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TITLE: Peptidylarginine Deiminase 2 and Citrullination of IgG in Immunity and Rheumatoid Arthritis

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CONTRACTING ORGANIZATION: University of Wisconsin System

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14. ABSTRACT

The purpose of this application is to identify mechanisms by which peptidylarginine deiminases (PADs) and citrullination regulate antibodies in immunity and rheumatoid arthritis. To this end, this project will (1) determine how PADs and IgG citrullination regulate a normal antibody response to immunization and normal antibody-based immunity to influenza, (2) identify how PADs and citrullinated IgG pathologically contribute to rheumatoid arthritis, and (3) determine if smoking increases IgG citrullination leading to autoimmune antibodies in genetically susceptible people. To date, we have discovered that PAD2 is not required for plasma cell numbers or arthritis severity in collagen-induced murine arthritis, but is required for anti-collagen IgG levels. Further, PAD2 is required for some antibodies formed in response to murine influenza. Experiments are ongoing to further understand these findings as well as to evaluate citrullination in autoimmune antibodies in humans.

15. SUBJECT TERMS

Rheumatoid arthritis, Antibodies, Anti-citrullinated protein antibodies, Rheumatoid factor, Citrullination, Peptidylarginine Deiminase 2

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

Rheumatoid arthritis, an autoimmune arthritis with a lifetime risk of about 3 percent, can lead to pain, disability, and early mortality despite lifelong treatment. Moreover, many of the treatments are unpleasant to inject and extremely costly. With about 1 percent of Veterans affected by rheumatoid arthritis often costing more than $15,000 per year, this is a major problem. Many people with rheumatoid arthritis produce antibodies against immunoglobulin (Ig) G, called rheumatoid factor (RF), and anti-citrullinated protein antibodies (ACPAs). These autoantibodies underpin the main diagnostic tests for rheumatoid arthritis. Unfortunately, about 25% of rheumatoid arthritis patients are seronegative for these tests, which delays diagnosis and treatment. In addition to these clinical dilemmas in rheumatoid arthritis, important pathophysiologic mysteries remain. Despite decades of research on ACPAs and RF, why these two different types of autoantibodies develop or why immune tolerance is broken against IgG is unknown. Further, the peptidylarginine deiminases (PADs) catalyze citrullination, the post-translational conversion of arginines to citrullines, and PAD2 and PAD4 are found in immune cells. However, our understanding of how citrullination and PADs regulate immunity and arthritis beyond simply generating the targets for ACPAs is rudimentary at best. Identifying the mechanisms by which the PADs and citrullination impact the immune system is critical to define fundamental pathways in immunity and aberrant pathways in rheumatoid arthritis. Moreover, gaps in our understanding of pathophysiology hinder the development of optimal diagnostics and treatments. The objective of this application is to identify mechanisms by which PADs and citrullination regulate antibodies in immunity and rheumatoid arthritis. The central hypothesis is that PAD2 regulates antibody-secreting plasma cells and citrullinates IgG, enhancing immunity and exacerbating rheumatoid arthritis. To test this hypothesis, Aim 1 will determine how PADs and IgG citrullination regulate a normal antibody response to immunization and normal antibody-based immunity to influenza. Aim 2 will identify how PADs and citrullinated IgG pathologically contribute to rheumatoid arthritis as well as determine how smoking, a major problem among Veterans, may increase IgG citrullination leading to autoimmune antibodies in genetically susceptible people. The successful completion of these Aims, in the short term, will establish a new mechanistic basis for how PAD2 and IgG citrullination regulate immunity and drive inflammation through immune cell function and citrullinated antigen generation. In the long term, these advances will usher in new translational opportunities to innovate diagnostics incorporating novel autoantibodies and therapeutics targeting the PADs ultimately to allow for faster diagnosis and more effective treatment of rheumatoid arthritis.

2. KEYWORDS:

Rheumatoid arthritis
Antibodies
Anti-citrullinated protein antibodies
Rheumatoid factor
Citrullination
Peptidylarginine Deiminase 2

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Obtain appropriate approvals.
- Target completion Date: January 31, 2019
- Completed: April 19, 2019

Major Task 2: Determine which arginines in IgG are citrullinated by PAD2.
- Target completion date: 7/31/2023
- Percent Completed: 15%

Major Task 3: Determine how PAD2 regulates plasma cell numbers (Evaluate METs in PAD2$^{-/-}$ mice)

- Target completion date: 4/30/2023
- Percent Completed: 90%

Major Task 4: Define the role of PAD2 in antibody-based immunity to influenza.
- Target completion date: September 29, 2021
- Percent Completed: 100%

Major Task 5: Define the pathologic role of PAD2 in autoantibody-dependent inflammatory arthritis.
- Target completion date: July 31, 2023
- Percent Completed: 90%

Major Task 6: Determine how anti-citrullinated IgG antibodies develop including the role of smoking and HLA variants.
- Target completion date: 7/31/2023
- Percent Completed: 50%

Major Task 7: Prepare/publish manuscripts
- Target completion date: 9/29/2023
- Percent Completed: 65% (lower than previous since more papers have been added)

What was accomplished under these goals?

Major Task 1:
1. Specific Objectives: Obtain appropriate approvals
2. Major activities: ACURO and HRPO protocols submitted and approved.
3. Significant results: All protocols approved.
4. Other achievements: None
5. Goals not met: None

Major Task 2:
1. Specific Objectives: Determine which arginines in IgG are citrullinated by PAD2
2. Major activities: Mass spectrometry optimization was unsuccessful by two groups (Dr Coon and Dr Li). Work has been moved to Dr Van Eyk's team at Cedars Sinai Medical Center. Several steps have been taken in optimizing the mass spec.
3. Significant results: Several citrullines were identified.
4. Other achievements: None
5. Goals not met: None, per new NCE timeline

Major Task 3:
1. Specific Objectives: Determine how PAD2 regulates plasma cell numbers (Evaluate METs in PAD2$^{-/-}$ mice)
2. Major activities: Backcrossing to the C57BL/6 background, flow cytometry, ELISpot and limiting dilution assays (LDAs) were optimized and completed. MET assays were optimized and experiments have been completed unless reviewers request additional work.
3. Significant results: With a larger sample size than our preliminary data, we saw no difference in plasma cell numbers in immunized PAD2-/- vs WT mice. Similar findings were seen in arthritis (See Task 5). These data suggest that reduced plasma cell numbers do not explain lower IgG levels in PAD2-/- mice. In contrast, we found that PAD2 is required for total and citrullinated MET formation and for anti-citrullinated protein antibody binding to METs, suggesting that citrullinated METs may drive the production of at least some antibodies in a PAD2-dependent manner.
4. Other achievements: None
5. Goals not met: None, per new NCE timeline.

Major Task 4:
1. Specific Objectives: Define the role of PAD2 in antibody-based immunity to influenza.
2. Major activities: All necessary influenza experiments have been completed.

3. Significant results: PAD2 is required for normal levels of persistent hemagglutination inhibiting antibodies and full protection from lethal influenza rechallenge
4. Other achievements: None.
5. Goals not met: None.

Major Task 5:

1. Specific Objectives: Define the pathologic role of PAD2 in autoantibody-dependent inflammatory arthritis.
2. Major activities: All necessary experiments have been completed except for mass spec.
3. Significant results: PAD2 is required for maximal anti-collagen antibody levels, but not collagen-specific plasma cell numbers, T cell activation or polarization, or arthritis severity in CIA.
4. Other achievements: None.
5. Goals not met: None, per new NCE timeline.

Major Task 6:

1. Specific Objectives: Determine how anti-citrullinated IgG antibodies develop including the role for smoking and HLA variants.
2. Major activities: Mass spectrometry was initiated and is being optimized as discussed above. Experiments to identify the different epitopes of anti-IgG antibodies in clinical subsets have been completed in all groups but smokers. Epitope identification in smokers has been initiated. HLA typing has been performed.
3. Significant results: Linear IgG epitopes bound by multi-reactive anti-citrullinated protein antibodies (ACPAs) and IgG in RA, but not lupus, contain citrulline or homocitrulline, unifying the autoantibody repertoire in RA and revealing novel and unique IgG epitopes that are disease-specific.
4. Other achievements: None.
5. Goals not met: None, per new NCE timeline.

Major Task 7:

1. Specific Objectives: Publish manuscripts
2. Major activities: See publication list below.
3. Significant results: Publication
4. Other achievements: None
5. Goals not met: None, per new NCE timeline

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

All trainees received one-on-one mentoring approximately weekly and have attended lab meetings and seminars at the UW. Additionally, trainees have attended virtual national/international conferences.

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?

Major Task 1: Obtain appropriate approvals

- Completed, nothing to do.

Major Task 2: Determine which arginines in IgG are citrullinated by PAD2.

- Optimize mass spectrometry.
- Identify citrullines in IgG from $PAD2^{+/+}$ and $PAD2^{-/-}$ mice.

Major Task 3: Determine how PAD2 regulates plasma cell numbers.

- Evaluation of METs in PAD2$^{+/+}$ and PAD2$^{-/-}$ mice is likely complete unless reviewers request additional important experiments.

Major Task 4: Define the role of PAD2 in antibody-based immunity to influenza.
- Completed, nothing to do.

Major Task 5: Define the pathologic role of PAD2 in autoantibody-dependent inflammatory arthritis.
- IgG from mice with CIA will be evaluated by mass spectrometry.

Major Task 6: Determine how anti-citrullinated IgG antibodies develop including the role for smoking and HLA variants.
- Identify citrullines in purified IgG from clinical subsets by mass spectrometry
- Identify specific epitopes bound by anti-IgG antibodies in smokers.
- Determine which HLA types bind which IgG peptides bound by IgG

Major Task 7: Prepare manuscripts
- Manuscript preparation, submission, and revision will continue as findings are completed.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

1. We demonstrated for the first time that PAD2, or any PAD, is required for the antibody response to influenza. Interestingly, no role was found for PAD4 in the antiviral response to influenza.
2. We created a new model of influenza infection using an attenuated virus in DBA/1J mice.
3. We demonstrated that PAD2 has a limited role in collagen-induced arthritis.
4. We developed novel statistical methods to evaluate antibody binding to peptide array data.
5. We identified novel epitopes of IgG bound by rheumatoid factors only in rheumatoid arthritis and not in other inflammatory diseases, specifically citrulline- and homocitrulline-containing epitopes. These findings unify the autoantibody repertoire in rheumatoid arthritis (i.e. anti-citrullinated protein antibodies and rheumatoid factors) and differentiate rheumatoid factors in different diseases. These novel epitopes may prove to be important diagnostic tools in rheumatology and also may help to determine how rheumatoid arthritis develops. Indeed, these epitopes will be used in a project to be funded by a DoD Discovery Award that will evaluate how loss of tolerance against IgG after a viral infection may drive rheumatoid arthritis.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

WIS0066US, P220084US01, Title: IgG EPITOPE PEPTIDES THAT BIND RHEUMATOID FACTOR AND METHODS OF USE THEREOF, Serial Number: 63/289749, Filed: 12/15/21

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

There were no significant changes in objectives or scope.

Actual or anticipated problems or delays and actions or plans to resolve them

Major Task 1: Obtain appropriate approvals

- **Problem/Delay:** HRPO protocol was not approved by the projected time.
- **Action/Plan:** Protocol was ultimately approved and work was initiated, but some time was lost.

Major Task 2: Determine which arginines in IgG are citrullinated by PAD2.

- **Problem/delay:** Since citrullination is a difficult post-translational modification to detect, we established collaborations with experts. However, it has become clear that IgG is an extremely difficult protein to evaluate by mass spectrometry, likely due to glycosylation. We spent a year working with Dr Joshua Coon's team at the University of Wisconsin (UW) before he declared that his group was unable to continue the project. We then started to work with Dr Lingjun Li's group, also at UW. After a year, it became clear that her group was not going to be successful. We then started to work with Dr Jennifer Van Eyk's group. Her group has worked closely with us to identify the causes of the failures and optimize protocols. We have discovered that there are three major challenges. As background, to detect citrullines in IgG, we need a negative control (IgG known to have no citrullines) and a positive control (hyper-citrullinated IgG). The first challenge is that mammalian IgG may be citrullinated at baseline and there are no good sources of bacteria-produced IgG to use as a negative control. The second challenge is that IgG appears to be resistant to *in vitro* citrullination. The third challenge is that the mass spectrometry coverage of IgG is poor, i.e. we are only able to identify a small percentage of the IgG molecule due to digested fragments that are too large or too small.
- **Action/Plan:** To overcome these obstacles, we will first modify the IgG digestion protocol (i.e. different enzymes) to enhance coverage of the IgG heavy chain. Once coverage is optimized, we will purchase peptides of the same length as those detected by mass spectrometry in native form (negative control) and in a form with each arginine replaced by citrulline (positive control). We will then complete Major Task 2, 5, and 6.

Major Task 3: Determine how PAD2 regulates plasma cell numbers (Evaluate METs in PAD2$^{-/-}$ mice)

- **Problem/delay:** With a larger sample size than our preliminary data, we saw no difference in plasma cell numbers in immunized PAD2-/- vs WT mice. Similar findings were seen in arthritis (See Task 5). These data suggest that reduced plasma cell numbers do not explain lower IgG levels in PAD2-/- mice.
- **Action/Plan:** We changed focus to how PAD2 in macrophages might be regulating IgG levels unrelated to plasma cell numbers, specifically by evaluating its role in METosis.

Major Task 4: Define the role of PAD2 in antibody-based immunity to influenza.

- **Problem/delay:** We discovered that DBA/1J mice were extremely susceptible to influenza infection, so many mice died during infection reducing sample size. Moreover, we had to limit mouse breeding, and we were unable to infect more mice due to COVID-19 from March to June of 2020.
6. **Action/Plan:** We created a new model of influenza infection using an attenuated virus in DBA/1J mice. All necessary experiments now have been completed.

Major Task 5: Define the pathologic role of PAD2 in autoantibody-dependent inflammatory arthritis.

- **Problem/delay:** Mass spec problems noted above in Major Task 2
- **Action/Plan:** As above.

Major Task 6: Determine how anti-citrullinated IgG antibodies develop including the role for smoking and HLA variants.

- **Problem/Delay:** HRPO protocol was not approved by the projected time.
- **Action/Plan:** Work was initiated, but time was lost.
- **Problem/Delay:** Challenges with mass spectrometry (as above)
- **Action/Plan:** As above.

- **Problem/Delay:** Roche dissolved Nimblegen so new arrays could not be performed.
- **Action/Plan:** ELISA replaced array in large part, which was much more time consuming. Also, we were able to analyze previously acquired array data funded by different awards to assist in ELISA design.
- **Problem/Delay:** HLA typing was delayed in order to complete the anti-IgG ELISA experiments in order to determine the correct subjects and correct number of subjects on which to perform HLA typing.
- **Action/Plan:** HLA typing was recently completed.

Major Task 7: Prepare/publish manuscripts
- No delays

All Tasks:
- **Problem/Delay:** The COVID-19 pandemic caused almost all work on the project to cease for months. Then, personnel absences due to illness and mental health issues as well as loss of personnel due to childcare needs, requiring new hires and training of new staff in the absence of senior staff caused additional delays.
- **Action/Plan:** Time at home was optimized with data analysis, manuscript preparation, and planning for the return to the lab. New staff were hired and trained.

Changes that had a significant impact on expenditures

The delays described above delayed spending. These expenditures are expected to be made in subsequent years and thus total expenditures are expected to be unchanged over the whole period of the grant.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

No significant changes were made.

Significant changes in use or care of vertebrate animals

No significant changes were made.

Significant changes in use of biohazards and/or select agents

No significant changes.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Journal publications.

Publications:

Shelef MA. New Relationships for Old Autoantibodies in Rheumatoid Arthritis. Arthritis & Rheumatology. 2019 Sep;71(9):1396-1399
Zheng et al. Disordered antigens and epitope overlap between anti-citrullinated protein antibodies and rheumatoid factor in rheumatoid arthritis. Arthritis & Rheumatology. 2020 Feb;72(2):262-272.
Zheng et al. MixTwice: large-scale hypothesis testing for peptide arrays by variance mixing. Bioinformatics. 2021. Mar 8;37(17):2637-43
Mergaert et al. Peptidylarginine Deiminase 2 in Murine Antiviral and Autoimmune Antibody Responses. Journal of Immunology Research. 2022 Jan 17;2022:5258221.

Mergaert et al. Rheumatoid Arthritis: Methods for Two Murine Models. Methods in Cell Biology. 2022;168:125-137.
Mergaert AM et al. Rheumatoid factor and anti-modified protein antibody reactivities converge on IgG epitopes. Arthritis & Rheumatology. 2022. Jun;74(6):984-991.

Books or other non-periodical, one-time publications.

None

Other publications, conference papers and presentations.

2019 Disordered Antigens and Overlap Between Anti-Citrullinated Protein Antibodies and Rheumatoid Factor Unify Autoantibodies in Rheumatoid Arthritis, Department of Medicine Research Day, University of Wisconsin-Madison, Madison, WI
2019 Citrullination, Autoantibodies, and Rheumatoid Arthritis. Rheumatology Research Seminar Series. University of Wisconsin-Madison, Madison WI
2019 Citrullination, PADs, Autoantibodies, and Rheumatoid Arthritis. Joint Biology Consortium. Brigham and Women's Hospital and Harvard University, Boston, Massachusetts, USA.
2019 Citrullination, Autoantibodies, and Rheumatoid Arthritis. Pediatric Rheumatology Grand Rounds. Boston Children's Hospital, Boston, Massachusetts, USA.
2019 Citrullination, PADs, and Autoantibodies, in Rheumatoid Arthritis. University of Minnesota Center for Immunology, Minneapolis, Minnesota, USA.
2019 Citrullination, PADs, Autoantibodies, and Rheumatoid Arthritis. Baylor University, Houston, Texas, USA.
2020 Antibodies in RA: Beyond Citrullination & Back to Rheumatoid Factor, American College of Rheumatology Annual Meeting, Washington DC, USA.
2021 Anti-modified protein antibodies and rheumatoid factor: convergence and divergence. La Jolla Arthritis Conference. Virtual.
2021 Revisiting Autoantibodies in Rheumatoid Arthritis, Turkish Rheumatology Congress. Virtual
2022 New Insights into ACPAs and RFs in RA. Rheumatology Research Conference. University of Colorado. Virtual.

- **Website(s) or other Internet site(s)**

None.

- **Technologies or techniques**

1. A/PR/8/34 H1N1–OT-I (PR8-OVA) infection of DBA/1J mice
2. CIA with 2 IP boosts.

- **Inventions, patent applications, and/or licenses**

WIS0066US, P220084US01, Title: IgG EPITOPE PEPTIDES THAT BIND RHEUMATOID FACTOR AND METHODS OF USE THEREOF, Serial Number: 63/289749, Filed: 12/15/21

- **Other Products**

None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project? (Information is provided for the past year)

Name:	*Miriam Shelef*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*4*
Contribution to Project:	*Leading projects, coordinating scientists, mentoring trainees, reviewing experiments, participating in data analysis, and writing manuscripts.*
Funding Support:	*UW-Madison, Wisconsin Partnership Program, Sjögren's Foundation, NIH*

Name:	*Marulasiddappa Suresh*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*<1*
Contribution to Project:	*Oversight of influenza experiments.*
Funding Support:	*NIH, UW-Madison*

Name:	*Janna Bashar*
Project Role:	*Graduate student*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*12*
Contribution to Project:	*Experiments anti-IgG antibody, MET, and HLA experiments.*
Funding Support:	*UW-Madison*

Name:	*Zihao Zheng*
Project Role:	*Graduate student*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*8*
Contribution to Project:	*Analysis of array data and development and use of improved statistical methods.*
Funding Support:	*none*

Name:	*Maxwell Parker*
Project Role:	*research intern*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*5*
Contribution to Project:	*Experiments evaluating IgG epitopes*
Funding Support:	*UW-Madison*

Name:	*Lydia Smith*
Project Role:	*research intern*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*1*
Contribution to Project:	*Experiments evaluating IgG epitopes, lab management*
Funding Support:	*none*

Name:	*Ryan Adyniec*
Project Role:	*research intern*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*2*
Contribution to Project:	*Experiments evaluating IgG epitopes*

Funding Support: *none*

Name: *Adam Titi*
Project Role: *undergraduate researcher*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *2*
Contribution to Project: *Experiments evaluating IgG epitopes*
Funding Support: *none*

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

The following are active and pending other support for Dr Shelef during the award period:

COVID-19 Response Award: 4647 (Shelef) 05/01/2020 – 10/31/2021
Wisconsin Partnership Program 1.1 calendar
Title: Creating Infrastructure to Study the Immune Response to SARS-CoV-2 in Wisconsin
Goal: Establish a biorepository of longitudinally collected blood products and data from COVID-19 convalescent subjects to support numerous COVID-19-related research endeavors.
Role: PI
No overlap

Pilot Award (Shelef) 7/1/2020 - 6/30/2022
UW – Madison, Department of Medicine 0 calendar
Title: Creating Infrastructure to Study, Test for, and Track SARS-CoV-2 in Wisconsin
Goal: Build upon the WPP funded project to evaluate antibodies against SARS-COV-2 over time.
Role: PI
No overlap

1R41AR078063-01A1 (PI: Chamberlain) 09/01/2020 - 08/31/2021
DHHS/NIH 0.6 calendar
Title: Using Mineral Coated Microparticles as an Improved Sustained (60+ days) Delivery Method of Anakinra for Treatment and Prevention of Gout with a Single Injection
Role: Consultant
No overlap

High Impact Research Grant (McCoy) 7/1/2021-6/30/2022
Sjögren's Foundation 0.6 calendar
Title: Comprehensive Profiling of Sjögren's Syndrome Autoantibodies Identified from a Novel Whole Peptidome Array
Goal: Confirm candidate peptides identified from a whole peptidome array of Sjögren's Syndrome patients.
Role: Co-PI
No overlap

COVID-19 Response Award: 4791 (Yesilkoy) 09/01/2021 – 08/31/2023
Wisconsin Partnership Program 0.6 calendar total directs Title:
Widespread protective immunity screening against COVID-19 using a point-of-care serology-profiling biosensor
Goal: Develop a point-of-care serologic biosensor to detect past COVID-19 vaccination and infection.
Role: Co-PI
No overlap

Collaborative Health Sciences Program: 5084 (Shelef) 08/01/2022 – 07/31/2025
Wisconsin Partnership Program 2.4 calendar total directs Title:
Rediscovering rheumatoid factor as a unique antiviral agent in COVID-19
Goal: Define the unique epitopes bound by rheumatoid factors in COVID-19 as well as their antiviral functions.
Role: PI
No overlap

Discovery Award: PR220829 (Shelef) 04/1/2023 – 03/31/2025
PRMRP, CDMRP 2.4 calendar total funds
Title: Virus-induced loss of tolerance against IgG as a driving force in rheumatoid arthritis
Goal: Identify virus-induced loss of tolerance for IgG as a driver of rheumatoid arthritis.
Role: PI
No overlap

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

N/A

QUAD CHARTS:

Quad chart and generic award chart are included.

APPENDICES:

N/A