Nobel Prizes in 2009 Celebrate Key Insights into Telomeres, Ribosomes…

While the 2009 Nobel Prizes for Medicine and Chemistry separately celebrate progress in two distinct fields of structural biology, one focused on telomeres at the ends of chromosomes and the other on ribosomes, the research that led to both prizes depended on microorganisms for vital materials and accessibility. Moreover, several Nobelists in these two fields this year could be considered microbiologists, even if they are now located within modern interdisciplinary settings. Also noteworthy, two of the recipients of the medicine or physiology prize are women, and one of the chemists is a woman (see following story).

Thus, Elizabeth H. Blackburn of the University of California, San Francisco, Carol W. Greider of Johns Hopkins University School of Medicine in Baltimore, Md., and Jack W. Szostak of Harvard Medical School and Massachusetts General Hospital in Boston, Mass., are sharing the Nobel in Medicine or Physiology for their discoveries involving telomeres in single-celled eukaryotes. The chemistry prize is going to Venkatraman Ramakrishnan of the MRC Laboratory of Molecular Biology, Cambridge, United Kingdom, Thomas A. Steitz, at Yale University in New Haven, Conn., and Ada E. Yonath at the Weizmann Institute of Science in Rehovot, Israel, for their efforts to understand ribosomes.

The chromosome of the unicellular ciliate *Tetrahymena thermophila* became the first subject of the telomere research that was recognized this year, tracing back to when Blackburn was doing research at Yale University. Before long, Blackburn and Szostak began collaborating, taking end pieces of the *Tetrahymena* chromosomes and inserting them into yeast plasmids as a way of easing the telomeric analytic burden—yeast being one of the more tractable eukaryotes for research purposes. From this series of experiments, they concluded that DNA end sequences, the telomeres, provide chromosomal stability in *Tetrahymena*. They also realized that yeast chromosomes contain functionally similar sequences, a realization that gained momentum and broadened the concept of telomeres as these two researchers and their collaborators looked at other examples of *Tetrahymena* species as well as the molds *Physarium* and *Dictostelium*.

Greider began to work as a graduate student with Blackburn during the 1980s, after Blackburn moved from Yale University to the University of California, Berkeley. Soon after Blackburn, Szostak, and their respective collaborators figured out that telomere sequences were being extended within cells, Greider came up with evidence for a specialized enzyme, now called telomerase, that builds telomeres onto the ends of replicated DNA chromosomes. Telomerase contains RNA as well as protein, and that RNA component serves as the template for building a specific DNA sequence, which varies from one species to another. Telomerase provides a platform that enables DNA polymerases to copy the entire length of the chromosome without missing the very end portion.

Meanwhile, the 2009 Nobel for Chemistry recognizes pioneering efforts to analyze ribosomes, and those early efforts depended on examining ribosomal particles from microbial sources. Early on, for instance, Yonath analyzed crystal structures of 50S subunits from *Geobacillus stearothermophilus* (formerly known as *Bacillus stearothermophilus*) and also the archaeon *Halocarcina marismortui*. Soon efforts broadened to include yet another microbial source, *Thermus thermophilus*—in this case, to furnish analytically suitable crystals of the 70S ribosome and 30S subunit.

Microbiology provided yet another avenue for approaching ribosomal...
structural challenges, namely through a series of ribosomal ambiguity mutations (ram), which reduce the accuracy of tRNA selection. Ramakrishnan and his collaborators in particular relied on ram mutations combined with crystallographic analysis to begin to explain the accuracy of codon reading during mRNA translation.

On a separate track, by 2005, Steitz and collaborators obtained resolution of about 2.5Å for the 50S ribosomal subunit, while developing detailed views of the peptidyl-transfer center and clarifying how ribosomes catalyze peptide bond formation. Earlier, Steitz and collaborators were the first to solve the profoundly challenging phase problem of the 50S structure from H. marismortui.

These insights into how ribosomes work, while important at a fundamental level for understanding how cells make proteins, also serve practical ends. For example, several types of antibiotic act by blocking microbial ribosomal functions. Thus, the research of Ramakrishnan, Steitz, Yonath, and their respective collaborators not only helps other researchers to better understand where those antibiotics bind to ribosomes and how they work, but it also is providing them guidance as they strive to develop novel, ribosome-targeting antibiotics.

Jeffrey L. Fox
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... Women 2009 Nobelists Comment on Gender Issues in Science

When the Nobel Foundation, which is based in Stockholm, Sweden, notifies winners of their new lofty status early each October, its representatives routinely interview those recipients after offering their formal congratulations. New winners, typically caught off-guard, are inclined to be candid in the first glow of such good news. This year, several foundation representatives included questions for the women recipients about the role played by gender in their careers. Here are excerpts from responses from Carol Greider of Johns Hopkins University and Elizabeth Blackburn of the University of California, San Francisco, who shared the Nobel Prize in Medicine or Physiology this year with Jack Szostak of Harvard Medical School, and also the response from Ada Yonath, who shares the 2009 Nobel Prize in Chemistry with Thomas Steitz of Yale and Venkatraman Ramakrishnan of the MRC Laboratory of Molecular Biology in the United Kingdom.

“I think actively promoting women in science is very important because the data has certainly shown that there has been an underrepresentation, and I think that the things that contribute to that are very many social . . . subtle, social kinds of things,” Greider says. “So, yes, I think that one should definitely be cognizant of that and be aware of it.”

Asked whether there is anything particular about telomerase research that attracts women to study these chromosomal structures, Greider says: “I think it’s one of those examples of a jackpot effect, where you have somebody that trains a lot of women, and then there’s a slight gravitation of women to work in the

Several Microbially Noteworthy Reports from NAS and IOM

The National Academy of Sciences (NAS), the Institute of Medicine (IOM), and the National Research Council (NRC), all in Washington, D.C., issued several reports of interest to microbiologists in September. They include:

• The NRC report “Responsible Research with Biological Select Agents and Toxins” concludes that instilling “a culture of trust and responsibility in the laboratory [is] the most effective way to prevent the deliberate misuse of biological select agents and toxins.” Further, it says, “efforts to ensure reliable personnel should come from within the laboratories.”

• The IOM-NRC report “Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases” offers a plan “for establishing and funding a comprehensive, globally coordinated system to identify novel zoonotic disease threats.” It recommends that the U.S. Agency for International Development “spearhead” these efforts and that the World Organization for Animal Health be given “the power to declare animal health emergencies.”

• The NRC report “A New Biology for the 21st Century: Ensuring the United States Leads The Coming Biology Revolution” recommends that the federal government undertake “a new multiagency, multiyear, and multidisciplinary initiative” in biology. It calls for “a timeline of at least 10 years and funding in addition to current research budgets.”
labs of other women. I don’t think it’s a large effect but a small effect. And so, because the founding group was women, it tends to . . . grow out as a jackpot effect. So then, Joe Gall (of Yale University), with whom Blackburn worked, was extremely supportive of the women in his lab, and he trained a number of telomere biologists. . . . It’s a founder effect.”

Similarly asked about the seemingly high numbers of women studying telomeres, Blackburn points out that the gender balance in the field is “close to the biological ratio of men and women. It’s all the other fields that are aberrant.”

However, asked about her efforts to maintain that balance, Blackburn demurs. “I’ve only actively promoted what we always hope is good science,” she says. “And, then it’s not as if one would favor a woman researcher in the area over a man. But, women have come into this field perhaps because . . . Carol [and I] were women, [and] we tended to have women students and postdocs. And so there’s a sort of self-perpetuating aspect.”

Nonetheless, Blackburn favors the current gender balance in her field. “You really do hope that when people see something like this working, that this . . . would be the norm,” she says. “That’s what I’d like to see, because you want women to have access to science because it’s such a wonderful thing to do. Anything that makes it more feasible for women to be in science and do the science they like, that’s good.”

Yonath works in chemistry, a field that was notorious for being inhospitable to women. Indeed, she is only the fourth woman to receive a Nobel for chemistry, and the first since Dorothy Hodgkin, also an X-ray crystallographer, was awarded the prize in 1964. “Dorothy Hodgkin and now it’s me,” she says. “During my time I had some very difficult years, and I had very pronounced competition, all by men,” she says. “But I don’t think that this is because I was a woman . . . And, I don’t think that I did something that is special for women, or the opposite.”

Jeffrey L. Fox

Salmonella Depend on Chemotaxis, Photosynthesis To Invade Lettuce Cells

Salmonella bacteria on lettuce penetrate the leaves to enter inner tissues via stomata, while also actively swimming toward photosynthetically produced nutrients, according to Shlomo Sela and other members of an Israeli research team. Although other bacterial plant pathogens also enter plant tissues, the Israeli experiments provide the first known evidence of bacteria responding chemotactically to photosynthetic products as part of this invasive process. Speculating that other types of bacteria similarly gain entry to leaf tissues, he suggests that measures to limit this process in leafy vegetables could improve food safety. Details of the research appear in the October Applied and Environmental Microbiology (75:6076–6086).

“Following completion of a series of attachment experiments between Salmonella and romaine lettuce, we realized that our results were different from those reported by others, who worked with iceberg lettuce,” says principal investigator Sela of the Agricultural Research Organization at the Volcani Center in Bet Dagan, Israel. To probe those differences, doctoral student Yulia Kroupitski began experimenting with iceberg lettuce. One day, she and technician Eddy Belausov saw that the salmonellae were “swimming toward and disappearing inside stomata,” Sela says.

However, the salmonella cells did not enter the plant cells when the let-
mata do not respond to collaborators. However, lettuce stochastic (USDA) and a former Sela Brandl of the U.S. Department of Agronomic bacteria, according to Maria plant’s initial response to those invaders also do not enter lettuce cells. Because of defective flagellar genes or failure at chemotaxis. Both types of mutants also do not enter lettuce cells.

Some plant pathogens force open stomata after they close as part of the plant’s initial response to those invasive bacteria, according to Maria Brandl of the U.S. Department of Agriculture (USDA) and a former Sela collaborator. However, lettuce stomata do not respond to Salmonella by closing, she notes. “Is salmonella so foreign to the plant that it is not recognized by the stomata, or does salmonella have its own stealth mechanism to enter the stomata without triggering basal plant defenses?”

“Because stomata are the portals into the plant for many bacterial species that cause plant disease, these observations have implications far beyond that of contamination of leafy vegetables with foodborne pathogens,” Brandl continues. Adds Robert Mandrell, also of USDA, “If this is more than a laboratory artifact as a result of a particular lab strain or unrealistic inocula, then it is an interesting area for further studies related to food safety, but also for plant pathology.”

Salmonella’s apparent behavior on lettuce leaves is surprising, agrees Joe Frank of the University of Georgia in Athens, who also studies how bacterial pathogens such as Salmonella and Escherichia coli O157:H7 behave on the leaves of green plants. “Salmonella, not being a plant pathogen, would not be expected to have such an adaptation,” he says.

Contaminated leafy greens are a principal source for foodborne illnesses in the United States, and were responsible for 363 outbreaks between 1990 and 2007, leading to a total of 13,500 reported and confirmed cases of illness, according to the Center for Science in the Public Interest (CSPI) in Washington D.C., a nongovernmental organization that tracks foodborne illnesses. Several types of microorganisms give rise to such illnesses, including several kinds of virus as well as bacteria such as E. coli and several types of salmonella, says Sarah Klein of CSPI.

“Contamination for most major [foodborne illness] outbreaks associated with fresh produce occurs pre-harvest,” says Mandrell of USDA. Some of those outbreaks involved produce that had been “washed multiple times with chlorinated water, indicating that the pathogen is either attached tenaciously to the surface or that pathogen has become internal either through the root system, cut edges or lesions, stomata, or some other unknown mechanism.” However, he adds, “A definitive explanation for most outbreaks is lacking.”

The Israeli findings plus information from investigations of a series of notorious outbreaks during the past few years implicate but do not prove whether chemotactic salmonella invade stomata to cause foodborne illnesses to individuals who consume contaminated leafy vegetables, agrees Frank of the University of Georgia. “We do not know if this happens to any significant extent in the field.”

David Holzman
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At 49th ICAAC, a Diverse Mix of Novel Antimicrobial Agents

The diversity of candidate antimicrobial drugs this year is “reassuring” and indicative of the “potential to move forward,” says Karen Bush of Indiana University in Bloomington, referring to a slate of novel compounds described during the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in San Francisco, Calif., last September. She was a co-convener of the ICAAC poster summary session “All New Antimicrobial...
Agents,” that featured some of the more promising agents that researchers brought forward this year. Although new quinolones were “not prominent” this year, she says, 76 novel compounds were submitted from that and other antimicrobial classes, including aminoglycosides, lipopeptides, cephalosporins, other β-lactam antibiotics or β-lactamase inhibitor combinations, and novel antifungal compounds.

One of those new compounds, called vancomycin PA1409 (PA1409), contains vancomycin covalently bound to 4-aminoquinoline. It is a very potent bactericidal agent, with good activity against a variety of bacterial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) as well as vancomycin-resistant *Enterococcus faecalis*, according to Bernard Meunier, a founder of Palamed, which is based in Castanet-Tolosan, France. It acts by inhibiting peptidoglycan synthesis, disrupting cell-wall integrity and thereby increasing the permeability of target cells, he says. It shows some renal toxicity but only at “very high doses,” about 250-fold higher than “curative doses.”

Another of the new compounds, MX-2401, is a “genuinely new-generation lipopeptide” with broad-spectrum bactericidal activity against a variety of gram-positive pathogens and “low toxicity,” says Bob Hancock of the University of British Columbia, who also chairs the scientific advisory board of Migenix; both the company and university are based in Vancouver, British Columbia, Canada. The compound apparently inhibits the translocation step of peptidoglycan biosynthesis in *S. aureus* or other gram-positive bacteria, interfering mainly with MrA but also with a subsequent transpeptidase step in cell-wall synthesis, he says. “Its activity is synergistic or additive with β-lactam antibiotics.” Further, MX-2401 has a “benign toxicity profile,” and its use appears to be “compatible with other classes of antibiotics,” including those that do not target bacterial cell walls. Moreover, when introduced at subinhibitory concentrations, it “transforms MRSA from β-lactam resistant to sensitive,” he points out.

ACHN-490, which is being called a “neoglycoside,” has broad activity against both gram-negative and gram-positive pathogens, including drug-resistant strains of *Escherichia coli* that cause urinary tract infections, according to Jon Bruss of Achaogen in South San Francisco, Calif. A chemically modified aminoglycoside, ACHN-490 overcomes some of the shortcomings of other members in this class but “behaves similarly” to them, he says. In phase-I clinical trials, ACHN-490 is “well tolerated.” It also shows “very exciting synergy” with daptomycin, a lipopeptide antibiotic active against gram-positive pathogens that was licensed in 2003 (expanded from skin infections to include bacteremia in 2006) through the Food and Drug Administration (FDA).

Yet another new compound, amycolamicin, obtained from the culture broth of an actinomycete strain MK575-1F5 (identified as *Amycolatopsis* sp. from soil), is also active against both gram-positive and some gram-negative bacteria, albeit not *E. coli* or other enteric bacteria, according to Yoshio Nishimura of the Microbial Chemistry Research Center in Tokyo, Japan. This compound has “very potent bactericidal activity against MRSA in vitro,” and it also is active in mice that are infected with this or several other bacterial pathogens, he says. It acts by inhibiting DNA gyrase, and it appears to have low toxicity.

CEM-101 is a “next-generation macrolide ketolide” that is being developed initially to treat respiratory tract infections, including those caused by *Legionella* spp. as well as antibiotic-resistant strains of *S. aureus*, according to Prabhavathi Fernandez of Cempra Pharmaceuticals in Chapel Hill, N.C. It is a “very stable fluoroketolide, with enhanced binding to bacterial ribosomes, [that was] well tolerated in phase-I clinical studies,” Fernandez says. Moreover, unlike telithromycin, “CEM-101 is not expected to affect or blur vision.”

In contrast to several of the foregoing antimicrobial agents, NVB302 has a very narrow spectrum of activity and is being evaluated specifically for treating *Clostridium difficile* infections, according to Mike Dawson of Novacta Biosystems Ltd. of Welwyn Garden City, United Kingdom. The compound itself is a semisynthetic, chemically modified peptide containing 19 amino acids whose parent compound is a lipantibiotic from *Actino-planus liguriae*. The in vitro activity of NVB302 is better than that of either metronidazole or vancomycin, both of which are used clinically for treating patients infected with *C. difficile*, whereas its activity against other microbes in the gastrointestinal (GI) tract is very poor, “which bodes well,” he says. “It appears to be stable [under] GI conditions, is absorbed orally, and is recovered in feces [without] going to the kidneys.” It apparently acts by binding to lipid II of gram-positive bacteria.

CXA-101 is another narrow-spectrum antimicrobial agent, in this case a new cephalosporin antibiotic with “potent activity” against *Pseudomonas aeruginosa* along with other *Pseudomonas* species, says James Ge of Calixa Therapeutics in San Diego, Calif. It has a “good safety profile” and is being developed as a “monotherapy and in combination with ta-zobactam.” Also noteworthy and in contrast to other antibiotics, CXA-101 retains “potent bactericidal activity” against *P. aeruginosa* in biofilms, he points out.

Finally, amid these many antibacterial agents is a new compound, designated AS2077715, with antifungal activity. This natural product, which is similar to funiculosin, was isolated...
from broth of the fungus Capnodiaceae strain No 339855, according to Keisuke Ohsumi of Astellas Pharma in Ibaraki, Japan. The compound has “selective antifungal activity,” he says, and looks promising as a topical agent for treating skin infections, including athlete’s foot. It is a “potent inhibitor of mitochondrial complex III.”

**Retrovirus Linked to Chronic Fatigue Syndrome**

As many as 95% of patients with chronic fatigue syndrome test positive for the retrovirus XMRV, according to Judy Mikovits of the Whittemore Peterson Institute (WPI) for Neuro Immune Disease in Reno, Nev., and her collaborators at the National Cancer Institute in Bethesda, Md., and the Cleveland Clinic in Cleveland, Ohio. Further, XMRV particles can be isolated from the blood of such patients, and those particles “can be transmitted between blood cells,” she says. Thus, the cumulative evidence implicates the XMRV “retrovirus as a significant contributing factor in this illness.” Researchers at WPI now are validating a blood test to detect the virus. Details appear in the October 8 online *Science*. Another recent study links this same virus to prostate cancer (see *Microbe*, November 2009, p. 494).

**Mycobacteria in the Mist**

The showerheads of city dwellers are strongly enriched for *Mycobacterium avium*, a chlorine-resistant, biofilm-forming opportunistic pathogen and its nontuberculous mycobacterial (NTM) cohorts, according to Norman Pace at the University of Colorado in Boulder and his collaborators. “While everyone was busy looking for *Legionella*, mycobacteria derived from municipal water systems were successfully building their empires inside showerheads,” says Pace, referring to well-known pathogen *Legionella*, whose notoriety is linked to its capacity to cause deadly pneumonias (initially among Legionnaires during their 1976 convention in Philadelphia) and, like mycobacteria, is associated with cooling systems and similar moisture-laden sites.

“The showerhead is a warm, moist, and dark place frequently replenished with low-level nutrient resources and seed organisms,” Pace notes. “A shower’s aerosol-generating particles are small enough to carry bacteria deep into the airways, and mycobacteria are readily aerosolized, probably because of their waxy hydrophobic cell walls.” Moreover, this waxy quality also helps mycobacteria resist the shear forces. And, because so many of the biofilm-forming members of this bacterial group are chlorine-resistant, widely used disinfection protocols promote their proliferation. A detailed report appears in the September 22 *Proceedings of the National Academy of Sciences* (106:16393–16399).

Mycobacteria, especially *M. avium*, are a well-recognized danger for patients with lung diseases, including asthma, bronchitis, and hypersensitivity pneumonitis, as well as for those suffering immune deficits such as HIV/AIDS. However, even seemingly healthy people are proving susceptible to NTM infections following exposures to hot-water aerosols, which is why, says Pace “identification of the anthropogenic reservoirs of these potential pathogens is an immediate public health concern.”

Until recently, identifying biofilm residents was technically challenging and unreliable, Pace continues. “Most bacteria living in natural microbial communities don’t grow well in cap-

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**Scanning electron micrograph of *Mycobacterium avium* cells. Researchers using metagenomic methods identified populations of this opportunistic pathogen in showerhead biofilms. (Magnification, ×12,700; image © Dennis Kunkel Microscopy, Inc.)**
Nanoparticles Enhance Photodynamic Killing of Bacteria

Nanoparticles made from porous zeolites and coated with photosensitizers and amino groups provide an enhanced means for killing bacteria with activated oxygen, according to Luisa De Cola at Westfälische Wilhelms-Universität Münster, Germany, and her collaborators. The nanoparticles bind to bacterial cell surfaces via the amino groups along their surfaces. When light of the appropriate wavelength impinges on the photosensitizers, they excite nearby oxygen molecules into the singlet state. In turn, they react with molecules along the surfaces of the nanoparticle-bound bacterial cells, damaging those molecules and effectively killing the cells, the researchers note. For instance, a two-hour period of irradiation proved effective at killing antibiotic-resistant cells of *Escherichia coli* and, separately, gonococcus cells. Details appear in the October 5 Angewandte Chemie, International Edition.

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