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MEETING REVIEW

25th Annual Midwest Microbial Pathogenesis Conference

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ABSTRACT The 25th annual Midwest Microbial Pathogenesis Conference (MMPC) was held at the University of Iowa from 28 to 30 September 2018. The conference has a long-standing tradition of providing scientists from the Midwest with a forum to present and discuss cutting-edge advances in microbial pathogenesis with particular focus on bacterial interactions with the environment, host, and other microbes. This review summarizes the genesis of the MMPC, topics presented at the conference, and articles found in the special MMPC sections of this issue of the *Journal of Bacteriology*.

KEYWORDS bacteria, conference, host-pathogen interactions, immunology, pathogenesis, viruses

The first Midwest Microbial Pathogenesis Conference (MMPC) convened in 1994, and the conference has been held every year since. The origins of the MMPC are rooted in the Buffalo Conference on Microbial Pathogenesis (currently in its 31st year) held in Buffalo, NY. The Buffalo meeting was started in 1988 by Michael Apicella and included presentations by Gerald Byrne (then at the University of Wisconsin) and Bob Munson (then at Washington University). Following his move to the University of Iowa, Apicella joined forces with Byrne and Munson to develop a similar meeting focused on microbial pathogenesis research being conducted in the Midwest. The first meeting was held at the University of Iowa in Iowa City, and thereafter the meeting was held annually at different midwestern institutions. Since its inception, the MMPC has provided an important forum for students, postdoctoral fellows, junior faculty, and established investigators from the Midwest to network and to present and discuss cutting-edge research in the field of microbial pathogenesis. A major objective of the MMPC is to promote young investigators as they develop into the next generation of research scientists. The MMPC also fosters scientific collaboration between investigators and institutions from within the region.

The MMPC returned to the University of Iowa from 28 to 30 September 2018 to celebrate the 25th anniversary of the conference and included 265 registered participants from 15 states and 47 institutions. The conference was chaired by Craig Ellermeier and Timothy Yahr from the University of Iowa. The 22 oral and 165 poster presentations focused on microbial physiology and signaling, intracellular pathogens, host-microbe interactions, viral pathogens, immune responses to pathogens, and microbial interactions.

Second messengers such as cAMP and cyclic di-AMP/GMP play critical roles in many signal transduction cascades. Joshua Shrout, a 2017 MMPC coorganizer and 2018 keynote speaker from the University of Notre Dame, discussed second-messenger signaling during swarming of *Pseudomonas aeruginosa*. Tu Huynh, from the University of Wisconsin, discussed how the second messenger cyclic di-AMP regulates osmolyte transport and maintenance of cell wall biogenesis in *Listeria monocytogenes*. Additional oral presentations focused on the potential for disrupting signal transduction systems as a strategy for treating bacterial infections. Erin Carlson, from the University of Minnesota, presented work showing that benzothiazole-based histidine kinase inhibi-

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tors perturb multiple *P. aeruginosa* virulence pathways in a burn wound model. Artemis Gogos, from the University of Illinois at Chicago and a trainee in the laboratory of Michael Federle, presented evidence that small molecules disrupt the *Streptococcus pyogenes* Rgg 2/3 quorum-sensing system, which is required for oropharyngeal colonization of mice. Paul Jensen, from the University of Illinois at Urbana-Champaign, described the use of transcriptional profiling and large-scale mutagenesis studies to observe that a microbe's stress response can be either coordinated or chaotic, depending on the type of stress. Additional work in this issue of the *Journal of Bacteriology* draws from poster presentations at the 2018 MMPC that were also related to signal transduction. Sinha et al. describe the identification and characterization of the small RNA (sRNA) transcriptome of the *Streptococcus pneumoniae* TIGR4 strain and found that 15% of the sRNAs identified in TIGR4 are not present in the D39 genome, suggesting that differences in sRNA may contribute to strain-specific virulence properties (1). A study by Tran et al. describes the role of a phage regulatory switch in controlling β-toxin production in *Staphylococcus aureus* during biofilm growth and when interacting with human aortic endothelial cells (2). Work by Williams McMackin et al. shows that the nucleoid proteins MvaT and MvaU regulate the *Pseudomonas aeruginosa* type III secretion system by directly silencing the P_{exsA} promoter (3). DeAngelis et al. present work showing that the phage shock protein system senses and responds to inner membrane damage and exhibits a colonization defect in a zebrafish model (4).

Matrix components released following cell death and lysis are important for biofilm formation. Vinei Thomas, from the University of Nebraska, presented evidence that acetate-mediated intracellular acidification and generation of reactive oxygen species constitute an active mechanism of cell death in *S. aureus*. Rajendar Deora, from Ohio State University, discussed the importance *Bordetella pertussis* biofilms as a pathogenic strategy that promotes survival and persistence in the mouse respiratory tract. Chronic carriage of *Salmonella enterica* serovar Typhi involves biofilm formation on gallstones (5). In this issue, Neiger et al. demonstrate that hyperbiofilm variants can be generated *in vitro* by culturing under gallbladder-mimicking conditions (6). Those variants, however, are negatively affected for systemic virulence. Mario Feldman, from Washington University, presented data showing that uropathogenic strains of *Acinetobacter baumannii* have specific adhesins for human bladder epithelia that are required for survival. Jonathan Hardy, from Michigan State University, described the use of *in vivo* bioluminescence imaging to investigate the process and effects of prenatal *Listeria monocytogenes* infections. Jeffrey Bose, from the University of Kansas, reported that *S. aureus* FakA, which is required for *S. aureus* to acquire fatty acids from the environment, modulates both the physiology and virulence of *S. aureus* (7).

Another conference theme focused on mechanisms of intracellular survival by bacterial and viral pathogens. Following host cell invasion, *Mycobacterium marinum* and *Listeria monocytogenes* escape to and replicate in the cytoplasm. The *M. marinum* ESX-1 secretion system participates in phagosome lysis to promote intracellular growth in macrophages. Patricia Champion, a 2017 MMPC coorganizer and 2018 keynote speaker from the University of Notre Dame, discussed an EXS-1 regulator with activity that is coordinated with assembly of the EXS-1 secretory apparatus. Additional work from the Champion group in this issue identifies MMAR_2894 as a ESX-1 secretion substrate that is required for optimal secretion of other ESX-1 substrates and for hemolysis but not cytolysis of macrophages (8). Cytoplasmic survival of *L. monocytogenes* is dependent upon 1,4-dihydroxy-2-naphthoate (DHNA), an intermediate of menaquinone biosynthesis (9). Cheng-Yen Kao, a trainee with John D. Sauer at the University of Wisconsin, reported that transcription factor Lmo1576 controls DHNA fermentative flux and may regulate metabolic programs to promote cytosolic survival.

Whereas *M. marinum* and *L. monocytogenes* both escape from the phagosome and replicate within the cytoplasm, *Chlamydia trachomatis*, *Coxiella burnetii*, and *Legionella pneumophila* replicate within membrane-bound compartments. Formation of the *C. trachomatis*-containing vacuole requires effector proteins delivered by a type III secretion system. Mary Weber, from the University of Iowa, presented work showing that

different *C. trachomatis* serovars have unique repertoires of secreted proteins and that the different effector sets may account for vaginal, cervical, and HeLa cell tropism. While residing in the vacuole, *C. trachomatis* transitions between an infectious elementary body (EB) form and a replicative reticulate body (RB). Derek Fisher, from Southern Illinois University, discussed how global protein phosphorylation events are balanced by kinases and phosphatases to control the EB-to-RB developmental cycle (10). Although *C. trachomatis* is the most common sexually transmitted pathogen, there is currently no vaccine. Stephen Jordan, from Indiana University School of Medicine, reported that $CD4^+$ gamma interferon (IFN-γ) responses are infrequent in *C. trachomatis*-infected women and may correlate with protection against reinfection. Intracellular *Coxiella burnetii* resides in a phagolysosome-like parasitophorous vacuole (PV) containing cholesterol (11). Tatiana Clemente, a trainee with Stacey Gilk at Indiana University School of Medicine, reported that *C. burnetii* expresses a eukaryotic-protein-like sterol reductase that prevents toxic effects resulting from cholesterol accumulation in the PV. Lubov Grigoryeva, a trainee from the laboratory of Nicholas P. Cianciotto at Northwestern University, examined signaling events in human macrophages following infection with *L. pneumophila* and found that endosomal Toll-like receptors and cytosolic DNA sensors are important for sensing the organism. These findings differ from those of similar studies with murine cells, raising questions about overreliance on the murine model. Replication of *L. pneumophila* in phagocytes requires the Dot/Icm type IVb secretion system. A study in this issue by Ngwaga et al. reports that the LegC4 effector restricts *L. pneumophila* replication in macrophages activated with tumor necrosis factor and thus appears to promote clearance from the immunocompetent host (12).

While the MMPC is focused largely on bacterial pathogens, several talks discussed viral pathogens. Formation of infectious viral particles is dependent upon host cell components including polyamines, which assist in the packaging of some viral genomes into capsids. Bryan Mounce, from Loyola University, demonstrated that a Rift Valley fever virus vaccine candidate is sensitive to polyamine depletion by FDA-approved pharmaceuticals and that depletion late in the viral life cycle significantly reduces viral titers. The interferon system restricts viral replication. Saurabh Chattopadhyay, from the University of Toledo, described a novel interferon-stimulated gene (TDRD7) that inhibits paramyxovirus replication by blocking virus-induced cellular autophagy (13).

Several talks focused on the contribution of the microbiome/virome to different disease states. Sarah Lucas, a trainee with Ryan Hunter at the University of Minnesota, compared 16S rRNA in patients with chronic rhinosinusitis (CR) to that in healthy controls and reported that CR-associated organisms have a distinct anaerobic phenotype and degrade host mucins as a nutrient source. Patrick Seed, from Northwestern University, provided evidence that maternally derived bacterial species asymptomatically colonize the olfactory tract in mice and that within a specific neonatal window of susceptibility the organisms trigger behavioral alterations that persist into early adulthood. Intestinal bacteria can enhance the replication and pathogenesis of poliovirus (14). Using coxsackievirus B3 (CVB3) replication as a model, Chris Robinson, from Indiana University School of Medicine, discussed how depletion of the microbiota reduces viral replication and enhances survival of CVB3-induced disease. Matthew Olson, from Purdue University, discussed a potentially novel subset of small-intestine-resident $CD4^+$ T cells that produce the serine protease granzyme A in response to segmented filamentous bacteria. These cells appear to maintain intestinal homeostasis but can also contribute to autoimmune-driven inflammation.

Műh et al. describe the use of a xylose-inducible clustered regularly interspaced short palindromic repeat interference (CRISPRi) system for targeted knockdown of gene expression in *Clostridioides difficile* (15). This work was featured in a commentary in this issue by Aimee Shen of Tufts University, who discusses this and other methods of genetic manipulation of *C. difficile* (16). Allen and Hauser describe the *in silico* analysis of contact-dependent growth inhibition (CDI) systems in *P. aeruginosa*, finding diversity

among strains isolated within a limited geographical region, which suggests that CDI systems play a role in the ecology of *P. aeruginosa* (17).

The keynote address was delivered by Michael Welsh from the University of Iowa. Welsh discussed immune deficiency resulting from mutations in the cystic fibrosis (CF) conductance regulator (CFTR) and advances using the porcine cystic fibrosis model. Humans and pigs lacking CFTR have acidified airway surface fluid which impairs innate defense mechanisms, including the activity of some cationic antimicrobial peptides. Acidification is dependent on a specific acid channel (ASC12) that could be targeted as a therapeutic approach (18). The same channel is lacking in mice, which may explain why CF mice fail to develop airway disease. The porcine model has also revealed that submucosal glands release long strands of mucus that contribute to mucociliary clearance by sweeping away large particles (19). In CF animals the mucus strains fail to properly detach from the submucosal glands, adding to the long list of clearance defects associated with CFTR dysfunction.

In summary, the 25th annual MMPC highlighted diverse microbial science occurring in the Midwest and continues to provide an important venue for promoting young scientists. The 26th annual MMPC will be chaired by Jason Huntley and Mark Wooten on 20 through 22 September 2019 at the University of Toledo.

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