AWARD NUMBER: W81XWH-20-1-0204
PR191079

TITLE: Key Autoantibody and Inflammatory Factors in the Initiation, Propagation, and Transition to Clinically Apparent Rheumatoid Arthritis

PRINCIPAL INVESTIGATOR: Kevin D. Deane, MD/PhD

CONTRACTING ORGANIZATION: University of Colorado Denver Anschutz Medical Campus

REPORT DATE: May-2021

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
May-2021	Annual Technical Report	15-Apr-2020 to 14-APR-2021

4. TITLE AND SUBTITLE Key Autoantibody and Inflammatory Factors in the Initiation, Propagation, and Transition to Clinically Apparent Rheumatoid Arthritis

5a. CONTRACT NUMBER
W81XWH-20-1-0204

5b. GRANT NUMBER
PR191079

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Kevin D. Deane MD/PhD

E-Mail: kevin.deane@cuanschutz.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Colorado Denver
Mail Stop F428
Anschutz Medical Campus, Building 500
13001 East 17th Place, Room W1126
Aurora, Colorado 80045 USA

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with the hallmark clinical finding of inflammatory arthritis (IA). RA affects ~1% of the population leading to substantial morbidity, increased mortality and high financial costs. The current paradigm for management of RA is to identify a patient with disease and treated once clinical signs of disease (e.g. joint pain and swelling) have been identified. However, there is now known to be a 'Pre-RA' period of RA during which circulating biomarkers including autoantibodies are present on average 3-5 years prior to the first appearance of clinically-apparent IA. Importantly, elevations of serum autoantibodies (e.g. antibodies to citrullinated protein antibodies [ACPA] and rheumatoid factor [RF]) can be used to accurately predict future RA in individuals without *current IA.* Indeed, the predictive ability of these autoantibodies has underpinned the development of several clinical prevention trials for RA. However, there are still substantial limits in prediction models for future RA; furthermore, specific biologic pathways that could be targeted in Pre-RA for prevention need additional exploration. As such, the primary objective for this project is to build on our initial findings from a prior CDMRP project and utilize a unique sample set of individuals from pre- and post-RA diagnosis obtained from the Department of Defense Serum Repository (DoDSR) to expand our knowledge about the development of RA and in particular improve prediction of future RA as well as identify potential pathways/targets for prevention by utilizing state-of-the-art biomarker testing.

15. SUBJECT TERMS

Pre-rheumatoid arthritis, prediction, pathogenesis, prevention

16. SECURITY CLASSIFICATION OF: Unclassified			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	11	USAMRMC

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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Project Title: Key Autoantibody and Inflammatory Factors in the Initiation, Propagation, and Transition to Clinically Apparent Rheumatoid Arthritis
Contract/Grant #: W81XWH-20-1-0204/ PR191079
PI: Kevin D. Deane, MD/PhD
Period of Report: 15-Apr-2020 to 14-Apr-2021

1. INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with the hallmark clinical finding of inflammatory arthritis (IA). RA affects ~1% of the population leading to substantial morbidity, increased mortality and high financial costs. The current paradigm for management of RA is to identify a patient with disease and treated once clinical signs of disease (e.g. joint pain and swelling) have been identified. However, there is now known to be a 'Pre-RA' period of RA during which circulating biomarkers including autoantibodies are present on average 3-5 years prior to the first appearance of clinically-apparent IA. Importantly, elevations of serum autoantibodies (e.g. antibodies to citrullinated protein antibodies [ACPA] and rheumatoid factor [RF]) can be used to accurately predict future RA in individuals without *current IA.* Indeed, the predictive ability of these autoantibodies has underpinned the development of several clinical prevention trials for RA. However, there are still substantial limits in prediction models for future RA; furthermore, specific biologic pathways that could be targeted in Pre-RA for prevention need additional exploration. As such, the primary objective for this Expansion Project is to build on our initial findings from a prior CDMRP project and utilize a unique sample set of individuals from pre- and post-RA diagnosis obtained from the Department of Defense Serum Repository (DoDSR) to expand our knowledge about the development of RA and in particular improve prediction of future RA as well as identify potential pathways/targets for prevention by utilizing state-of-the-art biomarker testing.

2. KEYWORDS:

Antibodies to carbamylated proteins (anti-CarP)
Antibodies to citrullinated protein antigens (ACPA)
Antibodies to peptidyl arginine deiminase (anti-PAD)
Pre-rheumatoid arthritis (Pre-RA)
Prediction
Prevention
Rheumatoid arthritis (RA)
Rheumatoid factor (RF)

3. ACCOMPLISHMENTS:

What were the major goals of the project?

- Goal/Objective 1 – Obtain final Human Research Protection Office (HRPO) approval June 2020.
- Goal/Objective 2 (Aim 1): Complete autoantibody testing on sample set (Table 1):

Table 1. Aim 1 Autoantibody testing		
Biomarker Testing	**Collaborator**	**Planned date of completion**
ACPA	Stanford, Inova	April 2021
Anti-PAD	Inova Research Laboratories	April 2021
Anti-CarP	Inova Research Laboratories	April 2021
Autoantibody glycosylation	Inova Research Laboratories	April 2022
Anti-nuclear antibody and anti-thyroid immunity	Oklahoma Medical Research Foundation	April 2022
Anti-malondialdehyde-acetaldehyde	University of Nebraska Medical Center	April 2022

- Goal/Objective 3 (Aim 2): Complete non-autoantibody biomarker testing (Table 2).

Table 2. Aim 2 Non-autoantibody testing		
Biomarker Testing	**Collaborator**	**Planned date of completion**
Proteomic measures	Olink Proteomics, Inc.	April 2022
C-reactive protein	University of Colorado	April 2022
Serum Calprotectin	Inova Research Laboratories	April 2021

- Goal/Objective 4 (Aim 3): Complete analyses and manuscript/abstract submission Nov 2022-April 2023.

What was accomplished under these goals?
Major activities
The contract for the project was fully executed on 15-April-2020 which was several weeks after the University of Colorado as well as multiple collaboratives sites were shut-down for research a shut-down around COVID-19. The shut-down including limits on personnel access to the laboratory and alterations of research laboratory testing which required high levels of sample processing safety (e.g. Biosafety Level 2+ [including need for human tissue processing in a hood]) at the University stuttered but was basically persistent until February 2021. As such, while we competed HRPO approval 29-May-2020, we have been delayed in sample disbursement and testing. However, with current (May 2021) availability, we estimate to ship all samples for planned testing (see Tables 1 and 2 above) by June 2021 with estimation that testing will be complete by November 2021. Notably this includes delay of some testing, but accelerating other testing. Therefore, overall, we will complete testing within 24 months of the initiation of the study and be on-track for completing analyses and publications as planned.

Specific objectives

- *Goal/Objective 1 – Obtain final Human Research Protection Office (HRPO) approval June 2020.* **Completed May 2020**
- *Goal/Objective 2 (Aim 1): Complete autoantibody testing on sample set as outlined in Table 1.* **Delayed; estimated completion Nov 2021**
- Goal/Objective 3 (Aim 2): Complete non-autoantibody biomarker testing as outlined in Table 2. **Delayed; estimated completion Nov 2021**
- Goal/Objective 4 (Aim 3): Complete analyses and manuscript/abstract submission Nov 2022-April 2023. **Estimated completion on-track for Nov 2022-Apr 2023**

Significant results

No scientific results are available at this time.

Other achievements

Not applicable.

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

- Not applicable at this time. However, we will utilize rheumatologists-in-training (e.g. fellows) for analyses once data available.

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 will complete biomarker testing and analyses as listed above.

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

The contract for the project was fully executed on 15-April-2020 which was several weeks after the University of Colorado as well as multiple collaboratives sites were shut-down for research a shut-down around COVID-19. The shut-down including limits on personnel access to the laboratory and alterations of research laboratory testing which required high levels of sample processing safety (e.g. Biosafety Level 2+ [including need for human tissue processing in a hood]) at the University stuttered but was basically persistent until February 2021. As such, while we competed HRPO approval 29-May-2020, we have been delayed in sample disbursement and testing. However, with current (May 2021) availability, we estimate to ship all samples for planned testing (see Tables 1 and 2 above) by June 2021 with estimation that testing will be complete by November 2021. Notably this includes delay of some testing but accelerates other testing. Therefore, overall, we will complete testing within 24 months of the initiation of the study and be on-track for completing analyses and publications as planned. Of note, there have not otherwise been changes to the original plan.

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

- Please see above.

Changes that had a significant impact on expenditures

- Please see above.

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

- There have been no changes in use of human subjects, etc.

Significant changes in use or care of human subjects

- No changes at this time.

Significant changes in use or care of vertebrate animals.

- Not applicable.

Significant changes in use of biohazards and/or select agents

- Not applicable.

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.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Kevin Deane*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	0000-0003-2211-4861
Nearest person month worked:	*0.6*
Contribution to Project:	*Project oversight, sample set selection*
Funding Support:	N/A

Name:	*Marie Feser*
Project Role:	*Study Coordinator*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*0.9*
Contribution to Project:	*Project oversight, sample set selection*
Funding Support:	N/A

Name:	*Ted Mikuls*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*0.6*
Contribution to Project:	*Project oversight, autoantibody testing*
Funding Support:	N/A

Name:	*Geoff Thiele*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*0.6*
Contribution to Project:	*Project oversight, autoantibody testing*
Funding Support:	N/A

Name:	*William Robinson*
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	*N/a*
Nearest person month worked:	0.6
Contribution to Project:	*Project oversight, autoantibody testing*
Funding Support:	N/A

Name:	*Laurie Moss*
Project Role:	*Data Manager*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*0.3*
Contribution to Project:	*Data management*
Funding Support:	*N/A*

Name:	*Brandie Wagner*
Project Role:	*Statistician*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	0.12
Contribution to Project:	*Analyses*
Funding Support:	N/A

Name:	*Colin O'Donnell*
Project Role:	*Statistician*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	0.12
Contribution to Project:	*Analyses*
Funding Support:	N/A

Name:	*Masoud Asadi-Zeydabadi*
Project Role:	*Statistician*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	0.12
Contribution to Project:	*Analyses*
Funding Support:	N/A

Name:	*Michael Holers*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	0.12
Contribution to Project:	*Project oversight, sample set selection, biomarker testing*
Funding Support:	N/A

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

- *There have been no changes in Other Support that have impacted this project for any personnel.*

What other organizations were involved as partners?

Organization name:	*Inova Research Laboratories*
Location of organization	*San Diego, California, USA*
Partner's contribution to the project	*Biomarker testing*

Organization name:	*Oklahoma Medical Research Foundation*
Location of organization	*Oklahoma City, Oklahoma, USA*
Partner's contribution to the project	*Biomarker testing*

Organization name:	*Olink Proteomics, Inc.*
Location of organization	*Boston, Massachusetts, USA*
Partner's contribution to the project	*Biomarker testing*

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** Not applicable.
- **QUAD CHARTS:** Not applicable.

9. APPENDICES

Not appliable.