**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

**REPORT DATE:** October 2020

**TYPE OF REPORT:** Annual

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

# REPORT DOCUMENTATION PAGE

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| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| Oct 2020 | Annual | Sep 15, 2019 - Sept 14, 2020 |

**4. TITLE AND SUBTITLE**
Exercise Effects on Synuclein Aggregation, Neuroinflammation, and Neurodegeneration

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**
W81XWH-19-1-0772

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Sheila M. Fleming, Ph.D.

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**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

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

Northeast Ohio Medical University
4209 State Route 44, PO Box 95
Rootstown, OH 44272-0095

**8. PERFORMING ORGANIZATION REPORT NUMBER**

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

The United States Army Medical Acquisition Activity
Fort Detrick, Maryland 21702-5012

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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. The present application seeks to use 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. We have completed the behavioral analyses of the first rat cohort and established a treadmill exercise-induced signal of improvement in spontaneous activity and decreased anxiety. We also have observed that treadmill exercise may improve deficits in forelimb movement initiation induced by synucleinopathy. Results from this research could help individuals afflicted by PD. If exercise is truly disease-modifying then it would provide a much needed, 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 | | | USAMRMC |
| Unclassified | Unclassified | Unclassified | Unclassified | 17 | 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.*

*Please note that dates indicated in black font were original target dates for completion whereas dates in red indicate projected completion dates due to delay from COVID-19 research shutdown.*

**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 – **Completed 12/15/19 (Sortwell MSU)**

Major Task 2: Exercise regimen and behavioral assessments conducted with 40 adult male F344 rats – **Completed 2/15/20 (Fleming NEOMED)**

**Complete COVID-19 Research Shutdown 3/15/20 – 6/15/20.**

**Partial COVID-19 Research Shutdown (slowed due to social distancing requirements) 6/15/20-8/15/20**

Major Task 3: Necropsy and postmortem assessments of 40 adult male F344 rats – **6/15/20** **50% completed 10/15/20 - New projected 100% completion date 12/31/20 (Sortwell MSU)**

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 – **4/15/20**

**New projected completion date 1/15/21 (Sortwell MSU)**

Major Task 5: Exercise regimen and behavioral assessments conducted with 40 adult male F344 rats – **7/15/20** **New projected completion date 3/31/21 (Fleming NEOMED)**

Major Task 6: Necropsy and postmortem assessments of 40 adult male F344 rats – **11/15/20**

**New projected completion date 6/30/21 (Sortwell MSU)**

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

Major Task 1: Intrastriatal injection of 60 adult male F344 rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – **12/15/20**

**New projected completion date 4/15/21 (Sortwell MSU)**

Major Task 2: Exercise regimen and behavioral assessments conducted with 60 adult male F344 rats – **6/15/21**

**New projected completion date 10/15/21 (Fleming NEOMED)**

Major Task 3: Necropsy and postmortem assessments of 60 adult male F344 rats – **9/15/21**

**New projected completion date 2/30/22 (Sortwell MSU)**

Major Task 4: Intrastriatal injection of 60 adult male F344 rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – **12/15/21**

**New projected completion date 1/30/22 (Sortwell MSU)**

Major Task 5: Exercise regimen and behavioral assessments conducted with 60 adult male F344 rats – **3/15/22**

**New projected completion date 7/15/22 (Fleming NEOMED)**

Major Task 6: Necropsy and postmortem assessments of 60 adult female F344 rats – **9/15/22**

**New projected completion date 11/15/22 (Sortwell MSU)**

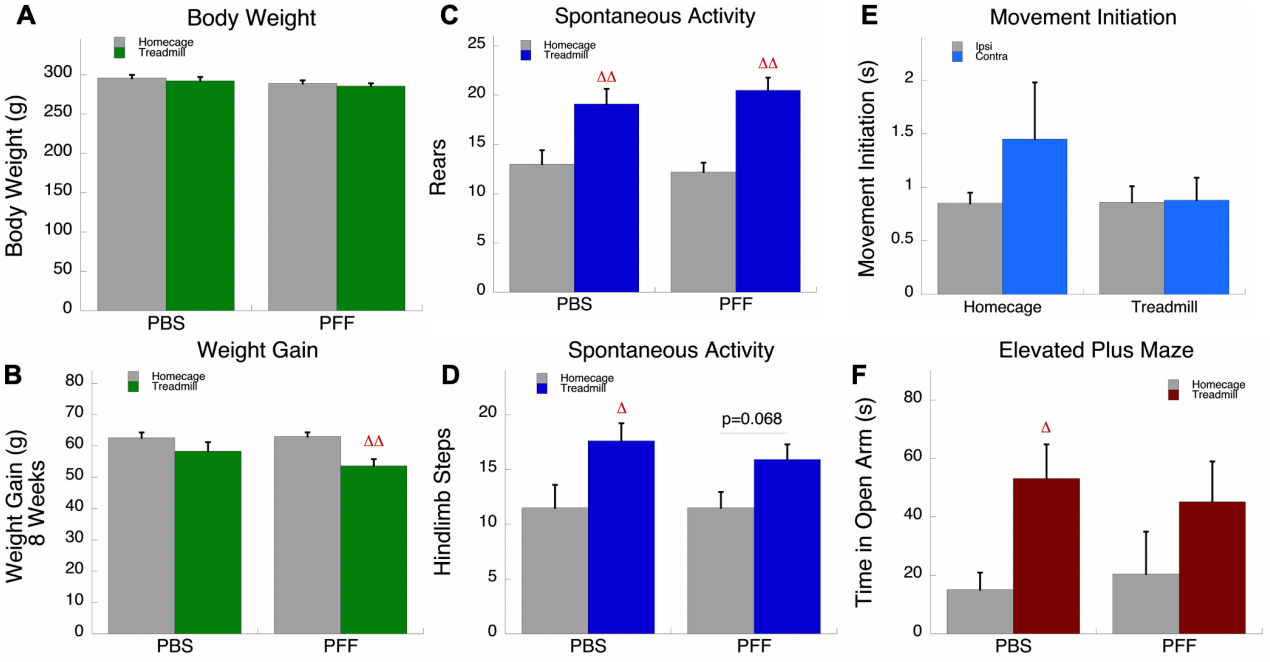
Altered timeline absorbs 6-month COVID-19 delay/slowdown and ultimately decreases delay to 2 months by the end of the project.

## What was accomplished under these goals?

1. Major activities: Mouse alpha-synuclein preformed fibrils (a-syn PFFs) were generated and validated in the Luk laboratory. Unilateral intrastriatal injections of PBS or a-syn PFFs were performed on 40 Fischer 344 rats at Michigan State University in the Sortwell lab, length of PFFs post-sonication was validated (approximately 50 microns). Following surgery the rats were shipped Northeast Ohio Medical University where the Fleming lab acclimated the rats and then began treadmill testing (Exercise) on half of the cohort. Cagemates served as controls (No Exercise) and remained in the homecage during treadmill testing. Treadmill exercise was performed five days/week (Monday-Friday) at the same time of day and in the same order during each session for the next seven weeks. During the last 10 days of Exercise or No Exercise, sensorimotor and nonmotor testing also was performed. Sensorimotor testing included assays for spontaneous activity (cylinder test), movement initiation, and bracing. For nonmotor testing animals were assessed for olfactory abilities using the block test, anxiety-like behavior using the elevated plus maze, and cognitive abilities using an object recognition test. At eight weeks post injection, animals were shipped back to the Sortwell lab for necropsy. Rats were perfused and are presently halfway through postmortem analyses.

2. Specific Objectives: The objective of this experiment is to determine the impact of exercise on alpha-synuclein aggregation (pSyn), neuroinflammation, and trophic factor expression within the nigrostriatal system at an early timepoint where peak pSyn and neuroinflmmation are observed in the substantia nigra but prior to frank neurodegeneration.

3/4. Key Outcomes/Other Achievements: The behavioral analysis reveals effects of treadmill exercise on several outcome measures in both PBS and PFF injected rats. Exercise did not significantly affect body weight in PBS (homecage=10, treadmill=10) or PFF (homecage=10, treadmill=10) rats (Figure 1A). However, weight gain over the course of the experiment was affected by exercise. PFF rats receiving exercise gained less weight compared to PFF rats that remained in the homecage (Figure 1B). Exercise also increased spontaneous activity in the cylinder. Both PBS and PFF rats receiving treadmill training made more rears in the cylinder compared to their no exercise homecage controls (Figure 1C). Hindlimb stepping in the cylinder was also increased in the PBS treadmill group and there was a strong trend for PFF rats to make more hindlimb steps (Figure 1D). In the movement initiation test there were no statistically significant differences but within the PFF rats, the data shows a trend for increased movement initiation time with the contralateral forelimb in the homecage rats but not in the treadmill exercise rats (Figure 1E). For nonmotor testing, treadmill exercise significantly increased time spent in the open arm in PBS injected rats and there was a trend for a similar increase in PFF rats (Figure 1F). There were no differences the block test of olfaction and object recognition is currently being analyzed. For weight, spontaneous activity, and movement initiation a 2x2 randomized ANOVA was performed followed by Tukey's HSD post hoc. For the elevated plus maze data the nonparametric test Mann-Whitney U was used. For all graphs Δ, ΔΔ represents p<0.05, 0.01, respectively, compared to same injection homecage control group.




To date, the data suggest that the seven week treadmill exercise regimen does affect behavioral performance in both PBS and PFF rats. Specifically, exercis e increases spontaneous activity and reduces the fear response in the elevated plus maze. Although not statistically significant, the movement initiation data shows the potential development of an initiation asymmetry in PFF rats that remained in the homecage similar to what we have observed in our previous work in PFF rats (*Fleming et al. 2020. Intrastriatal injection of alpha-synuclein preformed fibrils results in cognitive dysfunction and L-DOPA reversible sensorimotor impairments in rats. International Congress of Parkinson's Disease and Movement Disorders*) and that there is no potential asymmetry developing in the exercise PFF rats.

**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.*

Nothing to report.

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

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

**Planned for the next reporting period (Sept 15, 2020 – April 14, 2021)**

**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 3: Necropsy and postmortem assessments of 40 adult male F344 rats –
Completion date 12/31/20 (Sortwell MSU)
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 –
Completion date 1/15/21 (Sortwell MSU)
Major Task 5: Exercise regimen and behavioral assessments conducted with 40 adult male F344 rats –
Completion date 3/31/21 (Fleming NEOMED)

*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:*

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.*

We experienced a 6-month delay in research productivity due to the COVID-19 pandemic related research shutdown. We have accelerated our research schedule moving forward in order to reduce this delay and now anticipate finishing the project only two months behind schedule.

**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.*

Due to the COVID-19 pandemic related research shutdown expenditures and effort were less than expected during the first year of the award. Now that research productivity has increased these expenditures are expected to rise during the next year and be back on track by the start of the third and final year of the award.

**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 Rcvd 3/27/2019.
NEOMED IACUC approval Rcvd 10/07/2020.

**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: Jacob Howe, BS*
*Project Role: Graduate Student*
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked: 2 calendar months (over the 12 month interval)*
*Contribution to Project:*
*Mr. Howe has assisted Mr. Kemp with post mortem tissue assessments.*

**NEOMED:**

*Name: Sheila Fleming , Ph.D No Change*

*Name: Josephine Lepp, M.S. No change*

*Name: Edward Hamad, B.S.*
*Project Role: Research Technician*
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked: 3 calendar months (over the 12 month interval)*
*Contribution to Project:*
*Mr. Hamad 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 impact the effort on this project.

R01NS105826 09/01/18-08/31/23 0.6 months
Steece-Collier, PI ADC
NINDS
*changes or for changes in the levelfor active support reported previously. The awarding*
"Impact of dysfunctional BDNF on dopamine terminal remodeling in the parkinsonian striatum"
This proposal examines the role of the rs6265 BDNF variant in dopaminergic graft efficacy.

R61NS111347 12/01/19 - 11/30/22 0.36 months
Tepe, PI ADC
NINDS
"Development of cellular HTS for 20S proteasome enhancers"
This proposal seeks hit-to-lead candidates of 20S proteasome enhancers.

R01AG066223. 09/15/19-05/31/23 0.5 months
Tepe, PI ADC
NIA
"Small molecule induced proteolytic destruction of intrinsically disordered proteins"
This proposal seeks to validate lead novel drug candidates to clear α-synuclein aggregates in vitro.

No Number 1/1/2021 – 12/31/2023 0.0 months
Purcell, PI TDC
Strategic Partnership Grant, MSU
"A next-generation, all-diamond ultramicroelectrode sensor for clinical applications in the nervous system"
The project goals are to translate an all-diamond ultramicroelectrode sensor from the bench into the brain, and into a model of human disease (Parkinson's Disease) to facilitate drug and biomarker discovery.

No Number 08/01/20-02/28/22 0.6 months
Patterson, Sortwell Co-PIs TDC
Michael J. Fox Foundation
"Assessment of the neuroprotective potential of terazosin via PGK1-enhanced glycolysis and mitochondrial function"
This proposal will examine whether terazosin can provide protection from synucleinopathy or 6-OHDA induced degeneration.

No Number 08/01/20-07/31/21 0.12 months
Yurek, PI ADC (MSU Sub)
Michael J. Fox Foundation
"Gene therapy approach to reduce alpha-synuclein aggregation in an animal model of PD"
This proposal will examine whether viral vector mediated overexpression of RAB3 can provide protection from synucleinopathy.

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

1R41MH121119-01
“Extending WAAVES+: An animal and environment-agnostic, automated USV scoring platform for high-throughput social, behavioral, and neuropharmacological studies”
PI: Cornerstone Research Group, Inc. 9/1/19-8/31/21
Consultant: **Sheila Fleming, Ph.D.** 0.96 months
Agency: NIH/NIMH STTR FOA PA-18-579
This grant will develop an approach for a generalized, automated scoring tool for ultrasonic vocalizations (USVs) to be used when studying neuropsychiatric conditions.
**No Overlap**

1R01ES031124-01
“ATP13A2 and susceptibility to neurodegeneration” 9/28/2020-6/30/2025
**PI: Sheila Fleming, Ph.D.** 4.2 months
Agency: NIH/ NIEHS
This grant will investigate how loss of ATP13A2 function affects manganese and alpha-synuclein toxicity in mice.
**No Overlap**

**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

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

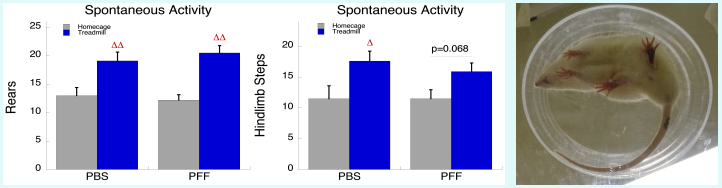
### Study/Product Aim(s)

- 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.




**Treadmill exercise increases spontaneous activity in the cylinder in PBS and PFF injected rats compared to rats that remained in the homecage without exercise.**

**Accomplishments: We have completed the behavioral analyses of the first rat cohort and established a treadmill exercise-induced signal of improvement in spontaneous activity and decreased anxiety. We also have observed that treadmill exercise may improve deficits in forelimb movement initiation induced by synucleinopathy**

## Timeline and Cost

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

**Updated:** (04/21/2020)

**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 and 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/behavior/postmortem analysis

**Budget Expenditure to Date (4-14-2020)**

Projected Expenditure: (MSU - $220K) (NEOMED - $210K) Direct Costs
Actual Expenditure: (MSU - $125K) (NEOMED – $150K) Direct Costs