

Accelerating Medicines Partnership®

Systems Biology of Inflammation (SBI)
Virtual Roundtable
June 13, 2022



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[Video Link](#)

Passcode: 6@ @f2jV?

Agenda

TIME	TOPIC
11:30AM – 11:45AM <i>15 minutes</i>	Welcome and & Review Goals of the Meeting
11:45AM – 12:20PM <i>35 minutes</i>	Overview of NIH-Funded Proof-of-Concept Pilots
12:20PM – 1:00PM <i>40 minutes</i>	Discussion of Research Concepts and AMP® SBI Scale & Scope
1:00pm – 1:15PM <i>15 minutes</i>	Data Coordination/Enablement Needs for AMP® SBI
1:15PM – 1:30PM <i>15 minutes</i>	Review of Next Steps & Action Items (Closed Session – Design Phase Stakeholders)

FNIH

Welcome & Goals of the Meeting

Robert Carter, MD

Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

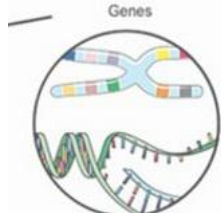
Suzana Petanceska, PhD

Director, Office for Strategic Development and Partnerships, National Institute on Aging (NIA)

Goals of the Meeting

- 1 Learn about SBI proof-of-concept pilots and proposals for scale up
- 2 Understand data enablement needs and challenges
- 3 Provide an opportunity for stakeholders to identify topics of highest interest
- 4 Review Design Phase participation and timeline

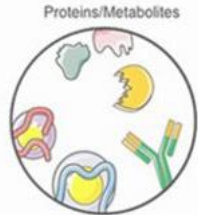
Why develop an AMP Systems Biology of Inflammation?



Genes

Problem: Diseases are defined by their manifestations but treatments target mechanisms

Solution: Develop a comprehensive, integrative, mechanistic understanding of diseases so that treatments target causative pathways irrespective of the clinical label



Proteins/Metabolites

Opportunity: Leverage the rich AMP datasets to identify shared and distinct mechanisms active in subsets of patients across multiple diseases



Cells/Tissues

Focus: A systems biology of inflammation approach across major complex diseases

Deliverables: Data, analytical tools, and mechanistic insights regarding shared and distinct inflammatory pathways



Organs

Outcomes: A new landscape for developing, selecting, and using targeted therapies across diseases

Concept approved at
AMP EC Meeting (Feb 2022)

Addressing fundamental questions key to successful translation

There are shared inflammatory pathways amongst diseases that you won't necessarily know about unless you look under the surface



- What are the cellular subtypes and cell-specificity of these pathways?
- Which inflammatory molecular changes observed in diseases are reactive vs. causative vs. aggravating for disease?
- How does the immune state of the individual influence responsiveness to treatment?

Example of potentially shared mechanisms

Are there related cell-types in different tissues that have unique tissue specific properties (e.g., tissue resident macrophages and microglia) that utilize similar inflammatory programs in the context of disease?

Zhang et al. *Genome Medicine* (2021) 13:64
<https://doi.org/10.1186/s13073-021-00881-3>

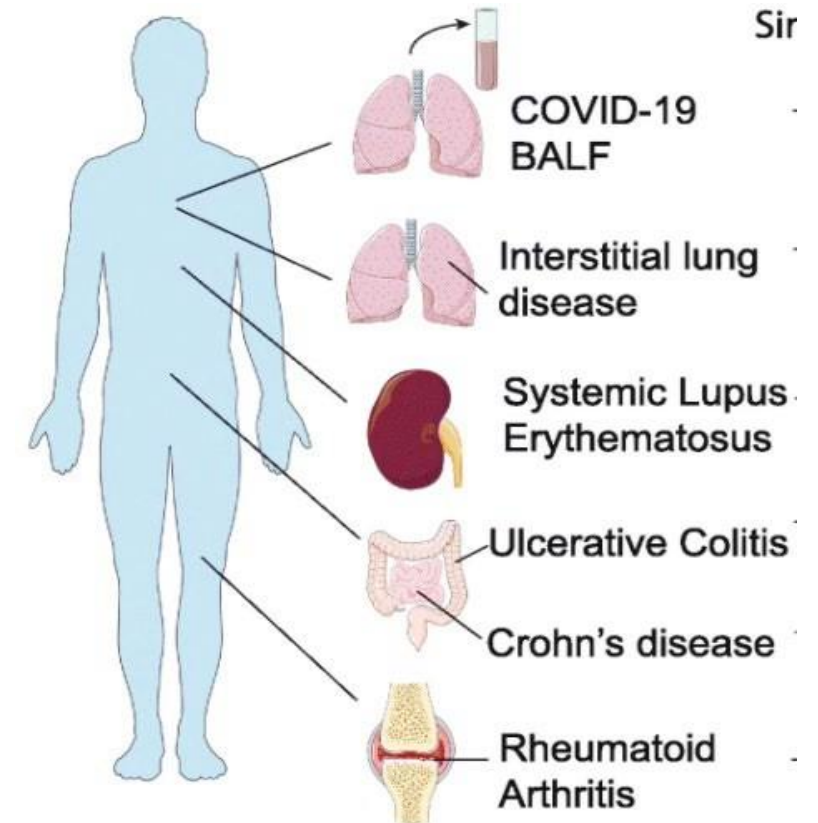
Genome Medicine

RESEARCH Open Access

IFN- γ and TNF- α drive a CXCL10+ CCL2+ macrophage phenotype expanded in severe COVID-19 lungs and inflammatory diseases with tissue inflammation

Fan Zhang^{1,2,3,4,5}, Joseph R. Mears^{1,2,3,4,5}, Lorien Shakib⁶, Jessica I. Beynor^{1,2,3,4,5}, Sara Shanaj⁷, Ilya Korsunsky^{1,2,3,4,5}, Aparna Nathan^{1,2,3,4,5}, Accelerating Medicines Partnership Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP RA/SLE) Consortium, Laura T. Donlin^{6,7*} and Soumya Raychaudhuri^{1,2,3,4,5,8*†}

Check for updates



- Are the cellular states of immune cells similar across multiple organ systems?

Qu W, et al. *Microglial TREM2 at the Intersection of Brain Aging and Alzheimer's Disease. Neuroscientist.* 2021. PMID: 34470515. Kim K et al. *Therapeutic B-cell depletion reverses progression of Alzheimer's disease. Nat Commun* 2021. PMID: 33846335

Zhou M et al. *Tumor Necrosis Factor (TNF) blocking agents are associated with lower risk for Alzheimer's disease in patients with rheumatoid arthritis and psoriasis. PLoS One.* 2020. PMID: 32203525

Real-life applications of this type of approach

J Alzheimers Dis. 2018 ; 66(1): 97–104. doi:10.3233/JAD-180619.

A precision medicine model for targeted NSAID therapy in Alzheimer's disease

Sid E O'Bryant^{a,*}, Fan Zhang^b, Leigh A Johnson^a, James Hall^a, Melissa Edwards^c, Paula Grammas^d, Esther Oh^{e,f}, Constantine G Lyketsos^f, and Robert A Rissman^{g,h}

Anti-Inflammatory therapies for Alzheimer's disease

- Alzheimer's Disease Cooperative Study (ADCS) → No overall benefit for AD progression, BUT.....
 - Pro-inflammatory (TNF α , CRP, IL-6, and IL-10) endophenotypes may respond to anti-inflammatory therapy
 - Higher baseline plasma levels predict positive cognitive response to NSAID therapies

AMP SBI would provide a systems biology framework to help define a molecular taxonomy of disease through the lens of inflammation

- De novo drug development and drug positioning based on mechanisms active in each individual, irrespective of clinical label
- Using blood omics data to link systemic inflammation to tissue-level disease
- Understanding the contribution of chronic inflammation to disease progression and treatment response
- Testing multi-omic risk scores

A molecular taxonomy of disease define diseases based on their intrinsic biology in addition to traditional physical "signs & symptoms"

[National Research Council \(US\) Committee on A Framework for Developing a New Taxonomy of Disease](#)

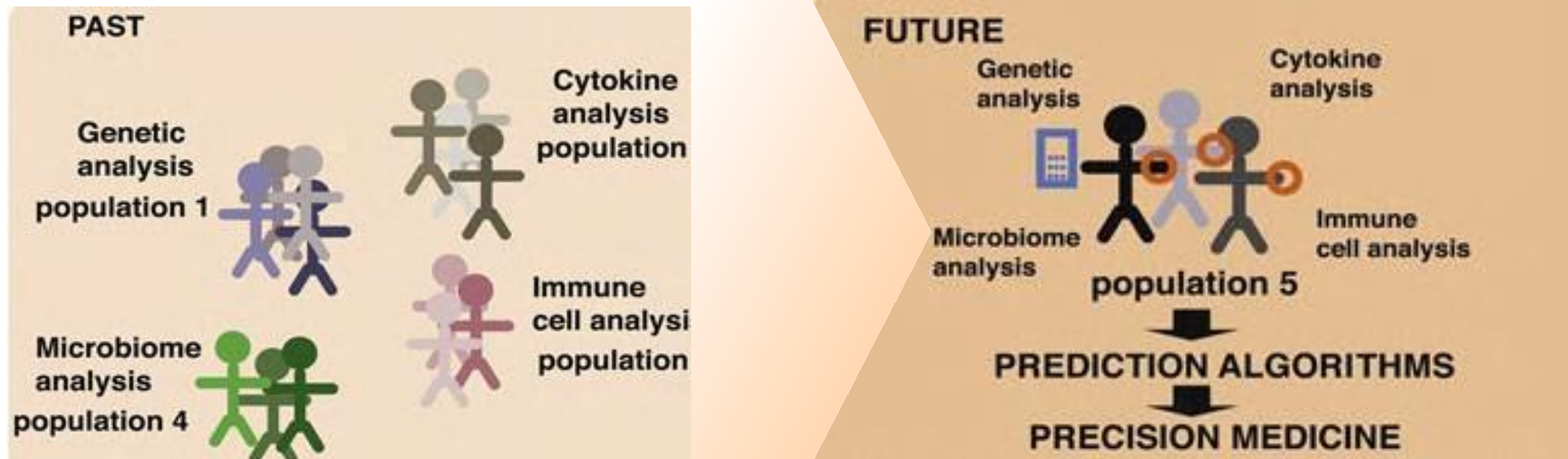
Washington (DC): National Academies Press (US); 2011.

Integrated Model

Develop integrated molecular map(s) of shared and distinct inflammatory pathways linked to disease outcomes

Deliverables

- Model inflammation across diseases at a tissue level and its relationship to other disease-relevant biological processes (metabolism, proteostasis, autophagy, etc.)
- Novel biomarkers and targets → advance understanding in the context of inflammation
- Enable a new precision medicine approach & knowledge network for a new molecular taxonomy of disease



NIH supporting Proof of Concept Pilot projects* to demonstrate feasibility of identifying shared inflammatory pathways across diseases and inform Research Plan

Use of existing datasets from first four AMP programs (AD, PD, T2D, RA/SLE) and external datasets

DATA SOURCES

Where available:

- Genome-wide association study (GWAS)/Whole genome sequencing (WGS)
- RNA sequencing (RNAseq)

DATA TYPES AND ANALYSES

- Establish feasibility to integrate and harmonize AMP data/metadata
- Conduct an initial set of systems/network biology analyses
- Develop and make available new web-based tools for integrated data analysis

Outcomes

**Each pilot project is ~\$250K direct costs per year for 2 years, see details in the appendix*

FNIH

Overview of NIH-Funded Proof-of-Concept Pilots

Overview of NIH-Funded Proof-of-Concept Pilots

The PIs listed below will provide a high-level update on the project goals and progress.

Title of Project	PI
1. Precision Medicine Approach to Dissect the Inflammatory Mechanisms of Aging and Chronic Disease	PI: Panos Roussos Icahn School of Medicine at Mount Sinai
2. Mapping Convergent and Divergent Inflammatory Mechanisms of Aging and Chronic Disease by Cross-tissue Integrative Multi-Omics for Therapeutic and Biomarker Discoveries	PI: Nilufer Ertekin-Taner Mayo Clinic, Jacksonville
3. Multiscale Network Modeling of the Inflammation in Major Human Diseases: Systematic Identification and Validation of Inflammation Targets and Therapeutics	PI: Bin Zhang Icahn School of Medicine at Mount Sinai
4. A shared foundation for single genetic investigations of immune responses (in collaboration with Rima Kaddurah-Daouk, Duke University)	PI: Phil DeJager Columbia University
5. Molecular Crossroads of Inflammation, Metabolism and Non-Communicable Diseases (in collaboration with Phil DeJager, Columbia University)	PI: Rima Kaddurah-Daouk Duke University
6. Integration of immune cell subtypes across diseases & tissues	PI: Phil DeJager Columbia University
7. Defining shared proteomic signatures of brain inflammation in CSF and plasma*	PI: Nick Seyfried Emory University

**Additional Proof-of-Concept Project – not currently funded*

Precision Medicine Approach to Dissect the Inflammatory Mechanisms of Aging and Chronic Disease

Panos Roussos
Icahn School of Medicine at Mount Sinai

Precision Medicine Approach to Dissect the Inflammatory Mechanisms of Aging and Chronic Disease

The Accelerating Medicines Partnership (AMP) has been investigating traits, including Alzheimer’s disease (AD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Parkinson’s disease (PD), Schizophrenia (SCZ) and Type 2 diabetes (T2D), which have complex and partially shared polygenic architecture, and their pathophysiology involves inflammatory mechanisms regulated by the innate and adaptive immunity found in the brain and periphery. We will utilize EpiXcan, a novel machine learning approach, which leverages expression reference panels (eQTLs cohorts with expression and genotype data) to understand the genetically driven perturbations of shared and distinct immune mechanisms across AMP-related traits.

Our group has generated high dimensional single-cell data in human purified microglia and peripheral blood mononuclear cells (PBMCs) from matched donors and population-level RNA-seq and ATAC-seq data in human purified microglia.

Aim 1. Leverage an expanded in-house population-level RNA-seq and ATAC-seq data in human purified microglia combined with external (from AMP related projects and other consortia such as GTEx and TOPMED) omics data of brain immune cells, PBMC and synovium to train GREx using the EpiXcan method, a novel machine learning approach that integrates epigenetic annotation to improve transcriptomic imputation (TI) predictive performance, which increases power compared to other published methods.

Aim 2: GREx models will be applied across multiple GWAS summary statistics for AMP-related traits to define the shared and distinct transcripts and regulatory mechanisms associated with these traits.

Aim 3. To further understand the relatedness among AMP traits, we will construct a network based on pairwise trait comparison of GREx to identify pairs of shared gene associations across trait categories. We previously utilized GREx to construct networks indicating shared genes within/across trait categories

DELIVERABLES: Transcriptomic imputation (TI) analysis across AMP-related traits using GREx across different immune cells. **(b)** Explore trait-trait correlations and gene-trait associations and identify molecular pathways associated with shared genes implicated across AMP-related disease traits.

TIMELINE:

Activity	Y1				Y2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Omics data preprocessing	█	█	█					
Training GREx models		█	█	█				
GWAS TI analysis					█	█		
trait-trait correlations							█	█

Progress to date

1. Data accessed:

To increase the power of the in-house generated data for developing EpiXcan models we are gaining access to data from AMP and external consortia. We have **gained AMP-PD data access approval** and are in the **process of getting access to AMP-T2D, AMP-RA/SLE data. TOPMED data access application has been submitted to dbGAP. GWAS summary stats** to be used in the analysis have been collected from publicly available resources.

2. Analyses conducted:

We have done QC on the in-house data to prepare it for the EpiXcan pipeline to generate GREx models.

3. Timeline for achieving the first deliverable(s)/milestone(s):

Within a year we aim to train the GREx models for the AMP-related traits across different immune cells to identify shared and distinct transcripts and gene regulatory networks and examine the overlap with common and rare genetic risk variants across AMP-related traits.

Mapping Convergent and Divergent Inflammatory Mechanisms of Aging and Chronic Disease by Cross-tissue Integrative Multi-Omics for Therapeutic and Biomarker Discoveries

**Nilufer Ertekin-Taner (PI)
Mariet Younkin (Presenter)
Mayo Clinic, Jacksonville**

Mapping Convergent and Divergent Inflammatory Mechanisms of Aging and Chronic Disease by Cross-tissue Integrative Multi-Omics for Therapeutic and Biomarker Discoveries

Aim 1: Identify genetic variants and transcriptional networks in inflammatory pathways that are shared between as well as distinct across diseases and in aging.

Aim 2: Discover inflammatory signatures that are shared across tissues as well as tissue-specific.

Aim 3: Determine inflammatory cell-subtype proportion and cell-specific molecular signature perturbations across diseases and in aging.

DELIVERABLES

Phase 1: Successful completion of this pilot will yield well-curated, uniformly processed and QC'ed cross-AMP multi-omics datasets (highlighted in green, Table 1).

Phase 2: Signatures that are preserved between diseases and their key molecules will represent common therapeutic targets for which resources and expertise can be collated across the AMPs (and beyond AMPs) for prioritized target validations and their longitudinal assessments. Those signatures that are also observed in healthy aging may be de-prioritized in the therapeutic and biomarker development process. Inflammatory molecular signatures that are preserved between central (CNS/kidney) vs. peripheral tissues (blood/CSF) can be prioritized as peripheral biomarkers that can inform on the inflammatory changes occurring in difficult-to-access central tissues.

Phase 3: Increased sample sizes afforded by meta- and joint-analyses can uncover novel signatures that could be validated in future studies

Dataset:	AMP-AD		AMP-PD	AMP-RA/SLE	AMP-T2D
Tissue	Brain	Blood/CSF	Blood/CSF	Tissue (synovium, kidney)/Blood/Urine	Pancreas, Liver, adipose, Heart, kidney, muscle
N	3000-5000+	3000+	300-10,000+	100+- 300+	200K+
Diagnoses	AD, PSP, Controls, other brain pathologies (vascular, DLB, PD)		PD, Control, Others	RA, SLE	T2D, CMP
Genome	GWAS/WES/WGS		WGS	GWAS	GWAS
Transcriptome	Bulk RNAseq	PaxGene RNAseq	Paxgene RNAseq	Bulk RNAseq	
	sn/scRNAseq			sn/scRNAseq	
Epigenome	RRBS/H3K27ac/H3K9ac /ATACseq	RRBS			
	snATACseq			snATACseq	
Proteome	Proteomics	Proteomics	Proteomics	Proteomics (urine ELISA)	
Metabolome	Metabolomics	Metabolomics			

AMP-datasets and omics measures. Green boxes (Genome and Transcriptome) indicate datasets proposed to be analyzed

TIMELINE/MILESTONES

Phase	Task	Deliverables	1-6	7-12	13-18	19- 24
1	Curate and consensus process, QC: genetic (WGS/WES/GWAS) and transcriptomic (bulkRNAseq, sc/snRNAseq) data	Harmonized and QC'ed genetic and transcriptomic datasets across AMP-efforts with standardized documentation.				
2	Characterization of known inflammatory multi-omics signatures for preservation and specificity: a) between diseases, b) in aging, c) a cross tissues.	Data analysis results shared through relevant knowledge portals in preparation for manuscript(s)				
3	Discovery of novel inflammatory multi-omics signatures by leveraging increased power of combined cohorts.	Data analysis results shared through relevant knowledge portals in preparation for manuscript(s)				

Progress to date

1. AMP-AD

- **Have access to and familiarity with multiple datasets** having integrated into published and ongoing studies (Allen. M *et al*, *Nat Sci Data* 2016, Allen.M *et al Alz and Dem* 2018; Wang.X *et al*, *Mol Neurodegener*, 2020; Wang.X *et al*, *JCI*, 2021; Reddy.J *et al*, *Acta Neuropathol Commun*, 2021; Patel. T *et al*, *Aging Cell*, 2022; Is.O *et al*, under review).
- Inventory of additional bulk tissue RNAseq datasets and metadata ongoing in preparation for reprocessing with AMP-PD, AMP-RA/SLE RNAseq data.

2. AMP-PD

- Data access request (DAR) by each team member was **submitted and approved** by AMP-PD. All team members have access and awaiting data transfer to/from Synapse.

3. AMP-T2D

- **Signed DUA** listing all team members has been approved by signing official at Mayo Clinic, awaiting IRB modification required for submission of DAR. Once this is done, DAR will be submitted to AMP-T2D.

4. AMP-RA/SLE

- **DUA to be sent** to signing official for approval, awaiting IRB modification to access data. Once these are completed, DAR will be submitted.
- **Expected Phase 1 timeline:** Submit DARs to AMP-T2D and RA/SLE and begin transfer and consensus processing of transcriptomics data either from Synapse or directly from the AMP consortia by end of June/early July.

Multiscale Network Modeling of the Inflammation in Major Human Diseases: Systematic Identification and Validation of Inflammation Targets and Therapeutics

Bin Zhang, Minghui Wang
Icahn School of Medicine at Mount Sinai

Multiscale Network Modeling of the Inflammation in Major Human Diseases: Systematic Identification and Validation of Inflammation Targets and Therapeutics

Aim 1. Assemble large multi-omics cohorts at the bulk tissue and single cell levels to identify molecular signatures of inflammation in complex diseases (AD, PD, RA, T2D and schizophrenia (SCZ)).

Aim 2. Conduct mRNA expression and protein quantitative trait locus (QTL) analyses to identify genetic regulators of inflammation signatures.

Aim 3. Perform integrative network analysis of bulk and single nucleus multi-omics data to identify essential gene networks and key drivers underlying complex diseases.

Aim 4. Identify FDA approved compounds targeting predicted molecular signatures and networks of AD through drug repositioning.

Deliverables: The outcomes from this study will include: 1) molecular signatures of each disease, 2) disease specific and pan-disease molecular signatures, 3) genetic regulators of inflammation signatures, 4) gene/protein co-expression and causal networks for each disease, 5) core inflammation coexpression and causal networks across the major diseases, 6) pan-disease key inflammation drivers, 7) *in silico* validation of inflammation drivers in multiple diseases, and 8) prediction and *in silico* validation of FDA approved drugs targeting pan-disease inflammation signatures and networks.

Timelines & Milestones:

Month 1-6: Data Curation & QC*

Month 7-12: Differential expression and eQTL analyses to identify shared inflammation signatures and genetic regulators;

Month 13-18: Multiscale network analysis to identify shared inflammation subnetworks and drivers;

Month 19-24: Identification and *in silico* validation of FDA approved drugs targeting the shared inflammation subnetworks and drivers.

Data Accessed

AMP-AD (processed)

Program	Dataset	Tissue	GWAS/WGS	Sulk RNA-seq	scRNA-seq	snRNA-seq	IT Proteom	free Proteo	ected proteo	etabolomic	A methylat
AMP-AD	MSBB	Brain	339	1067			289	189			201
AMP-AD	ROSMAP	Brain	805	2581	37	80	656	111		514	748
AMP-AD	ROSMAP	Blood	391	615							
AMP-AD	Mayo	Brain	349	586			286	199			
AMP-AD	Mayo	Blood		422							

AMP-T2D (accessed)

- WGS of 1171 cases and 1177 controls from The Genetics of Type 2 Diabetes Consortium (GoT2D, dbGAP phs000840.v1.p1).
- External datasets: RNA-seq and SNP array datasets from METSIM (n = 770) and AAGMEx (n = 256) cohorts for insulin resistance studies.

AMP-PD (approved)

- WGS: 3379 PD, 4153 control, and 2906 other diagnosis
- Blood RNA-seq: 1624 PD, 1097 control, and 267 other
- Proteomics in Plasma and CSF: 185

AMP-RA/SLE (DUA in review)

- AMP-RA
 - dbGap (phs001457.v1.p1): 4 phenotype datasets, 21 variables, 1 molecular datasets, SRA, 55 subjects, 10193 samples
 - ImmPort (SDY998): CyTOF (175), Flow Cytometry (309), Microscopy (421), RNA sequencing (10189)
- AMP-SLE
 - dbGap (phs001459.v1.p1): 4 phenotype datasets, 22 variables, 1 molecular datasets, SRA, 60 subjects, 26073 samples
 - ImmPort (SDY998): CyTOF (259), Flow Cytometry (171), Protein microarray (96000), RNA sequencing (13417)

Analytic Pipeline for Analyzing scRNA-seq Data in AD

Wang et al. *Molecular Neurodegeneration* (2022) 17:17
<https://doi.org/10.1186/s13024-022-00517-z>

Molecular Neurodegeneration

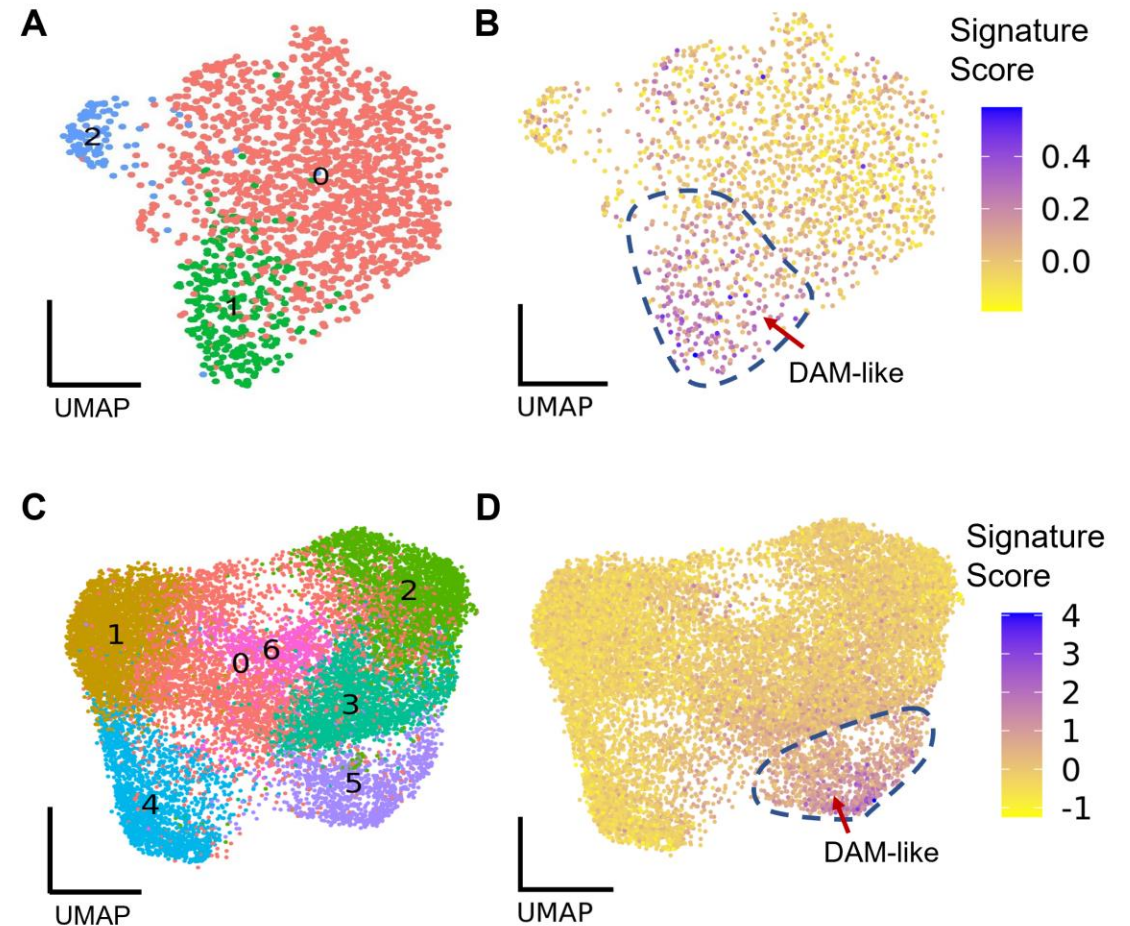
REVIEW

Open Access



Guidelines for bioinformatics of single-cell sequencing data analysis in Alzheimer's disease: review, recommendation, implementation and application

Minghui Wang^{1,2†}, Won-min Song^{1,2†}, Chen Ming^{1,2†}, Qian Wang^{1,2†}, Xianxiao Zhou^{1,2†}, Peng Xu^{1,2†}, Azra Krek^{1,3}, Yonejung Yoon^{1,2}, Lap Ho^{1,2}, Miranda E. Orr^{4,5}, Guo-Cheng Yuan^{1,3} and Bin Zhang^{1,2,6,7*}



Identification of DAM-like cell clusters by using signature scores plotted on UMAP representations of microglia in a single nucleus (Mathys et al; A-B) and a single cell (Olah et al; C-D) RNA-seq dataset. A & C show the clustering, and B & D show the signature scores.

Timelines & Milestones

- ❖ Month 1-6: Data Curation & QC.
- ❖ Month 7-12: Differential expression and eQTL analyses to identify shared inflammation signatures and genetic regulators.
- ❖ Month 13-18: Multiscale network analysis to identify shared inflammation subnetworks and drivers.
- ❖ Month 19-24: Identification and in silico validation of FDA approved drugs targeting the shared inflammation subnetworks and drivers.
- ❖ Month 6-24: Resource sharing.

The first milestone and the part of the 2nd milestone will be achieved by the end of August 2022.

A Shared Foundation for Single Genetic Investigations of Immune Responses

Phil DeJager
Columbia University

A shared foundation for single genetic investigations of immune responses

Aim 1: Assemble a database of all pertinent genetic associations (including other inflammatory diseases – MS, psoriasis, IBD,... as well as QTL results for immune traits) from existing published studies and assemble groups of diseases and immune traits by the extent of shared genetic architecture.

Aim 2: Deploy a mendelian randomization approach to evaluate (a) the relationship – if any – among the various diseases and traits characterized in the AMP programs, (b) whether the latter relationships are mediated by immune responses (i.e. individual analytes like TNF α or a short chain fatty acid or a “module” of correlated molecular features or a cell type proportion) using their genetic architecture.

Aim 3: Prioritize immune cell subtypes and cell states that are enriched for genetically defined groups of traits and disease susceptibility variants using enrichment approach.

Aim 4: Weighted GWAS. Using summary statistics, weigh the results of each GWAS for disease susceptibility by the effect size of the variant's effect on a pertinent immune-related endophenotype (such as a metabolite, module of coexpressed genes,...) to prioritize those variants who display some evidence of association to disease but have not yet reached genome-wide significance. This will also prioritize sets of disease-related variants that may be participating in the same molecular pathway or cell type.

Aim 5: For individual variants influencing disease susceptibility and immune responses, map the propagation of the functional consequence of each variant from epigenomic alterations, changes in the transcriptome, proteome, and ultimately altered metabolite profiles and cellular function. This leverages the integrated reference assembled by the Duke-led team.

Deliverables

1. 6 months: we will have completed Aim 1: a new database containing all of the AMP disease-related variants and all variants influencing immune traits/endophenotypes. This creates the matrix essential for the accomplishment of the other aims. **Plan for coordination and integration with Duke-led team completed (see Kaddurah Daouk proposal).**
2. 12 months: we will complete Aim 3, prioritizing immune cell subtypes and cell states that are enriched for susceptibility variants in each AMP disease
3. 18 months: Aim 2 is completed
4. 24 months: Aims 3, 4, 5 are completed.

Progress to date

1. Data accessed:

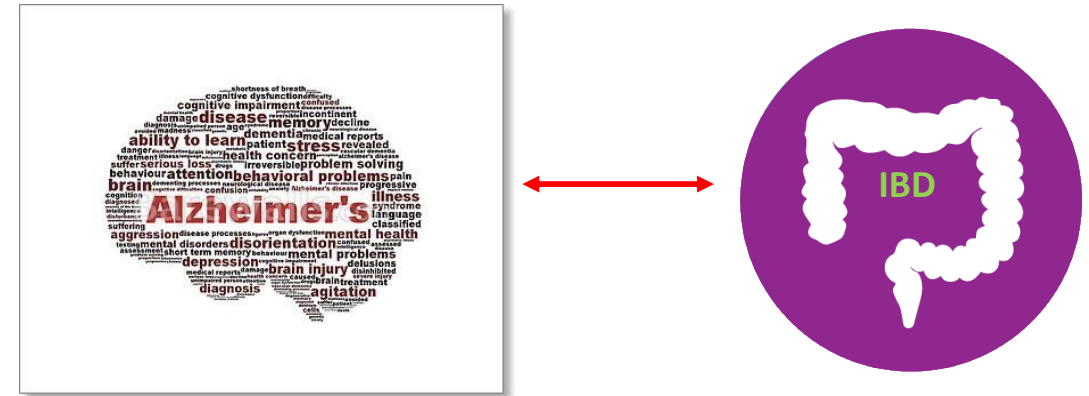
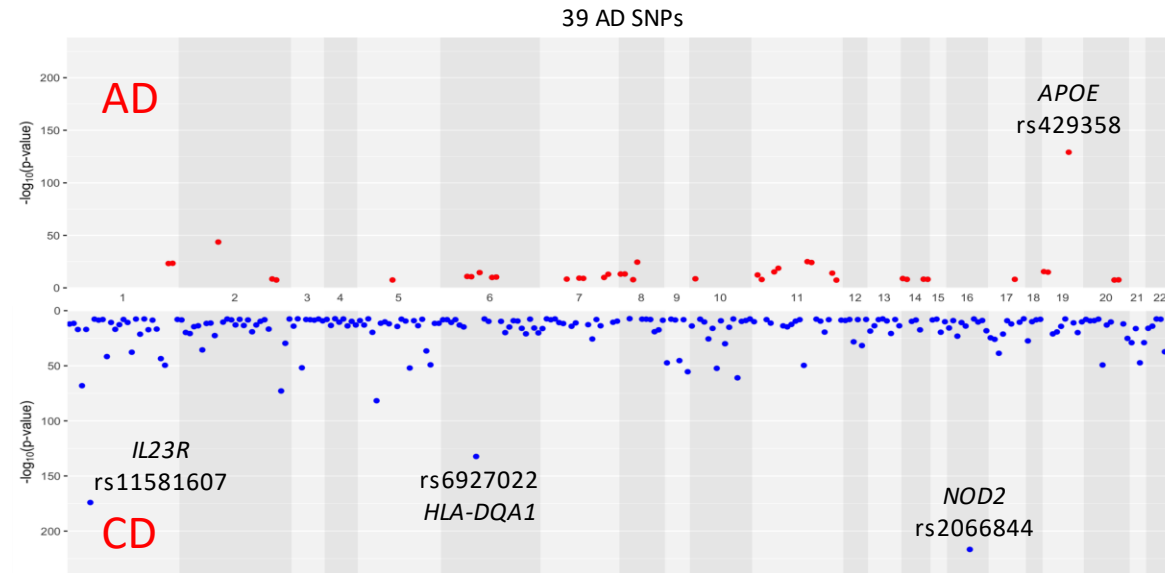
- AMP PD DUA finalized; access obtained. AMP T2D and AMP RA/SLE DUAs access ongoing: requests for access submitted, awaiting clarification/next steps

2. Analyses conducted:

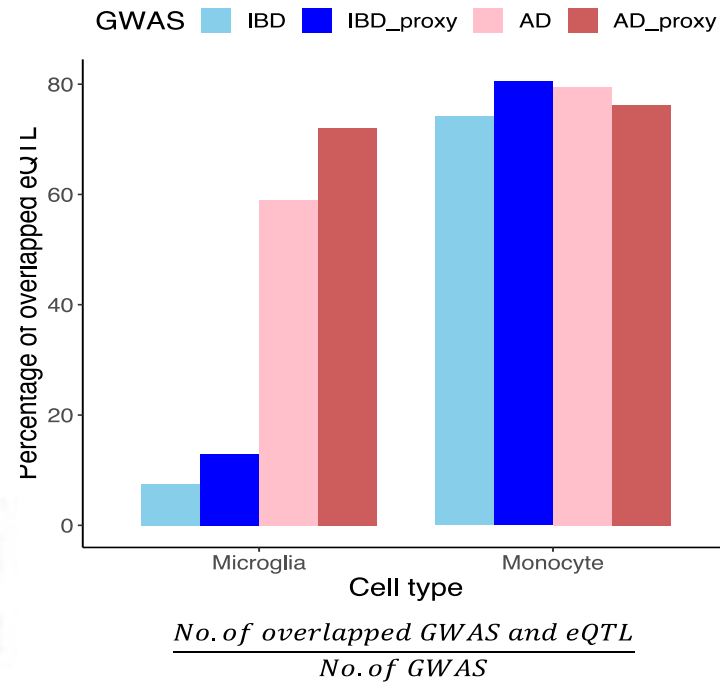
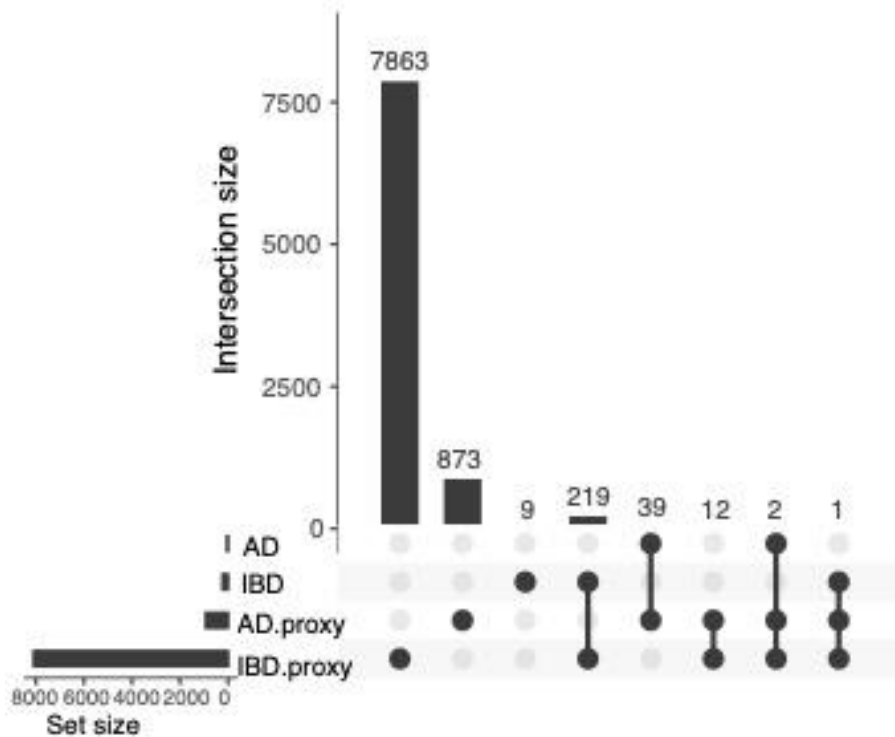
- Building an xQTL pipeline with detailed documentation to integrate QTL mapping across different datasets and omic dimensions
- Pilot integrating Crohn's disease GWAS, AD GWAS, microglial QTL and monocyte QTL completed. Report being written

3. Timeline for achieving the first deliverable(s)/milestone(s): 9/1/2022

- Database of genetic variants associated with disease susceptibility across inflammatory diseases, with direction of effect.
- Assemble published genome-wide QTL results to enable integration



228 IBD SNPs



Cell type	AD	IBD
Microglia	USP6NL PTK2B BIN1 CD2AP NUP160 PILRB CASS4 EPDR1 ZKSCAN1	ETS2 PTK2B TOM1 CCR1 RPS6KA2
Monocyte	44 unique eGenes	186 unique eGenes

PTK2B
BNIP3L

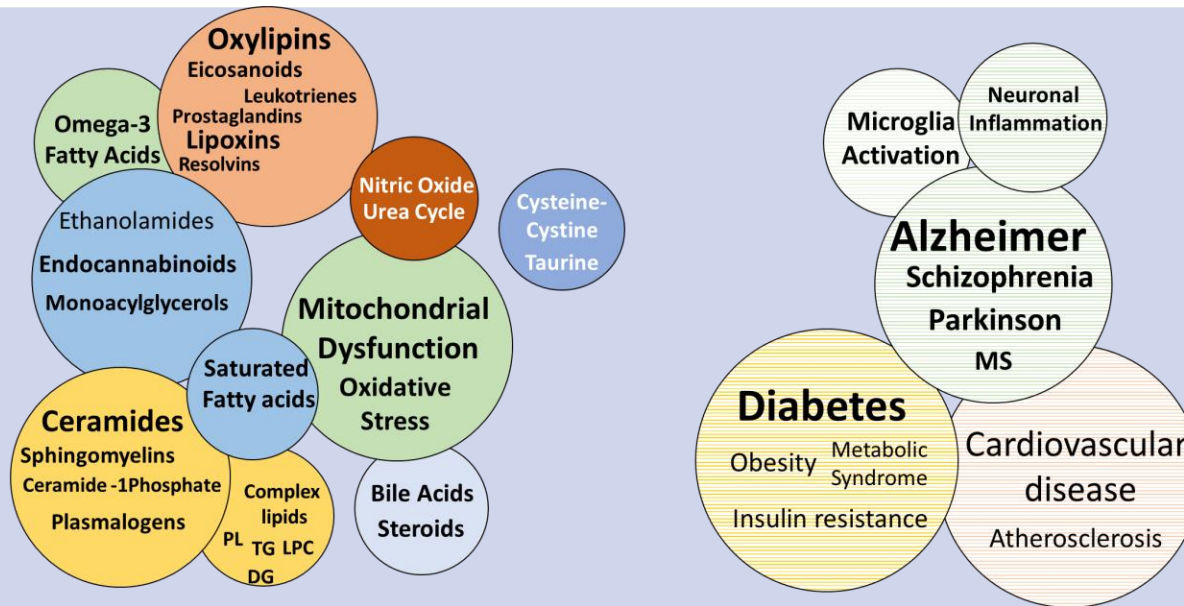
Molecular Crossroads of Inflammation, Metabolism and Non-Communicable Diseases

Rima Kaddurah-Daouk, Gabi Kastenmüller, Matthias Arnold
Duke University

Project title

Molecular Crossroads of Inflammation, Metabolism and Non-Communicable Diseases

Objective / Rationale



- Inflammatory and immune-related processes are strongly interlinked with metabolic homeostasis and signaling.
- A broad spectrum of metabolic pathways are affected, influenced by genetic and lifestyle factors.
- Metabolomics and lipidomics technologies provide insights into common inflammatory processes across diseases.
- The metabolome provides a readout for net influences of genomics and other omics on metabolic processes linked to inflammation.

Aims

Aim 1a: Build a genetically-anchored integrative molecular disease map.

Aim 1b: Extract genetic associations shared across immune traits and inflammatory diseases.

Aim 2: Leverage Alzheimer Disease Metabolomics Consortium Resources and Data Available across AMP Projects to Define Metabolomic Signatures for Inflammation and Immune-dysregulation Across Diseases.

2.1. Create biochemical map of inflammation and immune function dysregulation in AD.

2.2. Create biochemical map of inflammation and immune function dysregulation across CNS and metabolic diseases within AMPs.

Aim 3: Integrate all evidences collected in Aims 1 and 2 in a web-based cross-AMP inflammation portal.

Timelines Milestones Deliverables

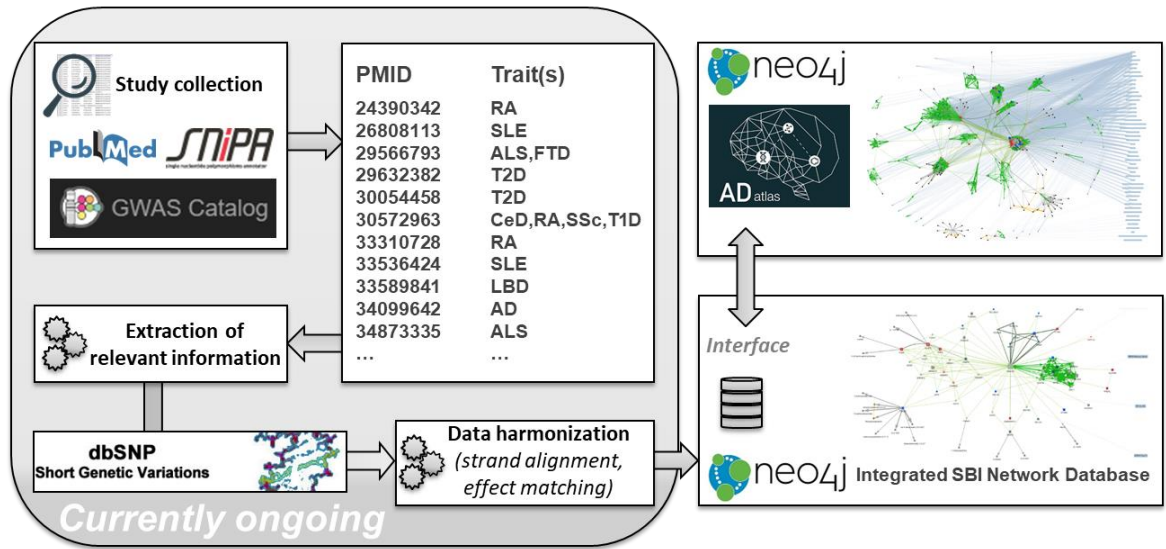
Aim 1: Complete GWAS integration framework and database (months 0-10), sharing of harmonized data (months 10-12), share genetic influences on molecular/metabolic (dys)regulation linked to inflammation (months 10-18)

Aim 2: Collect metabolic datasets from AMP projects/literature (months 0-6), analyze those data for evidence that implicates shared metabolic markers of inflammation in AMP-studied disorders (months 6-24)

Aim 3: Implement and make available a searchable web-based version of the network database (months 12-24)

Progress to Date

Conceptualization of GWAS integration pipeline completed



Metabolomics/Lipidomics studies in Parkinson's Disease Review Ongoing

- AMP datasets limited (BioFind), PIs contacted.
- Evaluated PPMI: longitudinal rich omics data and inflammatory markers with plans for metabolomics, PIs being contacted.
- Literature interrogated for datasets available, Key PIs being contacted to try to engage in AMP SBI.
- Key pathways implicated in disease identified from the literature being compared to AD.

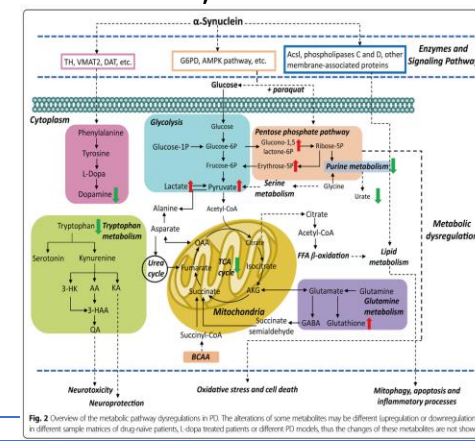
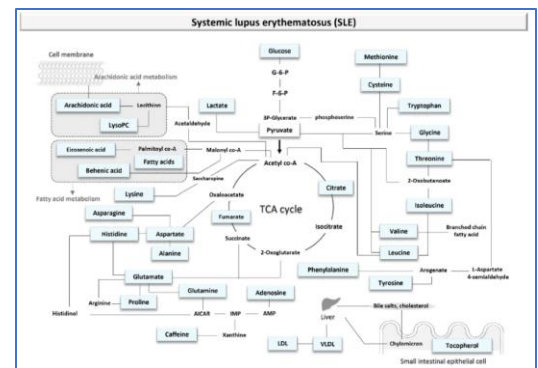
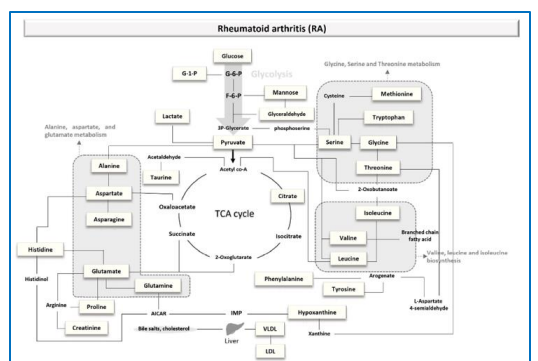


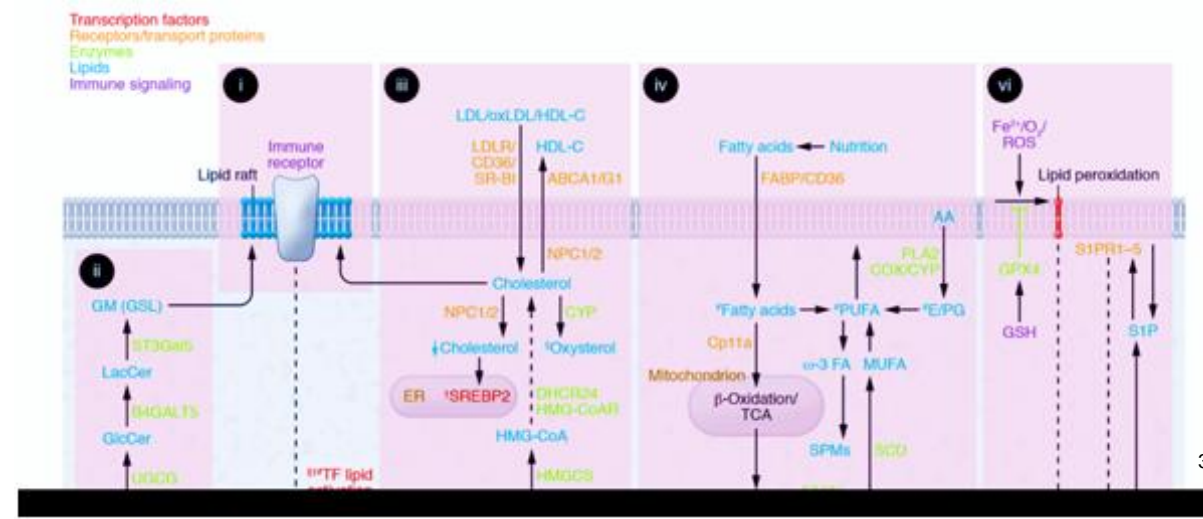
Fig. 2 Overview of the metabolic pathway dysregulations in PD. The alterations of some metabolites may be different (upregulation or downregulation) in different sample matrices of drug-naïve patients, L-dopa treated patients or different PD models, thus the changes of these metabolites are not shown.

NIAMS disorders – Literature and Pilot Proposal Completed

- Identified and reviewed metabolomics/lipidomics studies in RA/SLE, psoriatic arthritis, among others.
- Defined common pathways impacted and links to inflammation.
- Identified and reviewed metabolomics/lipidomics studies in drugs used in the treatment of these disorders and pathways affected.



Inflammation related pathways in AD – Compare and contrast to other AMP diseases (in progress)



Progress to date (continued)

Data Access for AMP-PD, RA/SLE, T2D

- Blanket IRB approved, DTAs/DUCs signed by team and routed through Duke for institutional signature, applications underway to access data.

Proposal for NIAMS developed and shared to generate metabolomics/lipidomics data

- SLE Response to Treatment
- SLE Stratification
- RA Early vs late disease
- Anti-TNF responders vs non-responders

Investigating Diabetes and metabolic processes implicated in inflammation will be investigated over the next quarter

Development of a GWAS integration pipeline

- Conceptualization of GWAS integration pipeline completed.
 - Implementation of the informatics framework is based on ~20 GWAS/meta-analyses of AMP-studied diseases; minimally-required set of variables was identified; additional studies are being collected to be added consecutively
- Data harmonization ongoing.
 - *Manual:* extraction of study-specific information (variables, reference assembly, effect alleles, type of effect estimate);
 - *Automation:* alignment of variants to same genome assembly (+ strand), mapping to dbSNP; consolidation of effect estimates; output in standardized file format (*est. to be completed by Aug 2022*)

Integration of Immune Cell Subtypes Across Diseases & Tissues

Phil DeJager, Vilas Menon
Columbia University

Integration of immune cell subtypes across diseases & tissues

Work packet 1: Integrate tissue-derived immune cells (frozen nuclei and purified cells such as microglia) and PBMC (and other biofluid) single-cell/nucleus RNAseq data into a common framework using Harmony and similar methods to integrate disparate datasets. Use of multiple methods would allow for assessing robustness of cross-data set integration.

Work packet 2: After integration, identify the full ensemble of gene expression programs in each major cell class/type in the unified data set. This is broader than standard trajectory analysis approaches, in that we allow for intersecting (in addition to branched) pathways.

Work packet 3: Using the integrated dataset, evaluate the role of individual immune expression programs in each cell type across available datasets (for tissue and other biosamples) to identify which cell types program fulfill roles in different diseases with RA/SLE/AD/T2D/PD...

Work packet 4: Integrate AMP data with Human Cell Atlas data (from De Jager and others) – including PBMC scRNAseq from 400 diverse (racial/ethnic) individuals + samples accounting for the impact of biological rhythms (diurnal, seasonal and menstrual) on expression patterns at single cell resolution. Also CSF scRNAseq on a subset of these healthy, diverse individuals (n=100) with matching PBMC scRNAseq.

Work packet 5: Integrate multiple sclerosis PBMC, CSF and brain sc/snucRNAseq data into the AMP integrative analysis as a bridge between the neurodegenerative diseases and inflammatory diseases (from De Jager and external sources).

Work packet 6: Identify molecular programs in the non-immune cells from the target tissue that correlate to the immune programs in #3. This should identify cellular response in the target tissue.

Work packet 7 Validate associations using emerging sc/snuc data as well as bulk data (RNA but also proteomic, metabolomic).

Deliverables

Each Work Packet represents one deliverable. Reprocessing of data is performed as part of the respective work packets involving data integration (1, 4, and 5)

Timeline/Milestones:

6 months: Identify the AMP datasets to integrate into the joint framework & finalize method selection for integration.

12 months: Complete Work Packet 1, integration of AMP data

18 months: Complete Work Packets 4 and 5, integration of external data. Also, Work Packet 2.

24 months: Complete Work Packets 3, 6 and 7.

Progress to date

1. Data accessed:

- Internal data – brain single nucleus, purified microglia single cell, purified CSF cells, PBMC single cell data from diverse individuals

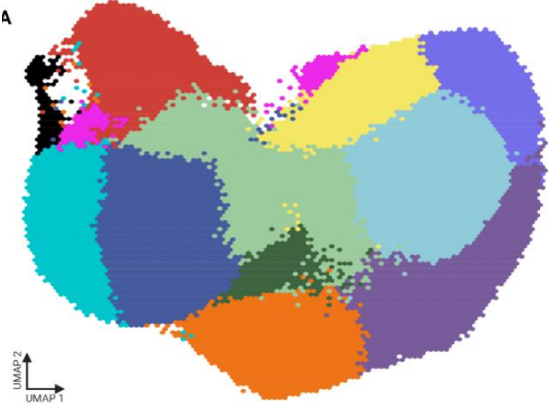
2. Analyses conducted:

- Tested different approaches to deploy a reference population structure model into external data and model system data (reported in: <https://www.biorxiv.org/content/10.1101/2022.06.04.494709v1>)
- Testing analytic methodologies for integration of datasets across technology versions (V2/V3 chemistry on Chromium), batches and projects/sample source: prioritized single cell Hierarchical Poisson Factorization (scHPF) as an approach to develop a shared framework for immune cells.
- Initial analysis to deploy the method in a large microglial dataset is ongoing.

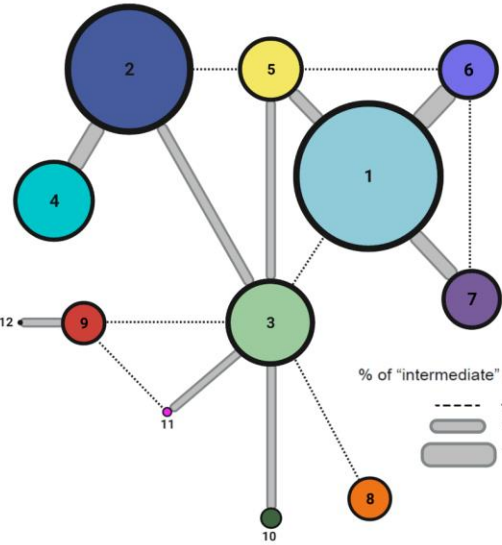
3. Timeline for achieving the first deliverable(s)/milestone(s): 9/1/2022

- Datasets downloaded and frozen
- Integration method selection finalized

Deploying a reference population structure into external scRNAseq data



Reference: based on 215,000 transcriptomes from live human microglia purified from 74 participants → 12 microglial subtypes



Constellation diagram of the 12 microglial subtypes

Deploying the model: single cell data from model systems, non-sampled condition (GBM), and single nucleus data

Defining shared proteomic signatures of brain inflammation in CSF and plasma

Nick Seyfried, Erik Johnson (presenter), Allan Levey

Emory University

(future proof-of-concept funding opportunity)

Defining shared proteomic signatures of brain inflammation in CSF and plasma

**Nick Seyfried, Erik Johnson, Allan Levey and
the AMP-AD Team**

**Associate Professor
Departments Biochemistry and Neurology
Director, Emory Integrated Proteomics Core
Goizueta Alzheimer's Disease Research Center
Emory School of Medicine**

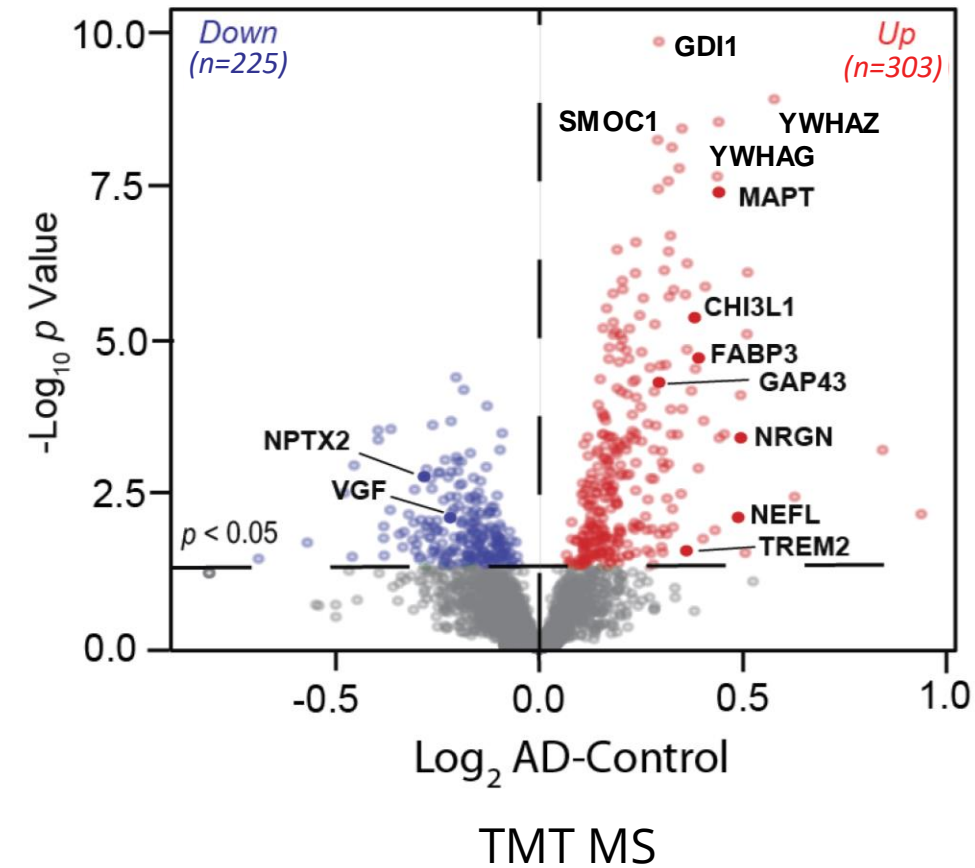
Disclosures: Nothing to disclose



CSF Biomarker Panels that Reflect Diverse Biology in AD Brain

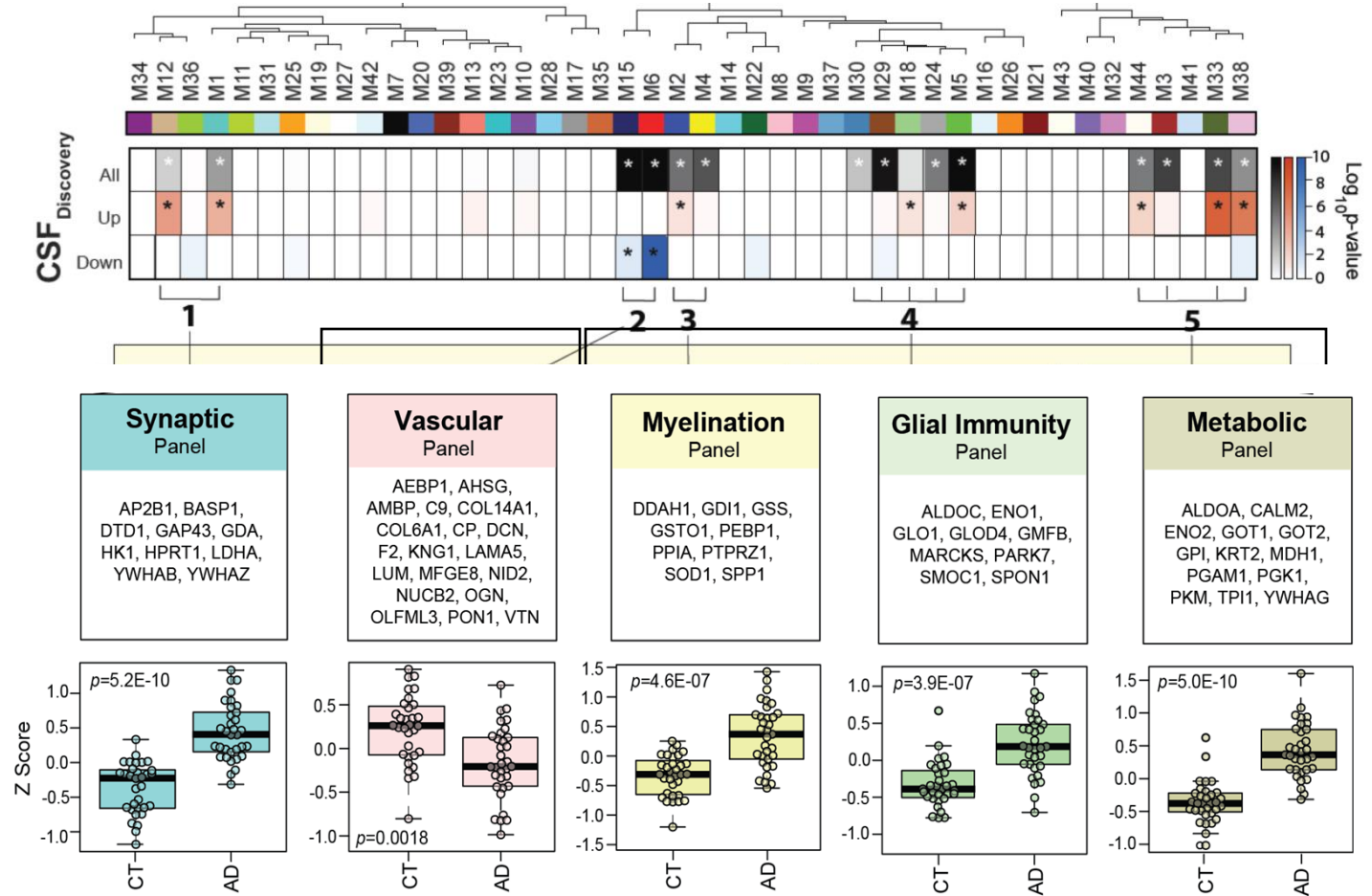
CSF

Brain



n=2,785 proteins across 40 CSF samples

~67% overlap with brain



Systemic/
Vascular

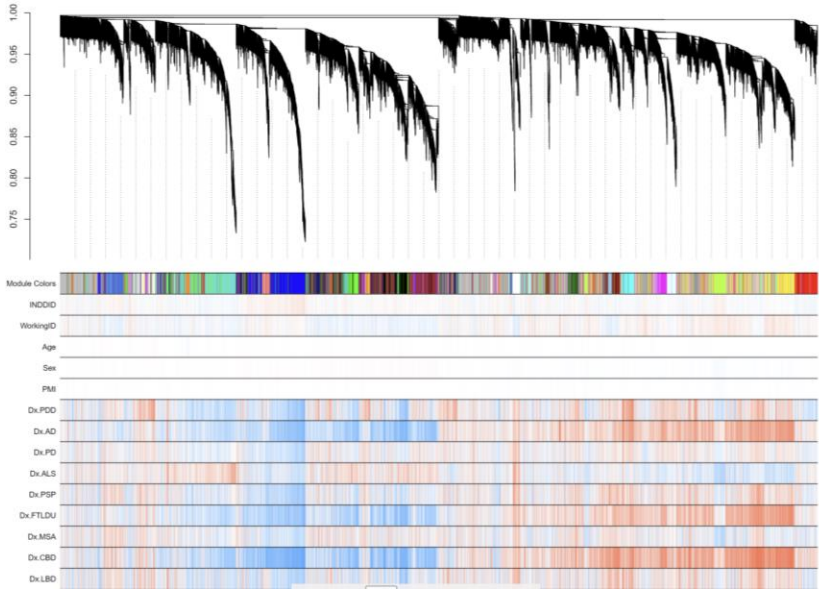
Glia Biology/Inflammation

Aim 1: Define common pathways linked to inflammation in brain across neurodegenerative diseases

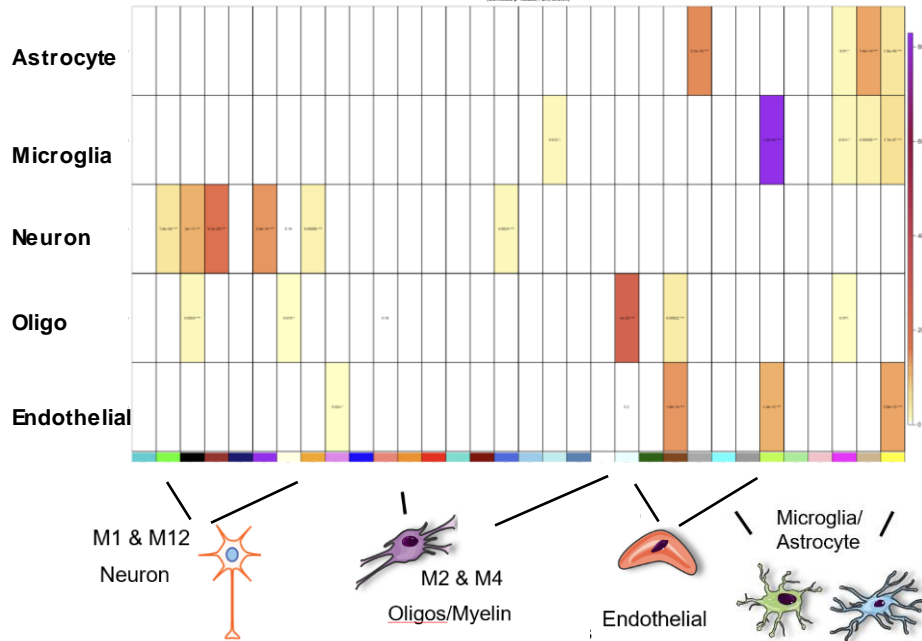
Rationale: Brain networks across AD and ADRDs are needed to enable the mapping of brain-linked protein markers of inflammation

- 1.1 Data Generation:** Deep TMT proteomic datasets (9,200 proteins) across AD and ADRDs (PD, PDD, LBD, FLTD, AD Tauopathies, ALS, MSA etc.). Total of ~360 tissues
- 1.2 Analyses:** Co-expression networks to prioritize modules related to inflammation, vascular and microglia biology that increase are shared across ADRDs.

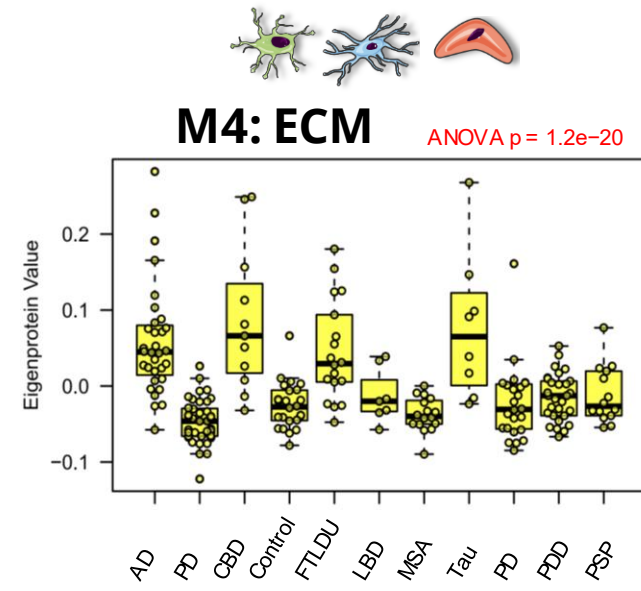
Co-expression Network in Brain



Cell Type Enrichment



Module-Phenotype

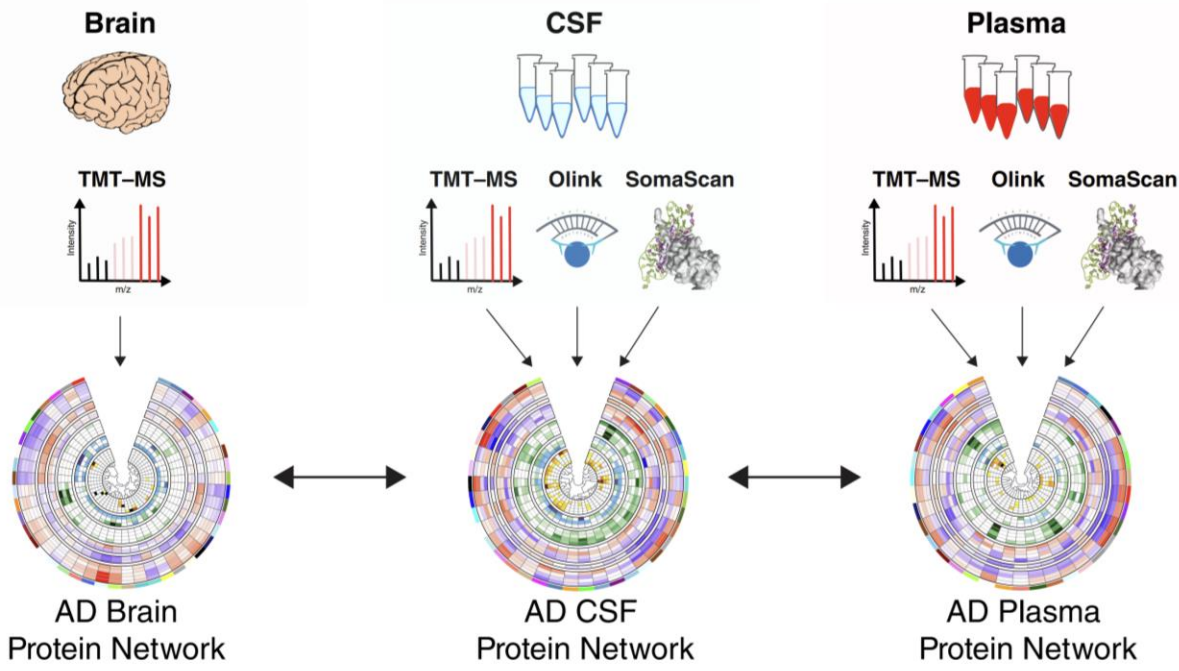
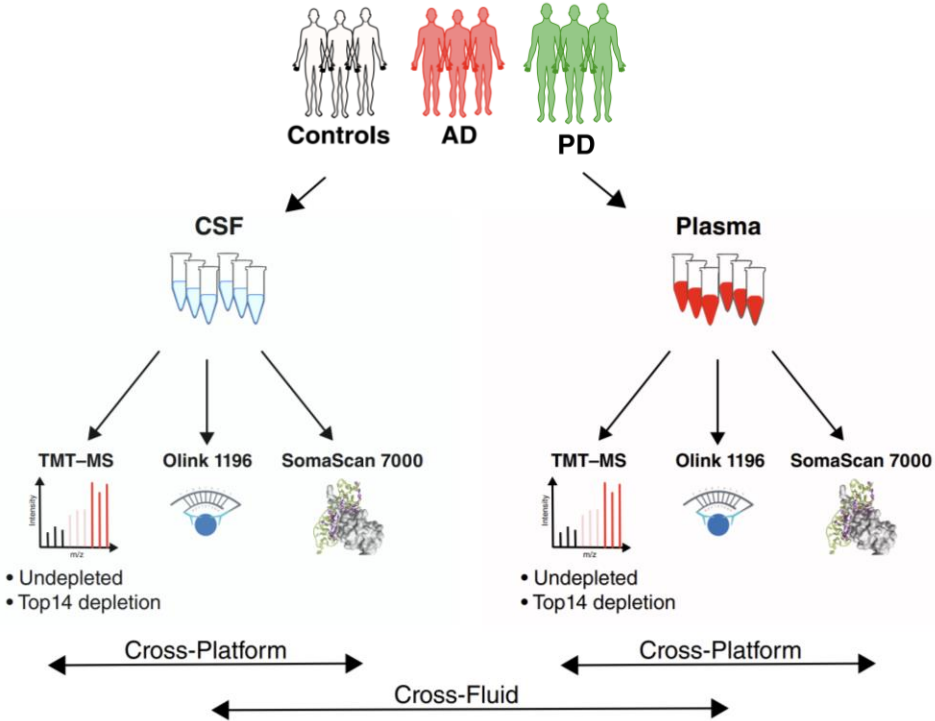


Aim 2: Define brain-linked inflammatory biomarkers in plasma and CSF across orthogonal proteomic platforms (MS, SomaScan and O-link)

Rationale: Integrating CSF and Plasma expression data from multiple proteomic platforms and diseases (e.g., AD and PD) will generate robust and reproducible biomarkers of inflammation

2.1 Data Generation: O-link, TMT-MS and SomaScans on Emory and ADNI CSF and plasma samples (AMP-AD 2.0)

2.2 Analyses: Perform integrated cross biofluid and cross disease (AMP-PD O-link samples n=208) analyses to assess changes in biomarkers linked to inflammation in brain



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Discussion of Research Concepts and AMP[®] SBI Scale & Scope

Research Concepts: AMP[®] Systems Biology of Inflammation

Industry participants will have the opportunity to ask questions and provide feedback on each of the research concepts.

Title of Research Concept
1. Precision Medicine Approaches to Dissect the Inflammatory Mechanisms of Aging and Chronic Diseases
2. Mapping Convergent and Divergent Inflammatory Mechanisms of Aging and Chronic Disease by Cross-tissue Integrative Multi-Omics for Therapeutic and Biomarker Discoveries
3. Multiscale Network Modeling of the Inflammatome in Major Human Diseases: Systematic Identification and Validation of Inflammation Targets and Therapeutics
4. Molecular Crossroads of Inflammation and Metabolism in Non-Communicable Diseases Integrated into a Multi-Omics Map
5. Integration of Immune Cell Subtypes across Diseases and Tissues
6. Estimating and Evaluating the impact of Immunosenescence across Diseases
7. Defining Proteomic Signatures of Brain Inflammation in Plasma as Biomarkers for Neurodegeneration



Precision Medicine Approaches to Dissect the Inflammatory Mechanisms of Aging and Chronic Diseases

Precision Medicine Approaches to Dissect the Inflammatory Mechanisms of Aging and Chronic Diseases

Goal 1: Dissect shared and distinct inflammatory mechanisms across AMP-related traits by building an integrated reference framework to catalogue all immune cell subtypes and states in brain and periphery.

Pilot Phase: Leverage in-house and external (AMP) single cell data of brain immune cells, PBMC and synovium to identify full repertoire of common and rare immune cells that are shared and distinct across brain and periphery.

Scale-Up Phase: Increase resolution of immune cell characterization by adding multi-modal (scRNA-seq + proteomics) multi-tissue data (brain prefrontal cortex, hippocampus, caudate and thalamus, choroid plexus and PBMCs).

✓ **Deliverables:** Shared and distinct transcripts and gene regulatory networks and examine the overlap with common and rare genetic risk variation across AMP-related traits.

Goal 2: Identify shared and distinct immune mechanisms across AMP-related traits, through integrative statistical fine-mapping to define the credible causal variants, transcripts and regulatory sequences, in relevant tissues and cell types.

Pilot Phase: Leverage in-house and external (AMP, GTEx and TOPMED) omics data of brain immune cells, PBMC and synovium to perform a comprehensive analysis of chromatin accessibility and gene expression QTLs.

Scale-Up Phase: Increase resolution of immune cell QTL mapping in human brain tissue by single cell profiling (sc and snRNA-seq and sc and snATAC-seq) in immune cells.

✓ **Deliverables:** Define credible causal variants, transcripts and regulatory sequences that are shared and distinct across AMP-related traits.

Goal 3: Precision Medicine approaches through multi-modal omics and detailed clinical data to identify the genetically-driven perturbations at the individual level

Pilot Phase: Leverage in-house and external population-level RNA-seq, ATAC-seq data in human purified microglia, PBMC and synovium to train genetically regulated expression models (GREx) using [EpiXcan](#) method.

Scale-Up Phase: Impute human brain immune cells scRNA-seq and scATAC-seq in the Million Veteran Program Biobank (MVP) (658,310 patients with genotypes, high ancestry diversity ~30% non- Europeans).

✓ **Deliverables:** Define the shared and distinct transcripts and regulatory mechanisms associated with AMP traits.

✓ Imputed GREx models and the availability of multiple AMP-related traits can be analyzed using deep learning methods to infer complex relationships of comorbid scenarios and transcriptional regulatory networks.

Datasets	AMP datasets, GTEx, TOPMED, Million Veteran Program (multiple diseases, diverse, >30% non-European samples)
Diseases	AD, PD, SCZ, T2D, RA SLE
Analyses	scRNA seq, scATAC seq, proteomic, chromatin accessibility, eQTL



Mapping Convergent and Divergent Inflammatory Mechanisms of Aging and Chronic Disease by Cross-tissue Integrative Multi-Omics for Therapeutic and Biomarker Discoveries

Mapping Convergent and Divergent Inflammatory Mechanisms of Aging and Chronic Disease by Cross-tissue Integrative Multi-Omics for Therapeutic and Biomarker Discoveries

Aims: 1) To identify genetic variants, transcriptional networks, epigenetic signatures in inflammatory pathways that are shared between as well as distinct for diseases and aging. 2) To discover inflammatory signatures that are shared between tissues as well as tissue-specific. 3) To determine inflammatory cell-subtype proportion and cell-specific molecular signature perturbations in disease and aging.

Tissue	AMP-AD		AMP-PD	AMP-RA/SLE	AMP-T2D
	Brain	Blood/CSF	Blood/CSF	Tissue (synovium, kidney)/Blood/Urine	Pancreas, liver, adipose, heart, kidney, muscle
N	3000-5000+	3000+	300-10,000+	100+-300+	200K+
Diagnoses	AD, PSP, Controls, other brain pathologies (vascular, DLB, PD)		PD	RA, SLE	T2D, CMP
Genome	Genome (GWAS/WES/WGS)	Genome (GWAS/WES/WGS)	WGS	GWAS	GWAS
Transcriptome	Bulk RNAseq	PaxGene	PaxGene	Bulk RNAseq	
	Sn/scRNAseq			Sn/scRNAseq	
Epigenome	Bulk Epigenomics (RRBS/H3K27ac/ATACseq)	Bulk Epigenomics (RRBS)			
	snATACseq			snATACseq	
Proteome	Proteomics	Proteomics	Proteomics	Proteomics (urine ELISA)	
Metabolome	Metabolomics	Metabolomics			

Table 1. Existing AMP datasets. Yellow: Datasets to be harmonized and utilized in primary analyses in this concept. Green: Datasets to be utilized for orthogonal validations in this concept.

Phase 1-Data processing: *Approach:* Compile existing **same-type/same-platform-omics data** (i.e. GWAS, WES, WGS, bulk RNAseq, RRBS, ATACseq, snRNAseq, scRNAseq, snATACseq) from different AMPs and **process them jointly** through the same analytic pipelines. *Deliverables/timeline:* Genome, bulk and sn/sc transcriptome, epigenetic data from AMPs processed jointly and subjected to uniform QC. 12-18 months, done in waves.

Phase 2-Cross-AMP comparison of known inflammatory molecular signatures: *Approach:* Inflammatory molecular **signatures already discovered** in each AMP **tested across all tissues and diseases** using processed AMP datasets. These signatures include but are not limited to disease risk variants, DEGs, networks, cell subtypes. *Deliverables/timeline:* Characterization of known inflammatory multi-omics signatures for their a) preservation between diseases vs. disease-specificity. b) preservation in aging (i.e. conserved with aging control samples) vs. disease conditions. c) preservation across tissues vs. tissue-specificity. 12-18 months after Phase 1.

Phase 3-De novo inflammatory signature discoveries: *Approach:* **Meta-analyses** and where possible also **joint analyses**. *Deliverables/timeline:* Discovery of novel inflammatory multi-omics signatures by leveraging increased power of combined cohorts. 12-18 months following Phase 1.



Multiscale Network Modeling
of the Inflammatome in Major
Human Diseases: Systematic
Identification and Validation of
Inflammation Targets
and Therapeutics

Multiscale Network Modeling of the Inflammation in Major Human Diseases: Systematic Identification and Validation of Inflammation Targets and Therapeutics.

Pilot Phase

- **Aim 1.** Assemble large multi-omics cohorts at the bulk tissue and single cell levels to identify molecular signatures of inflammation in complex diseases (**datasets from all AMP programs and Common Mind**).
- **Aim 2.** Conduct mRNA expression and protein quantitative trait locus (QTL) analyses to identify genetic regulators of inflammation signatures.
- **Aim 3.** Perform integrative network analysis of bulk and single nucleus multi-omics data to identify essential gene networks and key drivers underlying complex diseases.
- **Aim 4.** Validate the most significant network-modulating pan-disease inflammation drivers of major human diseases by integrating CRISPR technologies and human iPSC-based model systems. Apply a multiplexed CRISPR gene editing system to perturb a number of most significant causal inflammation driver genes for AD, PD, SCZ and diabetes in human iPSC-derived cell cultures.

Scale-Up Phase

- **Aim 5.** Identify FDA approved compounds targeting predicted molecular signatures and networks of AD through drug repositioning.
- **Aim 6.** Test iPSC validated pan-disease inflammation drivers using disease specific mouse models.
- **Aim 7.** Validate FDA approved drugs and drug combinations in disease specific iPSC and mouse models.

Deliverables:

- ✓ An inflammation signature shared by multiple diseases under study will be identified through intersection analysis.
- ✓ Characterize unique and shared regulators underlying the fundamental molecular mechanisms of how genetic variants affect inflammation regulation and complex diseases in humans.
- ✓ Identify disease specific and pan-disease inflammation subnetworks and drivers. Drivers are prioritized by network connectivity and disease relevance for subsequent validation.
- ✓ Molecular signatures of validated inflammation drivers in disease specific iPSC and animal models, prediction and validation of FDA approved drugs targeting pan-disease inflammation signatures and networks.



Molecular Crossroads of
Inflammation and Metabolism
in Non-Communicable
Diseases Integrated into a
Multi-Omics Map

Molecular Crossroads of Inflammation and Metabolism in Non-Communicable Diseases Integrated into a Multi-Omics Map

Pilot Phase:

Aim 1a: Build an integrative molecular disease map through a network-based molecular integration framework.

Aim 1b: Deploy the power of human genetics for causal modeling and broadening the set of susceptibility variants. Integrate results of GWAS studies with molecular associations of metabolomic, proteomic and transcriptomic data.

Aim 2: Determine shared and specific metabolic antecedents of inflammation across diseases.

Deliverables:

- ✓ Integrative molecular disease map with web-based access
- ✓ Disease network linked by shared molecular signatures of inflammation extracted from the integrative map
- ✓ Searchable version of the inferred graphical model of phenotypic and molecular entities inflammation related.

Datasets	AMP datasets Fenland study FL100 cohort at USDA
Analytics	Integrate GWAS, metabolomic, proteomic and transcriptomic data Targeted lipidomics

Scale-up Phase:

Aim 3: Enrich evidence of common mechanisms of dysregulated inflammation and immune function across disorders of interest using a targeted lipidomics approach.

Quantify plasma lipid mediator profiles in individuals with Parkinson's Disease (PD), schizophrenia (SCZ), and healthy controls within AMPs and related networks. Integrate lipid mediator profiles with existing proteomic and transcriptomic data to identify new associations between inflammatory pathways and other metabolic processes. Identify common inflammatory pathways affected in neuroinflammation and type 2 diabetes.

Deliverables:

- ✓ Comprehensive, quantitative dataset of oxylipins, endocannabinoids, bile acids, steroids and lipoproteins in cohorts related to AD, PD, SCZ and type 2 diabetes.



Integration of Immune Cell Subtypes across Diseases and Tissues

Integration of Immune Cell Subtypes across Diseases and Tissues

Pilot phase:

Work packet (WP) 1: Integrate tissue-derived immune cells (frozen nuclei, purified cells e.g. microglia) and PBMC (other biofluid) sc/snRNAseq data into a common framework using Harmony (or similar methods) to integrate disparate datasets.

WP2: Identify full ensemble of gene expression programs in each major cell class/type in the unified data set. This is broader than standard trajectory analysis approaches, in that we allow for intersecting (in addition to branched) pathways.

WP 3: Using the integrated dataset, evaluate role of individual immune expression programs in each cell type across available datasets (tissue, other biosample) to identify which cell types program fulfill roles in different diseases with RA/SLE/AD/T2D/PD. Evaluate the role of these cells and programs through course of disease, exploring the hypothesis that while factors at disease onset may be distinct, the chronic state within target tissue may be similar, offering an opportunity for influencing cross-disease resilience. The approaches could include some of the neighborhood-based analyses from AMP RA/SLE.

WP 4: Integrate AMP data with Human Cell Atlas data (PBMC scRNAseq from racial/ethnic diverse individuals + samples accounting for the impact of biological rhythms (diurnal, seasonal and menstrual) on expression patterns at single cell resolution. CSF scRNAseq on a subset of individuals.

WP 5: Integrate multiple sclerosis, PBMC, CSF and brain sc/sn RNAseq data into the AMP integrative analysis as a bridge between the neurodegenerative diseases and inflammatory diseases (from De Jager and external sources).

WP 6: Identify molecular programs in non-immune cells from target tissue that correlate to immune programs in #3 to identify cellular response in target tissue.

WP 7: Validate associations using emerging sc/sn data as well as bulk data (RNA but also proteomic, metabolomic).

Scale-Up Phase:

WP 8: Establish a reference multi-omic healthy immune system set building on existing sample/datasets. Generate shotgun proteomic and metabolomic (including microbial metabolites) profiles from matching plasma and CSF samples.

WP 9: Establish a parallel multi-omic cross-disease set including each AMP disease: scRNAseq data is generated from PBMC and any available target compartment (synovium, skin, CSF); shotgun proteomic and metabolomic profiles are generated from each type of available fluid.

Datasets	AMP RA/SLE/AD/T2D/PD datasets Human Cell Atlas Multiple Sclerosis (as bridge)
Analytics	sc/snRNA seq in relevant tissues, blood, CSF Shotgun proteomic and metabolomic profiles

Deliverables

- ✓ A new, up-to-date single cell atlas resource spanning across the entire AMP program which provides a key foundation for all cross-disease immune-related investigations in AMP and prioritizes individual cell subtypes/states for each disease.



Estimating and Evaluating the
impact of Immunosenescence
across Diseases

Estimating and Evaluating the impact of Immunosenescence across Diseases

Pilot Phase:

Work packet 1: Estimate “immunological age” from existing bulk tissue and single cell/nucleus data in available AMP datasets. Contrast “immunological age” to chronological age to yield a “delta immune age” variable from each available profile. Assess which age measures relate to disease measures and/or whether these influence the relation of known risk factors on disease outcomes. For example, the effect of APOEε4 on risk for Alzheimer’s disease is influenced by an immune system whose aging appears to be accelerated.

Scale-Up Phase:

Work packet 2: Generate a multi-omic cross-disease set of data of (~100 donors in each AMP diseases: AD, new onset RA SLE, PD T2D, healthy controls) to enhance the prediction of immunological age. Biosamples include relevant tissues (skin, synovium, kidney, PBMC and fluids (e.g. plasma, CSF, synovial fluid) to create a new reference set from which to generate new biomarkers to measure immunological age in a variety of contexts.

Work packet 3: Isolate cell subtypes or cell states that best mediate effect of age on disease outcomes to enable more detailed characterization of their characteristics and function, based on pilot results.

Deliverables:

✓ Evaluation of utility of “immunological age” or “delta immune age” in AMP diseases. This may highlight which measures should be further developed as biomarkers to help with patient selection in trials or as a covariate in human studies of disease.

✓ Characterization of immune cell populations that appear to be involved in the effect of immune aging in different diseases could yield new therapeutic targets and biomarkers.

✓ New reference map across diseases offers an opportunity to generate a consistent reference set across a broad range of conditions, assessing the translatability of the immune age measures and resolving the impact of immune age from that of other disease-related risk factors.

Cohorts and samples	Subjects with new onset RA (synovial fluid), SLE (skin biopsy), PD (with CSF), AD (with CSF), T2D, reference individuals
Diseases	AD, new onset RA SLE, PD T2D
Analytics	Cytometric profile, single cell RNAseq profiles, a measure of T cell proliferation to anti-CD3/CD28 stimulation, and bulk PBMC RNAseq profile



Defining Proteomic Signatures of Brain Inflammation in Plasma as Biomarkers for Neurodegeneration

Defining Proteomic Signatures of Brain Inflammation in Plasma as Biomarkers for Neurodegeneration

Pilot Phase:

Aim 1: Define common pathways linked to inflammation in brain across neurodegenerative diseases

- Currently analyzing > 300 individual cortical tissues by TMT-MS from a diverse number of neurodegenerative diseases in the UPENN brain bank. Harmonize data with TMT-MS datasets from the Banner (n=198) and ROSMAP cohorts (n=400). Identify modules linked to inflammation and microglia biology from across all tissues using WGCNA analysis.
- Molecular subtypes or 'proteotypes' based on the deep proteomic profiles will be used to classify association with neuropathology, APOE genotype, inflammatory modules, and clinical phenotypes.

Aim 2: Identify inflammatory biomarkers in plasma that reflect the underlying pathological changes in brain

- Compare brain and plasma AD proteome quantified by TMT-MS in AMP AD.
- O-link proteomic data available from AMP-PD will also be compared to TMT-MS profiles to assess shared and unique inflammatory signatures across the diseases.

Deliverables:

- ✓ A framework for patient specific changes in neuroinflammation across neuro-degenerative disorders.
- ✓ Identify 'hub' proteins from inflammatory and microglia networks in brain as potential biomarkers in plasma.

Scale-Up Phase:

- Capture and harmonize O-link plasma profiles from AMP PD, AMP AD, ADNI and Emory UDS cohorts to harmonize datasets. Cross-validate with TMT-MS assays.
- Proteomic-metabolomic integration with data from Duke AMP-AD metabolomic team (ADMC)

Deliverables:

- ✓ Integration of proteomic and metabolomic AMP AD data
- ✓ Associations between inflammatory pathways in brain and other metabolic processes.

Cohorts and samples	Brain tissue from University of Pennsylvania brain bank, Banner Brain Bank, ROSMAP Plasma from AMP PD, AMP AD, ADNI, Emory UDS
Diseases	AD, PD, FTD, ALS, and tauopathies.
Analytics	- Quantitative multiplex tandem mass tag (TMT) mass spectrometry (MS) based proteomic - O-link Ab-based proximity extension assay ₅₇

Additional Discussion Questions

The discussion questions below are meant to guide our conversation based on the input provided in the pre-session questionnaire:



1. We received feedback about additional projects that address disease stage(s) where immune mechanisms are under or overactive. Is this of specific interest to the group?
2. Are there other areas that are not covered by these research concepts that would add value to you and your organization?

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Data Coordination / Enablement Needs for AMP[®] SBI

Anna Greenwood, PhD
Sage Bionetworks

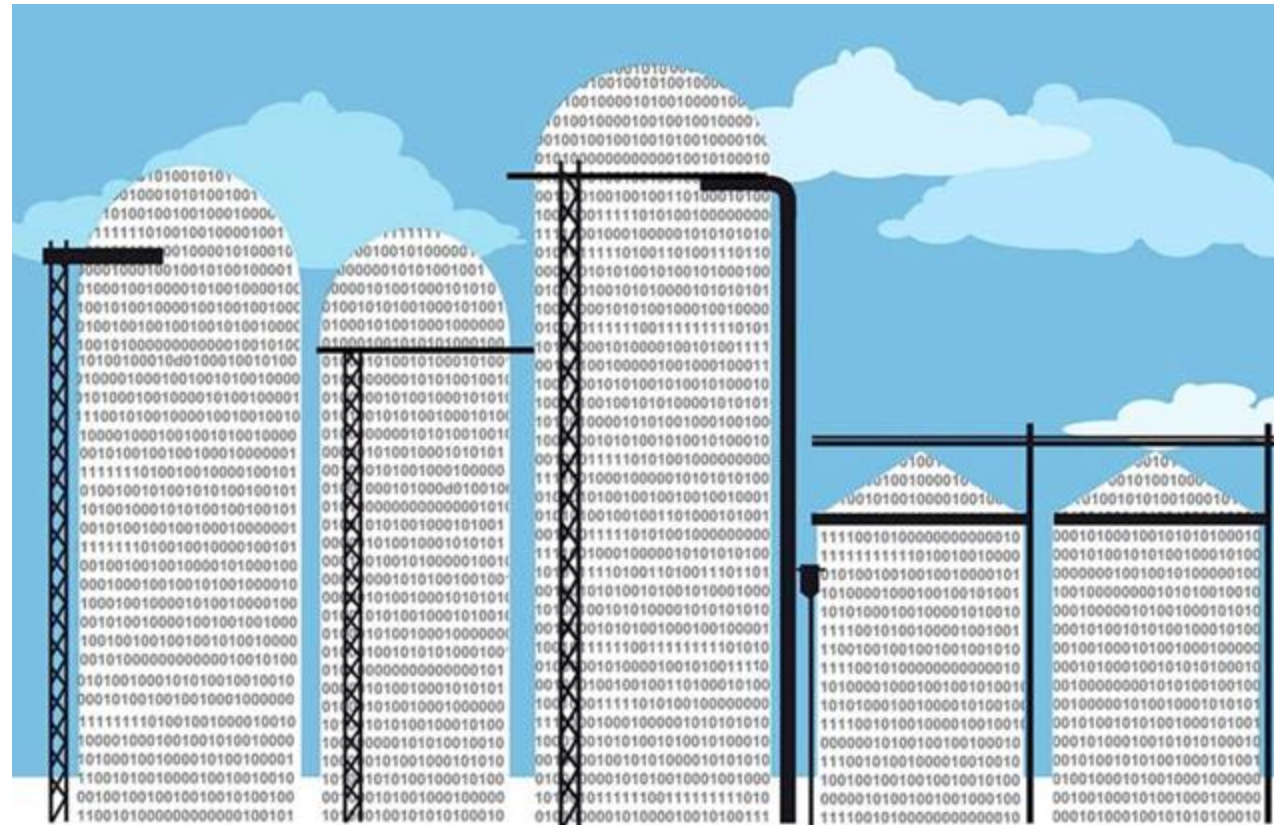
AMP-SBI: Data Coordination and Data Enablement Needs and Solutions

Anna Greenwood, PhD

Sage Bionetworks
AMP-AD DCC

June 13, 2022

Interoperability: Forming bridges across data "silos"

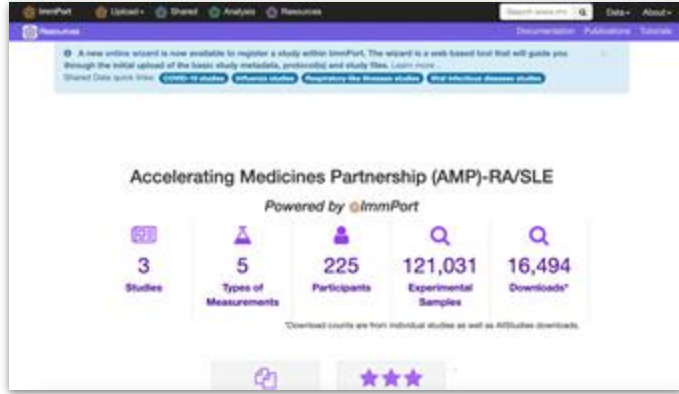


Vision for data repository interoperability

Interoperability from a user perspective:

1. Easily find compatible data across systems
2. Seamlessly access data across systems
3. Compute on all data in a common environment

AMP-RA/SLE
AMP-AIM



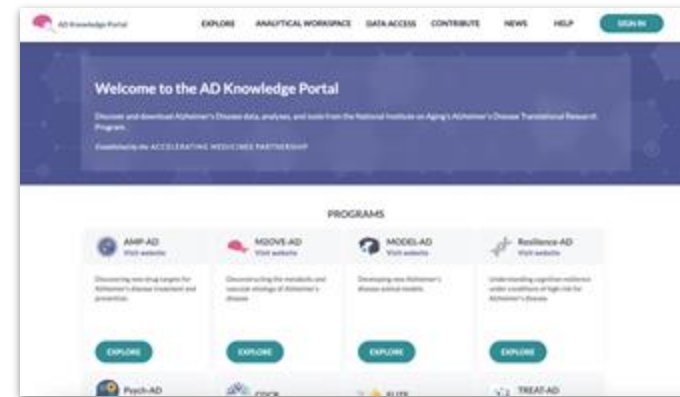
AMP-SCZ



AMP-PD



AMP-AD

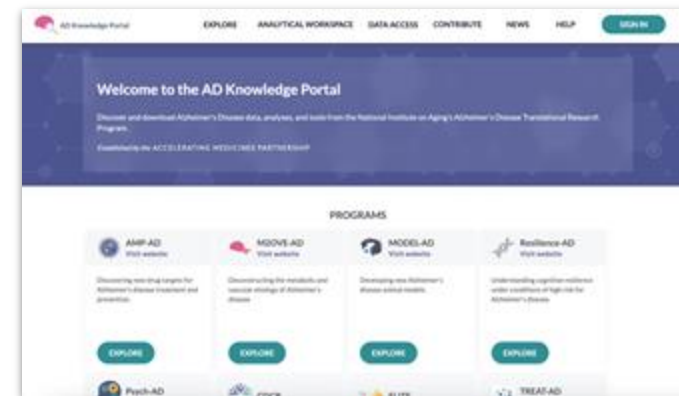
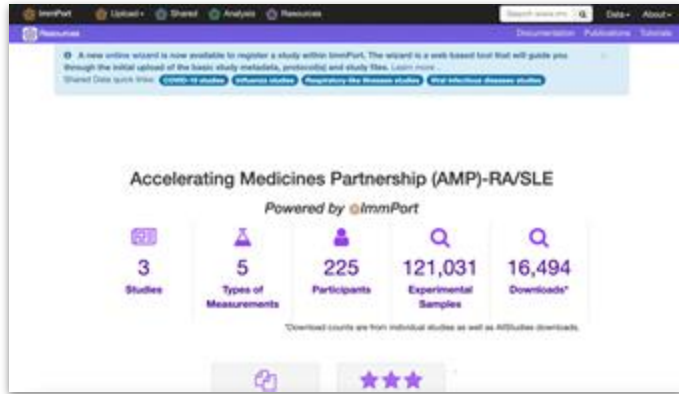


AMP-T2D



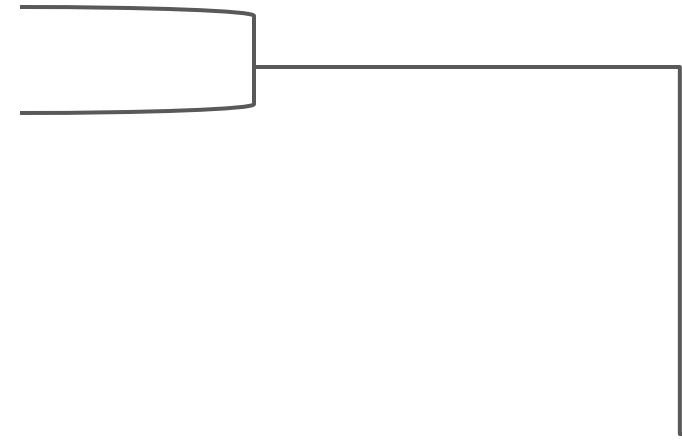
AMP-HF and future projects

AMP-SBI



AMP-SBI - Pilot phase

1. Easily find compatible data across systems
2. Seamlessly access data across systems
3. Compute on all data in a common environment



NIH investment for pilot:

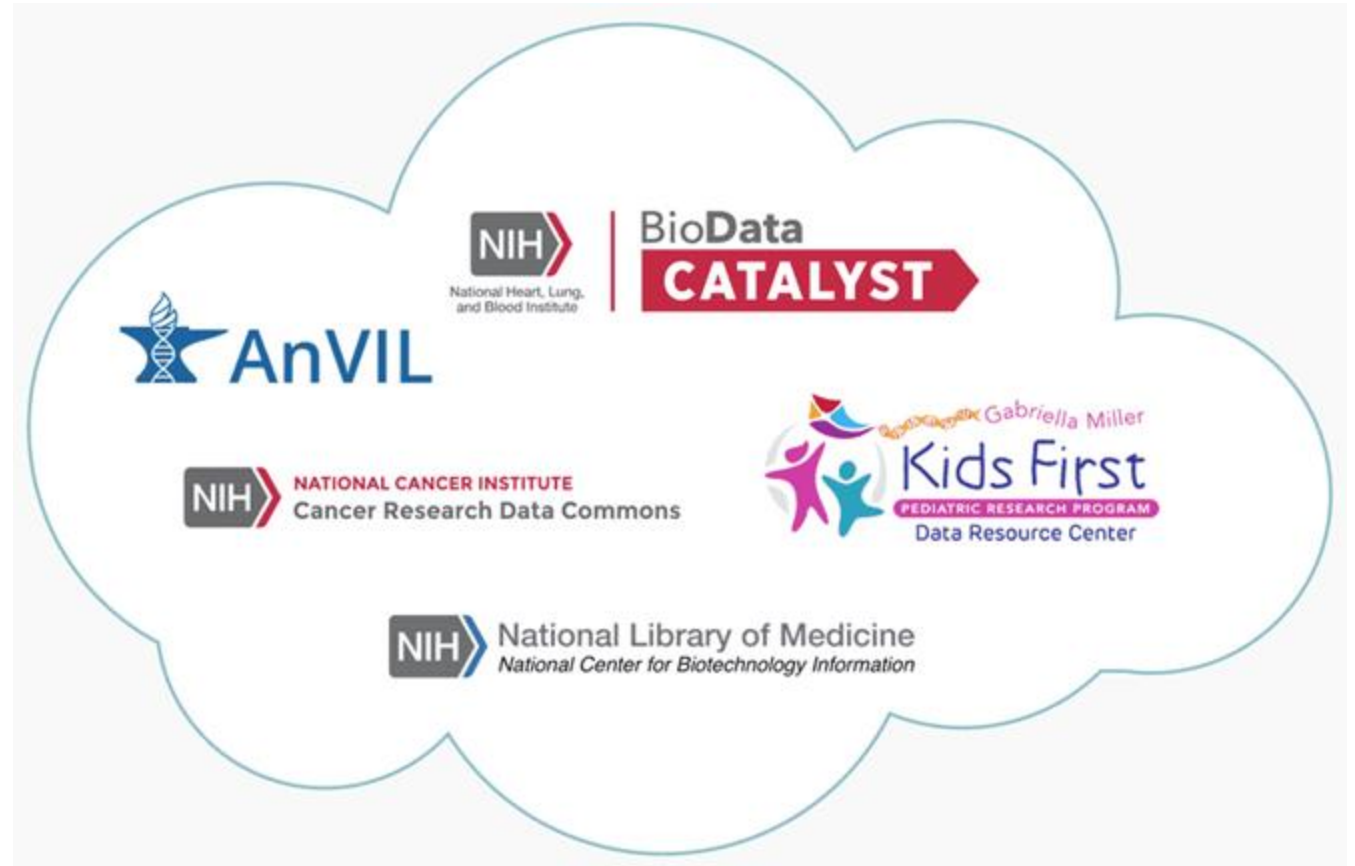
- Copy AMP datasets and host in a common environment
- Distributed effort by pilot teams to harmonize data across diseases

AMP-SBI scale up necessitates investment in true interoperability

NIH-funded efforts are leading the way for interoperability

NIH Cloud Platform Interoperability effort (NCPI)

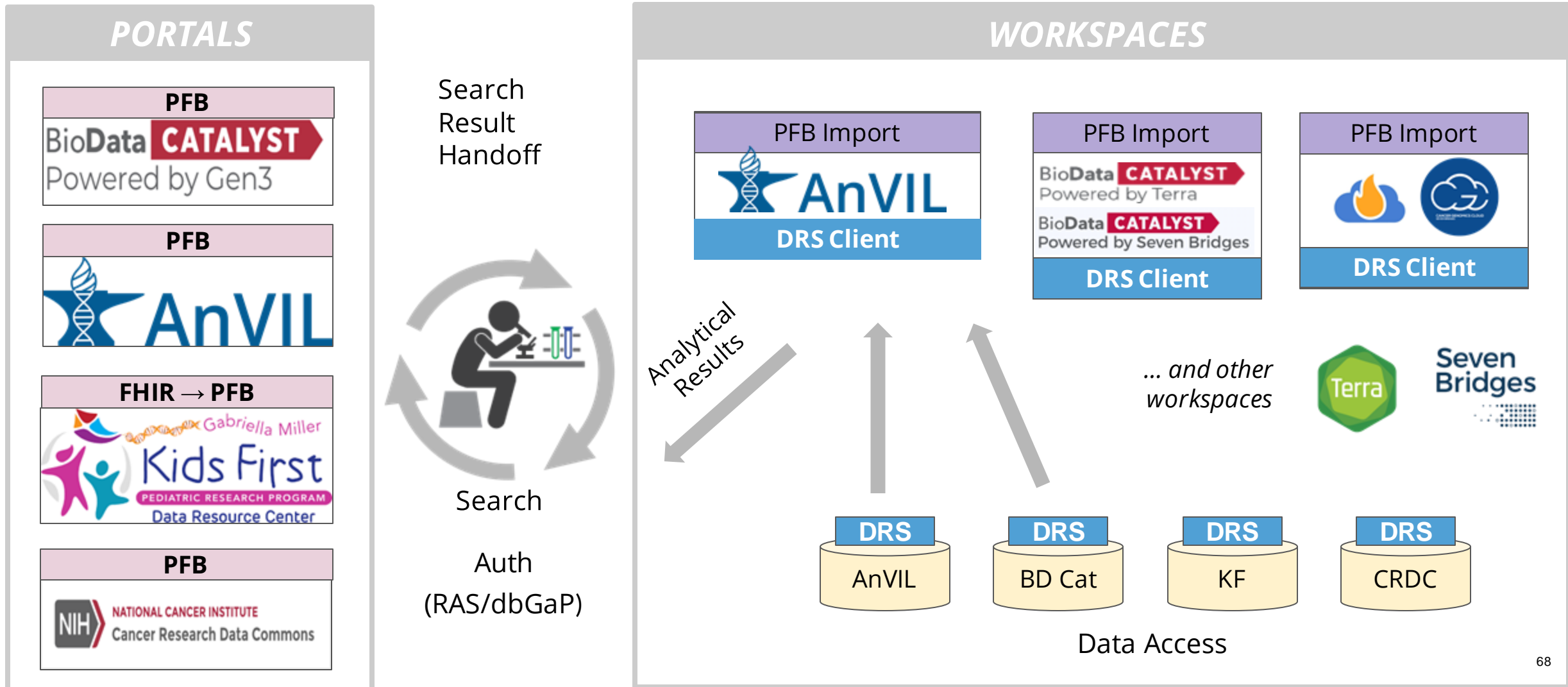
Facilitating the realization of a trans-NIH, federated and FAIR data ecosystem by establishing and implementing guidelines and technical standards.



<https://anvilproject.org/ncpi>

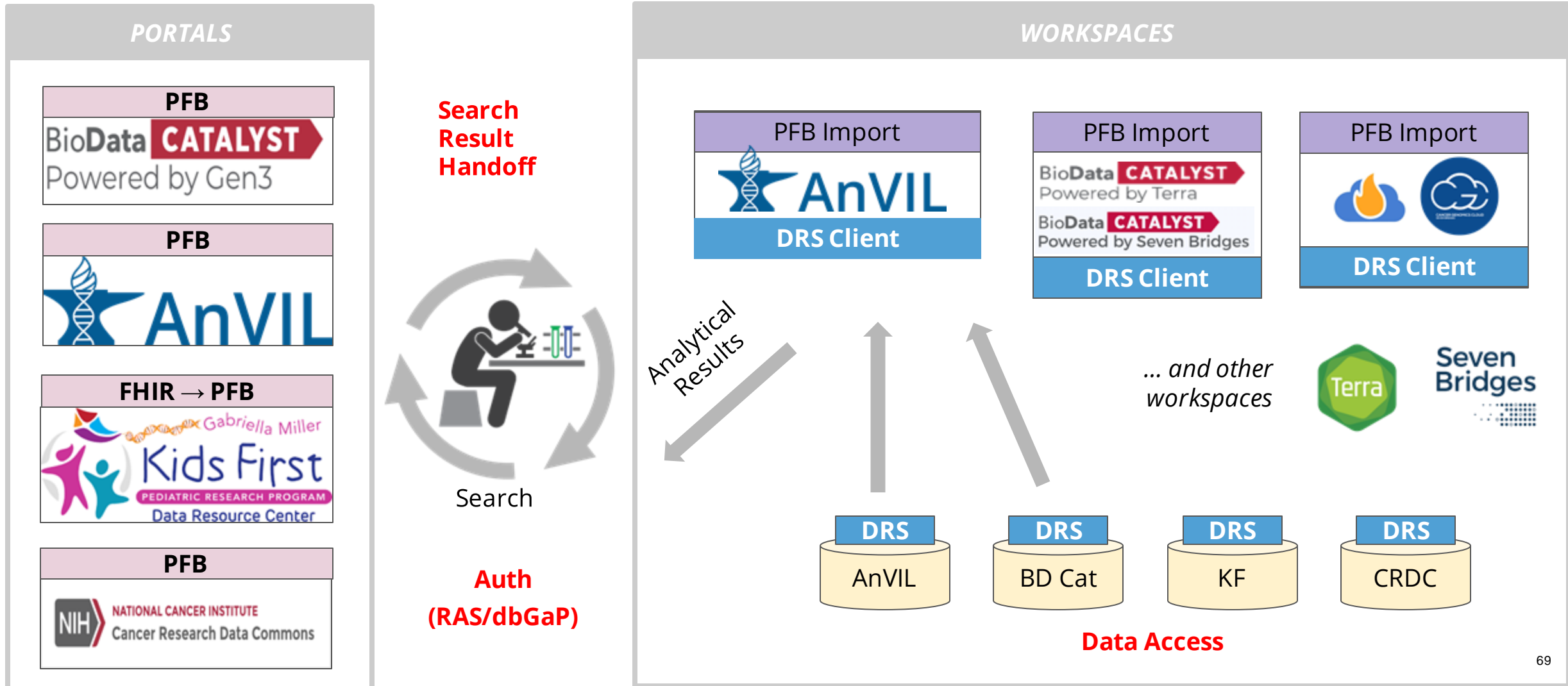
NCPI Vision for FAIR Systems Interoperability

Data portals connect to **workspaces**, workspaces access **data**



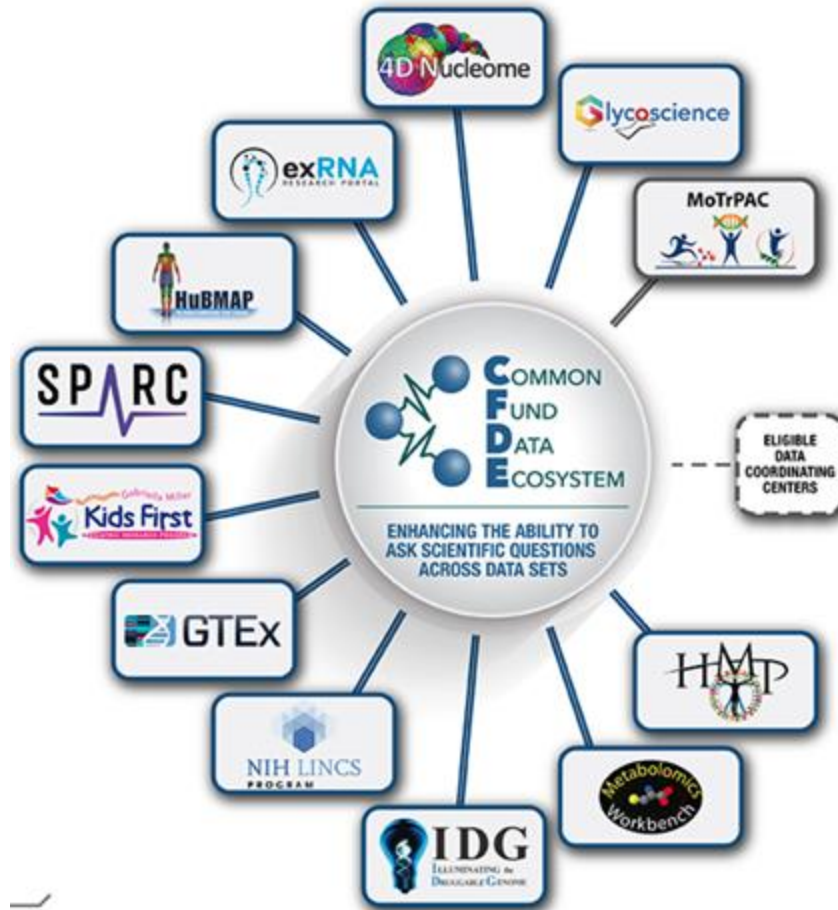
NCPI Vision for FAIR Systems Interoperability

Developing and implementing key building blocks to enable interoperability



Another interoperability example: Common Fund Data Ecosystem

Common Fund Data Ecosystem has built a common portal to bring multiple repositories together



Realizing interoperability for AMP-SBI

Accelerating Medicines Partnership (AMP)-RA/SLE
Powered by @ImmPort

3 Studies	5 Types of Measurements	225 Participants	121,031 Experimental Samples	16,494 Downloads*
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*Download counts are from individual studies as well as RTD/tee downloads.

AMP PD Accelerating Medicines Partnership® AMP Program

Accelerating Medicines Partnership®
Parkinson's Disease

Collaborating toward biomarker discovery to advance the development of Parkinson's disease therapies.

Get the AMP PD story Register for Access

Already registered? [Log In](#)

TYPE 2 DIABETES KNOWLEDGE PORTAL

Providing data and tools to promote understanding and treatment of type 2 diabetes and its complications.

Gene, region or variant Phenotypes

Search

Example: [SCN9A, 141229924, chr4:21,940,000-22,190,000](#)

Accelerating Medicines Partnership®
SCHIZOPHRENIA

Home About Participating in the Study For Scientists News & Updates

CLINICAL HIGH RISK FOR PSYCHOSIS

Young people may start to show signs of risk for psychosis months or even years before they receive a diagnosis. Learn about these signs and why early treatment is important.

Read More

LATEST NEWS

- Leaders of AMP Schizophrenia Describe International Collaboration to Find Biomarkers for Psychosis Risk
- Big Data for Psychosis Prediction
- Leading Science With Lived Experience

Read More

AD Knowledge Portal

EXPLORE ANALYTICAL WORKSPACE DATA ACCESS CONTRIBUTE NEWS HELP SIGN IN

Welcome to the AD Knowledge Portal

Discover and download Alzheimer's Disease data, analyses, and tools from the National Institute on Aging's Alzheimer's Disease Transitional Research Program.

Powered by ACCELERATING MEDICINES PARTNERSHIP

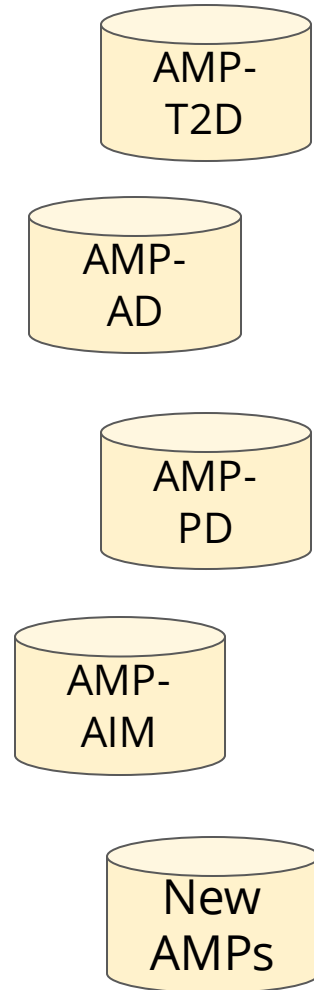
PROGRAMS

AMP-AD Visit website Discovering new drug targets for Alzheimer's disease treatment and prevention.	MOVID-AD Visit website Discovering the molecular and genetic etiology of Alzheimer's disease.	SADELLAD Visit website Developing new Alzheimer's disease clinical trials.	Resilience-AD Visit website Understanding cognitive resilience with conditions at high risk for Alzheimer's disease.
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EXPLORE EXPLORE EXPLORE EXPLORE

Psych-AD COG-AD ELIZABETH TREAT-AD

Interoperability work within each AMP repository

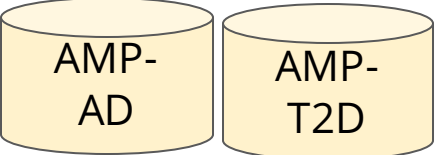


Adopt common data model

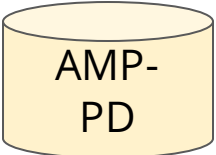
Implement key set of standards

- Data Repository Service (DRS)
- Researcher Auth Service (RAS)

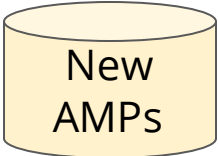
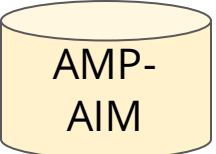
Interoperability work within AMP-SBI program



Develop central AMP-SBI portal for data discovery



Harmonize data from different sources



Raw omics data

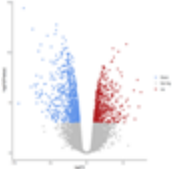


Processing Workflows

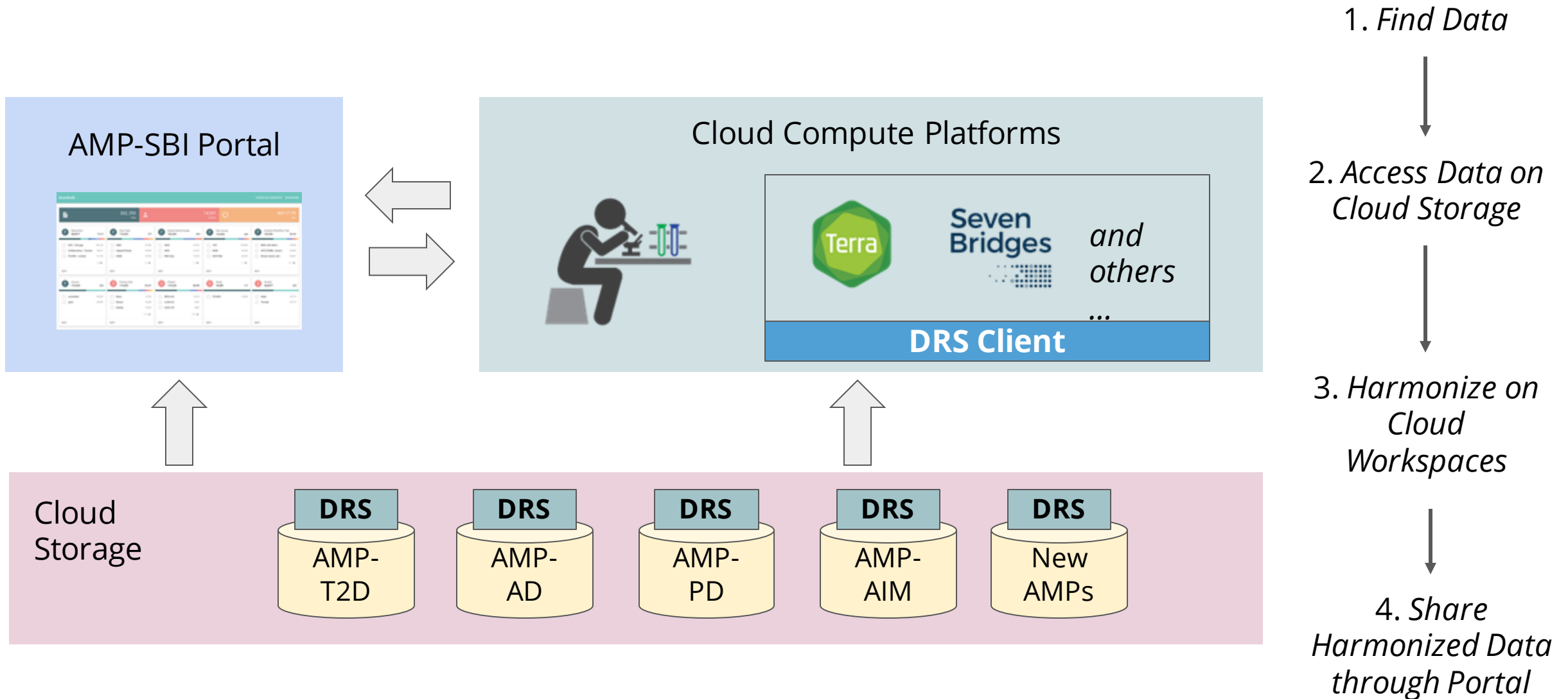


Compatible, harmonized data

gene	chr1	chr2	exp_1	exp_2
geneA	10	11	56	45
geneB	0	0	128	54
geneC	42	41	59	41
geneD	103	122	1	23
geneE	10	23	14	56
geneF	0	1	2	0



Vision for an interoperable AMP-SBI system



Questions/Discussion?

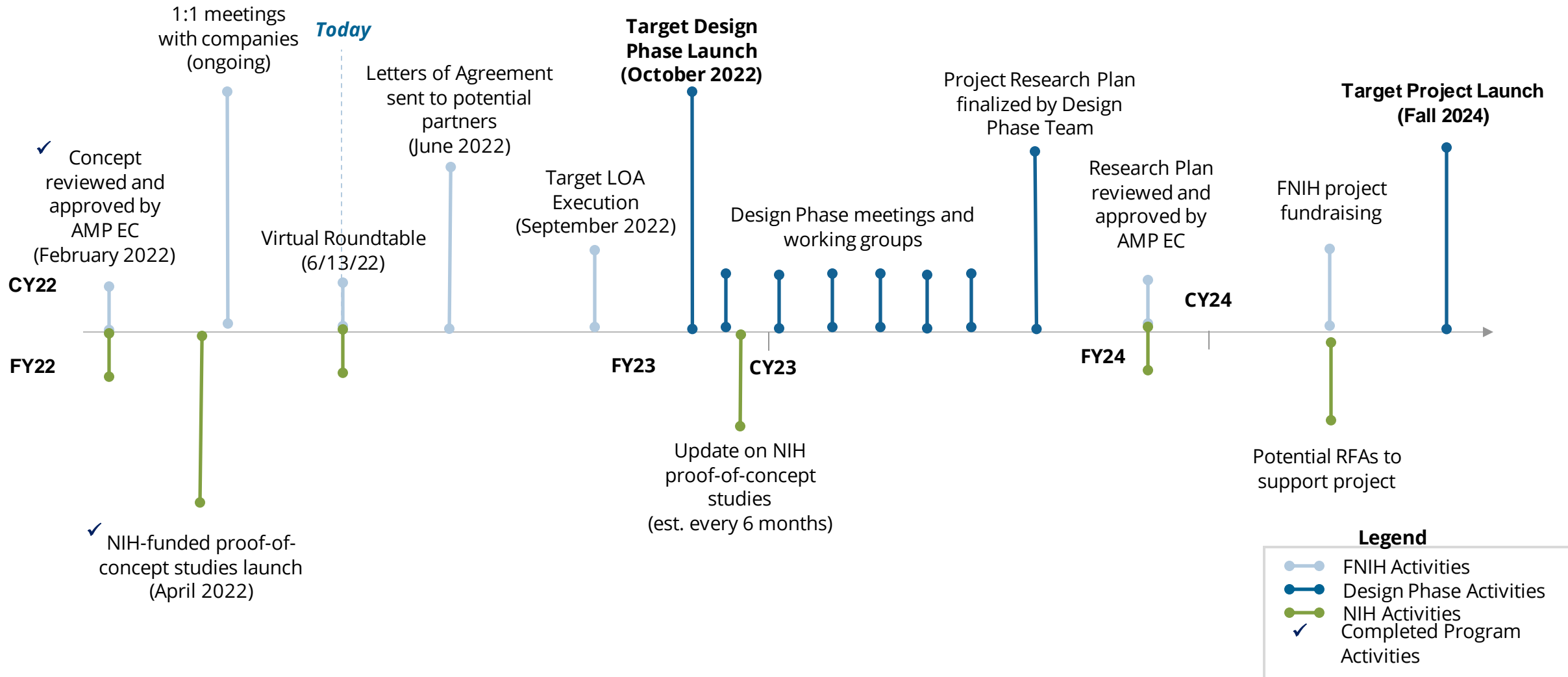
FNIH

Next Steps & Action Items (Design Phase Stakeholders)

Courtney Silverthorn, PhD

Associate Vice President, Research Partnerships, Foundation for the National Institutes of Health

Timeline

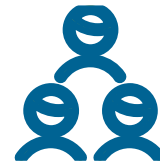


Next Steps

NEXT STEPS: AMP SBI



Letters of Agreement



**Identify
Representative from
Each Organization**

**NIA Pilot Project
Update in ~6 Months**

Contact Information

For information on the **SBI Design Phase** or **NIH-funded proof-of-concept pilots**

Courtney Silverthorn, PhD
Associate Vice President,
Research Partnerships

csilverthorn@fnih.org

For information on the **FNIIH Letter of Agreement** to join the **Design Phase**

Heidi Blythe
Director of Development

hblythe@fnih.org

FNIH

Appendix

Co-development of AMP SBI Research Plan to:

Decide Data To be Generated

- Identify longitudinal cohorts with phenotypic information and biosamples available in different disease areas
- Decide platforms for multi-omic data generation
- Design experimental validation & perturbation studies

Soliciting Inputs

- Liaising with private sector
- Liaising across AMP SCs
- Liaising across NIH Ics
- Seeking insights from SMEs and KOLs

CONCEPT

Create Cross-Disease Teams

Identify of Multi-omic datasets in more disease areas

- Private partner datasets
- Public partner datasets
- Other, e.g., Datasphere

Ideate Data Infrastructure

- Data integration, QC, harmonization
- Data hosting
- Platform sustainability
- Web interface - queryable analytics
- Central info web resource

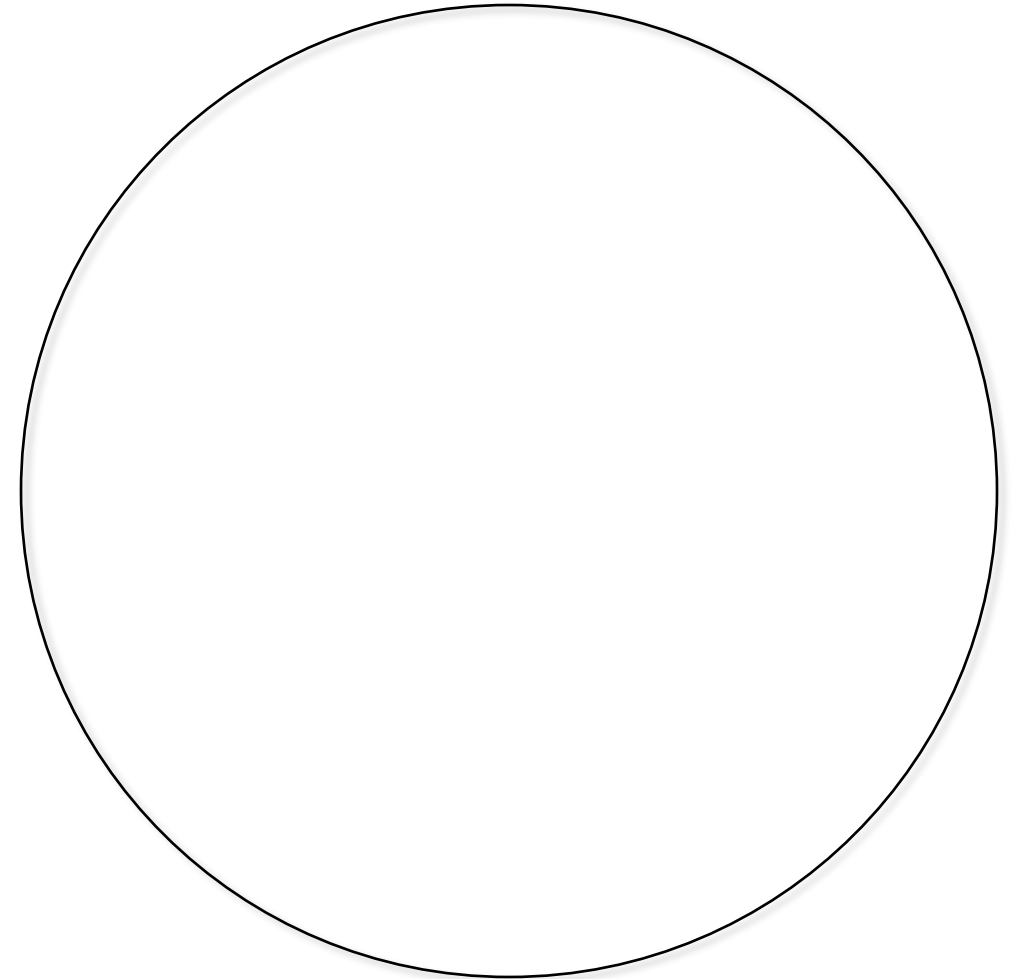
RESEARCH PLAN
to inform RFAs

Benefits

- Participation in face-to-face or virtual meetings with others engaging in this space
- Opportunities for private partner scientists to participate and contribute to project development working groups
- Ability to shape the goals and direction of the project
- Chances to align design with internal company pipeline efforts
- Opportunity to engage with the AMP SBI pilot ecosystem to provide impactful progress for AD patients (and potentially others)
- Receive insights on AMP SBI Pilots

Next Steps

- Requesting \$25K per industry partner for 2-year design phase
- FNIH hopes to leverage internal private donor funding to match industry contributions
- Letters of Agreement to be sent in early May to interested partners
- Send contact details for AMP SBI webinar participants



Calcagno et al. Systems Biology and Noninvasive Imaging of Atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2016;36:e1–e8. <https://doi.org/10.1161/ATVBAHA.115.306350>

Incorporating enthusiastic and strategic guidance from AMP Steering Committees



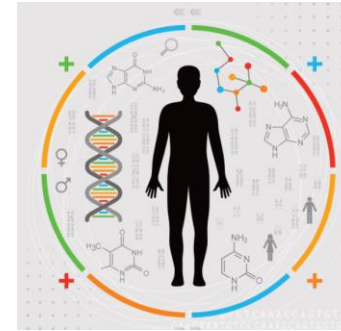
Need and value for consortium approach to predict cross-disease targets



ID patient subsets with similar inflammatory mechanisms regardless of clinical manifestations



Drug Repositioning



Diagnostic & prognostic BMx tools to identify, stratify and treat patients based on inflammation pathways



Useful for understanding of off-target effects

Accelerating Medicines Partnership®

Systems Biology of Inflammation (SBI)
Additional Background Slides



AMP SBI Timeline

NIH/NIA/NIAMS COMMITTED SUPPORT FOR FOUNDATIONAL PILOTS TO INFORM FURTHER DEVELOPMENT

INTEGRATED MODEL

Identify common pathways and biomarkers of inflammation across diseases

PILOT

Use existing data and tools within the current AMP programs as a platform for discovery

0-2 years

SCALE-UP

Generate additional cross-AMP resources

2-3 years

3-6 years

Research Plan Development

RFA/RFP

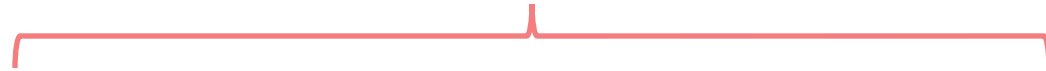
Scale-up Project Collaborative Agreements



TARGET LAUNCH

AMP SBI Research Plan Development and Funding Timeline

NIH/NIA/NIAMS COMMITTED ~\$6M SUPPORT FOR PILOTS TO KICKSTART & DE-RISK SCALE-UP DURING DEVELOPMENT



AMP SBI Pilot: ~\$6M

NIH to conduct pilot systems-level analysis of omics data across diseases to demonstrate the value of integrating cross-disease datasets

AMP SBI Research Plan: Dollar amount TBD

Systems biology of inflammation plan to include purpose built new data and resource generation with components selected per funding partner priorities



~\$300K DEVELOPMENT COSTS



FULL FUNDING COMMITMENT



TARGET LAUNCH 2024

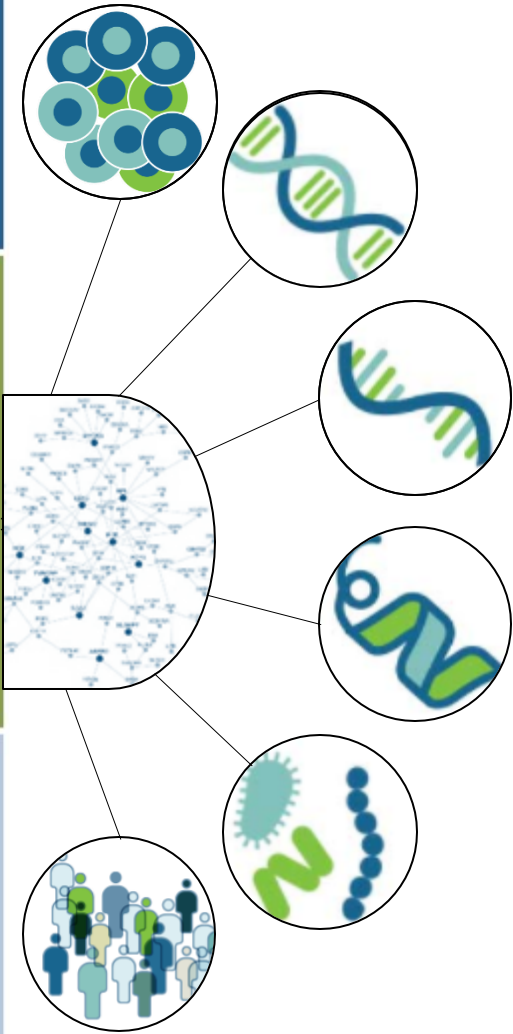
AMP Systems Biology of Inflammation (SBI) concept development

To create the AMP SBI concept, we have

- ✓ Created an inventory of datasets and tools from AMP
- ✓ Hosted AMP SBI strategy webinars
- ✓ Consulted with AMP SBI Steering Committees
- ✓ EC Approved, with resounding support from NHLBI, NIA, NIAMS, NINDS, and ODSS
- ✓ NIH Supported pilots

NIA will support six pilot projects*

NIAMS has committed additional support



Molecular crossroads of inflammation & metabolism across diseases

Dr. Kaddurah-Daouk (*Duke University*)

A shared foundation for single genetic investigations of immune responses

Dr. De Jager (*Columbia University*)

Mapping convergent & divergent inflammatory mechanisms using cross-tissue multi-omics

Dr. Ertekin-Taner (*Mayo Clinic*)

Multiscale network modeling of the inflammatome in major human diseases

Dr. Zhang (*Icahn School of Medicine at Mount Sinai*)

Integration of immune cell subtypes across diseases & tissue

Drs. De Jager and Mennon (*Columbia University*)

Molecular pathways associated with shared genes implicated across diseases

Dr. Roussos (*Icahn School of Medicine at Mount Sinai*)

**Each pilot project is ~\$250K direct costs per year for 2 years*

AMP inventory of immediately and soon-to-be accessible data

AMP AD

AMP PD

AMP RA/SLE

AMP T2D

	Brain	Blood/CSF	Blood/CSF/Brain	Tissue (synovium, kidney)/Blood/Urine	Pancreas, liver, adipose, heart, kidney, muscle
Tissue	Brain	Blood/CSF	Blood/CSF/Brain	Tissue (synovium, kidney)/Blood/Urine	Pancreas, liver, adipose, heart, kidney, muscle
N	3000 to 5000+	3000+	100+ to 15,000+	100+ to 300+	1.5 Million+, across disease states ¹
Diagnoses Available	Yes	Yes	Yes	Yes	Yes
Genomics	Genome (GWAS/WES/WGS)	Genome (GWAS/WES/WGS)	WGS/Genotype	GWAS	GWAS
Transcriptomics	Bulk RNAseq	PaxGene	PaxGene	Bulk RNAseq	
	Sn/scRNAseq and more expected		Sn/scRNAseq	Sn/scRNAseq	
Epigenomics	Bulk Epigenomics (RRBS/H3K27ac/ATACseq)	Bulk Epigenomics (RRBS)			
	snATACseq			snATACseq	
Proteomics	Proteomics	Proteomics	Proteomics and more expected	Proteomics (urine ELISA, blood)	
Metabolomics	Metabolomics	Metabolomics		Metabolomics	

External Data

e.g., PsychENCODE, and SNiPA, GTEx, Human Cell Atlas data, multiple sclerosis, TopMed, amongst others

New AMPS, new biosamples, new opportunities
e.g., AMP AIM and SCZ Salivary samples

Green represents soon to be accessible data

Scale-up to enable and expand systems-level analysis of omics datasets across different diseases/tissues

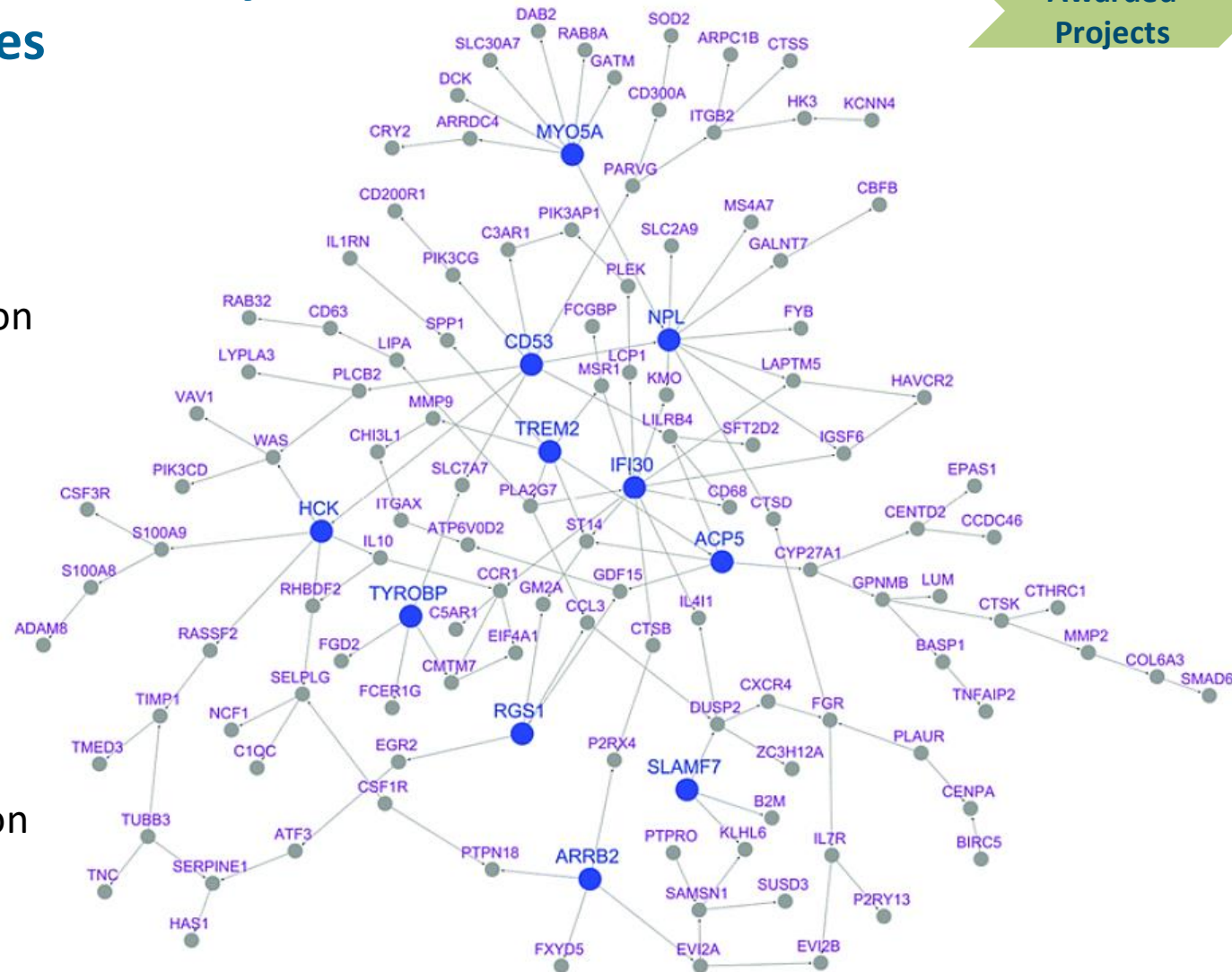


To expand results from the demonstration and any emerging studies the scale-up will:

- Expand cross-AMP multi-omic data integration
- Generate new data conducive to systems analyses
- Further cellular characterizations (e.g., scRNAseq-ATACseq, CyTOF)

Deliverables:

- Link systemic inflammation to tissue-level disease
- Identify contributions of chronic inflammation to disease outcomes
- Test the concept of multi-omic risk scores



Example: Gene core causal network conserved across tissues and species (e.g., HCK, CD53 and TYROBP) involved in multiple inflammation-related disorders

Accelerating Medicines Partnership®

General Background Slides



About the FNIH

Mission

The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people's lives.

Founded by Congress

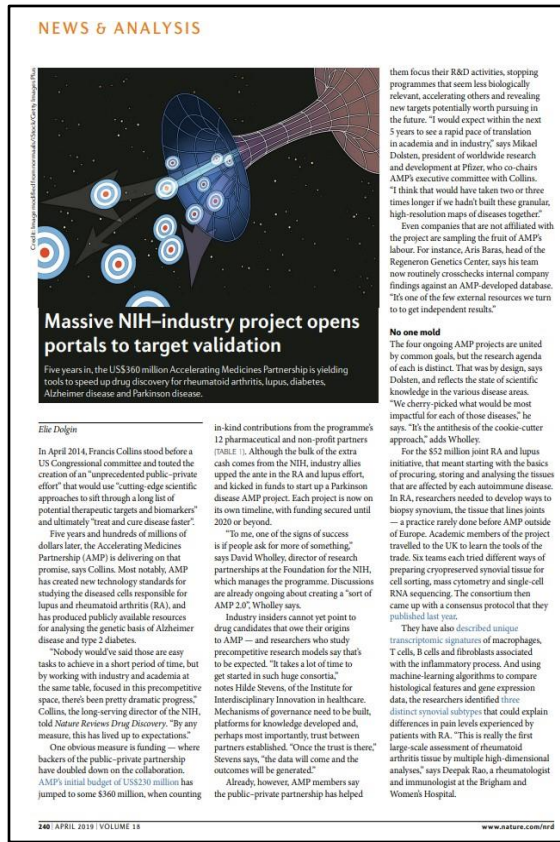
The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.

Why Collaborate?

- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in marketplace
- Disseminate knowledge
- Enhance credibility
- Reduce costs
- Support training & education
- Manage complexity

The Accelerating Medicines Partnership® (AMP®)

Precompetitive public-private collaboration started in 2014



- **Unite resources of 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
 - Generation of consensus platforms and procedures
- **Launched initiatives**
 - Alzheimer's Disease 1.0 and 2.0 (2014)
 - Type 2 Diabetes (2014)
 - Rheumatoid Arthritis & Lupus (2014)
 - Parkinson's Disease (2018)
 - Schizophrenia (2020)
 - Alzheimer's Disease 2.0 (2020)
 - Common Metabolic Diseases (2021)
 - Bespoke Gene Therapy Consortium (2021)
 - Autoimmune and Immune-Mediated Diseases (2021)

For an overview of the AMP Initiative, see:

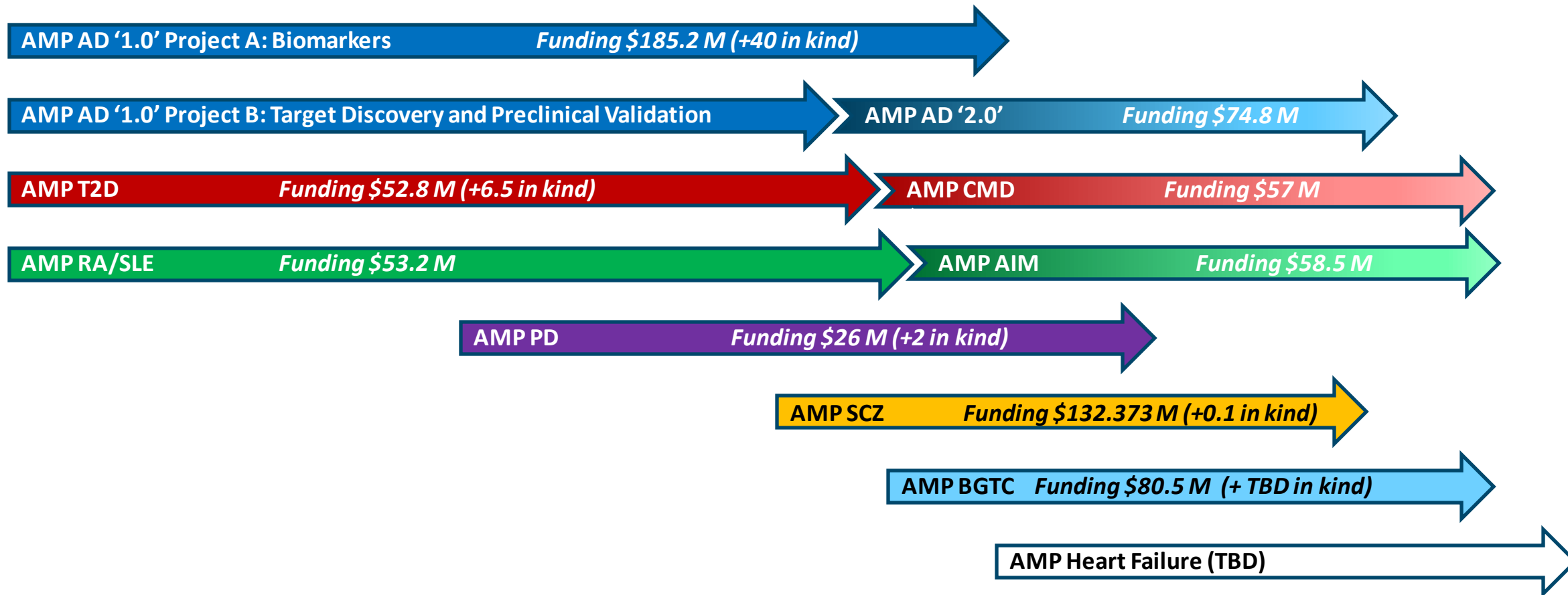
Nature Reviews Drug Discovery - February 27, 2019

<https://www.nature.com/articles/d41573-019-00033-8>

The Accelerating Medicines Partnership® (AMP®) by the numbers



AMP Timelines



AMP Data and tools available for systems biology of inflammation

AMP AD 1.0 *Launched 2014*

Platform: AD Knowledge Portal/Synapse

Relevant Data: Human brain bulk tissue RNAseq, proteomics (brain/CSF) WGS, metabolomics/lipidomics (blood), subset of samples with matched metabolomics (blood), proteomics (CSF), & RNAseq (blood).

Tools: Molecular network models

Ready: all data, analytical results & candidate targets are available in the AD Knowledge Portal & Agora. Strong neuroimmune brain & peripheral signatures

AMP AD 2.0 *Launched 2021*

Platform: AD Knowledge Portal/Synapse

Relevant Data: Human bulk and single-nucleus transcriptomics from post-mortem samples; brain/CSF/plasma proteomics; brain/plasma metabolomics, multi-omic sn/sc data on brain immune cells (autopsy/biopsy tissue); RNAseq & functional assays for longitudinal peripheral immune system profiling

Tools: Being updated & multi-scale models built

Ready: data will be made available over the next few years as it is generated (post-QC) to interrogate the immune etiology of AD

AMP RA/SLE/AIM

Launched 2014 | 2021

Platform: IMMPORT/Synapse

Relevant Data: Genomics, esp. scTranscriptomics from tissue (synovium, kidney, and blood), urine proteomics & digital histology from tissue

Tools: Harmony, developing additional cluster analytics

Ready: Immune profiles, cell group/type algorithms for data interrogation across diseases

More AMP Data and tools available for systems biology of inflammation

AMP T2D/CMD

Launched 2014 | 2021

Platform: HuGeAMP and DGA (ENCODE DCC)

Relevant Data: Human Genetics, Genomics and Epigenomics from metabolic disease relevant tissues and cells including pancreas, liver, adipose, heart, kidney, muscle, others

Tools: Variant search, gene finder, predicting effector genes

Ready: Emerging immune cell genomic data

AMP PD

Launched 2018

Platform: Google Cloud / Terra

Relevant Data: Human genomics, transcriptomics, & proteomics from blood|CSF. Single-nucleus transcriptomics and genomics from post-mortem brain tissue planned

Tools: Being built to visualize and analyze

Ready: To analyze 'Omics data derived from blood and CSF

AMP SCZ

Launched 2020

Platform: NIMH Data Archive

Relevant Data: Blood samples for genetic analysis and salivary cortisol to be collected and data generated. Additional fluid biomarkers and immune measures to be determined

Tools: Being built

Ready: To learn from outcomes of any cross-AMP analyses

AMP HF

To be Launched

Platform: Biodata Catalyst

Relevant Data: WGS data and other omics data to be generated longitudinally – methylation, RNAseq, metabolomics, and proteomics derived mainly from blood rather than tissue. Echocardiography and imaging phenotypes will be available from some participants

Tools: will include those that can enable a systems biology approach

Getting An AMP from Concept to Launch

