FNIH

Foundation for the
National Institutes of Health

# ACCELERATING MEDICINES PARTNERSHIP® PROGRAM SYMPOSIUM

February 5-6, 2024
Bethesda North Marriott Hotel &
Conference Center

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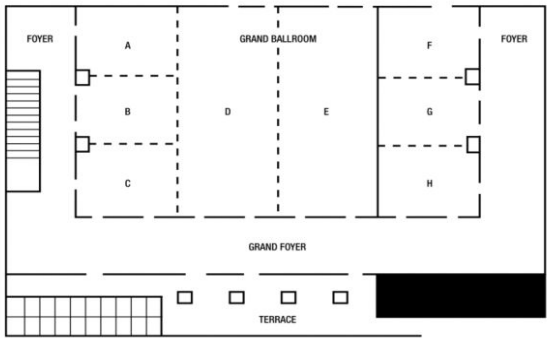
# CONFERENCE CENTER FLOORPLAN

MAIN LEVEL

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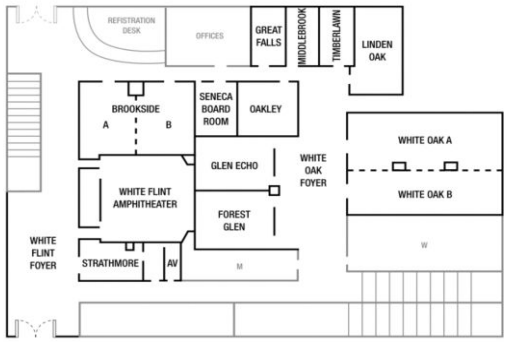


# WI-FI INFORMATION

**Network Name:** MarriottBonvoy_Conference

**Network Password:** AMPSYMP2024

FNIH.ORG

## VISIONARY

Alzheimer's Association®

GSK

Pfizer

## INNOVATOR

Boehringer Ingelheim

Bristol Myers Squibb®

novo nordisk®

## PIONEER

AMGEN

Otsuka

ucb Inspired by patients. Driven by science.

## EXPLORER

Cytokinetics

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## AMBASSADOR

American Heart Association.

American Psychiatric Association Foundation

Arthritis Foundation®

autoimmune association

Lupus Research Alliance

National Scleroderma Foundation

One Mind

NAMI National Alliance on Mental Illness

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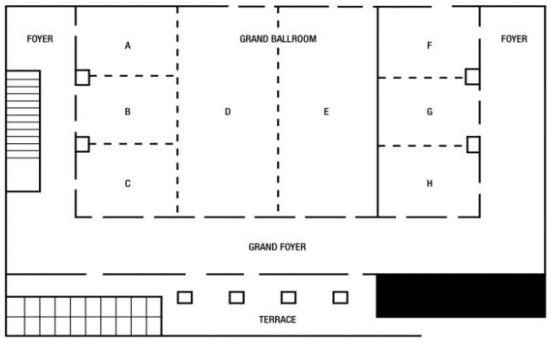


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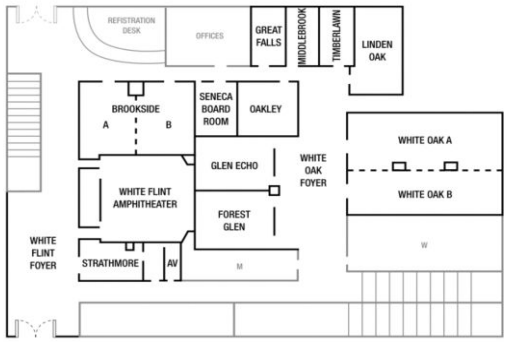



# WI-FI INFORMATION

**Network Name:** MarriottBonvoy_Conference

**Network Password:** AMPSYMP2024

FNIH.ORG

# AMP PROGRAM OVERVIEW

A PRECOMPETITIVE PUBLIC-PRIVATE COLLABORATION started in 2014, the Accelerating Medicines Partnership® (AMP®) program unites the resources of the National Institutes of Health (NIH) and private partners to improve our understanding of disease pathways and transform current models for developing new treatments by:

- Identifying new targets, biomarkers and development paradigms
- Developing leading-edge tools and technologies
- Collecting large scale datasets and supporting analytics for open analysis by the public
- Generating consensus platforms and procedures

The core AMP principles are as follows:

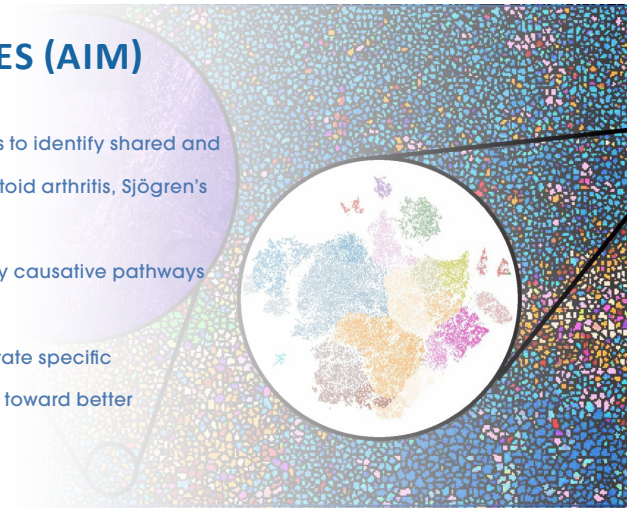
- Shared governance and funding
- Broad, prompt access to data and results
- Freedom to operate with regard to IP and IP protection

# AMP BY THE NUMBERS


MANAGED BY THE FNIH SINCE THE 2014 LAUNCH OF THE LARGE-SCALE INITIATIVE. THE AMP PARTNERSHIPS USE CUTTING-EDGE SCIENTIFIC APPROACHES TO BRING NEW MEDICINES TO PATIENTS THROUGH PRE-COMPETITIVE ADVANCEMENTS IN CLINICAL TARGET VALIDATION, DATA ANALYTICS, AND CONSENSUS PROCESSES. THE FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH (FNIH) IS A NOT-FOR-PROFIT ORGANIZATION THAT SUPPORTS THE MISSION OF THE NATIONAL INSTITUTES OF HEALTH (NIH), TO ACCELERATE BIOMEDICAL DISCOVERIES THAT IMPROVE THE QUALITY OF PEOPLE'S LIVES.

# PROGRAMS AT-A-GLANCE

## AMP AUTOIMMUNE & IMMUNE-MEDIATED DISEASES (AIM)

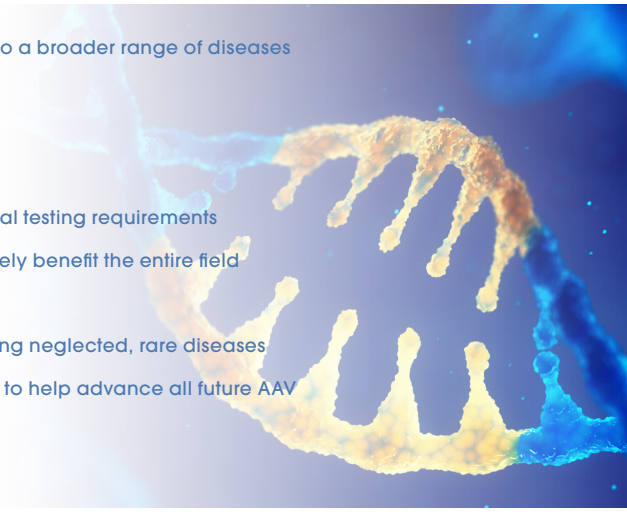


- Synthesize spatially-informed tissue and blood interrogations to identify shared and unique determinants of psoriatic spectrum disorder, rheumatoid arthritis, Sjögren's disease, and systemic lupus erythematosus
- Reconstruct cellular environments and interactions to identify causative pathways of diseases initiation, progression and damage
- Advance understanding of how cell-to-cell interactions activate specific mechanisms of disease to identify target molecules to move toward better therapeutic interventions

## AMP ALZHEIMER'S DISEASE (AD 2.0)

- Identify and validate new targets and biomarkers for various subtypes of Alzheimer's disease, aiding drug developers in selecting suitable patients for targeted treatments in clinical trials
- Enhance understanding of Alzheimer's progression at cellular and molecular levels, offering researchers detailed longitudinal data to understand the disease more comprehensively
- Prioritize data inclusion from racially and ethnically diverse cohorts, particularly Black and Latinx populations, utilizing a centralized knowledge portal to broaden access to de-identified data
- Facilitate global research and therapy development by providing researchers with subject-level data, analytical outputs, and target nominations for basic research, fostering collaboration and advancement in the field

## AMP BESPOKE GENE THERAPY CONSORTIUM (BGTC)



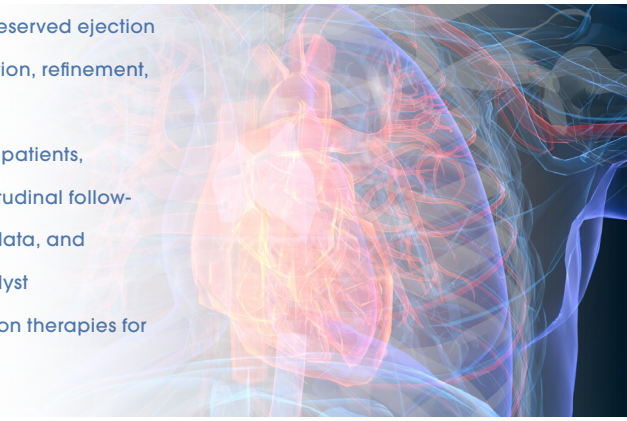
- Make adeno-associated virus technology more accessible to a broader range of diseases
- Optimize AAV vector production
- Improve AAV target gene expression
- Streamline preclinical and product testing
- Harmonize and validate sets of manufacturing and preclinical testing requirements
- Facilitate scientific and regulatory advances that will ultimately benefit the entire field
- Standardize regulatory submission package templates
- Bring gene therapies to affected populations sooner, including neglected, rare diseases
- Make publicly available a clinical development "playbook" to help advance all future AAV gene therapies for rare diseases

## AMP COMMON METABOLIC DISORDERS (CMD)

- Generate new and leverage existing genetic, genomic and biomarker data for all CMDs
- Develop analytical and visualization tools to support integrative analysis
- Deliver prioritized targets for these diseases with supporting mechanistic data

## AMP HEART FAILURE (HF)

- Identify potential subtypes/endotypes of heart failure with preserved ejection fraction (HFpEF) from existing datasets for prospective validation, refinement, and extension of "clinically actionable" endotypes of HFpEF
- Create a cohort and database of deeply phenotyped HFpEF patients, comparators, and matched controls with baseline and longitudinal follow-up of electronic health record, clinical, imaging and omics data, and biospecimens made available through NHLBI's Biodata Catalyst
- Establish the framework for master protocol for testing precision therapies for specific endotypes of HFpEF patients



## AMP PARKINSON'S DISEASE (PD)

- Address the absence of disease-modifying therapies for people living with PD, and address the challenge of consolidating data from numerous natural history studies, each with their own access pathway
- Improve clinical trial design and identify new pathways for therapeutic development by providing a platform to identify prognostic/disease progression biomarkers and enabling deep molecular characterization and longitudinal clinical profiling

## AMP SCHIZOPHRENIA (SCZ)

- Provide tools to enable the selection of enriched patient populations, to considerably improve success in developing pharmacologic treatments for patients with clinical high risk (CHR) for psychosis
- Develop and validate biomarkers and outcome measures that can establish early indicators of pharmacologic treatment efficacy

# CURRENT AMP PROGRAMS

### Alzheimer's Disease 2.0
Co-Chairs
Michael Nagel, Eisai
Suzana Petanceska, NIA

### Autoimmune and Immune-Mediated Diseases
Co-Chairs
Rab Prinjha, GSK
Bob Carter, NIAMS
Mary Collins, Lupus Research Alliance

### Bespoke Gene Therapy Consortium
Co-Chairs
Tim Miller, Thermo Fisher
P.J. Brooks, NCATS
Peter Marks, FDA

### Common Metabolic Disorders
Co-Chairs
Melissa Miller, Pfizer
Norann Zaghloul, NIDDK

### Heart Failure
Co-Chairs
William Chutkow, Novartis
Vandana Sachdev, NHLBI

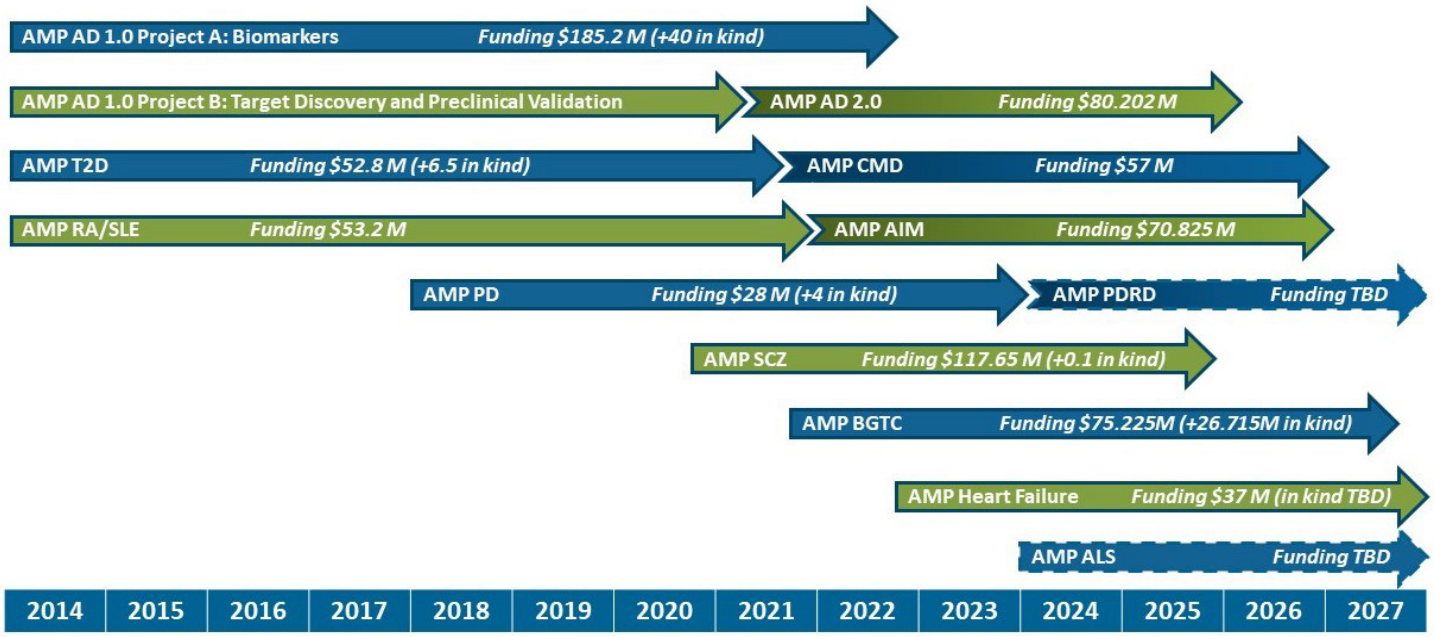
### Parkinson's Disease
Co-Chairs
Pablo Sardi, Sanofi
Deb Babcock, NINDS

### Schizophrenia
Co-Chairs
Carlos Larrauri, NAMI
Linda Brady, NIMH

FUTURE:
**Coming in 2024:**
AMP ALS
AMP Parkinson's Disease and Related Disorders

Learn more about our future programs

# AMP PROGRAM TIMELINES




**For more information, contact:**
**Courtney Silverthorn, PhD**
**AMP Director**
**csilverthorn@fnih.org**

To learn more about each AMP program, scan here

To visit our website, and learn how to support the AMP program, scan here

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# MONDAY, FEBRUARY 5

**8:00-8:55 AM**

## REGISTRATION/BREAKFAST

*REGISTRATION - GRAND BALLROOM C FOYER, MAIN LEVEL*
*BREAKFAST - GRAND BALLROOM E, MAIN LEVEL*

**9:00-9:15 AM**

## WELCOMING REMARKS

*GRAND BALLROOM A-C, MAIN LEVEL*

**Julie Gerberding**, MD, MPH, President and CEO, FNIH

**Lawrence A. Tabak**, DDS, PhD, Principal Deputy Director, National Institutes of Health

**9:15-10:00 AM**

## FIRESIDE CHAT: THE VISION AND LAUNCH OF THE AMP PROGRAM

**Francis Collins**, MD, PhD, Distinguished Investigator, National Human Genome Research Institute and former NIH Director

**David Wholley**, Executive Consultant and former Executive Vice President, Business Development, FNIH

**Courtney Silverthorn**, PhD, Associate Vice President, Science Partnerships and AMP Director, FNIH

**10:00-11:10 AM**

## AMP ALZHEIMER'S DISEASE

Scan here to view the AD 2.0 webpage

The AMP AD session will cover critical aspects of the program, including an overview of goals in both AMP AD 1.0 and AMP AD 2.0. Topics include the impact of sharing clinical trials data, enabling data infrastructure for systems biology research, and a precision medicine approach in AMP AD 2.0. Discussions will also focus on deconstructing disease complexity, integrative proteomics for novel targets, and developing a multi-omic atlas of Alzheimer's disease. These talks aim to provide insights into the program's advancements and contributions.

### SPEAKERS

**Suzana Petanceska**, PhD, Program Director, National Institute on Aging

**Laurie Ryan**, PhD, Chief of the Clinical Interventions and Diagnostics Branch, Division of Neuroscience, National Institute on Aging

**Anna Greenwood**, PhD, Director, Alzheimer's Disease Research Team, Sage Bionetworks

**David Bennett**, MD, Director, Rush Alzheimer's Disease Center, Rush University Medical Center

**Nick Seyfried**, PhD, Professor of Biochemistry and Neurology, Director, Emory Integrated Proteomics Core, Emory University

**Matthias Arnold**, PhD, Adjunct Associate Professor, Department of Psychiatry and Behavioral Sciences, Duke University & Team Leader, Helmholtz Munich

**Rebecca Edelmayer**, PhD, Senior Director, Scientific Engagement, Alzheimer's Association

**Michael Nagle**, PhD, Executive Director, Head of Human Biology Integration Foundation, Eisai

## 11:10 AM-12:20 PM AMP AUTOIMMUNE AND IMMUNE-MEDIATED DISEASES

Scan here to view the AIM webpage

The AMP Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP RA/SLE) successfully deconstructed, at the single-cell level, cellular states and intracellular pathways to identify cellular populations and effector pathways of autoimmune and immune-mediated disease. AMP Autoimmune and Immune-Mediated Disease Program (AMP AIM) continues to move toward better therapeutic interventions by integrating spatially-informed tissue and blood data to reconstruct cellular environments and interactions to identify causative pathways of disease initiation, progression, and damage in Rheumatoid Arthritis, Psoriatic Spectrum Disorder, Sjögren's Disease, and Systemic Lupus Erythematosus. The session will spotlight the tangible benefits achieved through AMP research, with insights from clinical research, industry perspectives, and patient impacts. Attendees can also anticipate exciting updates on the future trajectory of these projects.

### SPEAKERS

**Robert Carter**, MD, Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

**Judith James**, MD, PhD, Executive Vice President and Chief Medical Officer, Oklahoma Medical Research Foundation

**Anna Greenwood**, PhD, Director, Sage Bionetworks

**Michael B. Brenner**, MD, Elizabeth Fay Brigham Professor of Medicine, Harvard Medical School, Director, Cell and Molecular Immunology, Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital

**Jill Buyon**, MD, Director, Division of Rheumatology and Director of the Lupus Center, NYU Grossman School of Medicine

**Caroline Shiboski**, DDS, PhD, MPH, Professor, Department of Orofacial Sciences, School of Dentistry, UCSF

**Jose Scher**, MD, Director, NYU Colton Center for Autoimmunity

**Marc Levesque**, MD, PhD, Vice President, Immunology Discovery, Merck

**Rab Prinjha**, PhD, Vice President and Head of Adaptive Immunity and Immuno-epigenetics Research Unit, GSK

**Mary Collins**, PhD, Scientific Advisory Board, Lupus Research Alliance

## 12:20-1:40 PM LUNCH/SPEED NETWORKING

***LUNCH - GRAND BALLROOM E, MAIN LEVEL***
***SPEED NETWORKING - GRAND BALLROOM FOYER, MAIN LEVEL***

Structured networking from 1:00-1:35pm where small groups will rotate every 5 minutes, providing the opportunity to meet other conference attendees, interact in diverse groups and identify potential follow-up interactions.

## 1:40-2:50 PM AMP COMMON METABOLIC DISEASES

Scan here to view the CMD webpage

AMP CMD is built upon the federated knowledge portal developed for AMP T2D and is continuing to expand genetic, genomic and epigenetic data both from the community and data generated through directed efforts of the AMP T2D and AMP CMD SC. This session will begin with a historical perspective on AMP T2D and CMD, followed by updates on several of the active AMP CMD projects and from Pfizer. The session will conclude with a talk from AMP CMD industry partners on the next steps for AMP CMD.

### SPEAKERS

**Melissa Miller**, PhD, Senior Director of Human Genetics, Internal Medicine Research Unit, Pfizer Research and Development, Pfizer

**Norann Zaghloul**, PhD, Program Director, Division of Diabetes, Endocrinology, & Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH

**Kyle Gaulton**, PhD, Associate Professor in the Department of Pediatrics and Winkler Endowed Professor of Type 1 Diabetes, UCSD

**David Brenner**, MD, President and CEO, Sanford Burnham Prebys and Distinguished Professor of Medicine Emeritus, UCSD

**Panos Roussos**, MD, MS, PhD, Director, Center for Disease Neurogenomics, Icahn School of Medicine at Mt. Sinai

**Johan Bjorkegren**, MD, PhD, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mt. Sinai

**Josh Chiou**, PhD, Senior Principal Computational Geneticist, Pfizer

**Melissa Thomas**, MD, PhD, Vice President-Medical, Diabetes, Obesity, and Complications Research, Eli Lilly and Company

## 2:50-3:05 PM BREAK

*GRAND BALLROOM FOYER, MAIN LEVEL*

## 3:05-4:15 PM AMP PARKINSON'S DISEASE

Scan here to view the PD webpage

The AMP PD session will address key facets of the program, encompassing an overview of goals within AMP-PD. The session will delve into the construction of the AMP-PD platform, highlighting both successful and unsuccessful elements, along with achievements in harmonized data generation for identifying Parkinson's disease biomarkers. These presentations aim to offer valuable insights into the program's progress and contributions.

## 3:05-4:15 PM AMP PARKINSON'S DISEASE

**SPEAKERS**

**Debra Babcock**, MD, PhD, Program Director, Division of Neuroscience, National Institute of Neurological Disorders and Strokes, NIH

**Matt Bookman**, Solutions Architect and Manager, Verily

**Panos Roussos**, MD, MS, PhD, Director, Center for Disease Neurogenomics, Icahn School of Medicine at Mt. Sinai

**Aparna Vasanth Kumar**, PhD, Senior Principal Research Scientist, AbbVie

**Ameya Kulkarni**, PhD, Senior Scientist, Genomics Research Center, AbbVie

**David Craig**, PhD, Vice-Chair, Department of Translational Genomics, USC Keck School of Medicine USC

**Mary Makarious**, National Institute on Aging, NIH

## 4:15-5:15 PM PANEL DISCUSSION: 10 YEARS OF AMP IMPACTS

Since the launch of the AMP program in 2014, these large-scale public-private partnerships have accomplished a number of scientific aims that have had impacts on the broad scientific, medical, and patient communities. This panel will focus on the impacts of the longest-running AMP projects in Alzheimer's Disease, Rheumatoid Arthritis and Lupus, Type 2 Diabetes (launched in 2014) and Parkinson's Disease (launched in 2017).

**MODERATOR**

**Courtney Silverthorn**, PhD, Associate Vice President, Science Partnerships and AMP Director, FNIH

**PANELISTS**

**Lindsey Criswell**, MD, MPH, DSc, Director, National Institute on Arthritis and Musculoskeletal and Skin Diseases, NIH

**Richard Hodes**, MD, Director, National Institute on Aging, NIH

**Walter Koroshetz**, MD, Director, National Institute of Neurological Disorders and Stroke, NIH

**Griffin Rodgers**, MD, MACP, Director, National Institute of Diabetes and Digestive and Kidney Diseases, NIH

**Melissa Thomas**, MD, PhD, Vice President - Medical, Diabetes, Obesity, and Complications Research, Eli Lilly and Company

**Maria Quinton**, PhD, Scientific Director, Precision Medicine Neuroscience, AbbVie

## 5:30-7:15 PM POSTER PRESENTATIONS & RECEPTION

***POSTER PRESENTATIONS - GRAND BALLROOM D, MAIN LEVEL***
***RECEPTION - GRAND BALLROOM FOYER, MAIN LEVEL***

Networking for conference recipients and poster presentations showcasing the breadth of research within the AMP program by highlighting the scientific outcomes, impacts, and ongoing work of AMP-funded research from individual AMP program awardees.

# TUESDAY, FEBRUARY 6

**7:30-8:15 AM**

## REGISTRATION/BREAKFAST

*REGISTRATION - GRAND BALLROOM C FOYER, MAIN LEVEL*
*BREAKFAST - GRAND BALLROOM E, MAIN LEVEL*

**8:15-8:20 AM**

## WELCOME/RECAP

*GRAND BALLROOM A-C, MAIN LEVEL*

**Courtney Silverthorn**, PhD, Associate Vice President, Science Partnerships and AMP Director, FNIH

**8:20-9:30 AM**

## AMP HEART FAILURE

Scan here to view the HF webpage

AMP HF will deconstruct the syndrome of heart failure with preserved ejection fraction (HFpEF), classify potential disease subtypes, and identify specific therapeutic targets through tissue-level phenotyping and advanced analytics.

### SPEAKERS

**Will Chutkow**, MD, Executive Director, Heart Failure Drug Discovery, Cardiovascular & Metabolic Diseases, Novartis Institutes for BioMedical Research

**Vandana Sachdev**, MD, Director, Echocardiography Laboratory, National Heart, Lung, and Blood Institute, NIH

**Ross Upton**, PhD, CEO, Ultromics

**Maggie Redfield**, MD, Consultant, Division of Circulatory Failure, Department of Cardiovascular Medicine, Mayo Clinic (pre-recorded)

**Cynthia Chauhan**, Stage III HFpEF patient (pre-recorded)

**Javed Butler**, MD, MPH, MBA, President, Baylor Scott and White Research Institute and Senior Vice President, Baylor Scott and White Health

**Svati Shah**, MD, MHS, Associate Dean of Genomics and Director, Duke Precision Genomics Collaboratory

**9:30-10:25 AM**

## PANEL DISCUSSION: DATA, DATA EVERYWHERE - AMP PORTALS AND INTEROPERABILITY

This panel session will delve into the successes and lessons learned from 10 years of collective effort across the AMP project data portals. There will be a special focus on the AMP Systems Biology of Inflammation's design phase strategy for cross-project data interoperability and integration and the opportunities and challenges involved. Additionally, the panel will showcase presentations from various AMP data portals, offering insights into their data management strategies and highlighting the impactful outcomes of the data generated by these projects. We hope that this session will play a pivotal role in achieving the symposium's broader goals, showcasing scientific progress, and fostering collaborative discussions within the AMP community and the wider scientific network.

## 9:30-10:25 AM PANEL DISCUSSION: DATA, DATA EVERYWHERE - AMP PORTALS AND INTEROPERABILITY

**MODERATOR**

**Susan Gregurick,** PhD, Associate Director for Data Science and Director, Office of Data Science Strategy, NIH

**PANELISTS**

**Suzana Petanceska**, PhD, Program Director, National Institute on Aging, NIH

**Noel Burtt**, Director, Operations & Development, Diabetes Research & Knowledge Portals in Medical and Population Genetics Program and Metabolism Program, Broad Institute

**Sweta Ladwa**, MPH, PMP, Chief, Scientific Solutions Delivery Branch, Information Technology and Applications Center (ITAC) and Scientific Program Director for BioData Catalyst Data Management Core, NHLBI Technology and Application Center, National Heart, Lung, and Blood Institute, NIH

**Matt Bookman**, Solutions Architect, Verily

**Anna Greenwood**, PhD, Director, Alzheimer's Disease Research Team, Sage Bionetworks

## 10:25-11:35 AM AMP BESPOKE GENE THERAPY CONSORTIUM

Scan here to view the BGTC webpage

The Bespoke Gene Therapy Consortium aims to deliver AAV gene therapies to patients suffering from rare monogenic disorders. The project is adapting the regulatory environment by developing minimum standards for analytical testing and preclinical testing of manufactured AAV gene therapy product. These minimum standards, along with learnings from BGTC clinical trials and best practices identified from our team of AAV gene therapy experts, will be coalesced into a gene therapy clinical development playbook, a publicly available resource.

**SPEAKERS**

**PJ Brooks**, PhD, Deputy Director, Division of Rare Diseases Research Innovation, National Center for Advancing Translational Sciences, NIH

**Tim Miller**, MD, Vice President, Enterprise Science & Innovation, Thermo Fisher Scientific

**Peter Marks**, MD, PhD, Director, Center for Biologics Evaluation and Research, FDA

**Jean Dehdashti**, PhD, Program Officer, Division of Rare Diseases Research Innovation, National Center for Advancing Translational Sciences, NIH

**Amritha Jaishankar**, PhD, Executive Director, Cell & Gene Therapy (CAGT) Center, IQVIA

**Carmen Sivakumaren**, PhD, Manager, Enterprise Transformation Strategy, IQVIA

**Jenny Fam**, Director, MBA, RAC, Director, Regulatory and Drug Development Solutions (RADDS) & Cell & Gene Therapy (CAGT) Center, IQVIA

## 11:35 AM-12:20 PM PANEL DISCUSSION: FNIH PATIENT ENGAGEMENT

This panel will feature discussion and audience Q&A with members of the FNIH's Patient Ambassadors Program, providing tangible examples of FNIH's commitment to patient engagement and enabling best practice sharing across the landscape of AMP programs.

## 11:35 AM-12:20 PM PANEL DISCUSSION: FNIH PATIENT ENGAGEMENT

### MODERATORS

**Julie Gerberding**, MD, MPH, President and CEO, FNIH

**Tania Kamphaus**, MSc, PhD, Director, Translational Science Metabolic Disorders and Director of Patient Engagement, FNIH

### PANELISTS

**Janet Church**, President and CEO, Sjogren's Foundation (AMP AIM)

**Terry Pirovolakis**, CEO, Elpida Therapeutics and Founder, CureSPG50 (AMP BGTC)

**Sharon King**, Manager, Advocacy and Community Engagement, Aldevron (AMP BGTC)

**Carlos Larrauri**, MSN, National Alliance on Mental Illness (AMP Schizophrenia)

**Rebecca Edelmayer**, PhD, Senior Director, Scientific Engagement, Alzheimer's Association (AMP Alzheimer's Disease)

**Maggie Kuhl**, Vice President, Research Engagement, The Michael J. Fox Foundation for Parkinson's Research (AMP Parkinson's Disease)

**Will Chutkow**, MD, Executive Director, Heart Failure Drug Discovery, Cardiovascular & Metabolic Diseases, Novartis Institutes for BioMedical Research (AMP Heart Failure)

**Joni Rutter**, PhD, Director, National Center for Advancing Translational Sciences, NIH (AMP BGTC)

## 12:20-1:10 PM LUNCH

*GRAND BALLROOM E, MAIN LEVEL*

## 1:10-2:20 PM AMP SCHIZOPHRENIA

Scan here to view the SCZ webpage

The AMP SCZ session ensures a thorough exploration of the program's key elements. Commencing with a warm welcome and an insightful overview of the AMP SCZ project, we'll establish a foundation for an in-depth discussion on digital assessment strategies and their implementation. Delving further, the session will illuminate the substantial contribution of regulatory science to schizophrenia research, offering a pharmaceutical perspective on unlocking the potential of digital measures. By centering the narrative around patient experience, we breathe life into the story with vivid anecdotes and best practices, infusing authenticity into the unfolding narrative. To conclude, the session invites active participation in an engaging Q&A, empowering participants to shape the ongoing adventure of learning and discovery with their voices.

### SPEAKERS

**Joshua Gordon**, MD, PhD, Director, National Institute of Mental Health, NIH

**Justin Baker**, MD, PhD, Associate Professor of Psychiatry, Harvard Medical School

**Gahan Pandina**, PhD, Senior Director, Compound Development Team Leader, Neuroscience at Janssen Research & Development

**Carlos Larrauri**, MSN, National Alliance on Mental Illness

**Brandon Staglin**, MS, President, One Mind

**Linda Brady**, PhD, Director, Division of Neuroscience and Basic Behavioral Science, National Institute of Mental Health, NIH

**Valentina Mantua**, MD, PhD, Clinical Team Leader, Office of Neuroscience, Division of Psychiatry, CDER, FDA

**2:20-3:00 PM**

## PANEL DISCUSSION: REGULATORY ENGAGEMENT IN THE AMP PROGRAM

This panel discussion will focus on how AMP projects engage with regulators to accelerate therapies and diagnostics through the regulatory process to the patients that need them. We will discuss how public-private partnerships promote innovation and efficiency in the development of regulated products. For example, in rare diseases, regulatory streamlining, data leveraging, and innovative clinical trial designs are among the approaches that may expedite cell and gene therapy products advancement to the clinical.

**MODERATOR**

**Stacey Adam**, PhD, Associate Vice President, Science Partnerships, FNIH

**PANELISTS**

**Norm Stockbridge**, MD, PhD, Director, Division of Cardiovascular and Renal Products, Center for Drug Evaluation and Research, FDA

**Jeff Siegel**, MD, Office Director, Office of Drug Evaluation Sciences, FDA

**Teresa Buracchio**, MD, Director, Office of Neuroscience, Center for Drug Evaluation and Research, FDA

**Gopa Raychaudhuri**, PhD, Associate Director for Special Programs, Center for Biologics Evaluation and Research, FDA

**Hilary Marston**, MD, MPH, Chief Medical Officer, FDA

**3:00-3:15 PM**

## BREAK

*GRAND BALLROOM FOYER, MAIN LEVEL*

**3:15-3:55 PM**

## CLOSING KEYNOTE: THE NEXT 10 YEARS OF THE AMP PROGRAM

**Mikael Dolsten**, MD, PhD, Chief Scientific Officer and President, Worldwide Research, Development, and Medical, Pfizer

**3:55-4:00 PM**

## CLOSING REMARKS

**Courtney Silverthorn**, PhD, Associate Vice President, Science Partnerships and AMP Director, FNIH

**4:00-5:30 PM**

## AMP LEADERSHIP RECEPTION

*LINDEN OAK, LOWER LEVEL*

**By Invitation**

# POSTER ABSTRACTS

### 1. AMP Alzheimer's Disease: Enabling a Precision Medicine Approach to Target and Biomarker Discovery

Francesca Cignarella, PhD

Foundation for the National Institutes of Health, North Bethesda, MD

The Accelerating Medicines Partnership® (AMP®) Alzheimer's Disease (AMP AD) has played a pivotal role in revolutionizing our comprehension of Alzheimer's disease (AD). Launched in 2014, AMP AD initiated a groundbreaking collaboration among government, industry, and nonprofits, with a specific focus on discovering novel, clinically relevant therapeutic targets and validating existing therapeutic targets for AD by embedding PET Tau imaging in clinical trials. Building on this success, AMP AD 2.0, an ongoing precompetitive public-private partnership, aims to elevate target discovery and enable precision medicine research for AD, utilizing data from diverse cohorts. The program's goals in AMP AD 2.0 are ambitious, aiming to identify and validate new targets and biomarkers associated with different molecular subtypes of AD, thereby facilitating targeted treatments. Furthermore, it endeavors to map AD progression at a cellular and molecular level, offering a dynamic understanding of the disease. AMP AD 2.0 is committed to increasing access to de-identified data from diverse cohorts, with a particular emphasis on prioritizing information from at-risk populations such as Black and Latinx communities. Results and accomplishments from AMP AD include the generation of rich, human multi-omic data accessed by thousands of users. This has led to the establishment of new mechanistic insights into the role of the genome, proteome, metabolome, and microbiome. Molecular network models of disease pathways have expanded, and the Agora Platform offers access to 900+ unique targets, accompanied by comprehensive druggability information. Overall, AMP AD and its subsequent iteration, AMP AD 2.0, exemplify significant strides in advancing our understanding of AD and pave the way for targeted therapies. The commitment to diverse data sources and the focus on at-risk populations underscore the program's dedication to combating Alzheimer's disease.

### 2. Using iPSC models to capture the genetic and molecular heterogeneity of human Alzheimer's disease

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The Young-Pearse lab focuses on the identification of the molecular mechanisms that cause Alzheimer's disease (AD), with the ultimate goal of finding novel therapeutic targets. Beyond the recently FDA-approved anti-beta amyloid monoclonal antibody therapies (i.e. Aducanumab, Lecanumab), there has yet to be a treatment for AD that efficiently slows progression in the majority of individuals. AD manifests along a spectrum of cognitive deficits and levels of neuropathology. Genetic studies support a heterogeneous disease mechanism, with around 70 associated risk loci to date, implicating biological processes that mediate risk for AD. These processes fall into a diverse set of molecular and cellular pathways such as synaptic maintenance, lipid metabolism, intracellular trafficking, and inflammatory response. Despite this heterogeneity, most experimental systems for testing new therapeutic strategies are not designed to capture the genetically complex drivers of AD risk. We have generated induced pluripotent stem cells (iPSCs) from over 100 individuals in the Religious Orders Study and Memory and Aging Project (ROS-MAP) cohorts. Data collected from these participants includes genome sequencing, longitudinal cognitive scores, quantitative neuropathology, and multi-omic characterization of brain tissue. Our approach leverages these rich datasets to cross-validate convergent molecular systems disrupted between our cellular models and the processes in the brain of the individuals from whom they were derived. To this end, we have shown the utility of this approach using a variety of experimental models that range from highly reductionist monocultures of single brain cell-types to complex microphysiological systems that incorporate several different brain cell fates. We have identified molecular processes disrupted with genetic risk for AD that are concordant between our cellular systems and brain tissue from the same individuals. We have also employed CRISPR technology in these models to evaluate how specific genes (SORL1, INPP5D) are involved in driving risk for AD across brain cell-types.

### 3. Integrative multi-omic analyses for identification of potential therapeutic targets in Alzheimer's Disease

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Alzheimer's disease (AD) remains a complex neurodegenerative challenge, and the dysregulation of sphingomyelin and ceramide metabolism has emerged as a crucial player in its pathogenesis. While genome-wide and transcriptome-wide studies have pinpointed genes and variants associated with lipid metabolism in AD, the molecular mechanisms underlying sphingomyelin and ceramide disruption remain unknown. In this study, we employed a comprehensive multi-omics approach to investigate the central and peripheral metabolic changes in AD patients, correlating them with imaging features for translational research. Our methodology encompasses a spectrum of analyses: (a) transcriptomics of 2114 human post-mortem brain to identify differentially expressed genes; (b) in silico metabolic flux analysis on context-specific metabolic networks to identify altered reaction fluxes; (c) multimodal neuroimaging analysis to associate genetic variants in the sphingomyelin pathway with AD pathogenesis; (d) performing plasma metabolomic and lipidomic analysis to understand associations between lipid species and AD dysregulation; and (e) executing metabolite genome-wide association studies to identify potential drug targets within the pathway. Using these orthogonal approaches, we were able to identify sphingosine-1-phosphate (S1P) as the key molecule in this pathway. We tested our hypothesis using Fingolimod (an FDA approved drug for MS treatment) that modulates the S1P receptor (S1PR) activity and using experimental data we showed that the APP/PS1 mice treated with Fingolimod shows cognitive improvement. Thus, repurposing of drugs that target sphingomyelin pathway and modulate S1P receptor activity could correct the dysregulation and potentially improve memory and synaptic function. Our integrative multi-omics strategy not only identifies potential therapeutic targets within the sphingomyelin pathway but also highlights modulators of sphingosine-1-phosphate (S1P) metabolism as promising candidates for treating AD. This translational research highlights the power of multi-omics analyses in understanding the molecular complexity in AD, providing insights for potential therapeutic interventions.

### 4. Resolving race and sex-based heterogeneity in Alzheimer's Disease through network-based molecular subtyping of the CSF proteome

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Alzheimer's Disease (AD) is categorized by the accumulation of amyloid-beta plaques and Tau tangles within the brain, leading to dementia and cognitive decline. A wide range of genetic and demographic factors, such as race, sex, and APOE genotype intersect to drive axes of AD pathology, resulting in a molecular heterogeneity that makes AD incredibly complicated to diagnose and treat. For example, recent data has shown levels of cerebrospinal fluid (CSF) Tau, a key AD diagnostic biomarker, are lower in African Americans, which leads to later diagnosis, lower enrollment in clinical trials, and exclusion from biomedical sample collection. Thus, there is a pressing need for an effective model for characterizing the differing molecular manifestations of AD across diverse populations. To better resolve this complexity, we have established a novel integrated protein co-expression network and modularity clustering approach to resolve six distinct proteomic subtypes across 483 CSF samples, including almost 150 from African American participants. Of these subtypes, Subtype 3, which was comprised evenly of AD and control subjects and enriched with African Americans and men, was of particular interest, as it displayed CSF amyloid-beta levels consistent with AD-like subtypes, but reduced levels of Tau, consistent with control-like subtypes. Subtype 3 also had very high levels plasma enriched components such as albumin, immunoglobulins, and proteolytic enzymes, likely indicating a breakdown of the blood brain barrier and infiltration of these components into the CSF, which we hypothesize is responsible for the cleavage and depletion of CSF Tau in this population.

### 5. Agora: An open-access platform for the exploration of nascent targets for Alzheimer's disease therapeutics

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Agora (https://agora.adknowledgeportal.org) is an open resource developed to enable a broad spectrum of Alzheimer's disease (AD) researchers access to target-based evidence generated within the translational research portfolio of the National Institute on Aging (NIA). Agora aims to accelerate AD research and maximize therapeutic discovery by sharing information using interactive tools, data visualizations, and summarized evidence. Agora users can browse a list of over 900 targets nominated by the NIA's Accelerating Medicines Partnership in AD (AMP-AD) consortium and Target Enablement to Accelerate Therapy Development for AD (TREAT-AD) centers, and by the broader AD research community; see visualizations and summarized information based on harmonized genome-wide analyses of high-dimensional human transcriptomic, proteomic, and metabolomic data; use interactive visualizations designed to enable non-bioinformaticians to evaluate and compare complex multi-omic data; and access the underlying data that drives the results and visualizations. The advancement of promising new AD therapeutics requires efforts that span research groups and specialties across academia and industry. The Agora platform enables the AD research community to unite around target hypotheses to accelerate the investigation of promising new therapeutic targets, pathways and mechanisms.

### 6. Creating bridges to data: connecting aging & dementia research from the AD Knowledge Portal to CAVATICA

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Integration of rich biomedical datasets with analytical environments can support enhanced data reuse and collaboration across research communities. The AD Knowledge Portal (https://adknowledgeportal.org) is a freely accessible, open platform for rapid sharing of well-annotated, high-quality data; including data generated from human brain, spinal fluid, and blood samples as well as animal and cell-based AD models. Data in the portal is contributed by nine research consortia affiliated with the National Institute on Aging's (NIA) translational research portfolio, and by the greater AD research community as part of the Community Data Contribution Program. As part of a goal to provide seamless, secure access to the biomedical datasets hosted in the AD Knowledge Portal, we used the open Data Repository Service (DRS) API to interoperate with CAVATICA, a cloud-based data analysis and sharing platform designed to empower analysis across diseases and geography. CAVATICA allows researchers to securely work with data from diverse repositories, including the Exceptional Longevity Translational Resources (ELITE) Portal (https://eliteportal.synapse.org), BioData Catalyst, and dbGaP; access standardized computational tool libraries and genomic workflows; and use collaborative workspaces to minimize the cost of downloading or transferring data from the cloud. With this integration, AD Knowledge Portal users can leverage new, sophisticated tools to further analyze portal data in combination with other research datasets and accelerate novel discoveries in the field of Alzheimer's Disease and related dementias.

### 7. Brain metabolic imprint of Alzheimer's disease (AD) and progressive supranuclear palsy (PSP)

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Neurodegenerative diseases exhibit selective vulnerability in specific brain regions, marked by higher neurodegeneration, synaptic loss, and pathological protein aggregation. This selective vulnerability observed is believed to arise, in part, from the differing metabolic demands of the brain regions. To investigate these metabolic differences, our study investigated AD and PSP-related metabolic alterations in approximately 800 brains from the dorsolateral prefrontal cortex (DLPFC), cerebellar cortex (CER), and temporal cortex (TCX). Within the DLPFC region (ROS/MAP cohort), our novel metabolic insights into AD include (1) Broad impairment of osmoregulation as a potentially relevant pathomechanism. (2) An imbalance between excitatory/inhibitory neurotransmitter ratios, determined by integrating our metabolomic findings with additional proteomic data. (3) Tau load as a potential driver of metabolic dysfunction in the AD brain, with minimal contributions from the b-amyloid load. In our analysis of the CER and TCX regions (Mayo cohort), we compared the metabolic changes in AD and progressive supranuclear palsy (PSP). Findings from this comparison include (1) CER, despite its limited gross neuropathology, showed higher AD-related metabolic alterations than the TCX. (2) in PSP, the TCX exhibited fewer metabolic changes than the CER. (3) Despite their differences, AD and PSP share alterations in certain metabolic processes. Overall, (1) we identified biochemical processes altered in AD, with findings supported across both metabolomic and proteomic data, indicating multimodal deregulation. (2) Our research pinpointed widespread AD-related biochemical changes across various brain regions with differing levels of neuropathology. While there are many overlapping changes across the brain regions, each region also has its distinct metabolic alterations. (3) We identified biochemical processes disrupted by AD, with parallel findings in other neurodegenerative diseases, hinting at broader implications in neurodegenerative research.

### 8. Multi-Omics Profiling of Brain Tissue in Alzheimer's Disease and Older Controls in Multi-Ethnic Populations: AMP AD Diversity Initiative

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Background: Alzheimer's disease (AD) disproportionately affects African Americans (AA) and Latin Americans (LA). The disproportionate risk is likely multifactorial including differences in molecular and exposomal risk factors. To address this knowledge gap, the Accelerating Medicine Partnership for Alzheimer's Disease (AMP-AD) Diversity Initiative was launched to generate and curate multi-omics and exposome measures from donors of predominantly AA and LA descent. Methods: Brain tissue from dorsolateral prefrontal cortex (DLPFC), caudate nucleus (CN), superior temporal gyrus (STG) and temporal pole (TP) regions of AA (N=299), LA (N=344) and NHW (N=532) donors was obtained through Mayo Clinic, Mt. Sinai School of Medicine, Emory, Columbia, Rush Alzheimer's Disease Center, Banner Sun Health, and 1Florida ADRC. Whole genome sequencing (n=621) and RNA sequencing (n=2,542) was conducted either at Mayo, Rush or New York Genome Center. Sequencing reads were processed for WGS and RNAseq data. Following quality control (QC), RNAseq data was normalized and assessed for sources of variation (SOV). Exposome measures, such as education, occupation, bilingualism, alcohol consumption, smoking history, Area Deprivation Index (ADI) and additional neuropathological data are being collected and deposited in the AD Knowledge Portal. Results: WGS data for 621 donors, and RNAseq data generated at Mayo (n=1,136 samples), Rush (n=627), and NYGC (n=779) sequencing centers, were deposited to the AD Knowledge Portal. Consensus processing of RNAseq data revealed site, sex, race/ethnicity, RIN, AD diagnosis, age at death and/or library batch as SOV across various sites and brain regions. Principal component analysis of gene expression measures revealed no major stratification by disease or brain region. Integration of downstream analysis of these omics measures is ongoing. Conclusions: These multi-omics data made available to the research community is expected to be an initial step towards bridging our data and knowledge gap to elucidate conserved and distinct AD related pathways across these underrepresented at-risk populations.

### 9. From Deconstruction to Reconstruction: AMP RA/SLE and AMP AIM are Redefining Autoimmune Disease Research Toward Better Therapeutic Interventions

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The Accelerating Medicines Partnership® (AMP®) Rheumatoid Arthritis and Systemic Lupus Erythematosus (RA/SLE) program launched in 2014 as one of the founding projects in the AMP program. AMP RA/SLE was a pivotal effort to "deconstruct" autoimmune disease at the single-cell level. Through the analysis of over 100 synovial biopsies in rheumatoid arthritis (RA) and over 200 renal biopsies in systemic lupus erythematosus (SLE), investigators explored cellular states and intracellular pathways to identify cell populations and effector pathways of autoimmune and immune-mediated disease. The success of AMP RA/SLE catalyzed the continuous transition to the AMP® Autoimmune and Immune-Mediated Diseases (AIM) program and the expansion of disease areas to include RA, SLE, Psoriatic Spectrum Disorder (PSD), and Sjögren's Disease (SjD). Launched in 2021, AMP AIM represents a paradigm shift, using spatially-informed tissue and blood data to "reconstruct" cellular environments and interactions to identify causative pathways of disease initiation, progression, and damage. AMP AIM continues the legacy of its predecessor by not only seeking to better understand and treat disease, but also redefining research methodologies in these disease areas and tissues with groundbreaking protocols and cutting-edge technologies. AMP AIM will enable the advances needed to move beyond treatments focused on reducing inflammation and limiting tissue damage, to providing the data and methods to empower 1) a comprehensive understanding of autoimmune diseases and their mechanisms for patients and their doctors, 2) the identification of novel biomarkers and pathways (shared and unique), and 3) the creation of better treatments targeted at specific patient molecular profiles.

### 10. Cell-type abundance phenotypes (CTAPs) classify heterogeneity of rheumatoid arthritis synovium into clinically relevant inflammatory subtypes

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Rheumatoid arthritis (RA) is an autoimmune disease that affects approximately 0.5-1% of the population. Many different classes of biologic and small-molecule treatment are approved to treat this disease, but only a limited percentage of patients respond well to a given therapy, and some patients do not respond to any available treatments. Despite extensive studies, no clinical factors (e.g. laboratory values, joint involvement patterns) have been found that can predict response to a given treatment, leading many patients to undergo a months- or years-long trial-and-error process. In this study, we used multi-modal CITE-seq to analyze 314,000 cells from synovial tissue from 70 donors with RA and 9 donors with osteoarthritis. We classified synovial tissue heterogeneity into six categories we call cell-type abundance phenotypes (CTAPs) based on the abundance of B cells, endothelial cells, fibroblasts, myeloid cells, NK cells, and T cells. While this classification system relies solely on the frequency of these coarse cell types, CTAPs are associated with specific cell subsets and molecular pathways, such as CD4+ peripheral helper T cells, CD11c+ autoimmune-associated B cells, mural fibroblasts, and MERTK+ myeloid cell states. These cell states and molecular associations provide insights into the molecular drivers of each inflammatory synovial subtype. Interestingly, CTAPs are dynamic with time and treatment and can predict treatment response. CTAPs can be inferred from bulk RNA-seq data or flow cytometry, putting classification systems within easier logistical reach of clinical trials and other large-scale translational studies. In summary, the CTAPs are a biologically relevant, tissue-based system to describe and classify heterogeneity in rheumatoid arthritis synovial tissue. A similar approach may be useful to consider for other tissue-based autoimmune and autoinflammatory diseases.

## 11. Blood immunophenotyping identifies distinct kidney histopathology and outcomes in patients with lupus nephritis

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Lupus nephritis (LN) is a frequent manifestation of systemic lupus erythematosus, and fewer than half of patients achieve complete renal response with standard immunosuppressants. Identifying non-invasive, blood-based pathologic immune alterations associated with renal injury could aid therapeutic decisions. Here, we used mass cytometry immunophenotyping of peripheral blood mononuclear cells in 145 patients with biopsy-proven LN and 40 healthy controls to evaluate the heterogeneity of immune activation in patients with LN and to identify correlates of renal parameters and treatment response. Unbiased analysis identified 3 immunologically distinct groups of patients with LN that were associated with different patterns of histopathology, renal cell infiltrates, urine proteomic profiles, and treatment response at one year. Patients with enriched circulating granzyme B+ T cells at baseline showed more severe disease and increased numbers of activated CD8 T cells in the kidney, yet they had the highest likelihood of treatment response. A second group characterized primarily by a high type I interferon signature had a lower likelihood of response to therapy, while a third group appeared immunologically inactive by immunophenotyping at enrollment but with chronic renal injuries. Main immune profiles could be distilled down to 5 simple cytometric parameters that recapitulate several of the associations, highlighting the potential for blood immune profiling to translate to clinically useful non-invasive metrics to assess immune-mediated disease in LN.

### 12. Spatial Reconstruction of Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation in the synovium. RA is clinically heterogenous, with patients having varied responses to therapies, likely reflecting distinct pathogenic mechanisms. A recent study showed that the fractional abundances of 5 cell types can help predict treatment response in some subsets of RA. With the goal of better understanding the spatial organization of cells in RA synovial tissues and mapping cell-cell interactions, we sought to take a key next step in defining RA heterogeneity and its relation to treatment response. Results: We successfully applied CosMX spatial transcriptomics to characterize 333,966 high quality cells across 10 RA synovial tissue samples. Cells were subclassified cells into 54 subtypes and activation states based on prior definitions from the AMP single-cell RNA-seq atlas of inflamed synovium. Next, we mapped annotated cells into tissue space, where they organized into anatomic structures: vasculature (endothelial and mural cells), lining (lining fibroblasts and MERTK+ macrophages), and immune aggregates (T, B, and plasma cells). We quantified the boundaries of these niches and identified all niches in most samples. We next quantified the relative composition of niches within and across donors and observed significant heterogeneity of niches within patient samples. We validated our spatial organization results in an independent inflamed synovial tissue cohort from 3 patients with treatment naïve RA. Using our pipeline, we found similar proportions of cell types and organization of cells into the canonical niches defined in our spatial atlas. Conclusion: We established a draft spatial atlas of RA synovium and provided spatial context for 54 cell types, subtypes, and activation states observed in dissociated tissue assays. This atlas will serve as a reference to map the cellular organization in different cohorts as demonstrated and eventually enable us to compare the effects of different therapeutics on the RA tissue.

### 13. Single-Cell and Spatially Aware Technologies offer New Pathological Insights into Sjögren's Disease

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Background/Objectives: Compare 3' and 5' scRNA-seq of viably frozen minor salivary gland (MSG) biopsies collected from Sjögren's disease (SjD) patients to single-cell transcriptomics of formalin-fixed paraffin-embedded (scFFPE), tissue classification, 10X Xenium, and Imaging Mass Cytometry (IMC) of FFPE MSG biopsies. Methods: For 3' and 5' scRNA-seq, viably frozen MSG (2 SjD, 5 healthy controls (HCs)) were thawed, dissociated, counted, and split (targeting 8000-10000 cells). Using the 10X Flex/scFFPE protocol, 25mm sections from FFPE MSG were dissociated. Cells were counted, labelled, and captured (8000-20000 per tissue). Sequencing data were analyzed (CellRanger), ambient RNAs corrected (SoupX), and doublets detected (scDblfinder). Cells with feature counts <200 or >5000, mitochondrial percent >5%, and doublets were removed. Tissue sections adjacent to scFFPE sections were H&E stained and analyzed (HALO AI-based tissue classifier). A 25-plex IMC panel stained major cell populations, then cell segmentation (Mesmer, DeepCell) and spatial analyses (IMACytE, Somarakis, 2019) were performed. Results: scFFPE, 3', and 5' scRNA-seq yielded similar feature/gene counts per cell (median= 4571, 5186, 7452, respectively). scFFPE exhibited superior ambient RNA reduction and discrete cell population identification. An expanded scFFPE dataset (8 SjDRo+, 9 HCs) yielded 371,454 cells among 23 cell states. Cells were separated into immune and non-immune clusters and annotated (CellTypist or MSG reference data), then differentially expressed (DE) genes ($p<0.02$) were identified using a pseudobulk approach (DESeq2) and subjected to Ingenuity Pathway Analysis. Immune and glandular cell DE genes mapped to both common and different pathways in SjD Ro+ vs. HCs, including Type I interferon: downregulation (plasma cells, plasmacytoid DCs, naive B cells) upregulation (migratory DCs, DC1, seromucous and mucous acini, macrophages, mast cells). Conclusions: scFFPE yielded superior single-cell data compared to 3' and 5' using viable cells. Hyperian IMC and Xenium analyses are ongoing. Going forward, scFFPE and Xenium followed by IMC datasets will be expanded.

### 14. AMP Autoimmune & Immune-Mediated Diseases Research Poster

Andrea Fava

Please view poster board for further information.

### 15. The Bespoke Gene Therapy Consortium (BGTC), a public-private partnership advancing AAV gene therapies for rare diseases

Brad Garrison

Foundation for the National Institutes of Health, North Bethesda, MD

The Bespoke Gene Therapy Consortium (BGTC) was formed by the Foundation for the National Institutes of Health (FNIH) as part of the Accelerating Medicines Partnership® programs to address the challenge of developing AAV gene therapies for diseases of no commercial interest. It brings together 35 partner organization from the NIH, FDA, industry, and non-profit partners with extensive experience in designing, developing and manufacturing AAV-based gene therapies to collaborate in a pre-competitive space. One objective of the BGTC is to increase efficiency by streamlining the development pathway for AAV gene therapies to conduct first-in-human clinical trials and facilitate more timely access for patients to promising new therapies. To achieve this objective, the BGTC will support up to 8 clinical trials for diseases of no commercial interest spanning ocular, CNS, and systemic routes of administration. The BGTC is taking an end-to-end approach utilizing established AAV serotypes, standardizing processes, and exploring opportunities for regulatory streamlining to accelerate product development and promote patient access. While the focus of the BGTC is on diseases that are currently of no commercial interest, it is anticipated that the program will have broader impact on the gene therapy field as the technologies, paradigms, and information gained can be applied to the development of AAV gene therapies for common disorders with higher prevalence.

### 16. AAV8 Gene Therapy Clinical Trial for Morquio A

Allison Bradford; Kimberly Klipner, RN, BSN, MS, CCRC; Shunji Tomatsu MD, PhD; W. G. Stuart Mackenzie, MD

Background. Mucopolysaccharidosis IVA (MPS IVA, Morquio A syndrome), is a rare genetic disorder caused by lysosomal enzyme deficiency of, N-acetylgalactosamine-6-sulfate sulfatase, resulting in the accumulation of keratan sulfate and chondroitin-6-sulfate in multiple tissues. This enzyme deficiency causes systemic skeletal dysplasia, cardiac valve abnormalities, limited endurance, corneal clouding, and cervical instability. Limited treatment options have been available, including surgical management, Enzyme Replacement Therapy (ERT), and Hematopoietic Stem Cell Transplant (HSCT). Study Description. AAV8LM-GALNS, an adeno-associated virus, serotype 8 (AAV8), expressing a functional copy of human N-acetylgalactosamine-6-sulfate sulfatase (hGALNS) under the control of the tissue-specific (liver-muscle tandem) promoter, will be administered via a single intravenous (IV) infusion. We hypothesize that transduced cells will provide supraphysiological levels of enzyme activity in circulation, resulting in systemic delivery of enzymes into target tissues, including bone, cartilage, connective tissues, and visceral organs, and successive improvement of critical symptoms, including skeletal dysplasia. The study duration will last approximately 72 months (about 6 years), including enrollment and follow-up. Objectives. The study aims to evaluate the safety and tolerability of the use of AAV8 gene therapy in Morquio A patients. Secondary objectives include preliminary clinical efficacy and long-term safety of AAV8 Gene Therapy. Study Population. A sample size of approximately 12 patients is expected to be comprised of 1 adult initially in each dose cohort and 10 pediatric patients. Pediatric patients will include only MPS IVA patients who have radiographically open growth plates with a minimum growth velocity of 2.0 cm/yr before treatment and have not undergone successful hematopoietic stem cell transplantation (HSCT) and otherwise meet the inclusion and exclusion criteria. Clinical Endpoints. Clinical endpoints will be evaluated by assessing biomarkers that reflect disease state from blood and urine samples, gait analysis, respiratory function, skeletal imaging, joint laxity, hearing function, questionnaires, echocardiograms, multi-domain response index, and iliac crest biopsy.

### 17. Preclinical studies supporting the use scAAV9/SUMF1 for the treatment of Multiple Sulfatase Deficiency

Rachel M Bailey[1,3], Maximiliano Presa[2], Somdatta Ray[2], Lauren Bailey[1], Saurabh Tata[2], Tara Murphy[2], Harold Combs[2], Steven J Gray[3], Cathleen Lutz[2]

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Multiple Sulfatase Deficiency (MSD; OMIM #272200) is a rare, autosomal recessive pediatric lysosomal storage disease. Currently no specific treatments exist for this disorder and patients have progressive neurologic dysfunction with multisystem involvement that is eventually fatal. The disease pathology is due to homozygous loss-of-function mutations in the SUMF1 gene. The SUMF1 gene encodes formylglycine-generating enzyme, which is required for post-translational modification and activation of sulfatase enzymes. As such, pathogenic mutations in the SUMF1 gene impact the function of all sulfatase enzymes, leading to a broad phenotypic spectrum that overlaps with known inherited sulfatase disorders. Gene therapy may provide a meaningful and long-term therapeutic benefit for MSD patients by delivering a functional copy of the SUMF1 gene to patient cells. We developed a self-complementary vector encoding a codon-optimized human SUMF1 gene (scAAV9/SUMF1), the unaltered design of which could be appropriate for human use. Using a severe Sumf1 knock-out (KO) mouse model of MSD, we tested the benefits of treatment with our vector in mice shortly after birth and later in the disease course by administering virus into the cerebrospinal fluid (CSF) alone or in combination with an intravenous injection. CSF administration of scAAV9/SUMF1 was sufficient to rescue early lethality, normalize behavior and improve newly identified visual and cardiac dysfunctions in KO mice, even when given at an advanced disease stage. We found dose-dependent and long-term restoration of sulfatase activity in tissues, which is accompanied by decreased accumulation of glycosaminoglycans, lysosomal defects and neuroinflammation in the brain. Even at the highest dose tested, scAAV9/SUMF1 was well-tolerated without toxicity from high transgenic SUMF1 expression in KO and wild-type mice or in rats that were treated as part of a GLP-toxicology study. Overall, our preclinical results attest to the safety of scAAV9/SUMF1 delivery and predict a benefit of this treatment to MSD patients.

### 18. Corneal intrastromal AAV8 delivery of human SLC4A11 gene rescues corneal edema in Slc4a11-/- mouse model of Congenital Hereditary Endothelial Dystrophy

Wenlin Zhang, Doug Chung, Matthew Hirsch, Anthony Aldave

Purpose: Congenital Hereditary Endothelial Dystrophy (CHED) is caused by biallelic mutations in SLC4A11. The Slc4a11-/- mouse model recapitulates the clinical phenotype of CHED, characterized as progressive corneal edema due to corneal endothelial dysfunction. We evaluated the efficacy of intrastromal delivery of a recombinant AAV8 vector encoding human SLC4A11 cDNA under transcriptional control of human elongation factor-1 alpha promoter - rAAV8-EF1a-hSLC4A11. Methods: A single corneal intrastromal injection of 3 µL rAAV8-EF1a-hSLC4A11 was performed in one eye of Slc4a11-/- mice at 4 weeks of age. Three dosages were tested: 10e9 (n = 13), 10e8 (n = 10), 10e7 vg/eye (n = 10). For each mouse, the eye receiving the AAV8 vector was randomized, and the contralateral eye served as the control. Anterior segment OCT was performed in both eyes before injection and bi-weekly after injection until post-injection week 8 to measure central corneal thickness (CCT, mean ± SEM). Results: AAV injected eyes showed a sustained reduction of CCT from baseline in a dose-dependent manner. The CCT (µm) at baseline and post-injection week 8 exams were: for 10e9 vg/eye group, 161.1 ± 3.3 and 144.8 ± 6.5 (Mixed-effects analysis post-hoc multiple comparison, $p = 0.02$) in AAV injected eyes and 160.2 ± 2.7 and 197.2 ± 6.6 ($p < 0.0001$) in contralateral control eyes; for 10e8 vg/eye group, 162.5 ± 3.2 and 150.7 ± 2.4 ($p = 0.001$) in AAV injected eyes and 166.7 ± 5.2 and 180.2 ± 5.0 ($p = 0.13$) in control eyes; for 10e7 vg/eye group, 152.8 ± 6.1 and 160.3 ± 5.7 ($p = 0.31$) in AAV injected eyes and 154.7 ± 3.4 and 218.7 ± 7.5 ($p = 0.0004$) in control eyes. Conclusions: Intrastromal delivery of rAAV8-EF1a-hSLC4A11 effectively rescues corneal edema in Slc4a11-/- mice, indicating a functional recovery of corneal endothelial pump function.

### 19. Natural history of CNGB1-associated retinitis pigmentosa 45

Promie R. Faruque, Aykut Demirkol, Marilyn S. Rodriguez, Jorge I. Pincay, Janet R. Sparrow, Stephen H. Tsang

Purpose: This study expands on previous research linking autosomal recessive retinitis pigmentosa (RP) 45 with mutations in the CNGB1 gene, a small gene with 12 exons located on chromosome 16q21. Our aim was to better understand the clinical manifestations and the natural trajectory of CNGB1-associated RP, particularly monitoring the ellipsoid zone (EZ) horizontal width as an indicator of disease progression. Methods: The cohort included 12 participants (7 females), each diagnosed with RP and with confirmed pathogenic mutations in the CNGB1 gene, as part of the comprehensive natural history study conducted at the Division of Ophthalmic Genetics, Harkness Eye Institute, Columbia University. Extensive ophthalmic evaluations were performed, including spectral-domain optical coherence tomography (SD-OCT), short-wave autofluorescence (SW-AF), and color fundus photography using the Optos 200Tx system. We employed manual segmentation of the EZ horizontal width on OCT images, taken initially and at subsequent follow-ups, to gauge disease severity and track its progression. Results: Participant ages at initial visit ranged from 16 to 72 years, with best corrected visual acuity varying from 20/20 to complete absence of light perception. The initial mean EZ horizontal width was 4866.25 micrometers (standard deviation (sd)=2372.38). The logarithmic scale of the initial EZ width averaged at 8.38 (sd=0.51). Annually, the raw EZ horizontal width showed an average reduction of 124.28 micrometers (sd=132.35, p-value<0.05). Similarly, the log-transformed EZ width had an average annual decline of 0.03 (sd=0.04, p-value<0.05). Conclusion: Our findings reveal a gradual yet statistically significant decrease in the EZ horizontal width among our patient cohort, indicative of marked disease progression. The observed rate of EZ width reduction is comparable to that in other genetic forms of autosomal recessive RP. Identifying more patients with CNGB1 mutations and conducting earlier baseline assessments, coupled with extended follow-up durations, are crucial for a deeper understanding of disease progression.

### 20. Knock-out, tissue specific transgenic, and knock-in mouse models of PCCB deficiency recapitulate of the clinical spectrum of propionic acidemia and enable the first successful proof-of-principle gene therapy studies

Randy J Chandler, Charles P. Venditti

Metabolic Medicine Branch, National Human Genome Institute, National Institutes of Health.

Propionic acidemia (PA) is rare autosomal recessive metabolic disorder caused by defects in the mitochondrial localized enzyme propionyl-CoA carboxylase (PCC). The PCC enzyme is composed of six nuclear encoded alpha- and six beta-subunits with causative variants in either of the PCCA or PCCB genes found at equal frequencies in the patients. Individuals with PA can suffer from poor growth, potentially lethal metabolic decompensations and cardiomyopathy despite current medical management, which has led to the pursuit of gene therapy as a new treatment option for patients. While murine models and genomic therapies have been published for PA caused by PCCA deficiency, there are currently no publication describing the same for PCCB deficiency. To explore the pathophysiology of PA and generate a platform to test new therapies for PA, we have developed five new murine models of PCCB deficiency, 2 are detailed here. CRISPR-Cas9 gene editing of the 14th exon of the murine Pccb gene yielded multiple alleles, including a 4 base pair deletion, designated Pccb-/-, that results in a frameshift and premature stop codon in Pccb gene. Pccb-/- mice manifest a neonatal lethal phenotype and elevated plasma 2-methycitrate but had a significant increase in survival in comparison to untreated mutant controls ($p<0.01$) when treated with AAV9.CAG.PCCB at a dose of 1e11 vg/pup at birth. Due to the severe lethality displayed by the Pccb-/- mice, we designed a germline transgene to express the murine Pccb cDNA under the control of a muscle specific promoter (TgMCK-Pccb) to rescue the Pccb-/- mice. The resultant Pccb-/- TgMCK-Pccb animals display increased survival, with most mice perishing at 1 month of age, moderate elevations of plasma methylcitrate in comparison to the Pccb-/- mice, and are growth retarded, like patients with PA. Next, we treated Pccb-/-;TgMCK-Pccb mice at weaning with a dose of 1e14 vg/kg with either AAV9.CAG.PCCB or AAV9.EF1a.PCCB vectors, which resulted in a significant increase in survival and growth in comparison to untreated mutants. These new murine models replicate the clinical and biochemical features of PA over a spectrum of severity and can be used to test the effects of new genomic therapies for PCCB deficiency, such as systemic AAV gene therapy.

### 21. Intrathecal Administration of MELPIDA (AAV9/AP4M1) for Hereditary Spastic Paraplegia Type 50 (SPG50): A Phase 3, Multi-center, Open-Label Trial with Matched Prospective Concurrent Control Arm

Souad Messahel[4], Terry Pirovolakis[4], Keith Gottlieb[4], Susan Walker[8], Xin Chen[1], Steven J. Gray[1], Tyler M. Pierson[7], Carsten Bonnemann[3], James J. Dowling[5], Susan T. Iannaccone[1,2], and Darius Ebrahimi Fakhari[6]

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Hereditary Spastic Paraplegia, Type 50 (SPG50) is a rare, autosomal recessive disorder affecting children. The disease is caused by bi-allelic variants in the AP4M1 gene that impact the function of adaptor complex proteins. This results in a neurodegenerative disorder characterized by a progressive complex spastic paraplegia with onset typically in infancy or early childhood. Early-onset hypotonia evolves into progressive lower-extremity spasticity. The majority of children become non-ambulatory and wheelchair dependent. We demonstrate that the AP-4-HSP subtypes (AP-4-related disease), SPG47 (AP4B1), SPG50 (AP4M1), SPG51 (AP4E1), and SPG52 (AP4S1), share the same molecular mechanism, clinical phenotype, neuroimaging, and disease progression. We present the design rationale of a pivotal gene therapy trial for SPG50 disease. The trial, conducted across three clinical sites, aims to evaluate the efficacy of MELPIDA (AAV9/AP4M1). Eight eligible subjects with SPG50 disease aged 1-6 years will be enrolled across 3 US sites: UT Southwestern Medical Center, Cedars Sinai Medical Center, and the NIH. Up to 16 age- and disease-stage matched children with AP-4-related disease will be enrolled in an untreated concurrent control group. The utilization of selected major motor milestone items from the GMFM-88 scale as the primary endpoint reflects a unique approach to evaluating improvements in gross motor function, offering a standardized and clinically relevant measure for assessing treatment efficacy in treated subjects. The primary analysis will be a test of superiority of MELPIDA treated SPG50 subjects versus SPG47, SPG51, and SPG52 control subjects after 156 weeks. The secondary outcome assessments include assessment of cognitive impairment, clinical global impression and the proxy reported quality of life as SPG50 disease is associated with cognitive impairment and intellectual disability. The trial design holds the potential to contribute significant advancements to the field of gene therapy for SPG50 disease and may pave the way for improved therapeutic options for affected individuals.

### 22. From Review to Readiness: CMT4J and the Road to Clinical Trials

Terry Pirovolakis[1]; Sydney Cooper, MS[2]; Keith Gottlieb, PhD[1]; Souad Messahel, PhD[1]; Rachel Thomas[1]; Jocelyn Duff, MPH[6]; Michael Shy[4]; Carsten Bonnemann[3]; John Day[5]; Susan Iannaccone[2]

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First described in 2007, Charcot-Marie-Tooth Disease Type 4J (CMT4J) is an autosomal recessive neurological disease caused by loss-of-function mutations in the FIG4 gene. It is characterized by progressive loss of motor and sensory neuronal function, with a wide spectrum of symptoms and varying severity. CMT4J is an ultra-rare, severe version of CMT found in less than 0.24% of patients. A review of over 50 published cases of CMT4J characterized the heterogeneity of symptom onset in this patient population. The majority of affected individuals exhibited symptoms before adulthood while a subset experienced adult-onset disease, and a smaller group had unspecified symptom onset. Earlier onset is associated with more severe disease progression, while later onset shows a slower progression, sometimes with symptoms that resemble Parkinsonism. Most common initial symptoms include muscle weakness, neuropathy, and gait difficulties. Progression of the disease can lead to respiratory impairment and dependence on a wheelchair. Treatment is currently limited to management of these symptoms. To address the unmet needs of CMT4J patients and facilitate future therapeutic interventions, the Bespoke Gene Therapy Consortium (BGTC) has selected CMT4J as a leading neurological program for its platform. Furthering this partnership, Elpida Therapeutics will conduct a prospective, observational natural history study aimed at characterizing CMT4J's clinical and genetic spectrum. In this study, 20 individuals will be recruited across four specialized medical centers. Over five years, annual evaluations will be conducted, encompassing a comprehensive array of assessments. These include clinical and neurological exams, laboratory tests to investigate potential biomarkers, CMT-specific outcome measures, neuropsychological tests, nerve conduction studies, muscle fat fraction as measured by MRI, pulmonary function tests, and scoliosis series x-rays. These assessments will provide invaluable insights into the disease course, inform future therapeutic strategies, and enhance readiness for clinical trials in this rare neurodegenerative disorder.

### 23. Accelerating Medicines Partnership® Common Metabolic Diseases

Rachel Fischer, PhD
Foundation for the National Institutes of Health, North Bethesda, MD

The increasing burden and prevalence of common metabolic diseases (CMDs), including obesity, atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF), type 2 diabetes (T2D) and pre-diabetes, nonalcoholic steatohepatitis (NASH), and chronic and diabetic kidney disease (CKD), represent a major challenge for global public health. Common pathogenic drivers likely exist for these diseases. The presence of one of these disorders is associated with increased risk for an individual to develop additional CMDs. As a result, patients may experience several of these diseases throughout their lifetime. Therapeutic interventions for these disorders have been primarily targeted toward single diseases. However, recent therapeutics discovered for diabetes also reduce risk for renal and cardiovascular outcomes, suggesting that intercepting common disease drivers may be tractable, with a potential to develop therapies to modify the course of these diseases. The Accelerating Medicines Partnership® Common Metabolic Diseases (AMP CMD) is a collaborative partnership among government (NIDDK) and private-sector partners (Pfizer, Novo Nordisk, Eli Lilly, and Amgen) that harnesses their collective capabilities, scale, and resources to therapeutically address multiple metabolic diseases that share common pathogenic drivers and overlapping molecular pathways and make them available in a precompetitive space. The AMP CMD Knowledge Portal (CMDKP) and Genome Atlas (CMDGA), the project's open access knowledge portals, aggregate, analyze, and display summary statistics of genetic, genomic, and epigenetic data from subjects with CMDs and related complications. The portals already host useful analysis and visualization tools, freely available to the community. The goals of AMP CMD are to amplify these resources by: 1) Expanding the CMDKP by generating new and leveraging existing genetic, genomic, and biomarker data on CMDs; 2) Addressing data gaps in all CMDs; 3) Evolving the CMDKP by developing analytic and visualization tools to support integrative analysis; and 4) Delivering prioritized targets for the CMDs with supporting mechanistic data.

### 24. A consortium-wide modular massively parallel reporter assay (MPRA) resource to assess cellular contexts of diabetes-associated variants

Adelaide Tovar on behalf of the AMP-CMD NEWS Team and MPRA Working Group

To meet the pace of discovery, new large-scale genetic and genomic resources are urgently required to translate genetic associations to specific disease mechanisms. To this end, we have developed a collection of MPRA libraries to assess regulatory activities of >25k diabetes-associated common and rare variants in four cell types (adipocytes, beta cells, hepatocytes, and skeletal muscle myocytes) across basal and stimulatory states. We plan to combine results from these libraries with those generated by other AMP-CMD activities (e.g., colocalization analyses, CRISPR screens) to inform and expedite future consortium efforts. I will present our design strategy, an overview of the library, and our experimental plan. Additionally, I will share some of our previous work using an MPRA in skeletal muscle cells in combination with single-nucleus multiome data from primary skeletal muscle biopsies and iPSC-derived fibro-adipogenic progenitors.

### 25. Identifying causal relationships between metabolites and complex disease using non-targeted metabolomics

Ruth M. Elgamal, Tao Long, Mohit Jain, Kyle J. Gaulton

High-throughput non-targeted metabolomics provides the opportunity to profile circulating small molecules at population scale and, when combined with sample genotypes, can identify genetic variants influencing metabolite levels. We performed quantitative trait locus (QTL) mapping and fine-mapping of 62,590 profiles derived from non-targeted metabolomics data of peripheral blood from 7,087 Finnish ancestry individuals. Mendelian Randomization was performed using fine-mapped metabolite QTLs to identify metabolites where circulating levels have evidence for a causal role in 2,272 complex traits and diseases using FinnGen data. In total, these results will provide unprecedented insight into metabolites causally involved in complex disease and reveal new disease mechanisms and biomarkers.

### 26. The generation of new floxed alleles for the validation of novel therapeutic targets in diabetes, obesity, and metabolic disorders

Eric L. Waite, Mark Tigue, Klaus H. Kaestner

Type 2 diabetes (T2D) is a rapidly growing global health concern and an enormous burden on health care systems. New therapeutic targets are needed to combat this complex disease. To that end, the UM1 team at the University of Pennsylvania created a list of promising T2D-associated genes that may play a role in disease pathology in one or several tissues of interest (i.e. skeletal muscle, adipose tissue, pancreatic endocrine cells, etc.). The following pipeline was used to prioritize targets: (1) significant GWAS hit in locus (or near gene), (2) significant GWAS for one other trait in relevant tissue of interest (e.g. adipose tissue and insulin resistance), (3) eQTL in tissue of interest, (4) evidence of chromatin looping in primary or cultured cells from tissue of interest (e.g. cultured human adipocytes), and (5) above specified threshold of mRNA expression. The targets that came out of this prioritization strategy include FAM13A, STEAP2, NDUFAF6, VPS11, and HMBS. Our group took that list and made floxed alleles in the C57BL6/J strain. We hope that these floxed murine lines will be of use to the field in determining gene function in health and disease in a variety of tissues associated with T2D.

### 27. Validating the SenKiller mouse, a novel cell-type specific senolytic mouse model

Kai Kelly, Eric L. Waite, Mark Tigue, Ben Glaser, Klaus H. Kaestner

Type 2 Diabetes (T2D) affects millions globally per year. Recent studies in the field have implicated beta-cell senescence as a significant contributor to T2D pathophysiology. However, current senolytic mouse models are not cell-type specific and ablate senescent cells across the entire body. We have developed the SenKiller mouse, a cell type-specific senolytic murine model, to ablate senescent beta-cells in the context of T2D. Mouse embryonic fibroblasts were employed to confirm activation of the transgenic cassette in vitro. This project qualitatively displayed increased expression of a mCherry fluorescent reporter, contained within the SenKiller transgenic cassette, using Immunofluorescence. These results were quantitatively confirmed at the mRNA level using Rt-qPCR. Additionally, p16Ink4A results were verified at the protein level using a western blot. The increased mCherry and p16Ink4A expression serves as a promising basis for further validation experiments before the onset of in vivo experiments using the SenKiller mice. The SenKiller mouse model could be used in conjunction with a host of existing cell type specific Cre mouse lines to study the contribution of various senescent cell populations in different diseases and at large, aid in the study of cellular senescence and its impact on the aging process.

### 28. Interrogation of T2D GWAS targets in muscle identifies VPS11 as a regulator of skeletal muscle cell differentiation

Lin Liu[1,2], Sijia Yang[1], Matthew C Pahl[3], Kim Lorenz[4], Yang Chen[2], Ryan Calhoun[2], Feikun Yang[1], James A. Pippin[3], Jeff Ishibashi[5], Benjamin F. Voight[4], Struan F. A. Grant[3], Patrick Seale[2*] and Wenli Yang[1,2*]

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Skeletal muscle is the primary site for glucose and lipid disposal and thus plays a central role in the control of systemic metabolism and type 2 diabetes (T2D) development. To identify T2D risk genes relevant in skeletal muscle, we performed variant-to-gene mapping by integrating GWAS signals with multi-omics datasets, including high resolution chromosome conformation capture, chromatin accessibility and gene expression in human primary myotube samples, together with colocalization analysis of muscle eQTLs from Genotype-Tissue Expression (GTEx) data. This framework led to prioritization of 26 candidate muscle genes for further investigation. We then mutated each gene individually in a human myoblast cell line using CRISPR/Cas9 and assessed cell differentiation. We found that loss of VPS11, a core subunit of the HOPS tethering complex that mediates endosome and autophagosome fusion with the lysosome, resulted in severe impairment of myocyte differentiation and upregulation of inflammation genes including the NF-kB pathway. We demonstrate this effect of VPS11 deficiency is in part due to defects in intracellular iron trafficking mediated by the HOPS complex. Lastly, using gene reporter assays and allelic gene expression analysis, we identify potential causal variants in linkage disequilibrium with the GWAS signal at the VPS11 gene locus that affect VPS11 gene expression in muscle cells.

### 29. Implementation and scaling of technologies for comprehensive single cell multiomic profiling of liver and heart in control and disease

Aga D'Antonio-Chronowska, Qian Yang, Michael Miller, Justin Buchanan, Charlene Miciano, Luca Tucciarone, Sierra Corban, Rebecca Melton, Henry Jiao, Emily Eisner, Carolyn McGrail, Sadatsugu Sakane, Jose Sandoval, Thirupura Sundari Shankar, Neil Chi, Stavros Drakos, David Brenner, Tatiana Kisseleva, Bing Ren, Kyle Gaulton, Allen Wang

We are currently advancing efforts to deploy single-nucleus technologies such as multiplexed 10x Multiome and droplet Paired-tag for comprehensive profiling of gene expression and the epigenome in single cells across liver and heart diseases. A significant challenge in generating high-throughput data for single-cell and single-nucleus multi-omics assays is the considerable time and resource costs associated with profiling large sample cohorts. By multiplexing 10x Multiome samples, we can dramatically increase the throughput of processed samples, achieving reductions in cost per sample and potential technical variability due to sample batching. The multiplexed 10x Multiome approach leverages genotype information to demultiplex pooled samples and enables more efficient and cost-effective profiling of gene expression and chromatin accessibility in larger cohorts of donor tissues, offering numerous benefits including improved doublet removal and more uniform background. The Paired-tag method complements this by enabling the profiling of histone modifications alongside gene expression in single cells. The advantages of these technologies are highlighted, along with preliminary discoveries from their application to 85 liver samples from control, NAFLD, or NASH individuals, and 120 heart samples encompassing all four chambers (left and right ventricle and atrium) from 30 individuals with control, ischemic, or non-ischemic heart failure.

### 30. Accelerating Medicines Partnership® Heart Failure (AMP HF)/HeartShare

Harina Raja
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Heart failure (HF) is a complex clinical syndrome leading to substantial morbidity, mortality, and cost to the United States healthcare system with more than six million people diagnosed in the U.S. and expected to exceed eight million by 2030. Heart Failure continues to be defined by left ventricular ejection fraction with over half of HF patients characterized under HF with a preserved ejection fraction (HFpEF). Despite significant investment towards developing new therapies, the HFpEF mortality rate remains at about 50% at five years post-diagnosis. A lack of understanding of the underlying molecular mechanisms and heterogeneity of the disease has contributed to the difficulty with diagnosis and lack of therapeutics demonstrating proven benefits for HFpEF. The AMP HF study, also referred to as HeartShare, is a collaboration among public- and private-sector partners seeking to significantly stratify HFpEF patients and ultimately drive the development of new therapies by defining underlying mechanistic biomarkers for etiologically defined subtypes of HFpEF. The AMP HF study is designed in two parallel and interconnected components. The first component aggregates existing phenotypic data, biomarkers, and omics data from the National Institutes of Health (NIH)-funded studies and industry-sponsored trials and cohorts to identify subtypes of HFpEF, investigate associated biomarkers, and link them to clinical outcomes. The second component prospectively enrolls a new cohort of approximately 1000 HFpEF patients and controls from seven clinical sites. A subset of these patients will have myocardial, skeletal, and visceral adipose tissue biopsies to increase the depth of phenotyping for validating, refining, and extending the potential endotypes identified in Component I. The ultimate deliverable of the AMP HF study is to establish biologically relevant subsets of HF to advance targeted precision medicine.

### 31. ECG-based Classification of Heart Failure Subtypes

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Background: More than half of heart failure (HF) cases are estimated to be HF with preserved left ventricular ejection fraction (HFpEF) while the majority of existing HF treatments are for HF with reduced left ventricular ejection fraction (HFrEF). It is also the case that diagnosis of HFpEF is more complicated than it is for HFrEF. As part of an Ancillary Study (R01HFL169451, Akbilgic) to HeartShare, our overarching goal is to develop low cost electrocardiographic artificial intelligence (ECG-AI) models to help with diagnosis, risk prediction, and phenotyping of HFpEF. Goal: The goal of this study is to classify HF types from ECG-alone. Methods: We used retrospective ECG, ECHO, and HF diagnosis data from Atrium Health Wake Forest Baptist from January 1, 2014 to June 1, 2023. We annotated HF patients into three categories based on EF values: HFrEF (EF<40), HFmEF (40≤EF<50), and HFpEF (EF≥50). A convolutional neural network based ECG-AI model was developed to classify patients into accurate categories. Results. There were 7400 HFrEF, 853 HFmEF, and 2736 HFpEF patients as well as 57780 controls with no HF. The ECG-AI model was developed on 70% of the data, validated on 15% data, and tested on 15% hold-out data. The detection accuracies measured as AUC for individual categories were 0.91 (0.91-0.92) for HFrEF, 0.83 (0.81-0.85) for HFmEF and 0.67 (0.65-0.70) for HFpEF. When controls were excluded and HFrEF and HFmEF categories were combined, the AUC of detection HFpEF was 0.79 (0.78-0.81). Conclusions: ECG-AI model utilizing only 12 lead 10 seconds ECG can detect HF and its categories with moderate to high accuracies. Further hyperparameter tuning, expanding training dataset, and including clinical data as predictors in addition to ECG have potential to lead to much higher detection accuracies. Future studies also include single lead based models to assist smartwatches-based remote monitoring.

### 32. Accelerating Medicines Partnership® Parkinson's Disease

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Parkinson's Disease (PD) is a progressive neurological condition caused by neuronal death in a part of the brain called the basal ganglia. Patients with PD classically develop resting tremors, rigidity, slow movement, impaired balance, and a shuffling gait, but may also have problems with cognition, sleep, and autonomic functions. In February 2018, the Accelerating Medicines Partnership (AMP®) PD initiative was established as a collaborative effort between the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), industry leaders (AbbVie, BMS, GSK, Pfizer, Sanofi, and Verily), and non-profit organizations (the Michael J. Fox Foundation; MJFF, Aligning Science Across Parkinson's; ASAP). Managed through the Foundation for the National Institutes of Health (FNIH), this public-private partnership aimed to address the absence of disease-modifying therapies for PD and streamline data consolidation from diverse natural history studies. The AMP PD program, launched to enhance the clinical trial design and identify new therapeutic pathways, established a cloud-native data portal with data access through the Terra platform. This platform facilitates access to AMP-PD data, allows the execution of analysis tools, and supports collaboration among investigators. With 1015 registered users, the AMP-PD platform has aggregated clinical and multi-omics data from eight unified cohorts, comprising approximately 10,800 participants, and encompassing various data types such as Clinical, Transcriptomic, Proteomic, Genomic, and Single nucleus Brain data. Despite notable progress in drug development through the AMP PD project, current treatment options only offer temporary symptom relief without halting the underlying decline and death of brain cells. The proposed second phase, AMP Parkinson's Disease and Related Disorders (AMP PDRD) seeks to employ a data-driven approach to identify and validate biomarkers distinguishing Parkinson's disease from Parkinsonism, aiming to enhance the clinical trial success and ultimately broaden treatment options for individuals affected by these conditions.

### 33. Polygenic Background Modifies Penetrance of Monogenic Parkinson's Disease Risk Variants

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This work leverages data from the Accelerating Medicines Partnership – Parkinson's Disease (AMP-PD) to examine the impact of aggregate genetic risk on PD and the interaction of monogenic and polygenic risk. We first compute a genome-wide polygenic risk score (GPRS) and compare its prediction performance with polygenic risk scores (PRS) based on fewer numbers of more highly significant variants. Then, for AMP-PD cohorts Control and PD subjects, we compare odds of Case and Control status for combined monogenic + GPRS and PRS score status. PRS and GPRS approaches identify patients at significantly increased risk for Parkinson's Disease using different variant sets for risk stratification. Polygenic background is observed to modify penetrance of monogenic Parkinson's Disease risk variants for all scoring methods. GPRS may identify a larger population of high score individuals at somewhat increased genetic risk for PD. We conclude that genetic risk for PD includes both monogenic and polygenic contributions. Complex genetic risk stratification may provide further insights for patient endotyping alongside monogenic variant carrier status.

### 34. Identifying enhancer RNAs in blood and their immunological role for Parkinson's disease

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Although less than 2% of the human genome encodes proteins, we previously found that a large portion (64%) of the human genome is transcribed in dopamine neurons. By developing a novel method integrating total RNA-seq with functional genomics and epigenomics data, we derived 71,000 transcribed noncoding elements (TNE) in human dopamine neurons. We found many TNEs act as enhancer RNAs (eRNAs) active in dopamine neurons and link genetic variation with neuropsychiatric disease (Dong et al. Nature Neuroscience, 2018). Here we seek to identify eRNAs in blood by analyzing the total RNA-seq dataset for 8356 whole blood samples from Parkinson's disease (PD) patients and healthy controls in the Accelerating Medicines Partnership Parkinson's Disease (AMP-PD) consortium. In total, 109,597 TNEs were identified, and annotation with external functional genomic datasets classified 45,174 as "likely eRNAs" supported by at least one enhancer characteristic such as DNase I hypersensitivity sites, transcription factor binding hotspot, transcriptional coactivator P300 binding sites, bi-directional CAGE signal, chromatin state-defined putative enhancers, or sequence conservation. The TNEs were most significantly enriched for cis-eQTL GTEx causal variants from whole blood tissues. Differential expression analysis conducted across genes and eRNA candidates reveals multiple PD-associated enhancer candidates near a transcription factor gene for TNF-a, which is a pro-inflammatory cytokine previously shown to elevate in PD serum and associated with cognitive impairment in PD patients. Hi-C and eQTL analysis suggests these enhancer candidates regulate this gene. We found several immune-related traits with GWAS risk variants significantly enriched in "likely eRNA" candidates, indicating their potential regulatory role in Parkinson's disease. This study generated a resource of novel regulatory non-coding RNAs in blood and provides a likely link explaining PD risk variants.

### 35. Transcriptomic Profiling of Whole Blood and Immune Cells Reveals Gene Expression Alterations in Idiopathic and Genetic Parkinson's Disease

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Background: Accumulating evidence across various modalities underscores the pivotal role of immune cells in Parkinson's Disease (PD). Numerous PD risk loci feature genes prominently expressed in immune cells, including peripheral monocytes and CNS microglia. Additionally, the association of the Human Leukocyte Antigen (HLA) with PD further underscores the relevance of the adaptive immune system. While the involvement of both innate and adaptive immune cells in PD pathology is undeniable, the precise nature of their activity remains uncertain—whether it is a reactive response to the disease or an integral part of the underlying mechanism. Methods: We utilized whole blood (WB) transcriptomic data from two cohorts (PDBP and PPMI) of the Accelerating Medicines Partnership: Parkinson's Disease (AMP-PD) (n=2634) for differential expression, expression quantitative analysis, and network analysis. Further, we generated bulk and single cell RNA-seq from peripheral monocytes of 265 PD cases and 257 controls. Results: Our investigation revealed significant alterations in phagocytosis, mitochondrial and proteo-lysosomal genes in PD blood and monocytes, with discordant expression of mitochondrial genes in the periphery versus the CNS. The transcriptional deregulation was accompanied by a functional decrease in phagocytic and proteolysosomal functions in PD monocyte-derived macrophages. Integrating genomics data, we demonstrated that PD alleles influence the expression of genes in peripheral immune cells. Notably, we observed that PD risk-associated HLA alleles (HLA-DRB1*04) shape the T-cell receptor repertoire in a disease-specific manner. Conclusion: These findings highlight extensive transcriptomic changes in PD peripheral immune cells, distinct from those in the CNS. They pave the way for a deeper understanding of the roles played by peripheral immune cells in PD and contribute to ongoing efforts in biomarker development.

### 36. Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ)

Linda Brady[1], Carlos Larrauri[2], Suzanne Garcia[1], Loni Ajagbe[3]

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The Accelerating Medicines Partnership® for Schizophrenia (AMP® SCZ), launched in 2020, is the first AMP initiative directed towards a neuropsychiatric disorder. AMP SCZ will recruit a large cohort (N=1,977) of individuals between the ages of 12 and 30 years who meet the criteria for being clinical high risk for psychosis (CHR) – based on the Positive SYmptoms for CAARMS Harmonized with SIPS (PSYCHS) interview, a new psychometric instrument for defining CHR and associated outcomes – and healthy controls (N=640) across 42 sites from 14 countries. This public-private partnership is focused on developing and implementing a set of biomarkers combined with clinical and cognitive assessments, to create algorithms that reliably distinguish course types in individuals that are at clinical high risk for psychosis (CHR). Employing a comprehensive deep phenotyping approach, including neurocognitive imaging, electrophysiology, fluid biomarkers, digital measures, and speech sampling, the observational study aims to create multimodal algorithms that distinguish trajectories and outcomes (conversion, remission, and unremitted symptoms) in CHR individuals. The Proof of Principle (PoP) trial will determine if a pharmacological treatment can produce a detectable signal on the same biological, digital, cognitive, and clinical outcomes measures as used in the observational study within a 12-week period of study. Data from the observational study and PoP trial will be uploaded to the NIMH Data Archive (NDA) and made available to the broader research community with approved NDA Data Use Certifications. The AMP SCZ Data Release 1.0 (DOI: 10.15154/18rd-ck75) contains quality-controlled screening and baseline data from 430 unique subjects. These include curated and tabulated behavioral and clinical measures, electroencephalography, imaging data, and associated data. Every six months new curated data sets will be shared through the NDA until the full data set from 2,617 study participants are made available.

### 37. Cross-domain Symptom Clustering of Clinical High Risk Youth in AMP SCZ: Risk Factors and Relationship with Functioning

Cassandra M. J. Wannan[1,2], Isabelle Scott[1,2], Dominic Dwyer[1,2], Kelly Allott[1,2], Stephen Wood[1,2], Suzie Lavoie[1,2], Andrew Thompson[1,2], Paul Amminger[1,2], Andrea Polari[1,2], Patrick McGorry[1,2], Scott W. Woods[3,4], Martha E. Shenton[5,6,7], Barnaby Nelson[1,2], The Accelerating Medicines Partnership Schizophrenia

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Background: As well as experiencing attenuated psychotic symptoms, young people at clinical high risk (CHR) for psychosis also present with increased non-psychotic symptoms compared to the general population1 and non-psychotic clinical populations2. The aims of the current study were to (1) identify symptom-based clusters within the CHR population, (2) characterize the risk factors that are associated with these clusters, and (3) compare functional outcomes between these clusters and healthy individuals. Methods: Baseline clinical data, childhood and current risk factors, and measures of functioning were obtained for 228 CHR individuals and 78 healthy controls (HCs) participating in the Accelerating Medicines Partnership Schizophrenia (AMP SCZ) study. Six distinct symptom domains (depression, anxiety, activation, disorganization, negative symptoms, attenuated positive symptoms) were used to perform k-means clustering in CHR youth. The NbClust package in R was used to determine the optimal number of clusters. Analysis of Variance (ANOVA) was used to characterize demographic, risk factor, clinical, and functional profiles across symptom clusters and healthy controls. Results: We identified a two-cluster solution. Cluster 1 (N = 108) represented CHR individuals with a higher cross-domain symptom burden, whereas Cluster 2 (N = 120) represented CHR individuals with a lower cross-domain symptom burden. The high symptom burden cluster had significantly higher scores on childhood and current risk factors, and poorer functioning, compared to both the low symptom burden cluster and HCs. Conversely, despite poorer functioning, the low symptom burden cluster only had minimal increases in risk factors compared to HCs. Conclusions: With increasing cross-domain symptom burden we observed increases in both childhood and current risk factors and decreases in functioning. Based on their risk factor and functioning profiles, CHR individuals with low vs high symptom burden may represent distinct illness subgroups.

### 38. Precision Medicine Approaches of the AMP® SCZ PRESCIENT Project

Dominic Dwyer, Cassandra Wannan, Isabelle Scott, Kelly Allott, Stephen Wood, Suzie Lavoie, Alison Yung, Scott Clark, Jessica Hartmann, Kate Buccilli, Christina Phassouliotis, Swapna Verma, Louise Genthoj, Merete Nordentoft, Bjørn Ebdrup, Stefan Smesny, Kerstin Langbein, Christy Hui, Pablo A. Ramos, Matthew Broome, Jack Rogers, Rachel Upthegrove, Lana Kambeitz-Ilankovic, Joseph Kambeitz, Luis Almeda, Philippe Conus, Sung-Wan Kim, Pat McGorry, Barnaby Nelson

### 38. Precision Medicine Approaches of the AMP® SCZ PRESCIENT Project (cont'd)

The PRESCIENT project is part of the Accelerating Medicines Partnership® Schizophrenia (AMP®SCZ) and brings together 10 international psychosis risk detection sites in Australia, Europe, Asia, and South America. The primary aim of PRESCIENT is to collect 937 individuals who are at high-risk of psychosis contribute to the worldwide vision of AMP®SCZ to prevent the onset of schizophrenia. A central component of this vision is to use multimodal data to identify subgroups of individuals who could be targeted with existing or new preventative treatments. To achieve this goal, PRESCIENT unites over 50 researchers whose research can be divided into five main analytic domains. The purpose of this poster is to outline these domains to facilitate collaborations between researchers from PRESCIENT and other AMP®SCZ projects. The first domain is supervised machine learning, where researchers have a clearly defined target (e.g., an outcome or endpoint) and attempt to predict this target using a variety of usually high-dimensional data. Second, unsupervised learning will be used where subgroups are detected automatically based on shared patterns of biological, psychological, social, and environmental attributes. Third, we will use targeted trial methodologies with the AMP®SCZ observational data to assess treatment response heterogeneity. Fourth, we will investigate the dynamics of illness-related time-series. Fifth, we are partnering with leading artificial intelligence experts to create foundational models of mental illness that can learn patterns in very high-dimensional data sources (e.g., video or audio). When combined, our projects will implement a multi-domain precision medicine approach for psychosis risk by identifying subgroups of high-risk individuals who share expected prognoses and treatment-response likelihoods to prevent schizophrenia.

### 39. Multi-modal and longitudinal analysis strategies for the Accelerating Medicines Partnership® Schizophrenia project

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The Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ) project strives to develop algorithms to predict clinical endpoints and symptom trajectories in individuals at clinical high-risk for developing psychosis (CHR). Approximately 2000 subjects, enrolled in 43 worldwide sites, undergo comprehensive assessments at baseline and multiple follow-up timepoints over two years. Conversion to psychosis and sustained remission, assessed using the PSYCHS tool, are the endpoints to be predicted from baseline data. The protocol assessments include MRI, electroencephalography, blood and saliva samples, and audiovisual recordings assessed twice during the first two months. Interview-based measurements are taken at each visit, and cognitive assessments are performed at the first five visits. The protocol also includes novel digital domains, actigraphy and smartphone-based measures. While data are collected, a dedicated workgroup of multidisciplinary experts develops the analysis design. Legacy data are reviewed to inform design decisions, and analysis approaches from similar international CHR studies. Activities include performing benchmark experiments (e.g., multimodal and longitudinal prediction analysis), quantifying clinical concepts (e.g., proportion of individuals experiencing remission), and identifying challenges encountered in previous studies. Within the AMP SCZ project, a 10% leave-out sample and strict internal cross-validation procedures are used to achieve generalizability of the algorithms. Another main design consideration is how to address the multimodal and longitudinal aspects of the data. We provide two examples of benchmark experiments using legacy data to support the analysis design for AMP SCZ: 1) Testing various techniques to demonstrate the capabilities of Multiple Kernel Learning as an intermediate fusion technique for multimodal data with superior prediction capabilities; 2) Evaluating Dynamic Time Warping as a prediction enhancing tool with different assessment frequencies, demonstrating improved prediction from a combination of clinical measures assessed at different timepoints. Based on these promising results, we will include these approaches in the analysis of the AMP SCZ data.

### 40. Predicting the Emergence of Psychosis and Other Clinical Outcomes from Language Biomarkers: Strategies from the AMP® SCZ Initiative

Eduardo Castro[1], Carla Agurto[1], Zarina R. Bilgrami[2], Einat Liebenthal[3], Michaela Ennis[3], Justin T. Baker[3], Isabelle Scott[4], Beau-Luke Colton[4], Kang Ik K. Cho[10], Linying Li[2], Zailyn Tamayo[5], Mara Henecks[5], Habiballah Rahimi Eichi[3], Patrick D. McGorry[4], Rene S. Kahn[6], John M. Kane[7,8], Carrie E. Bearden[9], Dominic Dwyer[4], Tashrif Billah[10], Sylvain Bouix[10,12], Ofer Pasternak[10], Martha E. Shenton[10], Scott W. Woods[5], Barnaby Nelson[4], Guillermo A. Cecchi[1], Cheryl M. Corcoran[6], Phillip M. Wolff[2]

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Language and speech disturbances, often evident in the early stages of psychosis, have emerged as potential biomarkers of psychotic disorders. Enhancements in Natural Language Processing (NLP) and Machine Learning (ML) have significantly improved the feasibility and accuracy of using language metrics as diagnostic tools. Although the results of several recent studies leveraging these methods have been promising, they have also been limited by small datasets, with associated concerns about overfitting. In this context, the Accelerating Medicines Partnership® – Schizophrenia (AMP® SCZ) is poised to advance our understanding of language as a biomarker, which is the focus of this work, and integrate it with other digital biomarkers, such as actigraphy watch data, smartphone daily surveys, and geolocation data. Here, we describe the standard operating procedures (SOPs) used to conduct large-scale acquisition of audiovisual data from interviews from a varied, international, and multilingual cohort, enabling analysis of language content, speech acoustics, facial expressions, and head gestures from both face-to-face and remote settings. We also report preliminary analyses, facilitated by Large Language Models (LLMs), revealing that different language sampling techniques yield distinct insights into the disease's characteristics, with certain techniques proving more effective than others in identifying individuals at increased risk. Additionally, we discuss how ML methods could be used to identify integrated, multimodal language markers indicative of psychotic disorders. The AMP® SCZ initiative, therefore, promises to improve our understanding of psychosis and our ability to predict the onset of the condition in clinically high-risk individuals.

### 41. Development of an FDA Clinical Outcome Assessment Qualification Plan for a New Instrument Measuring Attenuated Positive Symptoms in Young Persons at Clinical High Risk for Psychosis

Catalina Mourgues-Cordon, Alison Yung, Barnaby Nelson, Melissa Kerr, Sophie Parker, Barbara Walsh, Angela Nunez, Emily Farina, Lisa Calvocoressi, Carlos Larrauri, Gahan Pandina, Sharin Roth, Patrick McGorry, Michael Sand, and Scott Woods

Attenuated positive symptoms (APS) are defining characteristics of the Clinical High Risk (CHR) syndrome for psychosis (prevalence 20% in adolescent and young adult mental health referrals doi: 10.3390/brainsci11111544) and are associated with distress, functional impairment, and help-seeking. The Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) are two commonly used clinical outcome assessments (COAs) to evaluate APS. While these Clinician-Reported Outcomes (ClinROs) have similarities in content and structure, they differ in rating symptom severity. The Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS) (doi: 10.1111/eip.13457 and available at ampscz.org), created by merging SIPS and CAARMS, is now being used in the AMP® SCZ observational study designed to prepare for future clinical trials supporting drug registration. Such trials would benefit from a Food and Drug Administration (FDA)-qualified COA to evaluate severity of APS symptoms, but none are currently available. To potentially address this need, FDA has accepted a Letter of Intent to develop a qualification plan for the PSYCHS as a ClinRO instrument (DDT-COA-000163, https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=182) and has provided funding (U01FD008131) for two main activities: defining the instrument's conceptual framework and gathering information about its quantitative and qualitative psychometric properties. We will present: 1) the draft PSYCHS conceptual framework; 2) preliminary results from a focus group; 3) preliminary AMP SCZ observational data from the PRESCIENT and ProNET networks, including comparison of PSYCHS severity scores to APS scores from previous cohorts, stability data across baseline and months 1-3 that can be used to estimate future placebo response, convergent validity analyses and divergent validity analyses; and 4) potential methods to determine the appropriate recall interval. The findings support progress on the path toward potential FDA qualification of the PSYCHS as a ClinRO measure for use in clinical trials.

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