

MEETING REVIEW

The 52nd Annual Wind River Conference on Prokaryotic Biology—2008[∇]

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The 52nd Annual Wind River Conference on Prokaryotic Biology, which was held at the secluded Aspen Lodge only minutes from Estes Park, CO, concluded on 15 June 2008. The Conference, which was first held more than 50 years ago as the Transformation Meeting, was renamed the Wind River Conference on Genetic Exchange (1, 6). Its current name reflects the broader array of topics now represented at the meeting (1), which cover the major areas of prokaryotic biology. Although many participants study pathogenic microorganisms, the main emphasis of the Conference continues to be on fundamental issues in prokaryotic microbiology including molecular biology, microbial community interactions, and environmental microbiology. The relatively small size of the meeting (approximately 100 participants) allows for unique interactions, particularly between principal investigators, postdoctoral fellows, and students. Each year the Conference attracts an exceptionally diverse group of participants, and this year was no exception. In addition, students and young scientists are given the responsibility of chairing the scientific sessions and leading the discussions, reflecting the emphasis of the meeting on career development.

The Conference was organized by Don Ennis (University of Louisiana) and invited plenary speakers included Roberto Kolter (Harvard Medical School), Graham Hatfull (University of Pittsburgh), Robert Belas (University of Maryland Biotechnology Institute), and William Jacobs (Albert Einstein College of Medicine). In addition to the plenary addresses, about 50 oral presentations were given by graduate students, postdoctoral fellows, and principal investigators. Two sessions were scheduled to allow participants to interact and discuss 31 posters presented primarily by graduate students and undergraduates. A committee of graduate students, assisted by Gordon Churchward (Emory University School of Medicine), authored this review to highlight some of the high-impact science and career development activities presented at the conference.

SCIENTIFIC PRESENTATIONS

Heterogeneous biofilm development. The Neil Welker Plenary Address was given by Roberto Kolter (Harvard Medical School, Boston, MA), an invitee of the graduate students attending the meeting. Kolter discussed the idea that biofilm communities consist of a heterogeneous population of cells existing in diverse phenotypic states and that these diverse states are the result of an ordered process of differentiation that requires the bacteria to pass through distinct developmental checkpoints. He showed that *Bacillus subtilis* biofilms consisted of discrete subpopulations of cells in different regions of the biofilm which expressed reporter genes associated with either motility, biofilm matrix production, or sporulation. Sporulation is dependent upon biofilm matrix maturation, as a mutation in *tasA*, a gene previously shown to be required for the production of the extracellular matrix, resulted in a strain unable to sporulate in the context of a biofilm (19). He also showed that differentiation was enhanced by novel signaling pathways. Certain pore-forming antibiotics secreted by wild-type strains of *B. subtilis* that dissipate potassium ion gradients in the bacteria enhanced the production of biofilm matrix. This observation led to the identification of a novel two-component regulatory system essential for sensing intracellular potassium concentrations.

The theme of biofilm structure continued with discussions of the role of DNA as a structural component of biofilms. Members of the laboratories of Lynn Hancock and Kenneth Bayles (Kansas State University and the University of Nebraska Medical Center, respectively) showed that in both *Enterococcus faecalis* and *Staphylococcus aureus*, where extracellular DNA (eDNA) is present in the biofilms, eDNA release is facilitated through specific lysis events within the biofilm. A graduate student, Vinai Thomas (Kansas State University), showed that *E. faecalis* relies on lysis of a subset of cells within the biofilm to generate eDNA concentrations necessary for biofilm stability. Biofilm eDNA release is dependent on the activity of gelatinase, produced by *gelE*, and the upstream *fsr* quorum-sensing locus is required to activate the GelE-dependent biofilm phenotype described elsewhere (16). The GelE and SprE proteases contribute to biofilm formation through acting on a subset of cells to cause the release of eDNA. An *sprE* mutant strain had an increased rate of lysis compared to the wild-type

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parental strain, while a *gelE* mutant was defective for lysis, leading to a biofilm-deficient phenotype. DNase I treatment of the *E. faecalis* biofilms caused dispersion of the biofilm, suggesting that an *E. faecalis* biofilm is dependent on eDNA for structure and adherence. Members of the Bayles laboratory presented evidence that bacterial programmed cell death (PCD) affects *S. aureus* biofilm formation (15). The effector of lysis, *cidA*, is necessary for the release of eDNA presence in *S. aureus* biofilms, and the *lrgAB* gene is also essential for efficient biofilm formation, consistent with the shared functional homology of Cid and Lrg to the phage lambda holin/antiholin mechanism of lysis regulation. The PCD system is involved in the regulation of eDNA release in distinct subpopulations of cells within the biofilm community. The biofilm generated by the *lrgAB* mutant lacked tertiary structures, in contrast to a wild-type biofilm which readily formed tower structures in a flow cell model. However, in contrast to the *cidA* mutant, which is easily washed off a polycarbonate surface, the *lrgAB* mutant biofilm was strongly adherent. The heterogeneous nature of the cells comprising the wild-type *S. aureus* biofilm appears to arise from specific spatiotemporally regulated lysis of a subpopulation of cells comprising the biofilm. When a staphylococcal biofilm was treated with DNase I to mimic the effects of extensive extracellular nuclease release, dispersion of the previously adherent biofilm ensued. Thus, staphylococcal nuclease, in addition to playing a role in normal biofilm formation, could also at high concentrations be responsible for dispersion of the biofilm, permitting dissemination and infection of distant tissue sites. Mark Smelzer (University of Arkansas for Medical Sciences) showed that inhibition of extracellular proteases combined with an absence of staphylococcal nuclease due to mutation reverses the biofilm-deficient phenotype of a *sarA* mutant. This suggests that regulation of proteases and perhaps nuclease by *sarA* plays an important role in staphylococcal biofilm development.

New frontiers in mycobacterial research. The development of an efficient allelic exchange system in *Mycobacterium tuberculosis* has been hindered by high frequencies of illegitimate recombination and poor transformability. In the second plenary address of the Conference, Hatfull described a new recombineering system developed for mycobacteria which greatly increases the frequency of homologous recombination in both fast- and slow-growing mycobacteria such as *M. tuberculosis* (17). A graduate student, Julia Van Kessel, identified gp60 and gp61 from phage Che9c as distant relatives of the Rac prophage RecE and RecT proteins. Expression of gp61 in the presence of a short single-stranded DNA oligonucleotide is sufficient to introduce single-base-pair changes into the genome, and these can be identified in the absence of selection by using cotransformation with DNA carrying a selectable marker to identify transformed cells. The technique shows a substantial DNA strand bias, with a 10,000-fold-greater frequency of recombination when the oligonucleotide targets the lagging strand. Proof of the recombineering principle was demonstrated through the introduction, using oligonucleotides as short as 50 bp, of point mutations conferring antibiotic resistance to both fast- and slow-growing mycobacteria. This new system will help to speed the efforts to explore the roles of various genes in pathogenesis and antibiotic resistance.

A major problem with treatment of tuberculosis is the pres-

ence of a poorly understood subpopulation of *Mycobacterium tuberculosis* bacteria that are able to persist in a drug-tolerant, or possibly dormant, state. Ann Lenaerts (Colorado State University) is helping to define where the persister population resides during an infection. Histologic examination of tissues from diarylquinolone-treated guinea pigs revealed that the bacilli remaining in the lungs after drug treatment were present as extracellular microcolonies and clusters on the peripheral acellular rim of the granuloma (10). The bacilli in this hypoxic environment are hypothesized to be the persistent population and potentially exist in a biofilm. Such a biofilm may contribute to the survival of persisters and the drug-tolerant phenotype (14). Dhinakaran Sambandan (Albert Einstein College of Medicine) presented a poster describing studies in which screening a transposon-mutant library of *M. tuberculosis* for biofilm-defective mutants led to the discovery of mutants with both early and delayed biofilm defects. Interestingly, mutants with the delayed phenotype also lost rifampin tolerance, supporting the link between biofilm development and drug tolerance.

To facilitate the development of drugs targeting the persister population, Scott Franzblau (University of Illinois at Chicago) has developed the low-oxygen recovery assay as a high-throughput screen to identify drugs with activity against persistent populations. The low-oxygen recovery assay utilizes luciferase-producing bacteria to provide a quick and effective readout of drug effectiveness in growth conditions that are thought to mimic the environment inside a granuloma (4). Equally important to discovery of new drugs and targets against *M. tuberculosis* is an understanding of the mechanisms of resistance to drugs currently in use. Analise Zaunbrecher (CDC and Emory University) revealed the mechanism of low-level resistance to kanamycin, a significant issue in the treatment of multidrug-resistant and extremely drug-resistant tuberculosis. In his plenary address, Jacobs described the mechanism of isoniazid action and the multitude of resistance mechanisms discovered for this drug (18). It was recently shown that strains with mutations in *mshA*, whose product is in the biosynthetic pathway for mycothiol, are highly resistant to isoniazid. Jacobs also addressed the need to devise a better vaccine against tuberculosis, instead of using the poorly effective *Mycobacterium bovis* BCG vaccine used worldwide today. An attenuated auxotrophic mutant of *M. tuberculosis* was proven to be safer and provide a higher level of protection than the BCG vaccine when examined in a mouse model (8).

Jacobs discussed additional experiments that were intended to develop the genetic techniques in another global killer, *Plasmodium falciparum*. The successful development of a phage system in *Plasmodium* that utilizes the *hxbI* mycobacteriophage integrase has decreased the time to make a mutant of this protozoan from 120 days down to 9 days (13).

A different approach to a better vaccine against tuberculosis was described by Karen Dobos (Colorado State University), who discussed the identification of the components of purified protein derivative and the search for activators of non-classically restricted CD8⁺ T cells. She suggested that proteomic approaches could be used productively to define reagents for the diagnosis and prevention of tuberculosis. James Graham (University of Louisville) searched for secreted factors expressed during latency that enhance fibroblast attachment. The

results suggest that *sigK* and *mpt70* expression contributes to remodeling of lung tissue in granuloma formation. Finally, Don Ennis (University of Louisiana) and his collaborators described the use of Japanese medaka and *Mycobacterium marinum* as a model for studying tuberculosis, since in these fish *M. marinum* causes a tuberculosis-like granulomatous disease (2). Ennis emphasized the utility of this model in studying the impact of chronic infection on mutational loads and tumor promotion following exposures to environmental carcinogens.

Microbial communication and interaction. Plenary speaker Belas described the intricate relationship of the roseobacter *Silicibacter* sp. strain TM1040 and the dinoflagellate *Pfiesteria piscicida*. The bacteria belonging to the marine *Alphaproteobacteria* group have emerged as some of the most critical players in the oceanic sulfur cycle because they efficiently degrade dimethylsulfoniopropionate and live in close contact with dimethylsulfoniopropionate-producing algae like prymnesiophytes and dinoflagellates, including *Prorocentrum*, *Alexandrium*, and *Pfiesteria* species. The symbiotic relationship between *Silicibacter* strain TM1040 and *Pfiesteria* involves a chemotactic and motile attraction phase followed by biofilm formation by TM1040. The ability of this *Roseobacter* clade to exist in a biofilm and also to produce antibiotic compounds provides them with a selective advantage. By comparing the transporter, regulatory, and carbon acquisition systems of TM1040 with two other roseobacters, it was found that TM1040 has the ability to generate biologically active metabolites including the sulfur-containing antibiotic compound tropodithietic acid (TDA) (5). Haifeng Geng (University of Maryland Biotechnology Institute) observed spontaneous non-pigmented mutants of strain TM1040. Geng found a correlation between nonpigmented TDA-deficient colonies and loss of a previously unknown 130-kb plasmid in TM1040, which enabled the demonstration that pSTM3 contains the genes required for TDA biosynthesis.

Sophisticated communication mechanisms are common in microbial populations. Thomas Ficht (Texas A&M University) showed that in *Brucella melitensis* the quorum-sensing molecule C_{12} -homoserine lactone (C_{12} -HSL) interacts with the LuxR transcriptional regulator VjbR and changes the function of VjbR from an activator to a repressor for 131 genes. The addition of C_{12} -HSL to a *vjbR* mutant still positively regulates the expression of 56 genes during stationary phase. These data provided indirect evidence that while C_{12} -HSL represses the function of VjbR activity, it activates gene expression by interacting with a second regulator. The genes affected by C_{12} -HSL are important virulence genes such as genes encoding the type IV secretion system, antibiotic and toxin resistance genes, and DNA repair genes. In addition, VjbR and C_{12} -HSL regulate different transporters and genes involved in metabolic functions such as amino acid transport, metabolism, and carbohydrate and energy production. All of these virulence and metabolic genes contribute to the brucellae's ability to establish and maintain an infection within the host cell.

Members of Marty Roop's laboratory (East Carolina University) discussed how two iron regulators help the intracellular pathogen *Brucella abortus* survive life in the macrophage. Eric Anderson examined the role of *B. abortus* RirA, the homolog of which found in *Rhizobium leguminosarum* is a global regulator of iron-responsive genes. The *rirA* mutant has a de-

fect in iron metabolism, suggesting that RirA is a regulator for iron-responsive genes in *B. abortus*. One such gene is *bhuA*, a gene that encodes a *Brucella* heme transporter. Preliminary data indicate that RirA serves as a transcriptional activator of *bhuA* during growth in iron-depleted medium. Previous studies have demonstrated that BhuA is essential for virulence in a murine model of chronic infection, and consistent with a role for RirA as an activator of *bhuA*, a *rirA* mutant also displays significant attenuation in both cultured murine macrophages and BALB/c mice. Kendra Hitz discussed how the iron response regulator, Irr, combats oxidative stress. In the absence of oxidative stress, Irr represses the expression of *ahpCD*, whose gene products make up the alkyl hydroperoxide reductase complex, an antioxidant system that detoxifies hydrogen peroxide. When hydrogen peroxide is produced from aerobic metabolism, Irr is degraded by the hydrogen peroxide and no longer represses *ahpCD* expression. Both *ahpCD* and *irr* mutations display significant attenuation in C57BL/6 mice past 4 weeks, illustrating the importance of these proteins in allowing the brucellae to maintain an intracellular infection. Samantha Orchard (San Diego State University) described an unpredicted property of a synthetic antimicrobial peptide isolated as an inhibitor of Holliday junction resolution for site-specific and homologous DNA recombination in *E. coli* (7). This peptide has potent antibacterial activity which is dramatically enhanced in mutants defective in the siderophore enterochelin synthesis and uptake pathways. These results suggest that this peptide may act to disrupt alternative pathways for iron acquisition.

Other speakers described factors that affected the ability of bacteria to cause virulent infections. Matt Conover (Wake Forest University Health Sciences) described the identification of an extracellular polysaccharide that is essential for the formation of biofilms by *Bordetella pertussis*. Mutant bacteria that lack the ability to make the polysaccharide are avirulent in a mouse infection model. Kyle Cady (Dartmouth Medical School) discussed a novel interaction between *Pseudomonas aeruginosa* and phage DMS3. He found that infection suppresses group behaviors such as swarming and biofilm formation thought to be important in infection and that this suppression requires intragenic CRISPR sequences and associated *cas* genes. Adel Malek (Dartmouth Medical School) described a novel interaction of *Pseudomonas aeruginosa* with airway epithelial cells. The bacteria harvest choline from phosphatidylcholine (PC) in host cell membranes and use it to synthesize their own PC. Mutants defective in PC synthesis are defective in the development and maturation of biofilms on airway epithelial cells. Continuing the emphasis on microbes and their interactions in communities, Matthew Ramsey (University of Texas at Austin) described the effects of oxidative stress on the opportunistic pathogen *Aggregatibacter actinomycetemcomitans*. This bacterium grows in close association with hydrogen peroxide-producing oral streptococci, and Ramsey showed that only two genes are upregulated in response to exogenous hydrogen peroxide exposure—*katA* and *apiA*, which code for catalase and factor H binding protein, respectively. He hypothesized that hydrogen peroxide production by the oral streptococci is a cue for increased resistance of *Aggregatibacter* to complement activity.

Three speakers described environmental interactions occurring between microbes in natural communities. Robert Kysela

(University of Colorado, Boulder) showed that unfertilized soils can constitute an important reservoir of antibiotic resistance but the increased nutrient availability in the form of fertilizer can increase the abundance of antibiotic resistance. María Rodríguez-Mora (University of Louisiana, Lafayette) described the relationships between geochemical gradients and microbial population structure across oxic-anoxic transition zones in the Cariaco Basin of Venezuela (11), concluding that oxidation of sulfide or sulfide oxidation product is very important in fuelling chemolithotrophy. Finally, Diana Nemergut (University of Colorado, Boulder) described the results of large-scale population sampling from a large number of microbial communities. The most surprising result was that while some genera are ubiquitous, the overwhelming majority of genera are found in only a single community and that many of these "rare" organisms are highly novel. In addition, for those genera found in multiple communities there is evidence of patterns of co-occurrence, suggesting that interactions between species are key factors in shaping microbial population structure in the world outside the laboratory.

Microbial cell and molecular biology. Charles Moran (Emory University School of Medicine) discussed a new bioinformatic analysis of the products of the SpoIIIA operon in *Bacillus subtilis*. These genes are essential for σ_G activation in the forespore and for normal spore development. The forespore outer membrane protein, SpoIIIAH, shares homology with predicted pore-forming proteins in the YscJ/FliF family (3). This finding suggested that the interaction between SpoIIIAH and the forespore inner membrane protein SpoIIQ may form a channel between the forespore and mother cell cytoplasm. The predicted width of the putative channel (75 Å) is large enough for folded proteins to pass through. In the mother cell, sigma factor activation is known to be due to the proteolytic cleavage of pro-sigma factors (9), but activation of sigma factors in the forespore is not well understood. Moran discussed the development of a compartmentalized biotinylation assay to show that the organization of SpoIIIAH and SpoIIQ is consistent with the formation of a channel that is gated at the mother cell end. Although no putative substrate was identified, this sparked discussion about the possible protein or metabolic factors that may be translocated into the forespore through such a channel. Another forespore membrane protein, SpoIIIAA, was recognized to have homology to the ATPases present in type II and type IV secretion systems and is hypothesized to provide the driving force for translocation through the putative channel.

Mike Hornback (Emory University School of Medicine) discussed the role of a novel eukaryotic-type β ZIP protein, RsfA, in the regulation of spore formation in *B. subtilis*. Genetic analysis suggests that this transcription factor is involved in a previously undescribed regulatory pathway controlling the formation of the spore cortex. Salika Shakir (University of Oklahoma Health Science Center) described another example of a eukaryotic-type regulatory system in *Bacillus anthracis*. A mutant lacking a serine-threonine phosphatase, Stp-1, is impaired in survival within macrophages, and its spores are less virulent than wild-type spores in a mouse pulmonary challenge model. In vitro studies demonstrate that the phosphatase acts on an adjacently encoded kinase, which suggests the involvement of a serine-threonine-type signal transduction system in the physi-

ology and virulence of *B. anthracis*. Other investigators described regulation of virulence factors occurring at different levels beyond transcription initiation. Kelsi Anderson (University of Nebraska Medical Center) showed how the *sarA* locus of *S. aureus* regulates virulence gene expression. SarA regulates transcript stability by binding to specific target sequences within mRNA transcripts. Indranil Biswas (University of Kansas Medical Center) described how ClpP functions to regulate the response of *Streptococcus mutans* to oxidative stress. Regulation of ClpP expression involves repetitive DNA sequences upstream of the ClpP promoter which are not found and do not affect transcription in the closely related *Streptococcus pyogenes*, suggesting the presence of a regulatory system unique to *S. mutans*.

A series of talks addressed genome plasticity in microbial populations. Susan Rosenberg (Baylor College of Medicine) discussed stress-induced mutagenesis that arises from changes in the fidelity of DNA double-strand break repair. This mutagenesis occurs in a subpopulation of cells that are spontaneously SOS induced but also induced for the RpoS response. Phillip Hastings (Baylor College of Medicine) discussed a model of replication fork arrest and recovery which explains the more complex genetic rearrangements resulting from a combination of duplication, inversion, and deletion events. Holly Martin and Christine Pybus (University of Nevada, Las Vegas) described the role of transcription in stationary-phase mutagenesis in *B. subtilis*. Their experiments demonstrate that transcription of the target gene favors reversion to prototrophy. Katja Mertens (Texas A&M Health Science Center) described the role of the AddAB complex in the survival of *Coxiella burnetii* (12). This complex, analogous to the RecBCD complex, is uncommon in gammaproteobacteria, but in contrast to RecBCD, its expression is strongly upregulated in response to oxidative stress, which is presumably an adaptation for survival within macrophages. Stephen Sandler (University of Massachusetts at Amherst) described observations of SOS induction in single cells of *E. coli*. While RecA/DNA filaments are allosteric effectors of LexA autoproteolysis, not all filaments lead to an SOS response, and certain *recA* mutants show constitutive SOS induction in the absence of DNA damage. There are at least two different patterns of constitutive induction depending upon the particular mutations present in *recA*. Justin Courcelle (Portland State University) presented evidence that in *E. coli* the response to oxidative DNA damage has a distinct dependency upon RecBCD, and the rate of DNA replication is reduced by a factor of only 20%, suggesting that the loss of viability in these cells is not directly associated with disruption of replication.

The meeting began with Kolter describing the genetic regulatory network that controls differentiation in *B. subtilis*. As a counterpoint, several speakers described metabolic network interactions and their regulation in enteric bacteria. Jannell Bazarro (University of Wisconsin, Madison) described a comparative analysis of thiamine biosynthesis in *E. coli* and *Salmonella enterica*. Although these organisms are very closely related, a study of thiamine requirements of mutants affecting the initial steps of the thiamine biosynthesis pathway demonstrates distinct differences, implying that conservation of metabolic components does not predict conservation of a metabolic network. Mark Koenigsnecht (University of Wisconsin,

Madison) continued the discussion of metabolic networks by his demonstration that mutants in a biochemical pathway that suppress the activity of key enzymes (phosphoribosylpyrophosphate synthetase) resulting in the accumulation of substrates can lead to downstream product formation (phosphoribosylamine) by activities that are novel and uncharacterized even in organisms as well studied as *S. enterica*. Finally, Melissa Christopherson (University of Wisconsin, Madison) described the characterization of a protein of unknown function, YjgF, with altered accumulation of metabolites derived from threonine in *S. enterica*. This protein is highly conserved across all three domains of life and may interact with toxic metabolites.

WORKSHOPS

In addition to scientific presentations, the Conference also has workshops that cater to the interests of the participants. This year the organizer, Don Ennis, organized a workshop on antimycobacterial drug discovery and development. In addition to the benefit for mycobacterium aficionados present at the meeting, this workshop gave students and postdocs the opportunities to meet program directors from NIH (Barbara Mulach) and industry (Mark Dodson, Sanofi Aventis). Mulach and Dodson also participated in a career development workshop moderated by Uldis Streips (University of Louisville). This workshop covered careers in academia and industry, the workings of the NIH review process, and also education and teaching with presentations by William Wood (University of Colorado), Hatfull, and Streips. For the younger participants, Gordon Churchward (Emory University School of Medicine) and Streips led a discussion of what is required to impress review panel members who evaluate postdoctoral fellowship applications.

CONCLUSION

The meeting concluded with a final plenary address on Saturday evening, and discussions lasted late into the night before everyone retired. The benefits of the conference were plenty and included conversations sparking new ideas and approaches, job opportunities, and lasting friendships. Between scientific presentations people had the opportunity to interact outside the conference by participating in horseback rides, hiking, golf, and games. (One of the authors [G.C.] can enthusiastically recommend Curly to those neophyte riders who might appreciate a horse with character.) The ability to interact in a relaxed setting with leaders in several different fields over the course of just a few days presents students with a rare opportunity that is nowadays seldom found at scientific meetings. The Wind River Conference on Prokaryotic Biology is a well-established, unique meeting which affords an opportunity to those who enjoy productive interactions in a beautiful location with their fellow scientists regardless of seniority.

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