VA Office of Research and Development
National VA Research Week

Virtual Research Symposium
May 21, 2021
Recognizing the Under Secretary, Magnuson, Barnwell, and Middleton Awardees
Lina Kubli, Ph.D.
Program Manager, Sensory Systems, Communication Disorders
VA Rehabilitation Research & Development
Dr. Rachel B. Ramoni  
Chief Research & Development Officer  
VA Office of Research & Development  
Washington, D.C.
Dr. Marjorie A. Bowman
Acting-Assistant Under Secretary of Health
Discovery, Education & Affiliate Networks
Washington, D.C.
The Under Secretary’s Award in Health Services Research
Dr. David Atkins, Director
VA Health Services Research & Development
Dr. Matthew H. Samore
The Under Secretary’s Award
Director, Informatics, Decision-Enhancement, and Analytic Sciences Center
Salt Lake City, Utah
A story about people and places

• My circuitous path from Midwest to East to West

• In 2003, I became Director of the Salt Lake Informatics, Decision Enhancement and Surveillance (IDEAS) Center
Our Center in 2003

• Our center comprised three investigators: Charlene Weir, Jonathan Nebeker, and me.

• Our VA funding consisted of only one CDA, one merit, a VA informatics fellowship, and a modest amount of support for health information technology evaluation.
Our Center team in 2018
Why VA research

• Opportunity to combine a passion for improving health of Veterans and a zeal for generating new knowledge

• My research quest is to:
  • Leverage electronic health record (EHR) data to drive quality and safety
  • Characterize mechanisms of antibiotic selection pressure and modes of transmission
  • Create systems and tools to enhance decision-making and policy-making
State of affairs for EHR data in VA circa 2008

• Limited access to clinical notes and minimal capacity for natural language processing

• In the infectious disease realm, lack of national data on microbiology and antibiotic use

• Two informatics initiatives were launched by HSR&D, Consortium for Healthcare Informatics Research (CHIR) and Veterans Informatics and Computing Infrastructure (VINCI)
Through a joint effort of IDEAS, CHIR, VINCI:

- Created new national data resources
  - Microbiology
  - Antibiotic utilization based on bar coded medication administration data
Putting these new data resources to work

• New connections: The Jon Bon Jovi story

• Partnership with Antimicrobial Stewardship Task Force and National Infectious Disease Service

• Innovations in outpatient and inpatient antibiotic stewardship
Outpatient Antibiotic Stewardship in VA

• Analysis of variation in prescribing practices*
• Pilot implementation in Kansas City, Boise, and Salt Lake City
• With expanded CDC funding, roll-out to 15 VA facilities**
• National dissemination enabled by partnership with Pharmacy Benefits Management’s Academic Detailing

Empirical anti-MRSA therapy was not associated with reduced mortality for any group of Veterans hospitalized for pneumonia.
Overall, contact precautions reduced transmissibility of MRSA-colonized patients by an estimated 47%
Lessons from the COVID-19 pandemic

• Everyone was an epidemiologist

• Things that were important:
  • In the science: methodological rigor and model validity
  • In the response: preparedness and infrastructure
  • Learning about what policy-makers found useful
  • Purpose and mission
Thank you

“I can no other answer make but thanks, And thanks, and ever thanks.”

Twelfth Night, Shakespeare
The Paul B. Magnuson Award
Dr. Patricia A. Dorn, Director
VA Rehabilitation Research & Development
Dr. David X. Cifu
The Paul B. Magnuson Award
Senior VA Traumatic Brain Injury Specialist
Central Virginia Veterans Health Center
Richmond, Virginia

David X. Cifu, MD

Senior TBI Specialist, U.S. Department of Veterans Affairs
Central Virginia Veterans Affairs Health System

Associate Dean for Innovation and System Integrations,
Virginia Commonwealth University School of Medicine
Richmond, Virginia
Home of LIMBIC-CENC
Bottom Line Up Front: BLUF

- Mature, federal mTBI research consortium since 2013 with robust infrastructure.

- 10 research studies have been completed with 200+ publications and 12 additional grants funded.

- Currently, supporting 8 active research studies
  - 1,600+ (target 3,000) participant Prospective Longitudinal Study
  - Prospective Biomarker Discovery and Novel Neuroimaging studies
  - 2.2+ million-participant Retrospective Database, Phenotypes and Health Economics big data studies using extant federal datasets
  - Supporting 2 prospective intervention (sleep, cognitive dysfunction) trials

- Key deliverable: A range of Knowledge Translation products have been developed and additional ones are underway for consumers, family, clinicians and researchers.
The Chronic Effects of Neurotrauma Consortium (CENC 2013–19) identified a range of differences between SM’s and Veterans with and w/o mild TBI in the 1,700+ participant Longitudinal Study.

CENC’s unique combined dataset from the electronic medical, benefits, pharmacy and administrative records from VA and DoD of 2+ million unique Veterans revealed linkages between TBI and dementia, Parkinson’s disease, chronic pain and suicide.

The Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC 2019–24) commenced October 2019, is growing the Longitudinal Study to >3,000 participants, and continue to analyze large electronic dataset.

LIMBIC–CENC’s research teams have identified an association between TBI and dementia, biofluid markers of repetitive TBI and confirmation that pain and mental health disorders worsen dysfunction after mTBI.
- CENC Special Issue: *Brain Injury* 2016; 30(12): 1397–1514
  - Methodologies for 10 studies
  - Assessment Protocols and Tools
  https://www.tandfonline.com/toc/ibij20/30/12?nav=tocList

- CENC Special Issue *Brain Injury* 2018; 32(9): 1149-1294
  - Findings for 10 studies through Spring 2018
  - Integration of findings across 7 clinical studies
  https://www.tandfonline.com/toc/ibij20/32/10?nav=tocList

- LIMBIC Special Issue of *Brain Injury* scheduled for Fall 2021 on
  “Practical Approaches to Assessing and Mitigating the Risk of Cognitive Decline after Concussion: *Findings from the Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)*”
Research Cores

Coordinating Center
- Virginia Commonwealth University, Richmond, VA

Neuroimaging Core
- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

Biomarkers Core
- Uniformed Services University of the Health Sciences/National Institutes of Health, Bethesda, MD

Data and Biostatistics Core
- Hunter Holmes McGuire VA, Richmond, VA
- Virginia Commonwealth University, Richmond, VA
- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT
- University of Hawaii, Department of Speech, Honolulu, HI

Prospective Longitudinal Study

Enrollment Sites
- Hunter Holmes McGuire VA, Richmond, VA
- Michael E. DeBakey VA Medical Center, Houston, TX
- James A. Haby Veterans Hospital, Tampa, Florida
- South Texas Veterans Hospital, San Antonio, TX
- Fort Belvoir Community Hospital, Alexandria, VA
- VA Portland Health Care System, Portland, OR
- Minneapolis VA Health Care System, Minneapolis, MN
- VA Boston Healthcare System, Boston, MA
- WG Hefner VA Medical Center, Salisbury, NC
- Eisenhower Army Medical Center, Fort Gordon, GA
- VA San Diego Health System/University of California-San Diego/Camp Pendleton, San Diego, CA

Recruiting Sites
- MacDill Air Force Base, FL
- Joint Base Lewis McChord, WA
- Fort Stewart, Columbus, SC
- Naval Amphibious Base, Coronado, CA

Additional Research Studies

Retrospective Database Study
- San Francisco VA Medical Center/University of California- San Francisco, San Francisco, CA

Phenotypes Study
- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

Health Economics Study
- VA Palo Alto Health Care Systems/Stanford University

Biomarkers Discovery Study
- USUHS/NIH, Bethesda, MD

North Florida/South Georgia Veterans Health System, Gainesville, FL

Novel Neuroimaging Study
- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

LIMBIC-CENC Legacy Study Sites

Epidemiology of mTBI and Neurosensory Outcomes
- San Francisco VA Medical Center, San Francisco, CA
- Tau Modification Study
- Roskamp Institute, Sarasota, FL/Burrows Institute, Phoenix, AZ
- Otolith Dysfunction
- Mountain Home VA Medical Center, Mountain Home, TN
- Novel White Matter Imaging to Improve Diagnosis of Mild TBI
- VA San Diego Healthcare System, San Diego, CA
- ADAPT/EVOLVE
- University of Washington, Seattle, WA
- Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces
- WG Hefner VA Medical Center, Salisbury, NC
- UTH Phasios Study
- Baylor College of Medicine, Houston, TX
- Clinical and Neuroimaging Correlates of Neurodegeneration in Military mTBI
- Minneapolis VA Health Care System
- Visual Sensory Impairments
- Iowa City VA Health Center, Iowa City, IA
Long-Term Impact of Military-relevant Brain Injury Consortium (LIMBIC) 2013-2024

Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)

Program Oversight: Government Steering Committee

Consortium Director/M-PI
David X. Cifu, MD - VCU

LIMBIC Leadership Team
Kristine Yaffe, MD – UCSF/SF VAMC
Col Kris Radcliffe, MD, PhD – Lewis-McChord
Col(R) Sidney Hinds, MD - USU

Coordinating Center
Director: LTC(R) K. Sickinger - VCU

Advisory Boards
Scientific/Consumer

Core Facilities

Neuroimaging
Elizabeth Wilde, PhD - Utah

Database and Biostatistics
Amma Agyemang, PhD/Mary Jo Pugh, PhD – VCU/UU

Biomarkers
Kim Kenney, MD/Jessica Gill, PhD/ Lt Cmdr J. Kent Werner, MD, PhD – USU/NIH

Knowledge Translation
Ronald Seel, PhD/Amol Karmarkar, PhD - VCU

Novel Neuroimaging
Elizabeth Wilde, PhD/David Tate, PhD - Utah

Biomarkers Discovery
Kim Kenney, MD/Jessica Gill, PhD - USU/NIH

Phenotypes
Mary Jo Pugh, PhD - Utah

Prospective Longitudinal
William Walker, MD - VCU

Retrospective Database
Kristine Yaffe, MD - UCSF

Health Economics
Clare Dismuke, PhD – Palo Alto

8 Military Bases/Sites
13 VAMCs

Regulatory Oversight
IRB/HRPO

Current Research Studies

Completed Research Studies

Completed Research Studies

Basic Science
1 Study (3 Lab sites)

Prospective Clinical Trials
7 Studies (2,300 participants across 30 sites)

Retrospective Database
1 Studies (1.6 million participants)

Technology
1 Study (1 Patent)

Technology
1 Study (1 Patent)
So how did we get here?
Knowledge Translation Center
• Dementia Risk and Risk Reduction Tools
• Patient Education Videos
• Clinical Pearls Postcards
• Gold Standard Research Assessments
• Searchable Scientific Reference Catalog

Building research capacity and output from the research infrastructure

CENC 2013
- Develop research and administrative infrastructure.
- Initiate one 4-center prospective study.

2014-15
- Establish mega-database from 9 extant datasets.
- Implement Round 1 of research RFPs.
- Implement 3-site Basic Science project.

2015-16
- Add 4 additional centers to Prospective Longitudinal Study.
- Implement Round 2 of research RFPs.
- Publish initial research articles.
- Sponsor National Meeting.

2016-17
- Initiate one single center and one 3-center prospective studies.
- Initiate three single center prospective studies.
- Present approach and findings at national meetings.
- Obtain additional grant funding.
- Add Health Economist.

2018-19
- Publish Special Editions on Research Methodology and Findings.
- Present research findings at national meetings.
- Obtain additional grant funding.
- Add Knowledge Translation Center.

LIMBIC 2020-21
- Secured funding to expand into LIMBIC.
- Expand PLS to 17 recruitment and 11-testing sites
- Initiate prospective Biomarker and Neuroimaging Studies.
- Expand Database studies to 3 unique areas of focus:
  - Epidemiology
  - Phenotypes
  - Health Economics

LIMBIC-CENC: Progressively building upon the experience and infrastructure of an established consortium to study long-term effects
Key Findings

- Veterans with TBI have higher rates of dementia, pain, opioid usage, mental health diagnoses, cardiovascular disease, stroke, and sleep dysfunction.

- Veterans with mTBI or blast do NOT have increased rates of neuroendocrine dysfunction.

- Tau and p-tau levels increased by number of blast exposures in Veterans with mTBI.

- Greater # of mTBIs (3+) associated with increased symptom burden and serum NFL levels.

- Increased “brain age” by imaging associated with increased h/o combat mTBI, # mTBI’s, depression, PTSD, poor sleep.

- Veterans with TBI have higher costs, risk of death, risk of chronic kidney disease, more likely to be minority, and more likely to be homeless.
LIMBIC-CENC: Getting It Done Together

1.6+ Million Unique Participants' Database

8 YEARS OF LEADERSHIP

10 COMPLETED STUDIES

200+ PUBLICATIONS

Brain Injury SPECIAL ISSUE on Dementia Risk - 2021

LIMBIC 2013 - 2024: 75+ researchers; 19 Universities, 16 VAMCs and 8 DoD facilities
Dr. Miriam C. Morey
The Paul B. Magnuson Award
Associate Director
The Geriatric Research, Education, and Clinical Center
Durham VA Health Care System
North Carolina
Gerofit

- Gerofit is a *group-based* supervised exercise and health promotion program for older Veterans (ages 65+). Developed as a clinical demonstration project in Durham VA in 1986.

- Exercises are offered 3 days per week and are individually tailored to functional impairments and patient directed goals, *with no time limit on duration of participation.*
Gathering & Publishing Landmark Data

Evaluation of a Supervised Exercise Program in a Geriatric Population

Miriam C. Morey, MA, Patricia A. Cowper, PhD, John R. Feussner, MD, Robert C. DiPasquale, MS, Gail M. Crowley, RN, Delane W. Kitzman, MD, and Robert J. Sullivan, Jr, MD

Most studies that assess the effects of exercise in the elderly involve subjects who are in good health. The observations that were significant: Metabolic equivalents increased from 7.1 ± 2.3 to 8.3 ± 2.6 (P < .001), treadmill time increased from 3.2 ± 1.2 to 4.2 ± 1.1 (P < .001).

Exercise on the Psychological Well-Being and Health Status of Older Veterans

Patricia A. Cowper

Physical function in sedentary and exercising older veterans as compared to national norms

Matthew J. Peterson, MS; Gail M. Crowley, BSN, RNC; Robert J. Sullivan, MD, MPH; Miriam C. Morey, PhD Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Durham, NC; Claude D. Pepper Older Americans Independence Center/Centers on Aging and Human Development, Duke University Medical Center, Durham, NC, Department of Medicine, Duke University Medical Center, Durham, NC.
Developing the Research and Evidence-Base

The Veterans LIFE Study: A Randomized Trial of Primary Care Based Physical Activity Counseling For Older Men

Miriam C. Morey, Ph.D., Matthew J Peterson, Ph.D., Carl F. Pieper, Dr. PH., Richard Sloane, MPH, Gail M. Crowley, MSN, ANP-C, Patricia A. Cowper, Ph.D., Eleanor S. McConnell, Ph.D., P. Pearson, M.A.

1Duke University Medical Center, Department of Medicine, Institute for Health Research; 2Durham VA Medical Center

Enhanced Fitness: A Randomized Controlled Trial of the Effects of Home-Based Physical Activity Counseling on Glycemic Control in Older Adults with Prediabetes Mellitus

Miriam C. Morey, PhD, Jr., MD, Jennifer B. G Sloane, MPH, Patricia PhD, James T. Cavan Gregory A. Taylor, PhL

Published in final edited form as:

Effects of Home-Based Diet and Exercise on Functional Outcomes Among Older, Overweight Long-Term Cancer Survivors: The RENEW: Randomized Clinical Trial


1Department of Medicine, Duke University Medical Center (DUMC), Durham, NC
Transformation Initiatives – T21’s

• Provide funding for the spread of good programs

• Implementation
  • Gerofit awarded T-21
    • 2014 - Geriatrics and Extended Care
    • 2015 – Office of Rural Health
The VA Gerofit Program

A VHA Best Practice
• Designated Best Practice by the VHA Undersecretary of Health in 2016

Alternative Models of Non-Institutional Care
• Promotes well-being, QOL
• Ability to remain at home
21 Gerofit Programs Implemented

GEC Support
- If we keep 1-3 Veterans out of institutional care each year, the program pays for itself.

ORH Support
- Developing methods for rural Veterans

COVID Impact
- Enhanced methods for telehealth “Gerofit to the Home.”
- 7 new programs being mentored
- 4.6 Million CARES Act COVID Gerofit recovery program

~ 16.6 M since 2014
High Program Implementation Fidelity

4 Year Trajectories - Expected

Chair Stands

Six Minute Walk Distance (Yards)

Expected estimates from Magistro, et.al. JA Longitudinal Study on the Relationship Between Aerobic Endurance and Lower Body Strength in Italian Sedentary Older Adults. JAPA, 23:444., 2013
4 Year Trajectories Gerofit: Observed Versus Expected

Chair Stands

Six Minute Walk Distance (Yards)

Expected estimates from Magistro, et.al. JA Longitudinal Study on the Relationship Between Aerobic Endurance and Lower Body Strength in Italian Sedentary Older Adults. JAPA, 23:444, 2013
EVIDENCE & RESOURCES

✓ Increased Fitness
✓ Increased Physical Function
✓ Improved Cardio Metabolic Profile
✓ 25% Lower 10-year Survival
✓ Improved Psychological Wellness
✓ High Veteran Satisfaction
✓ Reduced PTSD symptoms
✓ Significantly Lower Medication Use
✓ 10% Lower 1-year Hospitalization Rate

• 21 Programs Across 15 VISNs
• Exercise Videos for Older Veterans on YouTube (YouTube #Gerofit exercises)
• Partner with VA Veterans News Network – exercise classes for 87 medical centers
• Published Methods for Remote Functional Assessment
• Provides Access to Gerofit-to-the-Home For Veterans without Access to Programs
Tele Health Innovations: Supervised Home-Based Exercise

Change Over Time (N=4)

- **Above Average**: > 75%
- **Average**: 25-75%
- **Below Average**: 11-24%
- **At Risk**: < 10%

**TIMELINE**
- **Baseline**
- **3-Month Follow up**
- **6-Month Follow up**

**AGE RELATED %TILES**

**TESTS**
- 30 Second Arm Curl
- 30 Second Chair Stand
- 2 Minute Step Test

**N=4**
Seeding Research Through Collaboration

- Multi-morbidity and Function
- Peri-operative Rehab
- Impact on Mental Health
- PTSD
- Cardio-metabolic status
- Obesity
- Disease Specific Interests
- HIV
- Diabetes/Obesity
- Parkinson’s
- Return on Investment
- Functional Trajectories
- Medication reductions
- Patient Satisfaction
- Resilience
- Motivation
- Statistical Methodology
- Telehealth
- CLC-Improving function
- Research in Implementation Science
- RE-AIM Framework
GEROFIT – Patient Impact

Gerofit HASHTAGS
#BestMoveIveEverMade, #Reason2getUp, #KeepingMyBloodFlowing
#HealthPromoting, #GoodSenseofWellbeing, #FeelBetter, #ActiveAging
#GoingToGetBetter, #GaveMeA_NewLife, #BeenA_GodSend, #NoMoreCrying
#Happiness, #AvoidDying, #Satisfaction, #Healthy, #Excellent, #Longevity
#Energy, #LessPain, #Stronger, #LifeSaver, #StopBeingDepressed
#LifeProlonging, #GerofitMakesMeHappy, #RefreshedAndAlive!, #NoMoreCane
#ProgramA_Lifesaver, #StrongerAtHome, #100%betterWithGerofit
#stayInShape, #Amazing, #Friends, #improveMyHealth, #HealthyEatingHabits
#BoostMySelfesteem, #BetterFeelingAboutLife, #HelpfulStaff
#GotMeOutOfA_Funk, #GerofitMeansEverything, #GoodHealth, #GreatProgram
#BPOfA_Teenager, #ConsistentExercise, #3xA_Week_Everyweek, #BetterHealth
#LowerA1C, #KeepingTrying, #EnjoyingWorkout, #HealthyFun, #Wonderful
#Greatstaff, #Veterans, #ReachingGoals, #FocusedStructuredGoals
#IncreasingStrength, #A_WayOfLife, #GoodHealth, #GreatTraining, #LikeFamily
#NoMorePain, #MovingAndGrooving, #Body, mind&spirit, #Rewarding
#NeededThis, #KeepItMoving, #Motivation, #UpAndMoving, #RightToolsHelp
#VeteranSupport, #Health&Happiness, #strongerThanEver
#GreatHealth&Wellness, #BestPartOfMyDay!
Thank you

IMPLEMENTATION TEAM

Miriam Morey, Ph.D.
Program Lead

Megan P. Pearson, M.A.
National Gerofit Program Manager

Katherine Hall, Ph.D
Associate Director of Gerofit

Kenneth Manning, MS
Gerofit Exercise Physiologist

Stephen Jennings, MS
Gerofit Exercise Physiologist

Janet Prvu Bettger, Dr.Sc
Gerofit Implementation Scientist

Geriatrics and Extended Care Data Analysis Center (GECDAC)
Jiejin Li, Ph.D,
Peter Veazie, Ph.D.
Orna Intrator, PhD.

22 Gerofit Program Collaborative

SUPPORT

VHA GRECCs, Durham VA GRECC, Durham VA Healthcare System, and national Geriatrics and Extended Care programs

GEC Mentored Partnership Program

VHA Office of Rural Health
EnterpriseWide Initiative

Partner Programs
Duke Center for the Study of Aging/ Duke OAIC
Pepper Center

Gerofit Resources
Please visit our website at Gerofit:
https://www.va.gov/GERIATRICS/pages/gerofit_Home.asp
Watch our exercise videos on YouTube: #Gerofit Exercise
The John Blair Barnwell Award
Dr. Theresa Gleason, Director
VA Clinical Science Research & Development
Dr. David W. Oslin
The John Blair Barnwell Award
Director, VISN 4 Mental Illness Research, Education and Clinical Center
Corporal Michael J. Crescenz VA Medical Center
Philadelphia, Pennsylvania
Home Away from Home

Integrity – Commitment – Advocacy – Respect - Excellence
Treatment of Alcohol Use Disorder

1993 - 1996
Naltrexone in the Adjunctive Treatment of Older Alcohol Dependent Patients
DuPont Merck Pharmaceuticals

1999 – 2002
Treatment of Depression Complicated by Alcohol Use in Late Life
Department of Veterans Affairs VA MREP

1999 – 2004
Treatment of Late Life Depression Complicated by Alcohol
NIMH K08
Primary Care Mental Health Integration (the BHL Model)

Figure 2: Unadjusted Mean (S.E.) CES-D Scores

Baseline 3 Months 6 Months

CESD Score

MD-Refer
MD-Integ
OD-Refer
OD-Integ

Major Depression (MD)
All Other Depression (OD)

* Paired t-test of crude mean difference in CESD change BL to 6 months significant at 0.003 level (integrated -7.49, referral -10.24; difference referral had 2.75 point steeper decline). Decline in CESD score indicates improvement (reduced depression severity).

Integrity – Commitment – Advocacy – Respect - Excellence
Primary Care Mental Health Integration (the BHL Model)
Integrity – Commitment – Advocacy – Respect - Excellence

Measurement-Based Care

Personalized Patient Resources
- Targeted education/tips based on reported symptoms
- Graphic representation of patient progress

Introducing BHL Touch iPad App
Technology Advancing the Delivery of Measurement-Based Mental Health Care

BHL Touch is a new iPad app for patient direct-entry of self-assessments. It is a complementary mobile application to the desktop BHL Software, a nationally...
Pharmacogenetics

Naltrexone for alcohol use disorder

Experiences ordering a genetic test in the past year

- Past treatment with an antidepressant predicted a greater likelihood of the next intended medication being one with a high potential for clinical significance (OR: 1.59, 95% CI: 1.08, 2.35)

- Ramsey et al (2021)
Teamwork

Integrity – Commitment – Advocacy – Respect - Excellence
Dissemination Outside the VA

Pennsylvania PACE program

U PENN Integrated Care (PIC)
Family

Integrity – Commitment – Advocacy – Respect – Excellence
What’s Next

• Addiction
  – Improve rate of pharmacotherapy use

• PCMHI
  – Enjoy the improvements others are making

• MBC
  – Continue to demonstrate utility
  – Continue BHL dissemination and informatics focus – text and email features
  – Develop direct to provider feedback

• PGx
  – Dissemination / Implementation
Thank You
Dr. Jeffrey L. Curtis
The John Blair Barnwell Award
Researcher, pulmonologist, and critical care physician
VA Ann Arbor Healthcare System
Michigan
"Fighting for every breath,"
*a career in COPD research*

Jeffrey L. Curtis, M.D.

VA Ann Arbor Healthcare System
& University of Michigan

Chair, VA CURES Executive Committee
Member, VA SHIELD Executive Committee
Disclosures

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  - Department of Veterans Affairs
  - NIH/NHLBI & NIH/NIAID
  - Department of Defense
How (and where) it began

Requirement of CD4-positive T Cells for Cellular Recruitment to the Lungs of Mice in Response to a Particulate Intratracheal Antigen
How (and where) it began
How (and where) it began

Requirement of CD4-positive T Cells for Cellular Recruitment to the Lungs of Mice in Response to a Particulate Intratracheal Antigen

Lung Lymphocyte Elimination by Apoptosis in the Murine Response to Intratracheal Particulate Antigen
How (and where) it began

Requirement of CD4-positive T Cells for Cellular Recruitment to the Lungs of Mice in Response to a Particulate Intratracheal Antigen

Lung Lymphocyte Elimination by Apoptosis in the Murine Response to Intratracheal Particulate Antigen

Endothelial Selectins and $\alpha_4$ Integrins Regulate Independent Pathways of T Lymphocyte Recruitment in the Pulmonary Immune Response$^{1,2}$

Deficient In Vitro and In Vivo Phagocytosis of Apoptotic T Cells by Resident Murine Alveolar Macrophages$^3$
Requirement of CD4-positive T Cells for Cellular Recruitment to the Lungs of Mice in Response to a Particulate Intratracheal Antigen

Lung Lymphocyte Elimination by Apoptosis in the Murine Response to Intratracheal Particulate Antigen

Endothelial Selectins and α4 Integrins Regulate Independent Pathways of T Lymphocyte Recruitment in the Pulmonary Immune Response

Deficient In Vitro and In Vivo Phagocytosis of Apoptotic T Cells by Resident Murine Alveolar Macrophages

CCR2 and CCR6, but Not Endothelial Selectins, Mediate the Accumulation of Immature Dendritic Cells within the Lungs of Mice in Response to Particulate Antigen

How (and where) it began
How (and where) it began

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Cigarette Smoke Exposure Impairs Pulmonary Bacterial Clearance and Alveolar Macrophage Complement-Mediated Phagocytosis of *Streptococcus pneumoniae*
Why study COPD?

• **Chronic Obstructive Pulmonary Disease (COPD)**
Why study COPD?

- **Chronic Obstructive Pulmonary Disease (COPD)**

- 3rd leading cause of US & worldwide death

- Significantly more common in Veterans
More lethal than an MI

- Mortality of an acute exacerbation of COPD (AE-COPD) is 3-10%
More lethal than an MI

- Mortality of an acute exacerbation of COPD (AE-COPD) is 3-10%
Three facts about COPD
Three facts about COPD
Three facts about COPD

- [Graph or image showing percent change in age-adjusted death rates, U.S., 1965-1998]

  - Proportion of 1985 Rate
  
  - Coronary Heart Disease: -50%
  - Stroke: -64%
  - Other CVD: -35%
  - COPD: +183%
  - All Other Causes: -7%

  Source: NHANES-I and NHANES-III
Three facts about COPD

- No current medical therapies arrest loss of lung function.
Research Questions

• Can we develop novel therapies to reduce the impact of existing COPD?

• Can we prevent progression to COPD
  ▪ by identifying those at-risk at early disease stages?
Some novel therapies worked…

EFFECT OF SYSTEMIC GLUCOCORTICOIDS ON EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Some novel therapies worked…

EFFECT OF SYSTEMIC GLUCOCORTICOIDS ON EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE


Randomized Trial of Zileuton for Treatment of COPD Exacerbations Requiring Hospitalization

Woodruff et al. COPD 2011
Randomized Trial of Zileuton for Treatment of COPD Exacerbations Requiring Hospitalization

Woodruff et al. COPD 2011

New concepts on COPD pathogenesis needed

The last new drug for COPD, roflumilast, was FDA-approved in 2011
Research questions

• Can we develop novel therapies to reduce the impact of existing COPD?

• Can we prevent progression to COPD
  ▪ by identifying those at-risk at early disease stages
Key insights from others

Key insights from others


A lung microbiome exists in health & changes in COPD

Dickson et al. *mBio* 2017
A lung microbiome exists in health & changes in COPD

Dickson et al. mBio 2017

Erb-Downward et al. PLOS One 2011
Smoking reduces small airway immune defenses by epithelial reprogramming

Healthy small airway

Smoker’s small airway

Martinez et al. Am J Respir Crit Care Med 2018
Smoking reduces small airway immune defenses by epithelial reprogramming

Healthy small airway

Smoker’s small airway

Martinez et al. *Am J Respir Crit Care Med* 2018
(based on data from Polosukhin et al. *Am J Respir Crit Care Med* 2011)
Non-invasive detection of functional Small Airways Disease (fSAD)

Labaki et al. Acad Radiol 2019
(COPDGene cohort)
Functional Small Airways Disease (fSAD) correlates with epithelial gene expression

Airway epithelial gene signature of IL-17-induced inflammation

Christenson et al. *J Clin Invest* 2019
(SPIROMICS Bronchoscopy sub-study)
Defining the pathobiology of early COPD
Acknowledgments

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- Kareem Hazem
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- Dawit Mengistu
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- Derek Linderman
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- Jeffrey Jennings
- Mohamed Kady
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- Sara Li
- Virginia Maxwell
- Alicja Milik
- Ali McCubbrey
- Huram Mok
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- Sophina Taitano
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- John Osterholzer
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- Katy Norman
- Marc Peters-Golden
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COPDGene Investigators
LTRC Investigators
LHMP Investigators
SPIROMICS Investigators
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VA Biomedical Laboratory
Research & Development
Dr. Stephen Plymate
The William S. Middleton Award
Associate Director, Geriatric Research, Education, and Clinical Center
VA Puget Sound Health Care System
Seattle, Washington
Stephen Plymate
VAPSHCS - GRECC
Targeting the Glycolytic Metabolome in Prostate Cancer

- **Dustin Maly PhD:** Professor, Raymond E. and Rosellen M. Lawton Distinguished Scholar in Chemistry, Kinase inhibitors, UW

- **Wesley C. Van Voorhis MD PhD:** Professor and Head, Division of Allergy and Infectious Diseases, Department of Medicine
  - Director, Center for Emerging and Re-emerging Infectious Diseases (CERID)
  - Kinase/Target based drug development, UW

- **Stephen Plymate MD:** Professor Dept of Medicine, Member Molecular and Cell Biology Program UW, GRECC-VAPSHCS
Screened Kinase Inhibitor library: Selective Inhibition of LNCaP95

![Graph showing relative proliferation vs. compound for PC3 and LNCaP95 with specific compounds highlighted.]

- **PC3 < 0.85**
  - GP212

- **PC3 > 0.85, LNCaP95 > 0.65**
  - Control
  - Lead
  - SGI
  - KD SGI
  - GP228
  - GP232

- **PC3 > 0.85, LNCaP95 < 0.65**

**Chemical Structures:**
- Pyridopyrimidine (PP)
- Pyrazofurin (PF)
- 1553 (PP)
- 1676 (PP)
- 1817 (PP)
- 228 (PF)
- 232 (PF)
SGIs inhibit prostate tumor growth in vitro and in vivo
Specific Glycolysis Inhibitors (SGIs) for Castrate Resistant Prostate Cancer (CRPC)

RNA seq data: SGI-LEAD suppresses AR signature (left) and cancer cell proliferation signature (CCP) (right)

AR+ PCa Cells

24 h treatment

20 µM SGI-DEAD

20 µM SGI-LEAD

RNA isolation

RNA-seq
# SGIs effect ATP production

<table>
<thead>
<tr>
<th>Time points</th>
<th>Gene name (decreased phosphorylation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min &amp; 2h &amp; 4h</td>
<td>PRKAA1</td>
</tr>
<tr>
<td>30 min &amp; 2h</td>
<td>PRPF4B, SRRM1</td>
</tr>
<tr>
<td>2h &amp; 4h</td>
<td>C2CD5, RIOK2, EI24, STK10, MAP1B, MARK2, AFF4, PRKD1, PTK2B, PIEZO1, SRRM2, SLC35A5, CAMKK2, PRKAB1, ARFGEF2, TBKBP1, CLK3, WEE1, SRC, NEK9, MAP3K2</td>
</tr>
</tbody>
</table>

**Figure**

- **Panel A**: Western blot analysis of P-ACC and total ACC in LN95, PC-3, and LN95 cells treated with DMSO, BKI228, BKI1553, and BKI228, DMSO, and BKI1553 for 2 hr, 6 hr, and 3 hr.
- **Panel B**: Graph showing changes in ATP levels in BKDC cells treated with BKI1553, BKI1633, and BKI1617 at 10 min, 30 min, and 120 min.
SGIs Inhibit Glycolytic Pathway

Extracellular acidification rate (ECAR) was measured by Seahorse XF analyzer.
**MOA:** Selective glycolysis inhibition

**SGI in h b glycolysis a 6C 3 C transition**

- **LNCaP95**
  - DMSO
  - SGI-LEAD (20 µM)

- **Harvest cells at 30 min, 120 min**

- **GC/MS to identify 3-carbon glycolytic intermediates**

**OBSERVATION:** Very early significant reduction in DHAP/GAP & 3-PG by SGI-LEAD, confirmed with 13C-glucose metabolomics
SGIs have Excellent Pharmacokinetics and Safety

### SGI-LEAD PK Demonstrates Scalable Bioavailability Across Species

<table>
<thead>
<tr>
<th>Species &amp; route</th>
<th>Mouse PO</th>
<th>Rat IV</th>
<th>Rat PO</th>
<th>Dog IV</th>
<th>Dog PO</th>
<th>Monkey IV</th>
<th>Monkey PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>10</td>
<td>5</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µM)</td>
<td>12.8</td>
<td>65.7</td>
<td>29.4</td>
<td>2.52</td>
<td>1.58</td>
<td>2.45</td>
<td>1.08</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (min)</td>
<td>320</td>
<td>480</td>
<td>60</td>
<td>132</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-tau&lt;/sub&gt; (min·µmol/L)</td>
<td>13,725</td>
<td>8524</td>
<td>31,884</td>
<td>1,229</td>
<td>1,100</td>
<td>981</td>
<td>656</td>
</tr>
<tr>
<td>Clearance (mL/min/kg)</td>
<td>1.4</td>
<td>1.5</td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>V&lt;sub&gt;z&lt;/sub&gt; (L/kg)</td>
<td>1.0</td>
<td>1.7</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%F (bioavailability)</td>
<td>93</td>
<td>88</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

- Implies human dose prediction should be reliable

### Summary of Safety and PK properties of BKI-1553

- **In vitro Toxicity**
  - >10 µM IC<sub>50</sub> Src3D, AbIKD
  - >40 µM CRL8155 cell CC<sub>50</sub>
  - >40 µM HEP G2 cell CC<sub>50</sub>
  - >30 µM hERG inhibition
- **Solubility** = 50 µM at pH 6.5
- mAMES, IV Micronucleus: negative
- Plasma protein binding (human) 97z
- PK established in mice, rats, dogs, monkeys and follows allometric scaling
- hERG inhibition >30 µM
- In vitro rabbit cardiomyocyte QT/inotrophy toxicity testing negative at >30 µM
- **Microsome Stability** T<sub>1/2</sub> >120 min (mouse, rat, beagle, cow & human)
- Probable major metabolite: glucuronide
- No CYP3A4, 1A2, 2C9, 2C19 inhibition at 20 µM
- Mouse toxicity: NOAEL (PO) 300 mg/kg single dose, repeat dosing: >70 mg/kg qd x 7 days
- Off target liabilities:
  - No activity on CEREPEP CNS panel or 25 G-protein receptors, ion channels, etc. at 10 µM except displacement of captopril from angiotensin converting enzyme
  - Protein kinase (80) inhibition limited to PKD <1 µM
New Pathway for CRPC Treatment

• For the first time it is possible to selectively target the metabolome, aerobic glycolysis (Warburg Effect) to treat CRPC
  
  • Composition of Matter Patents
    • US 10632122; US 10307425; WO 2016/123152 Al
  
  • Use Patent
    • US 10350211
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Michael Nyquist
Taran Gujral
Stella Shin
John Lee
Lucas Sullivan

Vancouver Prostate Centre
Amina Zoubeidi
Dr. Steven M. Dubinett
The William S. Middleton Award
Researcher, staff physician
VA Greater Los Angeles Healthcare System
California
Inflammation and Immunity in lung cancer

Bringing Research Discoveries to the Care of our Veterans

MAY 21, 2021

Steven Dubinett, M.D.
VA Greater Los Angeles Healthcare System
When does immune recognition or immune suppression occur?

How does inflammation promote the development and progression of lung cancer?

Does inflammation modulate the physical properties of premalignant cells?

Can we alter the tumor environment to augment the systemic immune response? Can this be translated to premalignancy?
Addressing critical unmet needs for lung cancer interception

- Identification of patients with precancerous lung lesions
- In those with premalignant lesions, determining which will progress to invasive disease
- Identification of targets to intercept progression in aggressive premalignant lesions
Range of subsolid lesion imaging features

**Pure GGO** in RML
- Slightly increased focal attenuation through which underlying lung structures (vessels) are visible

**GGO/Semi-consolidation RML**
- Moderately increased focal attenuation through which underlying lung structures are visible

**Part-solid nodules**
- Combines solid (≥ 2 mm) and ground glass

**Solid nodule RLL**
- Completely opaque nodule with no underlying visible lung structures

*GGO = Ground Glass Opacity*
Lung Cancer Progression

Initiating event
Premalignant lesion
In situ lesion
Invasion
Metastatic

developing tumor mass

ing Time

Adapted from Zitvogel et al, Immunity 39: 74-88, 2013
Lung Cancer Progression

- Elimination
  - developing tumor mass
- Equilibrium
- Escape

Adapted from Zitvogel et al, Immunity 39: 74-88, 2013
CD4 T and B cells are increased in subsolid and solid lesions compared to the associated non-involved lung tissues.

<table>
<thead>
<tr>
<th></th>
<th>Sub/Solid</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK</td>
<td>0.30</td>
<td>0.20</td>
</tr>
<tr>
<td>NKT</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>CD4+ T</td>
<td>0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>B</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Proportion of CD45+ cells

P = 0.005
P = 0.007
P = 0.03
P = 0.002

J. Yanagawa, L Tran
Tumor-derived interleukin-2-dependent lymphocytes in adoptive immunotherapy of lung cancer


Cancer Immunology and Immunotherapy (1987) 24:76-85
For Immune-Mediated Tumor Control
DCs first then effector T cells follow

Pfirschke et al *Cancer Cell* May 8, 2017
The Potential Advantages of Intra-tumoral DC Therapy

**In situ vaccination**

- Provides access to the entire repertoire of available Ags in situ
- Enhances the potential for a broader T cell immune response to tumor Ags
- All patients could be treated (no limitations re: tumor Ag or HLA)

**Uptake and processing of multiple tumor Ags in situ**

**Tumor in vivo**
Interferon induction in response to autologous tumor antigens

Lee et al Clin Cancer Res 2017

Increased infiltration of CD8 T cells and PD-L1 expression following in situ vaccination
Phase I Trial of Intratumoral Administration of CCL21-DC Combined with Pembrolizumab

Intratumoral Injection of CCL21-DC

Leukapheresis

PBMC Isolation

DC Differentiation

DC Transduction

CCL21

CCL21-DC Manufacturing Outline

CCL21-DC
Be curious, collaborate, persist

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Researcher, cardiologist
Ralph H. Johnson VA Medical Center
Charleston, South Carolina
Department of Veterans Affairs Funding

Produces Scientific Advances that Saves Lives and Reduces Disability in Veterans with Heart Failure

One example

Michael R. Zile, MD
Division of Cardiology
2019 Middleton Award Recipient
Ralph H. Johnson Department of Veterans Affairs MC
Charleston, South Carolina

Charles Ezra Daniel Professor of Medicine
Distinguished University Professor
Medical University of South Carolina
Department of Veterans Affairs Funding

- VA Investment (1983-2021, 38 years)
- CDA, Merit Review, REAP, SHEEP Awards
- Return on Investment
  - Discovery
  - Application
  - Lives improved / saved
- One example of “How, What, Why, and Results”
Process of Discovery: Supported by VA Funding

BEDSIDE ➔ Identify critical clinical questions
Process of Discovery: Supported by VA Funding

BEDSIDE ➔ Identify critical clinical questions

Define disease mechanisms
Discover novel treatments

Research Bench
Process of Discovery: Supported by VA Funding

BEDSIDE ➔ Identify critical clinical questions

BEDSIDE ➔ Clinical application of novel discoveries

Define disease mechanisms
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Research Bench
“TEAM Sport”: Collaborating VA Investigators

BEDSIDE → Identify critical clinical questions

Define disease mechanisms
Discover novel treatments

Research Bench

Amy Bradshaw, PhD
Catalin F. Baicu, PhD
Francis Spinale, MD, PhD
Jeffrey Jones, PhD
Donald Menick, PhD
Amanda Larue, PhD

BEDSIDE → Clinical application of novel discoveries

Kurt Baringhaus, MD
Louis Dell’italia, MD

Sheldon Litwin, MD
Terrence O’Brien, MD
Val Fernandes, MD
“TEAM Sport”: Collaborating VA Investigators

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BEDSIDE ➔ Clinical application of novel discoveries

Kurt Baringhaus, MD
Louis Dell’italia, MD

ONE TEAM, ONE MISSION
# 1 Cause of Death, Hospitalization, Disability

National VA

RHJ Charleston VA

Cardiovascular Disease

1 in 4 Veterans Die from Cardiovascular Disease
1 in 4 Veterans Die from Cardiovascular Disease

Cardiovascular Disease: Chronic Heart Failure
# 1 Cause of Death, Hospitalization, Disability
National VA
RHJ Charleston VA
Cardiovascular Disease
1 in 4 Veterans Die from Cardiovascular Disease

# 1 Cardiovascular Disease: Chronic Heart Failure

Normal
Heart Failure With Preserve Ejection Fraction
Heart Failure With Reduced Ejection Fraction
# 1 Cause of Death, Hospitalization, Disability

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RHJ Charleston VA

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1 in 4 Veterans Die from Cardiovascular Disease

# 1 Cardiovascular Disease: Chronic Heart Failure

Normal

Heart Failure With Preserve Ejection Fraction

Heart Failure With Reduced Ejection Fraction
Heart Failure With a Preserved Ejection Fraction (HFpEF)

Mortality: 50% / 5 yrs
HF Hosp: 50% / 6 mos
Disability: ~ Transplant
Treatment: None ➡️ M&M

1st- Identify critical unmet need
Heart Failure With a Preserved Ejection Fraction (HFpEF)

1st- Identify critical unmet need
- Mortality: 50% / 5 yrs
- HF Hosp: 50% / 6 mos
- Disability: ~ Transplant
- Treatment: None → M&M

2nd- Define Mechanisms
Propose Hypotheses

Diastolic Dysfunction: Increased Stiffness
Inability to fill the LV

LVH

Myocardial Fibrosis
Define Disease Mechanisms Based on \( \Delta \) Cell / ECM Structure

LV Myocardium (Heart Muscle)

Cardiomyocyte

Extracellular Matrix (ECM)
Extracellular Space

Cardiomyocyte

Cardiomyocyte

Extracellular Matrix (ECM)

H & E Stained LV Myocardium

Extracellular Space
Hypothesis

Normal

LV Myocardium

ECM

Cardiomyocyte

Sarcomere

Titin

Actin

Myosin

LV Myocardium

ECM

Cardiomyocyte

Sarcomere

Titin Phosphorylation

Actin

Myosin

LV Myocardium

Cardiomyocyte

Sarcomere

Fibroblast Activation

Zile & Litwin Braunwald’s Heart Disease, 2017

Concentric LVH

ECM Fibrosis

HFpEF

LV

LA

RV

RA

Normal

Hypothesis

LV Myocardium

ECM

Cardiomyocyte

Sarcomere

Titin

Actin

Myosin

LV Myocardium

ECM

Cardiomyocyte

Sarcomere

Titin Phosphorylation

Actin

Myosin

LV Myocardium

Cardiomyocyte

Sarcomere

Fibroblast Activation

Zile & Litwin Braunwald’s Heart Disease, 2017

Concentric LVH

ECM Fibrosis

HFpEF
In Series Sarcomerogenesis

HFrEF

Normal Cardiomyocyte

20 μm 20 μm
100 μm

20 μm 20 μm
150 μm
Normal Cardiomyocyte

**HFrEF**

In Series Sarcomerogenesis

**HFpEF**

In Parallel Sarcomerogenesis
Basic Animal Models of Human Disease

Circulation 2006; 113: 296-304

Myocardial Hypertrophy, ↑Stiffness, HFpEF

Sarcomeres added in parallel

Increased fibrillar collagen

Normal

HFpEF
Basic Animal Models of Human Disease

HFpEF

Normal

Sarcomeres added in parallel

Increased fibrillar collagen

Myocardial Fibrosis, ↑ Stiffness, HFpEF
Translation of Basic Science into Clinical Studies
HFpEF patients

Study Subjects
Referent Control
Hypertension (-) HFpEF
Hypertension (+) HFpEF

Biopsy site

Excision of specimen

Closure of site with pledget-supported Prolene mattress sutures

HFpEF Patients have Myocardial Stiffness & HF Symptoms

Myocardial Stiffness: Contribution of Cellular vs. ECM Mechanism

Myocardial Stiffness: Contribution of Cellular vs. ECM Mechanism

LV Myocardial Stiffness (Stress at SL = 2.6 μm)

Collagen dependent
Titin dependent
Total

*p<0.01 vs Referent Control
#p<0.01 vs HTN(-)HFpEF

Control Patient

Hypertensive Patient

HFpEF Patient

LV Myocardial Fibrosis

HFpEF Patient

Zile, Bradshaw et al, Circulation 131:1247-59;2015
BEDSIDE → Identify critical clinical questions

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Discover novel treatments

Research Bench

Myocardial Fibrosis

BEDSIDE → Clinical application of novel discoveries

Safe & Effective Treatment
Pathophysiologic Mechanisms in HFpEF: Fibrosis = Novel Target

1- Reduce Fibrosis

- Spironolactone - TOP-CAT
- Entresto – PARAGON-HF (sacubitril / valsartan)

Sponsor
- NHLBI
- Novartis

2- Reprogram Fibroblast

- Cardiosphere derived cells
- Advanced progenitor cells (Stem cells)

DOD
Spironolactone

Probability of Heart Failure Hospitalization or CV Death

HR = 0.82 (0.69-0.98)

P < 0.001

Circ 2015; 131: 34-42
Valsartan (n = 2389)
1009 events, 14.6 per 100 pt-years

Sacubitril/Valsartan (n = 2407)
894 events, 12.8 per 100 pt-years

Rate ratio 0.87 (95% CI 0.75, 1.01)
P = 0.059

Total HF hospitalizations and CV death
PARAGON-HF
Primary Composite Endpoint Results

Hazard Ratio

Ejection Fraction (%)
Process of Discovery: Supported by VA Funding

BEDSIDE → Identify critical clinical questions

Define disease mechanisms
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Myocardial Fibrosis

Limitations
RCT 3-5,000 pts
Myocardial Bx

BEDSIDE → Clinical application of novel discoveries

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Myocardial Bx

BEDSIDE ➔ Clinical application of novel discoveries

Biomarkers: Dx, Px, & Tx
Circulating Biomarkers

➢ Novel Biomarker Discovery
➢ Identify Fibrosis Mechanism
➢ Diagnostic Criteria
➢ Prognosis
➢ Target for Novel Therapy
➢ Measure Treatment Success
Abnormal Biomarkers Reflect Profibrotic Remodeling

Increased Hemodynamic, Metabolic Load

Fibroblast → Activated Fibroblast

Increased Collagen Synthesis

sST-2
PINP
PIIINP

Decreased Collagen Degradation

MMP-2
MMP-9
CITP
TIMP-1
Abnormal *Biomarkers* Reflect Profibrotic Remodeling

Increased Hemodynamic, Metabolic Load

**Fibroblast** → **Activated Fibroblast**

- Increased Collagen Synthesis
- Decreased Collagen Degradation

**sST-2**
- ↑ in HFpEF

**PINP**
- ↑ in HFpEF

**PIIINP**
- ↑ in HFpEF

**MMP-2**
- ↓ in HFpEF

**MMP-9**
- ↓ in HFpEF

**CITP**
- ↑ in HFpEF

**TIMP-1**
- ↑ in HFpEF
## Baseline Values of Profibrotic Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>PARAGON-HF Median (IQR)</th>
<th>Referent Controls Median (IQR) *</th>
<th>%Pts Above Referent Control Median</th>
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<tr>
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<td>38 (29, 51)</td>
<td>30 (25, 35)</td>
<td>▲ 70%</td>
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<tr>
<td>PIIINP (ng/mL)</td>
<td>4.4 (3.6, 5.5)</td>
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<td>▲ 76%</td>
</tr>
</tbody>
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Cunningham...Zile JACC 76:503-514, 2020
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Circulating Biomarkers

➢ Novel Biomarker Discovery
➢ Identify Fibrosis Mechanism
➢ Diagnostic Criteria
➢ Prognosis
➢ Target for Novel Therapy
➢ Measure Treatment Success
Changes in *Biomarkers* Reflect Treatment Dependent Antifibrotic Effects

**Increased Hemodynamic, Metabolic Load**

**Fibroblast** → **DE-Activated Fibroblast**

**Increased Collagen Synthesis**

**Decreased Collagen Degradation**

**Rx** that target profibrotic remodeling (Sacubitril / Valsartan and Spironolactone) normalize Biomarkers.

- **sST-2**, **PINP**, **PIIINP** ↑ in HFpEF
- **MMP-2**, **MMP-9**, **CITP** ↓ with Rx
- **TIMP-1** ↑ in HFpEF with Rx
Effects of Sac/Val 16 and 48 Weeks After Randomization in Paragon HF

- TIMP-1: p < 0.001
- sST2: p = 0.002
- PIIINP: p = 0.04
- PINP: p = 0.44
- CITP: p = 0.02*

* p < 0.05 vs. Valsartan

Cunningham…Zile JACC 76:503-514, 2020

Measure Treatment Success; Relate to Pro-Fibrotic Mechanism

↓ Synthesis

↑ Degradation
Circulating Biomarkers of Fibrosis Predict Prognosis

Baseline Values vs Outcomes

TIMP-1

sST2

Change from Baseline Values vs Outcomes

TIMP-1

sST2

Circulating Biomarkers of Fibrosis Predict Prognosis

Cunningham…Zile JACC 76:503-514, 2020 PARAGON-HF Study
Treatment Effect by LVEF
CV death or HF hospitalizations (time-to-first)

Biomarkers Suggest Anti-Fibrotic Effects

Spironolactone  Sacubitril / valsartan

Ejection Fraction (%)  Ejection Fraction (%)
Heart Failure With a Preserved Ejection Fraction (HFpEF)

Mortality: 50% / 5 yrs
HF Hosp: 50% / 6 mos
Disability: ~ Transplant
Treatment: None M&M

Diastolic Dysfunction: Inability to fill the LV
LVH
Myocardial Fibrosis

1st - Identify critical unmet need
2nd - Define Mechanisms
Propose Hypotheses
LVH

Myocardial Fibrosis

Mortality: 50% / 5 yrs

HF Hosp: 50% / 6 mos

Disability: ~ Transplant

Treatment: None ➔ M&M

Diastolic Dysfunction:
Inability to fill the LV

1st- Identify critical unmet need

Heart Failure With a Preserved Ejection Fraction (HFpEF)

Spironolactone
FDA PMA 12-16-20

Sacubitril/Valsartan
FDA PMA 12-15-20
Expanded indication 2/2021

2nd- Define Mechanisms
Fibrosis
Thank You

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