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

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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 to extend IgG half-life.
- Original target completion date: September 29, 2021
- New target completion date: September 29, 2022 (although an additional 1 year NCE is likely to be needed as outlined in the original NCE request)

- Percent Completed: 15%

Major Task 3: Determine how PAD2 regulates macrophage extracellular traps (Original goal: Determine how PAD2 regulates plasma cell numbers.)

- Original target completion date: January 31, 2021
- New target completion date: September 29, 2022
- Percent Completed: 50%

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.

- Original target completion date: September 29, 2021
- New target completion date: September 29, 2022
- Percent Completed: 90%

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

- Original target completion date: September 29, 2021
- New target completion date: September 29, 2022
- Percent Completed: 30%

Major Task 7: Prepare/publish manuscripts

- Original target completion date: September 29, 2021
- New target completion date: September 29, 2022
- Percent Completed: 65%

What was accomplished under these goals?

Major Task 1:

1. Specific Objectives: Obtain appropriate approvals
2. Major activities: ACURO protocol submitted and approved. HRPO protocol 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 to extend IgG half-life.
2. Major activities:
    a. Mass spectrometry optimization and identification of some citrullines of murine IgG. Methods were optimized for IgG purification **without** protein G. Project was switched from Dr Herbert and Dr Coon to Bin Wang in Dr Li's lab, but had limited success and was stopped in part due to COVID-19. Work has now been moved to Dr Jennifer Van Eyk's team at Cedars Sinai Medical Center. They are leaders in the field of citrullination detection with 10 publications on this topic in top journals. We sent them a first set of samples in June of 2021, which they are currently analyzing.
    b. As part of the experiments to rescue IgG half-life by in vitro citrullination of IgG with PAD2, we performed additional IgG transfer experiments.
3. Significant results:
    a. Several citrullines were identified.
    b. With the increased sample size in IgG half-life experiments, there was a less apparent difference in IgG half-life between PAD2-/- and WT mice.
4. Other achievements: None
5. Goals not met: Mass spectrometry experiments to identify citrullines in murine IgG were not completed in the predicted timeframe.

Major Task 3:

1. Specific Objectives: Determine how PAD2 regulates macrophage extracellular traps (METs) (Original: Determine how PAD2 regulates plasma cell numbers.)
2. Major activities: Backcrossing to the C57BL/6 background was completed. Flow cytometry was optimized and experiments to determine why plasma cells are reduced in PAD2-/- mice were initiated. To complement the flow cytometry experiments, ELISpot and limiting dilution assays (LDAs) were optimized and experiments performed. MET assays were optimized and experiments were initiated.
3. Significant results: ELISpot and LDAs showed no difference in plasma cell numbers in immunized PAD2-/- vs WT and in mice with CIA. PAD2 appears to be required for normal citrullinated MET formation in response to some stimuli.
4. Other achievements: None
5. Goals not met: Experiments were not completed in the expected timeframe.

Major Task 4:

1. Specific Objectives: Define the role of PAD2 in antibody-based immunity to influenza.
2. Major activities: All necessary influenza related experiments have been completed unless experiments are requested by reviewers upon manuscript review.
3. Significant results: There was no difference in weight loss (a sign of flu severity) in PAD2 KO vs WT mice in the primary influenza infection. However, there was more weight loss in PAD2 KO mice upon influenza reinfection, suggestive of incomplete immunity after the primary infection. Further, PAD2 KO mice had lower anti-viral antibodies at key time points.
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: Mass spec to identify citrullines in IgG from CIA mice with and without PAD2.

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. Some HLA typing has been performed.
3. Significant results: Different IgG epitopes, specifically citrulline-containing and homocitrulline-containing epitopes, are bound in RA, but not in lupus or Sjogren's Disease.
4. Other achievements: None.
5. Goals not met:
    a. HLA typing has not been completed.
    b. Correlation between HLA type and IgG peptides bound by IgG has not been determined.

Major Task 7:

1. Specific Objectives: Publish manuscripts
2. Major activities:
    a. An invited editorial was written and accepted for publication that includes many of Dr. Shelef's theories described in the grant application that led to the experiments in this project. (Shelef. Arthritis Rheum. 2019)

b. A manuscript that contains a small amount of data funded by this award related to anti-citrullinated IgG antibodies was published. (Zheng et al, Arthritis Rheum. 2020)
c. A manuscript about the murine flu and CIA studies has been written and submitted for publication. It was rejected and is being resubmitted.
d. A manuscript about one of Zihao Zheng and Michael Newton's new statistical methods has been accepted for publication (Zheng et al. Bioinformatics. 2021).
e. A manuscript about the novel IgG epitopes has been written, submitted, and is being revised for Arthritis and Rheumatology.

3. Significant results: Publication
4. Other achievements: None

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

All trainees and Michael Denny received one-on-one mentoring approximately weekly and have attended lab meetings and seminars at the UW.

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: Completed
- Nothing to do.

Major Task 2: Determine which arginines in IgG are citrullinated by PAD2 to extend IgG half-life.
- Optimize mass spectrometry and identify citrullines in IgG either with Dr Jennifer Van Eyk's team.
- We will continue to investigate the difference in IgG half-life in PAD2-/- vs WT mice to understand this phenomenon prior to continuing with PAD2 rescue experiments and mutation studies. Mass spec will help with this problem.

Major Task 3: Determine how PAD2 regulates plasma cell numbers.
- Since plasma cell numbers were unaltered in the absence of PAD2, we will no longer perform experiments to assess survival vs formation of plasma cells. We will continue to explore why IgG levels are lower, potentially through the originally proposed gene expression analysis of plasma cells as well as through revealing the role of PAD2 in METs.

Major Task 4: Define the role of PAD2 in antibody-based immunity to influenza.
- Any experiments required by reviewers will be completed.

Major Task 5: Define the pathologic role of PAD2 in autoantibody-dependent inflammatory arthritis.
- IgG 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.
2. We created a new model of influenza infection using an attenuated virus in DBA/1J mice.
3. We identified novel epitopes of IgG bound by rheumatoid factors only in RA and not in other inflammatory diseases, specifically citrulline- and homocitrulline-containing epitopes.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

We are in the process of preparing an application for a patent related to the novel epitopes of IgG bound by rheumatoid factors only in RA.

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 to extend IgG half-life.
- **Problem/delay:** Mass spectrometry experiments to identify arginines and citrullines of murine IgG were not completed with two different collaborative groups.
- **Action/Plan:** Work with Dr Jennifer Van Eyk's team.
- **Problem/delay:** As part of the experiments to rescue IgG half-life by in vitro citrullination with PAD2, we performed additional IgG transfer experiments. With the increased sample size, there was a less apparent difference in IgG half-life between PAD2-/- and WT mice.
- **Action/Plan:** We will continue to investigate the difference in IgG half-life in PAD2-/- vs WT mice to understand this phenomenon prior to continuing with PAD2 rescue experiments and mutation studies including evaluating the mass spec data. We will determine if sample size needs to be increased or if the differences are not sufficient to warrant further study.

Major Task 3: Determine how PAD2 regulates macrophage extracellular traps (Original: Determine how PAD2 regulates plasma cell numbers.)
- **Problem/delay:** PAD2 does not appear to be required for plasma cell numbers in a response to immunization or CIA, just IgG levels.
- **Action/Plan:** In addition to transcription studies on plasma cells to understand why Ig production might be lower, we will focus on 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:** Some 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.
- **Action/Plan:** Problems were overcome and all necessary experiments 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, but we were able to analyze array data funded by different awards to assist.
- **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 will be completed.

Major Task 7: Prepare/publish manuscripts

- No delays

All Tasks:

- **Problem/Delay:** From March to June, all work in the lab was stopped except for a single influenza experiment that had already been started due to COVID-19-related restrictions. Additionally, Michael Denny left his job due to family responsibilities related to COVID.
- **Action/Plan:** Time at home was optimized with data analysis, manuscript preparation, and planning for the return to the lab. Michael Denny was replaced by Janna Bashar.

Changes that had a significant impact on expenditures

The delays described above have 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.

1. **Shelef MA.** New Relationships for Old Autoantibodies in Rheumatoid Arthritis. Arthritis Rheumatol. 2019 Sep;71(9):1396-1399. Federal support acknowledged.
2. Zheng Z, Mergaert AM, Fahmy L, Bawadekar M, Holmes CL, Ong I, Bridges AJ, Newton MA, **Shelef MA.** Disordered antigens and epitope overlap between anti-citrullinated protein antibodies and rheumatoid factor in rheumatoid arthritis. Arthritis Rheumatol. 2020 Feb;72(2):262-272. Federal support acknowledged.
3. Zheng Z, Mergaert AM, Ong IM, **Shelef MA,** Newton MA. MixTwice: large-scale hypothesis testing for peptide arrays by variance mixing. Bioinformatics. 2021. Online ahead of print. Federal support acknowledged.

  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 How Not to Get Rheumatoid Arthritis, Department of Medicine Grand Rounds, University of Wisconsin – Madison. Virtual
  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.

- **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**

Patent application in preparation related to novel IgG epitopes bound by rheumatoid factors in rheumatoid arthritis only.

- **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:	*She has been leading the projects, coordinating all 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:	*He oversees and guides influenza experiments.*
Funding Support:	*NIH, UW-Madison*

Name:	*Aisha Mergaert*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*7 (90% effort on this award, starting 7/1/2020 cost-shared to a T32 position, then she graduated in the beginning of May 2021)*
Contribution to Project:	*She performed experiments related to CIA, flu, plasma cells, and anti-IgG antibodies.*
Funding Support:	*NIH*

Name:	*Janna Bashar*
Project Role:	*Graduate student*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*11*
Contribution to Project:	*She has been working on 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:	*100%*
Contribution to Project:	*He analyzes array data and develops improved statistical methods to do so as well as assists with other statistical analyses for this project.*
Funding Support:	*none*

Name:	*Maxwell Parker*
Project Role:	*research intern*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*3 (50% effort joining 4/26/2021)*
Contribution to Project:	*Mr. Parker performs 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?

Dr Shelef has additional support as follows:

COVID-19 Response Award: 4647 (Shelef) 05/01/2020 – 10/31/2021
Wisconsin Partnership Program 1.1 calendar total directs
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 total directs
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 total directs 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) Sjögren's Foundation 7/1/2021-6/30/2022
0.6 calendar total directs
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

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