FNIH AMP®AIM Research Project and Sjögren's Update

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Janet Church
President and CEO of the Sjögren's Foundation

Introduction

The Sjögren's Foundation is proud to participate in and support the Foundation for the National Institutes of Health (FNIH) Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP®AIM) collaborative. This, and other research managed by the FNIH are partnerships between the public (NIH), industry (pharmaceutical companies and other related businesses), and patients and the advocacy organizations who represent them, such as the Sjögren's Foundation — which ensures the patient voice is an influential part of the research process.

Historically, we know that Sjögren's is behind other autoimmune diseases in terms of research funding and existing datasets. In response to this, the Sjögren's Foundation believed it was important to support this project at the Steering Committee level, giving us an equal voice on program design and direction as the research and industry partners participating in the program. This commitment is a $500,000 research investment made across 5-years, and made possible by our generous donors.

The FNIH has several AMP® programs focused on different diseases, and the original AMP® for autoimmune disease focused on lupus and rheumatoid arthritis. In 2020, the FNIH expanded this particular AMP® to include Sjögren's and psoriatic arthritis – leading to the new AMP®AIM. The AMP®AIM project is a 5-year research project that will focus on each individual disease followed by looking at diseases across datasets to compare commonalities and differences. This is the single most important research project for Sjögren's to date and the most important translational research project analyzing data from multiple diseases as part of the same effort.

An important part of AMP®AIM are the teams that are assembled, which are made up of the country's top experts and researchers for each disease as well as designated centers where patients can participate in the research. The Sjögren's team is comprised of highly accomplished Sjögren's researchers and clinicians. They all know that Sjögren's is a serious and systemic autoimmune disease and are well versed in the need for multidisciplinary care for patients. This team is called Sjögren's Team for Accelerating Medicines Partnership, or STAMP for short. Dr. Caroline Shiboski from UCSF (and the contact principal investigator for STAMP), has written a comprehensive look at the AMP®AIM program and STAMP work to date. We encourage you to read about this important research project for Sjögren's!

Sjögren's Team for Accelerating Medicines Partnership (STAMP): An Overview

by Caroline H. Shiboski, Professor
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In December 2021, the Foundation for the National Institutes of Health (FNIH) announced a transformative partnership to identify and map key biological pathways that drive autoimmune and immune-mediated diseases.[1] The press release described how the FNIH and the National Institutes of Health (NIH) had launched "a new partnership to investigate how cells of the immune system interact in tissue to drive inflammation and autoimmune disease". It further noted how "the Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP®AIM) Program will advance our understanding of key disease pathways using new tools to map in three-dimensions how cell types, cell states, and cell-to-cell interactions map in three-dimensions how cell types, cell states, and cell-to-cell interactions network to cause inflammation, abnormal function, and tissue injury. The resulting data will accelerate our understanding of the fundamental mechanisms and causes of autoimmune disease, allow more informed

selection of patients for clinical trials, and generate new targets for drug development." Sjögren's disease (SjD) is among the four autoimmune diseases that are part of the AMP®AIM network, the other three being systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis and associated diseases (PsA). The inclusion of SjD in the AMP®AIM network, titled the Sjögren's Team for Accelerating Medicines Partnership (STAMP), is funded by the National Institute of Dental and Craniofacial Research (NIDCR).

The overarching goals of the STAMP project are to further our understanding of the phenotypic and molecular heterogeneity of SjD; the disease mechanisms inherent to progression from non-SjD to SjD, and from early to advanced SjD; the disease mechanisms and molecular overlap between SjD and SLE; and lastly, to identify therapeutic targets to stabilize early disease and reverse/improve advanced disease.

Thus, it is a very promising endeavor with respect to improving the prospect of discovering new treatments for SjD. The objective of this article is to describe the STAMP scientific agenda, study design and procedures, a broad overview of pilot studies conducted to-date, and current enrollment numbers.

STAMP within the AMP®AIM Program Infrastructure

In 2014 the first iteration of AMP® was launched to transform the model for developing new diagnostics and treatments by identifying promising biological targets.[2] The initial diseases studied in this public-private partnership included Alzheimer's disease, type 2 diabetes, SLE, RA, Parkinson's disease, and schizophrenia.[3-5] The initial AMP® infrastructure comprised several technology and clinical centers, as well as a network of clinicians who were collecting patient data and tissues.[6] These centers were supported by an administrative arm, shared across clinical centers, that oversaw data collection, tissue storage, and other logistics. The clinical centers were also supported by a network of scientific subcommittees each focused on a particular cell subtype or analytic approach.[6] A central goal of the AMP® Network was to catalog cell types and cell states present in tissues affected by specific diseases of interest using single-cell transcriptomics. To achieve this, the network developed standardized protocols to collect and store specific tissues for research and to generate single-cell RNA sequencing (scRNA-seq) data from cells obtained from these tissues, as demonstrated for lupus nephritis in SLE through extensive analyses of kidney tissues.[7]

When the AMP®AIM network initial funding cycle began in early 2022, in addition to the four multi-site disease teams (SjD, SLE, RA, and PsA), five centralized cores were established to support this momentous research endeavor with respect to research management, systems biology, and technology analytics. Specifically, these include the Research Management Unit and Tissue Research Center (RMU/TRC) at the Oklahoma Medical Research Foundation (OMRF), a single-cell sequencing/spatial technology group led by investigators at the Broad Institute of the Massachusetts Institute of Technology and Harvard, Systems Biology Groups (SRGs) at both Harvard and the University of Michigan, and a Microbiome Technology Group (MTG) led by investigators at New York University (NYU).

STAMP: A Multidisciplinary Multicenter Team

The STAMP project includes four clinical sites at: the University of California, both in San Francisco (UCSF) and Berkeley (UCB), Johns Hopkins Medical Institutions (JHMI), OMRF, and the NIDCR Intramural Sjögren's Disease Clinic. An additional site is currently being established at NYU that will focus on participants with both SLE and SjD. The team comprises clinician-scientists (with each site including specialists in rheumatology, ophthalmology, and oral medicine), experts in immunology, genetics, genomics, biology (molecular; oral; ocular), oral pathology, epidemiology, biostatistics, bioinformatics, and patient advocacy as summarized in **Table 1.** The STAMP project is led by three Principal Investigators (PIs) at UCSF (Caroline Shiboski, Contact PI), JHMI (Alan Baer), and OMRF (Darise Farris), and a Significant Contributor (NIH intramural research equivalent to PI) at NIDCR (Blake M. Warner). The STAMP Steering Committee (SC) comprises the four PIs and three co-investigators: Chris Lessard and Astrid Rasmussen (OMRF) and Stephen Shiboski (UCSF). In September 2023, the team welcomed Sara McCoy (University of Wisconsin), a recipient of a Team Science Leadership Scholar Program in Women's Health, Autoimmune, and Immune-Mediated Diseases, to the STAMP SC. The collaboration with Dr. McCoy is mutually beneficial given the topic of her project titled "Sjögren's disease salivary gland mesenchymal stromal cells: defining the transcriptional and epigenetic landscape changes in health and disease" that will be conducted using tissues from the ST AMP cohort.

Other important STAMP administrative entities include the Scientific Agenda and Review Committee (SARC) and the Protocol Development Team (PDT). The SARC, co-chaired by Alan Baer and Darise Farris, includes SC members, STAMP clinician-scientists representing each specialty (rheumatology, ophthalmology, oral medicine/pathology), members of AMP®AIM technology and systems biology cores, representatives from the Sjögren's Foundation (Kathy Hammitt, Vice President for Medical and Scientific

Affairs, providing the patient's perspective), from NIH, and industry partners with an interest in SjD. The PDT, co-chaired by Astrid Rasmussen and Alan Baer, includes STAMP clinical co-investigators who have previous experience in the diagnostic tests inherent to a comprehensive SjD work-up in the context of both clinical practice and research. This group was primarily responsible for the development of STAMP standard operating procedures (SOPs) and clinical research forms (CRFs)

Each clinical team includes a clinical research coordinator (CRC) who oversees the scheduling of participants, and coordinates study visits, which are further described in the STAMP Study Design and Procedures section of this article.

Table 1. Sjögren's Team for Accelerating Medicines Partnerships (STAMP): A multidisciplinary multicenter team

		UCSF - *Contact*		OMRF		JHU		NIDCR		UCB	NYU	NHGRI	SF	UWM
	MPI/Significant Contributor	Caroline SHIBOSKI*		Darise FARRIS*		Alan BAER*		Blake WARNER*						
	Co-Investigators	Kimberly Taylor Jimmie Chun Ye Stephen Shiboski* John Gonzales Ava Wu Krishna Chaganti Richard Jordan Francisco Quintanilla (CRC)		Chris Lessard* Astrid Rasmussen* Hal Scofield Chuang Li Kathleen Higgins Kamran Riaz Kimberly Hefner Janice Gales (CRC)		Esen Akpek Alexander Daniel Jean Kim Thomas Grader-Beck Freena Chaudhry (CRC)		Zohreh Khavandgar Margaret Beach Alan Baer Teresa Magone Regina Reyes (CRC) Ioana Ghita		Nancy McNamara (Site Lead) Nancy Carteron Lisa Barcellos Ava Wu Francisco Quintanilla (CRC)	Peter Izmirly Jill Buyon	Lindsey Criswell	Kathy Hammitt	Sara McCoy*
		PI	**Co-I**	**PI**	**Co-I**	**PI**	**Co-I**	**Significant Contributor**	**Co-I**	**Co-I**	**Co-I**	**Significant Contributor**	**Patient Advocacy**	**Scholar**
Areas of Research Focus	Oral Biology	■	■		■			■						
	Ocular Biology		■		■		■		■					
	Immunology		■	■	■									
	Genetics		■		■				■	■		■		
	Genomics		■		■			■	■	■		■		
	Molecular/Cellular Biology		■	■	■		■	■	■	■				■
	Clinical Rheumatology		■		■	■	■		■	■	■	■		■
	Oral Medicine	■	■		■		■	■	■	■				
	Clinical Ophthalmology		■		■		■		■	■				
	Oral Pathology		■		■			■	■					
	Epidemiology	■	■									■		
	Biostatistics		■		■									
	Bioinformatics		■		■		■	■	■					
	System Biology		■		■									
	Patient Perspective												■	

The STAMP Scientific Agenda

The STAMP project started in March 2022 with an initial planning phase as part of which the team developed its 5-year scientific agenda and study protocol. The overarching goals of the STAMP project are to further our understanding of the phenotypic and molecular heterogeneity of SjD, the disease mechanisms inherent to progression and explaining the SjD/SLE molecular overlap, to ultimately identify therapeutic targets for SjD. To address these goals, STAMP's 5-year scientific agenda aims to investigate:

Aim 1: the prediction of disease development and progression in salivary gland and systemic disease. As part of this aim, we are recalling individuals who participated in two previous study cohorts 10 to 20 years earlier, specifically U.S. participants in the Sjögren's International Collaborative Clinical Alliance (SICCA), and participants in the OMRF Sjögren's Cohort. This will enable the team to 1) explore molecular changes over time within labial salivary glands (LSGs) both in SjD development and progression; and 2) test hypotheses that specific phenotypic features of SjD may be associated with progression from non-SjD to SjD, or with worsening of the disease.

Aim 2: the interactions between immune cells and LSG secretory/ductal cells, and elucidation of SjD molecular and phenotypic heterogeneity using multi-omic data. Multiomic data refers to a comprehensive approach in biological research that integrates multiple "omes," such as genomics, transcriptomics, and proteomics. In this aim, we plan to investigate the impact of immune cells on LSG function/cellularity/phenotype among participants with "pure" SjD (no other systemic autoimmune-related diseases (SARD)) and healthy controls. We also plan to investigate the heterogeneity of SjD by studying the associations between molecular co-variates of SjD and phenotypic features of disease activity and damage to LSGs.

Aim 3: the determinants of exocrine gland tropism. Exocrine gland tropism in the context of SjD refers to the disease's predilection to affect the salivary-type exocrine glands (e.g., salivary, lacrimal) by inflammatory infiltration and ultimately damage to the glandular tissue. As part of this aim, we plan to compare individuals who meet criteria for SjD and who have antibodies that are specific to SjD in their blood (anti-SSA/Ro antibodies) to those who meet criteria for SLE and are anti-SSA/Ro antibody positive. The potential determinants we plan to study include genetic effects (glandular expression quantitative trait loci [eQTL]); specific self-antigens (T- and B- cell receptor [TCR/BCR] profiling; blood/saliva autoantibodies); nonself-antigens (virome; microbiome); and sex hormones.

Table 1. Sjögren's Team for Accelerating Medicines Partnerships (STAMP): A multidisciplinary multicenter team

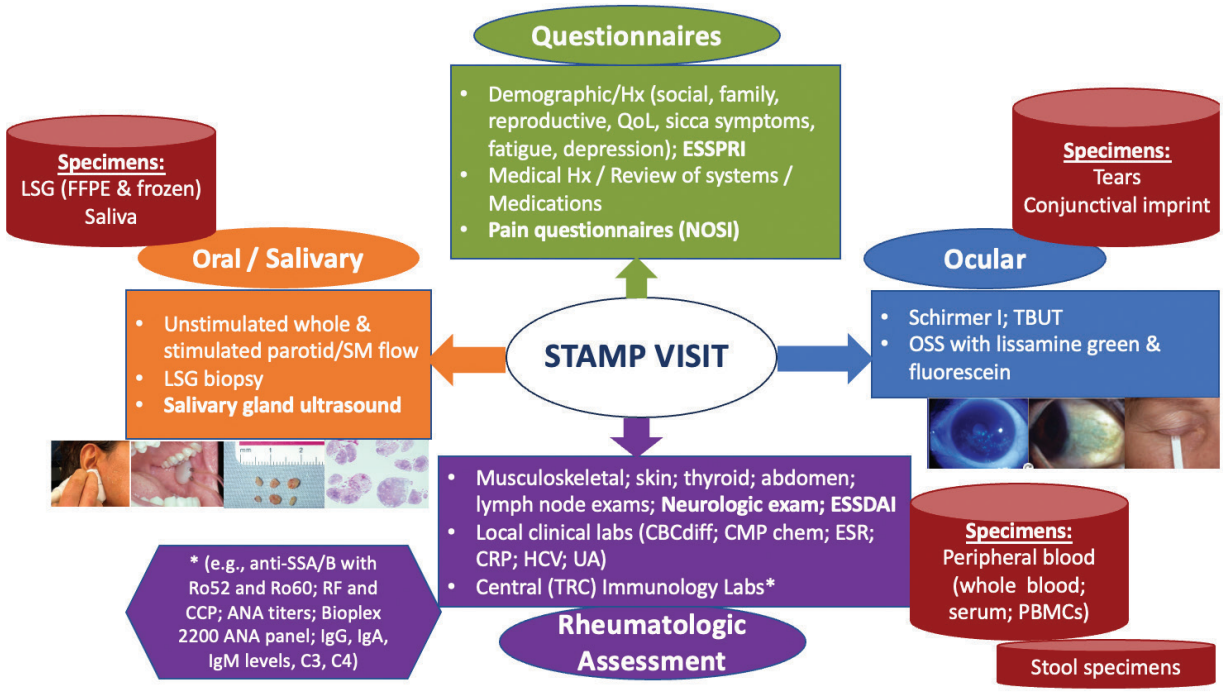
STAMP Main/New Cohort (N=300)	STAMP Follow-up Cohort (N=185)	STAMP SjD-SLE Cohort (N=20)	Healthy Controls (N=63)
At least one of the following: • Symptom of dry eyes/mouth (+ response to AECG Qs) • Previous dx of SjD • Bilateral parotid enlargement consistent with SjD • Multiple cervical or incisal dental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

STAMP Study Design, Inclusion Criteria, and Procedures

Study Design and Inclusion Criteria

The STAMP project is predominantly a cross-sectional study recruiting new participants (N=300) with signs/symptoms suggestive of SjD and healthy controls (N=63) that consists of a single study visit. The study also includes a longitudinal component recalling individuals who participated in the SICCA and the OMRF Sjögren's Project 10 to 20 years earlier (N=185). These participants are evaluated for SjD during a single study visit. Finally, a small group of participants with both SLE and SjD ("SLE/SjD overlap") will be recruited from the NYU site (N=20). Inclusion criteria for these four groups are summarized in **Table 2**. Following the NIH policy requiring a single Institutional Review Board (sIRB) for multisite research, our Human Subjects Research protocol (Pro00059668) was approved by Advarra(https://www.advarra.com/), which has been endorsed by each of the involved institutions. The study team developed a Data Safety Monitoring Plan (DSMP) approved by NIH and overseen by a Safety Officer who receives quarterly safety and enrollment reports from the STAMP team.

Figure 1. Sjögren's Team for Accelerating Medicines Partnerships (STAMP): Phenotypic Data and Specimens Collected



Study Procedures: Phenotypic Data and Specimens Collected

As part of the planning and pilot phases the team developed and tested SOPs, that provide step-by-step instructions on how to implement all study procedures to the clinical team, and CRFs. These enable a standardized way of recording study data such as patient answers to questionnaires and clinical findings. As summarized in **Figure 1**, the STAMP study data collection instruments comprise standardized patient questionnaires, clinical assessments, and laboratory tests and specimen collections. Standardized questionnaires have been developed to collect patient-reported information on: socio-demographic variables; medical history and review of systems; women's reproductive health; quality of life and other patient-reported outcomes (specifically, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)[8] and the Patient-Reported Outcomes Measurement Information System known as PROMIS-29).[9] The PROMIS-29 instrument assesses pain intensity using a single 0–10 numeric rating item and seven health domains; additionally, two pain-specific questionnaires evaluate pain catastrophizing and fibromyalgia related pain. Participants provide information related to current and past medication usage; lifestyle choices (specialized diet, tobacco, alcohol, drug use); reproductive history; oral and ocular health history; peripheral and autonomic neuropathy; history of signs and symptoms of lupus and other SARDs. These questionnaires are completed by participants accessing the AMP®AIM Research Electronic Data Capture (REDCap) Cloud platform (https://www.redcapcloud.com/data-collection-management/) after providing verbal consent prior to their visit.

During the study visit, after participants have signed the written informed consent form, they receive physical, ocular, and oral evaluations by a rheumatologist, ophthalmologist, and an oral medicine/pathology specialist or dentist, respectively, who have been trained to follow a specific SOP for each assessment. All clinical findings are recorded on standardized eCRFs that have been adapted and expanded from those previously developed for the SICCA project[10] and that were subsequently also used and adapted for the OMRF Sjögren's cohort project. All clinical assessments and diagnostic tests performed during the visit are well established standardized tests,[11-13] and are listed in **Figure 1**. New assessments and tests that were previously not performed as part of SICCA include a 28-joint count as part of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI),[14, 15] and a salivary gland ultrasound (SGUS).[16] Furthermore, a comprehensive neurological exam intended to identify signs of peripheral neuropathy and dysautonomia is part of the physical assessment. It was developed by the STAMP rheumatologists lead by Alan Baer and Astrid Rasmussen in consultation with neurologists using existing validated instruments.[17-21]

Biospecimens collected and shipped to the TRC for further processing and/or storage are also listed in **Figure 1**. The biospecimens include blood: viably cryopreserved peripheral blood mononuclear cells (PBMC), serum, plasma; LSGs: formalin-fixed paraffin-embedded (FFPE) for standardized histopathologic interpretation consistent with 2016 ACR-EULAR criteria[22, 23] and spatial "omics," and for cryopreservation (snap frozen and viably cryopreserved in CryoStor® CS10); saliva: whole unstimulated, major salivary gland stimulated; tears; and conjunctival imprints. Participants are also invited to participate in a stool microbiome sub-study conducted at NYU. In case they agree to participate, the stool samples are collected by the participant at home, and shipped directly to the site conducting the microbiome analysis through a pre-labeled and pre-paid biohazard compliant shipping kit.

STAMP Pilot Phase Completion and Enrollment

Four pilot studies have been completed to standardize clinical assessments and sample procurements (Pilot 1A), and to select the optimal tissue processing, cryopreservation methods, and spatial transcriptomic platforms to be used for this project (Pilots 1B-1D).

Briefly, as part of Pilot 1A, CRFs, SOPs, and a manual of procedures were finalized and tested across clinical sites. Formal calibration was performed among rheumatologists and other providers who perform the SGUS using the OMERACT scoring system to ensure standardization of their scoring against a gold standard. A set of 80 SGUS images from the Harmonic SS project that had been scored by a group of SGUS experts were obtained and used for this calibration exercise.[24] We also performed a formal calibration exercise between the two oral and maxillofacial pathologists, Blake M. Warner, NIDCR, and Richard Jordan, UCSF, who are interpreting all histopathologic hematoxylin and eosin (H&E) stained slides to assess them for focal lymphocytic sialadenitis and compute a focus score. A set of H&E slides previously read and scored by two pathologists as part of the SICCA project were used for this calibration exercise.[12, 25] Beyond the determination of the focus score and presence of the characteristic SjD histopathologic pattern, the pathologists provide a blinded description of additional, less common pathologies found in the LSG (e.g., germinal centers, lymphoma) and, when their assessments are discrep ant, reach a final diagnosis through a consensus process.

Pilots 1B-1D were tissue-focused and involved tissues collected from non-STAMP research participants at the NIDCR Division of Intramural Research protocols (NIDCR 15-D-0051, PI-Warner). These studies were conducted in the Warner Lab (NIDCR) and Lessard Lab (OMRF), and aimed at comparing various protocols for:

- Cryopreservation, dissociation, and logistics for central LSG processing using 10X 5' and 3' scRNA-seq chemistries, and head-to-head comparison of the sequencing data quality and determination of any biological or technological biases imparted by cryopreservation and individual chemistry selection (Pilot 1B)
- LSG fixation and spatial platforms (Pilot 1C)
  - Xenium and CosMx comparative studies performed on LSG sections
  - Customized panels for pilot spatial transcriptomics constructed using Warner Lab 3' scRNA-seq data shared with the TRC and the Spatial Technology Cores
- Testing the feasibility of using new 10X Genomics FLEX(which enables scRNA-seq analysis from FFPE LSGs) to assess historical (5-18 year-old) FFPE-preserved LSG samples from SICCA and OMRF cohorts (Pilot1D). The FFPE samples used were matched to those samples used for 3'- and 5'-scRNA-seq.

The tissue-focused pilot studies enabled the selection of complementary cutting-edge genomic analysis approaches to rigorously investigate salivary glands as the target tissue in SjD. To characterize the cell types and cells states, the team selected 10X FLEX single cell analysis which uses cells extracted from FFPE tissues to determine the compositional changes, RNA expression states, and dysregulated pathways of all cells in the salivary glands. Next, to understand the spatial arrangement of cells, the cell-to-cell interactions, and the between cell signaling pathways dysregulated in disease, the team selected the 10X Genomics Xenium Prime 5K. Xenium Prime 5K is a non-destructive 5000 gene panel that pro vides single molecule imaging of RNA expression in cells in up to 472 mm of tissue. This has been successfully combined with post-Xenium multiplex proteomics (e.g., imaging mass cytometry) for true multi-modal (RNA and protein) spatial biology analyses.

Following finalization of all our SOPs, CRFs, and operationalization of the study protocol, we scaled up enrollment, and as of August 7, 2024, a total of 166 participants have been enrolled in the STAMP project: 52 at UCSF/UCB, 41 at JHMI, 63 at OMRF, and 10 at NIDCR where recruitment is limited to healthy controls.

Conclusion

The AMP®AIM is highly innovative in its approach of dissecting autoimmune diseases down to the core genetic and biological mechanisms across the lifespan. It provides an unprecedented opportunity for potential rapid translation to drug discovery, which is especially relevant to SjD given its current lack of effective treatment. Furthermore, the systematic alignment of the data and biospecimen collection and curation across not only STAMP sites, but across three other autoimmune diseases, will enable a better understanding of disease mechanisms that may overlap across these diseases. It represents an opportunity of collaboration across not only STAMP sites, but across three other autoimmune diseases, will enable a better understanding of disease mechanisms that may overlap across these diseases. It represents an opportunity of collaboration across major SjD translational research sites and investigators across the U.S., using a multicenter multidisciplinary model spearheaded by the SICCA project 20 years ago, yet introducing cutting-edge "omics" technologies, and specimen collection protocols greatly updated make them analyzable through the new technologies. The STAMP project also includes a strong emphasis on succession planning, and the team is highly committed to the development of early and mid-career investigators across the spectrum of clinical, translational, and basic sciences. Finally, the STAMP multidisciplinary clinical sites provide participants with the opportunity to receive a comprehensive SjD evaluation within a single visit, which rarely occurs in the clinical setting. Participants then receive their test results that are necessary for assessment of SjD classification, which may facilitate their enrollment in future clinical trials.

On behalf of all STAMP investigators, I would like to extend our gratitude to STAMP study participants for their valuable contribution to Sjögren's disease research. We also acknowledge the valuable comments/edits made by members of the STAMP Steering Committee for this article, particularly Astrid Rasmussen, Blake Warner, Darise Farris, Alan Baer, and Chris Lessard.

If you are a healthcare provider interested in referring a patient with signs and symptoms suggestive of Sjögren's disease to the STAMP study, please contact Dr. Caroline Shiboski at caroline.shiboski@ucsf.edu or one of the STAMP clinical sites listed here:

- **Johns Hopkins Sjögren's Center (Baltimore, MD)**: (410) 550-6492 or (410) 550-9821
- **Oklahoma Medical Research Foundation (Oklahoma City, OK)**: sjögrens@omrf.org
- **UC San Francisco/UC Berkeley (San Francisco and Berkeley, CA)**: sjögrens@ucsf.edu

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