AWARD NUMBER: W81XWH-19-1-0772

TITLE: Exercise Effects on Synuclein Aggregation, Neuroinflammation, and Neurodegeneration

PRINCIPAL INVESTIGATOR: Sheila M. Fleming, PhD

CONTRACTING ORGANIZATION: Northeast Ohio Medical University

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6. AUTHOR(S)
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5d. PROJECT NUMBER
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5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT Preclinical and clinical studies suggest that exercise therapy may slow the progression of Parkinson's disease (PD) – however overall results are inconclusive. We have leveraged an optimized preclinical model of PD to examine whether exercise therapy can protect against alpha-synuclein accumulation and the subsequent loss of neurons in PD, the mechanism whereby the effects of exercise may occur and the effect on behavior affected in PD including motor, cognitive, and neuropsychiatric function. To date, we have observed that treadmill exercise improves motor and cognitive function in the rat alpha-synuclein preformed fibril model of PD, however treadmill exercise is not associated with increased survival of nigrostriatal dopamine neurons or reduced alpha-synuclein aggregation and associated neuroinflammation. We are presently investigating additional mechanisms whereby exercise could improve parkinsonian symptoms. Understanding the mechanistic underpinnings of exercise-associated enhancements in motor/cognitive performance could identify targets to improve this non-invasive, non-pharmacological, low-cost therapeutic strategy for PD patients and at-risk populations, including military veterans. Exercise therapy could be made readily available through hospitals and VA systems across the country.

15. SUBJECT TERMS
Parkinson's disease – exercise – neuroprotection – nigrostriatal system – alpha-synuclein – aggregation – glial cell line-derived neurotrophic factor – brain derived neurotrophic factor

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	16	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.*

Parkinson's disease is the second most common neurodegenerative disorder. An estimated 1,000,000 United States residents will be living with Parkinson's disease by 2020 which will create a profound health and economic burden. There exist treatments for the symptoms of the disease but as the disease progresses these treatments are no longer effective. Therefore, it is of critical importance that therapies that slow or halt the progression of PD are identified. Preclinical and clinical studies suggest that exercise therapy may slow the progression of Parkinson's disease – however overall results are inconclusive. Our ability to properly evaluate the disease-modifying potential of exercise has been hindered by two main issues. Firstly, in clinical studies it is difficult to determine whether any improvements observed are due to symptomatic improvement versus the sparing of neurons or slowing pathology in the brain since we have limited ability to quantify neurons and Parkinson's pathology in the living human brain. Second, our ability to turn to preclinical animal models has been limited by the model tools we have had, models that do not accurately reproduce the key pathological feature of the Parkinsonian brain, alpha-synuclein accumulation. The present application seeks to use an optimized preclinical model of Parkinson's disease to examine whether exercise therapy can protect against this hallmark pathology of Parkinson's disease and the subsequent loss of neurons. We also will examine the mechanism whereby the effects of exercise may occur and the effect on behavior affected in Parkinson's disease including motor, cognitive, and neuropsychiatric function. This research addresses the FY18 PRP IIRA Focus Area "*Biological mechanisms of impact from exercise on neurodegeneration in Parkinson's disease*" directly by examining the effect of exercise in this optimized preclinical Parkinson's disease model and mechanisms related to accumulation of the toxic protein alpha-synuclein, neuroinflammation and expression of substances in the brain called trophic factors. Results from this research could help individuals afflicted by Parkinson's disease. If exercise is truly disease-modifying then it would provide a much needed, non-invasive, non-pharmacological, low-cost therapeutic strategy for Parkinson's disease patients and at risk populations, including military veterans. Exercise therapy could be made readily available through hospitals and VA systems across the country.

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

Parkinson's disease – exercise – neuroprotection – nigrostriatal system – alpha-synuclein – aggregation – glial cell line-derived neurotrophic factor – brain derived neurotrophic factor

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.

Specific Aim 1: Impact of exercise on endogenous alpha synuclein aggregation, trophic factor expression, alpha synuclein inclusion-triggered neuroinflammation and alpha synuclein inclusion-induced behavioral deficits

Major Task 1: Intrastriatal injection of 40 adult male F344 rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle. **12/15/19 – 100% completed 12/15/19**

Major Task 2: Exercise regimen and behavioral assessments conducted with 40 adult male F344 rats – 1st cohort **- 2/15/20 – 100% completed 2/15/20**

Major Task 3: Necropsy and postmortem assessments of 40 adult male F344 rats – 1st cohort **6/15/20 – 100% completed 12/31/20.**

Major Task 4: Intrastriatal injection of 40 adult male F344 rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – 2nd cohort - **4/15/20 – 100% completed 1/15/21.**

Major Task 5: Exercise regimen and behavioral assessments conducted with 40 adult male F344 rats – 2nd cohort - **7/15/20 – 100% completed 3/31/20**

Major Task 6: Necropsy and postmortem assessments of 40 adult male F344 rats – 2nd cohort **11/15/20 – 100% completed 4/11/22**

Specific Aim 2. Impact of exercise on synucleinopathy triggered nigrostriatal degeneration and behavioral impairments

Major Task 1: Intrastriatal injection of 40 adult male F344 rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – 1st cohort - **12/15/20 – 100% completed 4/15/21**

Major Task 2: Exercise regimen and behavioral assessments conducted with 40 adult male F344 rats – 1st cohort - **6/15/21 – 100% completed 10/15/21**

Major Task 3: Necropsy and postmortem assessments of 40 adult male F344 rats – 1st cohort - **9/15/21- 75% completed 9/15/22**

Major Task 4: Intrastriatal injection of 40 adult male F344 rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle - 2nd cohort – **12/15/21- 100% completed 12/15/21**

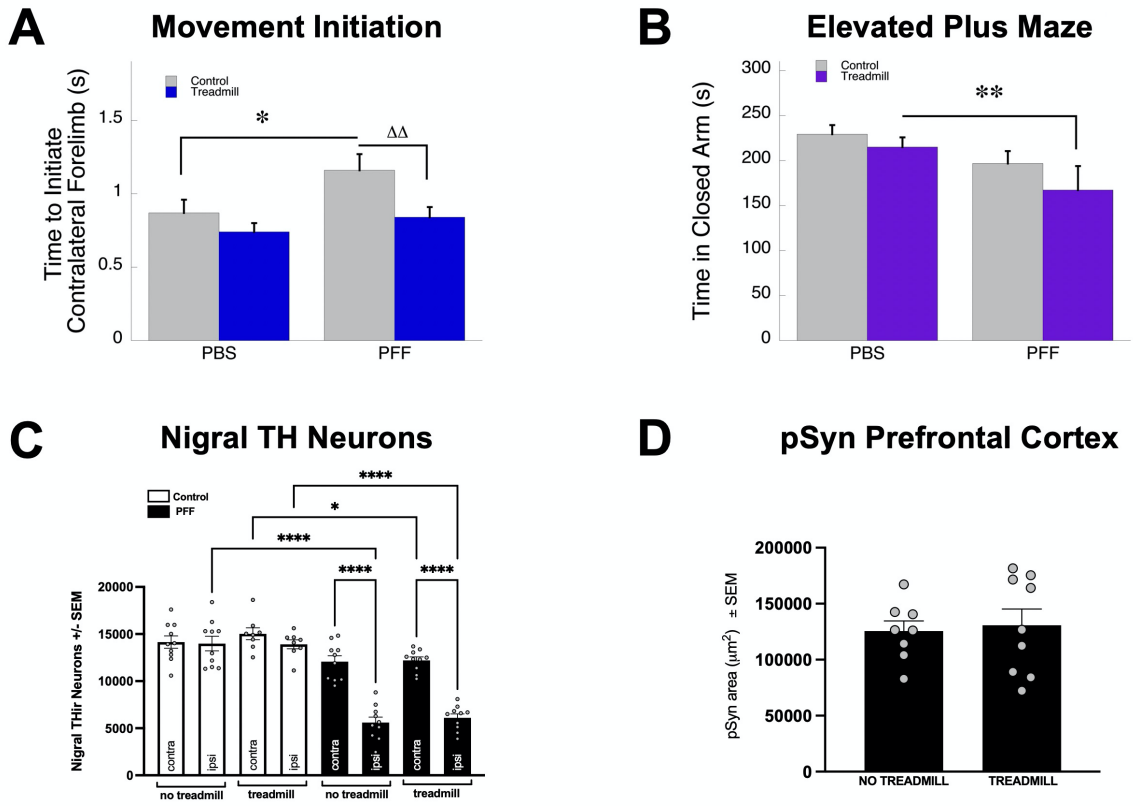
Major Task 5: Exercise regimen and behavioral assessments conducted with 40 adult male F344 rats – 2nd cohort - **3/15/22 – Exercise regimen 100% completed, behavioral assessments 50% completed 9/15/22**

Major Task 6: Necropsy and postmortem assessments of 40 adult male F344 rats – 2nd cohort – **9/15/22- Necropsy 100% completed, postmortem assessments 25% completed 9/15/22**

Note that proposed original completion dates were projected prior to the COVID-19 research shutdown in spring 2020.

Current status.

What was accomplished under these goals?



Major Activities during this reporting period include results representing outcomes from Specific Aim 2, Major Tasks 2, 3 and 5. Specifically, we examined the impact of treadmill exercise in control (PBS) and PFF-injected rats 6 months following surgery. PBS and PFF rats received treadmill exercise or no exercise for 5 months beginning 1 month after surgery.

The impact of treadmill exercise (Control or Treadmill) in PBS and alpha-synuclein preformed fibril (PFF)-injected rats (n=80).
A. Movement initiation. PFF/No Ex Control exercise rats took significantly longer to initiate a step with the contralateral limb compared to PBS/No Ex Control and PFF/Treadmill rats.
B. Elevated plus maze. PFF/Treadmill rats exhibited a reduction in emotional reactivity.
***, ** represents p<0.05, 0.01 respectively, compared to the corresponding PBS group,*
ΔΔ represents p<0.01 compared to PFF/No Exercise. 2X2 Randomized ANOVA, Tukey-Kramer post hoc.

The impact of treadmill exercise (no treadmill or treadmill) on pathological outcome measures in the rat PFF model (n=40).
C. Nigral TH Neurons. Number of tyrosine hydroxylase immunoreactive (THir) neurons in the subtantia nigra pars compacta (immunohistochemistry combined with unbiased stereology). PFF injection resulted in significant loss of ipsilateral THir neurons, PFF-induced nigral loss was not impacted by treadmill exercise injection. *Ipsilateral hemispheres 1 way ANOVA, comparisons between hemispheres via 2 way ANOVA, *, **** represents p<0.05, 0.0001 respectively.*
D. pSyn Accumulation in the Prefrontal Cortex. PFF injection resulted in accumulation of inclusions immunoreactive for alpha-synuclein phosphorylated at serine 129 (pSyn) in the prefrontal cortex. Treadmill exercise did not impact pSyn accumulation. *Unpaired t test.*

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."

Nothing to report.

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.

Results from Specific Aim 1 were presented at the *International Congress of Parkinson's Disease and Movement Disorders* in September 2022.
Fleming SM, Patterson JR, Kemp CJ, Lepp J, Hamad E, Scott S, Davis A, Szarowicz C, Lipton JW, Kubik M, Kuhn N, Stoll AC, Luk KC, Sortwell CE *The effect of short-term treadmill exercise in the alpha-synuclein preformed fibril rat model of Parkinson's disease.*

What do you plan to do during the next reporting period to accomplish the goals?

Planned for the next reporting period (Sept 15, 2022 – April 14, 2023)

Specific Aim 2. Impact of exercise on synucleinopathy triggered nigrostriatal degeneration and behavioral impairments
Major Task 5: Complete behavioral assessments of second cohort of 40 adult male F344 rats.
Major Task 6: Complete postmortem assessments of second cohort of 40 adult male F344 rats.

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."

Nothing to report.

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:*

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

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.

Nothing to report.

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

No human subjects research.

Significant changes in use or care of vertebrate animals

No significant changes in use or care of vertebrate animals.
MSU IACUC approval received 2/2022, ACURO approval received 3/2022.
NEOMED IACUC approval received 10/2020, ACURO approval receive 10/2020.

Significant changes in use of biohazards and/or select agents

No significant changes in use of biohazards. No select agents used.

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.

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

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.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the 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".

MSU:

Name: Caryl Sortwell, Ph.D. No change.

Name: Christopher Kemp, MS No change.

Name: Nathan Kuhn No change.

NEOMED:

Name: Sheila Fleming, Ph.D No Change

Name: Josephine Lepp, M.S. No Change

Name: *Sophia Scott*
Project Role: *Research Technician*
Researcher Identifier (e.g. ORCID ID): *0000-0002-6845-7395*
Nearest person month worked: *3 calendar months (over the 6 month interval)*
Contribution to Project:
Ms. Scott has been assisting in running and behaviorally testing the animals in the study.

Name: *Kendall Carter*
Project Role: *Research Technician*
Researcher Identifier (e.g. ORCID ID): *0000-0003-0870-3328*
Nearest person month worked: *6 calendar months (over the 6 month interval)*
Contribution to Project:
Ms. Carter has been assisting in running and behaviorally testing the animals in the study.

Name: *Reed Davis*
Project Role: *Postdoctoral Researcher*
Researcher Identifier (e.g. ORCID ID): *0000-0003-2735-2295*
Nearest person month worked: *2 calendar months (over the 6 month interval)*
Contribution to Project:
Dr. Davis has been assisting in running and behaviorally testing the animals in the study.

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."

Dr. Sortwell has received the following new active support since the previous reporting period. This new support does not overlap or impact the effort on this project.

***Title: Impact of BDNF Variants on Deep Brain Stimulation Outcomes**
Major Goals: The major goal of this proposal is to determine whether rs6265 BDNF genotype impacts patient response to DBS.
Project Number: No Number
Name of PD/PI: Sortwell, Caryl and Ali, Rushna (Co-PIs)
*Source of Support: Spectrum Health – Michigan State University Alliance *Project/Proposal Start and End Date: 04/01/22 -9/30/23 Total Award Amount (including Indirect Costs):
*Person Months: (Calendar) per budget period.

Year	Person Months
1. 2021 - 2022	1.2 calendar
1. 2022 - 2023	0.6 calendar

***Title: Further Investigation of the Neuroprotective Potential and Mechanism of the Rho Ki nase Inhibitor KL-00974**
Major Goals: This project will investigate the ability of optimized dosing of the Kadmon KL-00974 ROCK inhibitor to provide neuroprotection in the alpha-synuclein preformed fibril model and will investigate the mechanism of KL-00974-mediated neuroprotection in the AAV alpha-synuclein overexpression model using a transcriptomic approach.
Project Number: MJFF-021161
Name of PD/PI: Sortwell, Caryl and MacKeigan, Jeff (Co-PIs)
*Source of Support: Michael J. Fox Foundation
Project/Proposal Start and End Date: 02/22-08/23
*Total Award Amount (including Indirect Costs):
*Person Months: (Calendar) per budget period.

Year	Person Months
1. 2022 - 2023	1.2 calendar
1. 2023 - 2023	0.6 calendar

***Title: Synucleinopathy Triggered NLRP3 Inflammasome**
Major Goals: The major goal of this proposal is to determine examine and measure NLRP3 and related inflammasome components in the AAV alpha-synuclein overexpression and alpha-synuclein preformed fibril models of Parkinson's disease.
Project Number: No Number
Name of PD/PI: Sortwell, Caryl
*Source of Support: Takeda
Project/Proposal Start and End Date: 04/22-03/23
*Total Award Amount (including Indirect Costs):
*Person Months: (Calendar) per budget period.

Year	Person Months
1. 2022 - 2023	1.8 calendar

Dr. Fleming has received the following new active support since the previous reporting period. This new support does not overlap or impact the effort on this project.

Title: "Development of a protocol for ballroom dance therapy in Parkinson's disease"
These funds will support the development of a protocol for measuring the effect ballroom dancing on Parkinson's disease outcomes.
Project Number: No Number
Name of PD/PI: Amy Lee M.D., M.PH. and Sheila Fleming, Ph.D.
Source of Support: Northeast Ohio Medical University Translational Pilot Grant
Total Award Amount:
No salary support

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:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (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.*

Nothing to report.

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.*

Exercise Effects on Synuclein Aggregation, Neuroinflammation, and Neurodegeneration

PD180074 Semi Annual Technical Report W81XWH-19-1-0771 and 0772

PI: Sortwell and Fleming **Org: MSU/NEOMED** **Award Amount: $2,000,000**

Study/Product Aim(s)

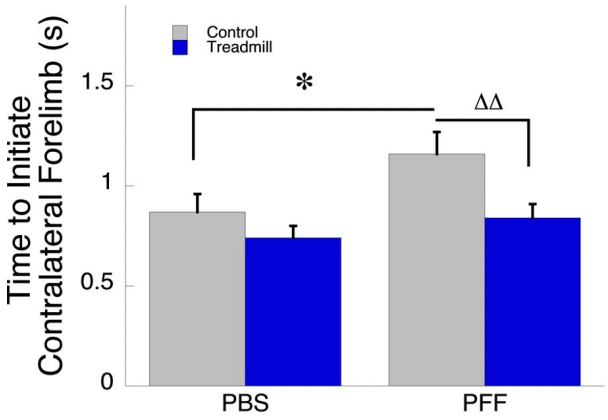
• Specific Aim 1: Impact of exercise on endogenous alpha synuclein aggregation, trophic factor expression, alpha synuclein inclusion-triggered neuroinflammation and alphasynuclein

•Specific Aim 2. Impact of exercise on synucleinopathy triggered nigrostriatal degeneration and behavioral impairments.

Approach

We will determine whether exercise can prevent the progression of early disease pathology or modify the consequences of disease pathology after it emerges using the the alpha-synuclein PFF rat model . We will measure the impact of exercise on protein degradation, the inflammatory response, and neurotrophic expression. Collectively, these studies will provide evidence to support or refute the disease-modifying potential of exercise against synucleinopathy in PD.

Movement Initiation



Treadmill exercise significantly improves forelimb step initiation deficits induced by intrastriatal injections of alpha-synuclein preformed fibrils (PFF). Rats received either treadmill exercise or no exercise 5x/week for 5 months.
** p<0.05 compared to the corresponding PBS group, ΔΔ p<0.01 compared to PFF/No Exercise. 2X2 Randomized ANOVA, Tukey-Kramer post hoc.*

Accomplishments: PENDING

Timeline and Cost

Activities	CY 19	20	21	22
Specific Aim 1				
Specific Aim 2				
Estimated Budget ($K)	$666	$666	$666	

Updated: (4/14/2022)

CY20 Goal – Initiate Specific Aim 1
- ☑ Generation of a-syn PFFs
- ☑Aim 1: Cohort 1 stereotactic surgeries
- ☑ Aim 1: Cohort 1 exercise regimen and behavioral assessments
- ☑ Aim 1: Cohort 1 postmortem analysis

CY21 Goal – Complete Specific Aim 1, Initiate Specific Aim 2
- ☑ Aim 1: Cohort 2 surgeries/exercise/behavioral assessments
- ☑ Aim 1: Cohort 2 postmortem analysis
- ☑ Aim 2: Generation of a-syn PFFs for SA2
- ☑ Aim 2: Cohort 1 stereotactic surgeries
- ☑ Aim 2: Cohort 1 exercise regimen/behavioral assessments
- ☑ Aim 2: Cohort 1 postmortem analysis

CY22 Goal – Complete Specific Aim 2
- ☑ Aim 2: Cohort 2 stereotactic surgeries
- ☐ Aim 2: Cohort 2 exercise regimen/behavioral assessments - *ongoing*
- ☐ Aim 2: Cohort 2 postmortem analysis

Budget Expenditure to Date (9/15/19-3/14/22)

Projected Expenditure: (MSU - $666K) (NEOMED - $624K) Direct Costs
Actual Expenditure: (MSU - $639K) (NEOMED – $425K) Direct Costs