

Welcome to the 2018 Q2 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](#)

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Multi-Drug Resistance Organism (MDRO) Network Global Investigator Meeting

On April 19-20, 2018, infectious disease (ID) physicians, microbiologists, pharmacists, principal investigators (PIs), and researchers from around the world participated in the CRACKLE II/ Multi-Drug Resistance Organism (MDRO) Network Program. The meeting in Madrid, Spain was the project's second international investigator meeting. The meeting included 49 attendees representing five continents, 18 of the 64 participating research sites, and 10 of the 12 collaborating countries.

MDRO NETWORK GLOBAL INVESTIGATOR MEETING

Madrid, Spain / April 19-20, 2018



Peggy Arias, ARLG project leader III, described the Network's [team science approach](#) to global data and isolate collection to study mechanisms of resistance. One of the Network goals is to build a scientific community, made up of highly productive and skilled research sites, to conduct future interventional strategy trials. Highlights and perspectives from attendees are captured below.

"The investigator meeting in Madrid brought together a unique mix of ID physicians, microbiologists, pharmacists, and clinical trials specialists from five continents. All who attended had a common purpose — to improve the outcome of patients infected with carbapenem-resistant Enterobacteriaceae (CRE). It was unanimously agreed that the CRACKLE II/MDRO program provides the opportunity to fulfill this purpose and to improve understanding of the epidemiology and treatment of CRE infections."

Dr. David Paterson (CRACKLE II Asia-Pacific Regional Coordinating Center PI, Australia site investigator, MDRO Network Publications Committee member)

"It was a real pleasure and honor for me to attend the MDRO investigator meeting for two main reasons. First, I benefited as a project manager. This was a very well organized event that was successful in bringing together international attendees to exchange their diverse experience and challenges with MDRO. The Duke Clinical Research Institute (DCRI) team managed to create a warm atmosphere that embraced a high-level scientific event! Second, I benefited as a scientist. The DCRI team engaged experts in brainstorming novel ideas for future landmark research studies. It was a unique experience for me to be in this expert panel!"

Maria Souli (ARLG project leader I)

"The CRACKLE II team is very grateful to our international collaborators for joining us during the investigator meeting in Madrid. The purpose of this meeting was to introduce the CRACKLE II study, learn from each other about global variability in the CRE epidemic, and to work together to evaluate ideas for future studies that will make use of the MDRO Network. It was a tremendously successful and also enjoyable meeting during which it was clear that antimicrobial resistance is a global problem that requires a global solution."

Dr. David van Duin (MDRO Network PI, U.S. site investigator, MDRO Network Publications Committee chair)



Dr. David van Duin speaking at the MDRO Network meeting

"The meeting is just an opening, which will lead us onto the new journey of global collaboration to resolve multidrug resistance. I feel the door is opened right in front of me, where I can see a great unobstructed view of

the bright future.”

Dr. Minggui Wang (CRACKLE II China Regional Coordinating Center PI, China site investigator, MDRO Network Publications Committee member)

“Participating in the ARLG investigator meeting in Madrid was an amazing experience for me and my team from Chile. It was an honor to attend a meeting with such a talented and experienced group of people. Seeing the level of commitment and energy of the team was a great way of boosting our own efforts to rise to the standards of the group. Organization of the meeting was impeccable!”

Dr. Jose Munita (Chile site investigator)

“The investigator meeting in Madrid this spring was an opportunity for investigators from around the world to meet face to face to share information about their local and regional antibacterial resistance patterns and the influencing factors. It was a great chance to learn from one another and discuss the design of clinical trials to better address antibacterial resistance.”

Dr. Robin Patel (MDRO Network Publications Committee member)

News and Upcoming Events

Congratulations to Dr. Marcus Zervos and his team at Henry Ford Health System for enrolling the first U.S. study participant in the [EVADE study](#) on March 22, 2018.

Duke Clinical Research Institute
Reception at IDWeek 2018

Save the Date



FRIDAY, OCTOBER 5, 2018

Please save the date to join your ARLG and DCRI colleagues for a private reception at IDWeek 2018 in San Francisco. More details will be shared in the coming months. While you are at the meeting, plan to stop by the DCRI booth (#501) to learn about the latest in fighting antibacterial resistance and advancing clinical research in infectious diseases.

 **Duke Clinical Research Institute** | **INFECTIOUS DISEASES**

Are you presenting an ARLG study at IDWeek or an upcoming conference? Let us know!

[Contact Us](#)

Be sure to check out our next newsletter for more details about events and ARLG meetings at [IDWeek2018!](#)

The [ARLG Mentoring Program](#) aims to train the next generation of researchers who will help support the mission of ARLG to reduce the public health threat of antibacterial resistance. In this issue, we speak with the program lead, Anthony Harris, MD, MPH, from the University of Maryland School of Medicine. Here are his thoughts on the ARLG Mentoring Program and how he sees it growing in the future.

The Mentoring Program has two funded opportunities: 1) [ARLG Fellowship](#) and 2) [ARLG Early Stage Investigator \(ESI\) Seed Grant](#). The ARLG Fellowship provides a two-year, fully funded, competitive opportunity to acquire expertise in clinical research. The ESI Seed Grant provides funds to researchers of all levels (MD, PhD, or Pharm D students, graduate or post-graduate trainees, or individuals with a faculty appointment for < 5 years) to work with a mentor on antibacterial resistance research that will hopefully lead to additional external funding. These opportunities provide guidance by established expert mentors in antibacterial resistance, training in research core competencies, and mentoring on specific research projects focused on antibacterial resistance.

We are very proud of how successful these two award programs have been. Since 2013, we have:

- *Provided seven ESI grants and five ARLG fellowships*
- *Mentored 35 individuals on ARLG projects*
- *Seen 12 peer-reviewed articles authored by our ESI mentees published in high-impact journals*
- *Seen nine peer-reviewed articles authored by our ARLG fellows published in high-impact journals*
- *Supported the publication of 43 additional manuscripts with ARLG mentees as authors*



Many of the mentees have used the ARLG funding as a launch point to subsequent successful funding. Thus, we believe the program has been successful at jump-starting young investigators on careers in antibacterial resistance research. All of the mentees are still pursuing academic careers focused on antibacterial resistance.

In the future, the goals of the program include continuing to grow the number of mentees and improving all aspects of the mentoring program via feedback and lessons learned.

Read on for spotlights on the great work of three of our award recipients!



**Post-Doctoral Fellow and Attending Physician
ARLG Research Fellow
Division of Infectious Diseases, University of
Pennsylvania Perelman School of Medicine**

About My ARLG Research Fellowship

I was awarded the ARLG Fellowship to study multidrug-resistant Gram-negative infections among solid-organ transplant recipients. More specifically, I am evaluating the clinical and molecular epidemiology of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae bloodstream infections among solid-organ transplant recipients. Solid-organ transplant recipients are particularly vulnerable to infection and can be the “canary in the coal mine” when new drug-resistant organisms are emerging. As a result, they represent an important piece of the global antimicrobial resistance puzzle. In order to minimize the morbidity and mortality related to these bacterial infections, it is important to study their clinical and molecular epidemiology. I have chosen to focus on ESBL-producing Enterobacteriaceae infections because they are the most common type of multidrug-resistant Gram-negative infections. I have chosen to focus on bloodstream infections, since they are arguably the most serious type of bacterial infection faced by this population.

Progress to Date

We have completed data collection at the Hospital of the University of Pennsylvania and continue to collect data from solid-organ transplant recipients at Johns Hopkins Hospital and the University of Maryland Medical Center.

Thus far, we have learned that among solid-organ transplant recipients who develop an Enterobacteriaceae bloodstream infection:

- Approximately 18 percent of infections are due to an ESBL-producing organism, and about 6 percent are due to carbapenem-resistant organisms.
- Outcomes are significantly worse for those recipients who develop an ESBL-producing or carbapenem-resistant Enterobacteriaceae bloodstream infection than those patients who have more susceptible infections.

Impact of ARLG Research Funding to My Career

Not only has this funding allowed me to develop a new line of research focused on multidrug-resistant bacterial infections among solid-organ transplant recipients, but it has also provided protected research time. This allows me time in my post-doctoral fellowship to collect data that will be used for an NIH K application submission. Exposure to ARLG leadership and the large-scale studies that they are performing has also provided me with an important education in the design and implementation of rigorous clinical trials and epidemiological studies. I have developed new mentorship relationships in the process that have cemented my interest in continuing to study antimicrobial resistance among immunocompromised hosts in the future.

Benefits of ARLG

ARLG is not merely a funding mechanism for research in antimicrobial resistance; rather, it is a community of scientists who ardently pursue improved human health through a better understanding of the optimal prevention, detection, and management of antimicrobial resistance. This community is the most valuable asset of the ARLG enterprise.

Michael A. Liss, MD, MAS, FACS
Assistant Professor of Urology
University of Texas Health San
Antonio
Principal Investigator, Micro-FIRE
(Microbiome of Fluoroquinolone Resistant
***E. coli*)**



About My ESI Grant

MY ESI grant supports Micro-FIRE. In this study, we are investigating the microbiome in men who harbor fluoroquinolone-resistant (FQR) *E. coli* compared to those who do not harbor the organism. FQR *E. coli* is the main cause of transrectal ultrasound-guided prostate biopsy needle infections.

Nearly one million biopsies are performed each year to diagnose prostate cancer, and sepsis rates have been steadily rising. We hope to understand the associated microbiome in this environment to identify pre/probiotics or other drugs to “decolonize” these men prior to prostate biopsy to reduce infection without increasing the use of antibiotics for prophylaxis.

Although, we are investigating specifically FQR *E. coli* as applied to prostate biopsy infection, this research could also be applied to recurrent urinary tract infections.

Along with ARLG, we are concerned that more antibiotics will be used to prevent infection, leading to more resistance. We are seeking means to reduce infections by understanding the surrounding microenvironment.

Progress to Date

We have enrolled 100 men prior to prostate biopsy and have found that there is a significant *E. coli* overgrowth in general. There are obvious changes in those carriers vs. non-carriers. We have also identified several bacteria that are lacking from carriers that should be repopulated in future studies. We are now conducting further research to identify specific *E. coli* sequence types that may be targeted.

What we have learned so far is that men colonized with FQR bacteria have:

- Less diverse bacterial communities (dysbiosis)
- Higher levels of Enterobacteriaceae
- Reduced levels of *Prevotella disiens*

Impact of ARLG Research Funding to My Career

Receipt of this grant from ARLG has had a positive impact on my career and future work in the following ways:

- I received an R03 grant from NIH AHRQ to study biopsy infection prevention with rapid diagnostics.
- I am writing a related grant to ARLG to target decolonization of these bacteria and also a separate antibiotic stewardship project.
- I joined our Veterans Affairs (VA) Antibiotic Subcommittee in charge of antibiotic resistance and stewardship and serve on the Quality Improvement Patient Safety Committee for the American Urologic Association.

Benefits of ARLG

ARLG not only provides a jump start to your funding but also opportunities to be paired

with leaders in the field. This is especially helpful for someone like me who has a urology background. ARLG mentors and staff have been a phenomenal group to work with; I very much appreciate their efforts to help me along my career path.



Jose M. Munita, MD
Associate Professor, Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

Adjunct Assistant Professor and Director of International Research, Center for Antimicrobial Resistance and Microbial Genomics (CARMiG), UTHealth, Houston, TX

Principal Investigator, VENOUS
(Vancomycin-resistant ENterococcus OUtcomes Study)

About My ESI Grant

My ESI grant supports VENOUS, which is a prospective, multi-site observational cohort study to evaluate the outcomes of patients with bloodstream infections due to vancomycin-resistant enterococci (VRE). In addition, parallel collection of clinical isolates is underway with the idea of identifying genomic microbial determinants of outcomes in this population of patients.

The main goal of VENOUS is to answer critical gaps of knowledge regarding the clinical and microbial factors determining the outcomes of VRE bacteremia and the best therapeutic approaches to deal with these multidrug-resistant organisms.

Clinicians have limited options to treat deep-seated VRE infections due to the lack of quality data. Through VENOUS we expect to fill a long-lasting void of good-quality data, providing prospective information about clinical outcomes and their relationship with the genomic bacterial background. This information will help us better understand what determining factors are involved in a patient's response to antibiotic treatment.

Enterococci is the third most common bacteria responsible for hospital-acquired infections in the United States, and the presence of VRE is strongly associated with worse clinical outcomes when compared with susceptible strains. Moreover, VRE has been highlighted as one of the top antimicrobial-resistant organisms by agencies such as the Centers for Disease Control and Prevention and the World Health Organization. Hence, this study is well aligned with ARLG's scientific agenda to reduce the public health threat of antibacterial resistance.

Progress to Date

We have enrolled 282 of an expected 300 patients from three large academic centers, including a major cancer center. We speculate that results will show that individuals with VRE bacteremia will have worse outcomes than those infected with susceptible organisms. In addition, we expect to find signals to better understand the best therapeutic approach to deal with VRE infections.

Impact of ARLG Research Funding to My Career

Receipt of this grant has been an enormous opportunity for me to lead a study as a principal investigator. I work closely with my mentor at University of Texas at Houston, Cesar Arias, who has supported me a great deal. Having Dr. Arias as my mentor has definitely been a tremendous opportunity and a distinct honor. I am also very

appreciative for the support and guidance from many others at ARLG, which has been another highlight of receiving this ESI award. Finally, working with the whole DCRI ARLG operations team has taught me many critical aspects about grant management, and I am deeply grateful for their relentless support.

Working on this seed grant has opened other doors for me. I am now the country PI for Chile on the CRACKLE II study.

Benefits of ARLG

For individuals interested in advancing their career in antimicrobial resistance, I would definitely encourage them to get involved with ARLG or apply for an ESI grant. For me, receipt of the ESI award was an unparalleled opportunity to propel my career. Everyone I have interacted with has been enormously knowledgeable, professional, stimulating, and welcoming. The work ARLG is doing today will have a tremendous impact on the way we approach the study of antimicrobial resistance, and being part of it is definitely very exciting.

Awards and Achievements



**Souha Kanj, MD,
FACP, FIDSA,
FRCP, FESCM,
FECMM
Abdul Hameed
Shoman Award for
Arab Researchers**

Souha Kanj of the American University of Beirut Medical Center (AUBMC)

received the Abdul Hameed Shoman Award for Arab Researchers for her outstanding research in the medical and health sciences category. Presented annually for the last 35 years, this award honors outstanding Arab men and women conducting scientific research in order to encourage young researchers. Dr. Kanj was selected out of more than 150 nominations in the medical and health sciences categories. A recognized expert in the field of infectious diseases, Dr. Kanj's main research focus is concentrated on hospital-acquired infection and antimicrobial resistance. Under her leadership, the AUBMC implemented a state-of-the-art Infection Control and Prevention Program operating in accordance with international standards. Read [more](#) about Dr. Kanj and this award.



**Robert A.
Bonomo, MD
2017 Middleton
Award**

Robert A. Bonomo, MD, of the Louis Stokes Cleveland VA Medical Center, was the recipient of the 2017 Middleton Award in recognition of his contributions

to the epidemiology, pathogenesis, diagnosis, prevention, and treatment of multidrug-resistant infections. Dr. Bonomo is a nationally and internationally recognized expert in the field of antibiotic resistance research. The Middleton Award is the highest honor awarded annually by the Biomedical Laboratory Research and Development Service to senior VA scientists in recognition of their outstanding scientific contributions and achievements in the areas of biomedical and bio-behavioral research relevant to the health care of veterans. The award was established in 1960 to honor William S. Middleton, MD, a distinguished educator, physician-scientist, and Department of VA chief medical director from 1955 to 1963. Read more about Dr. Bonomo and this award [here](#).

Recent Presentations

June 8, 2018: RAPIDS-GN abstract presentation at American Society for Microbiology (ASM) Microbe. Banerjee R, Dylla B, Schuetz A, Kohner P, Ihde S, Cole N, Hines L, Reed K, Rajapakse N, Virk A, Doernberg S, Finnemeyer M, Komarow L, Lok J, Patel R. Accelerate Pheno System (AXDX) performance during a randomized clinical trial

evaluating rapid identification and antimicrobial susceptibility testing for Gram negative bacteremia (RAPIDS-GN). American Society for Microbiology (ASM) Microbe, June 7-11, 2018, Atlanta, Georgia.

May 1, 2018: [Grand Rounds presentation](#) at University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, Department of Medicine, on “Antimicrobial Resistance Leadership Group (ARLG): What Has Been Accomplished” by Robert Bonomo, MD.



Recent Publications

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

Wenzler E , Bleasdale SC , Sikka M, Bunnell KL, Finnemeyer M, Rosenkranz SL , Danziger LH, Rodvold KA for the 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 (PROOF)**. Antimicrob Agents Chemother. Published [Online](#): June 11, 2018. doi:10.1128/AAC.00464.

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 Duijn 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;91(1):89-92.

Papp-Wallace KM, Barnes MD, Alsop J, Taracila MA, Bethel CR, Becka SA, van Duijn D, Kreiswirth BN, Kaye KS, Bonomo RA. **Relebactam is a Potent Inhibitor of the KPC-2 β -Lactamase and Restores the Susceptibility of Imipenem Against KPC-Producing Enterobacteriaceae**. Antimicrob Agents Chemother. 2018;62(6):69. pii:e00174-18. doi:10.1128/AAC.00174-18.
