

AWARD NUMBER: W81XWH-19-1-0562

TITLE: Transcription Factor Analysis Of SLE

PRINCIPAL INVESTIGATOR: Kathleen E. Sullivan

CONTRACTING ORGANIZATION: Children's Hospital of Philadelphia

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PREPARED FOR: U.S. Army Medical Research and Development Command
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13. SUPPLEMENTARY NOTES					
14. ABSTRACT The goals of this project are to understand the regulation of genes with differential expression in SLE. We are using ChIP-seq to define the epigenetic landscape that sets the transcriptional capacity for expression and we are using RNA-seq to define dysregulated expression. Bioinformatic approaches will extract transcription factor binding sites from regions of altered histone modifications. We will then alter those transcription factors to define effects on cell behavior. Due to COVID-19, we have begun recruitment and ChIP-seq/RNA-seq sample preparation but have not yet run any libraries. With accelerated recruitment, we will still be able to complete our proposed studies.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
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1. INTRODUCTION:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting many organs and cell types. The disease places an enormous burden on the patients who are typically young women just beginning careers. Treatment remains unsatisfactory and is based on global immune suppression and patients have a chronic course with periodic flares and end organ damage accruing over time. **The foundation of this proposal is the observation that SLE patients have a widely altered epigenome that implicates a limited number of transcription factors, opening the door for targeted therapeutics.** We hypothesize that targeting the epigenome will allow the immune system to be re-set rather than just suppressed. This project will measure changes at promoters and enhancers in SLE, specifically focusing on transcription factors that alter chromatin.

2. KEYWORDS:

Lupus, SLE, epigenetics, histone, ATF3, Transcription

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**
 - H3K4me3, H3K4me1, H3K27ac, p300 ChIP-seq in SLE T cells, B cells and monocytes. The goal is to define implicated transcription factors.
 - 60 SLE patients (including 10 cutaneous disease and 10 with nephritis)
 - 20 patients with rheumatoid arthritis
 - 40 healthy donors
 - Inhibit identified transcription factors and measure effects on the epigenome using ChIP-seq
 - 30 SLE patients
 - 30 healthy donors
- **What was accomplished under these goals?**
 - We had just set up our recruiting infrastructure and assay systems when clinical research at both institutions was halted due to COVID-19. We have just begun receiving samples from Johns Hopkins again and have >20 samples on site. They have been prepared and are in the freezer but have not yet been run.
 - Johns Hopkins has a plan for an accelerated schedule for recruitment
 - CHOP has a plan for accelerated processing and running.
- **What opportunities for training and professional development has the project provided?**
 - Nothing to report

- **How were the results disseminated to communities of interest?**
 - *Nothing to Report*
- **What do you plan to do during the next reporting period to accomplish the goals?**
 - *We have established an accelerated recruitment process so that we can “catch up” on our sample acquisition and complete all studies.*
 - *In the next 4 months, we will have run our test set of ChIP-seq assays (10 libraries each antibody) and analyzed for quality and have half of our samples recruited and stored.*

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**
 - *Nothing to Report*
- **What was the impact on other disciplines?**
 - *Nothing to Report*
- **What was the impact on technology transfer?**
 - *Nothing to Report*
- **What was the impact on society beyond science and technology?**
 - *Nothing to Report*

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**
 - *None*
- **Actual or anticipated problems or delays and actions or plans to resolve them**
 - *We believe that we will successfully execute all the studies in the statement of work. We are off to slow start due to delays in IRB approval and then COVID-19 but with our new recruitment plan in place, we should still complete all goals/tasks.*
- **Changes that had a significant impact on expenditures**
 - *CHOP had a hiring freeze and a key study member could not be hired until this month. This has not markedly impacted our progress since the effect of COVID-19 was greater than the effect of having to redistribute the work of the not-yet-hired person. Expenditures were overall delayed due to COVID-19.*

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
 - *No changes.*
 - *CHOP IRB has stated this project is not human subjects experimentation since we receive de-identified samples.*
 - *The Johns Hopkins IRB 00216558 was approved February 14, 2020*
- **Significant changes in use or care of human subjects**
 - None
- **Significant changes in use or care of vertebrate animals.**
 - N/A
- **Significant changes in use of biohazards and/or select agents**
 - None

6. PRODUCTS:

- **Publications, conference papers, and presentations**
 - **Journal publications. .**
 - *Nothing to Report*
 - **Books or other non-periodical, one-time publications.**
 - *Nothing to Report*
 - **Other publications, conference papers, and presentations.**
 - *Nothing to Report*
- **Website(s) or other Internet site(s)**
- *Nothing to Report*
- **Technologies or techniques**
Nothing to Report
- **Inventions, patent applications, and/or licenses**
Nothing to Report
- **Other Products**
Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

- *Provide the following information for: (1) PDs/Pis; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."*

Name:	Kathleen Sullivan
Project Role:	<i>CHOP PI</i>
Researcher Identifier (e.g. ORCID ID):	0000-0003-4018-1646
Nearest person month worked:	1
Contribution to Project:	<i>Dr. Sullivan is the program PI and oversees design and execution of the overall project.</i>
Funding Support:	<p>Lupus Foundation of America 10/1/14- 12/30/20 1.8 cm Title: HER2 in Lupus Nephritis</p> <p>NIH 6/12/18-5/31/21 1.2 cm 5R21AI130967-02 Title: Persistent Rubella</p> <p>NIH 9/20/18-6/30/22 1.2 cm 5U01HG010219-02 Title: UDN Clinical Site</p> <p>DOD 9/15/19-9/14/22 0.6 cm W81XWH-19-1-0562 Title: SLE Transcription Factor</p> <p>NephCure Foundation 1/1/20-12/31/20 .48 cm AWD-00000120 Title: Lymphocyte profile pre-rituximab in pediatric nephrotic syndrome</p> <p>CHOP 7/1/18-6/30/21 2.4 cm 28700RFRNT19002 Title: Frontier- Immune Dysregulation</p> <p>NIH 9/13/19-8/31/24 .36 cm 2U54AI1082973-11 Title: Primary Immune Deficiency Treatment Consortium</p>
Name:	<i>Michelle Petri</i>
Project Role:	<i>Johns Hopkins site PI</i>
Researcher Identifier (e.g. ORCID ID):	0000-0003-1441-5373

Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Petri oversees the clinical data, patient recruitment and provides expertise on SLE.</i>
Funding Support:	<p>NIH 7/1/2016 – 7/31/2021 4.0 cm R01 AR069572 Title: Hopkins Lupus Cohort</p> <p>NIH 3/8/2019 – 2/29/2024 0.8 cm R01 AR074096 Title: Monitoring Disease in Lupus</p> <p>NIH 9/1/2018 – 8/31/2023 0.2 cm 5R01AR073850 Title: Characterization of the lupus nephritis microRNAome - UAB PROFILE IV</p> <p>NIH 9/24/2014 – 5/31/2021 3.2 cm UH2AR067679 Title: Accelerating Medicines Partnership (AMP) in Rheumatoid Arthritis and Lupus: Network Research Sites</p> <p>DOD 9/1/2019 - 8/31/2020 0.7 cm W81XWH-19-1-0793 Title: A spatial temporal analysis of organ-specific lupus flares in relation to atmospheric and environmental factors</p> <p>Institutional funds pay the remainder</p>
Name:	<i>Li Song</i>
Project Role:	<i>Technician</i>
Researcher Identifier (e.g. ORCID ID):	<i>None</i>
Nearest person month worked:	<i>4</i>
Contribution to Project:	<i>Ms. Song processes all the ChIP-seq samples</i>
Funding Support:	<p>NIH 6/12/18-5/31/21 6.0 cm 5R21AI130967-02 Title: Persistent Rubella</p> <p>DOD 9/15/19-9/14/22 3.2 cm W81XWH-19-1-0562 Title: SLE Transcription Factor</p> <p>Institutional funds pay the remainder</p>
Name:	<i>Amrita Raj</i>
Project Role:	<i>Research Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	<i>None</i>

Nearest person month worked:	4
Contribution to Project:	<i>Patient recruitment and clinical database</i>
Funding Support:	<p>NIH 7/1/2016 – 7/31/2021 3.0 cm R01 AR069572 Title: Hopkins Lupus Cohort</p> <p>NIH 3/8/2019 – 2/29/2024 1.0 cm R01 AR074096 Title: Monitoring Disease in Lupus</p> <p>NIH 9/1/2018 – 8/31/2023 3.0 cm 5R01AR073850 Title: Characterization of the lupus nephritis microRNAome - UAB PROFILE IV</p> <p>Institutional funds pay the remainder - 2.0 cm</p>

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- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
 - Sullivan
 - Addition of this grant.
 - Reduction in effort on U01HG010219 from 2.4 calendar months to 1.2
 - Removal of effort on U24AI086037 due to project ending
 - Removal of effort on Lupus Foundation Award due to project ending
 - Removal of effort on 543769 – ALR due to project ending
 - Increase in effort on U54082973 from 0.24 calendar months to 0.36 calendar months
- **What other organizations were involved as partners?**
 - **Organization Name:** Johns Hopkins University School of Medicine
 - **Location of Organization:** *Baltimore, MD*
 - **Partner's contribution to the project (identify one or more)**
 - **Financial support;**
 - **In-kind support**
 - **Facilities X**
 - **Collaboration X**
 - **Personnel exchanges**
 - **Other**

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**
- **QUAD CHARTS:** *See attached*

9. APPENDICES: *N/A*
