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 define succinctly and clearly the proposed problem, background and rationale for the proposed program, what work is proposed, 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 out of 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 in Autoimmune and Immune-Mediated Diseases (AMP AIM)**
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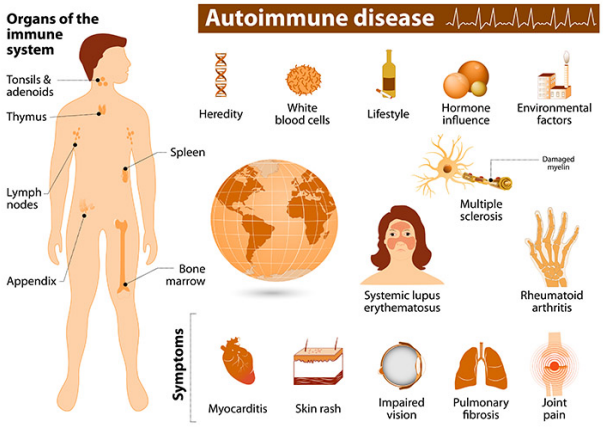
Submission Date:	July 31, 2020
Disease Area of Project	Autoimmunity and immune-mediated tissue inflammation in RA, lupus, psoriasis and other diseases affecting the synovial tissue and the skin
Estimated duration of the project	5 years
Estimated total cost of the project	~$63M

1. Problem statement –Describe the critical scientific problem or capability gap being addressed, and the clinical/scientific significance of the problem.

Combined, autoimmune diseases afflict more than 25 million Americans and recent studies suggest that the prevalence and incidence of these diseases are increasing. Rheumatoid arthritis, psoriasis spectrum diseases, Sjogren's syndrome and lupus are chronic autoimmune diseases characterized by profound abnormalities in the innate and acquired immune responses that result in persistent damage to multiple tissues and organ systems. They feature a self-propagating feedback loop that maintains and perpetuates systemic and local inflammation and tissue injury. The immune responses and inflammatory loops involve complex cellular and molecular components that may interface in blood and in the target organs. Many autoimmune diseases share common inflammatory pathways, clinical and laboratory features, associated comorbidity risks and even treatment response to disease modifying agents. However, there are multifactorial differences in genetics and immune dysregulation that generate disease heterogeneity, delay drug development and complicate patient care. Defining shared and unique immune mechanisms of disease at the systemic and organ level is critical for the design of new and specific interventions.



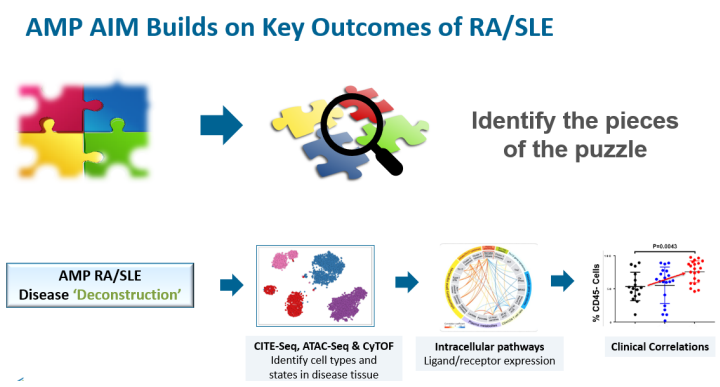
Over the last 6 years, the Accelerating Medicines Partnership – rheumatoid arthritis and systemic lupus erythematosus (AMP RA/SLE) program has brought together public and private communities to make unprecedented progress in understanding the cell populations, pathways and potential novel drug targets that drive these diseases. AMP RA/SLE is supported through a research partnership between seven pharmaceutical companies (AbbVie, BMS, GSK, Janssen, Merck, Pfizer, Sanofi and Takeda), the National Institutes of Arthritis and Musculoskeletal Disease (NIAMS) and the National Institute of Allergy and Infectious Disease (NIAID), multiple not-for-profit patient advocacy organizations (National Arthritis Foundation, Lupus Foundation of America, Lupus Research Alliance, and Rheumatology Research Foundation), and the Foundation for the National Institutes of Health (FNIH). The robust infrastructure, learned technologies, and analytical expertise of this existing program, provides an unprecedented opportunity to further accelerate the identification and validation of specific drug targets in other autoimmune diseases that may share immune and inflammatory pathways.

This proposal for AMP in Autoimmune and Immune Mediated Diseases (AMP AIM) outlines a plan for building a next generation public-private partnership across NIH, FNIH, and interested pharmaceutical companies and stakeholders focused on combining resources to advance and accelerate research enabling new target discovery in diseases such as rheumatoid arthritis, lupus, Sjogren's syndrome and psoriasis. Significant input from participating organizations, key academic investigators, and NIH is reflected in this proposal. If approved, we will seek additional partners to refine and strengthen this project proposal and partnership.

2. Overview describing how you would propose that AMP address the problem, with goals and a summary of key objectives.

The AMP RA SLE program has advanced the concept of disease ***deconstruction*** by establishing the value and feasibility of using high dimensional analytics on biopsy samples in RA and lupus to discover the molecular and cellular pathways active in the tissues from patients with these diseases**.** In order to deconstruct disease components, AMP has generated multi 'omic' (protein, mRNA, open chromatin) characterization of thousands of single cells in >100 synovial biopsies in rheumatoid arthritis and >200 renal biopsies in lupus nephritis. Analysis of associated samples (peripheral blood, urine, skin) from the same patients is underway. These studies have led to the discovery of new cell populations and states and biomarkers. Careful phenotyping and longitudinal follow-up of patients will allow discovery on linkages between patients and disease mechanisms. Indeed, this project has changed the research landscape for understanding RA and lupus.

We envision the next phase of the AMP program ("AMP AIM") as an equally great leap in the use of technical innovation to accelerate the discovery of new mechanisms of autoimmune diseases and new targets for intervention and therapeutic development. The new cornerstone of AMP AIM will be the concept of disease ***reconstruction*** based on high dimensional study of cell interactions.

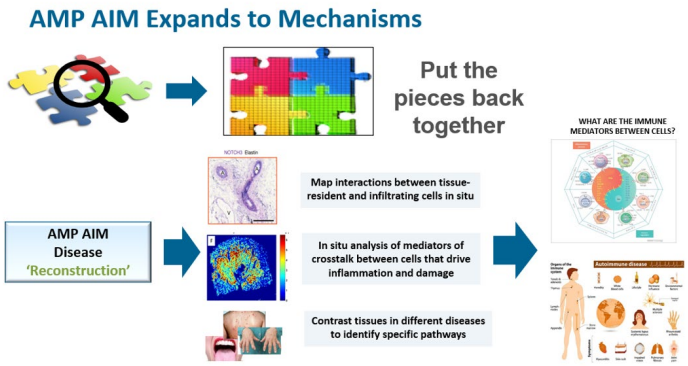


AMP AIM will not only refine and extend the single cell analysis of tissue to other autoimmune diseases (disease deconstruction), but will also bring in high dimensional novel analytics to discover how innate and adaptive cells of the immune system and tissue resident cells network with each other to cause inflammation, injury, abnormal function and clinical disease (disease **reconstruction**).

AMP AIM will focus on:

- ✓ Dissecting mechanisms of disease at the organ level in RA, lupus, Sjogren's and PSD, leveraging current resources and infrastructure.
- ✓ Spatial mapping of cell types and states will identify the pathways of crosstalk between cells that drive inflammation and damage.
- ✓ Network modeling of integrated single cell multi- 'omics and identification of inflammatory mediators, mapped in a spatial context, to uncover the regulatory mechanisms governing functions within and between cells that cause disease.
- ✓ Comparisons between and across tissues to understand how different cell types, states and interactions may lead to different disease manifestations.
- ✓ Upgrading data storage platforms and accelerating data sharing.

The **AMP AIM** new dataset will provide another order of magnitude increase in our understanding of how infiltrating and resident cells interact to cause tissue end-organ damage in different autoimmune diseases, while providing exciting new opportunities for drug development.



We envision at the end of the 5-year period, AMP AIM will have:

- A robust clinical data set that can support rigorous interrogation of clinical correlates of molecular data.
- A highly curated data set that includes high dimensional information about tissue resident and infiltrating cells at the single cell level in blood and tissues that are affected in different autoimmune diseases. This will potentially include data on gene expression, spatial mapping of cell types and states, and mediators that drive inflammation and tissue damage.
- Modelling of pathways active in target tissues, synovium, kidney, skin and blood, in RA, PSD, lupus and Sjogren's, syndrome, including identification of pathways involved in early and pre-clinical disease
- A suite of proven tools, technologies and SOPs, to investigate blood and tissues at the single cell level that can be applied to other autoimmune and immune-mediated.
- New computational tools to analyze and integrate high dimensional, multi modal data sets into disease pathways.
- A roadmap for how to apply contemporary molecular technology to similarly assess therapeutic strategies in additional inflammatory diseases of interest.
- A knowledge and data portal to enable data sharing and make data accessible to all stakeholders.

There will be a substantial return on investment for all stakeholders. For industry partners, the value of the data generated in this project will far exceed a similar internal investment made to jump start and prioritize drug discovery programs. The value proposition is as follows:

- The network will produce a dataset of hundreds of patients with one of multiple diseases, and different stages of diseases. Data may include single cell resolution spatial maps of inflamed tissue, as well as disaggregated single cell atlases. Individual level meta-data will make it possible to define whether the populations and the interactions between them are specific to disease, or whether they are being driven by other non-pathogenic factors (tissue,

demographics, or drugs). Samples will be fully genotyped, and it will be possible to assess the molecular impact of disease alleles (e.g. eQTLs, cell-cell interaction QTLs, etc.).

- ❖ The final annotated data set will be a very rich resource, which far exceeds anything any one partner could produce individually to support basic and translational research.

- ❖ The high-level deliverable of data access and an interrogation portal for systems biology mapping of the critical disease pathways and networks will provide an unprecedented tool to mine for drug targets.

- ❖ The data will include stratification of patients by stage of disease, organ involvement, and treatment responder status. The comparisons between diseases will allow development of strategies for enrichment for therapeutic response within a disease and broadening of drug application across autoimmune disease indications.

This analysis of immune modules will transform the approach to defining the pathogenesis of autoimmune diseases, improve patient enrichment strategies to ensure the best use of existing therapies, and enable the identification of new targets for potentially curative therapies across diseases.

3. Scientific strategy and proposed logistics

Project Design. The AMP AIM program will establish a pre-competitive partnership to further advance the findings of the RA/SLE program in three key areas: 1) Refine the exploration of mechanisms of autoimmune diseases through high dimensional single cell technologies to improve the identification of new targets; 2) Expand the analysis of tissue and blood to other inflammatory and autoimmune diseases beyond systemic lupus erythematosus and rheumatoid arthritis; and 3) Create robust clinical, molecular and genetic datasets, standard operating procedures and optimized technologies, and computational tools through a managed knowledge and data porta to allow rapidly and efficiently sharing and interrogation with the research community.

Novel and established technologies and approaches will be used to:

1. Expand the high dimensional analysis of tissue and blood to other autoimmune and inflammatory diseases beyond systemic lupus erythematosus and rheumatoid arthritis to other conditions depending on stakeholder interest. We anticipate adding 2 diseases initially. These conditions include initially psoriasis (PsO)/psoriatic arthritis (PsA) and Sjogren's. In the future, based on advances on tissue analytics and availability of funds, we will consider including atopic dermatitis (AD), scleroderma, or ankylosing spondylitis.

    - **Psoriasis/Psoriatic Arthritis**. The greatest challenge to therapeutic advances in the management of PsA is the heterogeneity of disease phenotype, which can affect a variety of domains, including skin, joints, spine, the eye and the intestine. Intriguingly, the remarkable advances witnessed in psoriasis therapeutics based on targeting TNF, IL-17 and IL-23 pathways have not translated into equally effective outcome in PsA.
      Therefore, an integrated precision medicine approach is desperately needed to understand pathogenesis of progression from psoriasis to PsA and response to therapy in

those with musculoskeletal disease. Perhaps the biggest unmet needs are a) the discovery of prognostic and predictive biomarkers (molecular insights) to identify targets that track with disease progression from psoriasis to PsA, and b) those features that presage response or non-response to a specific targetable pathway. AMP 2.0 represents an opportunity to leverage the infrastructure of AMP1.0 in skin lupus/synovial RA and expand to at-risk psoriasis and PsA patients that initiate biologic therapies which will serve both as a resource of new targets and as a biomarker of transition and clinical response.

- **Sjogren's Syndrome** is a common autoimmune disease with a prevalence of approximately 0.5% to 1% of the population, affecting an estimated 4 million in the United States. The syndrome manifests over a wide spectrum of disease ranging from, a limited, organ-specific disease to a systemic disease with widespread autoimmune manifestations. The two main symptoms of Sjogren's syndrome are extensive dryness of mouth and eyes caused by destruction of salivary and lachrymal glands. Systemic manifestations may include arthritis, skin lesions, gastrointestinal and hematologic complications, renal, lung and liver disease and lymphoma development. Currently, there is no single medication to treat Sjögren's and treatment is aimed at symptomatic relief of dryness. While symptomatic therapy helps patients with mild disease, the lack of disease-modifying drugs has a debilitating impact on patients with more severe and systemic organ involvement. There is very little known about the pathophysiology of the disorder. Sjogren's patients display clinical and molecular heterogeneity, which has not been well characterized beyond basic autoantibody profiles and some whole blood gene expression profiling. New information is needed to understand the molecular heterogeneity which will help identify targetable pathways and stratify patients for clinical trials or to help best select therapies for established patients.

- **Atopic dermatitis (AD)** is an immune-mediated skin disease that adversely impacts most aspects of everyday life. While it affects all ethnic populations, it has higher prevalence rates in certain ethnic populations that are also associated with a disproportionate impact on healthcare. AD is characterized by increased T-cell and dendritic cell (DC) infiltrates, upregulation of inflammatory mediators, epidermal hyperplasia, and epidermal barrier defects with downregulation of differentiation proteins, and lipids. AD is increasingly recognized as a heterogeneous disease with significant variation in molecular phenotypes across different ethnic, and other populations, although Th2 and Th22 play key roles. AMP RA/SLE has developed outstanding infrastructure, resources, methods, and datasets that can be readily replicated and expanded to study inflammatory skin diseases. Datasets from skin can be readily compared with existing RA/SLE datasets from synovium, skin, kidney and blood, potentially identifying genes, pathways and mechanisms that cross multiple diseases.

- **Systemic sclerosis (SSc)**, also called scleroderma, is a chronic immune-mediated multisystem disorder that is characterized by fibrosis of the skin and internal organs. Vascular damage, immune activation and excessive synthesis and deposition of connective tissues are prominent features of SSc. The degree of skin and internal organ involvement varies, and survival is impacted by the extent of damage to internal organs including, lungs, heart and kidney. There are no disease-modifying drugs for systemic sclerosis and the disease is associated with a high morbidity and mortality rate. Compounding the problem of treatments are issues of clinical and molecular

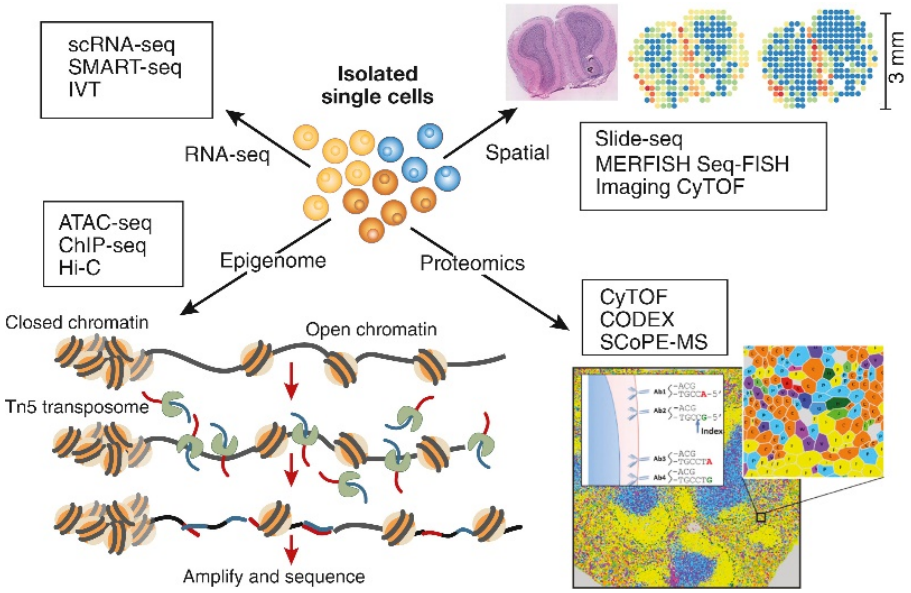
heterogeneity. Single cell studies in systemic sclerosis (SSc) have lagged other autoimmune diseases including RA and lupus. There is strong interest in developing better approaches to identify common and disease specific, targetable pathways to address the clinical and molecular heterogeneity which is found within SSc and across other autoimmune diseases.

Candidate tissues/diseases (to be defined with stakeholders) might include:

a. Synovium: rheumatoid arthritis, psoriatic arthritis, lupus, ankylosing spondylitis and/or others.
b. Skin: lupus, psoriasis, AD and scleroderma.
c. Blood: a wide range of inflammatory diseases including psoriasis, rheumatoid arthritis, psoriatic arthritis, and lupus.
d. Other tissues such as salivary glands in Sjogren's and mucosal biopsies in ankylosing spondylitis.

2. Refine the exploration of mechanisms of autoimmune and immune-mediated disease using novel and emerging high dimensional technologies to improve the identification of new targets:

a. Define the role of different cell states, cell types trajectories and pathways within affected tissues, and within different autoimmune and inflammatory diseases. Potential technologies include single cell transcriptomics, single cell epigenomics, metabolomics and proteomics.
b. Identify the mechanisms of interactions between cells that mediate tissue damage, using spatial data at the transcriptional, proteomic and metabolic level.
c. Identify the serological and tissue changes that occur prior to and in the earliest stages of disease.
d. Apply these technologies to define the mechanisms of disease progression in patients with multi-treatment failures.



Park et al., Kid Intl 96(4) 852-870, 2019 (https://doi.org/10.1016/j.kint.2019.03.035)

3. Create robust clinical, molecular and genetic datasets, standard operating procedures and optimized technologies, and computational tools to be shared rapidly and efficiently with the research community. This includes:
    a. Consent all patients for widespread data collection and data sharing, follow best practices in collecting and tracking sample metadata across all workflows and share annotated data linked to all relevant patient, sample and protocol metadata data with the network and funding partners.
    b. Establish best practices in organizing, curating, and annotating data, including metadata data, raw and processed molecular data and sharing data within the network and the public.

4. Develop an organized virtual home for the consortium enabling one-stop dissemination of relevant administrative and scientific information, including a dedicated data portal (AIM Knowledge/Data Portal). This will:
    a. Develop and include queryable analytics to facilitate the use and re-use of high-dimensional data by teams lacking dedicated computational expertise.
    b. Provide timely access to all available pre-publication data to partners.
    c. Facilitate subsequent public releases.

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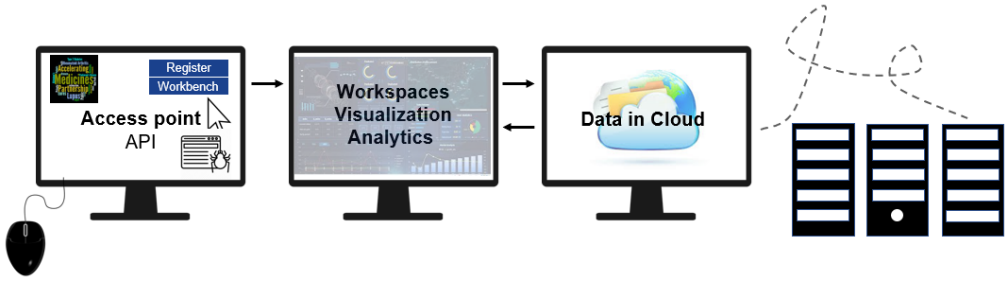

Portal: Public website with user registration and all program resources

Project Structure. The AMP AIM Network will include several key Disease Teams, and Shared Functional Teams and Structural Components. The following are core element of the future program. The final structure, interactions and governance will be further developed during the project plan development process.

Disease Focused Teams

Composed by disease experts from academia and industry, they will identify key research questions, establish priorities, organize the clinical studies and direct the data analysis. They will:

a. Define the criteria for patients to be recruited, the clinical parameters to be monitored, organize the clinical studies, guide the sub-phenotyping studies and analyze and integrate disease specific data.
b. Work collaboratively with other Disease and Functional Teams and Structural Components to develop key questions in disease pathology, and critical data elements to extract from optimized tissue processing and analytic pipelines.
c. Each disease will require a recruitment arm to identify and recruit patients into the AMP study.

Shared Network Functional Teams

a. Technology and Molecular Analysis Groups. This group will focus on developing, optimizing, and implementing standard procedures and pipelines to process tissues and conduct high dimensional analysis of tissue and blood. They will explore new and emerging technologies and together with the Network teams establish the feasibility of using them in specific diseases.
b. Systems Biology Group. The focus of this group will be to analyze and interpret large scale molecular data and integrate data from a range of technologies across multiple cell-types, tissue types and cell states. They will share tools and technology with other Teams and Groups in the Network and provide expertise and support for data analysis plans.

Shared Network Structural Components

a. Tissue and Biospecimen Repository. This component will store and bank blood, DNA, and other tissues for all recruited samples, provide them for molecular studies, pipeline studies, and follow up studies
b. Clinical Data Management. They will provide data management support of clinical data for all different diseases. This group might be managed by a Contract Research Organization (CRO).

Project Management and Project Funding Mechanisms

The Steering Committee for AMP AIM will be comprised of representatives from participating companies as well as members from government, and non-profit organizations, and will operate under the direction of the overall AMP Executive Committee (EC). The EC is in turn advised by an Extended Executive Committee comprised of R&D heads of companies involved in the partnership. The AMP AIM Steering Committee is responsible for defining and prioritizing the research agenda and project plan, for review of ongoing projects, and for the detailed assessment of milestones. The EC will also review the assessment of milestones and any revision to the project plan**.**

Research awards

The Steering Committee comprised of members of NIH and partner company leadership, will guide project workflow through project working group meetings, consortium meetings, and through issuing request for proposals (RFPs) for the duration of the project. It is anticipated that some FNIH, and other partner organization awards, may be considered by the Steering Committee to be invaluable to support the AMP AIM project. In addition, we expect to explore leveraging established disease-specific networks, awards and infrastructure of parallel knowledge/data portals from other AMP programs (e.g. AMP T2D).

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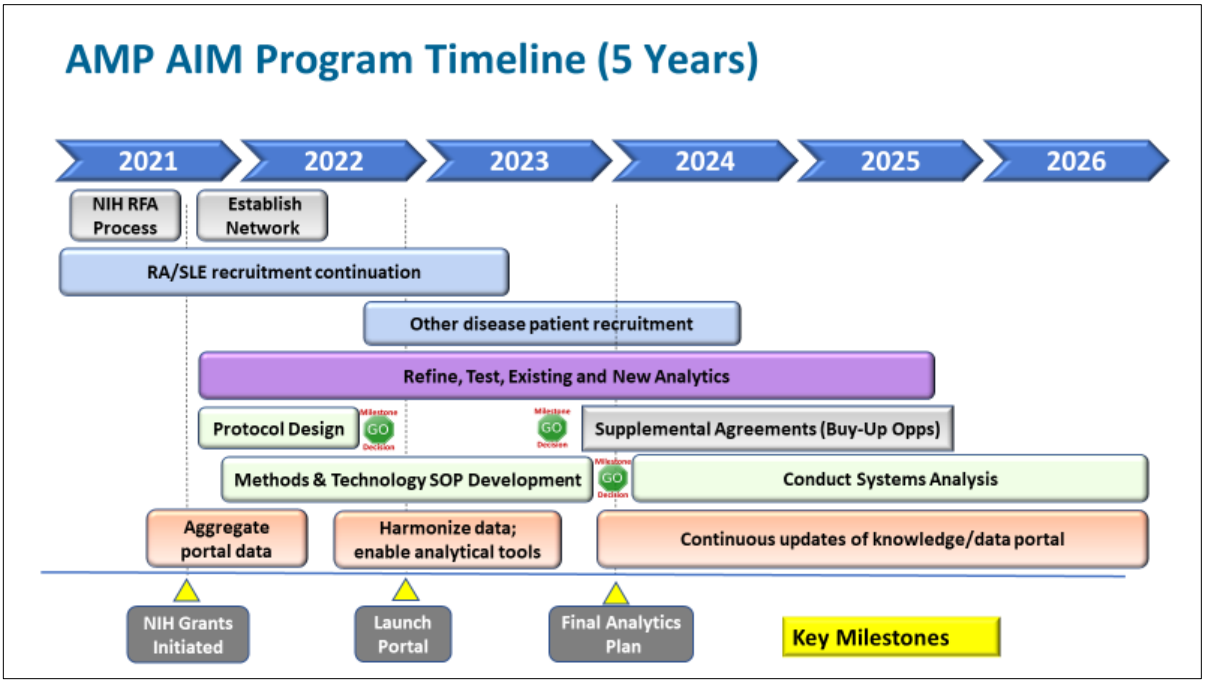
Timeline and Key Milestones



Key Milestones

- **Proposed Milestone 1**: *(6 months)* Establish AMP AIM Network, rapidly building on foundation of AMP RA/SLE.
- **Proposed Milestone 2**: *(9 months)* Decision on pipeline technologies and clinical inclusion (diseases, stages of disease, tissues, responder /non-responder status)
- **Proposed Milestone 3**: *(12 months)* Initiate patient recruitment
- **Proposed Milestone 4**: *(12 months)* Launch of Knowledge/Data Portal
    - Visualization and Analytical tools along with incorporation of the AMP RA/SLE program data
- **Proposed Milestone 5**: *(18 months)* Complete SOP work for new technologies (e.g. single cell spatial technologies, metabolomics) and tissues (e.g. salivary gland)
- **Proposed Milestone 6**: *(24 months)* Implement analytics for pipeline studies
- **Proposed Milestone 7**: *(24 months)* Buy-up Opportunity if applicable (AD, SSc and AS)

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

We have provided a sample core program budget based on the assumption that the available funds for the entire program, including a core set of autoimmune **and immune-mediated** diseases, 'enhanced package', are estimated to be $76.5M over 5 years, to be split approximately equally between industry and NIH. The average cost per company is $0.7 to 1M annually for 5 years with the current participation projected to be from ten companies**.** This preliminary budget was constructed from a model that determined a cost per sample for each analytic technology and multiplied that by the number of patients per cohort and the number of samples obtained from each patient, for both

tissue and other samples (blood, urine, etc.,) for each cohort in each phase. Costs for patient characterization, sample processing and storage were similarly calculated. Additional costs for start-up, investigator salary support, computational requirements (data management and knowledge portal) were added. The AMP AIM leadership is focused on the enhanced package to produce the most comprehensive and informative dataset. However, if potential partners align around a reduced number of diseases or fewer industry stakeholders come onboard the program, a core package it outlined as well, estimated to be $63M over 5 years with a private sector commitment of ~$0.63M annually.

AMP AIM Program	Total/ Annual Costs ($M)	
	'Core' Disease Pkg	'Enhanced' Disease Pkg
Patient Recruitment, Clinical Phenotyping Sample Acquisition & Processing	$24 Total Costs $8 Year 1, $4/Per Year/ Years 2-5	$30 Total Costs $11.8 Year 1, $4.55/Per Year/ Years 2-5
Systems Biology & Molecular Analytics	$9.5 Total Costs $2.2 Total Costs/Year/ Years 1-5	$11.5 Total Costs $2.3 Total Costs/Year/ Years 1-5
Clincial Coordination & Tissue Repository	$14 Total Costs $2.8 Total Costs/Year/ Years 1-5	$17 Total Costs $3.4 Total Costs/Year/ Years 1-5
Knowledge / Data Portal Data Coordinating Center	$13 Total Costs $4 Total Costs/Years/ Years 1-2 $1.66 Total Costs/Year/ Years 3-5	$15.5M Total Costs $4 Total Costs/Years/ Years 1-2 $2.5 Total Costs/Year/ Years 3-5
FNIH Program Management (meetings, travel, legal, comms)	$2.5 Total Costs $0.5 Direct Costs/Year/ Years 1-5	$2.5 Total Costs $0.5 Direct Costs/Year/ Years 1-5
Total Budget	$63M	$76.5M

Although this approach was used to calculate a detailed budget, it is important to note that the members of the Steering Committee recognize that the methods described here are evolving, particularly the technical analytic tools. The actual project will depend on what is proposed by applicants for funding, including approaches that improve on the plan as described above.

5. What prior results support the proposed program? (Please include references) (~300 words)

The AMP rheumatoid arthritis and systemic lupus erythematosus (AMP RA/SLE) program is the precursor to the program proposed here. That program combined expertise from clinical. basic science, and computational investigators to deconstruct tissue inflammation in rheumatoid arthritis and lupus. Careful phenotyping and longitudinal follow-up of patients will allow discovery on linkages between patients and mechanisms. Indeed, this project has changed the research landscape for understanding RA and lupus.

This program has established the value of conducting high dimensional analytics of tissue biopsy samples in immune-mediated diseases to discover the molecular and cellular pathways active in the tissues from patients with these diseases. **In order to deconstruct disease components**, AMP has generated multi 'omic' (protein, mRNA, open chromatin) characterization of thousands of single cells in >100 synovial biopsies in rheumatoid arthritis and >200 renal biopsies in lupus nephritis (see **Figure** 1A and 1B).

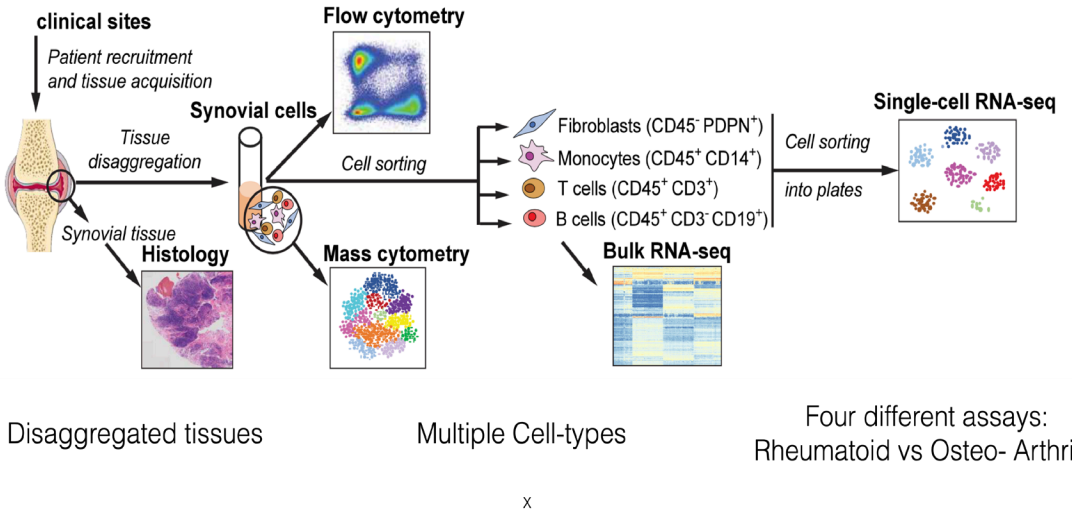


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Figure 1A. An Integrated pipeline to analyze RA synovial samples. RA synovial samples for AMP RA/SLE phase 1 were obtained at multiple clinical sites, disaggregated centrally, and analyzed using histology, flow cytometry, mass cytometry, bulk RNA-seq, and single cell RNA-seq.

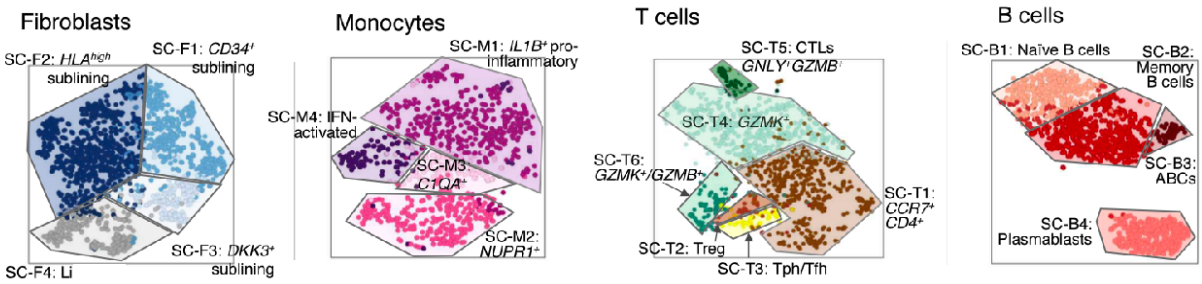

Figure 1B. These analyses led to the discovery of 18 dominant stromal tissue populations, including inflammatory HLA+THY1+ fibroblasts, autoimmune associated B cells, T peripheral helper cells, and inflammatory IL1B+ monocytes.

These studies have not only led to the discovery of new cell populations and states and biomarkers but have also provided a roadmap to use high dimensional single cell technologies to the application of clinical cohorts. Key learnings to date include the development of experimental protocols to disaggregate renal and synovial tissues [1, 2], the development of computational strategies to analyze and interpret large-scale single cell data [3, 4], and the discovery of novel cellular populations essential to tissue inflammation in the kidney and the synovium [1, 5, 6]. Recent and ongoing work has now turned the focus to exploit the knowledge of these key populations to define clinical biomarkers for disease progression, severity and treatment in blood and tissue [7, 8, 9, 10]. A prime example of the unexpected insights that AMP RA/SLE has offered us is the discovery of the inflammatory fibroblast, an essential component of RA synovitis [6]. Recent follow-up work has now shown that this population is the consequence of NOTCH signaling [8], and its presence in the blood can indicate the onset of flare [10].

6. Describe why this is a good fit for AMP (~150 words)

a. How does the proposed research fit the mission of AMP?

This program leverages the strengths of an ongoing, successful partnership on AMP RA/SLE and plans to improve on the lessons learned during this program. In addition to the supplemental investment and resources needed from the private sector to achieve these goals, the expertise and active participation of industry drug development and non-profit organizations is critical to ensure the proposed research program results and data that will be practically useful in developing effective new therapies that are relevant to patients.

This program is focused on defining the components of tissue inflammation and translating these findings to human diseases. The strategy we undertake requires patient recruitment in multiple diseases areas, obtaining tissues from patients, processing tissues to generate high dimensional molecular data, powerful computational and statistical strategies to define cellular and molecular pathways and translate these pathways back to mechanisms that increase or maintain disease activity. Inherently, the approach is broad in scope and cannot be carried out by any one organization. It merges the interests of all stakeholders in the field.

b. Why is the research uniquely suited to being executed by AMP as opposed to other entities?

Collaboration between public and private partners is essential to leverage effectively the expertise and resources of both. The focus of this project has value to both parties, as it seeks to define basic mechanisms of tissue inflammation to elucidate therapeutic opportunities that address patients underserved by current therapies and to ultimately provide avenues for normalizing tissue function and induce stable disease remission. Autoimmune and immune mediated diseases have common immune and inflammatory features that include response to immune modulating therapies. A public-private partnership will be able to tackle the challenges of discovering new effective therapies through complementary scientific and clinical expertise that is focused on the needs of the patient. The strategy outlined here greatly exceeds the scope of a project that could be undertaken by any single entity on its own and will lead to interactions between clinical investigators, data scientists, and basic scientists from both the public and private sectors.

This project will continue to utilize advanced methodologies and technologies not generally available. The focus on ‘omic level data from single cells (in tissue) or highly purified subsets (in blood) is fundamentally different than common systems approaches and will require the synergized engagement, expertise, infrastructure, and computational tools for pooling of data and resources that will stimulate and coordinate commonalities among disease pathways; and will identify and validate therapeutic targets. Collaboration between public and private partners is essential to enable directed research to solve the challenges posed in AMP AIM; and fostering open scientific interaction in the public domain.

c. 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?

No current patents or applications are expected to impact the program and study. This project will operate under the general policies of the Accelerating Medicines Partnership. Note: these are the general principles of the entire Partnership; their specific application to various aspects of the AMP AIM research agenda are discussed above in this concept. The policies for governance of AMP projects is now well-established and provided in Attachment A.

Any novel findings that might be generated from biomarker identification and validation would be published and thus made available in the public domain so as to facilitate the broadest possible application to enabling the development of treatments for AMP AIM, including development of downstream IP, without any pre-emptive patent restrictions. There is a potential for intellectual property to be developed around the methods and technologies needed to generate any validated data, but these too would be downstream inventions (e.g., xxx) that could be broadly enabled by but would not be part of the proposed AMP activities.

d. How will data be shared, consistent with AMP policies?

AMP AIM will share data according to AMP policies and aligned (and refined) from existing data sharing and use policies from the AMP RA/SLE Program. These include appropriate agreements for access and use of raw data obtained under NIH grants, data aggregation, transfer, use, sharing and publication policies and process. These policies are consistent with the AMP mission and guidelines for partnership. The current AMP RA/SLE program utilizes NIAID's ImmPort (https://www.immport.org/shared/home) as a data repository for sharing research data collected and makes the data available to qualified researchers.

It is anticipated the AMP AIM will develop a knowledge/ data portal within the program, ideally leveraging existing AMP portals infrastructure, visualization and analytical tools. Development of this portal will include specific development of policies and processes that are aligned with AMP.

7. Please identify known and potential funding partners.

e. Who would fund the project and why? (List likely government, company, non-profit, etc. sources)

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research at multiple levels, ranging from basic studies to enable comprehensive understanding of the molecular mechanisms underlying disease processes to preclinical research in model systems to translational studies to clinical and epidemiological research. Three areas of NIAM's core mission and portfolio focused on 1) Systemic Rheumatic and Autoimmune Diseases; 2) Skin Biology and Diseases and 3) Joint Biology, Diseases. NIAMS has a primary interest in emerging technologies, such as techniques to analyze single cells and innovative genomic approaches, have yielded a wealth of data that can be integrated with clinical information to build sophisticated new models of health and disease.

The National Institute of Dental and Craniofacial Research (NIDCR) has a significant investment in salivary gland research to extend general understanding of secretory organs as well as specific knowledge regarding health problems such as dry mouth and its oral complications. Knowledge gained through this research will be used to prevent and treat salivary gland dysfunction resulting from Sjögren's. NIDCR encourages research toward the identification and validation of predictive biomarkers in saliva for a variety of oral and systemic diseases will benefit disease screening and monitoring since, as a diagnostic fluid, saliva has many advantages over blood. NIDCR strives to be a leader in supporting the development of specialized tools for advancing knowledge about dental, oral, and craniofacial health, including, but not limited to, single-cell methods, stem-cell systems, multiscale imaging modalities, and disease models that accurately represent human biology.

National Institute of Allergy and Infectious Diseases. The study of autoimmune diseases is a priority for NIAID. The chronic and debilitating nature of these diseases, which can lead to high medical costs and reduced quality of life, is a burden on patients and affects their families and communities. Treatments are available for many autoimmune diseases, but cures have yet to be discovered. Although researchers have made considerable progress in understanding how the immune system causes organ, tissue, and cell injury in autoimmune diseases, much remains to be learned. By supporting a broad range of basic, preclinical, and clinical research in autoimmune diseases, NIAID enhances understanding of the causes of these diseases, the genetic factors that make people susceptible to them, and the regulatory mechanisms that control the production of self-destructive antibodies. NIAID-supported research on autoimmune diseases focuses on the immunologic basis of disease, including developing a greater understanding of the fundamental immunologic principles underlying disease onset and progression, developing improved animal models of disease, developing improved diagnostic tools, and identifying and evaluating more effective immune-based treatment and prevention strategies.

Representatives from the companies below (*) have committed funds in support of AMP RA/SLE and to support the concept design phase of the AMP AIM program. All have contributed expertise and experience to each of the core working groups described in this concept. FNIH has also reached out to several organizations for preliminary engagement and vetting of the primary aims, objectives and deliverables for AMP AIM (#). Discussions with these potential partners have been positive as well. Their participation and engagement portend an increased likelihood for further support for the program.

- AbbVie*
- Bristol Meyer Squibb*
- GSK*
- Janssen*
- Merck*
- Pfizer*
- Sanofi*
- Eli Lilly#
- Amgen#
- UCB#
- Gilead
- Roche/Genentech
- Regeneron
- Novartis

In addition, there is strong support in the disease-specific advocacy organizations, many of which have been engaged with AMP RA/SLE (*) and the planning efforts for this concept in AMP AIM, to ensure their communities see the benefit of the results of this program.

- Lupus Research Alliance*
- Arthritis Foundation#
- National Psoriasis Foundation#
- Sjogren's Foundation#
- Lupus Foundation of America*
- Rheumatology Research Foundation

The National Psoriasis Foundation (NPF) has a long history of providing funding to assist with the launch of investigators' research programs, study of specific topics and initiatives (https://www.psoriasis.org/grants). The NPF has recognized the importance of research to improve the lives of those living with psoriatic disease and the unmet needs in the community to drive innovative research in these areas. NPF is uniquely positioned to bring the research and clinical community together to change the face of psoriatic disease research utilizing successful, transformational and collaborative strategies and models to address these challenges. To this end and inspired by the Accelerating Medicines Partnership programs, NPF has established the Psoriasis Prevention Initiative (PPI) – a multi-institution, multi-disciplinary, team-based research network funding mechanism. Research will be given the highest priority based on their ability to:

1. Create, develop or support innovative collaborations among basic, translational, and clinical researchers.
2. Identify a multi-faceted, multi-disciplinary, collaborative team and research approach.
3. Explain how their approach will have the highest likelihood of developing an intervention to:
    a. prevent the onset of psoriatic disease
    b. prevent the onset of psoriatic disease relapse
    c. prevent the onset of related comorbidities

The initiative could also be integrated into or contribute to the infrastructure and success of the AMP AIM program.

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

The AMP AIM proposal has not been submitted elsewhere. There are complementary programs, particularly in the European Union (e.g. Innovative Medicines Initiatives), that are also exploring autoimmune disease research. These include 3TR, RTCure and BIOMAP.

3TR will integrate the analysis of seven autoimmune, allergic, and inflammatory conditions (RA, SLE, multiple sclerosis, Crohn's disease, ulcerative colitis, COPD and asthma) to identify the relationship between longitudinal molecular and microbiome profiles in blood cells and tissues, and disease trajectories to characterize and better predict, why certain patient groups do not respond to certain treatments.

The RTCure project aims to develop knowledge and tools to aid in the development of treatments for people in the earliest stages of RA as well as those at risk of developing it. The project team will develop and validate new methods to identify people at high risk for RA and tools to monitor the progress of the disease. They will also validate methods to monitor immune tolerance treatments; highly-targeted medicines that stop the immune system's attacks on the joints while ensuring the immune system remains able to fight off infections.

a. In September 2019, FNIH co-hosted the International Forum on RA with NIAMS and RTCure, providing a forum for alignment and results sharing of these programs. Several companies (and their AMP representatives) are also contributors and industry leaders for these EU initiatives. This will allow for continued communication between programs and the ability to make sure efforts are not duplicative.

The BIOMAP project, which launched in 2019, will examine the causes and mechanisms of inflammatory skin diseases from retrospective and ongoing clinical trials in the EU with the goal to identify biomarkers responsible for the variation in disease outcome. The project seeks to improve direct disease management by combining clinical, genetic and epidemiological expertise with modern molecular analysis techniques and newly-developed tools in bioinformatics.

AMP AIM and FNIH plan to engage leaders and participants in these programs on a regular basis and will consider joint workshops as well as collaborative meetings during global conferences (e.g. American College of Rheumatology, European League Against Rheumatism) to share insights, methods and results within program policies.

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SUMMARY OF THE ACCELERATING MEDICINES PARTNERSHIP (AMP)

The Accelerating Medicines Partnership (AMP) is a pre-competitive effort among government, industry, academia and non-profit organizations to harness collective capabilities, scale and resources toward improving current efforts to develop new therapies for complex, heterogeneous diseases. The focus of the partnership is on doing the research necessary to understand these diseases more fully, identifying the right targets to pursue for drug therapy, and thereby accelerating the ability to bring new medicines to patients in these diseases. To date AMP has established research programs in Alzheimer's disease, type 2 diabetes, rheumatoid arthritis, and systemic lupus erythematosus. 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 pre-competitive 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 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.