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The Antibacterial Resistance Leadership Group: Progress Report and Work in Progress

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The Antibacterial Resistance Leadership Group (ARLG), with funding from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, was created in June 2013. Its mission is to develop, prioritize, and implement a clinical research agenda that addresses the public health threat of antibacterial resistance. This article reports on the progress that the ARLG has made to date in fulfilling its mission. Since inception, the ARLG has received and reviewed >70 study proposals, initiated >30 studies, executed >300 agreements, included data from >7000 subjects, published >45 manuscripts, and provided opportunities for 26 mentees. Despite this substantial progress, there remains significant work to be accomplished. This article also describes the considerable challenges that lie ahead.

    Keywords. antibacterial resistance; network; stewardship; diagnostics; clinical trials.

The mission of the Antibacterial Resistance Leadership Group (ARLG) is to prioritize, design, and execute clinical research that will reduce the public health threat of antibacterial resistance (see http://www.arlg.org/). The ARLG focuses its efforts on 4 areas of greatest unmet need: (1) infections caused by gram-negative bacteria; (2) infections caused by gram-positive bacteria; (3) antimicrobial stewardship and infection prevention; and (4) diagnostics. The decision to pursue a project in these priority areas begins with the solicitation, review, approval, and preliminary development of clinical research projects, both interventional and observational. The ARLG also has allocated funds to support, mentor, and train the next generation of clinical investigators to meet future manpower needs in the area of clinical research in antibacterial resistance [1]. It has invested in innovative technologies and approaches for diagnosing infections and for detection of resistance to better inform use of antimicrobial therapies. Last, the ARLG has developed a number of innovative approaches to clinical trials, including adaptive design strategies to optimize enrollment in therapeutic trials, master diagnostic protocols to simultaneously evaluate more than one diagnostic test using specimens from a single patient, and novel trial designs to increase clinical trial efficiencies and to enable use of superiority trial designs.

ORGANIZATION

The organization of the ARLG is shown in Figure 1 [1–7]. To accomplish its research agenda and meet its goals, the ARLG works closely with the National Institute of Allergy and Infectious Diseases (NIAID). The ARLG Executive Committee provides overall guidance and direction to the enterprise and is responsible for high-level scientific and management decisions, establishing the research agenda, and approving and funding studies for development and implementation. The Executive Committee receives scientific input from the Steering Committee, whose primary role is to review and prioritize the >70 study proposals that have been received to date. The Executive Committee also coordinates the activities of the Statistical and Data Management Center [2], the Laboratory Center [3], and the Leadership and Operations Center [1], which together provide the critical infrastructure and operational expertise required for a successful clinical research enterprise.

    Essential to the work of the ARLG are panels of experts corresponding to each of the 4 prioritized research areas: the Gram-Negative Committee [4], the Gram-Positive Committee [5], the Stewardship and Infection Control Committee [6], and the Diagnostics and Devices Committee [7]. Three special emphasis panels provide expertise in topics that may involve more than one of the prioritized research areas: Special Populations, Pharmacokinetics, and Pediatrics. The ARLG has also engaged the broader scientific community and industry partners to

National Institute of Allergy and Infectious Diseases (NIAID)

Leadership and Operations Center (LOC)
Principal Investigator – Vance Fowler, MD, MHS, Duke University
Principal Investigator – Henry Chambers, MD, UCSF
Program Leader – Heather Cross, DPhil, Duke University

Statistical and Data Management Center (SDMC)
Director – Scott Evans, PhD, Harvard University
Program Manager – Jacqueline Huvane, PhD, Duke University

Laboratory Center (LC)
Director (Gram-positive) – Barry Kreiswirth, PhD, Rutgers University
Director (Gram-negative) - Robert Bonomo, MD, Case Western
Director (Diagnostics) - Robin Patel, MD, Mayo Clinic

EXECUTIVE COMMITTEE
Chair – Vance Fowler, MD, MHS, Duke University

Mentoring Committee
Chair – Anthony Harris, MD, MPH, U. Maryland

STEERING COMMITTEE
Chair – Henry Chambers, MD, UCSF

SCIENTIFIC COMMITTEES

Gram-Positive
Chair – Loren Miller, MD, MPH
UCLA

Gram-Negative
Chair – Yohei Doi, MD, PhD
U. Pittsburgh

Stewardship
Chair – Dev Anderson, MD, MPH
Duke University

Diagnostics
Chair – Kim Hanson, MD, MHS
U. Utah

SPECIAL EMPHASIS PANELS

Special Populations
Chair – Melinda Pettigrew, MD
Yale University

Pharmacokinetics
Chair – Thomas Lodise, PharmD
Albany College of Pharmacy

Pediatrics
Chair – Theoklis Zaoutis, MD
CHOP
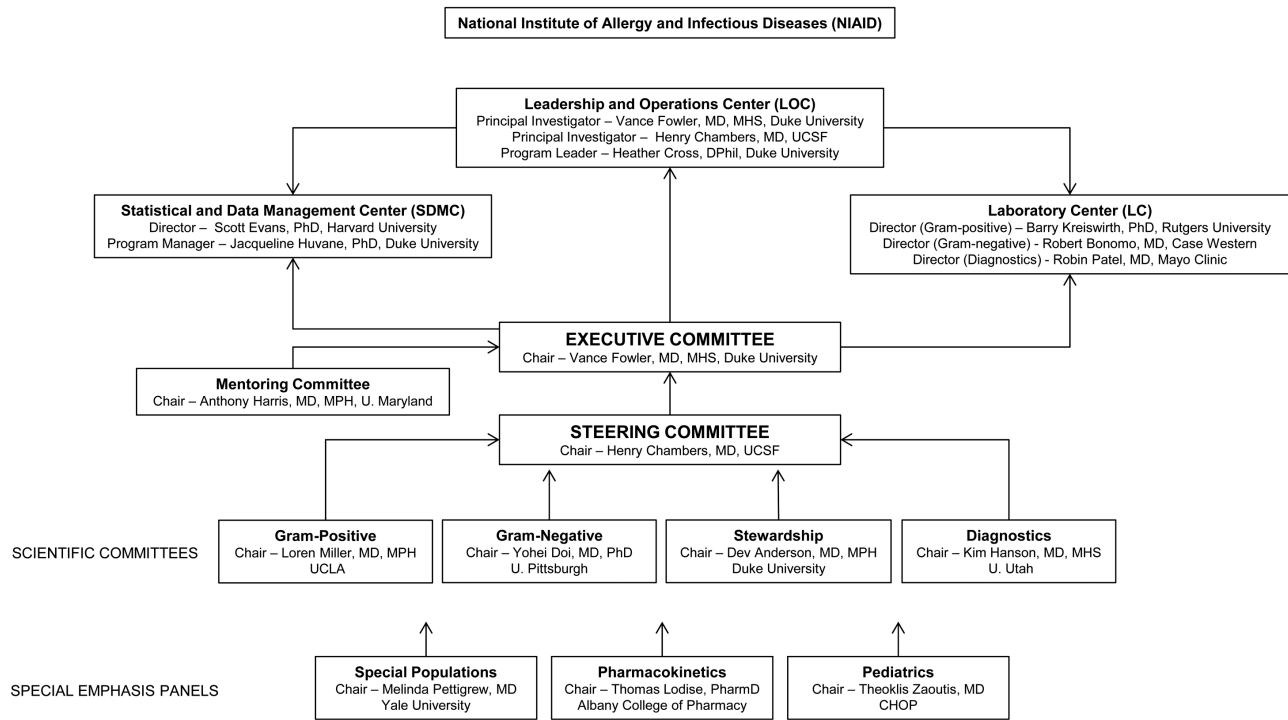
Figure 1. The Antibacterial Resistance Leadership Group (ARLG) works under the centralized leadership of an Executive Committee and 2 Principal Investigators (PIs). One PI, Dr Vance Fowler, Duke University, focuses primarily on operations and the other, Dr Henry "Chip" Chambers, University of California, San Francisco, focuses largely on the scientific agenda. The ARLG has 3 separate component centers: (1) Leadership and Operations Center (LOC) [1], coordinated by Dr Heather Cross, ARLG Program Leader, Duke University; (2) Statistical and Data Management Center (SDMC) [2], directed by Dr Scott Evans, Harvard University; (3) Laboratory Center (LC) [3], led by Dr Barry Kreiswirth, Public Health Research Institute/Rutgers University. The organizational structure features internationally recognized leaders in the field appointed to Scientific Committees, Special Emphasis Panels, and a Mentoring Committee, which are devoted to priority areas, including gram-negative bacterial infections [4], gram-positive bacterial infections [5], antimicrobial stewardship and infection prevention [6], and diagnostics and devices [7].

advance its clinical research agenda. The ARLG's research takes place in a variety of settings including universities and affiliated medical centers, community hospitals, outpatient clinics, the ARLG site network, and sites accessed through the NIAID-funded Vaccine and Treatment Evaluation Units. The fruits of this endeavor and specific accomplishments are summarized below and in other publications [1–7]. A current list of publications can be found on the ARLG website.

ACCOMPLISHMENTS AND OPPORTUNITIES

The ARLG has made considerable progress toward accomplishing its research goals (Table 1). Infections caused by drug-resistant gram-negative bacteria pose the greatest and most immediate public health threat and challenge. Accordingly, the ARLG has funded several observational cohort studies to better understand the magnitude of the problem [4]. Foremost among these is CRACKLE (Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae). CRACKLE is a prospective, multicenter cohort study designed to characterize the risk factors for and outcomes of infections caused by carbapenem-resistant Enterobacteriaceae (CRE) and to identify barriers to enrollment that will inform future clinical trials. Initially confined to the Eastern and Midwestern United States, the cohort has been expanded to sites throughout the United States and South America, and efforts are underway to include sites in Asia. To date, >1000 patients with CRE infection or colonization have been enrolled, >700 bacterial isolates have

Table 1. Antibacterial Resistance Leadership Group Accomplishments

Research Area	Projects (Active or Completed)	Manuscripts	Investigators/Institutions	Trainees
Gram-negative	15	17	>40	8
Gram-positive	4	8	>20	6
Stewardship	3	2	>10	5
Diagnostics	12	8	>10	7
Other		10		

been cataloged, and 12 original peer-reviewed manuscripts have been published [4]. CRACKLE promises to be a valuable resource for future pathogen-directed clinical trials, and it has already attracted the interest of potential industry partners. Other observational cohorts established by the ARLG include organ transplant patients infected or colonized by multidrug-resistant gram-negative bacteria, and patients with infections due to *Pseudomonas* and *Acinetobacter* [4].

Simultaneously, several interventional studies have been completed or are in advanced stages of planning. To address the problem of limited treatment options for drug-resistant gram-negative bacteria, the ARLG has focused on repurposing existing antibiotics by supporting clinical trials that inform their use in new ways [4]. This strategy can expedite the identification of new treatment options for gram-negative bacterial infections, and it supports studies that can inform clinical practice but would generally not be funded otherwise. The ARLG has undertaken development of fosfomycin tromethamine (Monurol) as an oral step-down therapy for complicated urinary tract infections [4]. Enrollment for a phase 1 pharmacokinetic study (Pharmacokinetics, Pharmacodynamics, and Safety/Tolerability of Two Dosing Regimens of Oral Fosfomycin Tromethamine in Healthy Adult Participants [PROOF]) to inform the dose of fosfomycin to be used in the step-down therapy trial has been completed. Results will be available in early 2017, and the randomized clinical trial is planned to follow shortly thereafter. The ARLG is also designing additional pharmacokinetic studies for a broad-spectrum tetracycline, which has efficacy against drug-resistant *Acinetobacter*, in patients with known or suspected gram-negative infections in the intensive care unit [4].

With respect to gram-positive infections, the ARLG designed, funded, and completed a prospective multicenter study to define the pharmacodynamic driver and predictor of outcome in 310 patients with methicillin-resistant *Staphylococcus aureus* bloodstream infections (BSIs) treated with vancomycin [5]. This study has completed enrollment, and results will be available in the coming months. The study has several advantages over others in this area because of its prospective and multicenter design, inclusive enrollment, validated sampling strategy, sample size, and rigorous vancomycin susceptibility determinations. The ARLG is also developing innovative approaches for assessing and ranking patient outcome in interventional studies of *S. aureus* BSI by applying global outcome measures that are specific to this infectious syndrome in order to classify patients based on outcome rather than the traditional approach of using individual patients to classify discrete outcomes. This methodology improves clinical trials efficiencies and enables use of a superiority trial design [8]. The ARLG has also funded an observational study of daptomycin for treatment of immunocompromised patients with infections caused by vancomycin-resistant enterococci [5].

The ARLG has funded or is developing several initiatives in the vital area of antimicrobial stewardship [6]. A study of stewardship program implementation and effectiveness in the community hospital setting (Duke Infection Control Outreach Network [DICON]) has completed data accrual and is undergoing analysis. A randomized controlled trial of short-course (5-day) vs standard (10-day) oral antimicrobial therapy for community-acquired pneumonia in children treated as outpatients (Short-Course Therapy in Pediatric Community-Acquired Pneumonia [SCOUT-CAP]) has also been initiated. In addition, a trial of rapid blood-culture identification of pathogens and a strategy trial of use of procalcitonin to identify patients with lower respiratory tract infections who do not need antibacterial therapy are in the late planning stages. A major goal of both of these studies is to define parameters by which overall antibiotic usage can be reduced while preserving good clinical outcomes.

Rapid and point-of-care diagnostics hold great promise for diagnosis and treatment of infectious diseases. The ARLG has developed several important programs and projects in this area. The Laboratory Center has established repositories of curated and annotated bacterial isolates [3]. These are available to approved individual investigators and industry representatives, and they constitute a valuable resource for in vitro and in vivo studies of new compounds and diagnostic tests. The PRIMERS (Platforms for Rapid Identification of Multidrug-Resistant Gram-Negative Bacteria and Evaluation of Resistance Studies) [9] have elucidated both the potential and the limitations of molecular diagnostics for identification of resistant pathogens and have demonstrated the importance of the interpretative framework and local prevalence in communicating these results. The ARLG designed MASTERMIND (Master Protocol for Evaluating Multiple Infection Diagnostics) [10] with elements of adaptive trial design to assess and compare sensitivities and specificities of molecular diagnostics [7].

Perhaps most exciting is a proof-of-principle study, RADICAL (Rapid Diagnostics in Categorizing Acute Lung Infections) that will evaluate the utility of host genome expression signatures [11] to distinguish viral from bacterial lower respiratory infections (and possibly noninfectious process as well). The near-term goal of this study is to develop and validate a point-of-care test platform that can be deployed in the clinic to improve diagnostic accuracy, and ultimately treatment, of one of the most common infections encountered in clinical practice. The longer-term goal is to improve antibiotic utilization and patient outcomes.

Particularly rewarding for the ARLG as it has matured is the development of public–private partnerships and the interest shown by industry in working with the ARLG to design innovative trials that have the promise of transforming the field. The strong support of the NIAID, recognition by the general public and the government that antibacterial resistance poses a major

medical threat, renewed interest of industry in antibacterial diagnostics and therapeutics, and availability of new funds to support much-needed research and clinical trials makes this a hopeful and exciting time for the field.

FUTURE CHALLENGES

There are signs of progress in meeting the challenge of antibiotic resistance, which is encouraging. Companies are again showing cautious interest in antibiotic development. Two new antibiotics active against drug-resistant gram-negative bacteria, ceftolozane-tazobactam and ceftazidime-avibactam, have been approved by the US Food and Drug Administration, and others are in the pipeline. The federal government has increased funding for clinical research aligned with the National Action Plan on Combating Antibiotic-Resistant Bacteria, including efforts supported by BARDA (Biomedical Advanced Research and Development Authority) and the ARLG. Antibacterial stewardship has gained the attention of the Centers for Medicare and Medicaid Services, which has mandated its incorporation into the hospital setting. New technologies, such as MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry), next-generation sequencing, and culture-independent methods of pathogen identification, could change how infectious diseases are diagnosed and treated and could enable development of pathogen-specific, targeted therapy.

More needs to be done. A hard look at the regulatory environment and approval process for antibiotics and diagnostics is warranted. How clinical trials are designed and conducted is a critical part of this process. Innovative trial designs could improve efficiencies and enrollment of relevant patient populations and overall study quality with respect to clinically meaningful outcomes.

Compared with other drug classes, antibiotics offer a poor return on investment, and a purely market-based approach (the failure of which contributed to the present predicament) is unlikely to be enough. An ongoing commitment for drug discovery and development will be needed in the United States and globally [12].

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APPENDIX

Antibacterial Resistance Leadership Group (*denotes former member). Executive Committee: John Bartlett, MD; Henry "Chip" Chambers, MD; Heather Cross, DPhil; Dennis Dixon, PhD; Scott Evans, PhD; Vance Fowler, MD, MHS; Richard Gorman, MD; Anthony Harris, MD, MPH; Jane Knisely, PhD; Barry Kreiswirth, PhD; Marina Lee, PhD; Baoying Liu, MD,