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TITLE: **A Novel Imaging Agent for Detecting and Monitoring Lupus Nephritis**

PRINCIPAL INVESTIGATOR: **Joshua Thurman**

CONTRACTING ORGANIZATION: **University of Colorado Denver**

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This is a project to develop methods for detecting and monitoring inflammation in patients with systemic lupus erythematosus (SLE) in order to non-invasively detect tissue inflammation. This method will allow clinicians to: 1) more accurately identify which patients with SLE need to be treated with immunosuppressive drugs, and 2) determine whether immunosuppressive treatment of these patients is effective. These imaging methods will provide the same information that can currently be obtained only by an invasive tissue biopsyBecause these imaging methods expose patients to very low levels of radiation, they can be repeated as needed to assess changes over time. These methods will directly improve the care of patients with SLE because an accurate method of monitoring tissue inflammation will reduce permanent organ damage by under-treatment of the disease while also reducing side effects caused by unnecessary treatment.

15. SUBJECT TERMS

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1. Introduction

This is an annual report for the project entitled: "A Novel Imaging Agent for Detecting and Monitoring Lupus Nephritis." The PI is Joshua Thurman, MD, and it covers the first year of this grant (7/01/19 – 6/30/20).

This is a project to develop methods for detecting and monitoring inflammation in patients with systemic lupus erythematosus (SLE). SLE is an autoimmune disease that can affect multiple different organs, including the kidneys, heart, intestine, and central nervous system. SLE is a lifelong disease marked by flares and remissions. The treatment of SLE almost always includes medicines that suppress the immune response. Immunosuppressive drugs, such as cyclophosphamide and mycophenolate mofetil, reduce tissue inflammation and injury, and the mortality for patients with SLE has improved in recent decades. Aggressive and prolonged immunosuppression reduces - but does not eliminate - the risk of future flares. Consequently, even patients who have remained in remission for prolonged periods need to continually be monitored for evidence of a disease flare, and these flares usually require patients to re-start treatment. However, the immunosuppressive drugs currently available also have many side effects. Most importantly, these drugs increase patients' risk of infections. Treatment, therefore, should be minimized in patients who are in remission and do not have active tissue inflammation.

The imaging methods that we are developing in this project offer the possibility of non-invasively detecting tissue inflammation in patients with lupus. It will allow clinicians to: 1) more accurately identify which patients with SLE need to be treated with immunosuppressive drugs, and 2) determine whether immunosuppressive treatment of these patients is effective. These imaging methods will provide the same information that can currently be obtained only by an invasive tissue biopsy. Furthermore, biopsies sample only a small portion of tissue, and these imaging methods will report on inflammation throughout the whole organ and throughout the entire body. Because these imaging methods expose patients to very low levels of radiation, they can be repeated as needed to assess changes over time. These methods will directly improve the care of patients with SLE because an accurate method of monitoring tissue inflammation will reduce permanent organ damage by under-treatment of the disease while also reducing side effects caused by unnecessary treatment.

2. Keywords

Kidney, complement, diagnostic, positron emission tomography

3. Accomplishments

What were the major goals of the project?
The major goals of this project as outlined in the Statement of Work (SOW) are:

1. Production of recombinant proteins and monoclonal antibodies.
2. Confirm in vivo targeting and specificity of anti-C3d probes
3. Test anti-C3d probes in a model of lupus-like glomerulonephritis.
4. Test anti-C3d probes in mice with lupus-like glomerulonephritis treated with conventional immunosuppression (cyclophosphamide.

What was accomplished to date under these goals?

Goal 1. We have produced a sufficient quantity of recombinant C3d and monoclonal antibody for the proposed studies.

Goal 2. We have produced sufficient Fab for the experiments, and we have begun generating the minibody. We have also begun generating the bioluminescence resonance energy transfer (BRET) construct to label the imaging probes for optical imaging.

Goal 3. We have obtained IACUC approval for the experiments, and we have expanded our colony of mice for the experiments (factor H knockout mice and factor H/factor B double knockout mice)

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?
During the next funding period we expect to:

- Complete production of the protein probes
- Label the probes for optical imaging and PET imaging
- Begin the proposed animal imaging experiments

4. Impact

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report at this phase of the project.

What was the impact on other disciplines?
Nothing to report at this phase of the project.

What was the impact on technology transfer?
Nothing to report at this phase of the project.

What was the impact on society beyond science and technology?
Nothing to report at this phase of the project.

5. Changes/Problems

Changes in approach and reasons for change
Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
The shutdown of our laboratories due to the COVID-19 pandemic has delayed the accomplishment of some of the experiments. As the labs re-open we will resume this work. If the work is not done at the end of the funding period we will request a no-cost extension.

Beyond a possible delay in competing the experiments, however, we do not expect that this will result in any changes to the project.

Changes that had a significant impact on expenditures
Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report.

Significant changes in use or care of human subjects
Nothing to report.

Significant changes in use or care of vertebrate animals.
Nothing to report.

Significant changes in use of biohazards and/or select agents
Nothing to report.

6. Products

Publications, conference papers, and presentations
Our plan is for all experimental results and analyses to be published. At this time there is 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?

Name:	Catherine Foss, PhD,
Project Role:	Co-investigator
Research Identifier:	
Nearest person month worked:	2.4 calendar months
Contribution to project:	Dr. Foss is an expert in radiochemistry and nuclear medicine.

Funding Support:	This project.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No change.

What other organizations were involved as partners?

There have been no changes from the original proposal regarding the organizations involved in the project:

University of Colorado Denver
1775 Aurora Court
Aurora, CO USA

Johns Hopkins University
733 N. Broadway, Suite 117
Baltimore, MD USA

8. Special Reporting Requirements

Not applicable.

9. Appendices

Not applicable.