**AWARD NUMBER: W81XWH-18-1-0577**

**TITLE: Preemptive Rituximab to Prevent Recurrent Focal Segmental Glomerulosclerosis Post-Transplant**

**PRINCIPAL INVESTIGATOR: Michelle Rheault, MD**

**CONTRACTING ORGANIZATION: Regents of the University of Minnesota**

**REPORT DATE: SEPTEMBER 2020**

**TYPE OF REPORT: Annual Report**

**PREPARED FOR:** U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

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**6. AUTHOR(S)**
Michelle Rheault, MD

E-Mail:

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

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**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
University of Minnesota
Children's Hospital
2450 Riverside Ave
Minneapolis, MN 55454

**8. PERFORMING ORGANIZATION REPORT NUMBER**

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U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

Focal segmental Glomerulosclerosis (FSGS) is a progressive chronic kidney disease that accounts for 4% of adults and 12% of children with end-stage kidney disease in the US. Kidney transplantation is the preferred treatment for end-stage kidney disease, however FSG can recur post-transplant in 30-50% of these patients, leading to poor graft survival. Treatment options for recurrent FSGS have included plasmapheresis or rituximab, neither of which are curative or effective in all patients. Recently, prophylactic approaches have been pursued as potential means to improve outcomes. Rituximab, an agent shown effective in the treatment of some patients with FSGS, prevented recurrence in a handful of high risk transplant patients. However, the role of pre-emptive treatment with rituximab combined with plasmapheresis in prevention of FSGS recurrence is unknown, necessitating a randomized controlled trial of this pre-transplant therapy plan.

**15. SUBJECT TERMS**

NONE LISTED

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| Unclassified | Unclassified | Unclassified | Unclassified | 14 | 19b. TELEPHONE NUMBER *(include area code)* |

## TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

This is a phase III, multicenter, randomized, open-label, clinical trial to test the hypothesis that plasmapheresis plus rituximab prior to kidney transplantation can prevent recurrent FSGS in children and adults. In addition, this study will collect DNA from patients treated in this study as well as prevalent patients with FSGS who have received a kidney transplant in order to identify genetic risk factors for recurrence.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Kidney disease, Focal Segmental Glomerulosclerosis, FSGS, kidney transplant.

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

**What were the major goals of the project?**
*List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

**Major Task 1: Clinical trial preparation and start up**

1. Hire and train project manager/coordinator for UMN, Month 1-2, Thu Danh, MPH hired 7/9/18, Training completed 7/15/18
2. Refine eligibility criteria, exclusion criteria, screening protocol, Month 1-2, Complete 10/12/18
3. Finalize consent forms, human subjects protocol and CRFs and submit to UMN IRB, Month 1-2, Submitted to UMN IRB on 10/12/18, Reviewed by IRB 11/26/18 with requested changes, Resubmitted 12/7/18, Scheduled for IRB review 1/7/19. Received UMN IRB approval 1/18/2019.
4. Finalize statistical analysis plan, Month 1-2: Started, not complete. Expected completion Q2 2020
5. Finalize clinical trial budget and clinical trial agreement (CTA) template for additional sites, Month 1-2: Complete 6/26/18
6. Coordinate with Sites for clinical trial agreements (CTAs), Month 2-6; 17 sites sent invitations, 20 sites confirmed participation and returned preliminary documents, 0 sites have completed subawards, 1 site will not be participating, 1 new site invited to participate. Subawards sent to sites 9/2019
7. Coordinate with Sites for material transfer agreements (MTAs) for DNA to be sent to Duke, Month 2-6: Not complete. MTAs sent to sites 9/4/19. UMN MTA complete 9/10/19.
8. Time required for submission and exemption of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration, Month 1-6, Complete 11/21/2017 Received "study may proceed" notification from FDA, IND #137324
9. REDCap database design and build, Month 1-6; Changed electronic data management system to OnCore to be in compliance with reporting and data security. CRFs and randomization functions built. Complete.
10. Submit to DoD Human Research Protections Office- Submitted on 3/11/2019. Received DoD approval 08/29/2019 to start enrollment for UMN site.
11. As of 9/29/2020, the study has 13 sites that have local IRB approval and 9 of those sites have DoD approval. Nine sites are open for accrual.

**Major Task 2: Clinical trial**

1. Initial Training of Site Coordinators and study staff, 6-9 months. Expected completion in Q1 of Year 2. Delayed due to IRB and DoD approval process.

**Major Task 3: Monitoring**

1. Invite DSMB members to participate and receive commitments, Month 2-6, Completed 9/30/18. DSMB will be composed of Ty Dunn, MD (Adult transplant surgeon, chair), Michael Somers, MD (Pediatric nephrologist), David Nelson, PhD (Statistician).
2. DSMB members convened on 8/2/2019 to go over the PRIVENT FSGS project and roles and responsibilities of members. Approved Charter of DSMB.

**What was accomplished under these goals?**

*For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

1) Major Activities: The second year of the grant have been dedicated to completing the start-up process; however, due to Covid-19, the project was suspended for 2-4 months. The study team worked on getting University of Minnesota IRB approval, which was granted on 1/18/2019. The study team received final approval by DoD ORP HRPO on 9/29/2019. The project is currently opened for accrual at the University of Minnesota site, 8/29/2019. We finalized protocol and subsequent forms, i.e. consent, assent, and parental permission, which were all approved by IRB and DoD. Those were sent out to participating sites. Subcontracts will be sent out to sites to complete in addition to clinical trial agreements and materials transfer agreement with Duke University. The study project has completed the electronic data management system for data collection. All CRFs have been added to the data capturing system. Finally the study convened the DSMB on 8/2/2019 to go over roles and responsibilities as well as the overview of the study. Due to Covid-19, the project was suspended for 2-4 months; however, in those months the study team focused on providing training to study coordinators and completing study start-up. The study was reopened for accrual on 6/22/2020 with the approval of a Sunrise Plan by the University of Minnesota Medical School and IRB. As of 9/29/2020, the project has 9 sites that are opened for accrual. One of those sites have consented a participants who is awaiting a transplant in a couple of months. The study team has been conducting monthly calls with study coordinators to provide updates of the project. Investigator calls were also scheduled to keep PIs apprised of the project.

2) Specific Objectives: The objectives for the first year of the grant period was to obtain study approval from local institution IRB and DoD approval, which were granted on 1/18/2019 and 8/29/2019, respectively; develop and complete the electronic data management system, and be opened for enrollment.

3) Significant Events: We have been approved by UMN IRB and DoD and are currently open to accrual for the study, 8/29/2019. Due to Covid-19, the study was suspended of March 2020-June 2020. The pandemic affect the project and pushed the enrollment goals.

**What opportunities for training and professional development has the project provided?**

*If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

Study staff were given one-on-one training with technical experts on the data collection tool that is being used, OnCore. The study team have conducted monthly calls for study coordinators to ask questions and voice any concerns. The team has also provided video trainings on the data collection tool for coordinators to review when needed.

**How were the results disseminated to communities of interest?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

| |
|---|
| Nothing to report. |

**What do you plan to do during the next reporting period to accomplish the goals?**
*If this is the final report, state "Nothing to Report."*

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

| |
|---|
| The study team plan to continue to enroll patients for Aim 1 and Aim 2 of the PRIVENT FSGS project. The study has received IRB and DoD approval for the University of Minnesota site and will be enrolling any individuals who screen and qualifies. In the meantime, the study staff at the University of Minnesota will be working to finalize the 20 sites to achieve IRB and DoD approval at their local institutions. Study staff at other institution will be trained on the protocol and data collection tool while awaiting IRB and DoD approval. The study team are working with the other sites to complete the clinical trial agreement and materials transfer agreement. The study expect majority of sites to be approved and ready for accrual by the end of Q4 2020.<br>For Aim 2 of the study, the UMN study site hope to enroll at least 10 participants in Q4 2020.<br>The study coordinators will hold monthly conference calls with the other sites. This will provide sites opportunities for questions, comments, and concerns. PI calls will be held quarterly. |

***4.*** **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

**What was the impact on the development of the principal discipline(s) of the project?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).*

| |
|---|
| Nothing to report. |

**What was the impact on other disciplines?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.*

Nothing to report.

**What was the impact on technology transfer?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

**What was the impact on society beyond science and technology?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:*

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report.

**Actual or anticipated problems or delays and actions or plans to resolve them**
*Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

The study has had some delays with the project due to Covid-19. The project was suspended from March-June 2020. The University of Minnesota Medical School and IRB approved a Sunrise Plan that provided a plan to keep participants and staff safe while still being able to conduct the project. As of mid-June 2020, the UMN site is opened for accrual as well as several other sites given their local institutions approval for enrollment.

**Changes that had a significant impact on expenditures**
*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

Nothing to report.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
*Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

**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:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  *Report only the major publication(s) resulting from the work under this award.*

  **Journal publications.** *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

**Books or other non-periodical, one-time publications.** *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

**Other publications, conference papers and presentations**. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

*List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.*

Nothing to report.

- **Technologies or techniques**
  *Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.*

Nothing to report.

- *research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.*

Nothing to report.

- **Other Products**

  *Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:*

  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

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".*

*Example:*

| | |
|---|---|
| *Name:* | *Mary Smith* |
| *Project Role:* | *Graduate Student* |
| *Researcher Identifier (e.g. ORCID ID):* | *1234567* |
| *Nearest person month worked:* | *5* |
| *Contribution to Project:* | *Ms. Smith has performed work in the area of combined error-control and constrained coding.* |
| *Funding Support:* | *The Ford Foundation (Complete only if the funding support is provided from other than this award.)* |

Michelle Rheault, MD
Co-PI
ORCID # 0000-0003-2494-3970
2 months
Dr. Rheault has provided oversight of IRB submission as well as DOD submission and contracting with additional sites. She has had oversight of the OnCore database build. She continues to be the primary person in contact with DoD and has complete oversight of the project.

Priya Verghese, MD, MPH
Co-PI
ORCID # 0000-0002-8836-0881
2 months
Dr. Verghese has recruited and managed the multi-site aspect of the project. She leads the team in developing recruitment strategies and site activation.

Thu Danh, MPH
Study Project Coordinator
ORCID # 0000-0001-7287-9980
12 months
Thu has worked with obtaining study IRB and DoD approval. He has worked with study team to draft and finalize case report forms and helped with the development of the study collection tool and OnCore Database. He has coordinated and managed other sites to maintain participation and to begin the onboarding process.

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

| |
|---|
| Nothing to report. |

**What other organizations were involved as partners?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.*

*Provide the following information for each partnership:*
*<u>Organization Name:</u>*
*<u>Location of Organization: (if foreign location list country)</u>*
*<u>Partner's contribution to the project</u> (identify one or more)*

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Please see attachment "Collaborating Sites."

**8. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

**QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

**9. APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*