ARLG
Antibacterial Resistance Leadership Group

September 28, 2018
Q3 Newsletter

Welcome to the 2018 Q3 ARLG Newsletter! Here, you will receive important updates from ARLG regarding recent events, grants, publications, and the committees that help us work toward our mission: to prioritize, design, and execute clinical research that will reduce the public health threat of antibacterial resistance.

Get Involved with ARLG

ARLG continuously accepts proposals for clinical studies designed to prevent, diagnose, treat, or eradicate antibiotic-resistant bacterial pathogens. We also award grants and fellowships to qualified investigators. If you are interested in getting involved with ARLG, apply now or contact us for more information.

Apply for a Grant | Contact Us

ARLG at IDWeek 2018™

The ARLG is pleased to be a part of IDWeek 2018™.

The ARLG will be featured in a Meet-the-Professor Session on Saturday, October 6, 7:15 a.m.– 8:15 a.m. in Room W2002. Updates from the ARLG session will focus on defining elements of a pragmatic clinical trial, discussing how host gene expression-based diagnostics distinguish bacterial and viral infection, and highlighting three future challenges of antimicrobial drug resistance. It will include case studies from research supported by ARLG as well as details on how to get involved with the group.

You are invited to the Duke Clinical Research Institute (DCRI) reception on Friday, October 5, 6.00 p.m. – 8:30 p.m. (see details below). You can also connect with the ARLG leaders, Vance Fowler, Chip Chambers, and Heather Cross, at the DCRI booth #501 on Saturday, October 6, 11:00 a.m. – 1:00 p.m.

Don't miss out on learning what's new from the ARLG and connecting with colleagues at IDWeek 2018™. Check out these featured ARLG sessions and a comprehensive list of all sessions.

News and Upcoming Events

Are you presenting at IDWeek 2018^{tm} or an upcoming conference on an ARLG study?

Let us know!

Contact Us

What's New from ARLG?

Check out the following new materials. Feel free to download, print, and share the fact sheets with your colleagues and the summary of results with your patients.

ARLG Fact Sheet

ARLG Laboratory Center Fact Sheet

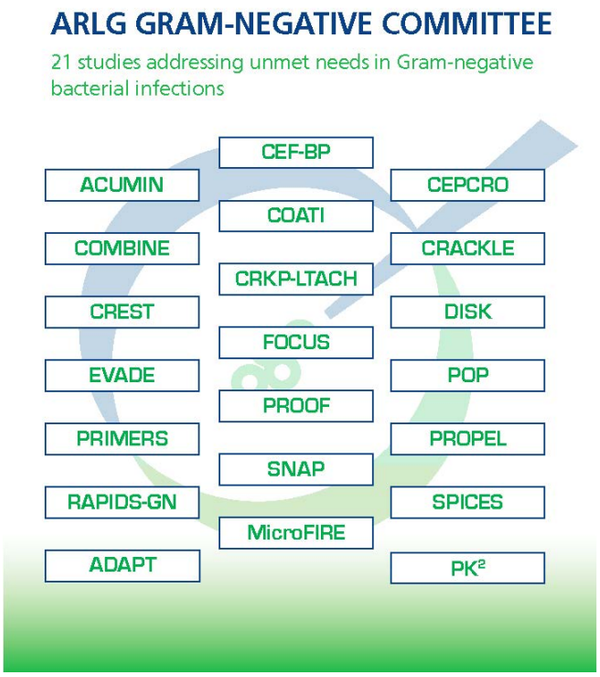
PROOF Summary of Results

RADICAL Summary of Results

Update from the Gram-Negative Committee

Yohei Doi, MD, PhD
Division of Infectious Diseases
University of Pittsburgh School of Medicine
ARLG Gram-Negative Committee Chair

The Gram-Negative Committee (GNC) strives to advance knowledge of challenging resistant Gram-negative infections and enhance patient outcomes. Dr. Yohei Doi, chair of the committee, provides thoughts and insights on contributions to date and future plans.



The GNC accomplishes its goals, often in collaboration with other committees and special emphasis panels, through:

1. Conceiving and designing clinical research studies, and
2. Reviewing and prioritizing clinical research protocols relevant to Gram-negative infections that are submitted to the ARLG Steering Committee.

Since its inception, the GNC reviewed and prioritized proposals have led to 21 ARLG studies addressing unmet needs in Gram-negative bacterial infections.

Implemented studies range from observational cohorts (e.g. CRACKLE, CREST), to those addressing pharmacokinetics (e.g. PROOF, ACUMIN), diagnostics (e.g. RAPIDS-GN, PRIMERS I-IV) and a randomized strategy trial (FOCUS). These studies have led to 46 manuscripts in peer-review journals and 40 abstract presentations at national and international scientific conferences.

Our committee is also going global as part of

ARLG's expanding international presence. The GNC has members from the U.S., Canada, Argentina, Israel, and Australia. We also provide mentoring opportunities to ARLG mentees whose research interests include Gram-negative infections. These junior investigators rotate through the committee and gain valuable experience through discussions and mentorship opportunities.

Moving forward, we plan to continue to generate and prioritize clinical studies involving resistant Gram-negative bacterial infections that will address knowledge gaps, inform the professional and lay communities, and ultimately advance clinical care.

ARLG SPOTLIGHT

Ephraim Tsalik, MD, PhD
Duke University Medical Center
Associate Director of Diagnostics and MASTERMIND (MASTER protocol for evaluating Multiple INfection Diagnostics)

About my role in ARLG

I have two primary roles in ARLG: 1) as a contributor and 2) and as recipient. As a recipient, I am the principal investigator for the **Ra**pid **D**iagnostics **i**n **C**ategorizing **A**cute **L**ung Infections (RADICAL) study. ARLG has been a supporter of RADICAL from the project's initial phase. We are currently in phase two of three expected phases. RADICAL-I focused on the development of a platform capable of measuring gene expression in a clinically meaningful way. RADICAL-II is testing the platform in a heterogeneous population with considerations for age, ethnicity, co-morbidities, and geographic location. We envision RADICAL-III as a clinical-utility study where real-time results will be used to determine the clinical value of the test in discriminating bacterial and viral infections. RADICAL results will be presented at IDWeek 2018^{tm} and ARLG created this summary of study results geared towards the public reader.

As a contributor to ARLG, I am the associate director of the ARLG Laboratory Center, where I work with other ARLG leaders. Our goal is to interface with industry, investigators, and other academic partners to leverage ARLG resources that include:

- Intellectual access to international thought leaders,
- Microbiological access to clinically well-characterized Gram-positive and Gram-negative bacteria through the Virtual Biorepository (VB) Catalogue, and
- Financial support of studies that advance or evaluate diagnostics for antibacterial resistance.

My work in diagnostics led to an interest in the MASTERMIND (MASTER protocol for evaluating Multiple INfection Diagnostics) concept that is based on the following premise: ***One single participant can provide information and samples for the simultaneous evaluation of multiple diagnostics.*** This concept, similar to platform studies used in oncology, represents the first standardized approach in the development of diagnostics.

An example of the MASTERMIND protocol in action is the MASTER-GC study. MASTER-GC evaluated three different platforms for the detection of extragenital gonorrhea and chlamydia infections. One of our biggest achievements of this study was the collaboration of three companies, who are typically competitors in this space, to work together towards one common goal: Use the study results to support their own FDA application for these new indications.

Extragenital infections are infrequent enough that no one company would be motivated to fund an individual research and diagnostic program; however, the companies agreed to participate knowing that ARLG was providing funding, resources, and support. In the end, the companies were happy with their participation and the study has the potential to be a win-win situation for all parties involved.

The next MASTERMIND study will focus on blood-stream infections. We are interested in evaluating diagnostics that detect pathogens directly from a blood sample, without the need

for culture.

Impact of ARLG Research Funding to my Career

My career has always focused on the type of questions that we are investigating in RADICAL and MASTERMIND. ARLG's support has been instrumental for the development and advancement of these studies by providing financial security that allows me to focus on the work and resources to hire and support research staff. In addition, I have received recognition in the institutional and scientific communities for this new and evolving approach to diagnosing illness that has the potential to answer larger questions in science and medicine.

Benefits of ARLG

Personally, what I have appreciated most from ARLG is their visionary and innovative approach to combat antimicrobial resistance. When I started out in my career researching new diagnostic approaches for host-gene expression, I often encountered skepticism and received many negative responses from conventional funding sources. However, ARLG recognizes that we cannot continue with the same approach and expect a different solution. I really want to express my gratitude to ARLG for their willingness to take a risk on an outlandish idea that has turned into an exciting and a promising RADICAL change to clinical practice.

Awards and Achievements

2018 SHEA William Jarvis Award

Maria Souli MD, ARLG project leader, will be the recipient of the 2018 SHEA William Jarvis Award for her article titled "Reduction of Environmental Contamination with Multidrug-Resistant Bacteria by Copper-Alloy Coating of Surfaces in a Highly Endemic Setting." ICHE (2017), 38(7): 765-771.

The award aims to recognize the most outstanding international clinical study published in Infection Control and Hospital Epidemiology (ICHE) in 2017.

The award will be presented during **ID**Week 2018^{tm}, October 5, at 4:30 p.m. in North Hall D, Moscone Center.

Recent Publications

Check out the following recent ARLG publications since March 1, 2018.

Gopalsamy SN, Sherman A, Woodworth MH, Lutgring JD, Kraft CS. Fecal Microbiota Transplant for Multidrug-Resistant Organism Decolonization Administered During Septic Shock. Infect Control Hosp Epidemiol. 2018 Apr; 39(4):490-492. doi: 10.1017/ice.2017.300. Epub 2018 Jan 18. PMID: 29343312. PMCID: PMC5996996.

Richter SS, Karichu J, Otiso J, Van Heule H, Keller G, Cober E, Rojas LJ, Hujer AM, Hujer KM, Marshall S, Perez F, Rudin SD, Domitrovic TN, Kaye KS, Salata R, van Duin D, Bonomo RA. Evaluation of Sensititre Broth Microdilution Plate for determining the susceptibility of carbapenem-resistant Klebsiella pneumoniae to polymyxins. Diagn Microbiol Infect Dis. 2018 May; 91(1):89-92. doi: 10.1016/j.diagmicrobio.2018.01.005. Epub 2018 Jan 9. PMID: 29456071. PMCID: PMC6083442.

Mamo Y, Woodworth MH, Wang T, Dhere T, Kraft CS. Durability and Long-term Clinical Outcomes of Fecal Microbiota Transplant Treatment in Patients With Recurrent Clostridium difficile Infection. Clin Infect Dis. 2018 May 17;66(11):1705-1711. doi: 10.1093/cid/cix1097. PMID: 29272401. PMCID: PMC5961001.

Miller WR, Seas C, Carvajal LP, Diaz L, Echeverri AM, Ferro C, Rios R, Porras P, Luna C, Gotuzzo E, Munita JM, Nannini E, Carcamo C, Reyes J, Arias CA. The Cefazolin Inoculum Effect Is Associated With Increased Mortality in Methicillin-Susceptible Staphylococcus aureus Bacteremia. Open Forum Infect Dis. 2018 May 23;5(6):ofy123. doi: 10.1093/ofid/ofy123. eCollection 2018 Jun 1. PMID: 29977970. PMCID: PMC6007512.

Wenzler E, Bleasdale SC, Sikka M, Bunnell KL, Finnemeyer M, Rosenkranz SL, Danziger LH, Rodvold KA; Antibacterial Resistance Leadership Group. Phase I Study To Evaluate the Pharmacokinetics, Safety, and Tolerability of Two Dosing Regimens of Oral Fosfomycin Tromethamine in Healthy Adult Participants. Antimicrob Agents Chemother.

2018 Jul 27;62(8). pii: e00464-18. doi: 10.1128/AAC.00464-18. Print 2018 Aug. PMID: 29891606. PMCID: PMC6105781.

Cheng YW, Phelps E, Ganapini V, Khan N, Ouyang F, Xu H, Khanna S, Tariq R, Friedman-Moraco RJ, Woodworth MH, Dhere T, Kraft CS, Kao D, Smith J, Le L, El-Nachef N, Kaur N, Kowsika S, Ehrlich A, Smith M, Safdar N, Misch EA, Allegretti JR, Flynn A, Kassam Z, Sharfuddin A, Vuppalanchi R, Fischer M. Fecal microbiota transplantation for the treatment of recurrent and severe Clostridium difficile infection in solid organ transplant recipients: A multicenter experience. Am J Transplant. 2018 Aug 7. doi: 10.1111/ajt.15058. [Epub ahead of print]. PMID: 30085388.

Patel R, Fang FC. Diagnostic Stewardship: Opportunity for a Laboratory-Infectious Diseases Partnership. Clin Infect Dis. 2018 Aug 16;67(5):799-801. doi: 10.1093/cid/ciy077. PMID: 29547995. PMCID: PMC6093996.

Kanwar A, Marshall SH, Perez F, Tomas M, Jacobs MR, Hujer AM, Domitrovic TN, Rudin SD, Rojas LJ, Kreiswirth BN, Chen L, Quinones-Mateu M, van Duin D, Bonomo RA; Antibacterial Resistance Leadership Group. Emergence of Resistance to Colistin During the Treatment of Bloodstream Infection Caused by Klebsiella pneumoniae Carbapenemase-Producing Klebsiella pneumoniae. Open Forum Infect Dis. 2018 Apr 23;5(4):ofy054. doi: 10.1093/ofid/ofy054. eCollection 2018 Apr.

Cheng YW, Phelps E, Ganapini V, Khan N, Ouyang F, Xu H, Khanna S, Tariq R, Friedman-Moraco RJ, Woodworth MH, Dhere T, Kraft CS, Kao D, Smith J, Le L, El-Nachef N, Kaur N, Kowsika S, Ehrlich A, Smith M, Safdar N, Ann Misch E, Allegretti JR, Flynn A, Kassam Z, Sharfuddin A, Vuppalanchi R, Fischer M. Fecal microbiota transplantation for the treatment of recurrent and severe Clostridium difficile infection in solid organ transplant recipients: A multicenter experience. Am J Transplant. 2018 Aug 7. doi: 10.1111/ajt.15058. [Epub ahead of print].

Evans S, Rubin DB, Powers JH, Follmann. Analysis Populations in Anti-Infective Clinical Trials: Whom to Analyze? Stat Commun Infect Dis. 2018. Doi:10.1515/scid-2017-0002. [Epub ahead of print].