AWARD NUMBER: W81XWH-19-1-0771

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

PRINCIPAL INVESTIGATOR: Caryl E. Sortwell, PhD

CONTRACTING ORGANIZATION: Michigan State University

REPORT DATE: October 2021

TYPE OF REPORT: Annual Technical Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2021	Annual Technical Report	Sep 15, 2020 - Sept 14, 2021

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

5a. CONTRACT NUMBER
W81XWH-19-1-0771

5b. GRANT NUMBER
PD180074

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER
0011351682 (SortwellMSU)

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
The United States Army Medical Acquisition Activity
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
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 nearly completed all the behavioral and postmortem analyses of Specific Aim 1 and have observed that treadmill exercise may: 1) improve deficits in forelimb movement initiation induced by synucleinopathy and 2) reduce synuclein pathology in the motor cortex. 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)*

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

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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 rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – **Projected 12/15/19; Completed 12/15/19**

Major Task 2: Exercise regimen and behavioral assessments conducted with rats – **Projected 2/15/20; Completed 2/15/20**

Major Task 3: Necropsy and postmortem assessments of rats – **Projected 6/15/20; Completed 12/31/20**

Major Task 4: Intrastriatal injection of rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – **Projected 4/15/20; Completed 1/15/21**

Major Task 5: Exercise regimen and behavioral assessments conducted with rats – **Projected 7/15/20; Completed 3/31/20**

Major Task 6: Necropsy and postmortem assessments of rats – **Projected 11/15/20; 50% Completed 9/30/21; *New Projected completion date 12/31/21***

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

Major Task 1: Intrastriatal injection of rats with either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – **Projected 12/15/20; Completed 4/15/21**

Major Task 2: Exercise regimen and behavioral assessments conducted – **Projected 6/15/21; Completed 10/15/21**

Major Task 3: Necropsy and postmortem assessments of rats **Projected 9/15/21; *New projected completion date 3/31/22***

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

Major Task 5: Exercise regimen and behavioral assessments of rats – **Projected 3/15/22; *New projected completion date 5/15/22***

Major Task 6: Necropsy and postmortem assessments of rats – **Projected 9/15/22; *New projected completion date 11/15/22***

What was accomplished under these goals?

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

Results represent results from Major Tasks 3 and 6 for a total of 80 adult male rats. We examined the impact of treadmill exercise in control (PBS) and PFF-injected rats 2 months following surgery.

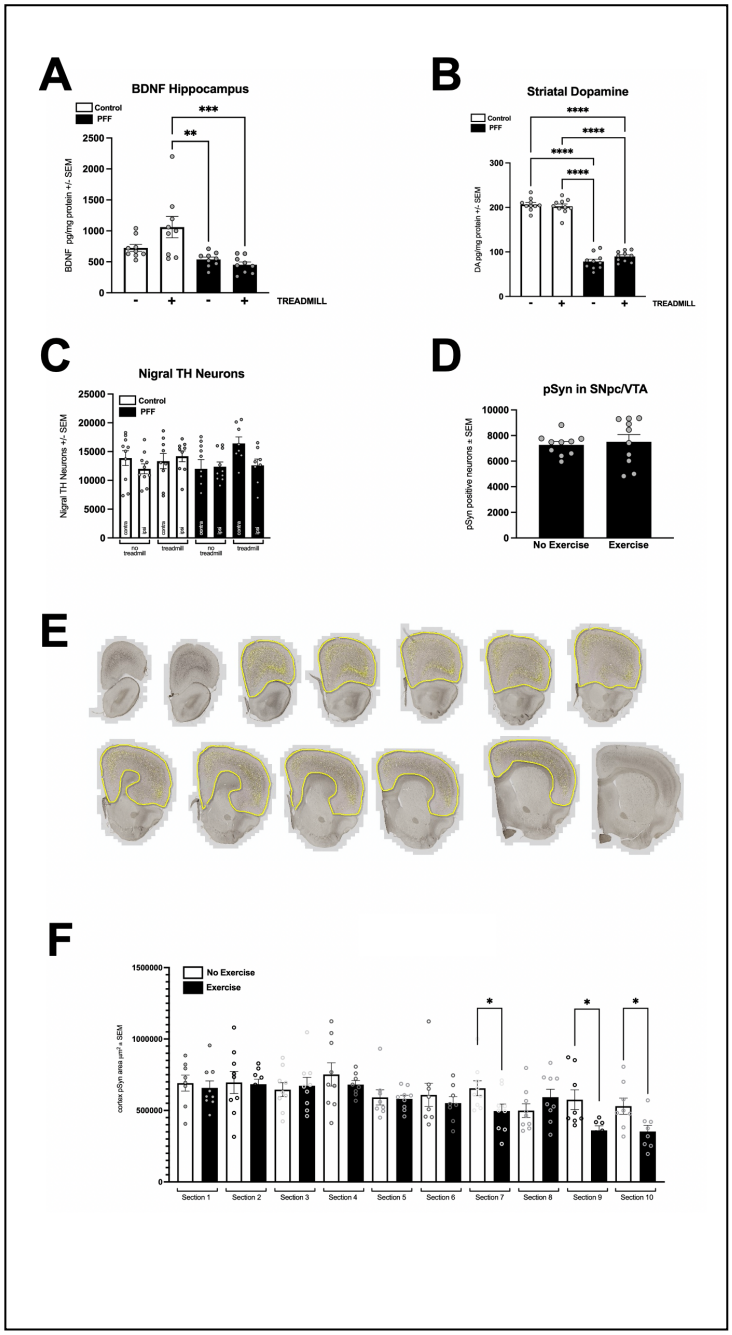
A. Brain-derived neurotrophic factor (BDNF) levels in the hippocampus (ELISA). We observe that treadmill exercise is associated with a significant increase in hippocampal BDNF, confirming the effects of exercise that has previously been observed and validating our treadmill exercise parameters.

B. Levels of dopamine (DA) tissue content in the striatum (HPLC). PFF-injected rats show a significant decrease in DA in the ipsilateral striatum with no impact of treadmill exercise.

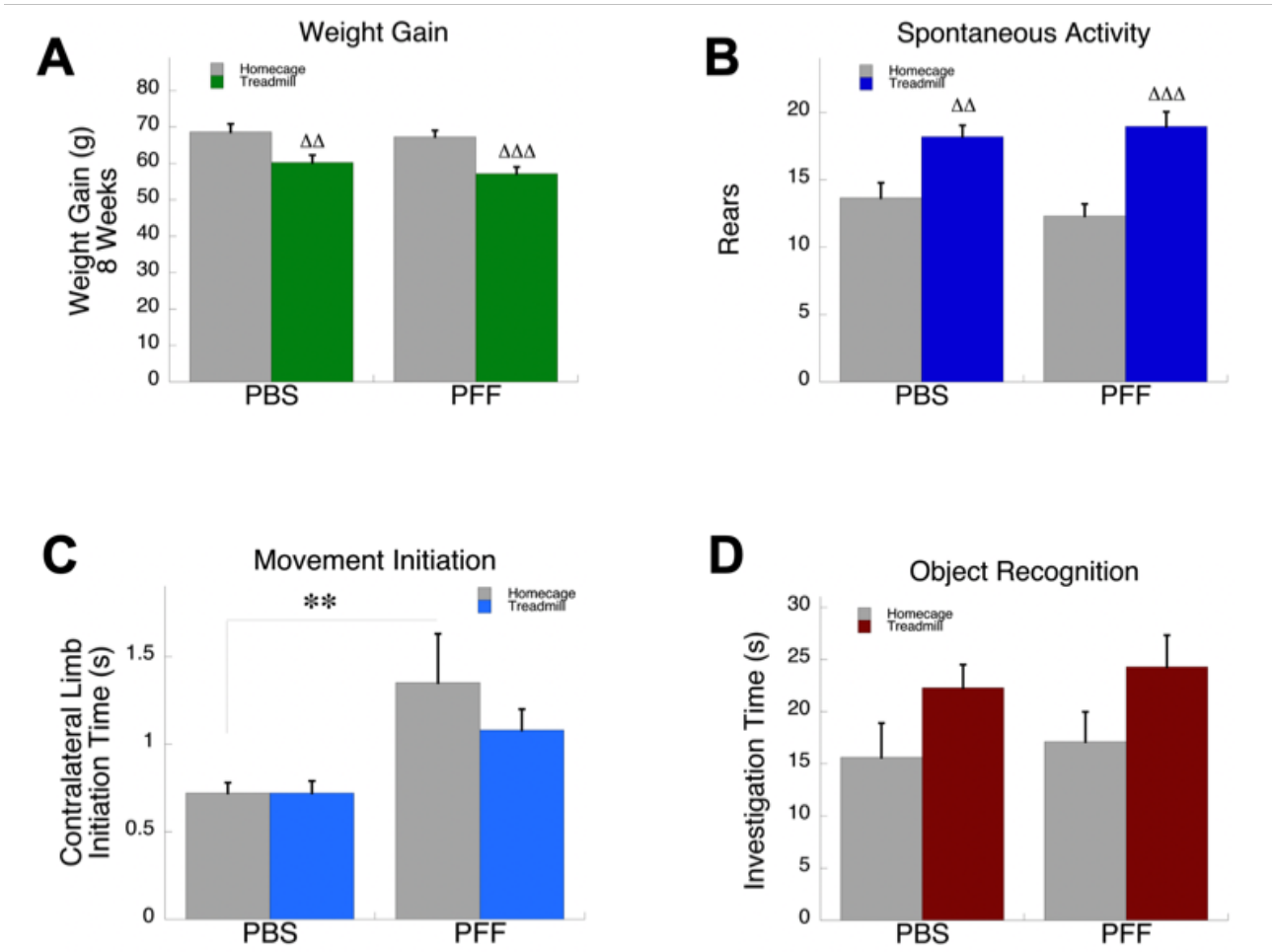
C. Number of tyrosine hydroxylase immunoreactive (THir) neurons in the SNpc (immunohistochemistry combined with unbiased stereology). Neither PFF injection nor treadmill exercise significantly impacts the number of nigral THir neurons observed at the 2-month time point.

D. Number of neurons in the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) that possess phosphorylated alpha-synuclein (pSyn) inclusions (immunohistochemistry combined with unbiased stereology). Treadmill exercise does not impact the number of nigral DA neurons that accumulate pSyn.

E, F. Total area of pSyn accumulation in the frontal cortex as measured by Halo Imaging software. Treadmill exercise significantly reduces accumulation of pSyn in caudal cortical sections, including cortical layers with large representation of primary and secondary motor cortex. Ongoing additional analysis will quantify pSyn accumulation within more specific cortical regions.



Results below represent combined results from Major Task 2 and 5 for a total of 80 adult male rats. Treadmill exercise in control (PBS) and PFF-injected rats 2 months following surgery results in a significant decrease in weight gain (**A**) and a significant increase in spontaneous activity (**B**, rearing activity in the cylinder) with no impact of PFF treatment. These two results validate the impact of our exercise regimen. **C.** PFF-injected rats that were not exercised exhibit significant impairments in contralateral limb movement initiation whereas **treadmill exercised PFF-injected rats did not show this significant impairment.** In light of our result demonstrating no exercise-induced increase in striatal DA tissue content in PFF-injected rats (B in previous figure), this finding suggests that treadmill exercise may attenuate forelimb impairments in the context of a synucleinopathy insult via mechanisms not yet explored (enhanced dopaminergic signaling). **D.** Investigation time in the object recognition task was significantly increased in both PFF and control rats by treadmill exercise, with no impact due to PFF injection at this time point.



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?

Planned for the next reporting period (Sept 15, 2021 – April 14, 2022)

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 6: Complete postmortem assessments including quantification of MHC-II immunoreactive microglia in the SN, in situ hybridization for BDNF and GDNF in the hippocampus and BDNF ELISA in the hippocampus (second cohort).

Specific Aim 2. Impact of exercise on synucleinopathy triggered nigrostriatal degeneration and behavioral impairments
Major Task 3: Conduct necropsy and initiate postmortem assessments (First neuroprotection cohort).
Major Task 4: Intrastriatal injection of either mouse alpha-synuclein preformed fibrils or an equal volume of control vehicle – (Second neuroprotection cohort)
Major Task 5: Exercise regimen and behavioral assessments – begin training and assessment.

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.

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 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: Nathan Kuhn No change.

NEOMED:

Name: Sheila Fleming, Ph.D No Change

Name: Josephine Lepp, M.S. No Change

Name: Ashley Davis, Ph.D. No Change

Name:	*Edward Hamad, B.S.*
Project Role:	*Research Technician*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-1484-3327*
Nearest person month worked:	*7 calendar months (over the 12 month interval)*
Contribution to Project:	

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.

R56 NS117549 07/01/21-6/30/26 1.2 months
Sortwell, PI
NINDS
"DBS effects on neuroinflammation and neurodegeneration induced by alpha-synuclein inclusions"
This proposal will examine the impact of STN DBS on neurodegeneration induced by injection of α-synuclein preformed fibrils to rats and the role of BDNF.
Overlap: None

No Number 02/01/21-7/31/22 1.2 months
Sortwell, PI
Michael J. Fox Foundation
"TM9SF2 Knockdown to Decrease Pathological Alpha-Synuclein Induced Degeneration"
The major goal of this proposal is to determine whether shRNA mediated knockdown of TM9SF2 decreases the degeneration induced by alpha-synuclein preformed fibrils.
Overlap: None

R01ES031237 1/1/2021-12/31/2025 0.6 months
Bernstein, PI
NIEHS
"Dieldrin-induced differential gene methylation and parkinsonian toxicity"
The major goal of this project is to determine whether differential gene methylation after developmental dieldrin exposure plays a functional role in the biological response to endogenous parkinsonian toxicants
Overlap: None

R21NS121393 05/01/21-10/31/22 0.6 months
Benskey, PI *Total Award Amount*
"Targeting complement component 3 in a model of synucleinopathy"
This proposal will examine whether viral vector-mediated knockdown of C3 in astrocytes can provide neuroprotection in a synucleinopathy model.
Overlap: None

No Number 04/12/21-08/12/22 0.6 months
Steece-Collier, Manfredsson, MPI *Total Award Amount*
REGENEXBIO, Inc
" Development and Functional Testing of miRNA CaV1.3 Knockdown in Striatal MSNs and SNc DA Neurons"
This proposal will evaluate the ability of a newly developed AAV.CaV1.3.miRNA vector to selectively knockdown CaV1.3 in striatum and substantia nigra and assess the impact of the CaV1.3 knockdown on neuronal excitability. This proposal will also perform proof-of-concept studies to test the AAV.CaV1.3.miRNA for preservation of substantia nigra dopaminergic neurons in four distinct "Parkinson's disease" rat models.
Overlap: None

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

1R56AG069116-01A1
"Mechanism of ZCCHC6 regulation of mitochondrial dysfunction in Alzheimer's disease"
PI: Tariq Haqqi, Ph.D. 4/01/2021-3/31/2022
Co-I: **Sheila Fleming, Ph.D.** 0.6 months
Agency: NIH/R01
This grant will determine the therapeutic potential of modulating ZCCHC6 in animal models of Alzheimer's disease.
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 and 0772

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

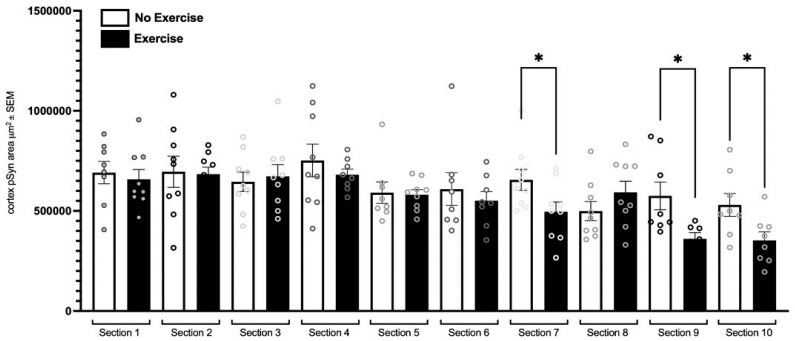
Study/Product Aim(s)

• 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.



Treadmill exercise significantly reduces accumulation of phosphorylated alpha-synuclein (pSyn) in caudal cortical sections, including cortical layers with large representation of primary and secondary motor cortex. Ongoing additional analysis will quantify pSyn accumulation in more specific cortical regions.

Accomplishments: PENDING

Timeline and Cost

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

Updated: (09/30/2021)

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 - *ongoing*
☑ 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/behavior/postmortem analysis

Budget Expenditure to Date (9/15/19-9/14/21)

Projected Expenditure: (MSU - $450K) (NEOMED - $405K) Direct Costs
Actual Expenditure: (MSU - $460K) (NEOMED – $356K) Direct Costs