Antibacterial Resistance Leadership Group (ARLG)

January 2016
Stockholm, Sweden

Principal Investigators:
Henry Chambers, MD  Vance Fowler, Jr, MD, MHS
## Disclosures

<table>
<thead>
<tr>
<th>Nature of Relevant Financial Relationship</th>
<th>Commercial Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant or research support</td>
<td>Cerexa, Pfizer, Advanced Liquid Logics, NIH, MedImmune, Cubist; NIH STTR grants pending: Affinergy; Locus, Medical Surface, Inc.</td>
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<td>Paid consultant</td>
<td>Astellas, Bayer, Merck, Medicines Company, Debiopharm, Durata, Achaogen, Biosynexus, MedImmune, Pfizer, Novartis, Galderma, Cerexa, Cubist; Genentech; Basilea; Theravance</td>
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<td>Speaker’s Bureau</td>
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<td>Employment</td>
<td>Duke University</td>
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<tr>
<td>Honoraria</td>
<td>Theravance; Green Cross</td>
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<tr>
<td>Membership on advisory committees or review panels, board membership,</td>
<td>Chair- Merck V710 Advisory Board Committee</td>
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<tr>
<td>Ownership Interest (e.g., stocks, stock options or other interests</td>
<td>NONE</td>
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<tr>
<td>Other relevant financial interests</td>
<td>Patent pending in sepsis diagnostic</td>
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</table>
What is the ARLG?

- **Mechanism**: *Grant from NIAID*

- **Duration**: 6.5y

- **Value**: - $62 million Grant support
  - Up to $45 million in kind support from NIAID
  - Supplements

- **Start Date**: *June 2013*
ARLG Mission Statement

“To prioritize, design, and execute clinical research that will reduce the public health threat of antibacterial resistance”
“Leverage existing partnerships, such as the NIH Antibacterial Resistance Leadership Group….to reduce obstacles faced by pharmaceutical companies”

“expand and strengthen the ARLG network”

“NIH will arrange for clinical trials networks such as the Antibacterial Resistance Leadership Group (ARLG), to test a Gram-negative therapeutic agent”
FACT SHEET: President’s 2016 Budget Proposes Historic Investment to Combat Antibiotic-Resistant Bacteria to Protect Public Health

“We now have a national strategy to combat antibiotic-resistant bacteria, to better protect our children and grandchildren from the reemergence of diseases and infections that the world conquered decades ago.”

— President Barack Obama’s remarks at the Global Health Security Agenda Summit, regarding the Executive Order to Combat Antibiotic Resistance, September 26, 2014

“Fourth, NIH will expand its Antibiotic Resistance Leadership Group to create a rapid response clinical trial network that is ready to test new antibiotics on individuals infected with highly resistant strains. The request includes $461 million, an increase of $100 million in FY 2016 to support the National Strategy.”
Research Agenda Priorities

<table>
<thead>
<tr>
<th>Significance</th>
<th>Long-Term Objectives</th>
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<tbody>
<tr>
<td>MDR Gram-negative Bacilli</td>
<td>Identify and design transformational clinical trials to improve outcomes of MDR-GNB infections and to minimize opportunities for further resistance</td>
</tr>
<tr>
<td>Antimicrobial Stewardship</td>
<td>Identify and develop institutional and provider-based strategies to reduce the use and environmental impact of antibacterials, and thus selective pressure for antibacterial resistance</td>
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<tr>
<td>MDR Gram-positive Bacteria</td>
<td>Design and develop innovative observational and interventional projects to determine safety and effectiveness of directed therapy and to improve outcomes of Gram-positive infections</td>
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<tr>
<td>Diagnostics</td>
<td>Develop studies to validate diagnostics that will enable early identification of MDROs in clinical trials to improve outcomes and lower cost.</td>
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Subcommittees

- **Scientific Subcommittees**
  - Gram-negative: Yohei Doi
  - Gram-positive: Loren Miller
  - Stewardship: Deverick Anderson
  - Diagnostics: Melissa Miller

- **Special Emphasis Panels (SEPs)**
  - Pediatrics: Theo Zaoutis
  - Pharmacokinetics: Thomas Lodise
  - Special Populations: Melinda Pettigrew
PRODUCTIVITY
25 projects and counting since June 2013...

Gram-negative (10)
Gram-positive (3)
Stewardship (4)
Diagnostics (12)
ARLG Metrics: Proposals & Publications since 6/13

- **Concept Research Proposals**

<table>
<thead>
<tr>
<th>Received</th>
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<th>Approved</th>
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<tbody>
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- **Early Stage Investigator (ESI) Seed Grants**

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- **Abstracts**

<table>
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<th>Submitted</th>
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- **Manuscripts**

<table>
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<tr>
<th>In Progress</th>
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<tr>
<td>3</td>
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</table>
ARLG Metrics: Site Contracts since 6/13

- Confidentiality Agreements
  - 101 executed

- Subawards to performing sites
  - 89 executed

- Site Agreements
  - 18 executed

- Rapid Start Agreements
  - 10 new executed (130 pre-existing)
Gram Positive
PROVIDE – Lodise

- Prospective Observational Evaluation of the Association between Day 2 Vancomycin Exposure and Failure Rates in Adult Hospitalized Patients with MRSA Bloodstream Infections

- Goal to determine if vancomycin AUC/MIC is related to patient outcome in MRSA bacteremia
PROVIDE Patient Enrollment

PROVIDE - Actual vs. Planned Enrollment (Target: 310 pts)

Total start-up duration: 6.5 months

- Concept approval: May 6, 2014
- Protocol final: Aug 29, 2014
- Database live: Nov 21, 2014
- 1st pt enrolled: Dec 1, 2014
DOTS – Holland

- **Overview:**
  - Randomized, Open-label, Superiority Trial of Daptomycin with Oral Tedizolid Stepdown Versus Standard Intravenous Therapy for *Staphylococcus aureus* Bacteremia

- **Study design:**
  - 7/14 days i.v. then continue on i.v. or step down to 7/21 days oral tedizolid
  - Non-inferiority and DOOR outcomes
  - Goal – change practice; possibly seek label change
Gram Negative
PROOF - Rodvold

- Overview:
  - PK/PD and Safety/Tolerability of Three Dosing Regimens of Oral Fosfomycin Tromethamine in Healthy Adult Participants

- Goal:
  - Determine optimal dosing for the FOCUS study while establishing PK/PD and safety/tolerability data on oral fosfomycin

- Progress:
  - Protocol submitted to DMID 9/2/15
  - IRB Approval 12/23/15
  - Enrolling
FOCUS - Spellberg

- Overview:
  - Oral Fosfomycin as Step-down for Complicated UTI
- Goal:
  - Compare treatment success of fosfomycin vs. levofloxacin. If non-inferiority established, hierarchical superiority analysis performed
- Progress:
  - Protocol development and site identification
  - NICE - Novel Investigational Clinical Endpoint (NICE) substudy to assess efficacy, and composite efficacy / safety
  - PAD – PK study characterizing disposition of oral fosfomycin or levofloxacin in plasma / urine among a subset of FOCUS subjects
Stewardship
SCOUT-CAP – Huskins/Zaoutis

- Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course Outpatient Therapy of Oral Antibiotics vs. Placebo in Children with Community Acquired Pneumonia

- Compare overall outcome of children after 5 days vs. 10 days of antibiotic therapy in outpatient pediatric CAP

- Change treatment guidelines

- First study to utilize innovative DOOR trial design
Diagnostics
Host gene expression classifiers diagnose acute respiratory illness etiology

Ephraim L. Tsalik,1,2,3,× Ricardo Henao,1,4,× Marshall Nichols,1 Thomas Burke,1 Emily R. Ko,1,5 Micah T. McClain,1,3,6 Lori L. Hudson,1 Anna Mazur,1 Debra H. Freeman,1,3 Tim Veldman,1 Raymond J. Langley,7 Eugenia B. Quackenbush,8 Seth W. Glickman,8 Charles B. Cairns,8,9 Anja K. Jaehne,10 Emanuel P. Rivers,10 Ronny M. Otero,10 Aimee K. Zaas,1,3 Stephen F. Kingsmore,11 Joseph Lucas,1 Vance G. Fowler Jr.,3 Lawrence Carin,1,4 Geoffrey S. Ginsburg,1,† Christopher W. Woods1,3,6,†
Host Gene Expression Signature

- A host-based mRNA classifier for differentiating viral and bacterial etiologies of acute respiratory tract infection

- Develop and validate 2 platforms (TLDA, BioFire)

- Planned enrollment: **500 subjects**

- Completed 5 months ahead of schedule

- Destination: Clinical trial of antibiotic prescribing based on gene signature
RADICAL Patient Enrollment

RADICAL - Actual vs. Target Enrollment (Target: 500 pts. total)

Total start-up duration: 5 months

Concept Approval: May 6
IRB Approval: Sept 5
1st patient enrolled: Oct 1

Target enrollment: 500 pts. total

- Target enrollment
- Actual enrollment
Rapid Molecular Diagnostics, Antibiotic Treatment Decisions, and Developing Approaches to Inform Empiric Therapy: PRIMERS I and II

Scott R. Evans,1 Andrea M. Hujer,2,3 Hongyu Jiang,1 Kristine M. Hujer,2,3 Thomas Hall,4 Christine Marzan,6 Michael R. Jacobs,5 Rangarajan Sampath,4 David J. Ecker,4 Claudia Manca,6 Kalyan Chavda,6 Pan Zhang,7 Helen Fernandez,7 Liang Chen,6 Jose R. Mediavilla,6 Carol B. Hill,8 Federico Perez,2,3 Angela M. Caliendo,9 Vance G. Fowler Jr,8,10 Henry F. Chambers,11 Barry N. Kreiswirth,6 and Robert A. Bonomo2,3,12, for the Antibacterial Resistance Leadership Group

Platforms for Rapid Identification of MDR-GNB, An Evaluation of Resistance Study

Objective: Compare molecular platforms in discriminating between resistance vs. susceptibility of key antibiotics by identifying and genotyping \( \textit{bla} \) genes in genetically characterized MDR-GNB isolates

Key Results:
- Detecting R/S genotypes in \( \textit{E. coli} \) and \( \textit{K. pneumoniae} \) strains accurately predicts phenotype
- Informed decisions regarding the choice of \( \beta \)-lactam therapy depends upon the geographic prevalence of \( \textit{bla} \) resistance genes
- Genotypic analysis can provide the clinician with clinically relevant, actionable drug susceptibility profiles within hours
INNOVATION
Innovation: Scientific Resource
Virtual Biorepository of MDR Bacteria

Laboratory Center Mission: To facilitate and support the ARLG research agenda by leading the development, implementation, and evaluation of the laboratory research.

Virtual Biorepository Goal: To provide investigators with unique access to clinically well-characterized Gram positive and Gram negative bacteria for the development of diagnostic tests, novel antimicrobial compounds and for studies evaluating mechanisms of resistance.

Please visit the Virtual Biorepository section of the ARLG website for additional information on how to use the catalogue, submit strains, and obtain strains of interest.

ARLG - Antibacterial Resistance Leadership Group (https://arlg.org/)
Supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health (http://www.niaid.nih.gov/)
Award Number UM1AI104681
Contact the VB Catalogue Support Team ccri-arlg-vbadmin@mc.duke.edu
Innovation: Operations
Duke Clinical Research Institute (DCRI)

- Operations Center for ARLG
- World’s largest Academic Research Organization
- > 1.3 million patients enrolled to date
- > 37,000 sites in > 65 countries
- > 1,300 employees and 200 faculty
- > 1,000 phase I-IV clinical trials and other studies
- > 9,300 manuscripts in peer-reviewed journals
- Full service trial operations (data, stats, monitoring, etc)
Innovation: Operations
DCRI ARLG Rapid Start Network

- Flexible, on-demand agreements for each study
- 50 sites currently active on ARLG studies
- > 370 feasibility surveys completed by additional sites
- 140 rapid start master agreements executed
  - reduces start-up by 2 months
- ARLG studies have included: **7,406 subjects** to date
Innovation: Operations Networks & Collaborations

- CRE National Network (CRACKLE)
  - 27 sites in 16 states
  - Prospective enrollment of CRE & other MDR Gram-negatives

- Innovative Medicines Initiative (IMI)
  - HABP/VABP Natural History
  - Dually funded with FDA and IMI

- Arias Network (Colombia, Brazil, and Ecuador)
- Stryjewski Network (Argentina & Chile)
Innovation: Trial Analyses

Classifies patients according to totality of benefit & harm

Creation of an ordinal scale to assess outcome: desirability of overall outcome response (DOOR)

Avoids non-inferiority design, smaller sample sizes

Higher ranks for patients:
- Patients with better overall clinical outcomes
- Oral > IV or shorter > longer treatment for same DOOR
### A simple example of DOOR

<table>
<thead>
<tr>
<th>Rank</th>
<th>Survival</th>
<th>SAE</th>
<th>Rx Strategy</th>
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<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>PO (or 5d)</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>IV (or 10d)</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>PO (or 5d)</td>
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<tr>
<td>5</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
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Example: ARLG SCOUT-CAP

- RCT comparing 5-day vs. standard 10-day course of outpatient antibiotics in children with community-acquired pneumonia (CAP)

- Original design
  - Debate over appropriate NI margin
  - Questionable feasibility w/ N=800 required for 90% power

- RADAR design
  - Superiority trial
  - N=360 (>50% reduction in the required N)
Innovation: Trial Design
ARLG Master Diagnostic Protocol

- **Idea:** 1 patient informs >1 diagnostic platform
- **Example:** No FDA approved diagnostic for Extra-Genital Gonorrhea
- **Approach:** 1 trial to simultaneously support FDA registration submissions for 3 diagnostic companies
Innovation: Trial Design  
ARLG Platform trial work (ADAPT)

- Working group developing platform trial for multiple drugs, targeting resistant pathogens at multiple sites
- Utilizes adaptive technology/methods from ISPY2, IMI-EPAD, PREPARE, and GBM-AGILE
- Participation from industry, academics, statistical consultants
- Allows estimates of treatment benefit by body site and/or resistance profile of pathogen

<table>
<thead>
<tr>
<th>Body Site</th>
<th>Level of Resistance</th>
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<tr>
<td></td>
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<tr>
<td>Drug A</td>
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<tr>
<td>Drug B</td>
<td></td>
</tr>
<tr>
<td>Drug C</td>
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Integrated Model for Statistical Inference
ARLG

- Productive
- Innovative
- Open for Business