Version 1.0

ACCELERATING MEDICINES PARTNERSHIP®
NEW PROGRAM PROPOSAL FORM

Individuals or groups interested in proposing a new program area for the Accelerating Medicines Partnership® (AMP®), whether in an existing or new disease area, should complete this proposal form and submit it via email to the Foundation for the National Institutes of Health at AMP@FNIH.org.

The purpose of the submission is to clearly define the proposed problem, background, and rationale for the proposed program, what work is offered, how it will be done, and how it might be funded. (**Please note that AMP does not have pre-existing funding for new programs; funds must be raised or prioritized from public and private sector sources).** It should also be made clear why this is a good fit for AMP. Please see the attached summary of AMP and relevant policies.

Proposed program name/descriptor	**Accelerating Medicines Partnership for Systems Biology of Inflammation (AMP SBI)**
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Submission Date:	01/28/2022
Disease Area of Project	Spans across disease areas
Estimated duration of the project	Five years
The estimated total cost of the project	~$70M

Problem statement –Describe the critical scientific problem or capability gap being addressed and its clinical/scientific significance. (~100 words)

Problem: Diseases are defined by their manifestations, yet treatments target mechanisms

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

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

Focus: A Systems Biology of Inflammation across major complex diseases.

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

Outcomes: A New Landscape for developing, selecting and using targeted therapies across diseases

An overview describing how you would propose that AMP address the problem, with goals and a summary of key objectives. (~300 words)

Diseases are defined by their clinical manifestations, yet treatments are developed based on targeting mechanisms. However, specific mechanisms often play a role in the clinical manifestations of only a subset of patients. One solution to this challenge is to shift from a taxonomy of diseases based on a clinical presentation to one based on mechanisms. This new approach provides an integrative mechanistic understanding of diseases so that treatments target pathways irrespective of the clinical label a patient may carry.

AMP provides an opportunity for us to identify shared and distinct mechanisms active across multiple diseases. The rich molecular and clinical data available through the AMP programs in tandem with unbiased systems biology approaches offer an opportunity to quickly recognize dynamic molecular networks at the tissue/cellular level across disease states/traits within a global pathway/pathway interaction context.

Inflammation alongside tissue repair and maintaining tissue homeostasis determines the initiation and progression of many complex diseases, suggesting that there may exist common inflammatory molecular signatures. AMP SBI aims to provide a systems biology framework to help define a molecular taxonomy of disease through the lens of inflammation.

Some findings from both AMP and other datasets have already highlighted possible common inflammatory mechanisms that could be used to (A) identify new targets across disease; (B) ID patient subsets with similar inflammatory signatures; or (C) understand off-target effects. For example, AMP Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP RA/SLE) identified TREM2-positive myeloid cells within Rheumatoid Arthritis-impacted tissues. TREM2 is also expressed within microglial cells during Alzheimer's Disease, indicating that similar mechanisms may be activated in these diseases (Qu W, 2021). In this instance, the identification of TREM2 across diseases has not yet led to more therapeutic options, yet others may. Clinical trials testing NSAIDs for AD treatment did not show an overall positive effect on cognition. A posthoc analysis that measured a panel of inflammatory markers (TNFα, CRP, IL-6, and IL-10) in baseline blood samples in

the participants of the ADCS NSAID trial showed that those participants with high levels of inflammatory markers at baseline had a positive response to the treatment (O'Bryant, 2018).

Deliverables of this effort include integrated datasets, analytical tools, and mechanistic insights into shared and distinct inflammatory pathways across complex diseases, all of which can be used to inform disease-modifying therapy development.

The current concept involves using existing data and tools to determine the feasibility of integrating and harmonizing cross-AMP datasets and identifying appropriate and informative use cases for integrated data. AMP SBI will then generate cross-AMP resources, including interoperable and integrated datasets, new tools for data analysis, perturbation datasets, and artificial intelligence-based and predictive modeling methods. The third step in the framework will focus on identifying common inflammation pathways across diseases to expand the understanding of biomarkers and drug targets.

Scientific strategy and proposed logistics

(Outline project design, who would do what, use of novel or established technologies, timeline, critical decision and funding milestones)

AMP Overview

The Accelerating Medicines Partnership (AMP) is a public-private partnership (PPP) launched in February 2014 between the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), 25 biopharmaceutical companies, and 22 non-profit organizations that are managed through the Foundation for the NIH (FNIH) to 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 biomarkers and targets
- Developing leading-edge tools and technologies
- Collecting large scale datasets and sharing broadly to research community
- Generating consensus on platforms and procedures

The ultimate goal is to increase the number of new therapeutic options for patients and reduce the time and cost of developing them.

Launched inititiatives include:

- Alzheimer's Disease 1.0 (AD 1.0) - 2014
- Type 2 Diabetes (T2D) - 2014
- Rheumatoid Arthritis & Systemic Lupus Erythematosus (RA/SLE) - 2014
- Parkinson's Disease (PD) - 2018
- Schizophrenia (SCZ) - 2020
- Alzheimer's Disease 2.0 (AD 2.0) - 2021
- Common Metabolic Diseases (CMD) - 2021
- Bespoke Gene Therapy Consortium (BGTC) - 2021
- Autoimmune and Immune-Mediated Diseases - 2021

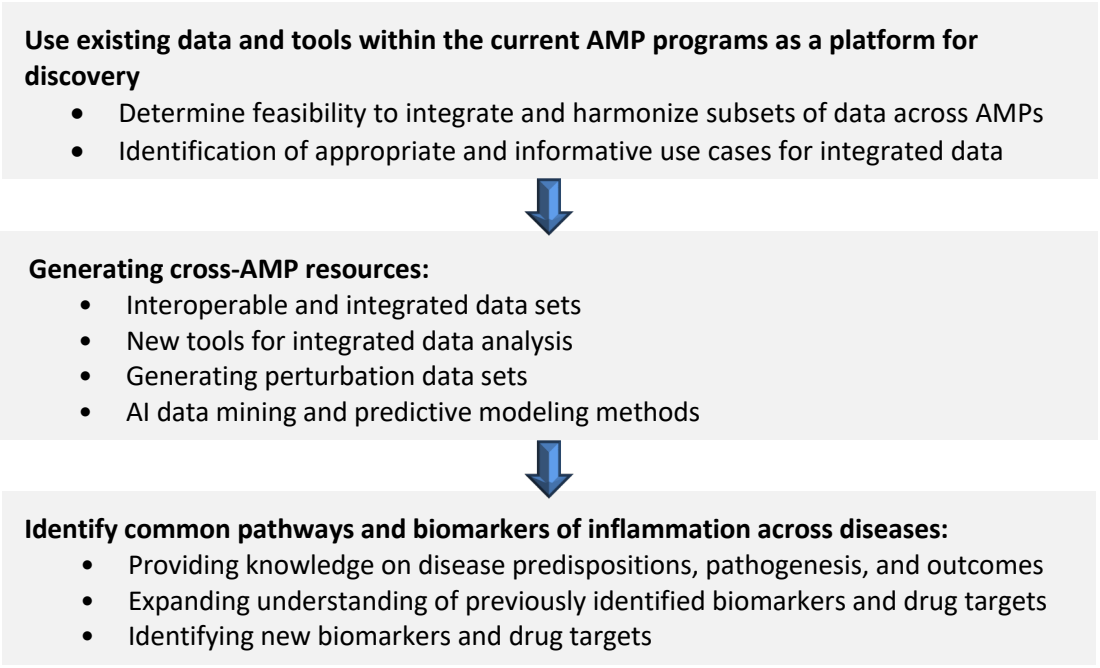
Many AMP programs aim to shorten the development time of new therapies by characterizing molecular indicators of disease and distinguishing biological targets most likely to respond to new

treatments. Although the programs differ in their focus, most AMPs include molecular and/or cellular analysis of specimens from patients with the condition, providing an accessible dataset. Some programs have also linked to additional such datasets derived elsewhere. The currently proposed effort builds on the accomplishments of the original four AMP programs, AMP AD, AMP PD, AMP T2D, and AMP RA/SLE. It seeks to enfold in data from newer AMPs actively being generated, *e.g., biomarkers from salivary AMP SCZ and AMP AIM*.

This initiative would initially use AMP to identify inflammation pathways across diseases using integrated systems biology analyses of the AMP datasets and relevant external datasets. Later it would generate new AMP resources and data.

AMP SBI enables a new precision medicine approach by building a knowledge network for biomedical research and a new disease taxonomy.

Figure 1. AMP SBI Overview



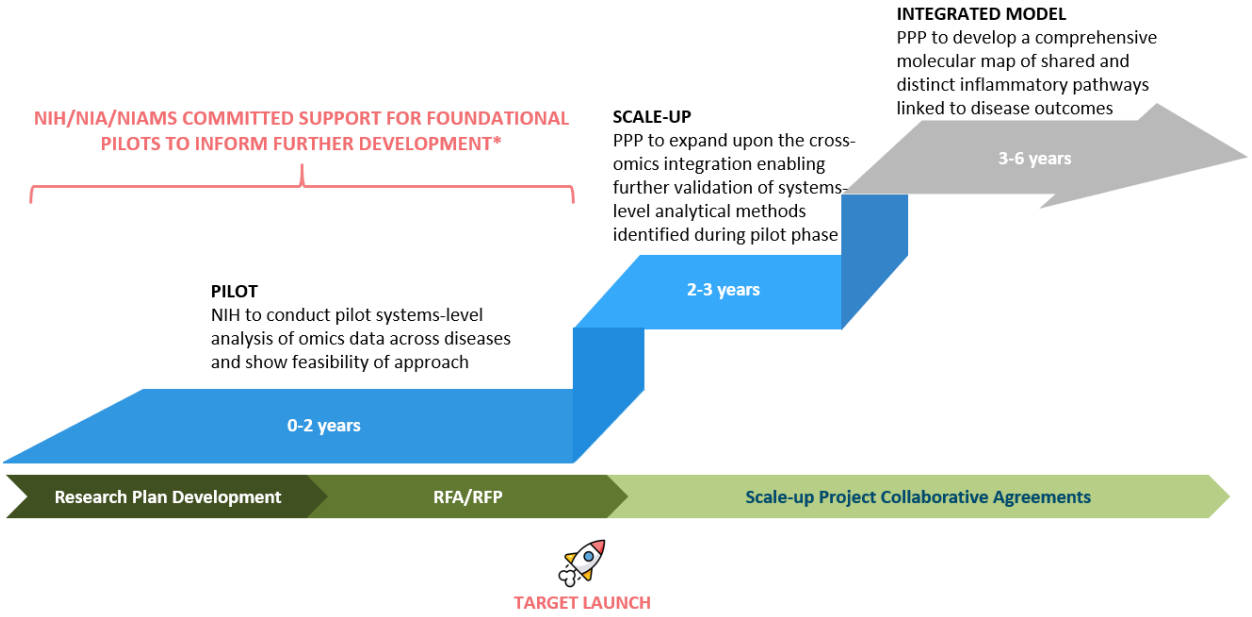
AMP SBI will occur in three phases, summarized below:

- **Pilot (0-2 years):** AMP SBI will conduct six 2-year pilot studies, each involving systems-level analysis of omics data across diseases to assess the feasibility of the overall approach.

- **Scale-Up (1 year):** AMP SBI will expand upon the cross-omics integration enabling further validation of systems-level analytical methods identified during the pilot phase

- **Integrated Model (3 years):** AMP SBI will develop a comprehensive molecular map of shared and distinct inflammatory pathways linked to disease outcomes.

Figure 2. AMP SBI Timeline



Pilot: Conduct systems-level analysis of "omics" across diseases to determine the feasibility of such an approach

The pilot phase of the AMP SBI program leverages a robust NIH investment (NIA and NIAMS) of over $6M over 2 years through a set of administrative supplements to existing cooperative agreement grants; see below. The proposed pilots would be best accomplished working with the close collaboration of AMP investigators. Initiating private partner input investment would enable public-private and cross-AMP collaboration and AMP SBI program research plan development during this period.

Table 1. NIA-supported pilot projects – each pilot will be executed over 2 years.
NIAMS has committed support for additional pilots

Title	Contact Principal Investigator and Institution
Molecular crossroads of inflammation, metabolism, and non-communicable diseases integrated into a multi-omics disease map	Dr. Rima Kaddurah-Daouk, Duke University
Mapping convergent and divergent inflammatory mechanisms of aging and chronic disease by cross-tissue integrative multi-omics for therapeutic and biomarker discoveries	Dr. Nilufer Ertekin-Taner, Mayo Clinic
Cross-AMP inflammatory research: a shared foundation for single genetic investigations of immune responses	Dr. Philip De Jager, Columbia University

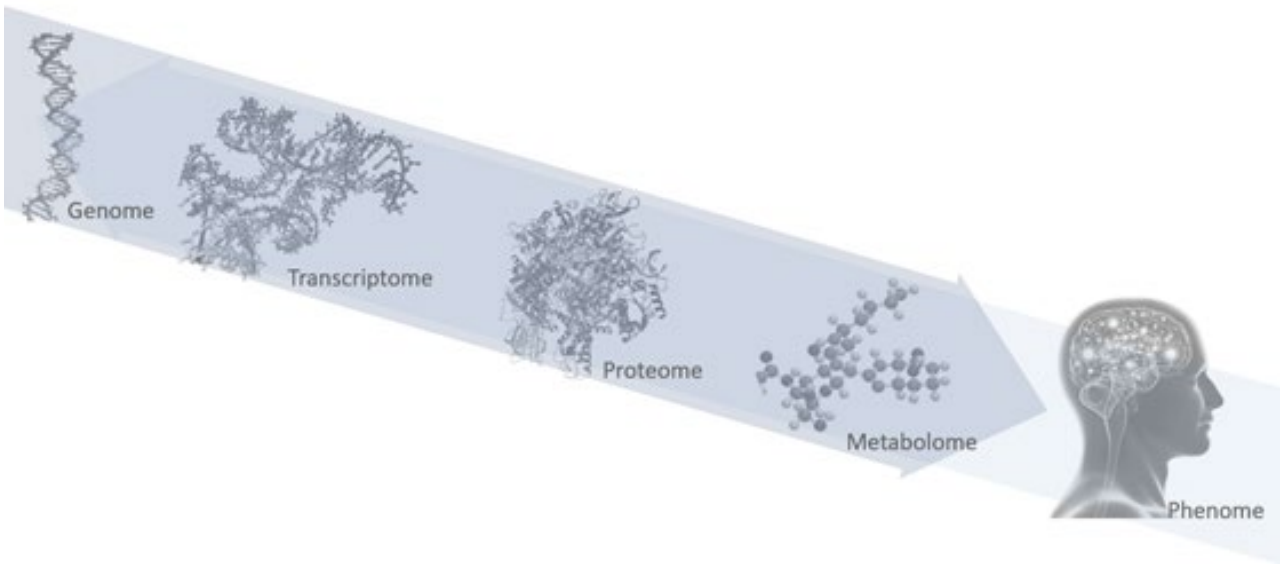
Multiscale network modeling of the inflammasome in major human diseases: systemic identification and validation of inflammation targets and therapeutics	Dr. Bin Zhang. Icahn School of Medicine at Mount Sinai
Cross-AMP inflammatory study: integration of immune cell subtypes across diseases and tissues	Dr. Philip De Jager and Vilas Menon, Columbia University
Trait-trait correlations, gene-trait associations, and molecular pathways associated with shared genes implicated across AMPs	Dr. Panagiotis Roussos, Icahn School of Medicine at Mount Sinai

AMP SBI foundational work will bring the cutting-edge, cross-disciplinary expertise in these supplements to bear to pilot approaches that utilize the readily available blood and tissue-derived omics and phenotypic data from AMP to link systemic inflammation across diseases.

The two-year pilot projects will run in parallel to assess the feasibility of harmonizing and integrating subsets of AMP omics and phenotypic data and the ability to conduct coordinated data analyses of the following data types **with existing genetic data**:

- Metabolomics – *NIH Funded*
- Transcriptomics – *NIH Funded*
- +/- Proteomics (Neurodegeneration focus) – *Unfunded Buy-Up Option*

Figure 3. Genome to Phenome



Additionally, this plan step will demonstrate the ability to map inflammatory mechanisms across diseases and tissues using a single or a multi-omic approach on selected conditions.

The precompetitive open science research model and the enabling data infrastructure will remain a central feature of the AMP SBI program. All harmonized data and data harmonization, integration, and analysis tools created for this program would be made available and be open source.

Table 2. AMP inventory of immediately and soon to be accessible data

	AMP AD		AMP PD	AMP RA/SLE	AMP T2D
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 expected Q1 2023	Sn/scRNAseq	
Epigenomics	Bulk Epigenomics (RRBS/H3K27ac/ATACseq)	Bulk Epigenomics (RRBS)			
	snATACseq			snATACseq	
Proteomics	Proteomics	Proteomics	Proteomics and more expected Q2-3 2022	Proteomics (urine ELISA, blood expected)	
Metabolomics	Metabolomics	Metabolomics		Metabolomics expected	

External Data
PsychENCODE, SNiPA, GTEx, Human Cell Atlas data, multiple sclerosis, TopMed, amongst others

Summaries of goals and deliverables of the NIH -funded pilot projects (*each pilot will be executed over 2 years*) :

Integrative metabolomics – NIH Funded

Molecular crossroads of inflammation, metabolism, and non-communicable diseases integrated into a multi-omics disease map (Contact PI: Rima Kaddurah Daouk, Duke University)

Inflammatory and immune-related processes are strongly interlinked with metabolic homeostasis and signaling (Kotas ME, 2015), affecting a broad spectrum of different metabolic pathways (Pietzner M, 2017), which, in turn, are influenced by genetic and lifestyle factors. The underlying complex molecular relationships are not fully understood. The growing number of systematic omics studies using standardized technologies have the potential to provide new insights into the molecular connections of inflammatory (and other shared) processes across diseases in a hypothesis-free manner, putting less focus on the historical definition of diseases based on symptoms and affected organ systems. In a recent study in 11,000 participants, it was demonstrated that 65.5% of 640 significant metabolite-disease associations were shared between at least two of 27 incident non-communicable diseases (NCDs) ((Schimke I, 1992); When integrating data on over 50 clinical risk factors, shared metabolite signals were able to capture low-grade inflammation as well as other shared pathogenic factors such as liver and kidney function, lipid and glucose metabolism, surrogates of gut microbial diversity and specific health-related behaviors. Shared metabolic signals served as antecedents of common NCD multimorbidity in these participants. Combining the vast molecular (omics) data and results (e.g., associations) generated across AMP projects provides a unique opportunity to cross barriers of current disease definition and to eventually move to a mechanism-based definition of disease and a better understanding of disease-overarching and -specific roles of inflammation and immune processes.

This pilot project aims to build a basis for a metabolomic network-based, genetically-anchored integration framework. The aims are:

1. Extract genetic associations shared across immune traits and inflammatory diseases
2. Identify shared and specific metabolomic signatures for inflammation and immune-dysregulation across diseases
3. Integrate evidence collected in Aims 1 and 2 and communicate via a web-based portal

Transcriptomics Pilot Project(s) – NIH Funded

Bulk, single-cell, and single nucleus transcriptome profiling have revolutionized the ability of researchers to understand cellular signaling and identity. There are growing datasets within AMP and externally available. However, these resources have yet to be brought together to create a joint reference relating the different immune cell subtypes and cell states together in a single framework to accelerate the translation of insights across the AMP spectrum. The following 5 pilots propose a path towards integrating and analyzing these resources.

Cross-AMP Inflammatory Research: A shared foundation for single genetic investigations of immune responses (Contact PI: Dr. Philip De Jager, Columbia University)

Many functional consequences of disease-related immune responses remain poorly characterized. AMP SBI enables us to determine the sequence of intermediate immune-related endophenotypes contributing to disease.

The goal of this pilot project is to map the propagation of the functional consequence of each variant from epigenomic alterations, to transcriptomic, proteomic, and metabolomic changes, with aims to:

1. Assemble a database of pertinent genetic associations and QTL results for immune traits from existing published studies
2. Evaluate the immune-mediated relationship among the various diseases and traits characterized in the AMP programs
3. Prioritize immune cell subtypes and states that are enriched for genetically defined groups of traits and disease susceptibility variants
4. Prioritize sets of disease-related variants that may be participating in the same molecular pathway or cell type

Mapping convergent and divergent inflammatory mechanisms of aging and chronic disease by cross-tissue integrative multi-omics for therapeutic and biomarker discoveries (Contact PI: Dr. Nilufer Ertekin-Taner, Mayo Clinic)

Expanding molecular characterization across biosamples types and diseases over time provides an ability to understand the multi-dimensional role of the immune system in disease pathogenesis in the context of co-morbidities.

The goal of this pilot project is to yield Inflammatory molecular signatures likely to be preserved between central and peripheral tissues, with aims to:

1. Identify genetic variants and transcriptional networks in inflammatory pathways that are shared and distinct for diseases and aging
2. Discover inflammatory signatures that are shared between as well as tissue-specific
3. Determine inflammatory cell-subtype proportion and cell-specific molecular signature perturbations in disease and aging

Multiscale Network Modeling of the Inflammatome in Major Human Diseases: Systematic Identification and Validation of Inflammation Targets and Therapeutics (Contact PI: Dr. Bin Zhang. Icahn School of Medicine at Mount Sinai)

Inflammation alongside tissue repair and maintaining tissue homeostasis determines the initiation and progression of many complex diseases, suggesting that there may exist common inflammation molecular signatures and networks. Systems and network biology offer a framework for omics and clinical data integration to dissect the disease pathways.

The goal of this pilot project is to assemble large multi-omics cohorts at the bulk tissue and single-cell levels to identify molecular signatures of inflammation across diseases, with aims to:

1. Conduct mRNA expression and protein quantitative trait locus (QTL) analyses to identify genetic regulators of inflammation signatures
2. Perform integrative network analysis of bulk and single nucleus multi-omics data to identify essential gene networks and key drivers underlying complex diseases
3. Identify FDA-approved compounds targeting predicted molecular signatures and networks of Alzheimer's Disease through drug repositioning.

Cross-AMP Inflammatory Study: Integration of immune cell subtypes across diseases & tissue (Contact PIs: Dr. Philip De Jager and Vilas Menon, Columbia University)

Bulk, single-cell, and single nucleus transcriptome profiling have revolutionized the ability of researchers to understand cellular signaling and identity. AMP SBI offers the ability to create a joint

reference relating the different immune cell subtypes and cell states together to provide insights into the disease etiology, mechanisms, and drug targets.

The goal of this pilot project is to build a joint reference relating the different immune cell subtypes and cell states together, with aims to:

1. Integrate tissue-derived immune cells and PBMC single-cell/nucleus RNAseq data into a common framework using Harmony
2. Identify the full ensemble of gene expression programs in each significant cell class/type in the unified data set.
3. Using the integrated dataset, evaluate the role of individual immune expression programs in each cell type across available datasets
4. Integrate AMP data with Human Cell Atlas, multiple sclerosis PBMC, CSF, and brain sc/snucRNAseq data into the integrative analysis
5. Identify molecular programs in the non-immune cells from the target tissue that correlate to the immune programs.

Trait-trait correlations, gene-trait associations, and molecular pathways associated with shared genes implicated across AMP (Contact PI: Dr. Panagiotis Roussos, Icahn School of Medicine at Mount Sinai)

To advance Precision Medicine, we need to understand better the molecular mechanisms underlying common and complex traits. AMP SBI will enable the interrogation of diseases with complex and partially shared polygenic architecture.

The goal of this pilot project is to identify shared gene associations and omics across AMP outcomes categories, with aims to:

1. Leverage population-level RNA-seq and ATAC-seq data in human purified microglia centrally and peripherally combined with external omics data to train GREx using the EpiXcan method
2. Apply GREx models across multiple GWAS summary statistics to define the shared and distinct transcripts and regulatory mechanisms associated with AMP traits
3. Construct a network based on pairwise outcome comparison of GREx to identify pairs of shared gene associations across AMP traits

Proteomics Pilot Project – Unfunded Buy-Up Option (Contact PI: Dr. Allan Levey and Nick Seyfried, Emory University)

A theme among neurodegenerative diseases is the co-occurrence of diverse disease protein aggregates in the same patient, underscoring the need to delineate common inflammatory pathways associated with related neurodegenerative disorders. By identifying brain, CSF, and plasma proteomic signatures from various NCDs from data previously generated in the AMP consortiums, it may be possible to identify common inflammatory biomarkers that lead towards more effective early detection and potentially reveal therapeutic strategies to combat diseases of inflammation.

This pilot project uses AMP AD and PD proteomics to define common inflammatory pathways across neurodegenerative diseases.

1. Identify molecular subtypes or ‘prototypes" based on the in-depth proteomic profiles associated with neuropathology, APOE genotype, inflammatory modules, and clinical phenotypes.

2. Identify inflammatory biomarkers in plasma that reflect the underlying pathological changes in tissue.
3. Provide a framework for patient-specific changes in inflammation across neurodegenerative disorders

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Going from Pilot to Scale-up

The further development of the AMP SBI program requires a contribution of $300K. This contribution would enable the FNIH to work together with government, private-sector, and academic key opinion leaders (KOLs) to co-develop a white paper for the scale-up phase utilizing available information from the foundational pilots to:

- Enable and expand systems-level analysis of "omics" datasets across different diseases/tissues
- Develop molecular map(s) using findings of shared and distinct inflammatory pathways linked to disease outcomes

Funding partners will prioritize components of the research plan and assess milestones for the scale-up. Activities to enable research plan components to include:

- Creating cross-disease teams and soliciting inputs across sectors
- Deciding data to be generated
- Identifying other datasets in prioritized disease areas
- Selecting the supporting data infrastructure

The finalized funded research plan will inform the Request for Applications (RFA's) to be issued.

The scale-up research plan is expected to require $64M over 4 years in public and private partner funds to support the selected Research Collaborative agreements, enable public-private and cross-AMP collaboration and AMP SBI program management.

Scale-up: Enable and expand systems-level analysis of "omics" datasets across different diseases/tissues

The scale-up phase of the AMP-SBI program is predicated on the successful finalization of the AMP SBI research plan and completion of the RFA process, and competitive selection of research collaborations. The preliminary scale-up and integration include purpose-built new data and resource generation with components selected per funding partner priorities with buy-down and buy-up options to be available. The estimated public-private partner contributions that FNIH would seek for all concepts outlined below is $63.7M.

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

- Expand cross-AMP multi-omic data integration and analyses
- Generate new data types to expand upon pilot findings conducive to systems-level analyses

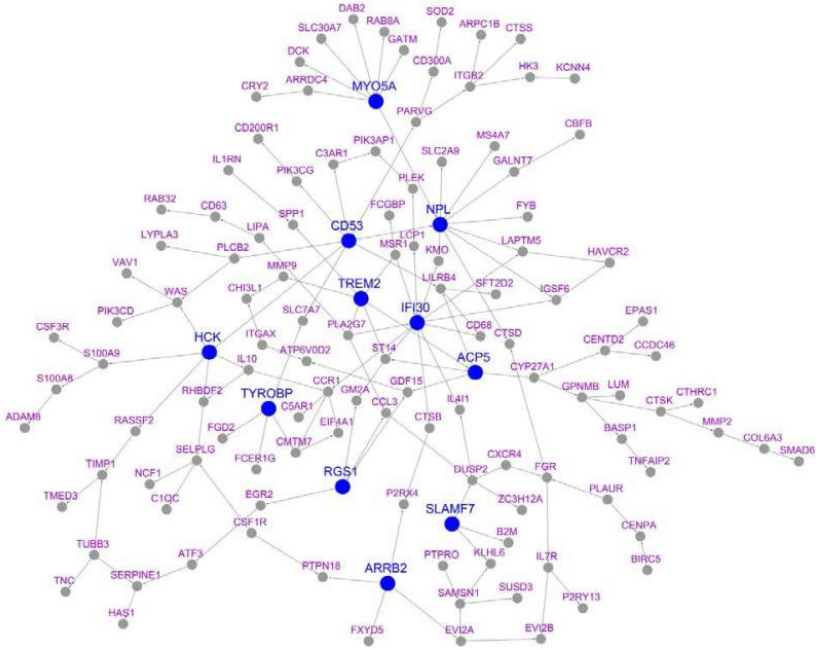
- Provide further cellular characterizations based on fresh tissue (e.g., scRNAseq-ATACseq, CyTOF)

1-year initial deliverables

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

Create a core gene causal network conserved across tissues and species and its key drivers. Highly consistent driver genes such as HCK, CD53, and TYROBP are involved in many inflammation-related disorders.

Figure 4. Molecular and Genetic Inflammation Networks in Major Human Diseases



Zhao et al. Molecular and Genetic Inflammation Networks in Major Human Diseases. Mol Biosyst. 2016 July 19; 12(8): 2318–2341. doi:10.1039/c6mb00240d.

Concepts for transonic scale-up are outlined below that can be considered in addition to any others identified with potential (public and private) funding partners during research plan development. *(each scale-up could be executed over 1 to 2 years)*:

The following scale-up would enable a deeper understanding of mediators central in inflammation, testing a common mechanism across diseases. Identifying common and distinct biochemical and metabolic imbalances across multiple conditions will provide enhanced resolution, biomarkers, and novel therapeutic approaches inflammation centric.

The goal of this scale-up project is to enrich evidence of common metabolic mechanisms of immune dysregulation across disorders, aims to:

1. Further, quantify metabolomic/lipidomic profiles in the case and healthy control participant samples across AMPs
2. Integrate metabolomic/lipidomic profiles generated with existing proteomic and transcriptomic data to identify new associations between inflammatory pathways and other metabolic processes.
3. Evaluate peripheral and central connections where imaging data is available

Studies remain modest in size, so the aggregate data from AMP and many other relevant will provide an integrated reference framework of immune cell subtypes and states to dissect immune responses' shared and distinct aspects.

The goal of this scale-up project is to generate data from deeply phenotyped longitudinal cohorts to establish trajectories of inflammatory signatures likely to be preserved between central and peripheral tissues as peripheral biomarkers that can inform on the inflammatory changes occurring in difficult-to-access central tissues, with aims to:
1. Collect PBMCs, PaxGene blood, tissue, plasma from neurodegenerative disease and metabolic disease patients
2. Perform scRNAseq (PBMC, Liver), immunophenotyping (PBMC), PaxGene RNAseq, and GWAS on all samples and process as per pilot
3. Characterize the longitudinal trajectory of inflammatory signatures identified in the pilot and discover novel inflammatory signatures

The goal of this scale-up project is to expand data generation to create a definitive genetic foundation to the shared immune signatures for all diseases represented in AMP, with the aim to:
1. Generate multiple layers of omic data from the healthy control and case participants to validate mapping the propagation of functional consequences. That will be guided by the pilot phase results and in conjunction with STEP 2 from other proposals.

The goal of this scale-up project is to expand data generation to create a definitive genetic foundation to the shared immune signatures for all diseases represented in AMP, with aims to:
1. Test iPSC validated pan-disease inflammation drivers using disease-specific mouse models
2. Validate FDA approved drugs and drug combinations in disease-specific iPSC and mouse models

The goal of this scale-up project is to validate associations using emerging bulk and sc/sn RNAseq data and omics, with aims to:
1. Establish through collaboration a reference multi-omic healthy immune system set the building on existing sample/datasets: using the diverse Healthy Control participants with scRNAseq data, generate shotgun proteomic and metabolomic (including microbial metabolites) profiles from matching plasma and CSF samples.
2. Establish a parallel multi-omic cross-disease set including each AMP disease

The goal of this scale-up project is to expand the integrated reference framework to catalog all immune cell subtypes and states in the brain and periphery, with aims to:
1. Increase the resolution of immune cell QTL mapping in human brain tissue through additional single-cell profiling (scRNA-seq and scATAC-seq) in immune cells
2. Add power for QTL discovery by leveraging snRNAseq and snATACseq being generated in complementary grants

3. Utilizing the updated single-cell QTL mapping, validate pilot analyses and uncover the credible causal variants, transcripts, and regulatory sequences shared and distinct across AMP-related traits.

Impute human brain immune cells scRNA-seq and scATAC-seq in the Million Veteran Program Biobank (MVP).

This scale-up will use a state-of-the-art untargeted or targeted proteomics approach providing a novel set of peptide and protein data across common mechanisms across diseases to harmonize with plasma data collected from other AMP programs where proteomics is available, including AMP-PD.

The goal of this scale-up project is to validate findings identified through further proteomic data generation across diseases, with the aim to:

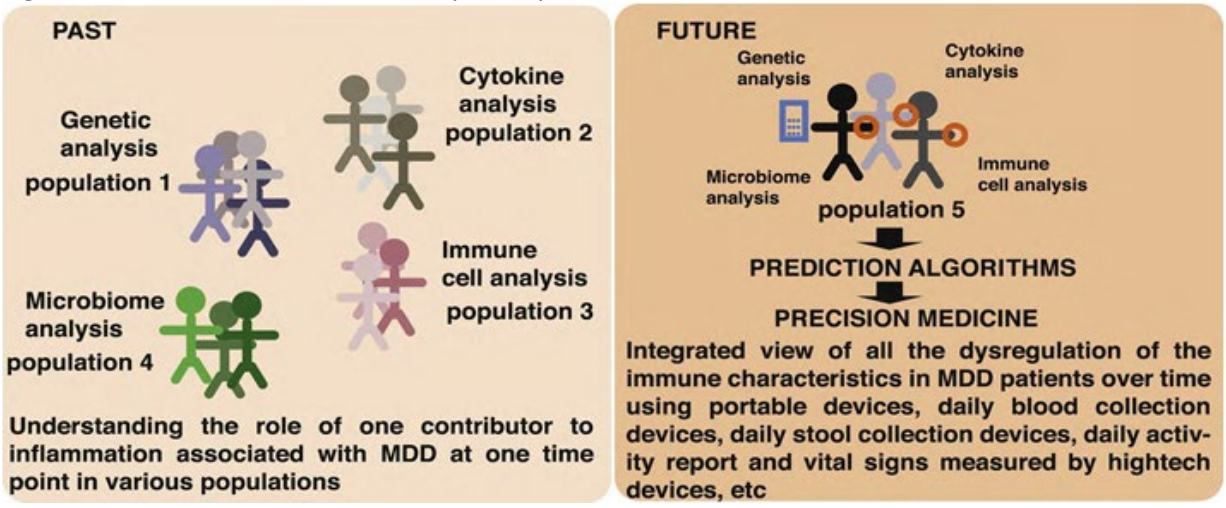
1. Enrich evidence of common mechanisms of dysregulated inflammation and immune function across disorders of interest across AMPs using untargeted or targeted proteomics platforms to generate new data that informed existing AMPs.

Integrated Model: Develop a comprehensive map of shared inflammatory pathways linked to various disease states and traits that span peripheral and central tissue types

Final deliverables

- Modeling inflammation across diseases at a tissue level and its relationship to other disease-relevant biological processes (metabolism/proteostasis/autophagy etc.)
- Provide a deeper understanding of previously identified biomarkers and drug targets in the context of inflammation
- Discover new biomarkers and drug targets
- Enable a new precision medicine approach by building a dynamic knowledge network as a basis for a new molecular taxonomy of disease

Figure 5. The Bidirectional Relationship of Depression and Inflammation



Beurel et al. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. NEURON 2020 Jul 22;107(2):234-256

What are the estimated costs? (Provide a rough breakdown of projected cost elements if possible).

Pilot and Development

PROGRAM ELEMENTS	TOTAL COSTS ($M) *Direct And Indirect*	FUNDING SOURCE
Pilot Projects	Over $6M committed over 2 years	Public partners, NIH
FNIH Management During Development and Pilot Phase	~$300K over 2 years	Private partners
Total	**~$6.3M**	**Public and private partners**

Scale-up and Integration

PROGRAM ELEMENTS	TOTAL COSTS ($M) *Direct And Indirect*	FUNDING SOURCE
Multi-omic Data Generation	~$20M over 4 years	Public and private partners
System Biology Analyses and Analytical Tool Development	~$20M over 4 years	Public and private partners
Experimental Validation / Perturbation Studies	~$10M over 4 years	Public and private partners
Data Enablement/Infrastructure	~$10M over 4 years	Public and private partners
FNIH Program Management	~$3.7 M over 4 years	Private partners
Total	**~$63.6M over 4 years**	**Public and private partners**

Pilot Buy-up Option

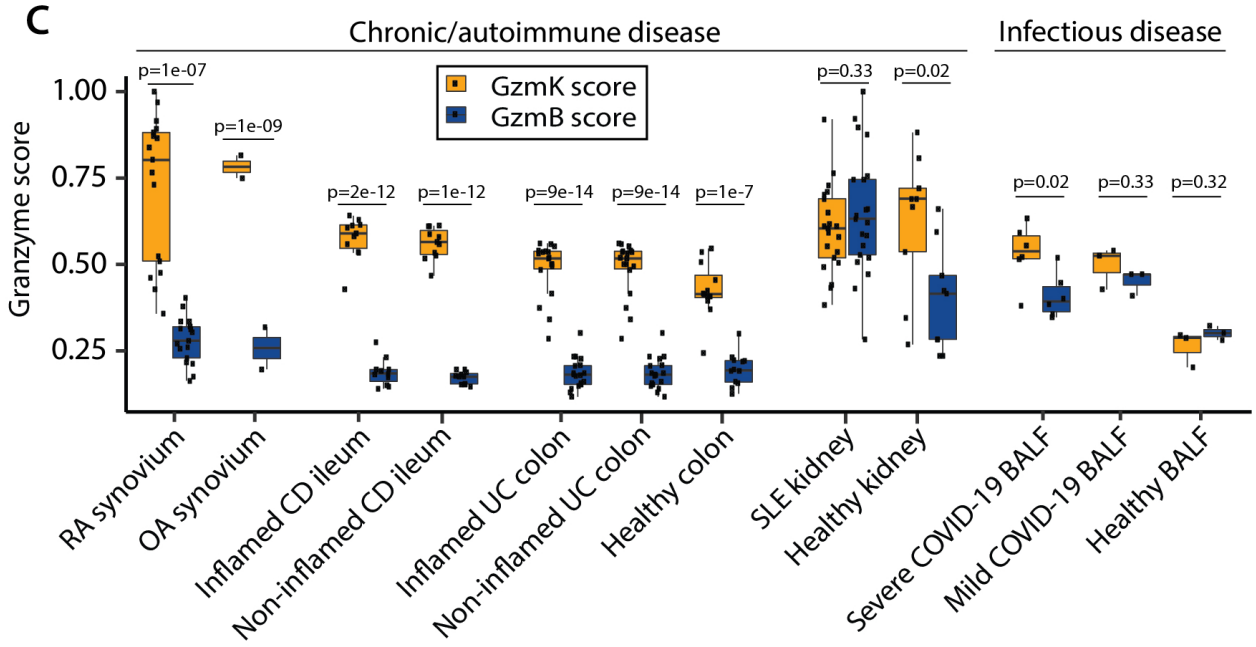
PROGRAM ELEMENTS	TOTAL COSTS ($M) *Direct And Indirect*	FUNDING SOURCE
Proteomics Pilot Project (Neurodegeneration focus)	Over $300K over 2 years	Public and/or private partners
FNIH Management	~$60K over 2 years	If FNIH managed
Total	**~$360K over 2 years**	**Public and private partners**

What prior results support the proposed program? (Please include)

As previously stated, some findings from AMP programs have already highlighted possible common inflammatory mechanisms. In addition, these studies suggest that GzmK+ GzmB+ CD8 T cells from a

core population of tissue-associated T cells in humans can drive inflammation both by production of inflammatory cytokines and by direct effects of granzyme K on other cell (Jonsson , 2021).

Figure 6: Granzyme K+ CD8 T Cells Form the Core Population of Inflamed Human Tissue-associated CD8 T Cells



Jonsson A et al. Granzyme K+ CD8 T Cells Form the Core Population of Inflamed Human Tissue-associated CD8 T Cells [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 10). https://acrabstracts.org/abstract/granzyme-k-cd8-t-cells-form-the-core-population-of-inflamed-human-tissue-associated-cd8-t-cells/.

Existing AMP Data and tools available for systems biology of inflammation

AMP T2D/CMD

- Platform: HuGeAMP and DGA Knowledge Portals
- 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 RA/SLE/AIM

- Platform: ImmPort, AIM Portal (2022)
- 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

AMP AD

- Platform: AD Knowledge Portal/Synapse

- 1.0 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).
- 1.0 Tools: Molecular network models
- 1.0 Ready: all data, analytical results & candidate targets are available in the AD Knowledge Portal & Agora. Strong neuroimmune brain & peripheral signatures

- 2.0 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
- 2.0 Tools: Being updated and multiscale models built
- 2.0 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 PD
- Platform: Google 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
- 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 Heart Failure (AMP HF)

An AMP HF research plan focuses on Heart Failure with preserved ejection fraction (HFpEF). The goal is for the data that results from the effort to be made available in the future through a public data portal. Some aspects of the data planned to be generated include the following:

- The portal will include WGS data from 180,000 participants
- Other multi-omics data will be generated longitudinally – methylation, RNAseq, metabolomics, and proteomics. Most of these data are derived from blood rather than tissue, however.
- Echocardiography phenotypes and imaging phenotypes will be available from some participants

Tools will include those that can enable a systems biology approach, including the potential for discovering inflammatory pathways.

Describe why this is a good fit for AMP (~150 words)
How does the proposed research fit the mission of AMP?
In collaboration with public and private partners, NIH will leverage previous investments into AMP to create a map of inflammatory mechanisms across disease by cross-tissue integrative multi-omics multiscale analyses for

therapeutic discoveries. The expertise and active participation of the private sector are critical to ensure the proposed research program results in tools that will be practically useful in developing effective new therapeutic options for patients that are acceptable to patients.

Leading towards a new precision medicine approach by building a knowledge network for biomedical research and a new disease taxonomy.

> "A Knowledge Network of Disease could embrace and inform rapidly expanding efforts by the biomedical research community to define at the molecular level the disease predispositions and pathogenic processes occurring in individuals. This network has the potential to play a critical role across the globe for the public-health and health-care-delivery communities by enabling the development of a more accurate, molecularly-informed taxonomy of disease."

Why is the research uniquely suited to being executed by AMP instead of other entities?

This public-private partnership utilizes existing resources developed by AMP, and stakeholders involved in AMP are uniquely capable of providing input and direction to enable successful implementation. We are aware of no comparable existing partnership structure that can effectively address these goals.

Is the proposed research dependent on any existing patents or applications? How would any intellectual property that is generated be handled, consistent with AMP policies?

Rights to existing IP used to generate AMP data or interrogate AMP data remain with the inventor. AMP SBI will not 'reach through' to any background IP. However, no new IP may be generated using AMP or AMP SBI data. AMP SBI is committed to open science and creating a resource for the research community at large.

How will data be shared, consistent with AMP policies?

AMP-SBI will share data according to AMP policies utilizing existing AMP infrastructure or NIH infrastructure where relevant.

Please identify known and potential funding partners. Who would fund the project and why? (List likely government, company, non-profit, etc. sources)

Strong involvement and program leadership from multiple NIH ICs

NIA*	NIDDK	NIMH

NIAMS*	NINDS	NHBLI
ODSS		

Representatives from the following companies have expressed interest in discussion on the further development of this concept. Their participation and engagement portend an increased likelihood for additional support for the program. We will continue outreach to private partners outside of those listed to assess their interests.

Takeda Pharmaceutical Company Limited*	Janssen Research & Development, LLC	Sanofi Pharmaceutical industry company
AbbVie	Otsuka Pharmaceutical Development & Commercialization, Inc.	Boehringer Ingelheim
GlaxoSmithKline plc (GSK)	Pfizer	

Steering Committees across AMP have been consulted and are invited to have a liaison involved in further developing this concept.

AMP AIM, RA/SLE	AMP CMD, T2D	AMP PD
AMP AD	AMP SCZ	

Other developing AMP leads have been made aware, and there are presentations planned to other FNIH programs in the future, e.g., Biomarkers Consortium Cancer Steering Committee.

Has this project been submitted elsewhere for funding; is there any potential funding overlap with other projects, ongoing or proposed?

No.

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SUMMARY OF THE ACCELERATING MEDICINES PARTNERSHIP (AMP) POLICIES

As AMP is designed as a precompetitive research partnership, new program proposals should be intended to observe the following AMP policies:

Antitrust

The project participants agree that all research activities funded by the partnership fall into the precompetitive space. There is to be no discussion of marketing activities.

Confidentiality

The project participants agree that there is to be no sharing of confidential information as a "blanket rule." If sharing is required, a specific CDA will be established by relevant parties and FNIH.

Solicitations

Solicitations will be open where practicable (or required by federal regulation).

Conflict of interest

Any conflicts of interest that arise are to be documented and reviewed with FNIH and the Executive Committee, who will jointly develop a mitigation strategy.

Publications

Projects will generally operate under a "team science" approach, and publications will have joint authorship where feasible. Specific publication strategies will be developed as part of each project plan.

Data sharing

Findings will be shared broadly and quickly, in the interest of patients and the public health; in certain cases, partnership participants may have access to findings during the assessment of data quality (up to 6 months of QA/QC).

Intellectual property

Pre-existing IP must be free to be used by the partnership. All research discoveries are intended to be released into the public domain, with no pre-emptive patenting. In rare instances when this is not possible, FNIH will determine fair strategies for distributing IP to encourage broad commercialization and balanced public health benefit and review them with the Steering Committee and Executive Committee.