS
virus, and it fell into the wrong hands?
This and similar questions continue to
fuel this debate, and help to explain
these recurrent pauses. “We’ve been
kicking the can down the road,” says
Robert Lamb of Northwestern Univer-
sity in Evanston, Ill. “What is the path
forward? We need to develop enduring
structures to air diverse points of view.”
Whether NSABB can again serve that
purpose or another forum needs to be
developed remains an open issue.

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

RESEARCH ADVANCES
Pathogenesis Puzzle: Norovirus Infects B Cells, Needs Bacterial Factors

Carol Potera

The notorious norovirus, long known
as an agent responsible for causing de-
bilitating gastrointestinal disease, sur-
prisingly infects B cells of the immune
system that lie beneath the gut epithel-

ium rather than the gut itself, accord-
ing to virologist Stephanie Karst of the
University of Florida, Gainesville, and
her collaborators there and at the Cen-
ters for Disease Control and Preven-
tion (CDC) in Atlanta, Ga. Details ap-
peared November 7, 2014 in Science
(doi:10.1126/science1257147). Its tar-
geting of immune system cells raises
questions about norovirus pathogene-
sis and poses new challenges to efforts
to prevent or combat infections that
this virus causes—an estimated 20 mil-

lion each year in the United States.

This research began more modestly
with efforts to cultivate norovirus in
vitro, according to Karst. After trying
mouse B and epithelial cells, she and
her collaborators learned that the virus
will replicate only in B cells, provided
they are supplemented with bacterial
histo-blood group antigen (HBGA).
Subsequently, they learned that mutant
mice lacking B cells resist norovirus in-
fection better than mice with intact B
cells. Additionally, norovirus replica-
tion is reduced 60-fold in antibiotic-
treated mice. These findings suggest
that norovirus infects B cells and intes-
tinal bacteria enhance these infections,
she says.

Human norovirus behaves simi-
larly. GII.4-Sydney, the current dominant
human strain circulating worldwide,
replicates in human B cells, but only
when H antigen, a type of HBGA car-
rried on the surface of the common
gut bacterium Enterobacter cloacae, is
present, allowing norovirus to attach to
B cells, according to Karst. Escherichia
coli, which lacks H antigen, fails to
stimulate norovirus infection. Other
viruses, including poliovirus, reovirus,
and mouse mammary tumor retrovi-
rus, also require bacteria to replicate,
she says. “Bacterial stimulation of viral
intestinal infections is a new emerging
theme,” says Karst.

“The missing link needed to move
the norovirus field forward is now in
hand,” says Stacey Schultz-Cherry of
St. Jude Children’s Research Hospital
in Memphis, Tenn. The system for cul-
turing norovirus in vitro along with the
realization that it infects B cells “will
allow us to create vaccines and antiviral
treatments,” she adds. “This is incredi-

bly exciting.”
MINITOPIC
By Adding a Constant Volume Each Generation, Bacterial Cells Maintain the “Right” Size

To control their size at the top end of the range of growth, bacterial cells add a constant volume each generation, regardless of the size they were at first after being released as daughter cells, according to Suckjoon Jun and Massimo Vergassola of the University of California San Diego, La Jolla, and their collaborators there and at Washington University in St. Louis, Mo. “Combined experimental results and quantitative analysis…conclusively support the so-called constant Δ model,” they note. “This ‘adder’ principle quantitatively explains experimental data at both the population and single-cell levels, including the origin and the hierarchy of variability in the size-control mechanisms and how cells maintain size homeostasis.” Details appeared December 24, 2014 in Current Biology (doi:10.1016/j.cub.2014.12.009).

How does norovirus infecting intestinal B cells trigger diarrhea and vomiting? “It’s a big black box,” Karst says. “You need effects on the epithelium in order to get secretion of fluids for diarrhea.” Perhaps norovirus-infected B cells release a protein that alters epithelial cells, she speculates. Immunological questions also remain unanswered, she adds, noting that norovirus infections do not generate a strong immune response. “If the virus infects a cell that’s supposed to mount an immune response to it, then the cell’s immune function could be impaired.”

“The full meaning of the observations that norovirus targets B cells and needs HBGAs from commensal bacteria to enter cells is not yet clear,” says Ken Cadwell of New York University School of Medicine in New York, N.Y. Certain B cell subsets may have special properties that allow them to be infected by norovirus, yet not be killed, he suggests. These new findings also may “partially explain why individuals vary in their susceptibility to different norovirus strains,” he adds. “Both HBGAs and commensal bacterial populations differ among individuals.”

Carol Potera is a freelance writer in Great Falls, Mont.

NEW IN ASM JOURNALS
Instead of Harming, Murine Norovirus Benefits Germfree Mice

David C. Holzman
Viruses of the gastrointestinal tract appear to be an integral component of the broader gut microbiome, providing “many of the same signals to the host that are attributed to commensal bacteria,” notes Ken Cadwell of New York University School of Medicine in New York, N.Y. The “recent surge in microbiome research” should be doing more to explore these viral influences, he says. Details appeared 10 December 2014 in the Journal of Virology (doi:10.1128/JVI.02966-14).

Recent experiments with germfree mice and those infected with the murine norovirus (MNV) help to make this case, according to Cadwell. Unlike the norovirus that infects and sickens humans, the mouse version of this virus does not make mice ill, he says, noting that this research with MNV builds on “pioneering studies” with lymphocytic choriomeningitis virus, which prevents diabetes in mice, as well as other epidemiological observations in humans, suggesting that viruses can be beneficial.

“Virologists have long suspected that viruses are beneficial,” says virologist Vincent Racaniello of Columbia University in New York, N.Y. “This paper provides very strong evidence that norovirus plays a role in development of the intestine and its immune system.” Although definitive evidence for viruses directly benefitting humans may be lacking, examples can be found of benefits for plants and animals from insects to mice. (See the 2014 report on beneficial viruses from the American Academy of Microbiology at http://academy.asm.org/index.php/browse-all-reports/5180-viruses-throughout-life-time-friends-foes-change-agents.)

Germfree mice exhibit many abnormalities of the intestine and its mucosal immune system due to the absence of bacterial flora, Cadwell says. “Remarkably, we found that MNV was able to partially and, in some cases, completely reverse many of the abnormalities that are present in germfree mice.” For example, furnishing mice with MNV boosted their CD4 and CD8 T cells generally, and replenished T cells within the gut villi, where they had been deficient.

MNV also helps to correct other abnormalities in germfree mice, including raising otherwise low numbers of granules that contain antimicrobial agents and abnormally low levels of expression in lysozyme Paneth cells, of interferon and of other genes associated with the immune system, according to Cadwell and his collaborators. Further, he says, the MNV-treated mice no longer show an increased susceptibility to intestinal damage from chemical injury and bacterial infection. Details appeared 4 December 2014 in Nature (doi:10.1038/nature13960).

“I am amazed at the huge impact of norovirus,” Racaniello says. “Not only can it correct morphological defects in the intestine of germfree mice, but it also plays a role in educating the immune system.”

Despite these responses, the MNV-treated but otherwise germfree mice differ from conventional mice in a variety of ways, Cadwell says. For instance, they remain unable to reverse many other intestinal abnormalities. A key question is whether MNV provides...
benefits beyond those furnished by commensal bacteria, he says, noting “Its ability to trigger inflammatory pathology in particular mutant mice even in the presence of commensal bacteria “suggests that this virus and commensal bacteria evoke nonoverlapping responses from the host, at least under certain conditions.”

David C. Holzman is the Microbe Journal Highlights Editor.

RESEARCH ADVANCES

By Dominating Wastewater Niche, Candidatus Microthrix Orchestrates Resource Use

Barry E. DiGregorio

While growing as part of microbial consortia in wastewater tanks, the filamentous bacterium Candidatus Microthrix parvicella (Microthrix) fine tunes resource use within its community, orchestrating overall yields of fatty acids, according to Paul Wilmes of the University of Luxembourg in Esch-sur-Alzette, Luxembourg, and his collaborators there and at other institutions in the United States and Europe. In practical terms, their detailed analysis of microbial dynamics within this setting could help in making it a source for biodiesel fuels, they note. Details appeared November 26, 2014 in Nature Communications (doi: 10.1038/ncomms6603).

“Such knowledge will be of paramount importance once we try to reengineer biological wastewater treatment plants to favor growth of Microthrix for subsequent lipid reclamation and biofuel synthesis from chemical energy-rich wastewater,” Wilmes says. Instead of yielding energy, however, it usually requires energy to run wastewater treatment plants, he points out. The comprehensive use of mixed culture processes is not likely to prove successful until microbiologists and biotechnology experts learn how to engineer specific niches into such systems, he and his collaborators note.

Lipid-accumulating microorganisms are found on the surface of the anoxic tank at the wastewater treatment plant in Schifflange, Luxembourg, throughout the year, according to Wilmes and his collaborators. Furthermore, colder temperatures apparently enhance lipid production at this particular facility, they note. “We link this pronounced lipid accumulation phenotype to optimal foraging behavior by Microthrix,” he says. Indeed, the bacteria continues to accumulate large amounts of fatty acids during the coldest part of winter.

“The prevalence of lipid-rich biomass at the air-water interface of such systems is a well-known fact worldwide and absolutely not limited to the Schifflange biological wastewater treatment plant,” and there is nothing “peculiar” about this particular facility, Wilmes continues. Thus “findings are generalizable to other biological wastewater treatment plants worldwide.” Whether the Microthrix-dominated consortium can be transferred to other similar facilities will depend on developing a better understanding of “the ecology of biological wastewater treatment systems,” he adds. Then it may become possible to “predictably steer them towards particular endpoints, such as enrichment and maintenance of lipid-accumulating organisms in bio-

MINITOPIC

New, Unusual Approaches to Testing Antibiotic Susceptibility, Flu, and Tracing Foods

Recent developments involving devices, software, or tests for detecting infections agents and, in some cases, determining their susceptibility to antimicrobial drugs include:

- A test called single-cell analysis morphological (SCMA) for tracking growth and changes in shape of individual bacterial cells can be used to determine antibiotic susceptibilities within about four hours, according to Sungmoon Kwon at Institute for Basic Science in Seoul, Republic of Korea, and collaborators. Details appeared 17 December 2014 in Science Translational Medicine (doi/10.1126/scitranslmed.3009650).
- A software package, called OSPREY, can help to predict specific mutations that enable methicillin-resistant Staphylococcus aureus—and, likely, other microbial pathogens as well—to develop resistance to particular antimicrobial drugs, according to Bruce Donald of Duke University in Durham, N.C., Amy Anderson at the University of Connecticut at Storrs, and their collaborators. Details appeared 31 December 2014 in Proceedings of the National Academy of Sciences (doi: 10.1073/pnas.1411548112).
- The U.S. Food and Drug Administration in January granted its first CLIA waiver to allow the marketing of a rapid, nucleic acid-based test for the influenza virus. The Alee i Influenza A & B test, which is conducted on nasal swab specimens and can be completed within 15 minutes, is manufactured by Alere Scarborough, Inc., of Scarborough, Maine.
- DNA Trax, particles consisting of carbohydrate and DNA molecules, can be sprayed on foods (or other materials) that, if and when they become contaminated by microbial pathogens, can serve as barcode markers for use in tracing those contaminated products, according to officials at DNA Trek in Livermore, Calif., who licensed this technology from scientists at nearby Lawrence Livermore National Laboratory.
logical wastewater treatment systems."

“There are two aspects of this paper that I find particularly exciting,” says Holly Bik of the University of Birmingham in Birmingham, England. “First, the authors used an extraction protocol that obtained DNA, RNA, proteins, and small molecules all from the same sample fraction—ensuring that the different omics datasets are focused on the same slice of the microbial community. Second, the reconstruction of composite genomes from environmental data is a great result. Previously, genome binning has mostly been focused on simplistic microbial communities such as acid mine drainage, and here the authors show that this method is now becoming possible for much more complex microbial assemblages.”

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

RESEARCH ADVANCES

Uncertainties in Tracking West Nile Virus Undermine Vaccine Development

Jeffrey L. Fox

Soon after West Nile virus (WNV) appeared in the United States (US) in 1999, several vaccine efforts were launched, leading to a vaccine deemed suitable for horses by 2001, according to Thomas Monath of Harvard Medical School in Boston, Mass. By last year, however, nearly all other WNV vaccine development efforts had stopped, leaving human populations fully vulnerable to this mosquito-transmitted disease, he says. The practical abandonment of vaccine efforts is “not technical,” Monath says. Instead, they are mainly matters of economics along with regulatory idiosyncrasies. For example, although the elderly are particularly vulnerable to WNV, it is difficult to say who within this population group would take a vaccine, if one were available, in large part because outbreaks tend to be regional but do not follow regular patterns from year to year. Another challenge is that Food and Drug Administration (FDA) officials indicated that they would require efficacy data from a human vaccine trial to approve a WNV vaccine and would not rely on the FDA Animal Rule, a provision that accepts efficacy data from animal studies along with safety data from testing in humans. The irregular nature of WNV outbreaks would greatly complicate planning any clinical efficacy trials, he points out.

WNV infected as many as 5.2 million individuals in the US since 1999, but only about 1.2 million were made ill from those infections, says Lyle Petersen of the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. Although it now causes infections throughout the country, its geographic incidence pattern is highly irregular. In recent years, he notes, “South Dakota has had the highest incidence, which is odd for a ‘tropical’ virus.” The incidence is also high in densely populated states such as California and cities such as Chicago and Phoenix.

Another peculiarity is that the three biggest outbreaks of neuroinvasive WNV, the most serious form of such infections, occurred “during heat waves” in 2002, 2006, and 2012, Petersen adds. Whether weather affects such incidence patterns is under debate, however. “Our data don’t support the idea that heat waves are responsible for WNV outbreaks,” says Marm Kilpatrick of the University of California, Santa Cruz. “In Texas, for example, the severity of winters appears to be more important.” If human behaviors change in response to local fluctuations in weather, he adds, “predictions go out the window.”
In any case, climate is but one of several factors that appear to be driving WNV incidence while the virus infects different species of birds, adapting to different hosts as they develop immunity to it, Kilpatrick says. A larger “uncertainty” resides in potential evolutionary changes in this pathogen, which is considered a relatively stable virus, as well as in its vectors and hosts.

On top of such uncertainties is unevenness in the surveillance system for following such trends, says William Karesh of the EcoHealth Alliance in New York, N.Y. “I’m not comfortable about understanding the pattern when we’re investing so much less in surveillance. We need to get our surveillance system to be steady, not a roller-coaster.” Moreover, amid the steady emergence of still other insect vector-borne diseases, some of the expertise needed to understand them, particularly in disciplines such as ecology and entomology, is dwindling as are the resources to train such experts, according to Petersen of CDC. Losing this capacity is “a major problem,” he says.

NEW IN ASM JOURNALS

Post-Joint Replacement Infections Are Antibiotic-Defying, Biofilm-Like, Large Aggregates

Despite standard antibiotic prophylaxis, breakthrough infections still occur, with often devastating effects, following total joint arthroplasty. Now Noreen Hickok of the Thomas Jefferson University, Philadelphia, Pa., Michael Otto of the National Institute of Allergy and Infectious Disease, Bethesda, Md., et al. show that despite cefazolin at 100–200 times the required concentration, *Staphylococcus aureus*—including MRSA—survive in synovial fluid. “When we looked at the synovial fluid containing the bacteria under the microscope, we could see large aggregates of bacteria, large enough in some cases to see with the naked eye,” says Hickok. These aggregates, which are like floating biofilms, “are insensitive to antibiotics,” she says. The resulting infections are very hard to treat, and in the case of implants, can result in the need for additional surgeries. “Unlike classic biofilms, these aggregates appear to have protein which may be cross-linked to form a very dense cluster of bacteria,” says Hickok. “It will be a challenge both

NEW IN ASM JOURNALS

Stinkbug Pouches: Not Quite the Same Function as on Kangaroos

Stinkbugs not only are olfactorily offensive to most civilized H. sapiens; they inflict substantial agricultural losses. Yet these seemingly lowly creatures have much to offer the microbiologist: their gut-based bacterial symbionts are critical to their survival and growth, and the mother stinkbugs transmit their prokaryotic partners to their offspring by smearing excrement onto the egg surface upon oviposition. Newly hatched stinkbugs ingest their symbionts by sucking the eggshell. Now Takema Fukatsu of the University of Tokyo, Japan, et al. show that the posterior end of the gut develops conspicuously enlarged symbiont-harbouring pouches, which Fukatsu says “represent a female-specific organ specialized for vertical transmission of the beneficial bacteria.” These pouches “may provide a potential target for controlling the pests by, for example, disrupting vertical transmission of the symbiont,” he says. Next on the agenda: investigating pouch gene expression. Fukatsu predicts molecules that enable ex-host survival of the symbiotic bacteria.


NEW IN ASM JOURNALS

Sustained Release Pharma Platform Is Novel Infectious Disease-Fighting Device

Doron Steinberg et al. of the Hebrew University of Jerusalem, Israel, report that they have incorporated the anti-biofilm, anti-quorum sensing agent, Thiazolidinedione-8, into a sustained release membrane, and that it inhibited Candida albicans biofilm formation for 72 hours due to prolonged release of the agent. Additionally, it significantly eradicated mature biofilm. The sustained release membrane, which the team developed, “is a pharmaceutical platform in which different agents can be incorporated for different clinical purposes: teeth, orthodontic appliances, implants, catheters, and ear tubes.” The device can also be used on soft tissue, and “presents a promising novel avenue for combating infectious diseases, which may serve as an alternative to the conventional antimicrobial regime used nowadays,” says Steinberg.


NEW IN ASM JOURNALS

Encouraging News for Universal Flu Vaccine Development

Matthew Miller et al. of McMaster University, Hamilton, Ontario, Canada, report that despite having vastly inferior neutralization potency relative to strain-specific hemagglutinin head domain-binding antibodies (in a monoclonal context), within a polyclonal context, broadly neutralizing antibodies that bind to the hemagglutinin stalk domain function with comparable potency to strain-specific antibodies. “This is encouraging news with regard to development of a universal influenza virus vaccine development, since the natural immune response induced by vaccines is polyclonal,” says Miller. “Furthermore, we found that broadly neutralizing antibodies of IgA subtype are both more frequent and more potent than their IgG counterparts. IgA is particularly important for providing protection against respiratory pathogens like influenza, since it is secreted at mucosal surfaces. Thus, vaccine strategies that favor production of IgA may be especially useful for universal influenza virus vaccine delivery.”


NEW IN ASM JOURNALS

Antisense Compound Proves Promising against Ebola in Monkeys

Travis K. Warren of U.S. the Army Medical Research Institute of Infectious Diseases, Fort Detrick, Md., et al. report that the experimental antisense medication AVI-7537, which targets the gene for Ebola virus protein VP24, protected 75% of a group of rhesus monkeys from the virus. The monkeys showed substantial reduction of virus in their bloodstreams within eight days of treatment, compared to animals receiving a placebo. “The study demonstrates that we can protect nonhuman primates from Ebola virus, using only a single antisense agent,” said Warren. In contrast,
monkeys treated with saline succumbed within an average of eight days following infection, while those treated with AVI-7539, which targets Ebola virus protein VP35, died within an average of 10 days.


NEW IN ASM JOURNALS

Could Frog Skin Peptides Be Source of New Antibiotics?

Skin and soft tissue infections with *Staphylococcus aureus* are leading nosocomial infections. Now David Craik of the University of Queensland, Australia, reports that slightly modified peptides from frog skin had powerful activity against *S. aureus* in a mouse model of wound infection. This is not the first time that researchers have investigated the use of frog skin peptides as antimicrobial peptides. But Craik says this peptide is relatively small, and thus less likely to be immunogenic, and that it is also easy to synthesize, unlike most frog peptides in earlier research. To stabilize the proteins, Craik annealed cyclized them, so that they would not be vulnerable to proteases. Craik notes that the breakdown products of peptides, amino acids, are harmless, unlike breakdown products of many more conventional antibiotics.


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Point-of-Care Diagnostic Testing in Global Health: What Is the Point?

The main goal of such testing is to inform caregivers in ways that lead rapidly to their starting correct treatments for patients

Madhukar Pai, Marzieh Ghiasi, and Nitika Pant Pai

Although point-of-care (POC) testing is widely considered a good idea, there is little agreement on what exactly it entails. While regulatory agencies such as the U.S. Food and Drug Administration (FDA) categorize tests based on criteria such as complexity and Clinical Laboratory Improvement Amendments (CLIA) waivers, the choice of criteria becomes vastly more complex when moving from issues concerning national to global health diagnostics.

In the global health context, the dominant viewpoint is that POC tests must meet several “ASSURED” criteria—that is, they need to be affordable, sensitive, specific, user friendly, rapid and robust, equipment-free, and deliverable. This dominant definition of POC testing thus is product-oriented, and it restricts POC testing to a particular class of products: those that are inexpensive, simple, rapid (such as widely used pregnancy tests), and which health workers can use while working in the community. From this perspective, any test that needs to be conducted in a laboratory is not a POC test—creating a dichotomy between the two.

We believe that this paradigm needs to be re-examined and, in doing so, propose an explicitly goal-oriented redefinition for POC testing, particularly applicable to resource-limited settings. On the basis that the rapid initiation of correct treatment is the most critical goal of any POC testing, we reverse engineered an alternative definition: POC testing is diagnostic testing that will result in a clear and actionable management decision such as when to start treatment or to require a confirmatory test, within the same clinical encounter.

Why do we put rapid clinical decisions and beginning of treatment at the heart of our definition? Quite simply, correct and timely treatment saves lives, reduces morbidity, and reduces transmission. Thus, the impact of a POC test comes from implementing effective treatments rather than from the test itself. Thus, moving rapidly through the test-and-treat cycle in the same clinical encounter is the most important goal for any POC testing program. Needless to say, this goal is what patients want—to be rapidly diagnosed and put quickly on the right treatment. Unlike the conventional, product-oriented definition, our goal-oriented definition for POC testing is agnostic to issues such as cost, how the test or technological platform looks, size of the product, where exactly it is performed, and who performs it.

Thus, we argue that POC testing is not defined by technology but by the successful use of a technology at the point of care to make rapid decisions. The focus must be on POC testing programs or strategies rather than technologies.

SUMMARY

➤ In general, point-of-care (POC) testing refers to diagnostic products that are simple, low cost, and performed outside laboratories. This is a product-centric view of POC testing.

➤ We recommend redefining POC testing to make it goal-oriented, explicitly making the rapid initiation of correct treatment the most critical goal of any POC test.

➤ Unlike the standard definition, which creates a rigid dichotomy between POC versus laboratory tests, we suggest that POC testing should be viewed as a spectrum: of technologies (simplest to more sophisticated), users (lay persons to highly trained), and settings (homes, communities, clinics, peripheral laboratories, and hospitals).

➤ POC testing is not defined by technology but by the diagnostic process, making it important to think in terms of testing programs or strategies that lead to the rapid completion of the test-and-treat cycle.

➤ Health care systems interested in POC testing programs need to do more than purchase rapid tests; they also need to build systems for rapidly communicating test results and beginning appropriate treatments.
Tests or a Testing Program and Strategy?

A health care system can choose to implement a rapid test as a POC testing program or not. To introduce a test as part of a POC testing program, several elements need to be put in place, including systems for rapid communication of test results to patients and care providers, for rapid initiation of treatments, and to ensure appropriate follow-up of patients. The test itself is only one component of an overall POC testing program that might prove relatively costly to implement, even if some of the rapid tests within it are inexpensive.

Regardless of which technology is used, where, and by whom, the most critical elements of POC testing are rapid turnaround and communication of results to guide clinical decisions and completion of testing and follow-up action in the same clinical encounter, or at least the same day. Thus, systems for rapid reporting of test results to care providers and implementing a mechanism to link test results to appropriate counseling and treatment are as important as the technology itself. If systems for reporting the results and follow-up care, such as prescribing specific drugs to administer to a patient, are not in place, then POC testing is unlikely to have an important impact on clinical or public health outcomes.

The mere availability of rapid or simple tests does not ensure their use in POC testing programs. Various barriers prevent the successful implementation of POC testing programs, including economic, regulatory, and policy-related issues, as well as user/provider perceptions and cultural barriers. It is also important that POC testing fit within real-world workflow patterns, as well as economic and social structures. These requirements mean that POC testing programs will need viable business models to ensure that they are sustainable and will be used to make rapid treatment decisions.

Many test developers seem to consider the physical size of a technology to be a critical element of POC testing. While a small device or one that can work without a specialized instrument will certainly help, the size of the technology by itself is not a critical consideration for POC testing programs. If deployed well, even a microscope can be successfully used in POC testing programs. Although a lab-on-a-chip may be tiny, it might require a mass spectrometer to complete the analysis! Thus, it is not the size of a test that defines a technology as POC testing, but how it is implemented.

Similarly, while low cost will certainly help to increase the uptake of POC tests in resource-limited countries, cost is not an intrinsic characteristic of a POC test. Some tests such as solid cultures for *Mycobacterium tuberculosis* are inexpensive to conduct, but their low cost does not mean that they can be used in POC testing programs. On the other hand, some technologies such as handheld ultrasound devices or automated molecular tests such as the GeneXpert® technology being marketed by Cepheid Inc. of Sunnyvale, Calif., are expensive, but they can be and are being used effectively in POC testing programs. Another reason why cost should not be used to define POC testing is the fact that initiatives such as donor-led price buy down, advance market commitments, and volume-based discounts make cost an elastic concept. Willingness to pay is also elastic, and there is no easy way to separate low-cost from expensive products. While it is critical to make tests affordable, we believe cost should not be confused with the concept of POC testing.

Dichotomy or a Spectrum?

Unlike the standard definition which creates a false dichotomy between POC versus laboratory tests, we argue that POC testing should be viewed as involving several components, including technologies that range from simplest to more sophisticated, users including lay persons to highly trained workers, and settings including homes, communities, clinics, peripheral laboratories, and hospitals (Fig. 1). As illustrated, POC testing is happening in diverse settings, ranging from homes to hospitals.

In this broad framework, the use of rapid tests in the community by front-line health workers is only one of several types of POC testing. A good example of this is the use of malaria rapid diagnostic tests by community health workers in Africa. Other examples are in-home pregnancy tests and oral fluid HIV self-tests. Here, the goal is self-assessment and linkages to care. Such tests, whether done at home or in the community, need to be very simple, preferably instrument-free (although small devices such as glucometers show that even this restriction may not be necessary), and should involve very few steps. Additionally,
interpretation should be very simple and straightforward, and the requirement for training should be minimal.

At the other end of the spectrum, POC testing programs are being implemented within hospitals. For example, labor ward nurses in hospitals are using rapid, oral-fluid HIV tests to determine when to provide antiretroviral therapy to reduce the risk of mother-to-child transmission of this virus. Emergency room doctors are rapidly diagnosing and treating ectopic pregnancy and abdominal trauma using handheld ultrasound devices. Rapid tests are also being used in intensive care units to make timely decisions on patient treatments. At this level of the health care delivery system, tests do not need to be instrument-free or inexpensive, and users are often well trained. Fairly sophisticated technologies can be and are being used to achieve rapid results that can inform clinical decisions.

While the traditional definition of POC testing does not include laboratories, our framework acknowledges the important role that peripheral laboratories have in POC testing programs. In most developing countries, there are large numbers of primary health centers with small, attached microscopy laboratories that typically are run by laboratory technicians with minimal training. These peripheral laboratories have limited resources, but can perform simple microscopy tests such as malaria and sputum smears, lateral flow assays, and basic tests such as hemoglobin, urine sugar, albumin, and Gram stains (Fig. 2). Patients who visit these primary health centers typically are asked to wait for a few hours before being sent home on the correct treatment. As long as the test-and-treat cycle is completed in the same visit, we consider these to be excellent examples of POC testing.

### Diversity of Target Product Profiles

The diversity of settings, users, and technologies suggests that restricting product characteristics makes a lot of sense once a decision is made to limit a test to a particular setting or context. In other words, every POC test does not need to meet the same target product profile (TPP) such

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**FIGURE 1**

The spectrum of point-of-care testing. (Adapted from N. P. Pai et al., PLoS Med. 9(9):e1001306, 2012; copyright held by the authors under Creative Commons license.)

<table>
<thead>
<tr>
<th>Setting</th>
<th>User</th>
<th>Device</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOME</strong></td>
<td><strong>COMMUNITY</strong></td>
<td><strong>CLINIC/HEALTH POST</strong></td>
<td><strong>PERIPHERAL LAB</strong></td>
</tr>
<tr>
<td>Self-testing (home-based)</td>
<td>Testing in the community by health workers (e.g., village workers, paramedics)</td>
<td>Testing in the clinic by healthcare providers (e.g., doctors, nurses)</td>
<td>Testing in the peripheral laboratory</td>
</tr>
<tr>
<td>User: Lay person</td>
<td>User: Minimally trained health worker</td>
<td>User: Clinical staff</td>
<td>User: Lab tech</td>
</tr>
<tr>
<td>Device: RDT (pregnancy-type) or dipstick</td>
<td>Device: RDT, dipsticks, mobile phone-based</td>
<td>Device: RDT, handheld instruments</td>
<td>Device: RDT, microscopy, handheld devices, etc.</td>
</tr>
<tr>
<td>Purpose: Self assessment and referral</td>
<td>Purpose: Triage and referral</td>
<td>Purpose: Diagnosis and treatment</td>
<td>Purpose: Diagnosis treatment monitoring</td>
</tr>
</tbody>
</table>

**EXAMPLES**

- **SIMPKEST TECHNOLOGY**
  - Simplest
  - HIV self-testing
  - Malaria, HIV, dengue
  - HIV, malaria, syphilis, dengue, Strep A
  - Sputum microscopy, malaria smears and RDTs, POC CD4 counts, etc.

- **RELATIVELY SOPHISTICATED TECHNOLOGY**
  - HIV self-testing
  - Malaria, HIV, dengue
  - HIV, malaria, syphilis, dengue, Strep A
  - Sputum microscopy, malaria smears and RDTs, POC CD4 counts, etc.
  - TB, HIV, malaria, HIV, HCV, flu, CD4, Strep A, viral load, etc.
as the ASSURED criteria, for example. While a technology designed for laboratories and hospitals (right side of the spectrum, Fig. 1) is unlikely to work in community or home-based settings, the reverse is quite possible. For example, the OraQuick® In-Home, which is marketed by OraSure Technologies Inc. of Bethlehem, Pa., rapid test for HIV is being used in the full range of settings from home to hospital.

All TPPs, ideally, should include sufficient information on the intended purpose of the test, the setting, and likely users. TPPs could also provide guidance to product developers on the desired cost, based on public health needs in resource-limited settings. Indeed, such TPPs have been developed for HIV and TB diagnostics.

**Conclusion**

By framing POC testing as a goal-oriented spectrum of activities while de-emphasizing the restrictive, product-centric view, we believe our approach is more inclusive, more reflective of reality, and will allow more industries and test developers to develop a range of products that may be amenable for use in POC testing programs.

For example, several companies are developing robust, automated, molecular assays for tuberculosis that are potentially deployable in microscopy centers. Such devices are already being used for POC CD4 testing of individuals with HIV infections, and will also be available for viral load testing. These simple, battery-operated devices do not require sophisticated, centralized laboratories, and can help doctors make rapid decisions in community care settings. A traditional definition of POC testing would exclude these examples as they are neither inexpensive nor instrument-free, whereas a goal-oriented definition would include these devices based on how well they fit within the diagnostic process.

Lastly, we believe that an approach that focuses on rapid treatment decisions as the goal is closer to what all patients want from their care providers, and might inspire health care systems and donors to think beyond just procuring rapid tests and ensure that these testing technologies
are implemented as POC testing programs. Only then will we see the true impact of POC testing.

Madhukar Pai is the Director of Global Health Programs, and the Associate Director of the McGill International TB Centre, McGill University; Marzieh Ghiasi is a researcher at McGill Global Health Programs; and Nitika Pai is an Associate Professor in the Department of Medicine, McGill University, Montreal, Quebec, Canada.

Suggested Reading


Pai, M. 2013. Point of care (POC) testing for infectious diseases: diversity, complexity, and barriers in developing countries. Invited lecture at 2013 CEND Symposium at the University of California, Berkeley. Video available at http://www.youtube.com/watch?v=SqASU6uCh0o


The CREATE Strategy Benefits Students and Is a Natural Fit for Faculty

Analysis of scientific literature using the CREATE approach allows students to learn microbiology while involving them with the process of science

Sally G. Hoskins and Alison Krufka

Given how much time microbiologists spend reading and analyzing research articles, it is surprising that so many teach lecture courses based on textbooks, inadvertently depriving their students of the excitement of scientific discovery that comes with analyzing current research. Such faculty members typically spent years learning to do scientific research, designing experiments or carrying out observational studies, troubleshooting, and integrating findings from current literature with their hypothetical frameworks. As they developed more sophisticated insights into study design and data interpretation, including an awareness of the need to constantly challenge their own assumptions, future college faculty gained an ever-increasing fluency in the language of data analysis.

 Unfortunately, few bring this insider understanding of the scientific process to the courses that they teach. Instead, too many courses are lecture-based, presenting information that students memorize, while developing little sense of how important conclusions were reached. Some colleagues find this approach to be a time-saving necessity or may note that “lectures are the way I was taught, and that method worked for me.” Traditionalists suggest that lecturing is the only way to cover sufficient content. Even faculty with a sense that traditional teaching is overdue for an upgrade may not feel they have time to overhaul their assigned courses.

CREATE Moves beyond Lecture to Engage Students in the Research Process

Actively engaging students in classrooms can be more effective than are traditional lectures. Even after taking courses that include laboratory exercises, many undergraduate biology majors have difficulty grasping key ideas fundamental to working scientists. Persistent misconceptions among such students about fundamental issues in biology argue that repeated exposure to key ideas in traditionally taught courses does not produce understanding.

The lecture-with-slides approach forces students to be passive listeners without encouraging them to engage the topics at hand, undermining learning and understanding. Overall, lectures and textbooks tend to disconnect students from the process of scientific discovery, which can turn them away from science altogether. Another major problem with standard lectures is that they steer faculty away from conveying their mastery of the logic of scientific analysis to their students.

In response to these challenges, we and colleagues developed the “consider, read, elucidate hypotheses, analyze and interpret the data, think of the next experiment” (CREATE) strategy to demystify and humanize science through close analysis of research articles. We had three main goals: leveraging the unique insights of faculty

SUMMARY

➤ Students taught in traditional ways tend to have difficulty understanding or applying key scientific concepts, and retain misconceptions about important ideas in biology.

➤ The “consider, read, elucidate hypotheses, analyze and interpret the data, think of the next experiment” (CREATE) approach to teaching microbiology builds on the deep understanding faculty members have for the research process.

➤ In following this approach, students prepare for class using tools that consolidate their knowledge of key scientific concepts and how to design studies.

➤ This approach encourages faculty members to guide students into examining how studies were carried out and what data mean in a lab-meeting-like atmosphere.
members into the research process, helping students learn how scientific knowledge develops and why people choose research careers, and consolidating students’ understanding of key biological concepts. The CREATE approach makes the journal article, not the textbook, the focus of class discussion, using research reports to convey to students insights into authentic processes of science.

Courses focus on sets of papers published sequentially from a single laboratory or, alternatively, from competing labs chasing the same scientific question, and follow the progression of these scientific studies. Any topic can be explored, and faculty can choose papers based on course goals and their own expertise, including from a variety of topics in microbiology (Table 1 and www.teachcreate.org). Rather than telling students what data mean, faculty members run courses like lab meetings, discussing and interpreting charts, graphs, and photomicrographs. CREATE teaching thus challenges students to understand and explain figures and tables of research papers as if they had carried out the experiments themselves. In addition to analyzing data, students are asked to propose experiments related to the papers and to analyze one another’s proposals. Such activities allow students to experience the creativity and teamwork of science while also learning to argue collegially and defend their ideas. E-mail exchanges with the authors of those research reports, who voluntarily respond to student-generated questions, add a personal touch to the process, humanizing researchers and helping to dispel stereotypes about them. Traditional teaching rarely gives students the opportunity to “talk science,” and the open-ended discussions typical of CREATE classrooms provide opportunities for students to experience scientific analysis and discourse. This classroom experience aligns with recommendations set forth in the seminal 2011 Vision and Change document that focused on the teaching of undergraduate biology (Table 2).

**TABLE 1.**

<table>
<thead>
<tr>
<th>Sample Microbiology Modules Developed in CREATE Workshops</th>
<th>Author</th>
<th>Suggested Student Level</th>
<th>Module Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired or Specific Immunity? Miriam St. Clair, Northern Virginia Community College</td>
<td>Community college students in a pre-nursing program</td>
<td>Module investigates aspects of acquired and specific immunity, examining work of I Adlerberth at the University of Gothenburg, 2006–2012.</td>
<td></td>
</tr>
<tr>
<td>Discovery and Determination of the Mechanism of Action of Listeriolysin O Terri Ellis, Ph.D., University of Northern Florida</td>
<td>Senior undergraduates</td>
<td>Module follows issues of bacterial virulence, intracellular survival and immune system interactions, focusing on the DA Portnoy laboratory at University of California, Berkeley from 1988–2003.</td>
<td></td>
</tr>
<tr>
<td>Symbiosis Between Leaf-cutting Ants, a Parasitic Fungus, and a Bacterium Elizabeth Shank, Ph.D., University of North Carolina</td>
<td>Upper-level undergraduates</td>
<td>Module follows the evolution of ant-microbe symbiosis, exploring the work of the CR Currie lab at University of Wisconsin, Madison, from 1994–2009.</td>
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*See www.teachcreate.org for teaching outlines and additional modules.*

Properly Prepared Students Enable Faculty to Focus on Scientific Thinking in Classes

In contrast to courses that use research articles by having individual students present full papers, or by assigning different figures to different students, in CREATE courses all students are challenged to master all figures of each research report. The learning tools used in the CREATE approach are designed to facilitate students’ ability to begin to decode research papers be-
Before each class convenes, as preparation for in-class detailed analysis. Pre-class concept mapping, sketching of experimental designs, and annotation of figures are key tools in the CREATE strategy. These drive students' review of fundamental biological concepts, help students visualize how experiments were done, and promote engagement with the data, preparing students for active discussion in class.

Students compile their concept maps, annotated figures, and sketches as well as additional information about experimental techniques or foundational concepts that they looked up before class to bolster their understanding of each report in portfolios. These are brought to every class and serve as references for open-book exams given twice per semester.

This fine-grained preparation allows CREATE faculty to use their strengths as scientists to guide students through the complexities of each study and the development of data interpretation skills. Thus, in the CREATE classroom, faculty move beyond describing microbiology content and instead encourage students to apply their understanding of the content as they decipher experimental questions—for example, examining how techniques were applied and why particular controls were used. The faculty member coaches students into examining the hypotheses or questions that underlie each study, the design of each experiment in it, and the logic of the overall approach.

When students analyze the data, they are encouraged to think independently about what conclusions they would draw rather than to summarize outcomes stated by the authors. Small-group work in each class (Fig. 1) gives students the opportunity to work with peers while learning that different groups may reach different answers in response to the same scientific question.

The CREATE approach has been used primarily in elective courses with enrollments of 30 or fewer students. We have begun experimenting with ways to integrate CREATE into large-enrollment courses, possibly in single sessions during labs or recitation periods, or by initiating CREATE activities in such sessions and then

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**TABLE 2. How CREATE courses embody Vision and Change recommendations**

<table>
<thead>
<tr>
<th>Vision and Change Recommendation</th>
<th>CREATE Approach</th>
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<tbody>
<tr>
<td>“Introduce the scientific process to students early, and integrate it into all undergraduate biology courses.”</td>
<td>CREATE curricula integrate and reinforce scientific process at each year of a Biology major.</td>
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<tr>
<td>“Define learning goals so that they focus on teaching students the core concepts, and align assessments so that they assess the students’ understanding of these concepts.”</td>
<td>CREATE activities are narrowly focused and challenge students to review and apply key concepts as they interpret data and analyze published results in the context of a research question. Students demonstrate understanding through integrated course activities, discussion and homework.</td>
</tr>
<tr>
<td>“Relate abstract concepts in biology to real-world examples on a regular basis, and make biology content relevant by presenting problems in a real-life context.”</td>
<td>CREATE modules are based in bona fide published scientific studies providing real-world context for key biological principles.</td>
</tr>
<tr>
<td>“Develop lifelong science-learning competencies.”</td>
<td>CREATE courses build transferable analytical skills via the CREATE toolkit. This approach is fundamental to CREATE (see Hoskins et al., 2007; Hoskins and Stevens, 2009. &quot;Learning our L.I.M.I.T.S.—Less is More in Teaching Science&quot;)</td>
</tr>
<tr>
<td>“Introduce fewer concepts, but present them in greater depth. Less really is more.”</td>
<td>CREATE courses stimulate curiosity by encouraging students to develop their own interpretations of data and to devise their own creative follow-up studies, which are vetted in classroom grant panels.</td>
</tr>
<tr>
<td>“Stimulate the curiosity students have for learning about the natural world.”</td>
<td>CREATE students gain unique insight into individual scientists’ work and personal lives through paper authors’ thought-provoking written responses to class-generated e-mail surveys.</td>
</tr>
<tr>
<td>“Demonstrate both the passion scientists have for their discipline and their delight in sharing their understanding of the world with students.”</td>
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Completing them in larger classroom settings. Such approaches would likely entail training lab instructors, typically graduate students, to work with the CREATE approach.

Both Students and Faculty Members Like the CREATE Strategy

For students accustomed to passive learning through lectures and skimming abstracts instead of reading papers, the level of preparation and detailed analysis required of them in taking a CREATE course is surprising and challenging. Students may resist changes in teaching approaches, particularly if such students were successful in traditionally taught classes.

However, our students react largely positively to CREATE classes. In interviews, our students at City College of New York (CCNY) reported that CREATE strategies such as concept mapping, sketching, and annotation were helping them in other courses. Upper-level CCNY CREATE students also suggested that we develop a first-year version of the course, arguing that the strategy would have helped them throughout their academic careers. On the five New York and New Jersey campuses where seven faculty that we trained in CREATE strategies taught their first courses, 79% of the 103 anonymous student survey comments were positive. Thus, the fear of student backlash should not deter faculty from trying CREATE.

Like students, faculty members are satisfied with CREATE. Faculty surveyed five years after adopting CREATE all reported continuing to use the strategy in some or all courses. When asked about the extent to which CREATE changed them as a teacher, faculty members offered a variety of observations. One faculty member noted that CREATE teaching made him realize that he had not previously been aware of the extent to which students were learning, and another noted the need to make classes student-centered and focus on helping students own the material. A third respondent described her enjoyment of

CCNY CREATE students working in small groups pool their expertise to develop molecular models based on the findings of a research study. Models will be compared and contrasted by the whole class. (Photo: Joann Huang.)
high-level discussions where students had the “freedom to explore their own ideas” and described the CREATE strategy as “liberating.”

CREATE Prepares Students for 21st-Century Science

We view CREATE as a way to address practical challenges of teaching and the more fundamental problem of traditional courses producing students who neither retain content that was covered nor feel enthusiastic about science. Through CREATE, highly trained researchers bring their research expertise to the classroom, share their passion for discovery, and break from the linear path of “teaching by telling.” Requiring students to prepare for each class using CREATE tools also spares faculty from being the source of all basic facts, freeing them to bring stories from their own research experiences to the classroom.

For example, in one CREATE class, we looked at reports outlining the discovery that some ulcers have a bacterial origin. In it, students read some of the personal writing of Barry Marshall, in which he describes his difficulties with the scientific establishment. This example helps to illustrate how well-established scientific “facts” may change, and that new findings may not be met with universal acceptance. This portrayal of what science is and how it works is not typically a part of content-heavy traditional courses, but it helps to make the field vivid, illustrating creativity, controversy and its resolution, and the ability of individuals to make a difference. We think these classroom experiences can deepen our students’ understanding of science and may lead them into research careers.

This shift from merely covering content to using content to develop how students think while emphasizing how scientific knowledge develops will serve students well into the future. Microbiology knowledge is developing rapidly, with journal articles covering new developments far faster than textbooks. Intensive examination of this literature via the CREATE strategy can provide students with significant learning gains, transferable analytical skills, and unique insights. We encourage faculty members to bring the skills they already possess to the classroom, focus on the scientific process, and teach CREATE.

Suggested Reading


Microbial Extension Cords: Nanowires in *Shewanella oneidensis*

To connect with external electron acceptors, these bacterial cells extrude membrane vesicles that extend to form filaments called nanowires

Sarah E. Barchinger

As part of respiration in microbial and other cells, electrons transfer through an electron transport chain to produce energy as adenosine triphosphate (ATP). For most bacteria, the final electron acceptor is a soluble substrate such as oxygen, sulfate, or nitrate that can be brought into the cell and then reduced.

Bacteria such as *Shewanella oneidensis* reduce a variety of electron acceptors, ranging from oxygen and dimethyl sulfoxide (DMSO) to solid mineral oxides such as manganese oxide, or MnO₂, and iron oxide, or Fe₂O₃. When *Shewanella* species occupy sediments or soils, the availability of soluble electron acceptors tends to be limited, meaning suitable electron acceptors cannot be brought inside such cells. In such cases, these bacteria transfer their electrons to their exterior surfaces and from there to available external substrates to carry out respiration. Moreover, when these bacteria are not near enough to the external electron acceptors that they require, one way the cells close that gap is by producing nanowires. In a sense, those nanowires are like extension cords on electric appliances, enabling these bacterial cells to reach farther away—not for electric outlets but for the electron acceptors that they need.

**Some Bacteria Transport Electrons Extracellularly**

At least three ways have been identified for microorganisms to facilitate extracellular electron transfer (EET): (i) by secreting flavins to serve as soluble electron shuttles, (ii) by contacting electron acceptors directly via outer membrane multiheme cytochromes, and (iii) forming structures, called “bacterial nanowires,” that also may be used for long-range electron transport. EET may occur through one or some combination of these three means.

*Shewanella oneidensis* MR-1, for example, makes use of all three processes. At the center of these pathways is a set of multiheme cytochromes localized to the cell envelope (Fig. 1, left). Electrons transfer from the quinone pool of the electron transport chain to the periplasmic cytochrome CymA. These electrons continue to the decaheme cytochrome MtrA, anchored to the outer membrane by the beta-barrel protein MtrB, from which electrons transfer to outer membrane (OM) decaheme cytochromes such as MtrC and OmcA. These cytochromes then either directly reduce insoluble substrates (Fig. 1, left), reduce soluble flavins secreted by *S. oneidensis* (Fig. 1, center), or transfer electrons to bacterial nanowires (Fig. 1, right).

**Composition of Bacterial Nanowires**

Bacterial nanowires made by *Geobacter sulfurreducens* were first described about a decade ago. These structures form only when cells are grown

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**SUMMARY**

- When *Shewanella oneidensis* bacteria are not near enough to the external electron acceptors that they require, one way the cells can close that gap is by producing structures called nanowires.
- *S. oneidensis* cells facilitate extracellular electron transfer (EET) in at least three ways.
- Unlike the electrically conductive pilus-like appendages studied in *Geobacter sulfurreducens*, *S. oneidensis* nanowires arise from chains of outer membrane vesicles that eventually convert to filaments.
- Many other types of gram-negative bacteria, including some pathogens of humans, extrude similar vesicles but for other purposes.
- How these outer membrane vesicles form and how this process is regulated in *S. oneidensis* is poorly understood.
in the presence of insoluble electron acceptors. Subsequent studies indicate that these *G. sulfurreducens* structures are conductive, require the type IV pilin protein PilA, and are important for long-range extracellular electron transport through biofilms.

Soon after this research involving the nanowires of *G. sulfurreducens* was reported, “electrically conductive pilus-like appendages” were found associated with *Shewanella oneidensis*. Because the *S. oneidensis* appendages appeared to have functions like those found in *G. sulfurreducens*, they were also called nanowires. Researchers hypothesized that pilins would also be involved in forming these appendages in *S. oneidensis*. Experiments relying on nanofabrication and atomic force microscopy show that isolated *S. oneidensis* nanowires are conductive along the width and length of the wire. Nanowires from a strain lacking the OM cytochromes MtrC and OmcA, however, lose their conductivity.

For years, investigators referred to the *S. oneidensis* nanowires as conductive pilus-like appendages without establishing which genes encoded them or how they are made. Working with John Golbeck and our colleagues at Penn State University, I determined that expression of genes encoding decaheme cytochromes such as MtrC and OmcA increases when nanowires form on cells that are seeking external electron acceptors. Because these proteins are required for electron transfer, this was unsurprising.

What was unexpected, however, is that none of the genes encoding the type IV pilus or the msh pilus apparatus had increased expression. That result left us with two possibilities: pili are still involved, but their levels are regulated post-transcriptionally, or pili are not required for nanowire formation in *S. oneidensis*. We eliminated the first possibility by inducing nanowire formation in a strain that lacks the genes for producing the major type IV pili. Like wild-type cells, this strain produces nanowires, suggesting that pili are not required for making nanowires.

So what are the components of these nanowires? To address this question, our collaborators Mohamed El-Naggar and Sahand Pirbadian, at the University of Southern California, developed a perfusion chamber in which they introduce fluorescent compounds to label proteins or other biochemical constituents of cells, enabling them to limit electron acceptor availability and observe nanowires being formed under the microscope in real time. We knew that vesicles were often seen associated with nanowires, so to better see them,
We stained cells with a lipid-specific dye. To our surprise, the entire length of the nanowire structures fluoresced, indicating that *S. oneidensis* nanowires contain membrane materials (Fig. 2)! The outer membrane cytochromes MtrC and OmcA also localize to the nanowires, and we found evidence of periplasm but not cytoplasm components within these structures, suggesting that *S. oneidensis* nanowires are extensions of the outer membrane that contain soluble periplasmic components.

Perhaps these surprising features of *S. oneidensis* nanowires were staring us in the face the whole time. Earlier, investigators saw little to no difference in reduction of insoluble electron acceptors with *S. oneidensis* mutants lacking type IV pili compared to wild-type cells, and *Shewanella* nanowires are larger in diameter than a typical type IV pilus. Also, the OM cytochromes MtrC and OmcA are required for nanowire conductivity in isolated nanowires, suggesting they are associated with the wires. Now we realize that they are integral parts of these membrane extensions.

A recent crystal structure of the cytochrome OmcA shows its 10 hemes arranged in a staggered cross formation (Fig. 1), implying that electrons could move not only from the interior to the exterior of the cell through this cytochrome, but also laterally between adjacent cytochromes, consistent with previous measurements of conductance through *Shewanella* nanowires. By extending its outer membrane and periplasm containing important electron transfer components, *S. oneidensis* is poised to reduce an electron acceptor, even from a distance. But how are these long membrane extensions formed?

### Membrane Extensions in Other Bacteria

While observing the earlier steps of nanowire formation, we sometimes saw vesicles bud from, but remain connected to, the cell body, later fusing to form long filaments. These observations made us realize that *Shewanella* nanowires are not simply extensions of the outer membrane, but instead consist of chains of outer membrane vesicles (OMVs) that gradually form filamentous structures (Fig. 3).

There are other microbial examples of chains of OMVs or membrane tubes. For example, membrane extensions coating flagella were described 50 years ago in several species of bacteria, including *Vibrio metchnikovii*, *Bdellovibrio bacteriovorus*, and *Helicobacter pylori*, and have since been found in other bacterial species. The physiological functions of those membrane tubes are not known. In the case of pathogens, investigators speculate that those tubes help the bacteria to evade host immune responses, perhaps masking flagella, which can be highly immunogenic. However, in *Brucella melitensis*, cells that no longer make flagella continue to make empty membrane tubes, suggesting that these bacteria regu-
late production of the membrane extensions independently of flagellar biosynthesis.

Other examples of membrane extensions in a wide variety of bacterial species suggest that these structures are far more widespread than is generally appreciated. In Salmonella enterica serovar Typhimurium, for example, membrane tubules connect cells to surfaces, other bacterial cells, and to eukaryotic cells as part of pathogenesis. In Francisella novicida, the growth medium and phase appear to regulate similar structures, which, however, do not appear to contact neighboring cells. Meanwhile, membrane extensions connect the two types of cells that pair up in the phototrophic consortium Chlorochromatium aggregatum, and quinones may be exchanged through these extensions. In yet another example, chains of outer membrane vesicles connecting Myxococcus xanthus cells likely pass information between cells, helping to coordinate group behaviors such as fruiting body formation.

Our work with S. oneidensis is the first description of bacterial cells extending their membranes to facilitate extracellular electron transfer. These outer membrane vesicles containing periplasm are packed with each cell’s EET machinery, and

![Figure 3](image_url)  
*Shewanella oneidensis* nanowires are composed of chains of outer membrane vesicles. Fluorescence microscopy, *left*, and atomic force microscopy, *right*, show that early in nanowire production, these structures begin as fused chains of vesicles. Later, these appear as smoother wire-like structures (see Fig. 2). Scale bars are 5 μm (left) and 2 μm (right). (Images courtesy of Sahand Pirbadian and Mohamed El-Naggar, unpublished results.)

![Figure 4](image_url)  
Model of electron transfer along *Shewanella oneidensis* nanowires to another cell or an electrode.
are poised to reduce any acceptor that S. oneidensis cells encounter. Thus, these membrane-derived “extension cords” help Shewanella reach distant electron acceptors that are critical for energizing such cells.

Regulating Bacterial Nanowire Synthesis

Extending an outer membrane full of cytochromes and other proteins is likely a highly regulated and energetically expensive process for a bacterial cell. When Shewanella cells are limited for electron acceptors, particularly under microaerobic conditions, nanowires begin to form. In the sediments and soils where Shewanella are found, soluble electron acceptors may be scarce, making nanowire formation important for survival. Because S. oneidensis nanowires consist of chains of OMVs, we may learn more about how their synthesis is regulated by reviewing how vesicles form in other bacteria.

In gram-negative bacteria, vesicles are thought to form when the OM and peptidoglycan layer separate from one another, freeing the OM to bulge and bud into vesicles. Many transcription factors monitor the envelope for events leading to such breaks, such as accumulating proteins in the periplasm. These factors then coordinate responses that maintain the integrity of the envelope under stresses such as osmotic or heat shock, nutrient deprivation, or electron acceptor limitation.

Because of their role in responding to cell envelope stress, some transcription factors and

AUTHOR PROFILE

Barchinger: from Interests in Space and Music to Bacteria that “Breathe Solid Rocks”

Sarah Barchinger distinctly remembers being asked to declare a major. A high school junior applying for scholarships, she thought: “Well, I don’t like just chemistry. I don’t like just biology either. Maybe I’ll like biochemistry,” which is what she chose. Although “a backwards way to pick a field,” she says, “it has worked for me.”

Barchinger, 32, grew up in Houston a few miles from the Johnson Space Center. “My elementary school mascot was the Stars, and I went to Space Center Intermediate School for a year,” she says. In 4th grade, “we talked to the astronauts on the space shuttle via ham radio. Even my babysitter’s father was an astronaut.” After her family moved to Iowa when she was 12, Barchinger became the first student to teleconference directly with the International Space Station. “I’m kind of surprised I didn’t go into astrobiology or some other space-related discipline,” she says.

Her recent research—part of her postdoctoral work at Pennsylvania State University—focuses on how Shewanella oneidensis transfers electrons to insoluble acceptors. “Shewanella, along with some other bacterial species, can essentially ‘breathe solid rocks.’ S. oneidensis uses a few different methods of transferring electrons outside itself to these insoluble substrates, but our focus has been on wire-like structures referred to as nanowires.”

In January, Barchinger began working as a part-time evaluator at Western Governors University, a fully accredited online university based in Salt Lake City. She is telecommuting from Houston, where she recently moved with her husband Jonathan Schueth, a biostratigrapher with ConocoPhillips, and Roo, their 7-year-old dog. She is evaluating student work in biochemistry for the university, and also preparing another paper on the nanowires research for publication.

Barchinger was born in Houma, La., and moved to Houston when she was 5. Her father was a manufacturing engineer with degrees in physics and math. Her mother retired several years ago from teaching first and second grade. Her younger sister is a wedding and event planner. “My parents always told us that we could do whatever we wanted, as long as we worked hard and were happy,” she says. “My parents were the type that would tell you to ‘go look it up’ when you had questions.”

Barchinger played soccer for much of her childhood, but gave it up in favor of music after moving to Iowa. She received her B.S. in biochemistry in 2005 from the University of Nebraska-Lincoln, and her Ph.D. in biochemistry, microbiology, and molecular biology in 2012 from Pennsylvania State University. She did postdoctoral work there from January 2012 to July 2014.

Her first lab experience came during a summer program at the University of Nebraska Medical Center. “I remember going down to the clinical lab and collecting samples from tables marked ‘urine’ and ‘blood.’ That summer was completely full of new experiences, but I had so much fun being part of that research community that I just never left.”

Marlene Cimons

Marlene Cimons lives and writes in Bethesda, Md.
members of their regulons appear to be associated with vesicle formation. Indeed, manipulating the levels of some envelope stress response systems, such as the extracytoplasmic function sigma factor $\sigma^E$ or the two-component system CpxAR, can change how rapidly vesicles are made. Deleting these response systems, however, does not keep Escherichia coli or other bacteria from making vesicles. No mutation or condition found to date eliminates vesicle formation in any bacterial species, including the membrane tubes surrounding the flagella of Vibrio cholerae.

Regulating this process is likely to be complicated. Because the most robust process for inducing nanowires to form involves cells in late-exponential to stationary phase growth under microaerobic conditions, other signaling pathways may also be involved, including the CRP and ArcA pathways that are important for S. oneidensis cells shifting to anaerobic metabolism, as well as small molecule effectors such as (p)ppGpp or cyclic-di-GMP. Vesicle synthesis in Xylella fastidiosa is tied to cellular levels of cyclic-di-GMP—a molecule that regulates synthesis of surface structures in other bacteria.

Although it is clear that bacteria regulate vesicle synthesis and which proteins get packed into vesicles, the mechanisms determining how and when outer membrane vesicles are released from such cells are not as well understood. Vesicles from many pathogenic bacteria are enriched with toxins or other proteins and molecules that help these pathogens invade their hosts. Some bacterial vesicles are enriched with quorum sensing signals for cell-cell communication. Immunofluorescence experiments determined that the decaheme cytochromes MtrC and OmcA localize densely along the length of S. oneidensis nanowires. Future experiments will hopefully identify other proteins packed into the vesicles involved in Shewanella nanowire formation.

**Perspective and Potential Applications**

Instead of being conductive pili, the nanowires of S. oneidensis extend the outer membranes of such cells, and those extensions are lined with proteins that are important for extracellular electron transfer. Although membrane extensions derived from vesicles seem to be a widespread occurrence, how bacteria regulate their production is still unknown.

If we can learn what triggers nanowire formation in Shewanella oneidensis, we might also learn how to make and then use them for other purposes—for instance, to make electrical connections between cells of different bacterial species. Through such partnerships, it might become possible to shuttle electrons from one cell to another to produce value-added chemicals. Moreover, by connecting S. oneidensis cells through such biological extension cords to electrodes, it should be possible to generate electrical currents.

Sarah Barchinger recently completed a postdoctoral fellowship at Penn State University and is currently an evaluator in biochemistry and microbiology for Western Governors University.

**Suggested Reading**


Two New Academy Reports

Microbes Make the Cheese. Did you know that each piece of cheese that we eat may contain as many as 10 billion microbes? Cheese is one of the few foods we eat that contain extraordinarily high numbers of living, metabolizing microorganisms. Cheesemakers are able to generate the vast array of cheese textures, tastes, colors, and smells because of the activities of microbes used in the cheese-making process. Microbes Make the Cheese is a new report by the American Academy of Microbiology (Academy) that provides insights into the history of cheesemaking, how microbial communities are introduced during the cheesemaking process, and how microorganisms shape the development of cheese in terms of its aroma, taste, appearance, and texture. In June 2014, the Academy brought together scientists from food microbiology, microbial ecology, and the cheesemaking industry to discuss the role of microorganisms in the production of cheese. The result of those discussions was this FAQ report, which will be available at http://academy.asm.org/.

The Threat of MRSA. Disease-causing bacteria called pathogens can make us ill and if not treated and controlled, can lead to organ failure and even death. One such bacterial pathogen is methicillin-resistant Staphylococcus aureus (MRSA). This organism is capable of causing a range of infections from skin and soft tissue infections to more life-threatening illnesses such as pneumonia as well as bloodstream and surgical site infections. The acquisition of MRSA used to be confined to the hospital environment, but now this organism can be acquired from community settings. Proper hand hygiene can help reduce the risk for a MRSA infection in both hospitals and the community. The Academy convened a panel of experts in November 2013 to discuss the clinical significance of MRSA in hospitals, the community, and in livestock populations along with measures that can mitigate the risk of infection with this organism. The Threat of MRSA is based on the deliberations of the participants that attended this colloquium and will be posted at http://academy.asm.org/.

Update on the Executive Director/Chief Executive Officer Search

ASM is actively seeking a new Executive Director/Chief Executive Officer to provide leadership, guidance, and management for the organization. In the fall the Council Policy Committee and the Council delegated hiring authority to the Officers of the Society. In this capacity, the Officers’ duties also include a review of the role of the Executive Director position, appointment of a search committee, and appointment of an interim Executive Director.

Since the ED/CEO position affects every constituency within the Society, the Officers appointed a committee that provides a broad view of the scope and function of this critical role. The following individuals have agreed to participate on the search committee:
The Officers charged the search committee to hire an executive search firm and under the search committee’s guidance conduct an international search for the position. After a competitive process, Korn Ferry, an international firm with a history of recruiting for ED/CEO positions for similar types of organizations and a strong track record in leadership development programs, was selected to assist in the search. The anticipated timeline to have the position filled is the summer of 2015.

2015 General Meeting Award Laureates

The Committee on Awards is pleased to announce the 2015 General Meeting award laureates. Biographical sketches of the 2015 awardees appear below and in the next two issues of Microbe.

**Abbott Award in Clinical and Diagnostic Immunology**

Robert S. Lanciotti, Ph.D., is the 2015 Abbott Award in Clinical and Diagnostic Immunology awardee. Lanciotti is the Chief of the Diagnostic & Reference Laboratory within the Arbovirus Diseases Branch at the CDC. His research has focused on arthropod-borne viruses (arboviruses); specifically the development of novel diagnostic assays, as well as studying the biology, evolution, and phylogeny of these diverse viruses.

Over the past 25 years Lanciotti and his laboratory have been responsible for the identification and characterization of several emerging arboviruses, including West Nile virus in New York (1999) and chikungunya virus in the Western Hemisphere (2014). His laboratory has been responsible for the discovery of several novel arboviruses, most recently Bourbon virus. His laboratory is also involved in the development, training, and distribution of arbovirus diagnostic assays to numerous public health laboratories. He is the author/coauthor of 98 scientific manuscripts and has authored 6 textbook chapters on diagnostic technology of the arboviruses.

**ASM Lifetime Achievement Award (sponsored by Abbvie)**

John Roth, Ph.D., is the 2015 recipient of the ASM Lifetime Achievement Award (sponsored by Abbvie). Roth has spent his entire career doing genetics on the enteric bacterium Salmonella typhimurium. This organism has been used to approach problems of general biological importance that may also be relevant to pathogenicity. His lab studied control of histidine biosynthesis, the central role of vitamin B₁₂ in the lifestyle of Salmonella and the recycling of NAD in response to oxidative stress. Other metabolic projects involved B₁₂-dependent degradation of propanediol and ethanolamine and the role of the protein microcompartments that enclose the enzymes of these pathways. All of this work was aided by genetic tools developed in part in Roth’s lab, including
use of transposon Tn10 as both a mutagen and a portable promoter and use of the phage-derived Mud-lac elements as reporters of gene expression. Formal genetic work has dealt with characterization of frameshift mutations and their suppressors, transposable elements and genetic recombination. Most recent work has been on recombination mechanisms that underlie formation chromosome rearrangements. Thanks to the educational efforts of several remarkable postdoctoral fellows and colleagues, Roth’s work has been directed increasingly toward more evolutionary questions and the interface between genetic mechanisms and natural selection. His current work describes how amplification of near-neutral mutant alleles can speed genetic adaptation and mimic mutagenesis.

Teaching has been an integral part of Roth’s career. His has taught bacterial and general genetics to undergraduates. He co-taught the Bacterial Genetics course at Cold Spring Harbor. Most recently he has been teaching general biology with emphasis on origins of life. He has mentored 35 graduate students and 30 postdoctoral fellows.

The first 10 years of his career were at UC Berkeley in the Department of Molecular Biology, followed by 25 years in the Biology Department at the University of Utah and 12 years at UC Davis, in the Department of Microbiology and Molecular Genetics.

ASM Founders Distinguished Service Award

The winner of the 2015 ASM Founders Distinguished Service Award is Julius S. Youngner, Sc.D., who is currently Distinguished Professor Emeritus in the Department of Microbiology and Molecular Genetics, University of Pittsburgh, School of Medicine. Among his scientific achievements, Youngner was a member of the team that developed the inactivated poliovirus vaccine that was licensed in 1955. More recently, an internally administered attenuated equine influenza vaccine licensed in 1999 by the USDA was developed in his laboratory. Youngner has authored over 200 papers that have appeared in the scientific literature.

Youngner has been a member of ASM (originally the American Society of Bacteriology) since 1942 and has served the Society in many capacities. He served several terms as a member of the Public and Scientific Affairs Board and was chair of the Committee on Medical Microbiology and Immunology and the Committee on Biomedical Research. Youngner wrote the draft document “Code of Conduct” for members of the ASM and served several terms as chair of the Ethics Committee of the Society. He also was on the Committee on Awards of the ASM. Youngner was elected to the Board of Governors of the American Academy of Microbiology and was a member for two terms. During this time he also was on the Committee on Elections for the AAM.

Youngner is past President of the American Society for Virology and is an elected Honorary Member of the International Society for Interferon and Cytokine Research.

ASM Graduate Microbiology Teaching Award

Aaron Mitchell, Ph.D., is the recipient of the 2015 ASM Graduate Microbiology Teaching Award. Mitchell became interested in science when he took a Genetics course taught by Elizabeth W. Jones at Carnegie Mellon University in 1975. He worked in her lab as an undergraduate and learned yeast genetics, then carried out Ph.D. dissertation research on yeast glutamine synthetase under the guidance of Boris Magasanik at the Massachusetts Institute of Technology and did postdoctoral work on the control of yeast meiosis with Ira Herskowitz at the University of California San Francisco. His first faculty position was in the Columbia University Department of Microbiology in 1987. He began working in the area of infectious diseases during a sabbatical with Myra Kurtz at Merck Research labs and through a collaborative project with John E. Edwards, Jr., at Harbor-UCLA Medical Center. In 2008 Mitchell moved to Carnegie Mellon University, where his lab is the one in which he worked as an undergraduate. He teaches a graduate Microbiology course as well as the Genetics course that first inspired him to become a scientist.

Mitchell committed significant effort to training and mentorship of young scientists. He was co-principal investigator (PI) for three different training grants during his time at Columbia University. He served as PI for an HHMI Undergraduate Education Grant immediately upon his move to Carnegie Mellon University. He was an
instructor in the Cold Spring Harbor Yeast Genetics Course for five years, and a co-founder and co-director of the MBL Molecular Mycology Course for 14 years with P. T. Magee and John E. Edwards, Jr. He serves as an advocate for young scientists as a member of the Burroughs Wellcome Fund Advisory Board for Pathogenesis of Infectious Disease Awards.

**BD Award for Research in Clinical Microbiology**

Robin Patel, M.D., is the 2015 BD Award for Research in Clinical Microbiology awardee. Patel graduated from Princeton University with a BA in Chemistry in 1985 and from McGill University in Montreal, Canada, with an M.D.(C.M.) in 1989. She then moved to Rochester, Minn., where she completed residencies in Internal Medicine and Microbiology and a fellowship in Infectious Diseases at the College of Medicine, Mayo Clinic. In 1996, upon completion of postgraduate training, she joined the staff of Mayo Clinic. She is currently Professor of Medicine and Professor of Microbiology, Director of the Clinical Bacteriology Laboratory and the Infectious Diseases Research Laboratory, and Chair of the Division of Clinical Microbiology, Mayo Clinic.

Patel is board certified in Infectious Diseases (American Board of Internal Medicine), Medical Microbiology/Public Health Microbiology (American Board of Medical Microbiology), Clinical Pathology/Medical Microbiology (American Board of Pathology), and Internal Medicine, Medical Microbiology and Infectious Diseases (Collège des Médecins du Québec and Royal College of Physicians and Surgeons of Canada).

Patel’s research focuses on clinical bacteriology diagnostic testing, antimicrobial resistance, and microbial biofilms. She has published over 250 peer-reviewed manuscripts and has delivered numerous national and international presentations. She is a Fellow of American Academy of Microbiology, a past member of the IDWeek Program Planning Committee, the chair of the United States Medical Licensing Examination Microbiology and Immunology Test Material Development Committee, and the vice chair of the ICAAC Program Planning Committee. She is an associate editor for the Journal of Clinical Microbiology, and the course director for the Mayo Medical School Microbiology course.

**bioMérieux Sonnenwirth Award for Leadership in Clinical Microbiology**

James Jorgensen, Ph.D., is the recipient of the 2015 bioMérieux Sonnenwirth Award for Leadership in Clinical Microbiology. Jorgensen is Emeritus Professor and Research Professor of Pathology at the University of Texas (UT) Health Science Center, San Antonio. Until partially retiring in April, 2014, he served as Professor of Pathology, Medicine (Infectious Diseases), Microbiology and Immunology, and Clinical Laboratory Sciences at the UT Health Science Center and was Director of the Clinical Microbiology Laboratory of University Hospital for 38 years.

He is a past chairman of ASM Division C and past member of the ICAAC Program Committee. He has served as chairholder and vice chairholder of the Clinical and Laboratory Standards Institute (CLSI) Microbiology Area Committee. He previously was chairholder of the CLSI Antimicrobial Susceptibility Testing Subcommittee for seven years. He chaired the working group that wrote the first two editions of the CLSI guideline on susceptibility testing of fastidious or infrequently encountered bacteria and the working group to define the penicillin breakpoints for nonmeningitis infections due to *Streptococcus pneumoniae*. Most recently, he was co-chairholder of the ad hoc CLSI working group on the susceptible dose-dependent interpretive category. Jorgensen was the convener (chair) of the working group on antimicrobial susceptibility testing of infectious agents of the International Organization for Standardization (ISO, Geneva) from 2003–2012. The working group was charged with defining global standards for susceptibility testing of bacteria and fungi and defining acceptable performance criteria for in vitro susceptibility testing devices. He was a volume editor of the *Manual of Clinical Microbiology* 8th, 9th, and 10th editions and is Co-Editor in Chief of the upcoming 11th edition due to be published in 2015. He has been a long time member of the editorial board of *Antimicrobial Agents and Chemotherapy*, and serves as a reviewer for several journals including the *Journal of Clinical Microbiology*. 
Jorgensen’s research efforts have focused on antimicrobial resistance mechanisms, especially those responsible for drug resistance in *Streptococcus pneumoniae*, beta-hemolytic streptococci, *Neisseria meningitidis*, other fastidious bacteria, staphylococci, enterococci, *Enterobacteriaceae*, *Pseudomonas* spp., and *Acinetobacter* spp. His recent activities have focused on detection, characterization, and molecular epidemiology of extended-spectrum beta-lactamases and carbapenemases. His research also has explored improved or more rapid methods of antimicrobial susceptibility testing/detection of resistance, and evaluation of promising new antimicrobial agents active against resistant bacteria, most recently through support from the National Institutes of Health.

**Carski Foundation Distinguished Undergraduate Teaching Award**

**Susan Merkel**, M.S., is the 2015 recipient of the Carski Foundation Distinguished Undergraduate Teaching Award. Merkel received her M.S. in Microbiology from Cornell University in 1988. Currently a senior lecturer in the Department of Microbiology at Cornell, she teaches lab and lecture courses in general microbiology and public health microbiology. Her research focuses on the development and efficacy of small group activities in large lecture courses, including a number of Web-based case studies. In addition, she trains graduate students how to teach using evidence-based teaching and learning strategies. She is the current Chair of the ASM Committee on Undergraduate Education and is on the Education Board of ASM. Merkel was Cochair of the ASM Task Force on Curriculum Guidelines for Undergraduate Microbiology, and continues to work to promote the dissemination and adoption of the new ASM Curriculum Guidelines. She is active in her community and currently serves on the Board of Health for Tompkins County. In addition, *Journal of Biology & Microbiology Education* and an Editor of the ASM MicrobeLibrary. She was awarded the Cornell College of Agriculture and Life Sciences Award for Innovative Teaching in 1997 and 2011.

**Eli Lilly and Company-Elanco Research Award**

**Vanessa Sperandio**, Ph.D., is the recipient of the 2015 Eli Lilly and Company-Elanco Research Award. Sperandio is a Professor in the Departments of Microbiology and Biochemistry at UT Southwestern. She got her Bachelor’s degree in Biology, and her Master’s and Ph.D degrees in Molecular Genetics under the mentorship of Wanderley Dias da Silveira in the State University of Campinas in Brazil.

During her Ph.D. studies, she was the recipient of a fellowship from the Brazilian government to perform part of her Ph.D. research at the University of Maryland Medical School in James B. Kaper’s laboratory, where she later also pursued her postdoctoral training. She joined the faculty at the Microbiology Department at UT Southwestern. She was promoted to Associate Professor with tenure in 2007 and joined the faculty of the Biochemistry Department as a secondary faculty member in 2008. In 2011 she was promoted to Professor.

She was a Latin American Pew Fellow in Biomedical Sciences (1997), an Ellison Foundation New Scholar (2004), a Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Diseases (2006), and Kavli Frontiers of Science Fellow (2007). In 2013 she was elected a fellow of the American Academy of Microbiology. She is also chair elect of Division D of ASM.

Sperandio is currently a member of the editorial boards of mBio, *Infection and Immunity*, the *Journal of Bacteriology*, and *Gut Pathogens*, being a previous member of the editorial board of the journal *Microbiology*. Her research investigates chemical, stress, and nutritional signaling at the interface among the mammalian host, beneficial microbiota, and invading pathogens. The main focus of research in her laboratory is the study of how bacterial cells sense several mammalian hormones leading to rewiring and reprogramming of bacterial transcription towards host and niche adaptation. She has also identified the first bacterial receptors to mammalian hormones, and reported that invading pathogens hijack these inter-kingdom signaling systems to promote virulence expression. She then translated these basic science concepts into strategies to develop novel approaches to antimicrobial therapy.
ASM Comments on FDA Oversight of LDTs

ASM staff attended the Food and Drug Administration (FDA) public workshop “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)” on 8–9 January. The purpose of this workshop was to discuss FDA’s proposal for a risk-based framework for addressing the regulatory oversight of a subset of in vitro diagnostics referred to as laboratory developed tests (LDTs). This meeting provided an additional opportunity for public discussion, which was spirited and raised many concerns from members of the clinical laboratory community. To see the agenda and list of speakers, please go to http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm423537.htm. FDA also provided a 120-day period, beginning in October 2014 for interested parties to comment on the framework. You can see the ASM comments, issued jointly with the Pan American Society for Clinical Virology (PASCV), by going to http://www.asm.org/index.php/publicpolicy-2/statements-testimony/137-policy/documents/statements-and-testimony/93344-ldt-2015.

IQCP Session Planned for General Meeting

In anticipation of the upcoming changes from the Centers for Medicare and Medicaid Services (CMS) Individualized Quality Control Plan (IQCP) program, the ASM Public and Scientific Affairs Board Committee on Laboratory Practice has planned a special interest session explaining these new CMS regulations. IQCP plan will take effect January 2016 and will have major impact on laboratory testing, most notably, in the clinical microbiology laboratory where this will replace Equivalent Quality Control which is now commonly used. To read more about this program, go to the CMS Clinical Laboratory Improvement Amendments page on IQCP at http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Individualized_Quality_Control_Plan_IQCP.html.

ASM Attends CLSI Committee Week

ASM Public and Scientific Affairs Board Laboratory Practices Committee Chair Susan Sharp attended the Clinical and Laboratory Standards Institute (CLSI) 8–13 January Committee Week in Ft. Lauderdale, Fl., as an advisor to the CLSI Subcommittee on Antimicrobial Susceptibility Testing (AST). The goal of the AST is to provide useful information to enable laboratories to assist the clinician in selecting appropriate antimicrobial therapy for the best patient care. Laboratory Practice Committee members Melissa Miller and Audrey Schuetz are also advisors to the AST. The AST and their activities are online at http://clsi.org/standards/micro/sub-ast/.

ASM President Attends White House Microbiome Roundtable

On 18 December, ASM President Timothy Donohue attended the Microbiome Roundtable at the White House. The goal of the meeting was to gather microbiome experts to share individual views and identify research areas and approaches that can inform strategies for developing a roadmap for accelerating discovery within the field. The following crosscutting questions were addressed at the roundtable: (i) What might facilitate future microbiome-related breakthroughs? (ii) What game-changing applications are on the horizon? (iii) What techniques best engage diverse communities that may benefit from idea sharing?

ASM Endorses Letter Opposing Sequestration

In February, ASM signed onto a letter opposing sequestration. Sequestration is possible again as the temporary and partial relief that Chairman Ryan and Chairman Murray negotiated in the Bipartisan Budget Act expires at the end of FY 2015. With the very real threat of the return of these cuts in the upcoming FY 2016 budget cycle absent congressional action, the ASM joined other organizations to unite again to protect funding for federal programs that keep Americans safe, healthy, and secure. The letter supports increasing funding to nondefense discretionary (NDD) programs and highlights the importance of these programs.

ASM Congressional Science Fellow Secures Congressional Office Position

Clayton E. Cox, Ph.D., ASM’s 2014-2015 Congressional Science Fellow, has found a placement in the office of Representative Louise Slaughter (D-NY). Cox will be working on antibiotics in agriculture, genetics and public health issues. ASM has supported Congressional Fellows since 1977. The ASM Congressional Science Fellowship Selection Committee selects a postdoctoral to mid-career microbiologist to spend one year on the staff of an individual congressman, congressional committee, or with some other appropriate organizational unit of Congress. Prospective Fellows must be citizens of the United States, members of ASM for at least one year and must have completed their Ph.D. by the time the fellowship begins in September. The Congressional Science Fellowship is supported in part by the Frobisher Fund, a bequest made to ASM by Martin Frobisher. Contact the Office of Public Affairs at publicaffairs@asmusa.org for more information on the ASM fellowship or go to the ASM website for a program description: http://asm.org/index.php?option=com_content&view=article&id=7535.

Education Board

ASMCUE 2015: Registration Discount Ends 9 March

Register today for the 2015 ASM Conference for Undergraduate Educators
(AMCUE), set for 28–31 May at the Renaissance Austin Hotel in Austin, Tex. Many researchers and faculty have already signed up for conference – available at a discounted rate through 9 March—ensuring their access to AME’s unique blend of dynamic speaker insights, poster presentations in biology education research, networking opportunities, and comprehensive roster of vendors and events. Why not register now and join colleagues at the following sessions?

Preconference Workshops
Integrating Quantitative Reasoning in Biology Education: Making the Science More Authentic and the Learning More Robust. Get hands-on experience in exploring biological problems with the help of a variety of scientific tools, all of which are freely available and appropriate for use in introductory biology and microbiology course and laboratory settings.

Creating a Successful NSF Grant Proposal. Gain tips and strategies for writing NSF grant proposals. Topics will cover the criteria of intellectual merit and broader impacts, along with ways to develop aims and align measures that will maximize your chance of funding success.

Designing Courses Based on National Recommendations for STEM Education. Learn ways to reconsider an existing course or design a new course by using the principles of backwards design and evidence-based teaching. A particular focus will be on strategies for implementing national recommendations into the classroom.

Plenary Sessions
Teaching Naked: How Moving Technology out of your College Classroom will Improve Student Learning, by national award-winning educator and author José Antonio Bowen, President, Goucher College

Antibodies Against Ebola Virus: The Road Map, by Erica Ollmann Saphire, The Scripps Research Institute

Microbes and Spaceflight, by Duane Pierson, NASA Johnson Space Center

Mobility and Higher Education, by Education and Medical Development Executives, Apple Inc.

For full program details, visit http://www.asmstue.org.

ASM-NSF LINK Empowers Researchers to Incorporate Mentoring Strategies for Greater Research Productivity
In today’s competitive research climate, ASM investigators are seeking more effective strategies to build diverse research teams and increase research productivity. Quality mentoring is recognized as a key factor that affects both lab dynamics and research quality, yet few researchers ever receive formal training in mentorship. In an effort to strengthen the research enterprise, ASM partnered with the National Science Foundation in 2012 to establish the ASM-NSF Leaders Inspiring Networks and Knowledge (LINK) Program, a structured-mentoring initiative aimed at building connections between experienced scientists (mentors) and early-career scientists (mentees). Leveraging the ASM Conference for Undergraduate Educators (AMCU), Annual Biomedical Research Conference for Minority Students (ABRCMS), and ASM General Meeting, LINK has supported emerging partnerships and provided tools to improve mentoring relationships. To date, the program has reached nearly 500 participants representing over 200 national and international universities, institutions, and government agencies. Approximately 65% of LINK participants are active researchers, most of whom advise undergraduate, graduate, and postdoctoral trainees. In 2014, the LINK program created an online learning community; instituted workshops on mentor development, team building and grant writing; and sponsored research and mentoring symposia at AMCU, ABRCMS, and asm2014.

Specific activities included:

• AMCU speakers Beronda Montgomery (Michigan State University) and Gita Bangera (Bellevue College) led sessions on effective models of broadening participation in STEM fields, including research training integration at community colleges.

• abrcms2014 workshop facilitators (Christine Pfund, Christine Pribenow, Melissa McDaniels, Beronda Montgomery, and Kelly Diggs-Andrews) conducted active engagement exercises on mentoring and trained researchers on ways to address common mentoring challenges.

• ABRCMS speakers Jesse Kwiek (Ohio State University) and A. Oveta Fuller (University of Michigan) showcased innovative models of bench work impacting public health initiatives.

LINK also created Mentoring Mondays, a five-month structured-mentoring program with goals to build and expand a community of trained mentors, broaden awareness about the benefits of quality mentoring for research success, and support emerging partnerships and collaborations that strengthen the global research enterprise. Mentoring Mondays was designed as an all-encompassing mentor training series that blended three broadcast webinars, four interactive webinars, an online discussion forum, and an onsite workshop for research investigators. Mentoring exemplars, including Christine Pfund (University of Wisconsin), Michael Summers (University of Maryland–Baltimore County), and Keivan Stassin (Vanderbilt University), shared insights on how researchers could enhance lab productivity through quality mentoring. In addition, creativity experts Andy Burnett and John Cabra of Knowinnovation, Inc., taught participants useful ways to re-envision traditional mentoring strategies while also
capturing one’s personal best practices as a method to recognize, generate, and record transferable success stories. All mentoring resources and tools were shared through the LINK listserv and are available on the LINK website. At the culmination of the series, 26 LINK honorees were invited to build mentoring partnerships, share best practices, and brainstorm implementable projects that can broaden participation in STEM at a 3-day mentoring strategies workshop held in conjunction with ABRCMS 2014.

In 2015, ASM-LINK offerings will include professional development workshops at national conferences and grant opportunities to support collaborations based on broadening participation. LINK is cosponsored by ASM and the National Science Foundation (grant no. 1241970). For details on upcoming events and to join the LINK community, visit www.ASMLink.org.

ABRCMS 2014: Cultivating Student Pursuit of Research Careers and Leadership Roles in Science

One of the best ways to ensure a future generation of scientists is by capturing and encouraging the scientific interests of undergraduates. For this reason, ASM and NIH have sponsored the Annual Biomedical Research Conference for Minority Students (ABRCMS) for more than 14 years. ABRCMS 2014 took place 12–15 November in San Antonio, Tex., to wide participant acclaim.

Organized and managed by the Society since 2000, ABRCMS is a premier student conference with a special focus on aiding individuals from underrepresented minority groups or persons with disabilities. The conference is dedicated to guiding undergraduates in the pursuit of advanced training in the biomedical and behavioral sciences, including STEM, and committed to providing faculty mentors, advisors, and program leaders with resources for facilitating student success. While the ABRCMS focus is on supporting undergraduates, the conference is attended by postbaccalaureates, graduate students, postdoctoral scientists, faculty, and administrators.

ABRCMS hit record attendance highs in 2014, attracting more than 3,600 participants, including about 2,270 students, 510 faculty and program directors, and 610 recruiters for graduate and summer research programs. Attendees heard from nearly 72 speakers at the conference and took part in numerous information-rich scientific sessions, research skills-training opportunities, workshops, and networking events.

This conference theme, “Delivering Scientific Leaders through Research Training and Academic Excellence,” reminded students to make the most of ABRCMS’ opportunities and resources as they pursue research careers and leadership roles in the sciences.

Keynote speaker Derrick Pitts, Chief Astronomer and Planetarium Director at the Franklin Institute (Philadelphia, Pa.), launched the meeting with an impassioned call for students to understand the importance of science communication. Insightful lectures on topics such as protein design, astronomy, medicine, and environmental health were given by biophysicist Stephen L. Mayo and by leading U.S. journalists Richard Rodriguez and Sonia Shah.

Major highlights of the meeting included the poster and oral presentations delivered by ABRCMS undergraduate, postbaccalaureate, and graduate students. Each of the 1,700 undergraduate and postbaccalaureate poster and oral presentations was judged by three researcher scientists, and at the closing banquet, 210 students received awards for outstanding research presentations.

Another integral conference component was a multiday mentoring workshop offered by the ASM-NSF Leaders Inspiring Networks and Knowledge (LINK) Program.

Conference highlights also included the ABRCMS Career Development Skills Cafe and the comprehensive conference exhibit program. The cafe featured multiple small-group roundtable discussions among students and experts on preparing CVs, securing summer research internships, finishing dissertations, and other topics of critical importance for next-generation scientists. In the exhibits program, representatives from more than 300 colleges, universities, government agencies, foundations, or professional societies were on hand to discuss graduate programs, research opportunities, funding sources, and professional networks.

ABRCMS is supported by a grant from the Division of Training, Workforce Development and Diversity of the NIH National Institute of General Medical Sciences (award number T36GM073777). ASM is committed to making the conference available annually for students seeking advanced training in the biomedical and behavioral sciences. The 2015 conference will be held 11–14 November in Seattle, Wash. For more information, visiting www.abrcms.org.

Branches: ASM Activities at the Local Level

Illinois Branch: 67th Pasteur Award

The Pasteur Award was established in 1948, and has been presented annually to an individual who has made significant contributions to the field of microbiology. This year is the 67th year for the award, and the Illinois Society for Microbiology (Illinois Branch of ASM) is proud to present its 67th Pasteur Award to Lance R. Peterson, M.D.

Peterson earned his Bachelor of Science degree from the University of Minnesota, Minneapolis, in 1970. He received his medical degree also from there in 1975, specializing in Internal Medicine and continued his studies to complete a Fellowship in Infectious
Diseases in 1977. He is Board Certified in three areas: Internal Medicine, Sub-specialty of Infectious Diseases, and Special Competency in Medical Microbiology. He has had tenured professor appointments in the Department of Medicine at the University of Minnesota, Northwestern University and the University of Chicago.

Peterson has held a number of job titles at the VA Medical Center in Minneapolis; his titles included Medical Director of the Hospital Based Home Care, Staff Member of the Infectious Disease Section, Chief of the Microbiology Laboratory, Director of the Medical Microbiology Fellowship Program, and associate Chief of Molecular Biology. In 1992 he moved to Chicago, accepting the position of Director of Clinical Microbiology Division at Northwestern Memorial Hospital. There he also held positions of Staff Member of the Infectious Disease Division, Director of the Medical Microbiology Fellowship Program and from 1998 to 2002 he was the First Director of the NMH Infection Control and Prevention Project (a CDC Prevention Epicenter) for the study and management of Antimicrobial Agent Resistance and Healthcare-Associated Infectious Diseases. In 2002 he accepted a position at Evanston Northwestern Healthcare (North Shore University Health System) as the Director of Microbiology and Infectious Diseases Research. There he holds several titles—Staff Member of Infectious Disease Division, Epidemiologist, Director of the Medical Microbiology Fellowship Program, and is Vice-Chair for Research, Department of Laboratory Medicine and Pathology.

He is active in many professional societies—ASM, the American Academy of Microbiology, the Chicago Area Infectious Diseases Society, the Infectious Diseases Society of America, elected to Fellowship, the British Society for Antimicrobial Chemotherapy, the Illinois Society for Microbiology, the Association for Molecular Pathology, and the American Society for Clinical Pathology.

He has held many professional offices, including serving on the Board of Editors for the Journal of Clinical Microbiology and the Journal of Antimicrobial Chemotherapy, Section Editor for the Journal of Global Antimicrobial Resistance, and has served on the Medical Devices Advisory Committee for the Food and Drug Administration, to highlight a few.

He has organized the first and second ASM Conference on Emerging Technologies for Diagnostic Microbiology and Infectious Diseases, in Beijing, China in 2008 and San Juan, Puerto Rico in 2011.

He has authored and co-authored close to 300 journal publications, almost 400 abstracts, two books, and 26 book chapters, and he is a world-renowned speaker. From 1988 to the present, he has received many research grants and federal funding grants.

Peterson’s research and studies cover numerous areas of Microbiology; with special focus on antibiotics and their role on antimicrobial activity. He is the national leader in the United States for the MRSA screening of all hospitalized patients. He has taken the lead for the molecular testing for the detection of Clostridium difficile. His interests are in areas of antibiotic activity highlighting bacterial resistance, molecular test methods for infectious diseases, and information technology applications to leverage infection control activities for improved patient safety. He is an advocate for rapid detection of pathogens and quantifying the outcomes of hospitalized patients. We applaud him on all his achievements and congratulate him on receiving the 67th ISM Pasteur Award.

Linda Bruno
ACL Laboratories, Rosemont, Ill.
Illinois Branch ASM Councilor

Obituary

Norman P. Willett

Norman Willett died on 19 September 2014 at the age of 86. He obtained his bachelor’s degree in Agriculture from Rutgers University, N.J., in 1949. He decided to pursue graduate work and obtained an M.S. from Syracuse University in 1952, and a Ph.D. at Michigan State in 1955. He spent a year at Harvard, where he investigated carries production by strains of streptococci in genetically defined strains of rats. His career path then took him to industry for four years, where he worked at Squibb Institute for Medical Research screening new antibiotics. He came back to academia, taking a position at the University of Pennsylvania School of Veterinary Medicine, where he worked from 1962 to 1967 on developing a chemically defined medium and defining growth conditions for Streptococcus agalactiae, a cause of bovine mastitis.

In 1967 he was offered the position as Chair of the Department of Dental Microbiology at Temple University, where he became a strong leader, hiring faculty and expanding the department. Having settled in Philadelphia, he volunteered with the Eastern Pennsylvania Branch of the ASM. Norm served as Treasurer, Vice President, and 29th President (1975–77) of the Branch. He continued to be active in Branch affairs thereafter, serving on the Executive Committee and as Chair and later Co-chair of the Branch Education Committee.

At the national level, Norm devoted extraordinary energy to the Branch Organization Committee (BOC), which he co-chaired with Stephen Sonstein from 1999–2008. During this time, the regional funding initiative was imple-
mented, which for the first time provided financial support and encouraged Branches to expand their range and diversity of activities. The number of student chapters grew exponentially and were encouraged with limited funding for programming by the national organization. The first postdoctoral chapter was formed with his encouragement, and new ones continue to be formed across the country. Norm was an integral part of all of these changes, and his leadership did much to enhance the collaborative relationship between Branches and National ASM. Those who served as Branch officers during that time fondly remember Norm’s enthusiasm at the podium and his encouragement and support of activities at the grass-roots level.

To his core, Norm was an educator. He read voraciously and widely, and made conversation about the latest articles. All of this information percolated into ideas to educate a wider audience at Symposia that he organized with his friend Frank Biondo, at the national ASM General Meeting. Norm’s sessions cut across discipline lines and frequently touched on issues of science and the citizen. At the National ASM, Norm was educating everyone; he truly loved going to the General Meeting.

At Temple, Norm was awarded a SEPA (Science Education Partnership Award) grant from the National Institutes of Health (NIH) to promote science education. From 1991–1994 he brought teachers from area schools to Temple University School of Medicine in the summer, where they teamed up with a research faculty member and developed a science laboratory module to take back to their schools. Subsequently, he obtained a Howard Hughes grant, in which he held workshops given by the original teachers, who presented the science modules they had developed, to a new group of teachers who had not had the opportunity to participate in the summer program, and a “Precollege Science Education Initiative for Biomedical Research” grant from NIH to provide a year of supplemental studies for “bridge students” to help them obtain the skills and credentials necessary to qualify for graduate school.

Norm was a friend and mentor to many. He was particularly supportive of women and encouraged T.K.E. to become active in the Eastern Pennsylvania Branch and to volunteer to serve on the Branch Organization Committee of the National ASM. He was a loyal partner with SS during the years they co-chaired the BOC. When M.G.S. took over as Chair of the BOC, he offered support and counsel on the value proposition that Branches offer the Society, always having time to brainstorm new ideas that would help Branches continue being able to offer the best opportunities that would advance our discipline while serving our members. Norm made similar contributions to the lives of others, showing them their potential and encouraging them to participate, debate, create. He enriched so many of our lives. His passing leaves a space not easily filled.

Toby K. Eisenstein
Temple University School of Medicine

Stephen Sonstein
Eastern Michigan University

Michael Schmidt
Medical University of South Carolina
Reviews and Resources

BOOK

Regulation of Bacterial Virulence

Our understanding of the molecular basis of virulence gene regulation has evolved over the past 30 years, along with our view of virulence. This field started as primarily an attempt to understand expression of pathogen-produced virulence factors such as toxins. However, today our concept of virulence has expanded and is recognized as a response on the part of the pathogen to a new environment (the host). This concept of virulence includes gene expression adjustments to a changing nutritional environment, as well as the response to the non-host environment as this impacts the ability to be successfully transmitted. This excellent new book edited by M. Vasil and A. Darwin reflects this more inclusive viewpoint and reminds us that regulation of virulence is as relevant today as in the 1930s when iron was discovered to regulate diphtheria toxin production in Corynebacterium diphtheriae.

Regulation of Bacterial Virulence is thoughtfully organized, consisting of 28 chapters divided into six sections. The editors assembled leading scientists to provide thoughtful, comprehensive reviews on a broad array of topics covering a wide variety of pathogens. These chapters are nicely integrated throughout the book both in terms of overall style and direct referencing to related information in other chapters. Each section addresses particular aspects of adaptation to a host environment, and each chapter is self-contained providing historical context, excellent descriptions of the biological process being regulated, detailed analyses of the regulatory pathways and molecular mechanisms involved, as well as an outstanding bibliography.

Section one sets the stage with “Global Changes During and Between Different States of Infection” and includes discussions of broad topics such as the shift from acute to chronic infection, development of biofilms and their role in infection, quorum sensing and the role of iron in regulation. Many of these topics reappear in other more focused chapters. The final section (section six) finishes up with “Emerging Regulatory Mechanisms of Special Significance” providing a view of emerging regulatory paradigms and biological questions. This includes the role of small RNAs in regulation, the importance of negative regulation of virulence, inter-kingdom signaling, and regulation of exit from the host. In between are sections describing regulation of surface factors, toxins, protein export and stress response.

The content of this book will be a valuable reference for researchers on these topics and also could be used as a textbook providing foundational information for graduate level courses. In reading this book I was reminded of what drew me to this topic years ago when I started by graduate work, and of what keeps me excited about the topic today. While there are many common themes, regulatory systems seem to be infinitely varied reflecting the particular needs of the organism and its response to the environment. We are limited only by the questions we ask, and the infection models and technology (currently) available to answer them.

Virginia L. Miller
University of North Carolina, Chapel Hill
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Application Deadlines

American Board of Medical Microbiology (ABMM) Certification. Certifies the expertise of doctoral-level microbiologists seeking to direct public health or clinical microbiology laboratories. ABMM certification is achieved by passing an online multiple-choice exam that is offered daily in the month of June at testing centers worldwide.
WWW: www.asm.org/abmm
Deadline: 1 April 2015.

ASM Robert D. Watkins Graduate Research Fellowship. Senior-level graduate students are invited to apply for the 2015 ASM Robert D. Watkins Graduate Research Fellowship. As part of its goal to increase the number of students from underrepresented minority groups who complete doctoral degrees in the microbiological sciences, the Watkins fellowship provides students with support to complete and present microbiology research. Fellows attend the ASM Kadner Institute for Graduate Students and Postdoctoral Scientists in Preparation for Careers in Microbiology (see below) or the ASM Scientific Writing and Publishing Institute (http://www.asmgap.org/) and, dependent on abstract submission and acceptance, are supported to present research at the ASM General Meeting.
WWW: http://www.asm.org/watkins

ASM Kadner Institute. Senior-level graduate students and early-career postdoctoral scientists are invited to apply for the 2015 ASM Kadner Institute for Graduate Students and Postdoctoral Scientists in Preparation for Careers in Microbiology. Sponsored by the National Institute of Allergy and Infectious Diseases and the Burroughs Wellcome Fund, the institute will be held on 24–27 July in Washington, DC. Participants receive careful guidance and mentoring in key topics important for succeeding in the microbiological sciences: (i) career preparation and opportunities; (ii) preparation, review, and critique of research proposals; (iii) scientific presentations and communication; (iv) effective teaching methods; and (v) professional ethics development.
WWW: http://www.asmgap.org

American Board of Medical Laboratory Immunology (ABMLI) Certification. Certifies the expertise of doctoral-level scientists seeking to direct laboratories engaged in the immunological diagnosis of human disease. ABMLI certification is the highest credential available to practicing medical laboratory immunologists and is recognized under CLIA ‘88 as one of the acceptable personnel requirements for high complexity laboratory directors. ABMLI certification is achieved by passing an online multiple-choice exam that is offered daily in the month of August at over 700 testing centers worldwide.
WWW: http://www.asm.org/abmli
Deadline: 1 June 2015.

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

13–16 March 2015.
Mechanisms of Intercellular Cooperation and Competition.
Washington, D.C.
WWW, http://conferences.asm.org/

26–29 April 2015.
31st Clinical Virology Symposium.
Daytona Beach, Fla.
WWW, http://www.clinicalvirologysymposium.org/

8–11 May 2015.
Antimicrobial Resistance in Zoonotic Bacteria and Foodborne Pathogens.
WWW, http://conferences.asm.org/

ASM Conference for Undergraduate Educators.
Austin, Tex.
WWW, http://www.asmcue.org/

30 May–2 June 2015.
ASM General Meeting.
New Orleans, La.
WWW, http://gm.asm.org/

12–16 June 2015.
Prokaryotic Cell Biology and Development.
WWW, http://conferences.asm.org/

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/

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.
Discounted registration rates apply through April 13

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www.asm.org/asm2015
Small Things Considered

Two More Questions about CRISPRs
by Merry Youle

Over the past eight years, researchers established a basic understanding of the CRISPR defenses against foreign DNA so widely used by both bacteria and archaea. Still, questions remained. Here is an update on two of them.

Question #1: How do you survive lytic phage invasion long enough to acquire a spacer?

A CRISPR-Cas defense (CRISPR for short) can quite efficiently dispatch a phage invader, but doing so requires having crRNAs on patrol that target that phage. To have such guards on duty, not only must you have a spacer in your CRISPR library acquired from that phage, but you must have transcribed the library and processed the transcript into the short RNAs (crRNAs) that recognize and target the invader for destruction. This takes time. A lytic phage can cause irreversible damage more quickly. So how does a bacterium or an archaeon acquire a new spacer in time and live?

Perhaps it acquires the spacer from a “dead” phage, either one that arrives already inactivated by environmental factors such as UV irradiation or one whose DNA is cleaved by the host’s restriction-modification (R-M) system. Researchers tested both possibilities using Streptococcus thermophilus SMQ-1279. This strain carries two active type II-A CRISPR-Cas systems and a type II R-M system—two defenses that work in concert to provide a more effective anti-phage defense. This strain is a host for lytic phage 2972. It has no CRISPR protection against that phage because it lacks a corresponding spacer, but its R-M system reduces successful infection by five orders of magnitude. However, if the infecting phage chromosome is methylated at all of the cognate restriction sites, the host’s R-M system is useless and host survival depends on the rapid development of CRISPR immunity by acquisition of a spacer targeting the attacking phage—a rare event that yields few survivors. When researchers challenged the cells with a mixture of both methylated and unmethylated phage, the number of cells that survived by acquisition of a spacer was increased as much as 10-fold. Moreover, the higher the proportion of unmethylated phages, the more cells survived by spacer acquisition. A similar increase resulted when the unmethylated phage were replaced with UV-inactivated phage. These two experiments, plus related controls, strongly supported the hypothesis that the presence of non-infectious phage DNA can provide a route to safe spacer acquisition.

Question #2: Must you choose between hosting a prophage and having a CRISPR defense?

Not all phage infection is a bad thing. A prophage integrated into the host chromosome can reside peacefully long-term, all the while conferring benefits on the host. Benefits? Typically prophages block infection by related phages. Often they encode and express virulence factors or other metabolic genes that assist their host. However, given damage to host DNA or other stresses, a prophage can excise, replicate, and ultimately lyse the host. The truly canny host would want a CRISPR defense that would allow a prophage to integrate and persist but destroy it when it excises.

The accepted view has been that CRISPRs shoot on sight, attacking temperate and lytic phages alike. Type I and II CRISPR-Cas systems had been shown to be incompatible with prophages by preventing integration or striking the prophage itself. Researchers investigating type III found a different story. The type III-A CRISPR-Cas system from S. epidermidis RP62a reduced lytic infection by ϕNM1 by seven orders of magnitude without affecting the frequency of lysogenization. Somehow this CRISPR defense sensed a difference between a phage genome launching a lytic infection and the same genome when inserting as a prophage, and responded appropriately to both. What is that difference? Since most phage genes are silenced in the prophage, whereas most are actively transcribed during lytic replication, they hypothesized that type III-A CRISPR-Cas systems target only transcriptionally active targets. Further experiments supported this by demonstrating that DNA cleavage by this CRISPR-Cas system required transcription across the target DNA. The molecular mechanism underlying this CRISPR tolerance of prophages remains to be unraveled. This is one more example reminding us that although the basics of CRISPR defenses are well established, there are subtleties, adaptations, and nuances that we are just beginning to explore.

Merry is a phageophilic microbiology writer/editor and STC blogger emerita.


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