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

Accelerating Medicines Partnership®
Rheumatoid Arthritis/Systemic Lupus Erythematosus (AMP RA/SLE)
Autoimmune and Immune-Mediated Diseases (AMP AIM)

February 5, 2024

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Accelerating Medicines Partnership® Symposium

Rheumatoid Arthritis/Systemic Lupus Erythematosus (AMP RA/SLE) Autoimmune and Immune-Mediated Diseases (AIM)

Judith James, MD, PhD
Oklahoma Medical Research Foundation
for the AMP RA/Lupus and AMP AIM Networks
Why an Autoimmune/Immune-Mediated Disease Focused AMP?

- Arthritis leading cause of disability in the US
- Autoimmune diseases afflict up to 1 in 8 US women
- Encompass more than 100 lifelong and costly diseases
  - 2001 data: 20M people with 29 AiD, treatment cost $168 Billion
  - SLE still a top 10 medical cause of death in women (15-45), especially in women of color
- Difficult to diagnose, treatments are toxic and currently impossible to cure
- Autoimmunity and autoimmune diseases are on the rise (even before COVID)
  - > 50% increase in ANAs < 30 years, but > 300% in teenagers
Aims & Goals of AMP RA/Lupus Program

• Molecularly deconstruct and compare two major autoimmune diseases, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

• Define shared and disease-specific biological pathways to identify relevant drug targets for the treatment of RA, lupus and related autoimmune diseases.

• Achieve an enhanced systems-level understanding of gene expression and signaling in target tissues and cells from affected organs and peripheral blood.

• Establish a unique and novel infrastructure that uses a collaborative trans-disciplinary, integrated team science approach, to test high impact ideas.

• Tissue is the Issue!
AMP RA/Lupus Program Research Phases

Research Phase 0
- Develop Standardized Methods & Technology Selection
  - Test different means of obtaining and preparing tissue and initial analytic runs
  - Small number of samples

Research Phase I
- Disease-specific Expression Profile of Tissue Cells
  - Compare healthy with disease
  - Small number of homogeneous samples
  - Sufficient data to establish feasibility and design of Phase II

Research Phase II
- Patient Characterization
  - Cohorts:
    - RA: 90, Lupus: 200
    - Exceeded enrollment
    - RA: responder/non-responder status, early/established disease, comparison among DMARD treatments
  - Analyze responder / non-responder status, types of kidney disease, before/after treatment

Method Development and Optimization
Accelerating Medicines Partnership® (AMP®) RA/SLE

Primary Network Sites

• Albert Einstein College of Medicine – Chaim Putterman, MD
• Brigham and Woman’s Hospital – Michael Brenner, MD
• Broad Institute – Soumya Raychaudhuri, MD, PhD
• Feinstein Institute for Medical Research – Betty Diamond, MD; Peter Gregersen, MD
• Hospital for Special Surgery – Vivian Bykerk, MD; Lionel Ivashkiv, MD
• Johns Hopkins School of Medicine – Michelle Petri, MD
• New York University School of Medicine – Jill Buyon, MD
• Oklahoma Medical Research Foundation – Judith James, MD, PhD; Joel Guthridge, PhD
• Rockefeller University – Thomas Tuschi, PhD
• Stanford University – Bill Robinson, MD; PhD, PJ Utz, MD
• University of California, San Francisco – David Wofsy, MD
• University of Colorado – V. Michael Holers, MD
• University of Pittsburgh – Larry Moreland, MD
• University of Rochester – Jennifer Anolik, MD, PhD

Funding Partners

Supported by the Accelerating Medicines Partnership® Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP® RA/SLE) Program. AMP is a public-private partnership created to develop new ways of identifying and validating promising biological targets for diagnostics and drug development.
Vision AMP AIM

To provide pre-eminent disease-specific and trans-immune mediated disease datasets to allow reconstruction of novel disease-centric and common pathway-driven target organ damage while building shared clinical, technologic and analytic approaches to move these and related disease fields forward and identify crucial targets for therapeutic interventions.

- Systemic Lupus Erythematosus: 9:1
- Sjogren’s Disease: 7:1
- Rheumatoid Arthritis: 3:1
- Psoriatic Spectrum Disorder: 1.5:1

Female: Male
AMP® AIM: Expanded interrogation of infiltrating and resident cells interactions causing tissue end-organ damage in multiple inflammatory diseases & providing new targets and pathways for drug development

- Discover how innate and adaptive cells of the immune system and tissue resident cells interact to drive inflammation and clinical disease
- Map anatomic locations, neighborhood pathology, cell-to-cell and receptor-to-ligand interactions
- Define how these cell and molecular pathologies are common across diseases and across tissues

- Advance understanding of how cell-cell interactions activate specific mechanisms of disease through spatial analytics
- Accelerate the discovery of new mediators of disease through “interactome” analytics
- Systems level integration across tissues and diseases combining the above with epigenetics and genomics to Identify target molecules in causative pathways of disease
Amalgamate spatially-Informed AMP AIM Tissue and Blood Interrogations to identify shared and unique determinants of early disease

Spatial Multiomics

Single Cell Transcriptomics

Serial IHC

Imaging Mass Cytometry

Mass Cytometry

Metabolomics

Microbiome

Clinical Data
**AMP AIM Disease Team Protocols**

**Cohort 1:**
Newly dx RA, treatment naïve (MTX< 2 weeks)

**Cohort 2:**
MTX Incomplete Responders, bDMARD naïve

**Comparison Cohort:**
Refractory RA, failed 2 biologics or JAK inhibitors in addition to MTX

**Cohort 1:**
Cross-sectional, new participants with signs and symptoms suggestive of SjD with or without a previous diagnosis of SjD

**Cohort 2:**
Follow-up of a subset of participants previously enrolled in either the SICCA or OMRF cohorts 10 to 15 years earlier

**Cohort 1:**
PSO and PSA subsets including treatment naïve

**Cohort 2:**
Longitudinal follow up of PSO and PSA treatment groups to compare responders vs non-responders

**Cohort 3:**
PSO patients at-risk for PSA, cross sectional and longitudinal

**KP1:** Low proteinuria initial renal biopsies

**KP2:** Established LN and treatment non-response

**SP1:** Cross-sectional evaluation of lesional vs non-lesional CLE subsets

**SP2:** Longitudinal follow up of lesional vs non-lesional response to SOC therapies

**Trans-disease: Microbiome (gut, skin) - MicroTeach**
Team Science Leadership Scholars Program

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the NIH Office of Research on Women’s Health (ORWH) and the Office of Data Science Strategy (ODSS) partnered to launch this pilot program in 2022 which is designed to create a more robust cadre of researchers dedicated to women’s health research.

The goals of this program:

• Improve women’s health by supporting the research and development of women scholars who specialize in women’s health studies.

• Develop scholars' skillsets in team science through immersive cross-sectoral collaborative experiences.

• Enhance scholars' leadership and mentorship experiences by expanding networks outside of the current place of employment so they serve as effective mentors for future generations of team scientists.

• Integrate new emerging leaders with unique scientific questions and approaches including data science analysis that can leverage AMP AIM infrastructure, samples, cohorts and/or data.

• Integrate and synergize the scholars’ work with the AMP AIM Network scientific goals.

LSP 1.0

• RFA released: November 9, 2022, Application deadline: February 21, 2023
• Over 30 inquiries, 12 applications received
• 6 external reviewers, top 2/3 advanced to 5 internal reviewers
• Review criterion:
  • Candidate qualifications
  • Potential for Team Science Leadership role
  • Proposed study timeline
  • Institutional commitment
  • Significance and innovation of project
  • Scientific environment
• $500K total project cost over 2 years

LSP 2.0

• RFA released: November 21, 2023
• Application deadline: April 1, 2024
Team Science Leadership Scholars Program

Sheila Angeles-Han, MD  
Pediatric Rheumatology  
Cincinnati Childrens  
JIA/RA  
“Towards Personalized Use of MTX for the Treatment of JIA-Associated Uveitis”

Monica Guma, MD  
Rheumatology  
UCSD  
RA/PsA  
“Integrated scRNAseq and Lipidomics Reveals New Synovial Pathogenic Pathways and Therapeutic Targets”

Sara McCoy, MD  
PhD  
Rheumatology  
UW School of Medicine & Public Health  
SjD  
“Sjögren’s Disease Salivary Gland Mesenchymal Stromal Cells: Defining the Transcriptional and Epigenetic Landscape Changes in Health and Disease”

Paula Ramos, PhD  
Human Genetics  
MUSC  
Autoimmune Diseases  
“Cell Type-specific Epigenetic Effects Of Social Exposures On Autoimmune Disease Severity”

April Barnado, MD  
Rheumatology  
VUSC  
SLE  
“Quantifying the Predictive Value of Clinical, Genetic, and Molecular Data for Treatment Response In Patients with Systemic Lupus Erythematosus Nephritis”

Kelly Ruggles, PhD  
Computational Biology  
NYU School of Medicine  
SLE  
“Developing and Leveraging Multi-Omic Approaches to Elucidate Early Disease Pathogenesis in Lupus Nephritis”
Opportunity Funds:
Evaluate new technologies or analytic approaches; pilot approaches for potential use in the Network; new infrastructure to facilitate the work of the Network (Gudjonsson, Fava, Wei/Gravallese, Guthridge, Baer/Izmirly)

NIH Pain Supplement Awardees:
Award 1 (Drs. Buyon and Ogdie leads):
• Specific Aim 1. To delineate pain phenotypes in patients with SLE, PSD, and SjD.
• Specific Aim 2. To assess differences in skin biomarkers and functional brain MRI among patients with SLE, PSD, and SjD with and without concomitant FM or pain sensitization.

Award 2 (Dr. Anolik lead)
Specific Aim 1. To define pain phenotypes associated with peripheral and central mechanisms of pain in patients with RA and PsA.
Specific Aim 2. To identify novel mediators of pain in the RA and PsA synovium.
Accelerating Medicines Partnership® (AMP®) Autoimmune and Immune-Mediated Disease Program (AIM)

Primary Network Sites

- Brigham and Woman’s Hospital – Michael Brenner, MD
- Broad Institute – Nir Hacohen, PhD; Soumya Raychaudhuri, MD, PhD
- Hospital for Special Surgery – Laura Donlin, PhD
- Johns Hopkins School of Medicine – Alan Baer, PhD; Michelle Petri, MD
- Mount Sinai School of Medicine – Jose Clemente, PhD
- National Institute of Dental and Craniofacial Research – Blake Warner, DDS, PhD, MPH
- New York University School of Medicine – Adreiana Heguy, PhD; Jill Buyon, MD; Jose Scher, MD
- Ohio State University – Brad Rovin, MD
- Oklahoma Medical Research Foundation – Joel Guthridge, PhD; Darise Farris, PhD; Judith James, MD, PhD
- University of California, San Francisco – Caroline Shiboski, DDS, PhD, MPH; Wilson Liao, MD
- University of Colorado – Larry Moreland, MD, PhD
- University of Michigan – Lam Alex Tsoi, PhD; Johann Gudjonsson, MD, PhD; Josh Welch, MD; Xiang Zhou, PhD
- University of Pennsylvania – Alexis Ogdie, MD, MSCE; Victoria Werth MD
- University of Rochester – Christopher Ritchlin, MD, MPH; Jennifer Anolik, MD, PhD

Funding Partners

Supported by the Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Disease Program (AMP® AIM) Program. AMP is a public-private partnership created to develop new ways of identifying and validating promising biological targets for diagnostics and drug development.
Data Coordination for AMP-RA/SLE and AMP-AIM

Anna Greenwood, Sage Bionetworks

February 5, 2024
Importance of Data Sharing and Aggregation for Rare Diseases

Regulatory & Legal Definitions of Rare Diseases

- **US**
  - Rare Disease Act <200,000 patients in US
  - <6 per 10,000

- **EU**
  - EU Orphan Regulation
  - <5 per 10,000

- **Japan**
  - Legal definition is <50,000 patients in Japan or <1 per 2,500
  - <4 per 10,000

*200,000 patients per US 2019 population size of 329 million equals 6 per 10,000

https://bluematterconsulting.com/
Goals of AMP-RA/SLE and AMP-AIM

AMP-RA/SLE

- Perform molecular analyses of gene expression and signaling in specific subsets of immune cells and resident tissue cells
- Deconstruct and analyze relevant cell subsets or single cells in order to understand the mechanisms of disease

AMP-AIM

- Extend single-cell disease deconstruction approach to additional autoimmune diseases
- Leverage novel, high-dimensional research tools to uncover cellular interactions that cause inflammation, injury, abnormal function, and clinical disease
# AMP-RA/SLE and AMP-AIM Data Types

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<th>clinical</th>
<th>genotype</th>
<th>histology</th>
<th>biomarker data</th>
<th>flow cytometry</th>
<th>mass cytometry (CytOFLMC)</th>
<th>immune repertoire</th>
<th>single cell/nucleus ATAC-seq</th>
<th>single cell/nucleus gene expression</th>
<th>multiomics (CITE-seq)</th>
<th>proteomics</th>
<th>spatial transcriptomics</th>
<th>multiplex imaging</th>
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AMP-RA/SLE Phase I Data Initially in ImmPort

Accelerating Medicines Partnership (AMP)-RA/SLE

Powered by ImmPort

- 3 Studies
- 5 Types of Measurements
- 225 Participants
- 121,031 Experimental Samples
- 21,706 Downloads*

*Download counts are from individual studies as well as AllStudies downloads.

NIHME, NIH, pharmaceutical companies, and nonprofit organizations have formed the Accelerating Medicines Partnership (AMP) Rheumatoid Arthritis – Lupus Program to develop new ways of identifying and validating promising biological targets for diagnostics and drug development. An overview of the AMP Rheumatoid Arthritis – Lupus Program and its three research phases and a listing of the academic groups collaborating on the work are available.
Data Coordination Goals for AMP-AIM

- Leverage systems and processes in use for another AMP program (AMP-AD)
- Enable collaborative analysis by consortium members prior to public data release
- Create a community repository dedicated to autoimmune diseases
Sage’s Experience with Data Coordination for Rare Disease

A home for Neurofibromatosis research resources

The NF Data Portal was created to help openly explore and share NF datasets, analysis tools, resources, and publications related to neurofibromatosis and schwannomatosis. Anyone can join the NF Open Science Initiative (NF-OSI) to contribute!

PORTAL PROGRAMS AND GOALS

- **Initiatives**: 23
  - Initiatives are funded-organized programs, groups, consortia, cohorts, or awards, usually focused on a specific research area in neurofibromatosis.

- **Studies**: 232
  - Studies are hypothesis-driven projects with the goal of uncovering new knowledge about neurofibromatosis type 1, type 2, or schwannomatosis.

- **Files**: 29,063
  - Data are collected from human samples, animal models, and cell lines from a variety of assays.

- **Publications**: 219
  - Publications are preprints and peer-reviewed articles produced by NF Data Portal studies.

- **Tools**: 1,147
  - Find neurofibromatosis research tools: animal models, cell lines, genetic reagents, antibodies, and biobanks.
Evolving Data Coordination for AMP-AIM

External investigators

ARK: The Autoimmune and Related Disease Knowledge Portal

SYNAPSE

Consortium analysis

Individual Contribution Teams
Welcome to the ARK Portal

The ARK Portal hosts data generated by a network of research teams working collaboratively to deepen the understanding of Arthritis and Autoimmune and Related Diseases. It was established by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and includes data from the Accelerating Medicines Partnership® (AMP®).

Programs
Explore research Programs supported by the ARK Portal

Projects
Explore research Projects within each program

Dataset Collections
Explore Collections of data organized by topic

All Data
Explore all data in the ARK Portal.
How to navigate the portal to find data and resources

1. Use Explore Menu to select Projects, Datasets, or Data Files

2. Browse and filter to identify resources of interest
### Exploring all data files

The image shows a screenshot of a data exploration interface, likely from a database or a digital repository. The interface includes filters for data exploration, allowing users to search for specific datasets based on various criteria such as project, program, and data type. The screenshot highlights a user interface element with an arrow pointing towards a specific dataset or filter, indicating the ease of navigation and search capabilities within the platform.
Upcoming additions to the ARK Portal

New Data and Annotations

Explore Data by Participants

Explore Publications

Explore Tools
Acknowledgements: Sage Team

Data Coordination
- Tiara Adams
- Victor Baham
- Hayley Sanchez
- Amelia Kallaher
- Jessica Malenfant
- Elvira Mitraka

Portal Design and Development
- Nick Grossenbacher
- Adam Hindman
- Jay Hodgson

Funding: NIAMS supplements to grant U24 AG061340
AMP RA/SLE Network: Rheumatoid Arthritis

Michael Brenner, M.D.

Brigham Professor of Medicine, Brigham and Women’s Hospital, Harvard Medical School

AMP Symposium 2-5-2024
AMP RA/SLE Phase 2 RA pipeline: Single cell disease deconstruction consortium

Synovial biopsies (multiple sites, cryopreserved, banked)

Centralized Processing/Tissue Disaggregation

Flow sort

CITE-seq

Droplet-based cell capture (10X Genomics)

Protein library

mRNA library

Histology (Filer, Anolik) (H&E, IF, Hyperion)

Blood CyTOF (Lederer, Rao, Zhang) scRNAseq

Clinical Data Cohorts

Flow Cytometry

Sort T, B Cells

Fibroblasts

Monocytes

T cells

B cells

Bulk RNA-seq

Immune Cell Repertoire (Anolik, Rao)

Brenner lab

Zhang, Jonsson, Nathan, Millard …. Wei, Rao, Donlin, Anolik, Brenner, Raychaudhuri

Nature | Vol 623 | 616-624 (2023)
24 T cell clusters in RA synovium (94,056 cells)

- RA is a Th1 disease (No)
- RA is a Th17 disease (No)
- Major CD4 finding is expansion of Tph cells (drive B cell differentiation in the synovial tissue).

MAIT cells

T cell UMAP

Zhang, Jonsson, Nathan, Millard … Wei, Rao, Donlin, Anolik, Brenner, Raychaudhuri
Nature | Vol 623 | 616-624 (2023)

Rao DA, Front Immunol 2018


24 T cell clusters in RA synovium (94,056 cells)

- RA is a Th1 disease (No)
- RA is a Th17 disease (No)
- Major CD4 finding is expansion of Tph cells (drive B cell differentiation in the synovial tissue outside of B cell follicle.
- Major CD8 finding is that most CD8 T cells express Granzyme K (not B)


Evidence for Ectopic Lymphoid Structure formation and Extrafollicular B cell differentiation in situ in synovium

- B cells that express a family of orphan nuclear receptors, NR4A+ implicated in **ectopic lymphoid structure** development (LTα, LTβ, IL-6)
  *Meeidnu …. Anolik, 2022, Cell Reports 39, (2022)*

- Repertoire analyses of B cells finds clonal sharing between ABC, activated B cells, memory B cells and plasma cells
  *Dunlap … McDavid, Rao, Anolik, BioRxiv: https://www.biorxiv.org/content/10.1101/2023.03.18.533282v1*

**B cell UMAP**

Zhang, Jonsson, Nathan, Millard …. Wei, Rao, Donlin, Anolik, Brenner, Raychaudhuri
*Nature | Vol 623 | 616-624 (2023)*
Stratify RA patients by CTAP (Cell Type Abundance Phenotype)

Zhang, Jonsson, Nathan, Millard …. Wei, Rao, Donlin, Anolik, Brenner, Raychaudhuri

15 Myeloid clusters in RA synovium (76,181 cells)

Zhang, Jonsson, Nathan, Millard …. Wei, Rao, Donlin, Anolik, Brenner, Raychaudhuri

Nature | Vol 623 | 616-624 (2023)
Notch signaling drives inflammatory fibroblasts in RA

1,844 fibroblasts (AMP RA/SLE Consortium)


AMP RA Phase 1 Resource Paper Nature Immunology: 2019
CTAP F (fibroblast enriched) synovium linked to treatment non-response


Used AMP scRNA data converted to pseudo-bulk, to match up to bulk RNAseq in R4RA study. Then assess treatment response based on predicted CTAP.

Zhang, Jonsson, Nathan, Millard .... Wei, Rao, Donlin, Anolik, Brenner, Raychaudhuri
Nature | Vol 623 | 616-624 (2023)
Overall Outcomes:

- Stratifying RA into CTAPs (Precision Medicine for RA)
- Each CTAP made up of distinct cell types and cell states and predicts response to therapy
- Defining new pathologic cell T cell, B cell and macrophage states in each CTAP
- Role of inflammatory and destructive fibroblast states with special relevance in treatment inadequate responders
- Overall, essential role of synovial tissue interrogation in precision medicine and in deconstructing-reconstructing RA

Poster Session:
- Fan Zhang: CTAPs
- Kevin Wei: new AMP-AIM and its focus spatial transcriptomics
Mining the Fruits of the Accelerated Medicines Partnership (AMP): Clinical, Transcriptomic and Proteomic Insights in Lupus Nephritis Paving the Way to AMP AIM

February 5, 2024
Jill P. Buyon
**Phase 0**: Identify and refine the technologies to be leveraged in Phase 1.

**Phase 1**: Examine cells from blood, urine, and tissue (kidney and skin) in a limited number of patients with LN.


**Phase 2**:

a) Identify biological pathways that could serve as novel targets for therapeutic intervention.

b) Correlate cellular and molecular renal patterns with clinical response after 6 and 12 months of standard of care.

c) Identify blood and urine surrogates for renal biomarkers.

**Provide Insights into Clinical Management**
Obtaining Research Kidney Tissue was Safe: Sets Stage for AMPAIM (15 sites) (Deonaraine K, Lupus Sci Med, 2021)

N = 475 patients biopsied in Phases 0-2

449 patients with research tissue obtained
- 27 patients had possibly, probably, or definitely related AEs
  - Serious: 17
  - Requiring transfusion: 4
- 7 patients had unrelated or unlikely related AEs
  - Serious: 4
  - Requiring transfusion: 1

26 patients with no research tissue obtained
- 7 patients had possibly, probably, or definitely related AEs
  - Serious: 1
  - Requiring transfusion: 0

OVERALL 18/475 (3.8%) related SAE

* All SAE resolved except 1 cardiac arrest (unrelated)
Phase 1: Plate-Based Transcriptomic Analysis of Kidney Immune Cells
(cryopreserved tissue, CEL-Seq2, 24 LN = 3,541 cells, 10 Donors = 438 cells)

- Interferon response elevated and correlated with blood
- Cells expressed pro-inflammatory and inflammation-resolving responses
- Local activation of B cells correlated with an age-associated B-cell signature
- Evidence of progressive stages of monocyte differentiation
- Two chemokine receptors, CXCR4 and CX3CR1, were broadly expressed, implying a potentially central role in cell trafficking
Phase I: Fluidigm-Based Transcriptomic Analysis of Kidney Parenchymal Cells
(21 LN, 3 controls, 1,221 tubular cells)
(Der E, Nat Immunol. 2019, cited 138 times)

- Upregulated Type I IFN signature in tubular cells and keratinocytes of LN patients compared to controls
- High IFN and fibrotic signature in tubular cells correlated with no treatment response
- Tubular cells from mixed class LN had distinct expression profiles compared to membranous and proliferative LN
Phase 2: 369 SLE Patients with UPCR > .5 Consented

254 Eligible for Clinical Follow Up (3,6,12 months) and Transcriptomics (Class III, IV, V, mixed biopsies)

- 48 UPCR < 1 not analyzed for renal response
- 24 lost lost-to-follow-up (N=24)
- 2 repeat biopsies

180 Included in Responder Outcome Analysis UPCR > 1

Complete response (UPCR < .5, ≤ 10 mg pred)
Partial response (> 50% reduction UPCR, pred < 15mg)
No response
Phase 2: The Majority of Patients with Low Levels of Proteinuria had Clinically "Actionable" Histology: Supports the Importance of Evaluating Early Disease in AMP AIM

Carlucci P, Rheumatology, 2022
Phase 2: Both Low and High Levels of Proteinuria Associate with Increased Activity and Chronicity (Carlucci P, Rheumatology, 2022)
Phase 2: Patients with LN more often have no extrarenal manifestations and less commonly experience fatigue, pain, or impaired physical and social functioning. (Carlucci P, in revision, 2023)
Phase 2: Evaluation of Response Outcome
Demographics, Baseline Characteristics and Biopsy Class of Patients with Baseline UPCR ≥1 (Izmirly P, Arthritis Res Ther, in press)

<table>
<thead>
<tr>
<th>Sex: Female</th>
<th>156 (87%)</th>
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<tr>
<td>Age, mean (SD)</td>
<td>35.2 (11)</td>
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<tr>
<td>Ethnicity: Hispanic</td>
<td>59 (33%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>29 (16%)</td>
</tr>
<tr>
<td>Black</td>
<td>76 (42%)</td>
</tr>
<tr>
<td>White</td>
<td>53 (29%)</td>
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<tr>
<td>First biopsy</td>
<td>62 (34%)</td>
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<tr>
<td>UPCR, mean [IQR]</td>
<td>3.5 [1.6-4.4]</td>
</tr>
<tr>
<td>Serum creatinine mg/dL, mean [range]</td>
<td>1.25 [0.4-7.4]</td>
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<tr>
<td>Low C3</td>
<td>116 (65%)</td>
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<tr>
<td>Low C4</td>
<td>102 (57%)</td>
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<tr>
<td>Positive anti-dsDNA</td>
<td>124 (71%)</td>
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<td>[III]</td>
<td>30 (17%)</td>
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<td>[IV]</td>
<td>35 (19%)</td>
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<tr>
<td>[V]</td>
<td>51 (28%)</td>
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<td>3 (2%)</td>
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<td>36 (20%)</td>
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<td>[IV][V]</td>
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<td>Activity Index, mean [range] (n=143)</td>
<td>5.4 [0-18]</td>
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<tr>
<td>Chronicity Index, mean [range] (n=143)</td>
<td>3.3 [0-10]</td>
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Phase 2: Temporal Patterns in the Renal Response Status of AMP Patients

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<th>Baseline</th>
<th>Wk 12</th>
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<th>Wk 52</th>
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<tr>
<td>CR</td>
<td>0</td>
<td>19 (10.6%)</td>
<td>38 (21.1%)</td>
<td>40 (22.2%)</td>
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<tr>
<td>PR</td>
<td>0</td>
<td>22 (12.2%)</td>
<td>32 (17.8%)</td>
<td>39 (21.7%)</td>
</tr>
<tr>
<td>CR and PR</td>
<td>0</td>
<td>41 (22.8%)</td>
<td>70 (38.9%)</td>
<td>79 (43.9%)</td>
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N = 180

- Complete Response (4%)
- Partial Response
- Non Response

Sustained Complete Response

Never Responders (22%)

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<tr>
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<th>Baseline</th>
<th>Wk 12</th>
<th>Wk 26</th>
<th>Wk 52</th>
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<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>14 (11.9%)</td>
<td>27 (22.9%)</td>
<td>34 (28.8%)</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>14 (11.9%)</td>
<td>23 (19.5%)</td>
<td>30 (25.4%)</td>
</tr>
<tr>
<td>CR and PR</td>
<td>0</td>
<td>28 (23.7%)</td>
<td>50 (42.4%)</td>
<td>64 (54.2%)</td>
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N = 118

- Complete Response (7%)
- Partial Response
- Non Response

Missing data, response not determined
Phase 2: Predictors of Complete/Partial Renal Response (logistic regression)

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Odds Ratio Estimate (95% Confidence interval)</th>
<th>P value</th>
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<tr>
<td><strong>At both wk 26 and 52</strong></td>
<td></td>
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<tr>
<td>First biopsy</td>
<td>3.12 (0.89- 10.89)</td>
<td>0.075</td>
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<tr>
<td>Anti-dsDNA antibody positive at baseline</td>
<td>4.70 (1.19-18.51)</td>
<td>0.027</td>
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<tr>
<td>No Cyclophosphamide induction</td>
<td>5.08 (0.80-32.26)</td>
<td>0.084</td>
</tr>
<tr>
<td>UPCR &gt; 25% decrease from baseline to week 12</td>
<td>7.37 (2.31-23.49)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>At wk 52 only</strong></td>
<td></td>
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<tr>
<td>Anti-dsDNA antibody positive at baseline</td>
<td>2.61 (0.93- 7.33)</td>
<td>0.069</td>
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<tr>
<td>UPCR &gt; 25% decrease from baseline to week 12</td>
<td>2.61 (1.07-6.41)</td>
<td>0.036</td>
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<tr>
<td>Chronicity Index per unit decrease</td>
<td>1.33 (1.10-1.62)</td>
<td>0.003</td>
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<tr>
<td>UPCR &gt; 3 at baseline</td>
<td>3.71 (1.34-10.24)</td>
<td>0.012</td>
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</table>
Phase 2: In 123 AA LN Patients, APOL1 G1/G2 Risk Variants Did not Associate with Class, Activity, Chronicity, Baseline Serology, or Response but with Chronic Kidney Disease (Carlucci P, ACR abstr, 2023)

<table>
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<tr>
<th>Clinical Characteristic</th>
<th>0 RV N=56</th>
<th>1 RV N=52</th>
<th>2 RV N=15</th>
<th>p-value</th>
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<tr>
<td><strong>Class, %</strong></td>
<td></td>
<td></td>
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<td>0.53</td>
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<tr>
<td>Mesangial</td>
<td>11</td>
<td>6</td>
<td>20</td>
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<tr>
<td>Membranous</td>
<td>30</td>
<td>37</td>
<td>20</td>
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<tr>
<td>Proliferative</td>
<td>34</td>
<td>23</td>
<td>27</td>
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<tr>
<td>Mixed</td>
<td>20</td>
<td>27</td>
<td>33</td>
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<tr>
<td>Advanced Sclerosing</td>
<td>5</td>
<td>8</td>
<td>0</td>
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<tr>
<td><strong>dsDNA Positive, %</strong></td>
<td>69</td>
<td>62</td>
<td>50</td>
<td>0.42</td>
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<tr>
<td>Low C3, %</td>
<td>52</td>
<td>49</td>
<td>43</td>
<td>0.83</td>
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<tr>
<td>Low C4, %</td>
<td>48</td>
<td>47</td>
<td>43</td>
<td>0.94</td>
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<tr>
<td>Activity, median</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>0.76</td>
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<tr>
<td>Chronicity, median</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>0.35</td>
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| Response Week 52, %            |           |           |           | 0.47    |
| Complete or Partial Response   | 42        | 56        | 36        |         |
| No Response                    | 58        | 44        | 64        |         |
Proliferative lupus nephritis is characterized by upregulated neutrophil/myeloid activity signature.

IL-16, CD163, PRTN3 are urine proteins among the most highly correlated to the LN histologic activity index.

Decreasing uCD163 outperforms uPCR in tracking response (by 3 months).

Phase 2: Urine Proteomics Identify Class, Provide Biomarkers of LN Activity and Track Response
(Fava, A., JCI Insight 2020, Arthritis 2022, JCI Insight 2024)
Phase 2: Kidney Pipeline (N=155) with Establishment of a Dataset that Builds on and Expands Phase I Analysis

Sample collection → Cell dissociation → 10X V3 → Deplete MT reads (DASH) → scRNAseq data

Phase 1
- 24 renal biopsies
- 1,318 tubular cells

Phase 2
- 155 renal biopsies
- 408,915 tubular cells

- 159,761 Proximal Tubule
- 130,512 Loop Henle
- 118,642 Distal Tubule
- 8,976 glomerulus
- 48,435 Interstitial
- 36,131 T/NK
- 24,084 Myeloid
- 12,644 B/Plasma

Nuclei isolation → 10X V3 → snRNAseq
Phase 2: “Injury Associated”* Macrophages Increase with Lupus Nephritis Activity Index and are Enriched in Class IV

UMAP: Infiltrating LN kidney myeloid cells (annotated based on transcriptional similarity to known blood expression)

*SIGLEC1, SPP1, TREM2, LPL, CTSA, CTSB, FABP5
inferred trajectories suggest that injury associated macs derive from infiltrating CD14, CD16, and resident populations
Phase 2: “Injury Associated” Macrophages are Expanded in Class II Lupus Nephritis and Associate with Fibroblasts

(Schwetar J, Ruggles K, ACR abstract, 2023)

Injury Associated macrophages significantly expanded in de novo Class II and Class III, IV and mixed

p-value = 5 x 10^{-4}

spearman correlation = 0.76
Phase 2: Chronicity Index Associates Negatively with Cytotoxic T Lymphocytes in Blood and Kidney from Patients with LN

Decreased in LN biopsies with high chronicity

Increased in LN biopsies with high chronicity

Single-Cell Association with Chronicity in LN
FDR < 0.05,
p = 0.006

(Gurajala S, provided)
Blood Immunophenotyping Identifies Distinct Kidney Histopathology and Outcomes in AMP *(Horisberger, ACR, 2023, under review)*

Mass cytometry immunophenotyping of PBMCs in 145 LN AMP patients and 39 healthy.

**5 cytometric parameters:** type I IFN ((MX1, ISG15, SIGLEC-1), proliferative T-B cells, non-proliferative granzyme B+ T cells, altered naïve B cells, and low-density neutrophils

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<th>G0 39 healthy</th>
<th>G1 46 LN</th>
<th>G2 46 LN</th>
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<tr>
<td>IFN score</td>
<td>low</td>
<td>high</td>
<td>intermediate</td>
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<td>Proliferative T-B</td>
<td>low</td>
<td>intermediate</td>
<td>high</td>
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<tr>
<td>Cytotoxic T</td>
<td>low</td>
<td>Intermediate</td>
<td>high</td>
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<tr>
<td>Proliferative LN</td>
<td>39%</td>
<td>67%</td>
<td>85%</td>
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<tr>
<td>Activity Index</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Chronicity Index</td>
<td>6</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Complete Response</td>
<td>18%</td>
<td>18%</td>
<td>41%</td>
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AMP AIM Kidney Project 1
Study Early Disease

1. Patients with low-grade proteinuria who progress have repeat kidney biopsy and treated late

2. Patients with low-grade proteinuria that never progress-not treated

3. Patients with low-grade proteinuria, actionable LN histology treated early

4. Patients with low-grade proteinuria that never progress-not treated

5. Patients with low-grade proteinuria who progress have repeat kidney biopsy and treated late

Untreated UPCR 0.25-0.499

1 NYU Class III, MMF
3 JHU Class III, MMF
1 JHU Class V, MMF

No Actionable LN 
No Treatment
1 JHU Class II 1 NYU Class II
1 JHU Class I 1 JHU no LN

Actionable LN 
Treatment
2 NYU Class III, MMF
3 JHU Class III, MMF
1 JHU Class V, MMF

Treatment at physician’s discretion

Visit 1
1 JHU Class II
1 NYU Class III, MMF

Visit 2
1 NYU Class III, MMF

Visit 3
1 NYU Class III, MMF

Visit 1 3 mos
1 NYU Class III, MMF

Visit 2 6 mos
1 NYU Class III, MMF

Visit 3 12 mos
1 NYU Class III, MMF

UPCR>0.5
Biopsy

UPCR>0.5
Biopsy

UPCR>0.5
Biopsy

Screening

Baseline Visit

No Biopsy

Biopsy

Treatment at physician’s discretion

DAY -28 to -1
DAY 0
Month 3
Month 6
Month 12

Enrollment as of January 31, 2024
Where We are Headed…… AIMP AIM single-cell Data to Infer Cell-type in a Spatial Context in LN Class II Progression (provided by J Gudjonsson, A Tsoi, B Rovin)

AMP Single-cell kidney data

CosMX spatial data

Spatial gene expression

Spatial marker genes per cell type

Cell type assignment

PTGDS (podocytes)

Class II

Class V

Class IV/V

Thick ascending limb of Loop of Henle

CD8

endothelium

urothelium

myofibroblast

podocyte

principal cell

neutrophil

connecting tubule

proximal tubule

Thick ascending limb of Loop of Henle

NK

CD4

endothelium

urothelium

myofibroblast

podocyte

principal cell

neutrophil

connecting tubule

proximal tubule

Thick ascending limb of Loop of Henle

NK

CD4

endothelium

urothelium

myofibroblast

podocyte

principal cell

neutrophil

connecting tubule

proximal tubule
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<td>Northwell Health – Richard Furie</td>
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<td>University of California Los Angeles – Maureen McMahon, Jennifer Grossman</td>
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<tr>
<td>UCSF</td>
<td>Ann Davidson</td>
<td>University of California San Diego – Kenneth Kalunian</td>
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<tr>
<td>Lupus Nephritis Trial Network</td>
<td>David Wofsy</td>
<td>University of California San Francisco – Maria Dall’Era</td>
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<td>Maria Dall’Era</td>
<td>University of Cincinnati- David Hildeman</td>
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<td>University of Michigan - Matthias Kretzler, Celine Berthier</td>
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<td>Chaim Putterman</td>
<td>Jessica Li, Mimi Kim</td>
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<td>Jessica Li</td>
<td>Kristina Deonaraine, Devyn Zaminski, Katie Preisinger, Brooke Cohen</td>
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<td></td>
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<td>Wade DeJager, Philip Carlucci</td>
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</table>
Accelerating Medicines Partnership®
Autoimmune and Immune Mediated Diseases (AIM)

Sjögren’s Team for Accelerating Medicines Partnership (STAMP)

Caroline H Shiboski, UCSF PI for STAMP
AMP Symposium, February 5, 2024
Disclosures

- I am a consultant for Al Therapeutics, unrelated to Sjögren’s disease
- I have no conflict of interest related to this presentation
# STAMP: Multidisciplinary Multicenter Team

<table>
<thead>
<tr>
<th>UCSP - Contact</th>
<th>OMRF</th>
<th>JHU</th>
<th>NIDCR</th>
<th>UCB</th>
<th>NYU</th>
<th>NHGRI/NIAMS</th>
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<tr>
<td>MPI</td>
<td>Caroline SHIBOSKI</td>
<td>Danie PARRIS</td>
<td>Alan BAER</td>
<td>Blake WARNER</td>
<td>Nancy Rennert (site lead)</td>
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<tr>
<td>Co-Investigators / CRCs</td>
<td>Kimberly Taylor</td>
<td>Jamie Gowan</td>
<td>Bilal Khokher</td>
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<td></td>
<td>Jameselen Chido Ye</td>
<td>Stephen Shubinski</td>
<td>John Gonzalez</td>
<td>Ava Wu</td>
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<td>Kanada Chakravarti</td>
<td>Richard Jordan</td>
<td>Francis Quinlanilla (CRC)</td>
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## Areas of Research Focus

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<th>Oral Medicine</th>
<th>Clinical Ophthalmology</th>
<th>Oral Pathology</th>
<th>Epidemiology</th>
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## Collaborators

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<tr>
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<td>Nancy Rennert (site lead)</td>
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<td>Lisa Barcellos</td>
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## Scientific Advisor

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## Advocacy

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## Women’s Leadership Scholar

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**STAMP SPECIFIC AIMS**

**Aim 1: Planning Phase**

Develop 5-year scientific research agenda + SOPs for phenotyping participants with SjD

**Aim 2: Pilot Phase**

- Evaluation of clinical assessments/sample procurement SOPs
- Training/calibration across recruitment sites
- Preliminary analyses of molecular and clinical data to plan deconstruction-reconstruction model for SjD

**Aim 3: Scale up Phase**

Implement standardized clinical research protocols across sites and molecular deconstruction-reconstruction approach to:

- Understand phenotypic and molecular heterogeneity of SjD
- Understand disease mechanisms inherent to progression from non-SjD to SjD, and from early to advanced SjD
- Identify therapeutic targets to stabilize early disease and reverse/improve advanced disease
- Understand disease mechanisms and molecular overlap between SjD and SLE (and RA)
### Aim 1. Prediction of SjD development and progression in LSG and systemic disease:

Recall 10-18 yr follow-up cohort (SICCA and OMRF) with 1/1 SjD/non-SjD ratio

To explore molecular changes over time within LSG (in SjD development and progression)

To test hypotheses that specific phenotypic features may be associated with progression from non-SjD to SjD, or with worsening of disease

### Aim 2. Interactions between immune cells and glandular secretory/ductal cells and elucidation of SjD molecular and phenotypic heterogeneity using multi-omic data:

**Impact of infiltrate on glandular function/cellularity/phenotype** among participants with “pure” SjD (no other SARD) and healthy controls

**Heterogeneity in SjD**: associations between molecular co-variates of SjD (LSG spatial transcriptomics, and PBMC protein and autoantibody profiling) and phenotypic features of disease activity and damage (pure SjD; symptomatic and healthy controls; recalled SjD and non-SjD; SjD/SLE and SjD/RA)

### Aim 3. Determinants of glandular tropism

Compare Ro+ SjD vs. Ro+ SLE with or w/o gland involvement

Potential determinants: genetic effects (glandular eQTLs); specific self-antigens (TCR/BCR profiling; blood/saliva autoantibodies); non-self-antigens (virome; microbiome); and sex hormones
### STAMP Study Design and Inclusion Criteria

- **Cross-sectional study:** new participants with signs/symptoms suggestive of SjD; and healthy controls
- **Follow-up study:** participants enrolled in SICCA/OMRF 10-18 yrs earlier

<table>
<thead>
<tr>
<th>STAMP Main/New Cohort (N=300)</th>
<th>STAMP Follow-up Cohort (N=185)</th>
<th>STAMP SjD-SLE Cohort (N=20)</th>
<th>Healthy Controls (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one of the following:</td>
<td>SjD (N=90) or non-SjD (n=95) per 2016 ACR-EULAR Classification criteria 10-18 years prior</td>
<td>Meet 2016 ACR-EULAR classification criteria for SjD</td>
<td>Age and sex matched to SjD participants</td>
</tr>
<tr>
<td>- Symptom of dry eyes/mouth (+ response to AECG Qs)</td>
<td>- Previous participation in either the SICCA or OMRF cohorts with full evaluation, including minor salivary gland biopsy</td>
<td>- Meet SLE classification criteria</td>
<td>- To be recruited from sites and NIDCR</td>
</tr>
<tr>
<td>- Previous dx of SjD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bilateral parotid enlargement consistent with SjD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Multiple cervical or incisal dental caries (absence of other risk factors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Abnormal serology suggestive of systemic autoimmune disorder (elevated RF, ANA (&gt;1:320 titer), anti-Ro/SSA)</td>
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<td></td>
</tr>
<tr>
<td>18 years of age or older; able and willing to provide consent</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

---

**STAMP SjD-SLE Cohort (N=20)**
- Meet 2016 ACR-EULAR classification criteria for SjD
- Meet SLE classification criteria

**Healthy Controls (N=63)**
- Age and sex matched to SjD participants
- To be recruited from sites and NIDCR

---

**FNIH**

**AMP AIM**
**STAMP Phenotypic Data / Tests / Specimens**

### Questionnaires
- Demographic/Hx (social, family, reproductive, QoL, sicca symptoms, fatigue, depression); **ESSPRI**
- Medical Hx / Review of systems / Medications /COVID-19-related hx

### Oral / Salivary
- Unstimulated whole & stimulated parotid/SM flow
- LSG biopsy
- **Salivary gland ultrasound**

### Ocular
- Schirmer I; TBUT
- Ocular surface stain with lissamine green & fluorescein

### Rheumatologic Assessment
- Musculoskeletal; skin; thyroid; abdomen; lymph node exams; **ESSDAI**
- Local clinical labs (CBCdiff; CMP chem; ESR; CRP; HCV; UA)
- Central (TRG) Immunology Labs*

### Specimen Collection
- Unstimulated whole saliva
- Stimulated parotid and submd gland saliva
- LSG (FFPE and frozen)
- Peripheral blood (Whole blood; Serum; PBMCs)
- Tears
- Conjunctival imprint

* (e.g., anti-SSA/B with Ro52 and Ro60; RF and CCP; ANA titers; Bioplex 2200 ANA panel; ENA for SLE, Myositis, scleroderma; IgG, IgA, IgM levels, C3, C4; and SARS-CoV2 N-protein ELISA)
STAMP Planning and Pilot Phases Completed

- Pilot 1A: SjD Clinical Assessments, Sample Procurement, Training / Calibration
  - SOPs, CRFs, MOPs finalized and tested across 5 STAMP clinical sites
  - Training/Calibration: ESSDAI; SGUS (Rheum); LSG Focus score (Oral pathologists)
  - Data Safety and Monitoring: DSMP approved by NIAMS; NIDCR; Safety Officer (SO) identified/assigned

- Pilots 1B-1D: Tissue-focused (LSG) and comparing various protocols for
  - 1B - cryopreservation, dissociation, and logistics for central LSG processing using 10X 5' and 3' scRNA-seq Chemistries (Lessard/Warner labs)
  - 1C - LSG fixation and spatial platforms
    - Xenium and CosMx comparative studies performed on LSG sections (n=2)
    - Customized panels for pilot spatial transcriptomics constructed using Warner Lab 3’ scRNAseq data shared with the TRC and the Spatial Technology Cores
  - 1D - feasibility of using new 10X Genomics technology (enables scRNA-seq analysis from FFPE LSGs) to assess historical (5-18 year old) FFPE-preserved LSG samples from SICCA and OMRF cohorts
## STAMP Cohorts  Actual and Planned Recruitment

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>UCSF/UCB</th>
<th>JHU</th>
<th>OMRF</th>
<th>NIDCR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>As of 01/30/2024</td>
<td>26</td>
<td>26</td>
<td>28</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>Projected in Yr3</td>
<td>85</td>
<td>72</td>
<td>59</td>
<td>16</td>
<td>232</td>
</tr>
<tr>
<td>Projected in Yr4</td>
<td>93</td>
<td>78</td>
<td>65</td>
<td>16</td>
<td>252</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>176</td>
<td>152</td>
<td>36</td>
<td>568*</td>
</tr>
</tbody>
</table>

* Distribution by cohort:

- **300** New participants
- **185** Follow-up (10-18-yr; SICCA/OMRF)
- **63** Healthy controls
- **20** SjD/SLE
Accelerating Medicines Partnership® (AMP®) Autoimmune and Immune-Mediated Disease Program (AIM)

**Primary Network Sites**
- Brigham and Woman’s Hospital – Michael Brenner, MD
- Broad Institute – Nir Hacohen, PhD; Soumya Raychaudhuri, MD, PhD
- Hospital for Special Surgery – Laura Donlin, PhD
- Johns Hopkins School of Medicine – Alan Baer, PhD; Michelle Petri, MD
- Mount Sinai School of Medicine – Jose Clemente, PhD
- National Institute of Dental and Craniofacial Research – Blake Warner, DDS, PhD, MPH
- New York University School of Medicine – Adreiana Heguy, PhD; Jill Buyon, MD; Jose Scher, MD
- Ohio State University – Brad Rovin, MD
- Oklahoma Medical Research Foundation – Joel Guthridge, PhD; Darise Farris, PhD; Judith James, MD, PhD
- University of California, San Francisco – Caroline Shiboski, DDS, PhD, MPH; Wilson Liao, MD
- University of Colorado – Larry Moreland, MD, PhD
- University of Michigan – Lam Alex Tsoi, PhD; Johann Gudjonsson, MD, PhD; Josh Welch, MD; Xiang Zhou, PhD
- University of Pennsylvania – Alexis Ogdie, MD, MSCE; Victoria Werth MD
- University of Rochester – Christopher Ritchlin, MD, MPH; Jennifer Anolik, MD, PhD

**Funding Partners**

Supported by the Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Disease Program (AMP® AIM) Program. AMP is a public-private partnership created to develop new ways of identifying and validating promising biological targets for diagnostics and drug development.
**ELLIPSS: AMP AIM Psoriatic Disease Team**

**Principal Investigators**
- Christopher Ritchlin
- Alexis Ogdie
- Johann Gudjonsson
- Wilson Liao
- Jose U. Scher

**Co-investigators**

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- Bonnie Elewski UAB
- Shruti Naik NYU
- Andrea Niemann NYU
- Alex Tsoi Michigan

**Rheumatology**
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- Eric Ruderman Northwestern
- Rebecca Haberman NYU
- Monica Guma UCSD
- John Giles Columbia
- Lianne Gensler UCSF
- Ken Saag UAB
- Michelle Kahlenberg Michigan

**Synovial biopsy**
- Darren Tabechian URMC
- Norm Madsen URMC
- Art Mandelin Northwestern
- L. Geraldina-Pardillo Columbia
- Abba Singh UCSD

4 patient research partners
Psoriasis and Psoriatic Arthritis (PsA):
Unique research opportunity

- **Psoriasis** is one of the most common immune-mediated inflammatory skin diseases, affecting 3% of population

- **PsA** is a form of arthritis that occurs in 30% of people with psoriasis and is characterized by joint pain, stiffness, swelling and deformity

- **Unmet needs**
  - Understand immunoendotypes of psoriatic disease (psoriasis and PsA)
  - “Transition window” to discover new diagnostics and therapeutics

Scher JU et al., *Nature Rev Rheum*; 2019
ELLIPSS: 3 fundamental questions in Psoriatic Disease

1. What are the **key immune and effector cells** in the **skin and joints** that promote **specific phenotypes**?

2. Can we define the cellular and molecular signatures of **remission** and **treatment response** in PsO and PsA?

3. How can we characterize host, environmental (e.g., microbial), and other factors that contribute to the **transition from PsO to PsA**?
**ELLIPSS**: Discovering Novel Targets in Psoriatic Disease – scRNA-seq, Microbiomics and Spatial Transcriptomics

**Single-Cell RNA seq**
examines gene expression of individual cells in tissue

**Spatial transcriptomics**

**Psoriasis**
Swab
Biopsy

**Psoriatic Arthritis**

**Skin Microbiomics**
looks at abundance of all microbes in the skin surface

**PBMCs**

**Synovium**

**Spatial transcriptomics**
Non-lesional and lesional skin
ELLIPSS: Nanoarthroscopy to enhance Synovial Sampling

- First medical-grade, single-use chip-on-tip NanoScope system
- Combines latest technology in 1mm-imaging sensors with Nano arthroscopy 2mm-instrumentation
- Designed for precise, atraumatic insertion into joint spaces for efficient resection of synovium under local anesthesia
ELLIPSS: Spatial Transcriptomics of Healthy and Inflamed Skin

N=25 healthy, lesional, and non-lesional Patient biopsies

Lesional

Non-lesional

Healthy

Psoriasis

Castillo, Sidhu et al; Gudjonsson, Ritchlin, Scher and Naik; *Science Immunology* 2023
Thank You

**AMP AIM ELLIPSS Exec. Committee:**
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Johann Gudjonsson, MD, PhD
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Ricardo Cibotti, PhD
Disease Teams Investigators
Technology Core Investigators
System Biology Core Investigators
Funding partners
Patients!
Translating AMP’s Success into New Medicines

AMP Symposium
05 February 2024

Marc C. Levesque, MD, PhD
VP, Merck Immunology Discovery
MRL Cambridge Site Head
Scientific support for **Basic Science**: *Development of REAP-Seq*

Multiplexed quantification of proteins and transcripts in single cells

Vanessa M Peterson, Kelvin Xi Zhang, Namit Kumar, Jerelyn Wong, Lixia Li, Douglas C Wilson, Renee Moore, Terrill K McClanahan, Svetlana Sadekova & Joel A Klappenbach

**Affiliations | Contributions | Corresponding author**

*Nature Biotechnology* (2017) | doi: 10.1038/nbt.3973
Received 14 June 2017 | Accepted 24 August 2017 | Published online 30 August 2017

**REAP-Seq Workflow**

(RNA expression and protein sequencing (REAP))

**DRUG-Seq**

**Spatial Transcriptomics**

**Optical Pooled Screening**
Scientific support for New Drug Discovery: Targeting inflammatory fibroblasts and macrophages in RA synovium

Inflammatory Fibroblasts

Inflammatory Macrophages

Scientific support for Clinical Science: IL-2 mutein clinical trial in SLE patients

A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-6194 in Adult Participants With Systemic Lupus Erythematosus (NCT06161116)

• The MOA behind the biased IL-2Ra agonist (IL-2 mutein; MK-6194) program is to preferentially activate/expand regulatory T cells to restore immune homeostasis.

• Data from AMP SLE patient cohorts were leveraged to address the question: Is there evidence for a dysregulation in Tregs among SLE patients, to inform on whether SLE could be a relevant disease indication for a biased IL-2Ra agonist?

  ➢ The total numbers of circulating CD4+ Tregs and “naïve” Tregs were found to be elevated in the AMP SLE patient cohorts compared to normal healthy donors.

  ➢ The number of functional “effector” Tregs were significantly decreased in SLE patients along with significant decreases in expression of Treg functional markers (e.g. CD25/IL-2Ra, HLA-DR, CXCR3+).

• Collectively, the data suggest that there is a dysregulation in the Treg compartment in SLE patients and provides biological rationale for SLE as an indication to pursue with a biased IL-2Ra agonist – and/or other MOAs which would enhance Treg function.
Accelerating Medicines Partnership®
Rheumatoid Arthritis/Systemic Lupus Erythematosus (AMP RA/SLE)
Autoimmune and Immune-Mediated Diseases (AMP AIM)

Rab Prinjha, Ph.D., Vice President and Head of Adaptive Immunity and Immuno-epigenetics Research Unit, GSK

February 5, 2024
Impact of AMP-RA-SLE partnership across GSK in numbers - Thank you AMP!

Profound impact on targets, technologies, therapeutics and talent progression

200+ Target triage packages

16+ Target progression packages

3+ Target prioritization efforts

1+ New target ID effort

5+ Single cell capability acceleration

6+ Disease strategy informing insights

Deep subtyping for new target ID

Prototyping of single cell visualization capabilities

Disease Tissue Enrichment

Genetics-driven cell type prioritisation

Linking cell subtype abundance to disease activity

Assessing gene expression and co-expression across cell types

Disease activity (SLEDAI)

Fraction cDC (of myeloid)
The Patient Voice

Mary Collins, PhD
Lupus Research Alliance SAB member
Patients have been amazing contributors to the AMP RA/SLE and AIM studies!

- **475 SLE patients** consented for kidney biopsies in AMP RA/SLE through Phases 0-2.
- **205 RA/OA patients** consented for synovial biopsies, arthroplasty or synovectomy samples through Phases 0-2.
- **Many of these SLE and RA patients** also donated blood and urine samples to AMP RA/SLE.
- **103 tissue samples** have been donated by patients across AMP AIM to date, along with matched blood samples. Recruitment is ongoing.
We asked our Patient Advocacy Partners: What inspires patients to contribute to medical research?

- Patient Advocacy Organizations web sites have information about clinical trial participation.

- Patient Advocacy Organizations enabled studies to explore factors influencing patient participation in clinical trials.
Patients highlighted reasons to participate in survey results and testimonials

• Patients highly valued input from their physicians in providing background information and in helping them make their decision to participate.

• Patients wanted to contribute to research, to find a cure and to help future patients also afflicted with their disease.
Are we effectively communicating AMP study findings to participating patients?

- Web pages for Patient Advocacy organizations can be a major source of information for patients, and include summaries of AMP study outcomes. (excerpt from LRA website)

Lupus Research Alliance Congratulates NIH on 5-Year AMP Success
February 28, 2019

Accelerating Medicines Partnership Completes Key Phase
September 24, 2019

LRA Highlights Groundbreaking Lupus Research at ACR Convergence 2023
November 6, 2023
Feedback to patients: how can we do better?

• Partner with Advocacy Organizations to enhance information on their web sites about AMP research studies and clinical trials
  • Patient testimonial videos on their experience in joining AMP studies and trials
  • Summaries of research or trial results, emphasizing research advances and patient impact
  • Share videos summarizing relevant research conference highlights from AMP
  • Links to scientific publications for patients who want the details

• Can individual patient information be shared with patients?
  • As aspects of disease heterogeneity and response to therapy are uncovered, can patients find out how this might affect them personally?
Congratulations to the entire AMP RA/SLE and AIM Teams, especially our patients!
Accelerating Medicines Partnership®
Rheumatoid Arthritis/Systemic Lupus Erythematosus (AMP RA/SLE)
Autoimmune and Immune-Mediated Diseases (AMP AIM)

AMP Symposium

February 5, 2024