FEATURES

Q and A with New ASM CEO Dr. Stefano Bertuzzi

Applying Topological Principles to Genomic Analysis

Six Things You Might Not Know about Mitochondria

ASM News
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- David S. Perlin, Professor and Executive Director, Public Health Research Institute, New Jersey Medical School-Rutgers University
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July 31–August 3, 2016 | Washington, DC

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August 4–7, 2016 | Washington, DC

5th ASM Conference on Salmonella
August 29–September 1, 2016 | Potsdam, Germany

6th ASM Conference on Beneficial Microbes
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Long recognized as having bacterial origins, mitochondria are more complex and more specialized than is generally recognized (see p. 475). (Image © Thomas Deerinck, NCMIR/Science Source.)

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Antibiotic susceptibility testing is crucial for monitoring the efficacy of antimicrobial agents in the increasingly difficult battle against microbial pathogens

Highlights from the 31st Clinical Virology Symposium
Steven Specter, Richard L. Hodinka, and Randall Hayden
Participants debated whether to regulate laboratory developed tests, while learning about Ebola, other emergent viruses, and of new technologies for viral diagnoses

Microbiology Highlights from 2015
Jeffrey L. Fox
Some 2015 highlights trace to earlier times, but last year was packed with important policy and research developments involving microbiology
Trees versus Bushes
Stanley Maloy

When Charles Darwin wrote *On the Origin of Species* in 1859, he drew a diagram of a tree to represent divergence through natural selection. His work focused on plants and animals—he had no clue what microbes were or how they would impact his conclusions (R. Kolter and S. Maloy, *Microbes and Evolution: The World that Darwin Never Saw*. ASM Press, Washington, D.C., 2012). However, it was the comparison of gene sequences in microbes that provided the most conclusive evidence for a “universal tree of life.” In the late 1970s, Carl Woese argued that the 16S subunit of ribosomal RNA provided an ideal tool for evaluating genetic relationships between organisms—16S rRNA from different organisms shared regions with sufficient sequence similarity to recognize the 16S gene from divergent organisms, while having regions that were sufficiently variable to distinguish closely related organisms. This discovery led to a paradigm shift in our understanding of evolution, dividing all living organisms into three Domains: Bacteria, Archaea, and Eukarya.

Identification of microbes from 16S rRNA sequence comparisons also had many practical applications. This approach was widely used to answer the question “who’s there” in variety of environments, including the diagnosis of life-threatening infections in clinical laboratories. Although this approach only tells part of the story, it often gives insights into important aspects of the microbes. For example, quickly distinguishing between two pathogens in a sick patient is often sufficient to suggest an effective therapeutic intervention.

Nevertheless, it does not tell the whole story. In the early years of 16S rRNA sequencing, I recall scientists claiming that by simply knowing this sequence they could accurately predict the metabolism and ecology of a bacterium. With the advent of whole-genome sequencing, comparative genomics, and genetic tests of sequence predictions, we now know that although 16S rRNA sequences can provide valuable insights into a bacterium, it is impossible to predict many important features of bacterial genetics and physiology from this data alone. This conclusion didn’t surprise bacterial geneticists who recognized the potential impact of a single point mutation on the physiology of an organism, or the ease of acquiring genetic loci—like antibiotic resistance genes—from other organisms.

Furthermore, once genome sequencing became possible, comparative genomic approaches led to the surprising realization that horizontal gene transfer (HGT) resulted in major genetic differences between closely related bacteria. Two bacteria that seemed closely related based upon comparison of sequences of 16S rRNA and other housekeeping genes often differed by more than 10% of the genes in their genomes. The extent of HGT led to the idea that we should be thinking about evolution as a highly networked bush instead of a tree. This promiscuous perspective of horizontal gene exchange explains ecological differences between bacteria that seem closely related based upon 16S rRNA sequences, but focusing on the bush often obscures the underlying vertical evolution.

In this issue of *Microbe*, Raul Rabadan and colleagues describe an approach that integrates these ideas by using topological principles to visualize evolutionary relationships between microbes (p. 467). This computational approach relies on mathematical concepts that have useful applications in physics and engineering, but are not yet widely used in biology. They describe the basic framework of this approach, but the framework is likely to continue to evolve, and ultimately “natural selection” will determine which approach will endure.

*Stanley Maloy, Center for Microbial Sciences, San Diego State University, is the Chair of the Microbe Editorial Board.*
Letters

Ebola Diagnostics

It appears that there were omissions in your recent article on Ebola diagnostics (“Ebola Outbreak Spurred Sequencing and Diagnostic Efforts,” June 2015, p. 226). In the article, the author did not discuss the simple, sample-to-answer Ebola Zaire virus nucleic acid amplification tests that have already been issued Emergency Use Authorization by the FDA: Xpert Ebola (Cepheid, Sunnyvale, Calif.) and FilmArray Biothreat-E Test® (BioFire Defense LLC, Salt Lake City, Utah). Both of these moderate-complexity tests are capable of near-care or point-of-care testing on whole blood, with minimal hands on time and results in 1 to 2 hours. Xpert Ebola was developed with grants provided by the Bill and Melinda Gates Foundation and Paul Allen Family Foundation, and is undergoing field evaluation in Sierra Leone.

Benjamin Pinsky
Stanford University School of Medicine

The Early Challenges of Antibiotic Discovery

Professor Kim Lewis’ excellent review of the status of antibiotic research (“Challenges of Antibiotic Discovery,” Microbe, September 2015, p. 363–369) unfortunately includes a common microbiological misconception that should be addressed. He comments that Selman Waksman “introduced a simple screen which essentially replicates the accidental discovery of Fleming—a Streptomyces spot-inoculated on a plate with a lawn of the test pathogen, and a zone of growth inhibition indicates the presence of an antibiotic.” However, the variety of complex twists and turns of screening for antibiotics are illustrated by the theses of the following students of Waksman’s and not readily apparent from the published papers: H. Boyd Woodruff (actinomycin)(H. B. Woodruff, The production of antibiotic substances by soil microorganisms. Ph.D. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1942), Elizabeth Horning (clavacin and fumigacin)(E. S. Horning, Distribution and properties of antagonistic fungi and actinomycetes in nature. Ph.D. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1942), Doris Jones (antiviral screen)(D. Jones, The effect of micro-organisms and antibiotic substances upon viruses. M.S. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1945), Elizabeth Bugie (antibiotic production)(E. J. Bugie, Production of antibiotic substances by Aspergillus flavus and Chaetomium cochlodes, M.S. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1944), and Albert Schatz (streptomycin)(A. Schatz, Streptomyacin, an antibiotic agent produced by Actinomycyes griseus. Ph.D. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1945). In 1952 the Nobel Committee awarded the Nobel Prize in Physiology or Medicine to Selman Waksman for his “ingenious systematic and successful studies of soil microbes that led to the discovery of streptomycin.” Likewise, this year the Nobel Prize in Physiology or Medicine was in part awarded to Satoshi mura for the discovery of Avermectin, and the Nobel Assembly cited Dr. mura’s “extraordinary skills in developing unique methods” for the isolation of Streptomyces species. Screening methodology merits focus.

The variations in methodology of Waksman’s “simple screen,” which led to the discovery of many antibiotic-producing actinomycetes and fungi, were complex and required the combined efforts of a remarkable team. Waksman’s team at Rutgers used a variety of screening approaches, including: directly plating soil, using soils enriched with Escherichia coli to enhance antagonists active towards gram-negative pathogens, and recovery using selective media containing turbid suspensions of washed live target bacteria combined with phosphate and cleaned agar. In spite of the complex screening methods, it is ironic that one of the two original Rutgers streptomycin-producing Streptomyces griseus strains (D-1) was obtained from a chicken tracheal swab that was plated onto nutrient agar where it showed microbial antagonism (D. Jones, M.S. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1945).

In brief review (H. B. Woodruff, Appl. Environ. Microbiol. 80:2–8, 2014), the first of Waksman’s antibiotics, actinomycin (1940) was discovered by Boyd Woodruff (H. B. Woodruff, Ph.D. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1942) using soils enriched with E. coli for two months followed by plating onto live E. coli-laced agar medium. The recovered actinomycetes that produced haloes on the turbid media were tested for their antimicrobial activities towards gram-negative and gram-positive bacteria, including Mycobacterium tuberculosis. One microbe, Streptomyces antibioticus, a previously undescribed species, produced actino-
mycin that was active towards all three groups. Eureka! The discovery of the first broad-spectrum antibiotic and validation of the Waksman screening concept. Unfortunately, actinomycin was toxic in the subsequent animal trials. In continuing the development of screening methodology, Elizabeth Horning (E. S. Horning, Ph.D. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1942) addressed antagonistic fungi and bacteria. For fungi, she speeded up the procedure by sidestepping the several-week soil enrichment step and plated soil directly onto bacteria seeded plates. Any fungal antagonists (clearing zones) were subcultured onto dextrose peptone agar in an attempt to enhance antibiotic production. After incubation, these fungal plates were streak inoculated with Bacillus subtilis or Staphylococcus aureus up to the edge of the fungus colony. The fungi producing clearing zones were transferred to dextrose-peptone or Czapek agar. Horning discovered the antibiotics clavacin (Penicillium notatum) and fumagacin (Aspergillus fumigatus). She also addressed antagonistic actinomycetes by plating soils, lake mud, composts, and one bacterially enriched soil onto albumin and Krainskey agars. She recovered over 100 inhibitory strains, coincidentally showing that roughly 30% of the soil actinomycetes had inhibitory activities. However, the singular experiment using potting soil enriched with mixtures of bacteria, revealed that 93% of the recovered actinomycetes showed antagonism.

At this stage Waksman fully directed his attention to his beloved actinomycetes (S. A.Waksman and A. T. Henrici, J. Bacteriol. 46:337–341, 1943). Albert Schatz continued the primary direct screening method onto E. coli or M. tuberculosis based media and then with subsequent analysis of isolates using the cross streak plate method and also testing in liquid media (A. Schatz, Ph.D. Thesis, Rutgers, the State University of New Jersey, New Brunswick, N.J., 1945). Interestingly, he did not recover any antagonistic isolates from the tubercule plates. He isolated the S. griseus strains 18–16 and D-1, which displayed activities towards E. coli. S. griseus 18–16 was discovered through plating on E. coli turbid medium, but grew sparsely and without a clearing zone, and therefore, this strain may not have been discovered by a modern high-throughput screen. It was selected simply based on its sparse growth with E. coli cells as a source of nutrient. S. griseus D-1 was initially observed through plating from a chicken throat swab directly onto nutrient agar where it was antagonistic to other throat organisms. These two cultures produced the broad-spectrum antibiotic streptomycin, which was active towards both gram-positive and gram-negative bacteria, as well as tubercle bacteria. Eureka II! The discovery of streptomycin rocketed the screening for broad-spectrum antibiotics and revamped the pharmaceutical industry, which resulted in the discovery of diverse antibiotics resulting in a paradigm shift in medicine and society.


We also note that Selman Waksman’s name and S. griseus were unfortunately misspelled in the article (Waksman and grysus, respectively). Lewis’ report excellently represents the status of today’s antibiotic discovery and we applaud his group’s efforts and successes in bringing forth new and novel drugs from dirt, and thereby, revitalizing the interest in this important field of study.

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16S rRNA, 18S rRNA, 70S and 80S Ribosomes: What Does the “S” Stand For?

Sequence data of small subunit rRNA (16S rRNA for prokaryotes, 18S rRNA for eukaryotes) are an integral part of every paper describing new species of microorganisms. And because of the availability of extensive ribosomal RNA sequence databases, most “cultivation-independent” studies of microbial communities in natural environments target 16S or 18S rRNA genes. I estimate that 16S or 18S rRNA genes feature in at least 70–80% of all papers in journals such as FEMS Microbiology Ecology, ISME Journal, and Microbial Ecology.

Although the great majority of microbiologists use the terms 16S and 18S rRNA daily, hardly anybody appears to know what the “S” stands for. To prove this fact I devised a little quiz. The question asked was: “What is the dimension of the “S” unit (as used in 16S rRNA, 70S ribosomes, etc.) in SI Units (kg = kilogram; m = meter, s = second)”. I presented the following options: (1), Dimensionless; (2), kg; (3), m; (4), s; (5), kg/m; (6), kg/m². (7)
kg/m³; (8), m/s; (9), m/s²; (10), kg.m/s;
(11), kg.m/s²; (12), kg/m³.s; (14), kg/s;
(15), kg.s/m³; (16), No idea. I presented
this quiz at four different occasions: (i)
16 April 2015, The Winogradsky Insti-
tute of Microbiology, Moscow, Russia,
for an audience of 20 senior scientists
and 40 graduate and senior undergrad-
uate students; (ii) 15 May 2015, The
Interuniversity Institute for Marine
Sciences in Eilat, Israel, during a course
marine microbiology for 20 M.Sc. and
Ph.D. students and their teachers; (iii)
8 June 2015, at a session on “The Spe-
cies Concept in the Genomic Era” dur-
ing the 6th FEMS congress in Maa-
stricht, The Netherlands, attended by
90–100 participants; (iv) 28 August
2015 at the 7th National Conference of
Microbial Resources & the Interna-
tional Symposium on Microbial Sys-
tematics and Taxonomy, Hangzhou,
China, where 310 scientists and stu-
dents were present.

The result was interesting; out of the
total of almost 500 participants in the
quiz, nearly all of which were scientists
and students who are almost daily
confronted with the terms 16S rRNA
etc., only one (in Maastricht) give the
correct answer which is option 4: the S
(= Svedberg) is a unit of time and is
therefore measured in seconds. Except
for option 16 (“No idea”), popular
answers were “Dimensionless” and
“m/s²”. Once or twice someone hesi-
tantly commented that it may have
something to do with sedimentation.
Indeed the Svedberg unit is the ratio
between the speed of a particle in the
ultracentrifuge (measured in m/s) and
the centrifugal force (m/s²), 1 S being
equivalent to 10⁻¹³ s.

While biochemistry textbooks give
in-depth information on the use of the
analytical ultracentrifuge, most micro-
biology textbooks provide little expla-
nation. Some textbooks do not explain
the nature of the S unit (e.g., B. D. Davis
et al., Microbiology, 4th ed., 1990; A.
Salyers and D. Whitt, Microbiology. Di-
versity, Disease, and the Environment,
2001). The connection between the S
unit and sedimentation is given e.g. by
M. T. Madigan et al., Brock Biology of
Microorganisms, 13th ed., 2012 (“The
S-values are Svedberg units, which re-
fer to the sedimentation coefficients
of ribosomal subunits (30S and 50S) or
intact ribosomes (70S) when subjected
to centrifugal force in an ultracentri-
fuge”). The most accurate description
I found in a modern microbiology text-
book is “The rate of sedimentation per
unit of centrifugal force is called the
sedimentation coefficient and is gener-
ally expressed in Svedberg (S) units”
(R. Atlas, Principles of Microbiology,
2nd ed., 1997). I did not read the defi-
tion of 1 S = 10⁻¹³ s in any of the
microbiology textbooks I checked.
Thus it may not be too surprising
that so few microbiologists know
the meaning of a basic unit they use
every day.

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PRINCIPLES OF VIROLOGY
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- Ralf Bartenschlager, Department Head and Professor, Molecular Virology, University of Heidelberg

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Q and A with Dr. Stefano Bertuzzi

ASM’s incoming CEO talks about his background, the importance of associations, and his vision for ASM

Stefano Bertuzzi, Ph.D., MPH, has been named CEO of ASM effective 4 January 2016. Dr. Bertuzzi joins ASM after serving as the Executive Director at the American Society for Cell Biology (ASCB) for the past three years. Before leading the ASCB, Dr. Bertuzzi was a senior scientific executive at the National Institutes of Health, where he served as Director of the Office of Science Policy, Planning, and Communications at the National Institute of Mental Health, and as a science policy advisor to NIH Director Dr. Elias Zerhouni. He received his Ph.D. in Molecular Biotechnology from the Università Cattolica del Sacro Cuore of Milan, Italy, with a fellowship in the Microbiology Institute, and his Master’s in Public Health (MPH) from the Bloomberg School of Public Health at the Johns Hopkins University in Baltimore with a specialization in health policy. Dr. Erika Shugart, Director of Communication and Marketing Strategy, sat down with Dr. Bertuzzi for a brief Q&A.

What attracted to you to the position of ASM’s CEO/ED?

I would say two things. The first one is the microbial sciences. They are undergoing a total renaissance, triggered in part by the explosion of technology. Think about metagenomics, for example. What I find fascinating is the depth and breadth of the new microbial sciences. Here at ASM, it runs from very basic science to very applied. Beyond the biomedical applications, I am fascinated by the new work being done on the benign microbes. My favorite is the marine world. Pick a drop of water in the ocean and you will have 50,000 microbes in there—more than there are ASM members. Yet we can culture fewer than 1% of these. So think about what is there to discover. Just look at recent work on individual microbiomes. Then there are big problems like climate change, where, amazingly, microbes play a significant part in the equation. What is extremely exciting is that a large organization like ASM spans all of this.

The second reason is more operational, but equally important to me. I am extremely impressed with all of the ASM programs. I am so excited about the ASM strategic plan, because now we can really think about our programs and say how these will help us reach our goals.

You have worked in a variety of different roles. What is the most important lesson from your career that you will bring to ASM?

In my career so far, I have been many things—first a bench scientist, then a lab chief, then an NIH policy wonk, and most recently the Executive Director of a scientific society. So there are a lot of hats in my career closet, but the lesson I hope I can bring to ASM once I put on this newest hat is the need to listen to your people. There is first the ordinary but difficult job of listening to the people you work with every day, but as CEO there is another type of listening to be done—to our members. In today’s world of fast-flowing data and changing technologies, there is a new kind of listening that a CEO must do—listening to the data streams indicating what people say they want, and what they say they need. We are in business because of our members, so it is very important to listen to what they need, and to listen to what they can’t find elsewhere to satisfy their needs. However, while I want to do thorough listening through data, it is clear that we cannot relegate solely to technology those ever-important personal relationships with our members.
What is your favorite aspect of working in a scientific society?

I am going to go way back to Alexis de Tocqueville’s Democracy in America, a book I read this summer at the beach. There is a whole chapter devoted to associations, entitled “On the Use Americans Make of Associations in Civil Life.” De Tocqueville’s concept is that the Jeffersonian view of democracy in America, all focused on the individual, is fabulous because it gives each one of us the right to our most treasured value, which is freedom. However, Americans realized that in this model of democracy, individual freedom can be powerless. If you have all the freedom you want but you are but one individual, then no one will hear your problems. So this is the reason de Tocqueville says that associations became so important in early America, and it is why I believe that the engine of innovation in the U.S. today is powerful—because individuals band together to push for something that they need, to block something that is hurting them, and so on. I think that it is beautiful to think about the role of associations as the engine of innovation in society. We need to maintain and enhance this concept.

What are the most critical issues facing ASM?

First of all, I think that ASM is a very strong organization, otherwise I wouldn’t have decided to join it. Against this strong background, any problem we face is only critical to a certain extent. But these are rapidly changing times for scientific organizations. Many traditional successful models are laboring to keep up with technological, scientific, and economic changes. I am reminded of a quote from Jack Welch, the former CEO of General Electric. He said “When the degree of change outside of the organization is greater than the degree of change inside the organization, the end is near.” I am not suggesting the end of ASM is near, au contraire. ASM has always maintained a healthy degree of change and growth. Although ASM is a very strong organization, in today’s world all organizations must evolve to remain relevant for their members.

One of the areas that I think ASM needs to evolve is the governance. To me that is very important, because without that we can’t get anything done. I am very supportive of the work that has been done on modernizing the ASM governance. I want to implement that vision and the new governance system, but with a great degree of agility and nimbleness. We don’t want the governance to become a cage. I am looking for a board that asks the tough questions and discusses the strategic issues, but is not focused on implementation or operations. That is the role of the CEO and his staff. We need to strike a good balance at this level.

The second critical issue is technology. Technology in a broad sense is about understanding what people need. We need to be able to get data in order to make decisions, and in order to get data we need technology. As I said earlier, we need to analyze data in new ways, as a form of listening to what our members want and need. That way we can modularize our offerings, delivering tailored services to particular subgroups within ASM who have their strong identifies and needs, but without neglecting the power of the associative whole. I plan to spend a lot of time visiting with our members. We should have the statistical and technological means to crunch the big numbers, but I want also listen to our members, using a very old technology—the human ear.

The third critical thing for ASM is its scholarly publications. We are in a rapidly changing world. ASM has some fabulous journals, but we now have disruptive newcomers invading the scholarly publishing space from multiple levels. Technology, and innovation in general, is going to be key to keeping our scholarly publications relevant, authoritative, and sustainable.

The fourth is the visibility of ASM. We need to grow the ASM public visibility, especially around the emerging scientific issues for the mid-21st century. ASM has an impressive track record in public communication of its science, science policy issues, and education. But public communications is going through a revolution not seen since the invention of the radio or perhaps the printing press. This is not news to anyone in science news. If you want to stay a player in the new 24/7 information world, you have to raise your game.

What do you hope to achieve in your new role?

My ultimate goal is to have an engaged membership that understands that they are better off because of ASM, realizing that without ASM they wouldn’t be able to function at their personal and professional best. I don’t want an association where people say “I gave you my check, so stop bothering me.” The idea is to have an engaged membership that recognizes how ASM really helps them get what they need, be it career development; efficient, authoritative publishing in an ASM journal; or anything else. This to me is the quintessential role of an association. It is about the members.

There is one other thing, and that is diversity. I am very sensitive to the issue of diversity and have recently been influenced by a wonderful book by Scott Page called The Difference. We often think of diversity as something that we ought to pursue because it is the right thing, but it is much more than that. Scott Page
shows that in certain areas, and science is certainly one of those, a diverse workforce gets to your goals quicker. The complexity of science today calls on different skills and different approaches, and that is what diversity brings to the table.

Business development is another thing I am going to pay a lot of attention to. We need to engage for-profit partners and foundations in the microbial sciences. We face some very daunting problems in funding, education, and training that we won’t be able to manage on our own. I look forward to working with the Strategic Alliances director. We need to sit down with key partners and find the win-win, where we can achieve common goals, advance the field, and ultimately benefit both our outside partners and our community.

What are the most critical issues facing science?

There are so many. ASM has always worked in partnership with other associations and groups, but that has to expand as there are many issues that affect not only the microbial sciences. As de Toqueville would have it, we need associations of associations to be heard.

One of the critical issues I see in science is the sheer complexity of biology. What I mean by this is, after the big genetic wave, and then genomics, we really thought that we had done a lot. We now realize that we know very little. We probably know 5% of what we should know, because as we know more, we realize how complicated biology is. To tackle that complexity, to take our understanding to the next level, will require an unprecedented integration of the disciplines. Everything is becoming extremely quantitative. What were once the domains of the physicist or the engineer are now becoming necessary for the biologist. We must make sure that ASM facilitates these multidisciplinary forums; they are not easy, but it’s where the future will be. ASM has a great convening power, so we need to use it with our journals, our meetings, and our initiatives to bring the microbial sciences together.

The second critical issue broadly facing science is more exacerbated in the U.S. We are now deep in a seemingly never-ending funding crisis while the system presents a severe imbalance between supply and demand in its workforce. We have more people in the pipeline than there are opportunities in academia. ASM needs to protect the rising generations of scientists while broadening their career opportunities.

The third issue is to face up to the general public knowledge of science. It is appalling. I think that ASM has always had a big role in communicating the value of science, but we need to take it further. Things we took for granted as great public benefits like vaccination are under attack. Vested political interests have succeeded in painting scientists as whimsical doomsayers and government money hounds. We have to redouble our efforts to communicate the tenets of science—how it works, how it corrects itself, how small discoveries roll on into great changes in ordinary life. ASM has to be at the forefront of this effort.

And the fourth thing is diversity, which I mentioned before. In science, diversity is a high-value proposition. We must gather into our discipline the best scientists on Earth, hence the absolutely fundamental global role that I envision for ASM, but also we need to aggressively foster diversity at the ethnic, gender, and sexual orientation level, enhancing the potential that makes for better science.

You have talked about the important role the microbial sciences can play in tackling daunting problems. How can ASM help to find solutions to these problems?

Our human capital is our best asset. We don’t produce objects or products, per se. We produce knowledge. That is what our members hold in common. One thing that I haven’t mentioned that is very relevant to this is the American Academy of Microbiology. I would really like to see the Academy working closely with our policy actions, because I see the Academy as a one-of-a-kind think tank. The Academy could be a powerful strategic asset. Working in conjunction with ASM leadership, it could be a vehicle for engaging controversial or crisis issues. It can convene in a timely fashion working groups to study these issues, providing a factual ground floor for public discussion, and formulate policy responses. Advocacy backed by Academy working groups could be very effective, what a great synergy I see for the two!

What would like to tell members about your life outside of work?

My wife, Elena, and I have been together since high school, which was when the Earth was still cooling down! We met at summer camp. I have two kids, Davide, 11 years old, and Celeste, who is a 6-year-old. Davide is our biological son and Celeste was adopted from Washington, D.C. This is our own diverse family, and it’s why diversity resonates with me so much. I see all of the issues my little girl faces growing up black in a white family and I am acutely aware of how our society all too often looks first and judges too quickly.

I am also an avid reader, and all too often, an all-night reader. Is there a support group for that? I also love sailing, which I can’t do as much as I’d like to. I like to go running in the morning when the weather is good. I have been totally converted to baseball by my son, who
is an avid sports person. Growing up in Italy, I didn’t know the first thing about baseball, and after being here for 20 years I still didn’t know what baseball was until Davide was born. Now I am a total Nationals fan. When I moved from Milan to Washington, I still had season tickets to the legendary La Scala opera house. Now I have season tickets for the Nationals. I am delighted to think that I am probably the only person who converted La Scala season tickets to Nats season tickets!

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NEW FROM ASM

Microbial Collaborations in Edible Plants, Other Foods Affect Foodborne Pathogens

Shannon Weiman

Competition and cooperation between microbial species in foods contribute to growth and persistence of human pathogens, according to several researchers who presented recent findings during the 2015 ASM General Meeting, held last May in New Orleans. Examining microbial communities on foods from vegetables to cheeses, these researchers are unraveling the phylogenetic and molecular nature of these interactions, with the longer-term goals of better predicting, identifying, and preventing food contamination to improve food safety.

“During their interactions with plants, human enteric pathogens, such as Salmonella enterica, are known to benefit from interactions with phytopathogens,” says Andrée George of the University of Florida, Gainesville. S. enterica gains a better foothold in host plants through metabolic interactions with Pectobacterium carotovorum, which causes soft rot in tomatoes, he says. P. carotovorum carries enzymes that break down the oligosaccharide pectin in plant cell walls, releasing nutrients that S. enterica feeds on but cannot access itself because it lacks genes encoding such enzymes.

S. enterica thrives within soft-rot lesions of plant tissues, upregulating genes for transporters and enzymes encoded in its KdgR regulon that metabolize plant tissue breakdown products. “Bioinformatic, phenotypic, and gene expression analyses demonstrated that the KdgR regulon included genes involved not only in uptake and metabolism of molecules resulting from pectin degradation, but also those central to utilization of a number of other carbon sources,” says George. These regulatory changes enable S. enterica populations to become 10-1,000 times larger in soft rot lesions than on intact plants, he notes. These principles may also apply to pathogenic strains of Escherichia coli, which similarly thrive in soft-rot lesions and possess KdgR regulons.

However, some bacterial species protect plants against colonization by human pathogens, according to Maria Marco of the University of California, Davis. For example, the epiphyte Erwinia could help to stop E. coli O157:H7 from colonizing lettuce by outcompeting this human pathogen, she says. “These bacteria, Erwinia, might compete for nutritional resources available on the leaf surface.” E. coli O157:H7 tends to persist on plants that harbor fewer of these protective epiphytes, she adds.

Interactions between fungi and bacteria within cheese can promote the growth and dispersal of some bacterial species, including the human pathogen Listeria, says Benjamin Wolfe of Tufts University in Medford, Mass. Mucor fungi, a common component of microbial communities within cheeses, form hyphae that serve as superhighways for specific bacterial species, including proteobacteria and Listeria, to spread across the cheese blocks, he says.

Metabolic changes, rather than motility mechanisms, enable those bacte-
ria to interact with the fungi and thus spread across the surfaces of the cheeses, Wolfe points out. For instance, proteobacteria within cheeses alter their nitrogen metabolism, while downregulating chitinases, suggesting a symbiotic relationship to protect their fungal partners. “Several bacteria grew poorly without the presence of a fungal partner, demonstrating that the cheese environment may be unable to support the growth of some bacteria,” he says. However, this seeming deficiency is “rectified by the presence of several different genera of fungi.”

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

RESEARCH ADVANCES

Simulating Microbiome Activities in Silico—with Robots as Hosts

Barry E. DiGregorio

Because the interactions and influences between host and microbiome sometimes prove too complex to analyze directly, one simplifying alternative is to model them in silico, according to Warren C. Ruder of Virginia Polytechnic Institute and State University (Virginia Tech) in Blacksburg, Va., and his collaborators. Their approach “computationally simulates a hybrid robot-bacteria system,” and this virtual host-and-microbiome duet appears to “replicate a range of different biological ‘host’ behaviors,” they report. Details appeared in the July 2015 Scientific Reports (doi:10.1038/srep11988.)

In other words, the model incorporates an engineered bacterial population to stand in for the microbiome, while the robot stands in for an animal host, according to Ruder. “In our simulations, we borrowed Escherichia coli signaling machinery that drives the bacteria’s desire to acquire lactose or arabinose, but we modeled the system with normal culture media,” he says. The “host”—that is, the computer-simulated robot—was equipped with sensors and a miniature microscope.

This model system allows its users to make simple changes to engineered gene networks in the bacteria that are part of the virtual microbiome or to the host robot’s programming, and then watch complex behaviors emerge within the overall model, Ruder says. Such computer simulations belong to the growing field of synthetic biology, whose virtual birth traces more or less to the year 2000.

“In most simulations, the robot was passive and simply took commands,” Ruder says. “When we programmed it with a single additional subroutine whereby it detected when it got close to a fuel depot and injected a biochemical into the bioreactor, we saw a new behavior. The result was a system that exhibited stalk-pause-strike behavior. This showed that simple additions to the genetic circuitry and robot programming caused relatively complex behavior to emerge.”

“By integrating an engineered microbiome, a microfluidic chemostat mimicking the microbiome’s environment within an organism, and a robotic conveyance, we have designed, modeled, and simulated a biomimetic system that allows us to explore natural phenomena through both synthetic biological and robotic programming,” note Ruder and his collaborators. “We expect this model system will have implications in fields ranging from synthetic biology and ecology to mobile robotics.”

“The work will serve as a good foundation for other researchers in the fields of computational systems biology or synthetic biology,” says Rahul Sarapeshkar at Dartmouth College in Hanover, N.H. “Such control systems are very important in enabling these fields to engineer and to understand the noisy, analog, and complex feedback dynamical systems actually seen in living cells.” And adds Vikas Berry at the University of Illinois, Chicago, “I believe that a prototype of the proposed model can be built in a year or two. However, the complete development of this ‘biotechnology’ and the realization of the vast variety of functions and operations that can be possible will take a few decades of work.”

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

SCIENCE AWARDS

Lasker, National Academy “Convergence” 2015 Awards Recognize Microbiology

Jeffrey L. Fox

The 2015 Lasker Awards in several categories recognize microbiologists and
MINITOPIC
Several Recent Microbial Developments Impinge on Agriculture

Several noteworthy developments involving microorganisms that affect agriculture include:

- White grain disorder in wheat is caused by three previously unidentified fungi that belong to the Eutiarosporella genus and occur in different proportions in different diseased areas, according to Peter Solomon of the Wheat Biosecurity Laboratory at the Australian National University in Canberra and his collaborators. Details appeared 29 July 2015 in Australasian Plant Pathology (doi:10.1007/s13313–015-0367–2).

- N- and C-terminal extensions that connect to the core of bamboo mosaic virus by very flexible linkages allow for extensive interactions with many surrounding subunits and thus explain the “extreme flexibility” of this virus and likely account for its enormous capacity to damage crops, according to Edward H. Egelman of the University of Virginia School of Medicine in Charlottesville and his collaborators there and in Seattle, and Taiwan. Details appeared 13 July 2015 in Nature Structural & Molecular Biology (doi:10.1038/nsmb.3054).

- Efforts to improve food safety by clearing wild vegetation surrounding crops is not helping, and “has not led to the reductions in pathogenic Escherichia coli and Salmonella that people were hoping for,” say Daniel Karp at the University of California, Berkeley, and his collaborators there and in Stanford, Santa Barbara, Seattle, and Sweden. Details appeared 10 August 2015 in Proceedings of the National Academy of Sciences (PNAS)(doi:10.1073/pnas.1504788112).

- Having the right mixtures of soil microbiota directly influences the survival of Nicotiana attenuata, a species of wild tobacco and, for example, without those mixtures, the plants are susceptible to a infectious wilt disease that can quickly kill them, according to Ian Baldwin of the Max Planck Institute for Chemical Ecology in Jena, Germany, and his collaborators. Details appeared 8 September 2015 in PNAS (doi:10.1073/pnas.1505765112).

Although both Witkin and Elledge focused on cellular responses to DNA damage, her research established the existence of that response and its basic features in bacteria, whereas he studied similar phenomena in more complex organisms, including yeast and mammals. While the details of these organisms differ, all of them coordinate activities of large numbers of genes, avoiding or minimizing harm to their respective host cells.

In response to such damage, bacteria typically step up their DNA repair capabilities, halt cell division while repairs take place, and amplify their mutagenic capabilities as a way of increasing variation within the population, enhancing adaptability. Witkin’s early forays into this field involved examining the response of bacterial cells to X-ray and ultraviolet radiation. This work led to her uncovering the SOS response as well as some of its key components, including RecA and LexA.

While at the Waksman Institute as well as earlier during her career, Witkin usually worked with only a few immediate collaborators and preferred to do experiments on Escherichia coli, according to Waksman director Joachim Messing. “‘With E. coli,’ she would say, ‘you can do two experiments in one day,’” he says. “When she retired 25 years ago, she had concrete plans to do something completely different—to study a favorite poet.”

Elledge, at first working with Ronald Davis at Stanford University and later, independently, began making comparable observations while examining strains of yeast with damaged DNA. He and other investigators subsequently worked out features of the mammalian DNA-damage response pathway and showed that it closely resembles that of yeast. These organisms depend on a series of related kinases to drive activities that protect them from threats to genomic integrity.

Separately, the first-ever NAS Prize in Convergence Research goes to Chad A. Mirkin of Northwestern University...
in Evanston, Ill. His innovations led to new cancer therapeutics and also diagnostic tools such as Verigene™, a system used in hospitals to detect infectious pathogens and drug resistance markers without having to culture tissues from patients. The diagnostic technology, which is commercially available through Nanosphere, Inc. of Northbrook, Ill., is based on an automated, multiplex, and flexible nucleic acid test for identifying viruses and bacteria that cause infections of the bloodstream, respiratory tract, and gastrointestinal tract.

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

RESEARCH ADVANCES

Nanoparticles Containing Peppermint Oil, Cinnamon Flavor Disrupt Biofilms

Carol Potera

When encapsulated in silica nanoparticles, peppermint oil and cinnamaldehyde, which gives cinnamon its characteristic flavor, penetrate biofilms and potently kill drug-resistant pathogens within them, according to Vincent Rotello at the University of Massachusetts, Amherst, and his collaborators. These nanocapsules also promote fibroblast growth, which helps wounds to heal, they say, leading them to call these flavor-loaded nanoparticles a “promising natural disinfectant and wound cleanser.” Details appeared 17 June 2015 in ACS Nano (doi:10.1021/acsnano.5b01696).

Nanomaterials offer two advantages over other products when it comes to treating bacterial biofilms, according to Rotello. They breach otherwise impenetrable layers surrounding biofilms, and they can be engineered to kill bacteria once inside. “Nanomaterials are an ideal way to launch a sneak attack on bacteria in a way that bacteria aren’t ready for,” he says. Although these nanocapsules can be stored stably, the acidic environment within biofilms breaks down the silica shell, releasing the peppermint oil and cinnamaldehyde. This antimicrobial duo kills 99.9% of the bacteria within biofilms containing pathogens such as Pseudomonas aeruginosa, Staphylococcus aureus, Enterobacter cloacae, and Escherichia coli. Although peppermint oil or cinnamaldehyde can kill bacteria in biofilms when each ingredient is used alone, they work much better when combined, according to Rotello.

The loaded nanocapsules appear to be safe for host tissues, based on cell culture experiments. Thus, when E. coli biofilms...
are co-cultured with 3T3 fibroblasts, cinnamaldehyde, in particular, enhances fibroblast growth. “This was a surprise,” Rotello says. It turns out that cinnamaldehyde promotes insulin-like growth factor-1 signaling, a potent stimulator of collagen biosynthesis in fibroblasts, he adds, citing published findings by other investigators. He and his collaborators are beginning to test whether these flavor ingredient-loaded nanocapsules will promote wound healing in animals.

Plans call for developing these nanocapsules for use as a topical disinfectant to treat chronic skin wounds, according to Rotello. Treating wounds with topical preparations, which typically have fewer side effects, is preferable to using systemic drugs for individuals with chronic wounds, he says—imagining the nanocapsules as becoming “a super-charged version of Bactine” that works against biofilms”—referring to a popular, over-the-counter antiseptic that is widely used to treat minor skin wounds.

Perhaps these loaded nanocapsules also can be developed to treat challenging internal biofilm infections, such as those that form along knee and hip replacements, catheters, or other indwelling medical devices, according to Rotello and his colleagues. Toward that end, they are shrinking the size of the nanocapsules from 2 μm to 200 nm to test whether such smaller versions, when injected into infected animals, will safely and effectively disrupt internal biofilms.

Having such an approach for treating infections in biofilms “without harming underlying cells and tissues is the holy grail of antibacterial therapies,” says Y.S. Prakash at the Mayo Clinic College of Medicine in Rochester, Minn. Moreover, combining the nanocapsules with antibiotics or other therapeutics might make them even more specific while minimizing toxicities, he suggests. “I’m very enthusiastic about where this avenue of clinically important research is going.”

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

MINITOPIC
Another Set of Microbiota Studies Involving the Gut or Other Anatomic Sites

Here in brief are findings from several recent reports of efforts to understand how microorganisms in the gut or elsewhere in the body affect the host:

- Despite reports to the contrary, there is no significant association between body mass index (BMI) and the relative abundance of any bacterial species within the mammalian gut microbiome, based on a meta-analysis of multiple studies, according to Katherine Pollard of the University of California, San Francisco, and her collaborators. She presented their findings during the 2015 Joint Statistical Meetings in Seattle last August.
- In the gastrointestinal tracts of both fruit flies and mice, lactobacilli act in a “cytoprotective” way, turning on genes of the Nrf2 pathway within nearby host epithelial cells and thus helping them to withstand stress, according to Andrew Neish at Emory University School of Medicine in Atlanta, Ga., and his collaborators. Details appeared 13 August 2015 in Cell Reports (doi.org/10.1016/j.celrep.2015.07.042).
- Autoimmune uveitis, which in humans leads to blindness, appears to be triggered by a gut microbiota-produced molecule that mimics a retinal protein, according to experiments conducted in mice, says Rachel Caspi of the National Institutes of Health in Bethesda, Md., and her collaborators. Details appeared 18 August 2015 in Immunity (doi:10.1016/j.immuni.2015.07.014).
- The microbiota of the oral cavity and throat of individuals with schizophrenia seems to be richer than usual in lactobacilli, which may serve as a biomarker for this condition, according to Eduardo Castro-Nallar and Keith Crandall of the Computational Biology Institute at George Washington University in Washington, D.C., and their collaborators. Details appeared 25 August 2015 in PeerJ (doi:10.7717/peerj.1140).
- In mice with permissive genetics, reprogramming of the gut microbiota can “ameliorate development of metabolic syndrome,” according to C. Ronald Kahn of the Joslin Diabetes Center in Boston, Mass., and his collaborators in Boston, St. Louis, and Munich, Germany. Details appeared 1 September 2015 in Cell Metabolism (doi:10.1016/j.cmet.2015.07.007).
- In mice, gut bacteria share some of the responsibility for the beneficial effects of fish oil and the harmful effects of lard, according to Robert Caesar of the University of Gothenburg in Sweden and his collaborators. In particular, fish oil in the diet increases the abundance of Akkermansia muciniphila bacteria, supporting earlier reports suggesting that these bacteria promote a “healthy phenotype.” Details appeared 27 August 2015 in Cell Metabolism (doi:10.1016/j.cmet.2015.07.026).

NEW FROM ASM
Herpes Simplex Virus Turns on DNA Synthesis in Nearby Uninfected Cells

David C. Holzman

Through some unexpected and still-unidentified form of molecular texting, the herpes simplex virus (HSV) induces a hormone-like stimulation of cellular DNA replication in nearby, uninfected cells, according to Peter O’Hare of St. Mary’s Medical School, Imperial College in London, United Kingdom, and his collaborators. Details appeared 26 August 2015 in the Journal of Virology (doi:10.1128/JVI.01950–15/).
“This activation results in a propagating wave of host DNA synthesis in advance of infection,” says Sandra Weller of the University of Connecticut Health Center, Farmington. The observation may be relevant for other viruses and infections, she adds, calling the phenomenon a “novel and very surprising finding of considerable interest.” And, says James Alwine of the University of Pennsylvania, Philadelphia, “While paracrine effects by viruses have been suggested before, this is one of the most striking and convincing demonstrations.”

The research began as part of an effort to tag viruses and trace their entry into host cells, according to O’Hare. However, he and his collaborators quickly switched their focus when they noticed that uninfected cells began synthesizing DNA in response to viral infections in nearby cells.

At this point, the nature of the induced DNA synthesis remains unknown, O’Hare continues. It could be DNA duplication, DNA repair, “or some other type of DNA synthetic event,” he says. “Powerful new technologies can be brought to bear on these discoveries,” he adds, alluding to innovative techniques in chemical biology, known as “click-chemistry,” which allow tagged molecules to be tracked visually or biochemically.

The virus-induced signaling mechanism “appears not to require direct cell-to-cell contact, and thus must be due to some diffusible factor, but this factor must have limited diffusion ability as the effect is tightly concentrated around the infected cells, indicating that proximity is important,” points out Roger Everett of the Centre for Virus Research in Glasgow, Scotland, who was not involved in the research.

“It will be interesting to see if other cell processes or signaling are activated or altered by HSV or other herpesviruses,” says Alwine, who suggests that the research may have implications for virally induced cancers. “For example, the paracrine effectors from only a few infected cells may provide signaling to surrounding, uninfected cells that may potentiate them towards transformation, or make an already transformed cell more malignant,” he says.

The research raises other important questions, says Weller. The identity of the signaling molecules, and whether this is an antiviral response by the cell to try to slow virus infection or a proviral action by the virus to sensitize surrounding cells are among those deserving further investigation, she says. “Either scenario would be profoundly interesting. There is plenty of work to be done.”

Paracrine signaling, in which infected cells communicate over distances with other cells, is taken for granted by researchers in immunology and endocrinology, who are studying such effects in multicellular organisms, including mammals. However, this example of such signaling is unusual outside that field. The finding “will stimulate much investigation in the immediate future,” Everett says.

NEW FROM ASM

**Compound Spares Mice Symptoms and Death from Lethal Doses of Anthrax**


Bacillus anthracis elaborates a unique polypeptide capsule that enables the pathogen to cause lethal systemic infection following inhalation and germination of anthrax spores. Peter Taylor and David Negus of University College, London, United Kingdom, previously described a robust depolymerase derived from the soil bacterium *Pusillimonas noertemannii* BS8 that, in vitro, strips the protective capsule from the surface of vegetative *B. anthracis* bacteria. They now show that intravenous administration of this enzyme, EnvD, to mice infected by the inhalation route with lethal doses of *B. anthracis* spores prevents emergence of symptoms and death. Current recommended treatments are based on efficacy in animal studies, but are not always effective in humans, says Taylor. Further, engineering antibiotic resistance genes into this pathogen—which has been done—would render current treatments ineffective. Capsule removal during early infection prevents experimental systemic anthrax. Thus, “it could prevent and treat the disease in humans, and circumvent attempts to cause untreatable infections with engineered multidrug-resistant forms of the pathogen,” says Taylor.

**NEW FROM ASM**

**Zebrafish Model Shows Promise for Illuminating C. neoformans Modus Operandi, Screening New Drugs**


Cryptococcus *neoformans* is estimated to kill more than 600,000 people worldwide, annually. Existing mammalian models are costly, and challenging to use for analyzing pathogenic processes. But invertebrate models are limited. John Perfect and colleagues of Duke University Medical Center, Durham, N.C., confirm that some pathological features observed in mice can be replicated in zebrafish. This model illuminates the
interactions of pathogen with host immune system, and examines important sites of infection such as the central nervous system, enabling the investigator to follow the infection visually, in real time. Perfect notes that C. neoformans frequently invades the brain, an incompletely understood process that could yield to this model. Additionally, the model system could be used to screen for new anticryptococcal drugs—a critical need since mortality using current agents ranges from 15 to 50%.

NEW FROM ASM

Improved Understanding of Regulator Protein Could Boost Conversion of CO₂ to Biofuels, Organic Feedstocks


Carbon dioxide serves as the carbon source for a number of environmentally significant microorganisms. In a mini-review, F. Robert Tabita of The Ohio State University, Columbus, describes studies of the protein that regulates expression of genes important for CO₂ fixation. That master regulator, CbbR, must be activated in order for CO₂ to be metabolized. To that end, CbbR takes part in several complex interactions, including with various small effector metabolites, and with other regulatory proteins from two component regulatory systems, all of which influence CbbR-mediated gene expression. Studies of these interactions have enabled construction of improved CbbR proteins, “which are currently being used to boost bacterial conversion of CO₂ to organic matter,” says Tabita. Any strategy for using microbes to convert CO₂ to value added products such as biofuels or carbon feedstocks must maximize CO₂ fixation, for which an understanding of CbbR-mediated control is critical, he adds.

NEW FROM ASM

CRISPR-Cas Reviewed in Detail


CRISPR-Cas technology has opened up new ways for studying and manipulating the genome. In a new review article, Marie F. La Russa and Lei S. Qi of Stanford University describe recent advances of CRISPR-Cas for activating and repressing specific genes, and outline its advantages and disadvantages relative to alternative technologies. The dCas9 protein can be directly fused to proteins that switch gene expression on or off at the transcriptional level, says Qi. Since researchers only need to reprogram the sgRNA sequence to direct dCas9 to a new gene, it is now possible to modulate almost any gene’s expression by targeting a dCas9 fusion protein to that gene,” he adds. Thus, “we now have the ability to quickly and easily manipulate gene expression for any gene of interest. This could represent a new means of engineering cell behavior, which can be used both in the clinic and by basic scientists.“

NEW FROM ASM

Terrestrial Nanoarchaea, Likely of Ancient Vintage, Have Distinct Cellular Host from Marine Nanoarchaea


Nanoarchaea, originally isolated from a marine high-temperature vent, have highly reduced genomes and an obligate symbiotic lifestyle. Now Mark Young of Montana State University, Bozeman, et al. describe a third partial genome of a terrestrial nanoarchaea from a hot spring in Yellowstone National Park. Nanoarchaea appear ubiquitous in Yellowstone’s low-pH hot spring environments. The cellular partner for these terrestrial nanoarchaea is a Sulfolobales-related archaeal host, quite distinct from the Ignicoccus host detected in the marine system. The differences in genome content and host relationships between terrestrial and marine nanoarchaea lineages suggest that the former, and their parasitic lifestyle are of ancient vintage. Young also describes the first virus that is likely replicating within nanoarchaea and provides support for the proposition that foreign genetic elements could be responsible for the high number of split genes found in nanoarchaeal genomes. Nanoarchaea could be useful for understanding genome reduction, and the minimal requirements for viral replication, says Young.

NEW FROM ASM

New Test for Lyme Bests Standard for Early Cases in Sensitivity, Specificity

The current standard two-tiered testing algorithm for Lyme disease has limited sensitivity for detecting early Lyme disease. Now Lauren J. Lahey and William H. Robinson of Stanford University, et al. have developed a multiplex assay which includes a panel of 10 highly specific antigens that detect a patient’s antibodies’ response to early infection. “Early Lyme disease patients exhibit multiple positive markers on the panel, rendering this multiplex approach more sensitive for detecting *Borrelia burgdorferi* than two-tiered testing,” says Lahey. “A diagnostic for this early phase could make physician diagnosis more accurate and eliminate uncertainty in cases where the patient has another disease, such as southern tick-associated rash illness, that presents with similar symptoms.” The Stanford multiplex assay identified 87% of early Lyme cases, compared with 67% for the two-tiered assay, and specificity was 100%.
Join nearly 1,000 of your colleagues at the 2016 ASM Biodefense and Emerging Diseases Research Meeting to explore novel research in emerging infectious diseases, and its beneficial application in strengthening our biodefense systems. The 2016 meeting will feature daily plenary sessions, concurrent symposia (to include select oral abstract presentations), workshops, poster presentations, and This Week in Microbiology (TWiM) podcasts and more.

Program Highlights:

Global Threats—Collaborative Solutions
Michael V. Callahan
Massachusetts General Hospital
Boston, Massachusetts

Keynote Lecture
Tom Frieden
Centers for Disease Control and Prevention
Atlanta, Georgia

www.asm.org/biodefense2016
Applying Topological Principles to Genomic Analysis

Topological data analysis helps to overcome difficulties that conventional tree-based phylogenetic analyses have with horizontal gene transfers

Kevin Emmett, Joseph M. Chan, Daniel S. Rosenbloom, and Raul Rabadan

In On the Origin of the Species in 1859, Charles Darwin proposed phylogenetic trees to depict evolutionary relationships on the basis of phenotypic attributes. Since then, biologists have shifted to using molecular traits to characterize evolutionary relationships between and among species. These approaches typically assume that traits are inherited vertically, and that evolution is strictly clonal. However, several other modes of genetic exchange add complexity to this process, including lateral gene transfers in bacteria, recombination and reassortment in viruses, viral integration in eukaryotes, and fusion of genomes of symbiotic species.

For several decades, evolutionary relationships among microorganisms were inferred mainly from sequences of genes encoding 16S ribosomal RNA molecules, a highly conserved genomic region for both bacterial and archaeal species. However, this region accounts for less than 1% of the complete genome in most species, meaning that this approach omits the vast majority of genetic information. Moreover, because horizontal inheritance is pervasive among microorganisms, the remaining 99% of genes may tell a very different evolutionary story. This problem becomes more acute for viruses, which lack 16S or other universally shared genes.

Alternative Approaches to Depicting Evolutionary Relationships Are Needed

These challenges underscore the need for alternative approaches with which to analyze evolutionary relationships, going beyond the traditional phylogenetic tree representation (see Microbe, August 2015, p. 319). The rapidly growing number of sequenced microbial genomes provides fertile ground for developing such alternative approaches to analyzing and depicting both vertical and horizontal evolutionary processes. While recent developments in phylogenetic networks provide ways to identify instances of reticulate evolution, the field does not yet have a widely accepted framework for visualizing and quantifying the frequency, scale, and significance of horizontal evolution.

Although phylogenetic trees can look complicated, in a sense they are very simple mathematical objects. They are composed of one-dimensional objects—branches—and contain no loops (Fig. 1).

To represent horizontal evolution, though, more complex objects are needed. Topology gives us a framework for characterizing the global properties of mathematical objects. According to some mathematicians, topology was born with Bernhard Riemann in the mid-1800s. Through conversations and letters to friends and colleagues, Riemann characterized the minimal number of cuts needed to transform a complex object into something simpler and without loops,

SUMMARY

➤ Horizontal gene transfers, particularly among microorganisms, complicate efforts to analyze and depict phylogenetic relationships.
➤ Topological data analysis provides a novel approach to characterizing both vertical and horizontal modes of evolution that are embedded in genomic datasets.
➤ Aligned genomic sequences can be viewed as points in a high-dimensional sequence space; applying persistent homology analysis to these spaces then enables us to read off phylogenetic information from resulting barcode diagrams.
➤ This analytic approach can be used to gain insights into the recent evolution of viral and bacterial pathogens.

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like a tree. The number of cuts needed to make this change is called a topological invariant, meaning that if we deform the space continuously by stretching and compressing it, this number will not change. For example, an object with a loop can be continuously deformed into a circle (Fig. 1A). However if we cut that loop once, we obtain a tree that can be deformed into a point. The minimal number of cuts needed to transform an object into a tree is a topological invariant, called the first Betti number.

Here, we describe a topological approach to characterize both vertical and horizontal modes of evolution in genomic data simultaneously. The approach is based on recent developments in the field of computational topology and its application to large datasets, loosely known as topological data analysis.

Intuitively, our aim in applying topology to phylogenetic analyses is to represent and quantify loops in genomic space. We will approximate the space of genomes by an object that is neither a tree nor a network, but rather a higher-dimensional mathematical object known as a simplicial complex. Computational approaches can be used to read off properties of these complexes.

We first applied this approach to viral evolution—particularly that of the influenza virus, where genomic reassortment can lead to new versions of this virus that can cause pandemics.
Further work established the characteristic genomic scales at which recombination in bacteria leads to the emergence of antibiotic resistance in several strains of pathogens. While the application of topological data analysis to genomic data remains in its infancy, we hope our introduction to this elegant new framework spurs interest in its development and, more broadly, recognition that mathematical ideas once thought to be without application can help in addressing unsolved biological questions.

**Topology and Its Use in Data Analysis**

Topology is the branch of mathematics that characterizes spaces and how they can be deformed. If we take a tree and change the lengths of its branches or extend new branches from a point, the tree remains a tree. In the same way, if we take a cup, we can smoothly mold it into a donut without cutting or tearing it apart. We say that the cup and the donut have the same topology.

How can we assess if two separate spaces share the same topology? One trick is to assign to each space some algebraic object—a number, for instance—that does not change under deformation. That object is called a topological invariant. For instance, we can assign to an object the number of loops, which in the case of the cup will be one, and in the case of the tree will be zero. We can continuously deform only those spaces with the same invariants. Thus, for example, we cannot deform a tree into a donut without cutting or merging different sections. Algebraic topology provides tools to compute invariants of these spaces.

However, genomic sequence data—or other data from real-world analyses—does not come in the form of a perfect continuous space, as dealt with by classical topology. Instead, such data can be viewed as a high-dimensional point cloud forming a discrete representation of a space. Topological data analysis (TDA) refers to a framework that took shape during the last 15 years to compute topological properties from finite point clouds, building on developments in computational topology and statistics.

Our primary tool is persistent homology, a branch of TDA that computes topological invariants representing multiscale information about the connectivity and holes within a dataset. "Per-

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**Rabadan: from Stargazing and Physics to the New World of Biology and Genomics**

Raul Rabadan remembers reading the book by Carl Sagan that was based on his Cosmos television series and being so fascinated that he began reading technical physics books, even though they were beyond his understanding, he says, “I was completely puzzled about how mathematics could capture physical phenomena. I still am.”

Theoretical physics became his field, later expanding to systems biology. He is an associate professor in the Department of Systems Biology and Medical Informatics at Columbia University, and also director of the University Center for Topology of Cancer Evolution and Heterogeneity. The interdisciplinary team that he leads includes researchers from math, physics, computer science, engineering, and medicine, and their work focuses on developing tools to analyze genomic data for insights into molecular biology, population genetics, evolution, and cancer.

“The applications are manifold from data mining large genomic datasets to track infectious diseases, look for mutations in cancer, and find patterns in clinical information in large hospital databases,” Rabadan says. “Traditionally biology has been an extremely descriptive science. But biology is changing, with large amounts of high-quality data, presenting a sophistication and richness that was not foreseeable 50 years ago. While reading scientific journals, it is impossible not to become enthusiastic about biology every day.”

Rabadan, 41, a permanent resident of the United States, grew up in Madrid. His father is a physician who also holds a doctorate, his mother a retired computer scientist. He also has a sister who is a biologist. “Since I was a child, I was fascinated by science,” he says. “I remember spending nights with a little telescope chasing planets, nebulae, and galaxies. I had the good fortune of having a family that values science, and they were always very supporting with my inclinations. I had also good and motivating teachers in science. I have been very lucky in my life.”

He received his M.Sc. in 1998 and his Ph.D. in 2001, both in theoretical physics and both from the Autonoma University in Madrid. After that, he conducted research in that field at the European Laboratory for Particle Physics (CERN) in Switzerland and at the Institute for Advanced Study (IAS) in Princeton. In 2006 he joined the systems biology program at IAS, then left for Columbia in 2008.

“Probably my most transforming events occurred when I rediscovered biology at IAS,” Rabadan says. “I saw a new world. [At] IAS, I started interacting with biologists and learning about the new developments in genomics. I had the chance then to meet [cancer researcher] Arnold Levine, not only an astonishing biologist and a great mind, but a wonderful mentor.”

Rabadan and his spouse, who works at the United Nations, have twins, a boy and girl, age 3.

Marlene Cimons

Marlene Cimons lives and writes in Bethesda, Md.
Persistent" refers to the method’s ability to capture structures that persist across a range of spatial resolutions, while “homology” refers to the type of topological invariant that is being computed. Note that this concept of homology within mathematics is separate from the use of the term homology to refer to evolutionary similarities between individuals.

To compute persistent homology, data is first represented as a point cloud in a high-dimensional space with a notion of distance. Next, a scale parameter is defined. As the scale parameter is increased, points with pairwise distances less than the scale are connected with lines. When three points connect with a line, we fill in the triangle between them. The objects constructed in this way are called simplicial complexes, and the set of them across all scales is called a filtration. By performing simple algebraic manipulations on matrices representing these objects, we can compute homology (see Fig. 2 for a simple example).

Persistent homology is summarized by information at different dimensions. The term $H_0$—where $H$ stands for homology and 0 stands for the dimension—tells us about the number of connected components in the data and the relationships between them. It is equivalent to hierarchical clustering in conventional phylogenetic trees. Higher dimensions provide information not found in phylogenetic trees, including loops ($H_1$), spherical voids ($H_2$), and their higher-dimensional generalizations ($H_3, H_4, H_5...$), giving a quantitative estimate of the shape of the data. The topological invariants can be concisely represented in a barcode diagram, which tracks the shape across multiple scale parameters. Each horizontal line in the diagram represents a topological feature. Each feature is annotated with an interval, representing the scale at which the feature appears and the scale at which the feature disappears in the filtration.

Using TDA To Handle Genomic Sequence Data

Aligned genomic sequences can be viewed as points in a high-dimensional sequence space. As more genomes are sequenced, this space becomes better sampled. Using standard phylogenetic measures, we can compute a matrix of pairwise distances. We can then apply persistent homology analysis to this metric space, reading off phylogenetic information from the resulting barcode diagram.

If a population evolves in a tree-like pattern, no loops appear in the data. In other words, the only topology that is present appears within dimension zero. However, if the evolutionary history includes horizontal patterns of inheritance that cannot fit in a tree, this nontrivial topology...
will be captured in the barcode diagram as higher-dimensional homology.

Here is a simple example of how TDA can capture horizontal evolution from population data (Fig. 2). Consider this reticulate phylogeny (Fig. 2A): five genetic sequences sampled recently (yellow circles) originate from a single common ancestor due to clonal evolution (solid blue lines, tracing parent to offspring) and recombinant evolution (dotted red lines).

These five sequences can also be placed in the context of a larger sample, where the data are projected into two dimensions using PCA (Fig. 2B). PH is applied to this larger sample (Fig. 2C), resulting in a barcode pattern (Fig. 2D). The H₁ bar near the center (Fig. 2D) identifies a recombinant event involving the five highlighted sequences. The scale over which this bar persists represents the evolutionary distance between two parents of the recombinant offspring. PH additionally returns the set of sequences producing the loop, known as the homology generators. The number of H₁ bars is the first Betti number and can be used to measure the frequency of recombination events.

Applying Topological Analysis to Influenza

Our first application of TDA is to influenza A virus, a common human pathogen. It is well known that frequent reassortments punctuate the evolution of influenza, a segmented single-stranded RNA orthomyxovirus. Reassortant strains can lead to antigenic novelty when internal segments adapted to humans pair up with novel external segments. Such events led to the human influenza pandemics of 1957 and 1968.

To analyze recent trends in influenza evolution, we applied persistent homology to data for more than 3,000 avian influenza genomes from the NIH Influenza Sequence Database. Examining each genome segment separately, we recovered only zero-dimensional homology, consistent with the absence of intra-segmental recombination (Fig. 3A). In other words, segment-by-segment the evolution of influenza is tree-like and amenable to phylogenetic tree representation.

However, a similar analysis of the concatenated full genome reveals a complex topology, with a large number of loops in one and two
dimensions, reflecting pervasive reassortment (Fig. 3B). Statistical inference on the loops corresponding to reassortments identified segments that tend to co-segregate with each other during reassortment (Fig. 3C). In particular, polymerases are more likely to co-segregate, in contrast to envelope and capsid proteins that show independent reassortment patterns. Co-segregation of polymerases suggests that effective protein–protein interaction between the polymerase complex and the NP protein constrain reassortment. Finally, we identified two distinct scales of one-dimensional loops, corresponding to reassortment within a single subtype at smaller scales and reassortment across subtypes at larger scales (Fig. 3D).

**Applying Topological Analysis to Pathogenic Bacteria**

Horizontal gene transfers among bacteria are a well-known source of genetic diversity. As with viral reassortment, topology can be used to characterize bacterial lateral gene transfers. We constructed phyletic profiles for a range of pathogenic bacteria using FigFam annotations from the Pathosystems Resource Institute Center (PATRIC) database, which consists of more than 100,000 protein families curated from more than 950,000 unique proteins.

Protein family annotations group proteins into sets of isofunctional homologs, that is, clusters of proteins with both similar sequence compositions and functions. A particular strain is represented as a binary vector, indicating the presence or absence of a given protein family. Correlations between strains can reveal genome-wide patterns of genetic exchange.

For each strain, we can compute a transformation into FigFam space and construct a strain-strain correlation matrix on which we can then compute persistent homology. For example, we can show relative recombination rates between different species, computing them by using persistent homology (Fig. 4A). From this analysis, we see that different species have a diverse topological structure in this space over a wide variety of recombination scales. For instance, the large scales of genomic exchange in *Haemophilus influenzae* suggest that it acquires novel genetic material from distantly related strains.

In Fig. 4B we show a topological network representing *Staphylococcus aureus*, a gram-positive bacterium commonly found in the nostrils and upper respiratory tract. The network was generated using Ayasdi Cure, a program for topological analysis and visualization of biological data. In the network, color corresponds to enrichment for *mecA*, an antibiotic resistance gene.
resistance gene. The network depicts two large clusters connected by a narrow bridge of strains. Strikingly, we observe that while mecA enrichment is not as strong in the left cluster, there is a distinct path of enrichment emanating along the connecting bridge between the two clusters and into the less-enriched cluster. This suggests the hypothesis that antibiotic resistance has spread from the right cluster into the left cluster via strains intermediate to the two, and will likely continue to be selected for in the left cluster.

**Conclusions**

Horizontal genetic exchange is pervasive. Here we describe a novel framework for characterizing its presence in genomic data using ideas from topology and show how it can be used to analyze both viral and bacterial datasets. The method allows us to describe in quantitative terms both the scale and frequency of horizontal gene transfers. As the quantity and complexity of genomic data increase, we hope new approaches for analyzing and depicting those data while drawing from rich mathematical frameworks will continue to be developed.

**Acknowledgments**

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**Suggested Reading**


Postdoctoral Research Scientist in the Department of Biomedical Informatics, Columbia University, New York, N.Y., and Raul Rabadan is an associate professor in the Departments of Systems Biology and Biomedical Informatics at Columbia University, New York, N.Y.
Virtually all organisms contain multiple mobile DNAs that can move from place to place, and in some organisms, mobile DNA elements make up a significant portion of the genome. Mobile DNA III provides a comprehensive review of recent research, revealing the many important roles that mobile DNAs play in genome structure, function, and evolution.

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Six Things You Might Not Know about Mitochondria

Long-recognized as having bacterial origins, mitochondria are more complex and more specialized than is generally recognized

Marcia Stone

Mitochondria in virus-infected cells generate reactive oxygen species (ROS) to protect themselves and their host, but until recently no one could say for sure how they respond to invasive bacteria. However, next-generation genomic sequencing is making it easier for researchers to investigate this and other matters concerning mitochondria, according to Cole Haynes of the Sloan-Kettering Institute (SKI) in New York, N.Y., who spoke about recent mitochondrial research last April.

This differential response of mitochondria to microorganisms that invade the cells that they occupy is but one of several notable recent findings. Others include:

- The understanding that mitochondria do not float freely in the cytoplasm of their host cells but, instead, form chains whose dysfunctional segments can be readily deleted.
- That contrary to what many experts suspected, ribosomes found in mitochondria differ significantly from those found in other α-proteobacteria.
- Mitochondria make use of at least one set of co-opted phage genes; others are likely embedded in mitochondrial DNA awaiting discovery, experts say.
- Mitochondria adapt to differing energy needs, not only from organ to organ but also from cell to cell.
- Mitochondrial proteins might reverse stem-cell aging, which many experts predicted was inevitable.

Mitochondria Stress Responses Bolster Innate Immunity

In the microbe-eat-microbe world, various bacterial pathogens are armed with virulence factors aimed at mitochondrial targets. However, mitochondria can prove a formidable adversary.

One well-known bacterial pathogen, *Pseudomonas aeruginosa*, unleashes powerful factors, including a variety of protein inhibitors and iron chelators that can damage mitochondria. The mitochondria respond with a bactericidal form of ROS and by triggering host inflammatory reactions.

Recent research reveals that severely damaged mitochondria also commit a form of suicide called “mitophagy” and take advantage of the fact that most cell proteins have to fold into three-dimensional structures in order to function by evolving an “unfolded protein response” or UPR\textsuperscript{mt} which, as its name suggests, refolds unfolded proteins and returns them to their functional state.

“In very dire circumstances, however, the most severely damaged mitochondria are simply culled,” Haynes says. “Concomitantly, the cell tries to salvage or regenerate the least damaged among them by activating the UPR\textsuperscript{mt}. By killing off severely damaged mitochondria and preventing the corrupted ones from accumulating, a pool

**SUMMARY**

- New analytic technologies are enabling researchers to determine how mitochondria use anti-stress programs and other means to defend against bacterial invaders.
- Mitochondria are not free floating within host cells, but link together as chains that undergo fission and fusion.
- Some genes in human mitochondria derive from bacteriophage, an exception for this otherwise fully bacterial organelle.
- The ribosomes of mitochondria differ from those of other bacteria, their eukaryote hosts, and even from one host to another.
- Mitochondria in different tissues and organs appear to be specialized, enabling them to respond more effectively to varied physiologic demands.
of retained healthy organelles enables more viable mitochondria to be regenerated.”

“Recent work from a number of laboratories, including our own here at SKI, indicates a protective role for mitophagy and the UPRmt during a bacterial invasion,” says Mark Pellegrino, who works with Haynes. “When the UPRmt is activated by injured mitochondria, the host cell responds with genes that promote mitochondrial recovery and limit bacterial proliferation or kills the microbes outright,” Haynes adds.

Another pathogen, the fungus-like soil bacterium *Streptomyces*, targets the mitochondrial respiratory chains from hosts that include true fungi, insects, worms, and perhaps even plants. Although the precise targets of this pathogen differ from those of other bacteria, here, too, mitochondria counter *Streptomyces* with a range of defenses, including antibacterial ROS, inflammatory responses, programmed cell death, and the UPRmt to help recover mitochondrial function.

Mitochondrial stress responses can fine-tune innate immunity. “The bacteria that make mitochondrial toxins, *P. aeruginosa* and *Streptomyces*, for example, activate the mitochondrial UPRmt response which alerts the host cell to danger,” Haynes says. In contrast, commensals don’t produce mitochondrial toxins and do not, therefore, initiate an innate immune response. Thus, the UPRmt appears to be one of the ways mitochondria distinguish friend from foe and is particularly important in microbe-rich environments such as the intestines of animals and roots of plants.

**Mitochondria Form Rearranging Networks**

One way mitochondria recover from stress is by culling those that are severely damaged, thus enriching the pool of healthy — or least-defective — organelles. The fact that mitochondria are not free floating but rather belong to a network, within which whole sections can be deleted, is crucial to this removal process.

Fission, regulated by mitochondria, helps isolate the damaged segments within mitochondrial networks that need to be removed. Parkin, a host-encoded protein, binds to and thus protects the functioning sections within such networks. Several other proteins are also involved in the complicated fission-fusion process in which old or new mitochondrial segments are deleted from or added to such networks. Some of those proteins interfere with mitophagy, while others bind Parkin, blocking degradation of not-so-badly defective mitochondria that remain functional enough to warrant rescuing. These steps suggest to some researchers that, by preventing programmed cell death, anti-apoptotic proteins from host cells can fuse to components within mitochondrial networks and stabilize them.

Whether this fission-fusion lifestyle was adapted from an early α-proteobacterial relative and continues to be used by wild proteobacteria somewhere or is a specialized process that arose separately after primordial mitochondria broke away from free-living bacteria to form intracellular symbioses is unknown.

However, although mitochondria have taken familiarity to extremes, they are not unusual in their cozy relationship with eukaryotes. Other α-proteobacteria form intracellular partnerships with eukaryotic hosts, shuttling many or most of their genes into the host nucleus and making few of their own proteins, according to Didier Raoult of Aix Marseille Université in France. “Alphas are all over the place,” says J. Jeffrey Morris from the University of Alabama, Birmingham, and this ubiquity heightens the possibility that some undiscovered fission-fusion types are distributed somewhere in nature, waiting to be discovered. “They [α-proteobacteria] range from big, complicated *Escherichia coli*-like cells, the ‘Roseobacters,’ to very tiny bacteria with reduced genomes, SAR 11, and intracellular parasites, the rickettsia which cause Rocky Mountain Spotted Fever and are a lot like mitochondria,” he adds.
Genes of Human Mitochondria Are Partly Viral

The mosaic genetics of mitochondria is reflected in their protein translation machinery. Notably, the ribosome closely resembles that of its bacterial counterpart, whereas the DNA polymerase enzyme is phage-like, making it the only working viral gene acquisition yet reported in mitochondria. However, it would not be surprising to find other active genes from viral sources now that next-generation genomic sequencing tools are available. Gene transfer agents (GTAs) identified in some free-living α-proteobacteria may be common in a wide range of both bacteria and archaea, according to some researchers.

“The most amazing thing about GTAs is that they’re encoded in the α-proteobacterial genome and at least partially controlled by the cell,” says Olga Zhaxybayeva of Dartmouth College in Hanover, New Hampshire. “A small fraction of bacterial cells [in the lineages that carry GTA] produce phage-like particles that package seemingly random pieces of host DNA. We presume that this mechanism is maintained by the cells for gene transfer but don’t know for sure.”

Yet another reason to expect that mitochondria will have more than one set of viral genes is because they are so promiscuous when acquiring genetic material. For example, genes in mitochondria from lice, protozoans, and humans have origins in Rhizobiales, Rickettsiales, and other α-proteobacteria. Indeed, the fact that mitochondria are related more closely to microbial communities than to any single bacterial species supports the accepted scientific notion that the mitochondria appeared during evolution before many other α-proteobacteria—making the “rare event of a mitochondrial acquisition unique,” according to Raoult.

It is well-accepted among biologists that some form of α-proteobacterium was the key ancestor for mitochondria. However, they continue to debate whether that bacterial ancestor entered into symbiosis with an archaeon or with some other type of cell that was on its way to becoming a eukaryote, perhaps a proto-eukaryote.

Although this debate continues, findings by Thijs Ettema of Uppsala University in Sweden and colleagues published earlier in 2015 appear to speak directly to its outcome (Microbe, August 2015, p. 316). These scientists report identifying genetic evidence of a complex archaeon they named Lokiarchaeota, which seems to “bridge the gap between prokaryotes and eukaryotes.” One whole Lokiarchaeota genome and two segments were retrieved near an underwater volcano called “Loki’s Castle” in the Atlantic seabed south of Svalbard.

These particular archaea may be able to change shape like amoebae and engulf their prey, which could be how a much-earlier host Lokiarchaeota acquired the very special α-proteobacterium that eventually evolved into a mitochondrion, Ettema speculates. Furthermore, he says, “Our results provide support for hypotheses in which the eukaryotic host evolved from a bona fide archaeon. The rich genome of Lokiarchaeota provided the host with a ‘starter-kit,’ supporting the increase in cellular and genomic complexity that is characteristic of eukaryotes.”

The hunt is on for live Loki’s to test in the lab.

Mitochondrial Ribosomes Differ from those in Free-Living Bacteria

Eukaryotes carry two separate types of ribosomes: one in the cytoplasm that synthesizes most of the cellular proteins and the other in the mitochondria. In contrast to eukaryote cytoplasmic ribosomes, the mitoribosomes produce only a few respiratory chain proteins—a task that is so important for mitochondrial function that it apparently cannot be outsourced. Moreover, because mitochondrial energy production is so important, the mitoribosomes usually tether to the mitochondrial inner membrane, and then insert the proteins that they produce directly into that membrane, avoiding any circuitous transit of those valuable materials through the host cytoplasm.

High-resolution cryoelectron microscopy shows that mitoribosomes differ dramatically from ribosomes of other bacteria. Less surprisingly, the ribosomes in mitochondria also differ structurally from eukaryotic cytoplasmic ribosomes. Among the most unexpected findings of these recent structural studies is the discovery that a transfer RNA (tRNA) is incorporated into the center of the mammalian mitoribosome, where it replaces a ribosomal RNA (rRNA), which otherwise is considered a ubiquitous component of both bacterial and eukaryotic cytosolic ribosomes, according to Basil Greber, a member of the Nenad Ban laboratory at the Institute of
Molecular Biology and Biophysics in Zurich, Switzerland.

Mitoribosome structures also differ dramatically from one host species to another, which surprises some researchers. “Apparently, evolutionary tinkering has remodeled the bacterial ribosome of the endosymbionts in divergent ways,” reasons Gerber.

“The detailed insights into mitoribosomal structure [obtained in our studies] are enabled by recent technical advances in cryo-electron microscopy, particularly the development of direct electron detector cameras that can correct for movements of the specimen in the electron beam that would otherwise lead to image blurring,” says Ban, who heads the Zurich lab.

**Organs Contain Mitochondria that Are Specialized to Physiologic Demands**

In humans, for example, skeletal muscle mitochondria are adept at oxidizing fatty acids, while brain mitochondria are good at handling ketones, and adrenal mitochondria appear de-
signed to meet high demands for making steroid hormones. Mitochondria can differ even within individual cells. Specifically, intermyofibrillar and subsarcolemmal mitochondria have distinct fuel preferences and respond differentially to various signals. Notably, between 1,000 and 100,000 mitochondria supply the power to each cell.

Mitochondria from different human organs typically share only about 75% of their genes and the range of encoded proteins having specific functions. The mitochondrial ribosome is used exclusively to translate 13 essential mtDNA-encoded respiratory proteins in all tissues. In contrast, the genes encoding complex IV, crucial for responding to oxygen tension, are tissue-specific. Thus, mitochondria-based, cellular oxygen tension assessments differ widely from one tissue to another, but respiratory-chain complexes do not. Mitochondrial experts speculate that this contributes to the tissue-specific effects of various mutations that appear in mitochondrial genomes.

Mitochondrial movement, the genesis of new cells, mitophagy, and fission-fusion are the main processes underlying these tissue and cell differences, according to experts.

Mitochondrial Sirtuins—Nutrient-Sensing, Stress Resistance Proteins

Recent mitochondrial research findings challenge the long-held concept that the passive, chronic accumulation of cellular damage over a lifetime causes hematopoietic stem cell (HSC) aging.

Young adult HSCs are usually metabolically inactive and have few mitochondria. In contrast, HSCs from older adults appear prone to proliferate. One reason may be that most mitochondrial protein manufacture is outsourced to host genomes. Therefore, the finished products have to be delivered to replicating mitochondria via a circuitous cytoplasmic path, and protein transport is more likely to go wrong in old versus young stem cells. Proper import of proteins into mitochondria is emerging as a central regulator of cellular metabolism and stress responses.

Nutritional stress is also more likely to occur in older tissues, which is where sirtuin 7 (SIRT7) becomes a factor. Nutritional stress triggers repression of protein synthesis as well as the unfolding or degradation of corrupted proteins by SIRT7, limiting further mitochondrial activity, according to Danica Chen at the University of California, Berkeley, and her collaborators, including Haynes from SKI. As proof of concept, they added SIRT7 to aged HSCs, showing that it halts mitochondrial protein synthesis, thereby reducing stress and helping stem cells return to a quiescent state. Thus, some forms of cellular aging appear to be reversible, “giving hope that targeting the appropriate protective programs can rejuvenate tissue homeostasis,” Chen and her collaborators note.

Marcia Stone is a freelance writer in New York, N.Y.

Suggested Reading

Next-Generation Sequencing Initiative

Recognizing the significance of Next-Generation Sequencing (NGS) across the microbial sciences, ASM has established a new, multi-stakeholder mechanism to identify needs and opportunities associated with this technology across various scientific disciplines, including the capabilities of NGS in the biomedical, forensic, environmental, and agricultural sciences as well. This is a cross-departmental initiative at ASM, with the American Academy of Microbiology (Academy) and Strategic Alliances taking the lead on establishing the coalition. Anticipated projects that may be identified by the Coalition include the creation of a comprehensive database for interpreting NGS data; development of professional guidelines; establishment of mechanisms for validating the technology; and/or development of educational materials and/or meetings to explore current uses and future needs. The Steering Committee, which is comprised of senior, internationally recognized experts, will establish the coalition. Working Groups will be designated by the coalition to coordinate the activities for any recommended projects.

In April 2015, the American Academy of Microbiology, the honorific leadership group with the ASM, hosted a colloquium on next-generation sequencing (NGS) as a molecular diagnostic tool for faster pathogen detection and identification. The topics included the utility of NGS versus competing assays such as MALDI-TOF MS; feasibility for clinical laboratory workflow; requirements for standard operating procedures; data management concerns; regulatory issues; and creation and maintenance of a reference database. A review article on the applications and current status of NGS in the clinical microbiology laboratory is scheduled for publication in mBio.

ASM also hosted a meeting on this topic entitled “Rapid NGS Bioinformatic Pipelines for Enhanced Molecular Epidemiologic Investigation of Pathogens” on 24–27 September 2015 in Washington, D.C.

The Steering Committee convened in September 2015 to discuss the short and long-term goals of the Coalition; determine the initial areas of science to be covered by the Coalition; and identify relevant organizations and/or experts to serve on the Coalition. Steering Committee members were selected for their outstanding contributions to the field of NGS. The Steering Committee will be responsible for determining a strategic, step-wise approach for addressing each of the disciplines.

Next-Generation Sequencing Steering Committee Members
Gregory Armstrong, M.D., Centers for Disease Control
Mike Dunne, Ph.D., bioMérieux
Maria Giovanni, Ph.D., National Institutes of Health
Kelly Hoon, Illumina
Ramana Madupu, Ph.D., U.S. Department of Energy
Uwe Scherf, Ph.D., U.S. Food and Drug Administration
George Weinstock, Ph.D., Jackson Laboratory for Genomic Medicine
Catherine Woteki, Ph.D., U.S. Department of Agriculture

Ex-Officio Members
Joseph Campos, Ph.D., ASM Secretary
Michele Swanson, Ph.D., Academy Board of Governors Chair

For more information on the Coalition, please contact Connie Herndon, Director of Strategic Alliances (202–942-9327, cherndon@asmusa.org) or Marina Moses, Director of the Academy (202–942-9227, mmoses@asmusa.org).

ASM Meetings and Conferences
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2016 ASM Biodefense and Emerging Diseases Research Meeting
Recognizing that emerging infectious diseases serve as a paradigm for handling the public threat of bioterrorism, the 2016 ASM Biodefense and Emerging Diseases Research Meeting (8–10 February 2016, Arlington, VA) unites the individuals carrying out the research to defend against the growing threat of bioterrorism with the decision makers shaping the future biodefense research agenda. Join nearly 1,000 attendees at this event to stay up-to-date with the latest challenges and developments in the field. For more information, visit www.asm.org/biodefense2016.

Mark Your Calendar: 32nd Clinical Virology Symposium
Led by biomedical researchers and scientists involved in patient care, the 32nd Clinical Virology Symposium (19–22 May 2016, Daytona Beach, FL) provides an exceptional forum for the meaningful exchange of ideas dealing with viral infections. New for 2016: the Symposium will take place from Thursday through Sunday, and will include increased networking opportunities for you to expand connections with fellow laboratorians, physicians, and biomedical researchers involved in patient care and public health. View program schedule today at www.asm.org/cvs2016.

Upcoming ASM Conferences
ASM Conferences address the needs of the diverse scientific interests of microbiologists by providing a forum for international groups of scientists to discuss their specific area of concentration. Mark your calendar for these upcoming ASM Conferences. For more information, visit www.asm.org/conferences.

- @ASM Conference on The Individual Microbe: Single-Cell Analysis and Agent-Based Modeling (18–20 March 2016, Washington, DC)
- 13th ASM Conference on Candida and Candidiasis (13–17 April 2016, Seattle, WA)
- ASM Conference on Streptococcal Genetics (31 July–3 August 2016, Washington, DC)
- 5th ASM Conference on Salmonella (29 August–1 September 2016, Potsdam, Germany)
- 6th ASM Conference on Beneficial Microbes (9–12 September 2016, Seattle, WA)
- ASM Conference on Antibacterial Development (11–14 December 2016, Washington, DC)

2015 History of Microbiology Research Travel Award Recipient
The Center for the History of Microbiology/ASM Archives (CHOMA) is pleased to announce Lauren N. Ross, M.D., as the recipient of the 2015 History of Microbiology Research Travel Award. Ross, of the Department of History and Philosophy of Science at the University of Pittsburgh, used the award to conduct research at CHOMA on early American bacteriologists’ understanding of Koch’s postulates and more generally their ideas about disease causation as reflected in textbooks, lab manuals, and other materials.

The History of Microbiology Research Travel Awards are given to support historical research of the awardees’ choosing, in areas that can be supported by materials in the CHOMA collections. The CHOMA collections, located at the University of Maryland Baltimore County, include 9,000...
volumes on microbiology and related topics, photographs, biographical materials, topical files on various aspects of microbiology, records of the Society from its founding in 1899 to the present, and several collections of personal papers.

For more information on the Center for the History of Microbiology/ASM Archives, and to learn how to apply for a History of Microbiology Research Travel Award, visit the website at www.asm.org/choma (choose “History of Microbiology Research Travel Awards” from Sidebar Menu) or contact archives@asmusa.org.
ASM Public Affairs

ASM Comments on the List of Select Agents and Toxins

ASM submitted comments to the Centers for Disease Control and Prevention on the possession, use, and transfer of select agents and toxins. The comments addressed adding certain Influenza virus strains to the List of Select Agents and Toxins. To read the ASM’s comments go to: https://www.asm.org/index.php/public-policy/137-policy/documents/statements-and-testimony/93640-sa-8-24-15.

ASM Participates in White House Budget Meeting

On 15 September, Public Affairs staff participated in a White House meeting on the federal budget. Aviva Aron-Dine, Executive Associate Director, Office of Management and Budget, and Tamara Fucile, Associate Director of Legal Affairs, Office of Management and Budget, spoke about the fiscal year 2016 budget as well as the administration’s position on negotiations regarding a continuing resolution (CR). The fiscal year begins on 1 October, and as of this writing, it is believed that a short-term CR will be passed to fund the government as negotiations continue. For up-to-date information on the federal budget process, please visit the Public and Scientific Affairs Board public policy Web page at asm.org/policy.

Announcement of Public Consultation on Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge

As a part of the National Strategy for Combating Antibiotic-Resistant Bacteria, the U.S. Department of Health and Human Services (HHS) announced a prize competition for the delivery of one or more successful rapid point-of-care diagnostics that may be used by health care providers to identify bacterial infections. The prize will be up to $20 million, subject to the availability of funds. The National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) are sponsoring the prize competition, and seek public comments regarding the technical criteria and performance characteristics of the diagnostic(s) for which the prize(s) will be offered. For more information go to: http://www.asm.org/index.php/public-policy/98-policy/issues/93738-ar-prize.

ASM Attends Blueprint for Drug/Diagnostic Co-Development Forum

On 9 September, ASM staff participated in the Fourth Annual Blueprint for Drug/Diagnostic Development: Genetic Databases conference. The conference convened researchers, sponsors, advocates, and regulators for an annual forum addressing challenges in the co-development of drugs and companion diagnostics. As next generation sequencing (NGS) becomes an important tool in clinical microbiology, common regulatory concerns and standardization of practice and use are important to explore. The agenda for the conference can be seen at http://www.focr.org/events/blueprint-drug-diagnostic-development-genetic-databases.

ASM Raises Questions about IQCP Implementation

ASM has been assisting clinical microbiology laboratory personnel in the development of their Individualized Quality Control Plans (IQCPs) since June 2015, as can be seen at http://clinicalmicro.asm.org/index.php/lab-management/laboratory-management/445-iqcp-iqcp. During the course of creating these materials jointly with the College of American Pathologists (CAP) and the Clinical and Laboratory Standards Institute (CLSI), many concerns were raised, leading to a 8 September letter from ASM to Andrew Slavitt, the Acting Administrator for the Centers for Medicare and Medicaid Services on questions of implementation of IQCPs in clinical microbiology laboratories. To see the questions raised, go to http://www.asm.org/index.php/public-policy/2/137-policy/documents/statements-and-testimony/93728-iqcp-cms.

ASM Briefs Congressional Staff on Duodenoscope Issues

On 3 September, Melissa Miller, Chair of the Laboratory Practices Committee, was joined by Romney Humphries, member of the Practical Guidance for Clinical Microbiology review group, to brief House Committee on Oversight and Government Reform staff. Congressional staffers asked ASM for expert advice about its statement “On the Question of Culturing of Duodenoscopes”, authored by the Laboratory Practices Committee in April, available here http://www.asm.org/index.php/component/content/article/98-policy/issues/93456-lp-4-15. Also participating in this briefing were Eileen Burd, Laboratory Practices Committee member, and Punam Verma from Virginia Mason Medical Center; the volunteers participating in the briefing represent ASM in a joint FDA/CDC/ASM Endoscope Culturing Working Group, which is currently reviewing data on endoscope culturing in advance of issuing updated information for healthcare providers. To read the latest on FDA’s ongoing investigation of infections associated with duodenoscopes, see http://www.fda.gov/medicaldevices/productsandmedicalprocedures/reprocessingoffreusablemedicaldevices/ucm454630.htm.

ASM Attends Sept S-FAR Face to Face Meeting

ASM staff attended the U.S. Stakeholder Forum on Antimicrobial Resistance (S-FAR) 1 September meeting in Washington, D.C. The focus of the meeting was to discuss strategies for implementing the National Action Plan for Combating Antibiotic-Resis-
tant Bacteria. The group was addressed by Susan Coller-Monarez from the White House Office of Science and Technology Policy and involved several working session covering appropriations, antibiotic usage data collection, and research and development incentives. S-FAR consists of partners from both the public and private sectors who evaluate developments in antimicrobial resistance and to apply this information to policymaking. Learn more about S-FAR by going to http://s-far.org/.

**ASM Supports Agriculture Research**

In September, ASM as a founding member of the Supporters of Agricultural Research, or SoAR group, participated in a strategy meeting to discuss challenges facing agricultural research and competitive grants at the Department of Agriculture (USDA) and ways to increase awareness of the importance of R&D funding during the appropriations process in Congress. For more information on SoAR, please see http://supportagresearch.org/.

**ASM Attends CMS Advisory Panel on Clinical Diagnostic Laboratory Tests Meeting**

On 26 August, ASM staff attended the public meeting of the newly created Advisory Panel on Clinical Diagnostic Laboratory Tests at the Centers for Medicare & Medicaid Services (CMS). The second day of this inaugural meeting provided a forum for stakeholders to present and submit written comments on new test codes for 2016 and observe the deliberations of panel members on each code. Microbiology expertise is provided to the Panel by former Publica and Scientific Affairs Board Professional Affairs Chair Vickie Baselski. The Panel was authorized by Public Law 113-93, the Protecting Access to Medicare Act of 2014. To see the agenda and other relevant documents, please click https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/AdvisoryPanelonClinicalDiagnosticLaboratoryTests.html.

**Education Board**

**ASM Represented at National Student and Educator Meetings in Summer 2015**

The strategic directions of the ASM Education Board include collaborating with national organizations to promote microbiology education at all levels. In summer 2015, the Board sponsored the Society’s participation in several conferences for science students and educators.

**CourseSource Colloquium.** Samantha L. Elliott (St. Mary’s College of Maryland), editor in chief of the ASM Journal of Microbiology & Biology Education (JMBE), represented JMBE and ASM at the CourseSource Colloquium held 15–17 June 2015 in Minneapolis, Minn. Supported by the Howard Hughes Medical Institute, CourseSource is an online open-access journal of peer-reviewed teaching resources for undergraduate biological sciences. The colloquium convened CourseSource editors and advisory board members, along with representatives from select scientific societies, to further define the relationships between CourseSource and the societies and to evaluate the CourseSource article submission and review process.

**Gordon Research Conference on Undergraduate Biology Education Research.** Education Director Amy Chang and ASM Headquarters Fellow for Education Rachel Horak represented the Society at the 2015 Gordon Research Conference on Undergraduate Biology Education Research (GRC-UBER) held 12–17 July in Lewiston, Maine. The GRC-UBER is a biennial event that seeks to advance understanding of efforts to systemically and effectively improve biology programs and synthesize new directions for research; it also aims to communicate a unified message about the impact of UBER on student learning and success. The ASM Biology Scholars Program supported the attendance of five program alumni at GRC-UBER: Samantha L. Elliott (see “CourseSource” above), Mary Mawn (Empire State College SUNY), Laura Regassa (Georgia Southern University), Heather Seitz (Johnson County Community College), and Naomi L. B. Wernick (University of Massachusetts–Lowell).

**Leadership Alliance National Symposium.** Education staff member Tiffani Fonseca represented ASM at the 2015 Leadership Alliance National Symposium, held 24–26 July in Stamford, Conn. The Leadership Alliance is a consortium of more than 30 institutions of higher learning; its mission is to develop underrepresented students into leaders and role models in academia, business, and the public sector. At the meeting, Fonseca served on several session panels and shared information about ASM Education Board resources during the exhibits program.

**Society for the Advancement of Biology Education Research.** Samantha L. Elliott (see “CourseSource” above), and Kelly Gull, Education staff member, represented ASM and JMBE at the 2015 Society for the Advancement of Biology Education Research (SABER) National Meeting, held 31 July–2 August in Minneapolis-St. Paul, Minn. Begun by three ASM Biology Scholars Program alumni, SABER is a community dedicated to using scientific methodology to inform the practice of teaching and ensure that all students learn science. The SABER annual meeting convenes U.S. and Canadian biologists, with participants presenting about student learning and performance, student attitudes and beliefs, effectiveness of instructional strategies or training programs, and validation of new instruments to measure learning.
Obituaries

Charles R. Manclark

Charles R. (Chuck) Manclark, 86, died on 3 February 2015, after a brief illness. Upon receipt of an undergraduate degree in biology in 1952, Chuck enrolled in a graduate program at the University of California Los Angeles (UCLA) in the Department of Bacteriology. His studies, however, were delayed so that he could serve a tour with the U.S. Army, including one year as a microbiologist at the Army hospital in Korea. Upon his return to UCLA, he initiated studies on Vibrio (now Campylobacter) fetus under the mentorship of John Pickett, investigating immune responses at the mucosal surface and their potential involvement in spontaneous abortion in cattle and sheep. Following receipt of his Ph.D. in 1963, Chuck was a microbiology faculty member at Long Beach State College and subsequently at the University of California School of Medicine, Irvine.

In 1967, Chuck joined the Laboratory of Pertussis of the National institutes of Health Division of Biological Standards, the precursor to Center for Biologics Evaluation and Research of the Food and Drug Administration (FDA). Upon Margaret Pittman’s retirement in 1971, Chuck was named Chief of the Laboratory. As head of the laboratory, Chuck played a leadership role in the transition from whole-cell toacellular pertussis vaccines. He understood the strengths and limitations of the whole-cell vaccine, and had the vision to recognize that development of a new and safer vaccine required improved understanding in basic science, especially in the pathogenesis, immunochemistry, and genetics of Bordetella pertussis. Chuck moved on multiple fronts, including obtaining research funding, encouraging bright and talented scientists from around the world to tackle the problem, and building a strong laboratory at the FDA. As one example, Chuck had a key role in the landmark study conducted by investigators at UCLA (C. L. Cody, L. J. Baraff, J. D. Cherry, and S. M. Marcy) on the safety of whole-cell pertussis vaccines. Recognizing the need for objective data, Chuck secured funding, and then, as contracting officer and collaborator, contributed significantly to design and implementation. This published study provided a solid foundation of baseline safety data for subsequent evaluations of new-generation vaccines. Manclark’s laboratory at the FDA became an internationally recognized leader in research, regulation, and testing of pertussis vaccines, and regularly hosted scientists from around the world for collaborations and training. Chuck’s impact was felt internationally through organizing three international pertussis symposia, helping to write World Health Organization guidance documents on vaccine testing and quality control, and giving invited lectures around the world on techniques for research, testing and production of pertussis vaccine.

In recognition of his accomplishments, in 1993 he was elected an Honorary Member of ASM.

Following his retirement in 1993, Chuck and Doloras, his wife of 61 years, moved to Santa Barbara, Calif., where they built a home and became avid gardeners. Chuck is survived by Doloras, as well as two sons and five grandchildren.

Both of us worked in the FDA Pertussis Laboratory with Dr. Manclark, and we appreciated the opportunity he provided to work on an important public health problem with a team of talented scientists.

Bruce D. Meade
Hillsborough, N.C.

James L. Cowell
Holly Springs, N.C.

James T. (Ted) Park

Ted Park died on 15 July at the age of 92. He was an outstanding microbiologist who worked on the bacterial cell wall for almost 60 years. Park’s pioneering work began with the discovery that treating Staphylococcus aureus with penicillin led to the accumulation of unusual sugar-nucleotide precursors, initially called “Park nucleotides” and now known as nucleotide-sugars involved in cell wall synthesis. This breakthrough led to the simultaneous elucidation of two central phenomena: how cell wall peptidoglycan is synthesized and (as discovered together with J. Strominger) how penicillin kills bacteria. These findings revealed a novel aspect of bacterial cell wall synthesis, catalyzed our understanding of the mechanism of action of anti-cell wall antibiotics, and paved the way for the development of other drugs of this class.

Park’s lab went on to show that penicillin did not inhibit the polymerization of the cell wall backbone, as had been thought, but instead inhibits the reactions that crosslink the individual strands of peptidoglycan. In subsequent years, he and his colleagues worked on many cell-wall-related subjects, his later work focusing on the turnover and recycling of over 50% of the cell wall material at every cell division cycle. His discoveries revealed the mechanism by which growing bacteria insert new layers of cell wall peptidoglycan into pre-existing wall and how cell wall components are broken, recycled, and reconstructed to enable changes in cell structure. In the process, Park’s lab identified the genes involved in the process and biochemically characterized the dozens of reactions and proteins involved. Indeed, this was a pioneering effort that has been influential in the understanding of a number of key bacterial physiological processes, including antibiotic resistance, signaling in and among bacterial cells, and the immunological recognition of bacteria. Park’s work on
Howard V. Rickenberg

The passing of Howard Rickenberg severs one of the remaining links to the heroic age of molecular biology, and to the flood of emigres and refugees from war-torn Europe that transformed science in America and put it at the center of the whole enterprise. Howard was born Hans Reichenberger into a Jewish family in Nürnberg, Germany, in 1922. He experienced at first hand the rise of the Nazis, spewing their murderous intentions and virulent nationalism. His alarmed parents sent him to safety in England to finish high school, but when the war broke out Howard, in company with thousands of other refugees, found himself interned and shipped off to a prison camp in Australia (narrowly escaping being sunk by a German submarine). The Aussies had the “option” of enlisting in the army, and Howard spent four years defending the city of Darwin on the northern coast against a Japanese invasion that never came.

After the war he made his way to the United States, was reunited with his parents (who had made their own adventurous escape via Manchuria, just in the nick of time), and anglicized his name. He earned a B.S. at Cornell (where he was inspired by the geneticist Adrian Srb), and then a Ph.D. at Yale with David Bonner studying “adaptive enzymes” (today we refer to these as induced enzymes). Howard made the Big Time while a postdoc with Jacques Monod in Paris, where he discovered the beta-galactoside transport system, a member of the lac operon and the first transport carrier to be identified as a gene-specified protein. The lac permease has been a major focus of research ever since, culminating in the elucidation of its molecular structure and mechanism by Ronald Kaback.

Several faculty appointments followed, first at the University of Washington and then at Indiana University, and in 1966 Howard moved to Denver, Colo., as Director of the Division of Research at the National Jewish Hospital and Research Center (subsequently the Department of Cellular and Molecular Biology) and Professor of Microbiology at the University of Colorado School of Medicine. I worked closely with him for the next 20 years to build a successful unit dedicated to basic research within a hospital setting, and we became lifelong friends. Our small department made significant contributions to several areas, and provided a springboard for some distinguished careers. Howard’s own interests had come to center on cyclic AMP as a second messenger in the regulation of sugar catabolism in E. coli, and later on its role in the morphogenesis of slime molds. He also served on the editorial boards of several journals, and as Editor in Chief of Microbiological Reviews.

Following his retirement in 1987, Howard spent several years teaching (as a Fulbright lecturer in the Ivory Coast, and later in Soochow, China), and then returned to his beloved France to settle in Marseille. He died in June following a major stroke during a visit to Aachen, Germany, aged 93. Howard was a man of wide reading, lively mind and an engaging personality. He was keenly interested in the interplay between science and society, and therefore in politics; on this, as on everything else, Howard held strong opinions but seldom lost sight of the difference between opinion and fact. You could always engage him in argument, but could never move him off his bedrock faith in a wholly material universe, and in the preeminent role of science in making sense of it all.

Howard is survived by two daughters, Monica and Lisa, a son, Raoul, and three grandchildren. He was a joy to converse with, and he will be missed.

Franklin M. Harold

Michael Malamy
Moselio Schaechter
Abraham L. Sonenshein
Andrew Wright

cell wall metabolism was funded by the National Institutes of Health for more than four decades.

Park obtained his Ph.D. at the University of Wisconsin and got his first academic job at Vanderbilt. In 1962, he was asked to establish a Department of Microbiology at Tufts University School of Medicine and to serve as the first chair. Park recruited the scientists who became the heart of the department and who established it as one of the finest in the country. Park served as chair until 1970 and then returned to the lab bench, where he continued to work daily for the next 40 years. Park trained a large number of students and postdoctoral fellows, many of whom went on to distinguished careers in the US, Sweden, France, Israel, and other countries. Although obliged to retire officially at the age of 70, Park remained active in research, working with his own two hands until he reached the age of 87. At this, point he closed his lab and returned to his favorite pastime as a tennis player. As a student at the University of Wisconsin, Park had been a Big Ten tennis champion, and he continued to play competitively throughout most of his life.

Park’s strength as department chair was in his adherence to principles of honesty, decency, and respect for others. His outstanding contribution was to create a set of rules for how the department should be run. They were based on total democracy, an equal say for all. Who know the history of the department attribute its unusual success, at least in good part, to this set of principles. It made for collegiality, friendship, and concern for others in a way that is rare in academic circles. We cannot say enough about what respect this generated for him. Subsequent chairpersons have all tried to follow Park’s principles.
Microbe Mentor

Dear Microbiologist... 

Just one Post-It note of advice could change your career.

Mike May

At the General Meeting in New Orleans, students, postdocs and early career scientists wandering around the exhibit floor found a board that said: “Post your career questions here and receive a free gift!” This triggered a range of questions scribbled on Post-It notes, such as: “What are my options outside of academia for a career?” Although we all enjoy a free gift, the biggest “gifts” in this case came from seasoned professionals who stopped by to leave answers. This question-and-answer activity revealed the next generation’s biggest concerns and effective ways to address them.

The roughly 500 questions and answers stuck on the board stretched from basic career advice to the sociology of science. Despite the small size of the Post-It notes, the professionals filled them with “big” answers. For example the answer to “Problem with your lab work?” was “First try your best but then ask for help. Don’t suffer in silence!” In some ways, that answer forms the heart and soul of this exercise, and revealed the teamwork found within the ASM community of microbiologists of both today and tomorrow.

What Degree for Me? Many of the students asked questions about what the right degree level is for a job in microbiology. For example, they asked what they could do with a master’s degree, or if a Ph.D. was necessary. The answer really depends on what you want to do.

One professional wrote: “Talk to people at a variety of levels and degrees.” That person added, “An M.S. can be a very marketable degree. A Ph.D. can have you overqualified.” So not everyone needs a Ph.D. In fact, one person stopped by to write: “You don’t need to earn your Master’s or Ph.D. to be an accomplished scientist! Working at the bench as a tech is a rewarding job!”

Nevertheless, here’s a great incentive for more education: “A doctorate in Microbiology will open more career doors.” To get those doors open, though, it can take more than a specific degree. One person pointed out the value of learning a variety of advanced techniques. Several noted the value of an internship.

In the end, getting any degree is about learning, and as someone wrote: “The best way to learn something is to teach it. Even if you’re teaching your dog.”

Picking a Postdoc. Some questions revolved around timing. For instance, a doctoral student asked when to look for a postdoc. One answer: “Start looking for a postdoctoral position at least a year before you plan to graduate.”

To get the most from a postdoc, many suggested one thing: “Get out there and sell your skills!” Also, try to gain as much experience with, and meet as many professional contacts who are already in, the career you want to move into.

To do that, you need to be prepared and proactive. “Don’t be afraid to approach someone you don’t know to ask about their science,” one professional wrote. “Develop your own ‘elevator’ speech so you can quickly tell someone what your skills and interests are if they approach you!”

A Collection of Career Options. When it came to careers, many of the questions delved into nonacademic opportunities, from clinical research to government and industry and beyond.

Many professionals suggested considering all options. As one person wrote: “Go to every interview. It may not sound like something you want, but you might find it is wonderful and a perfect fit for you.”

The experts revealed the range of opportuni-
ties. One wrote: “Look into careers in Clinical Microbiology. There are lots of opportunities in health systems and biotech companies.” One professional even encouraged exploring opportunities beyond this world with: “Look to space. NASA wants to go back to the Moon to stay.” This person also talked about greenhouses on other planets, and concluded: “All this involves Microbes.”

A couple experts even pointed out jobs away from the bench. One wrote: “‘Off the Bench’, there is a world of opportunities: Clinical trials, policy, regulatory, quality, scientific/medical affairs, applications specialist/scientist…and the list goes on!”

Sociology of Science. Some of the questions explored the lifestyle of a professional scientist. One young scientist asked: “How do I stay motivated to write my paper when there are so many things to do in the lab that I enjoy more?” Although that question might need a personalized answer, one general comment provides a useful tactic: “Make a list every day of what you want to accomplish. It will help keep you on task with so many daily distractions.”

As a general approach to science, some of the experts encouraged taking risks. “Don’t be scared to take chances and talk to leaders in your field,” one expert wrote. “You will learn so much more! Life begins at the end of your comfort zone!” Another wrote: “Don’t be afraid to think outside the box. Creativity is amazing and can take you into uncharted waters!”

Exploring, though, takes courage. “The world of science can be brutal,” one expert pointed out, “but when times get tough always remember something amazing is just waiting to be discovered.” Ultimately, the exchange of scientific ideas and development of future opportunities comes from a community. Thus, many of the experts strongly endorsed the power of networking. As one wrote: “My most important piece of advice—Network, network, network!” The same person suggested that students join the local Branch of ASM or get involved with the Young Ambassador program. That suggestion combined with the other advice on this board, could help anyone get a jumpstart to a great career.

Mike May
Mike May is a freelance writer and editor living in Ohio. He earned a M.S. in biological engineering from the University of Connecticut and a Ph.D. in neurobiology from Cornell University. He can be reached at mikemay1959@gmail.com.
At the time of World War II, the vaccine against epidemic typhus that was most trusted by the Germans was the one developed by a Polish microbiologist, Rudolf Weigl. This vaccine was only available in his laboratory in Lwow. It was made by infecting body lice with the typhus rickettsiae, waiting a week for them to develop, and collecting the infected gut. This material was phenol treated and made into the vaccine. To accomplish this, Weigl needed a colony of healthy lice, which he bred using human volunteers as feeders. The Germans placed such priority of this endeavor that they left not only the outspoken Weigl to his work, but even sheltered the louse-feeding volunteers, which included scientists and other intellectuals, some of whom were Jewish. Moreover, the lab sent full-strength vaccine preparations to the underground and to some ghettos while diluting out those provided to the Germans.

This extraordinary story is the subject of this book, which goes into considerable detail regarding these events and its participants. One of them that figures prominently is the eminent, now-retired microbiologist Waclaw Szybalski of the University of Wisconsin, who worked in the Weigl lab as a young man.

Elio Schaechter
San Diego State University
San Diego, Calif.

Life’s Engines: How Microbes Made Earth Habitable

This short book, less than 200 pages of text, is a delight. It’s not clear for whom it is written. Falkowsky says it’s an outreach beyond that of a textbook. I doubt if most of its contents aren’t familiar in broad outline to most professional microbiologists, but I’m sure all of them would be rewarded by reading it. I was. It’s sprinkled with intriguing historical vignettes: when he was 22, Darwin collected fossils with Adam Sedgwick in north Wales; Darwin took a copy of Charles Lyell’s Principles of Geology along with the King James Bible on the HMS Beagle; Robert Hooke learned Dutch to read Van Leeuwenhoek, and wonderful sentences like, “In 1859, the same year that Big Ben chimed for the first time and the London publisher John Murray and Sons sent the first edition of The Origin of Species to press, on the other side of the Atlantic an American train conductor, Edwin Drake, drilled the first major oil well near Titusville, Pennsylvania.”

Falkowsky has intriguing ideas about a variety of microbiological happenings. He pays considerable attention to the delay between the emergence of oxygenic photosynthesis and the great oxygenation event, discounting the impact of iron’s being the major oxygen sump (as he used to believe) emphasizing instead that of sulfur and nitrogen. The topics are eclectic. He discusses, among others, the age of Earth, origin of life, panspermia, lateral gene transfer, climate change, and the consequences of our burgeoning human population. He’s intrigued by the origins and impact of biology’s “nanomachines:” particularly photosynthetic reaction centers and membrane-bound ATP synthases. Perhaps the book ought better to be titled A Chat with Paul Falkowsky, that, too, undoubtedly a delight.

John Ingraham
The University of California, Davis
Application Deadlines

ASM Scientific Writing and Publishing Institute The ASM Committee on Graduate and Postdoctoral Education welcomes applications to the 2016 ASM Scientific Writing and Publishing Institute (SWPI) Program, an effort that supports beginning researchers in understanding the writing, publishing, and review processes for scientific journals. Led by ASM members who have published widely, reviewed manuscripts, and served on the editorial boards of major journals, the program is a two-part training initiative. The first part, known as SWPI Online, consists of several introductory webinars, and the second part, known as SWPI Face-to-Face, is a multi-day in-person workshop. Participation in both programs is beneficial for attendees, but not required.

ASM offers the SWPI with partial support from the Burroughs Wellcome Fund. **SWPI Online.** SWPI Online is a three-month overview of scientific writing and publishing concepts. Open to graduate students, postdoctoral fellows, and early-career scientists, the experience includes six webinars, pre- and post-webinar assignments, structured mentoring, and a community of practice. The topics covered will include condensed discussions of titles and abstracts; introduction, results, discussions, and methods sections; figures and legends; and the manuscript review process. The 2016 program takes place in January through March, and the application deadline is **1 December 2015.**

**SWPI Face-to-Face.** At the SWPI face-to-face workshop, emphasis is placed on substantial time for participants to benefit from one-on-one feedback from facilitators, writing practice, and stimulating discussions and interactions. The institute is open to senior-level graduate students, postdoctoral fellows, and early-career scientists who are ready for an immersive and intensive writing experience. Before the institute, participants submit in-progress manuscripts for pre-SWPI assessment, and afterward, leave with detailed plans for improving their manuscripts, tools and resources for developing future publications, and a network of peers and mentors for critiques and advice. The next SWPI workshop will take place in the summer of 2016 in Washington, D.C, and the application deadline is **10 April 2016.**

**WWW:** [http://www.asmgap.org](http://www.asmgap.org)

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


**Deadline:** 15 December 2015.

**National Registry of Certified Microbiologist (NRCM) Certification.** The NRCM certifies microbiologist at the prebaccalaureate/baccalaureate, master's and doctoral levels. Certification is achieved by passing an online multiple-choice exam that is offered daily in the month of April at testing centers worldwide.

**WWW:** [www.asm.org/nrcm](http://www.asm.org/nrcm)

**Deadline:** 1 February 2016.

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**About Application Deadlines**

ASM Meetings Calendar

8–10 February 2016.  
ASM Biodefense and Emerging Diseases Research Meeting.  
Arlington, Va.  

@ASM Conference on The Individual Microbe: Single-Cell Analysis and Agent-Based Modeling.  
Washington, D.C.  
http://conferences.asm.org/

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

19–22 May 2016.  
32nd Clinical Virology Symposium.  
Daytona Beach, Fla.  
WWW, www.clinicalvirologysymposium.org

ASM Microbe 2016.  
Boston, Mass.  

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

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

29 August–1 September 2016.  
5th ASM Conference on Salmonella.  
Potsdam, Germany.  
http://conferences.asm.org/

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

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

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

About the Calendar

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

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

POSITIONS AVAILABLE

Assistant/Associate Professor of Food Science and Technology in Molecular Food Microbiology

12-month, tenure-track position; 100% Research. The Department of Food Science & Technology at the University of Tennessee Institute of Agriculture in Knoxville, TN, is seeking candidates who have the ability to develop a competitive and independent research program in molecular food microbiology. Focus areas may include functional genomics and proteomics, metabolomics, microbial pathogenesis, detection, gene expression, molecular characterization, virulence, control methods and/or microbial ecology of foodborne pathogens. Review of applications will commence November 1, 2015 and continue until a suitable candidate is identified. More information on the position and application process can be found at http://foodscience.tennessee.edu/ or by contacting Dr. Faith Critzer, Search Chair, faithc@utk.edu or (865) 974–7274.

Postdoctoral Scientist in Food Microbiology

A postdoctoral scientist position is available at the Institute for Food Safety and Health of the Illinois Institute of Technology in Chicago, Illinois. The postdoctoral scientist will work on an extramurally funded research project to study Listeria and Salmonella infiltration mechanisms in fresh and fresh-cut fruits using microbiological and genomic methods. Applicants should have a strong background in food microbiology, molecular biology and genomics, with a Ph.D. in food science or bacteriology or closely related fields. Prior research experience with foodborne pathogens is highly preferred. Competitive salary and benefits for three years will be commensurate with qualifications and experience. Applicants should submit a cover letter, CV, and contact information for three references to Professor Wei Zhang (zhang@wiit.edu). Review of applications will begin immediately. The expected start date for this position is January 2016.

Employment Advertising

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

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

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

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

Deadlines: Your ad must be received by the 1st of the month before the publication month to ensure timely publication (e.g., to appear in the January 2016 issue, your ad must be received by 1 December 2015).

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

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

Display

Display advertising closes the 1st of the month preceding publication. For specifications, rates, and deadlines for display ads, contact Rhonda Beamer at the address given above.
Professor, Associate Professor or Assistant Professor without Tenure Position

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

Abstract submission closes: March 17, 2016 at 5:00 p.m. ET
ASM Premium Member registration opened: November 5, 2015
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Small Things Considered

When Antibiotic Resistance In Vitro Does Not Tell You What You Need to Know
by Terry Roemer

Increasingly, it is becoming apparent that there is a deep difference between what happens in vivo and in vitro. Each field of biology has to learn this lesson, not the least that of antibiotic research. Gone are the days when a laboratory result alone was thought to reveal what goes on in a person sick with a microbial infection. Where do such distinctions show up and why do they matter?

Recently, Dan Andersson and colleagues from Uppsala University Sweden published an important study on the many mechanisms of mecillinam (aka amdinocillin) resistance in Escherichia coli. What separates this work from the previously published studies is that it provides an understanding of the genetic and environmental basis of an important drug resistance paradox of mecillinam, namely why resistance to this β-lactam antibiotic is so readily observed in the laboratory but rarely identified in clinical settings where this drug is widely used to treat E. coli urinary tract infections.

Indeed, resistance mutants arise in vitro at frequencies of $8 \times 10^{-8}$ to $2 \times 10^{-5}$ per cell, depending on the drug concentration used during selection, but at much lower rates in clinical isolates. The laboratory mutants involve many distinct functions and as many as 38 known genes, ranging from the drug target (pbpB) to other aspects of cell wall synthesis, cell division, respiration, ribosomes, tRNA synthetases, and the ppGpp-mediated stringent response pathway. This diversity is quite interesting and the subject of much research, but it is not the point here. What is startling is that the rare mecillinam-resistant E. coli clinical isolates all carry only mutations that cause loss of function of cysB, a gene involved in cysteine biosynthesis. How depletion of cysteine levels confers mecillinam resistance is not known.

The Andersson lab went on to demonstrate that whereas mutants selected in vitro all share similar fitness costs as assayed in vitro, the cysB mutations do not incur a fitness cost when grown in a more relevant, urine-rich medium. These experiments demonstrate that among the broad set of mutations that can confer mecillinam resistance under the standard way of determining drug resistance, only the rare cysB mutants possess sufficient fitness to persist in the setting of an infection. However, even these mutants are rarely found in an infected bladder, probably because mecillinam reaches levels so high as to be inhibitory even to them. A high growth rate of the pathogen is required in this environment to counter its constant expulsion from the urinary tract.

To assess the significance of resistance arising requires more complicated and expensive technologies that incorporate relevant environmental conditions. This is critical to all of us involved in early antibacterial discovery. So often we lower the priority of new leads based on traditional measures of resistance. I have the uncomfortable feeling that a large number of useful drugs are not further tested because they resulted in a “high rate” of resistance. Clearly, new methodologies are needed to measure antibiotic drug resistance in animal models of infection that capture (i) pathogen physiology, especially its fitness level, (ii) drug exposure levels, and (iii) host response mechanisms such as the innate immune system. Otherwise, we risk ignoring potentially effective, novel therapeutic antimicrobial agents based on faulty assumptions of their propensity for drug resistance.

Terry is a Distinguished Scientist at Merck & Co.


Talmudic Question of the Month*

Given that so many kinds of bacteria are intimately associated with animals and plants, why are so relatively few pathogenic?


*We use this term to denote questions whose answers cannot be found by a Google search.
METABOLISM AND BACTERIAL PATHOGENESIS

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

GROUNDBREAKING THINKING ON HOW BACTERIAL METABOLISM IS FOUNDATIONAL TO PATHOGENESIS

Useful for specialists in bacterial pathogenesis and specialists in metabolism as well as molecular biologists, physicians, veterinarians, dentists, graduate and undergraduate students, and laboratory technicians, Metabolism and Bacterial Pathogenesis is also essential reading for scientists studying the microbiome.

“Within these pages, leading experts in the field summarize research on a timely topic that connects research on the pathogenesis of infectious diseases to bacterial physiology. Metabolism and Bacterial Pathogenesis is a great addition for bacteriologists from both medical schools and colleges of biological sciences.”

-- Andreas Bäumler, Professor and Vice Chair of Research, Department of Medical Microbiology and Immunology, UC Davis School of Medicine

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Schedule at-a-Glance and more program information are now available.

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