Virtual Research Week Symposium
May 20, 2022
Recognizing the Magnuson, Barnwell, Under Secretary’s, and Middleton Awardees
Shakeria Cohen, Ph.D.
Program Manager, Military Exposures, Nephrology, & Pulmonology
VA Biomedical Laboratory Research & Development
Washington, D.C.
Dr. Rachel B. Ramoni
Chief Research &
Development Officer
VA Office of Research
& Development
Washington, D.C.
Dr. Carolyn M. Clancy
Assistant Under Secretary of Health
Discovery, Education & Affiliate Networks
Washington, D.C.
The Paul B. Magnuson Award
Dr. Patricia A. Dorn, Director
VA Rehabilitation Research & Development
Dr. Leigh Hochberg
The Paul B. Magnuson Award
Director, VA Center for Neurorestoration and Neurotechnology
Providence, Rhode Island
BrainGate: Toward the Restoration of Communication and Mobility

Leigh R. Hochberg, MD, PhD, FAAN, FANA

VA RR&D Center for Neurorestoration and Neurotechnology (CfNN)
Department of Veterans Affairs, VA Providence Healthcare

School of Engineering and Carney Institute for Brain Science, Brown University

Center for Neurotechnology and Neurorecovery, Neurocritical Care and Stroke Services, Department of Neurology, Massachusetts General Hospital, Harvard Medical School
Disclosures

Financial:
None. (US Patent 10,448,877 – potential COI if licensed)

Research support:
Rehabilitation R&D | ORD | U.S. Department of Veterans Affairs
NIH | National Institute on Deafness and Other Communication Disorders

*BRAIN Initiative | National Institute of Neurological Diseases and Stroke
Cullen Education and Research Foundation Prize
ALS Association

*CAUTION: Investigational device. Limited by Federal law to investigational use.
BrainGate: Simple goals (mission statements)

ALS: You will *never* lose the ability to communicate.

Brainstem stroke/LIS: You will communicate easily again, *tomorrow*.

Spinal cord injury/Stroke: You will be able to move again, *tomorrow*.
BrainGate Pilot Clinical Trials

BrainGate (14)
+ Pitt/CHI (3)
+ Caltech (5)
+ SU (1)
+ Hopkins (1)
+ Case (1)
+ San Sebastian (1)
+ China (1+)
+ Germany (1)
+ Philadelphia (1)
+ Utrecht (3)
+ CSF (2)
+ Melbourne (4)
Feasibility Study of the BrainGate Neural Interface System

• Participants must have limited use of their hands due to muscular dystrophy, motor neuron disease (ALS, PMA, adult-onset SMA), spinal cord injury, or stroke

• 18-75 years old; >1 year from injury; able to communicate; otherwise healthy; live within 3 hours of the study site.

• Recording and neural control trials occur in the participant’s place of residence.

• Recruiting: Boston, Providence, Palo Alto, Atlanta

clinicaltrials.gov/ct2/show/NCT00912041
Pioneering Participants

2004-2017:

✓ Motor cortex can be engaged for 2D and 3D control years after cSCI, brainstem stroke, ALS
✓ Range of age, duration of illness
✓ Cursor, Typing, TV/light/fan, robot arm, prosthetic limb, FES
✓ Array = Useful signals >5 years
✓ Participants are extraordinary
✓ Safety profile sufficient to continue research

Block 7
KalmanPK2 & StateDecoder (ncTX & SpikePower) | LDA (false clicks enabled)

T9 5/26/16
>39 correct characters per minute, without word prediction

Pandarinath, Nuyujukian, Blabe, et al. eLife 2017
BrainGate-enabled tablet computer control by people with ALS

Nuyujukian, Albites-Sanabria, et al, PLOS ONE 2018
Fast, Closed Loop, Automatically Updating Decoder

Participant T10 | Trial day 83
David Brandman et al, JNE 2018

Participant T5 | Trial day 30
Handwriting decoding from motor cortex (Participant T5; C4 AIS-C)

HHMI, Nature
Willett, Avansino, Hochberg, Henderson, Shenoy, Nature 2021
Brain-to-text handwriting by a person with tetraplegia

Willett, Avansino, Hochberg, Henderson, Shenoy, Nature 2021

Full vocabulary
> 90 characters/min
> 99% accuracy with language model
Wireless Communication of Neural Signals

Wireless link at 3.2-3.8 GHz transmitting 100 Mbits/sec over 1-3 meters

M. Yin, D. Borton et al, Neuron 2014;
Animal device commercially available 2015;
Human use in BrainGate research 2017
First-in-human: Broadband intracortical wireless recording

Simeral et al, IEEE TBME 2021
BrainGate Research Aims; Challenges for BCIs

**Neuroengineer**
Borton et al., JNE 2013
Simeral et al., IEEE TBME 2021

**Communicate**
24/7 Decoding and Communication Interface
Bacher et al., Neurorehab. Neural Repair 2014
Jarosiewicz et al., Science Trans. Med. 2015
Pandarinath et al., eLife 2017
Brandman et al., J. Neural Engin. 2018
Nuyujukian et al., PLOS ONE 2018
Stavisky et al., J. Neural Engin 2020
Burkhart et al., Neural Comp., 2020
Willett et al., Nature 2021

**Restore | Rehabilitate**
Bacher et al., Neurorehab. Neural Repair 2014
Jarosiewicz et al., Science Trans. Med. 2015
Pandarinath et al., eLife 2017
Brandman et al., J. Neural Engin. 2018
Nuyujukian et al., PLOS ONE 2018
Stavisky et al., J. Neural Engin 2020
Burkhart et al., Neural Comp., 2020
Willett et al., Nature 2021

**Assist**
Robot Assistants
Hochberg et al., Nature 2012
Collinger et al., Lancet 2013
Aflalo et al., Science 2015
Flesher et al., Science 2021

**Reanimate paralyzed limbs via**
Chadwick et al., J. Neural Engin. 2011
Bouton et al., Nature 2016
Ajiboye et al., Lancet 2017

**Functional Electrical Stimulation (FES)**
Chadwick et al., J. Neural Engin. 2011
Bouton et al., Nature 2016
Ajiboye et al., Lancet 2017

**Replace**
Prosthetic limbs
Hochberg et al., Nature 2012
Collinger et al., Lancet 2013
Aflalo et al., Science 2015
Flesher et al., Science 2021

**Soft Robotics, Rehabilitation Robotics**
CfNN | Some of our 43 @ VA + OSRI
The John B. Barnwell Award
Dr. Miriam Smyth, Acting Director
VA Clinical Science Research & Development
Dr. Louis Dell’Italia
The John B. Barnwell Award
Associate Chief of Staff for Research
Birmingham VA Health Care System
Birmingham, Alabama
• Favorable loading conditions in MR may falsely elevate ejection fraction despite underlying contractile impairment

• Therefore in order to preserve LV function and improve outcome surgery is recommended if LVEF < 60%
Patient with Isolated MR

Control

MR

ED

ES
Unique Hemodynamic Characteristics of the Primary Mitral Regurgitation (PMR)

A Neverland of Myocardial Compensation

- The molecular underpinnings of PMR has undergone less investigation.
- The inherent unloading of LV ejection into left atrium stymies normal trophic growth factors, renders RAS blockade useless, and confounds any conventional assessment of LV systolic function.
- This knowledge gap has resulted in the current conundrum of timing for surgical intervention to achieve full recovery of LV function after mitral valve repair.
It cannot be assumed that ACE inhibitors or AT₁ receptor blockers invariably protect the heart—particularly during the early phases of MR. The interactive effects of RAS, chymase and MMP systems during early adaptive and later phases of MR obviously warrant further study.
Mast cell chymase limits cardiac efficacy of ACE inhibitor therapy in rodents: *ACE Escape*  
*JCI* 120:1229-1239, 2010  
*In-vivo Cardiac Microdialysis*  
*Tissue vs. Blood Angiotensin II formation*
The inhibition of ACE has not been clinically successful in preventing progression in VO caused by AR or MR...

All LV remodeling is not the same.
Paradigm Shift: LV Chamber Dilates Before Cardiomyocyte Elongation in VO

A

LVESD (mm)

* * *

Time (weeks)

0 1 3 5 10 15

6 7 8 9 10 11 12

C

Myocyte length (μm)

* * *

Time (weeks)

0 1 3 5 10 15

110 130 150 170 190

Interstitial Collagen Loss

Sham

ACF 12h
Mitral Regurgitation

- Unique hemodynamic stress: low pressure volume overload due to ejection into the left atrium.
<table>
<thead>
<tr>
<th>Interstitial Collagen</th>
<th>Desmin (green)</th>
<th>TEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Incessant Stretch Stimulus, Neurohormonal Activation, Inflammation, and Oxidative Stress**

**Extracellular Matrix and Myocyte Cytoskeletal Breakdown**

**Mitochondrial Damage and Disarray**
Cardiomyocyte Stretch *in vitro*
Volume Overload *in vivo*

Extracellular Matrix Breakdown

Intracellular

mtDNA

$O_2^-$

ROS

Desmin Disruption
Mitochondrial Damage
Bioenergetic Dysfunction
Myofibrillar Breakdown

Differential Expression of Gene Pathways

Gene expression

Nucleus
Increased Sarcolipin Expression and Adrenergic Drive in Humans With Preserved Left Ventricular Ejection Fraction and Chronic Isolated Mitral Regurgitation

The current study suggests that biological perturbation occurs well before changes in ejection performance... and sets the stage for a large clinical trial testing whether β-blockade temporizes the need for surgery in mitral regurgitation.
Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function

Mustafa I. Ahmed, MD, Jason L. Guichard, MD, PhD, Namakkal S. Rajasekaran, PhD, Shama Ahmad, PhD, Nithya Mariappan, PhD, Silvio Litovsky, MD, Himanshu Gupta, MD, Steven G. Lloyd, MD, Thomas S. Denney, PhD, Pamela Cox Powell, MS, Inmaculada Aban, PhD, James F. Collawn, PhD, James E. Davies, MD, David C. McGiffin, MD, and Louis J. Dell’Italia, MD

EDITORIAL COMMENTARY

Left ventricular dysfunction after degenerative mitral valve repair: A question of better molecular targets or better surgical timing?

Jordan D. Miller, PhD, and Rakesh M. Suri, MD, DPhil

J Thorac Cardiovasc Surg 2016;152:1059-70
How VO Affects Both the Extra-and Intra-Cellular Skeleton of the Heart
LV Longitudinal and Circumferential Strains Decrease after Surgical Correction of Primary MR
Summary

• Despite preoperative LVEF > 60% in patients with isolated MR, there is

• Severe oxidative stress and disruption of cardiomyocyte desmin and mitochondrial sarcomere architecture that may explain post-operative LV functional decline, and further

• Supports the move toward earlier surgical intervention.
Current Research Directions

• New Guidelines for surgical intervention in isolated mitral regurgitation?

• Machine Learning has identified cardiac magnetic resonance LV circumferential strain and LV sphericity to predict LVEF < 50% after surgery

• Better Myocardial Protection during surgery CSR&D 2022-2026
Cardiopulmonary Bypass causes an increase in Red Blood Cell derived Exos Hb that mediates tissue injury.

RBC Exosomes from 30 cardiac patients

Exos Hb content post XCR

Patient RBC Exosomes \( \uparrow \text{Hb} \)

injected into

Sprague-Dawley rats (n=5-7)

Acute Cardiac Injury

Acute Kidney Injury
The Under Secretary’s Award for Outstanding Achievement in Health Services Research
Dr. David Atkins, Director
VA Health Services Research & Development
Dr. Donna Washington
The Under Secretary’s Award for Outstanding Achievement in Health Services Research
Center for the Study of Healthcare Innovation, Implementation, and Policy
Los Angeles, California
Women’s Health & Health Equity in VHA
Advancing Science to Improve Health and Healthcare of Vulnerable Veterans

Donna L. Washington, MD, MPH, FACP
Director, Health Equity – Quality Enhancement Research Initiative National Partnered Evaluation Center
Women’s Health Focused Research Area Lead, VA HSR&D Center for the Study of Healthcare Innovation, Implementation, and Policy, VA Greater Los Angeles Healthcare System
Professor of Medicine, Geffen School of Medicine at UCLA
VHA Women’s Health research ~2002

BOTTOM LINE UP FRONT: VHA WH research now advanced to intervention trials to improve care

Population characteristics
VA health care system characteristics
External environment

Individual health behaviors
Use of health services

Health outcomes
Patient experience
Foundational Research on Access to VA Care for Women Veterans

To Use or Not to Use
What Influences Why Women Veterans Choose VA Health Care
Donna L. Washington, MD, MPH,1,2 Elizabeth M. Yano, PhD,3,4 Barbara Simon, MA,3 Su Sun1

- Population-based regional study – VA users and nonusers in southern CA and NV
- Uncovered large gaps in women Veterans’ knowledge about VA eligibility and services
- Convened national leaders in an expert panel to develop practice, policy, research recommendations
Foundational Research on Access to VA Care for Women Veterans

Access to Care for Women Veterans: Delayed Healthcare and Unmet Need
Donna L. Washington, MD, MPH\textsuperscript{1,2,*}, Bevanne Bean-Mayberry, MD, MHS\textsuperscript{1,2,*}, Deborah Riopelle, MSPH\textsuperscript{1,*}, and Elizabeth M. Yano, PhD, MSPH\textsuperscript{1,*}

Assessment of the Healthcare Needs and Barriers to VA Use Experienced by Women Veterans
Findings From the National Survey of Women Veterans
Donna L. Washington, MD, MPH\textsuperscript{*}, Melissa M. Farmer, PhD\textsuperscript{*}, Su Sun Mor, MPH\textsuperscript{*}, Mark Canning, BA\textsuperscript{*}, and Elizabeth M. Yano, PhD, MSPH\textsuperscript{*,*}

Tailoring VA Primary Care to Women Veterans: Association with Patient-Rated Quality and Satisfaction
Donna L. Washington, MD, MPH\textsuperscript{a,b,*}, Bevanne Bean-Mayberry, MD, MHS\textsuperscript{a,b,*}, Michael N. Mitchell, PhD\textsuperscript{a,*}, Deborah Riopelle, MSPH\textsuperscript{a,*}, Elizabeth M. Yano, PhD, MSPH\textsuperscript{a,c,*}
2008-2009 National Survey of Women Veterans

- Confirmed information gaps re: VA eligibility/benefits/services
- Demonstrated prevalence of mental health comorbidities and need to integrate into 1º care
- Identified role of maintaining military social support as buffer against unmet needs

**IMPACTS**

- WV's call center
- Outreach campaign & updated web site with links
- VA Women’s health added to TAP program
- Peer support
VA Structure & Services for Women

• Foundational studies (w/ Yano) on organization and services for women
• Analytic studies to determine predictors of service availability
• Linked to National Survey of WV for multi-level models to identify drivers of WV health care quality and satisfaction

IMPACTS

• Informed revision of national VA policy for delivery of comprehensive care to WV – panel size, available services, Designated WH Providers
• Organizational measures adapted for annual measure
Increasing Visibility of VA Research on Women Veterans
Women’s Health Research Publications

Research among women in military & women Veterans

Special Issue on Women Veterans Health & Health Care

“…more papers published in the last 5 years, than the previous 25 years combined.”

Year of Publication

Number of Publications

Partial year

Homelessness in Women Veterans

Web of homelessness vulnerability

1. Childhood adversity
   - [Survivor instinct]

Military service

2. Trauma and/or substance abuse

3. Post-military abuse, adversity, and/or relationship termination
   - [Isolation]
   - [Lack of social support and resources]

4. Mental health, substance abuse, or medical problems
   - [Pronounced sense of independence]
   - [Access barriers]

5. Unemployment
   - [Lack of social support and resources]

Criminal justice involvement

HOMELESSNESS

Health Equity-QUERI National Partnered Evaluation Center Activities

- **Characterize Disparities**
  - Access / healthcare use
  - Quality
  - Outcomes

- **Evaluate Underlying Mechanisms**
  - Health system
  - Social determinants
  - Behavioral

- **Inform Equity-Focused Action**
  - Policy & practice partners
  - Dissemination

- **Improve Measurement**
  - Vulnerable Groups
  - Health factors or determinants

Health Equity QUERI Center (va.gov)
Improve Measurement

Evaluate quality of measures used to identify vulnerable Veteran groups


Identify strategies to enhance data quality

- Reduce amount of missing race/ethnicity data
- Develop residential-based social determinants of health measures
Characterize Disparities


- NVHER 2021
  — Focus on Health Equity & Action Cyberseminars
Time Trends in COVID-19 Infection by Race/Ethnicity, VHA 2020

Time Trends in COVID-19 Mortality by Race/Ethnicity, VHA 2020

VHA data, n=83,542 COVID-19 PCR positive Veterans, 3/1/20 – 11/30/20

Evaluate Underlying Mechanisms

Health Affairs

Addressing Inequities in Health Care


Racial and Ethnic Disparities Persist at Veterans Health Administration Patient-Centered Medical Homes

Disparities in Hypertension Control by Race/Ethnicity

2009 Hypertension

- AI/AN: 3%
- Asian: 4%
- Black: 6%
- Hispanic: 5%
- Multi-race: 7%
- NH/OPI: 0%
- White: REF

2014 Hypertension

- AI/AN: 6%
- Asian: 0%
- Black: 4%
- Hispanic: 2%
- Multi-race: 2%
- NH/OPI: 4%
- White: REF

Disparity in Control: AI/AN = American Indian/Alaska Native
Change from 2009-2014 in disparity (p<0.05): NH/OPI = Native Hawaiian/other Pacific Islander
*p<0.05 for comparison with Whites
## Disparities in Diabetes Control by Race/Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>2009 Diabetes</th>
<th>2014 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI/AN</td>
<td>7%*</td>
<td>9%*</td>
</tr>
<tr>
<td>Asian</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Black</td>
<td>6%*</td>
<td>6%*</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7%*</td>
<td>5%*</td>
</tr>
<tr>
<td>Multi-race</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>NH/OPI</td>
<td>5%*</td>
<td>3%</td>
</tr>
<tr>
<td>White</td>
<td>REF</td>
<td>REF</td>
</tr>
</tbody>
</table>

**AI/AN = American Indian/Alaska Native**  
**NH/OPI = Native Hawaiian/other Pacific Islander**  
*p<0.05 for comparison with Whites*
Disparities Reduction – Lessons Learned

Monitor Disparities

• Monitor outcomes of broad quality improvement projects by patient race/ethnicity
• Use multiple metrics to track progress toward achieving dual aims of high-quality health care and health equity

Build infrastructure for disparities reduction

• Incentivize achievement of health equity, identifying both quality goals and equity goals
• Integrate strategies tailored to social determinants of health into QI programs
Inform Equity-Focused Action

Increasing awareness of VA health and health care equity issues – Congressional briefings and testimony include:

- U.S. House Veterans Affairs Committee Subcommittee on Health (2/2020 oversight hearing, “Achieving Health Equity for America’s Minority Veterans”)
- U.S. House Veterans Affairs Committee Women Veterans Task Force (10/2019 research round table)
- Congressional Black Caucus Veterans Braintrust (9/2019 Forum on African American women Veterans)
Many Thanks!

- Mentors
- Mentees
- Collaborators
- Support
  - HSR&D, QUERI, CSHIIP
- Operations partners
  - Office of Health Equity
  - Women’s Health Services
- Veterans
  - patients
  - research participants
- Becky Yano
- Paul Shekelle
- Bob Brook
- Mark Canning
- Kristina Cordasco
- Susan Frayne
- Alison Hamilton
- LaShawnta Jackson
- Danna Kasom
- W. Neil Steers
- Su Sun
- Joy Toyama
- Michelle Wong
- Anita Yuan
& many others
The William S. Middleton Award
Dr. Christopher Bever, Director
VA Biomedical Laboratory
Research & Development
Dr. Robert Bonomo
The William S. Middleton Award
Director, Geriatric Research, Education and Clinical Center
Louis Stokes Cleveland VA Medical Center
Cleveland, Ohio
Journeys of Discovery: 
β-Lactamases and Antimicrobial Resistance

Robert A. Bonomo, MD
Associate Chief of Staff, Academic Affairs, Cleveland VAMC
Senior Clinical Scientist Investigator, Veterans Health Administration
Senior Associate Dean, Case Western Reserve University School of Medicine (Cleveland VA)
Director VA SHIELD Coordinating Center
Director, Cleveland GRECC
Distinguished University Professor, Case Western Reserve University, Cleveland
Director, Case VA Center for Antimicrobial Resistance and Epidemiology (Case VA CARES)

VA Presentation
It really takes a village.....THANK YOU

- Drs. Jane Battles, Grant Huang, Christopher Bever, Holly Krull, Rachel Ramoni, Vicky Davey, Merit Reviews, VA TEAMS
- VA SHIELD Team Drs. Saiju Pyarajan, Elizabeth Partan, Carey Shive, Jason Wertheim, Emerson Padiernos, Ian Robey, Osmara Molina De Rodriguez, Devin Bolz
- NIH (Drs. Dennis Dixon, Nancy Ernst, Jane Knisely, Karen Frank, John Dekker, Julie Segre, J. Gi, Erin Zeituni, Sudha Srinvasan, Steven Holland, Erica Raterman, Kenneth Oliver, Joel Goldberg, Brooke Decker, Andre Lisco, Jeff Cohen, and Ann Eakin)
- ARLG, Harrington Foundation.
- Drs. Karen Bush, Louis B. Rice, and David M. Shlaes
- My LAB- Ms. Kris Hujer and Andrea Hujer; Mr. Chris Bethel, Steve Marshal, Nick Domitrovic, Sue Rudin; Magda Taracila,
- Dr. Maria Fernanda Mojica and Dr. Laura Rojas Coy
- Dr. Kris Papp-Wallace
- “The KPC Club”: Drs. Federico Perez, M. Wright, Mark Adams, David van Duin, Keith Kaye, Cesar Arias, Michael Jacobs, Scott Evans, Barry Kreiswirth, Liang Chen, Marcelo Tolmasky, Maria Soledad Ramirez, Latania Logan, Pranita Tamma, and Sandy Richter
- “The Psda Club” Andrew Mack, Drs. Shozeb Haider, John Dekker, George Drusano
- Drs. Vance Fowler, Focco van den Akker, Fabio Prati, Emilia Caselli, Marisa Winkler, Roberto Viau, Paul Carey, Brad Spellberg
- “The NDM Club” Drs. Alejandro Vila, Jim Spencer, Walter Fast, Mike Crowder, Rick Page
- “The NTM Club” Drs. Khald Dousa, Sebastian Kurz, David Nguyen, Barry Kreiswirth, Dr. WH Boom;
- AstraZeneca, Allergan, Merck, Wockhardt, GSK, Roche, Achaogen, Shionogi, Entasis, VenatoRx
- Dr. Rita M. Bonomo
By 2050, increases in antimicrobial resistance (AMR) will be responsible for **300 million deaths**

**Total GDP Loss**

100.2 Trillion USD

Mechanisms of Resistance

Why is AMR so difficult to overcome?

Eichenberger and Thaden, Antibiotics, 2019
β-lactamases: 80 years of mystery
To overcome β-lactamases, we must understand the mechanism

Bush and Bradford, Nature Microbiology, 2019
I tell the folks in the lab......“BLIs live and die at the bench”

Bush and Bradford, Nature Microbiology, 2019
We will have lots of choices...... Cezanne
The β-lactam β-lactamase inhibitor pipeline

Many choices!

Chemical scaffolds

β-lactam-based

Boronic acid-based

DBO-based

<table>
<thead>
<tr>
<th>Chemical Scaffolds</th>
<th>Inhibitor Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactam-based</td>
<td>1. Ceftazidime/avibactam</td>
</tr>
<tr>
<td></td>
<td>2. Ceftolozane/tazobactam</td>
</tr>
<tr>
<td></td>
<td>3. Imipenem/relebactam</td>
</tr>
<tr>
<td></td>
<td>4. Meropenem/vaborbactam</td>
</tr>
<tr>
<td>Boronic acid-based</td>
<td>1. Cefepime/taniborbactam (VNRX 5133)</td>
</tr>
<tr>
<td></td>
<td>2. Cefepime/enmetazobactam (AAI 101)</td>
</tr>
<tr>
<td></td>
<td>3. Sulbactam/durlobactam (ETX 2514)</td>
</tr>
<tr>
<td></td>
<td>4. Meropenem/nacubactam</td>
</tr>
<tr>
<td></td>
<td>5. VNRX-7145/ceftibuten (oral formulation)</td>
</tr>
<tr>
<td>DBO-based</td>
<td>6. Cefepime/zidebactam</td>
</tr>
<tr>
<td></td>
<td>7. Cefpodoxime/ETX0282 (-1317)</td>
</tr>
<tr>
<td></td>
<td>8. Ertapenem/zidebactam</td>
</tr>
<tr>
<td></td>
<td>9. QPX7726 +</td>
</tr>
<tr>
<td></td>
<td>10. AV006 +</td>
</tr>
<tr>
<td></td>
<td>11. Cefidericol??</td>
</tr>
</tbody>
</table>

Here

On the near horizon

“A class by itself”
The Journeys

OHIO-1 β-lactamase resistant to mechanism-based inactivators
Robert A. Bonomo, C. Curnie-McCumber and David M. Shlaes
Division of Infectious Diseases, Department of Internal Medicine, Case Western Reserve University, Cleveland, Ohio, USA

MINIREVIEW
Carbapenems: Past, Present, and Future
Kristina M. Papp-Wallace,1,2 Andrea Endimiani,1,3 Magdalena A. Taraciak,1 and Robert A. Bonomo1,2,4,5*
Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH 44106; Institute for Infectious Diseases, University of Bern 2010, Bern, Switzerland; and Department of Medicine,1 Pharmacology,2 and Molecular Biology and Microbiology,3 Case Western Reserve University, Cleveland, Ohio 44106

Three Decades of β-Lactamase Inhibitors
Sarah M. Drawz1 and Robert A. Bonomo2,3,4,5
Departments of Pathology,1 Medicine,2 Pharmacology,3 and Molecular Biology and Microbiology,4 Case Western Reserve University School of Medicine, Cleveland, Ohio, and Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, USA

Extended-Spectrum β-Lactamases: a Clinical Update
David L. Paterson1 and Robert A. Bonomo2
Infectious Disease Division, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania,1 and Infectious Disease Division, Louis Stokes VA Medical Center, Cleveland, Ohio2

Crystal Structure of KPC-2: Insights into Carbapenemase Activity in Class A β-Lactamases
Wei Ke,1 Christopher R. Bethel1, Jodi M. Thomson,1 Robert A. Bonomo1,2 and Focco van den Akker1,2
Department of Biochemistry and Pharmacology, Case Western Reserve University, Cleveland, Ohio 44106, and Research Service, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio 44106

Analysis of Antibiotic Resistance Genes in Multidrug-Resistant Acinetobacter sp. Isolates from Military and Civilian Patients Treated at the Walter Reed Army Medical Center
Kristine M. Hujer,1 Andrea M. Hujer,1 Edward A. Hulten,2 Saralee Bajaksouzian,4 Jennifer M. Adams,6 Curtis J. Donnelly,1 David J. Ecker,1 Christian Masiore,1 Mark W. Eshoo,1 Rangarajan Sampath,2 Jodi M. Thomson,1 Philip N. Rather,1 David W. Craft,1 Joel T. Fishman,3 Alissa J. Ewell,1 Michael R. Jacobs,4 David L. Paterson,1 and Robert A. Bonomo1,2,5*

JMB
The Recent Adventure

Using β-lactamase inhibitors, we studied a novel and unwelcome “phenotype” in a clinically important carbapenemase (KPC)

The Result

Given us insight into cephalosporinase activity
CEFTAZIDIME/AVIBACTAM: a “gold standard”? 

• Avibactam resembles portions of the cephalosporin bicyclic ring system
New β-Lactamase Inhibitors: a Therapeutic Renaissance in an MDR World

Sarah M. Drawz, Krisztina M. Papp-Wallace, Robert A. Bonomo

Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA; Research Service, Louis Stokes Cleveland Department of Veterans Affairs, Cleveland, Ohio, USA; Departments of Medicine, Pharmacology, and Molecular Biology and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA.

**TABLE 1** MICs of β-lactam and β-lactam-avibactam combinations against select pathogens

<table>
<thead>
<tr>
<th>Pathogen with Multiple β-Lactamases, including KPC-2</th>
<th>CAZ (μg/ml)</th>
<th>CAZ-AVI</th>
<th>CPT</th>
<th>CPT-AVI</th>
<th>ATM</th>
<th>ATM-AVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>K. pneumoniae with OXA-48</td>
<td>256/512</td>
<td>0.25/0.5</td>
<td></td>
<td></td>
<td>&gt;=512/512</td>
<td></td>
</tr>
<tr>
<td>K. pneumoniae withCTX-M-15</td>
<td>8/64</td>
<td>0.06/0.25</td>
<td></td>
<td></td>
<td>&lt;=0.06/0.06</td>
<td></td>
</tr>
<tr>
<td>K. pneumoniae with KPC-2</td>
<td>&gt;=512/512</td>
<td>0.25/0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli with ESBL</td>
<td>16/64</td>
<td>0.12/0.25</td>
<td></td>
<td></td>
<td>&gt;=512/512</td>
<td></td>
</tr>
<tr>
<td>E. coli with AmpC</td>
<td>16/64</td>
<td>0.12/0.5</td>
<td></td>
<td></td>
<td>&lt;=0.06/0.06</td>
<td></td>
</tr>
<tr>
<td>E. coli with OXA-48</td>
<td>4</td>
<td>&lt;0.008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli with IMP-1</td>
<td>256</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteriacae</em> with multiple β-lactamases, including KPC-2</td>
<td>&gt;64/&gt;64</td>
<td>0.5/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteriacae</em> with multiple β-lactamases, including AmpC</td>
<td>256/&gt;256</td>
<td>0.5/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteriacae</em> with VIM</td>
<td>64-&gt;512</td>
<td>64-&gt;512</td>
<td>&gt;64/&gt;64</td>
<td>16/&gt;32</td>
<td>0.25-&gt;256</td>
<td>0.12-&gt;0.5</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>8/64</td>
<td>4/8</td>
<td>&gt;64/&gt;64</td>
<td>16/&gt;32</td>
<td>16/32</td>
<td>8/32</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> with ESBL PER-1</td>
<td>128/128</td>
<td>4/16</td>
<td>&gt;64/&gt;64</td>
<td>32/&gt;32</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>128/&gt;512</td>
<td>32/256</td>
<td>&gt;64/&gt;64</td>
<td>32/&gt;32</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>1/2</td>
<td>1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Data were adapted from references 15, 16, 19, 20, 21, and 24. Avibactam was added at 4 μg/ml. Abbreviations: CAZ, ceftazidime; AVI, avibactam; CPT, ceftaroline; ATM, aztreonam.
- Numbers separated by a forward slash indicate MIC₃₀/MIC₅₀ values. Empty cells indicate that values were not reported.
Why (how) does avibactam work?

1.80 Å KPC-2 avibactam complex

Avibactam - S70 residue

Chair-shaped conformation of avibactam

Slowly desulfates
In patients treated with TAZ AVI vs. colistin all-cause hospital mortality at 30-days after starting treatment was 9% vs 32%.

Thus.....In this prospective, observational, multi-center cohort, all-cause propensity adjusted mortality was decreased in patients with CRE infections started on ceftazidime/avibactam vs. colistin (absolute risk reduction 23% [95% CI 9%-35%], p=0.0012).

“One good drug is better than two bad ones”
A decade ago!

A novel mechanism?

Taz av R Mem S

...lem/Vabor S
Natural variants modify *Klebsiella pneumoniae* carbapenemase (KPC) acyl–enzyme conformational dynamics to extend antibiotic resistance

Different Conformations Revealed by NMR Underlie Resistance to Ceftazidime/Avibactam and Susceptibility to Meropenem and Imipenem among D179Y Variants of KPC β-Lactamase

Structural Characterization of the D179N and D179Y Variants of KPC-2 β-Lactamase: Ω-Loop Destabilization as a Mechanism of Resistance to Ceftazidime-Avibactam
Not expression levels...

“H bonding networks disrupted”

Protein NMR shows 3% “disorder”; SEC also!

D179Y variant is unstable....
Although we could not measure $K_i$, we observed it took longer to form an acyl enzyme complex with Avi.
Interactions of vabor in the active site.

Crystallography?
3.15 Å, Space group C1

D179Y
Unable to map residues due to Disorder!!!
Compared all the structures

FIG 7  Ω Loop position and disorder in β-lactamases related to ceftazidime resistance. (A) WT KPC-2 (PDB 5UL8) (34). (B) KPC-2 E166Q with ceftazidime bound (PDB accession number 6Z24) (32). (C) R164S SHV-1 in complex with SA2-13 (PDB accession number 3OPP) (26). (D) D179N KPC-2. (E) D179Y KPC-2.

Explaining the mechanism whereby D179Y KPC-2 hydrolyzes ceftazidime, we maintain that the observed conformational changes and disorder in the Ω loop observed in the D179Y structure permit ceftazidime to be accommodated without steric hindrance since residue N170, and the rest of the Ω loop, is displaced. This allows ceftazidime in the acyl-enzyme-bound state, and likely also in the Michaelis-Menten preacylation binding mode, to bind unhindered, thus contributing to the decreased $k_{cat}$ for the D179Y variant compared to WT KPC-2. The observed reduced $k_{cat}$ for D179Y KPC-2 is likely a direct consequence of the displacement of the E166/N170 residues that position the deacylation water; this deacylation water is needed for fast deacylation.
Conjugate Base or Substrate Assisted Catalysis?

“For the WT enzyme itself, the conjugate base mechanism may be well favored.”  Y Chen...Shoichet  Protein Science 2008.
In KPC variants? This aminothiazole ring could also aid substrate-assisted deacylation via positioning (and possibly activating) the deacylation water molecule for D179 KPC variants where E166 in the Omega loop is displaced.

Well.....you are trying to answer how it gets deacylated, you have not answered how it gets acylated.

Implications for drug design
Newer Journeys

- Allosteric Inhibitors of β-Lactamases
- New BLIs, New Applications
- New β-lactamases... “playing heavy metal”
- VA TEAMS “Bench to Bedside”
- Rapid Molecular Diagnostics in Long term Care Facilities
Conformational free energy surface (FES) reconstructed from metadynamics simulations of PDC-3

Hopefully, someday we can exploit these and use allosteric inhibitors

Enhanced sampling molecular dynamics simulations identified conformational changes in the E221K variant loop, where a hidden pocket adjacent to the catalytic site opens and stabilizes ceftolozane for efficient hydrolysis.
EXT2514+ Sulbactam

Form the basis of a phase III trial that was very successful.

ATTACK

ETX2514 overcomes resistance of the WRAMC isolates to sulbactam

<table>
<thead>
<tr>
<th></th>
<th>MIC (mg/L)</th>
<th>Sulbactam</th>
<th>Sulbactam-ETX2514</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli pBC SK (-) bla&lt;sub&gt;ADC-7&lt;/sub&gt;</td>
<td>32</td>
<td>&lt;0.03</td>
<td></td>
</tr>
<tr>
<td>A. baumannii MIC&lt;sub&gt;30&lt;/sub&gt;</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>A. baumannii MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>32</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4: MICs of the WRAMC A. baumannii isolates Medical Center Isolates were performed on agar broth dilution according to the Clinical and Laboratory Standards Institute.

ETX2514 effectively inhibits ADC-7 and OXA-58 β-lactamas

Figure 5: β-lactamas were mixed with increasing concentrations of ETX2514 using 100 μM NCF as a reporter substrate.
Inhibiting *Mycobacterium abscessus* Cell Wall Synthesis: Using a Novel Diazabicyclooctane β-Lactamase Inhibitor To Augment β-Lactam Action

Khalid M. Douas,*,† David C. Nguyen,*,‡ Sebastian G. Kurz,*,‡ Magdalena A. Tarzicla,*,‡ Tracey Bonfield,*,‡ Christopher R. Bethel,‡ Melinda D. Barnes,*,‡ Suresh Selvaraj,*,‡ Aynnas M. Abdelrahman,‡ Barry N. Kreiswirth,*,‡ W. Henry Boom,* Shannen H. Kasperbauer,‡ Charles L. Daley,‡ Robert A. Bonomo,*

Charles L. Daley,* Stew

**TABLE 1** Summary of activity of DUR, AMOX, IMI, or CXM alone or in various combinations against 101 clinical isolates of Mab*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Test method</th>
<th>MIC (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUR</td>
<td>Alone</td>
<td>2–8</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin (AMOX) alone</td>
<td>128 &gt; 256</td>
</tr>
<tr>
<td>IMI</td>
<td>Alone</td>
<td>1–4</td>
</tr>
<tr>
<td>IMI-AMOX</td>
<td>Titrate IMI + AMOX fixed at 4 μg/mL</td>
<td>0.25–8</td>
</tr>
<tr>
<td>AMOX-DUR</td>
<td>Fixed 1:1 ratio</td>
<td>1–4</td>
</tr>
<tr>
<td>IMI-DUR</td>
<td>Fixed 1:1 ratio</td>
<td>0.5–4</td>
</tr>
<tr>
<td>IMI-DUR-AMOX</td>
<td>Titrate IMI-DUR 1:1 + AMOX fixed at 8 μg/mL</td>
<td>≤ 0.06 (≤ 0.25)</td>
</tr>
<tr>
<td>CXM</td>
<td>Alone</td>
<td>4–128</td>
</tr>
<tr>
<td>CXM-AMOX</td>
<td>Titrate CXM + AMOX fixed at 8 μg/mL</td>
<td>0.5 to &gt; 64</td>
</tr>
<tr>
<td>CXM-DUR</td>
<td>Fixed 1:1 ratio</td>
<td>0.5–4</td>
</tr>
<tr>
<td>CXM-DUR-AMOX</td>
<td>Titrate CXM-DUR 1:1 + AMOX fixed at 8 μg/mL</td>
<td>≤ 0.06 (≤ 0.25)</td>
</tr>
</tbody>
</table>

*OXR, durbactam; AMOX, amoxicillin; IMI, imipenem; CXM, cefoxitin. OXR antimicrobial agent and susceptible breakpoints for testing rapidly growing mycobacteria are available only for imipenem and are as follows: susceptible (≤ 8 μg/mL), intermediate (16 μg/mL), and resistant (≥ 32 μg/mL).
AAI101 vs. tazobactam -- a strategically placed methyl group (CH3) on the triazole moiety in AAI101.

AAI101 -a net neutral charge that enhances potency. Thus, like its partner cefepime, AAI101 is a zwitterion.

Antibiotic zwitterions are able to penetrate the Gram-negative cell wall at a higher rate.

In some ways, the MERINO Study was not a surprise!
Is the β-lactamase inactivated by enmetazobactam modified?
CTX-M-15 crystals grown in the presence of enmetazobactam or tazobactam reveal formation of a cross-link between Lys73 and Ser70, two residues critical for catalysis, with concomitant loss of the Ser70 hydroxyl group.
Understanding basic mechanism to design more effective therapies

Successful Treatment of Bloodstream Infection Due to Metallo-β-Lactamase-Producing *Stenotrophomonas maltophilia* in a Renal Transplant Patient

Maria F. Mojica, Christopher P. Oullette, Amy Leber, M. Brian Becknell, Monica I. Ardura, Federico Perez, Masako Shimamura, Robert A. Bonomo

Mojica et al AAC 2016
Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing Klebsiella pneumoniae infection

Evelyn Shaw1,2, Alexander Rombouts1, Fe Tubau3,4, Ariadna Padullés5, Jordi Câmara3, Toni Lozano5, Sara Cobo-Socrístán5, Núria Sabe1,2, Imma Grau1,4,6, Raül Rigo-Bonnin7, M. Angeles Domínguez2,3,6 and Jordi Carratalà1,2,6

Favorable response
Clinical success was achieved in 6 of the 10 patients

A successful experience has also been recently reported using this combination for treating a patient with a suppurated thrombophlebitis and Persistent BSI due to an OXA-48/NDM-1-producing K. pneumoniae
The urgent need for metallo-\(\beta\)-lactamase inhibitors: an unattended global threat

Maria F. Mojica*, Maria-Agustina Rossi*, Alejandro J. Vila, Robert A. Bonomo

Figure 2: Metallo-\(\beta\)-lactamase inhibitors and reaction intermediate structures
(A) Chemical structure of some metallo-\(\beta\)-lactamase inhibitors: the boronates, taniborbactam and QPX7728; the chelator, Aspergillomarasmine A; and the bisthiazolidine, L-bisthiazolidine. (B) Reaction intermediate of meropenem hydrolysis bound to New Delhi metallo-\(\beta\)-lactamase-1.
Deciphering the evolution of metallo-β-lactamases: A journey from the test tube to the bacterial periplasm

Received for publication, September 22, 2021; and in revised form, January 13, 2022. Published Papers in Press, February 1, 2022.

Carolina López 1, Juliana Delmonti 1, Robert A. Bonomo 2,3,4,5, and Alejandro J. Vila 3,6,4

From the 1Laboratorio de Metaloproteínas, Instituto de Biología Molecular y Celular de Rosario (IBR, CONICET-UNR), Rosario, Argentina; 2Research Service, Veterans Affairs Northeast Ohio Healthcare System, Cleveland, Ohio, USA; 3Departments of Medicine, Pharmacology, Molecular Biology and Microbiology, Biochemistry, and Proteomics and Bioinformatics, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; 4Medical Service and GREECC, Veterans Affairs Northeast Ohio Healthcare System, Cleveland, Ohio, USA; 5U.S. Department of Veterans Affairs, CWRU-Cleveland VAMC Center for Antimicrobial Resistance and Epidemiology (Case VA CARES), Cleveland, Ohio, USA; 6Area Biofísica, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Rosario, Argentina

Edited by Wolfgang Petri

MBL Mechanism “on Steroids”
MBL Inhibitors

Fig. 2. Chemical structures of bisthiazolidine inhibitors. Bisthiazolidines 1a (L-CS319, blue), 1b (D-CS319, gray), 2a (L-VC26, orange), and 2b (D-VC26, cyan).
Bohacek and colleagues suggested that there are over $10^{63}$ drug-like molecules. Med Res Reviews 16, 30-50, 1996

**MICs**
- Meropenem $=$ 32 ug/ml
- Meropenem + MB 076 $=$ 0.06 ug/ml

**Inhibits ADC, KPC, SHV, AmpC, PDC**

**Survival Days Post Infection**
- Cefepime Only
- MB_076 Only
- Combo 1:4 (MB_076: Cefepime)
Applications to LTCFs?

R01 funding opportunity title- Rapid Diagnostics and Phenotypic Antibacterial Susceptibility Testing for Bacteremia or Hospital Acquired Pneumonia

Proposed workflow— Rapid Pathogen ID, genotypic AMR, and phenotypic AST for HAP. Sample type BAL, TAT – 4 hours, Detection method– qPCR. Pathogens to be detected *Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumonia, and Haemophilus influenzae*

Earliest start date if granted: March 2023. Expected start date for experiments with clinical sample: Dec 2024

Proposed workflow

Workflow will be developed at CID -Bangalore using simulated BAL samples. This workflow will then need to be tested using clinical samples.
Challenges ahead

• Identification of measureable biological correlates of β-lactamase inhibition in the cell are still elusive.

• New BLIs and β-lactams WHAT IS THEIR ROLE

• New collaborations; ......like getting married “right partner” is key.....”genius is knowing a good idea when you hear one”

• New ideas and new tools ...... protein science/NMR/peptide fragments/antibody based therapies/diagnostic platforms/analytical tools/cryoEM/AFM/SEM...
“No time to lose”: Forward looking science for the benefit of patients must be based upon sound theory and should be our mandate – need to marry hypothesis testing at the bench to the clinic.