Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** Drexel University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010-12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Anne Martella

4. **Grant Contact Person's Telephone Number:** (215) 895-6471

5. **Grant SAP Number:** 4100050893

6. **Project Number and Title of Research Project**: 3. *sPLA2 Inhibition Therapy for Epilepsy*

7. **Start and End Date of Research Project:** 1/1/2010- 6/30/2012

8. **Name of Principal Investigator for the Research Project:** Timothy Cunningham, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 153,343.

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Yao, Lihua	Sr. Research Assistant	100%	36,085
Andrew, Francis	Nurse Practitioner	10%	3,501
Chun, Shuyan	Fellow	100%	26,979

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Cunningham, Timothy	P.I.	40%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes___X_____ No_____

If yes, please describe your plans:

We plan to submit to the NIH for funding to continue our research (i.e. SBIR).

12. Future of Research Project. What are the future plans for this research project?

The proposed studies will focus on pharmacokinetics of CHEC 9, for which we have the majority of efficacy and pharmacodynamics data.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female			1	
Unknown				
Total			**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic			1	
Unknown				
Total			**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian			1	
Other				
Unknown				
Total			**1**	

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No____X____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes___X____ No_____

If yes, please describe commercial development activities that resulted from the research project:

The work contributed to the intellectual property portfolio of Pultis Biotechnology, a Drexel spin off.

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE

INSTRUCTIONS.

This project evaluted the efficacy of new secreted phospholipase A2 (sPLA2) inhibitors as therapy for both the excitability disturbances and inflammatory consequences of epilepsy. These inhibitors, called CHECs, consist of 7mer and 9mer peptides with demonstrated systemic efficacy in traumatic and autoimmune disease models. They are part of a portfolio of intellectual property (composition of matter, applications, diagnostic) held by Drexel University. The goal of this application is to expedite the clinical development of these peptides by expanding potential clinical applications. These compounds are especially suited for commercial development since it has been unequivocally demonstrated that they are active when taken by mouth. The present experiments are proof-of concept studies for treatment of epilepsy, where the inflammatory consequences of the disease have been largely overlooked. Interestingly, there is also evidence, including our own preliminary studies, that excitability changes during epilepsy are closely related to inflammation, raising the possibility that the CHEC peptides represent a unique monotherapy for this disease.

SPECIFIC AIM 1 - Inflammation, sPLA2 inhibition and seizure control.
We will screen two systemically active peptide inhibitors of sPLA2 enzymes CHEC-7 and CHEC-9 in a kainic acid seizure model applied to early postnatal and young adult rats. A wealth of data exists that demonstrates the anti-inflammatory and survival promoting activity of these compounds, and preliminarily, their influence of excitability and synaptic functions. We will now apply these peptides to the KA model to explore both contribution and consequences of sPLA2 enzyme activity in seizure disorders. We will measure the following in P13-16 and P35-40 KA models:
a. Motor seizure activity, including potential critical periods for effective sPLA2 inhibition.
b. The time course of changes in enzyme activity, lipid products and substrates (many of the latter are potent inflammatory mediators) using assays specific for sPLA2s, 2D TLC, and mass spectroscopy. These measurements include systemic activity (plasma, urine), and the activity found in the soluble and synaptosomal fractions of cerebral cortex (including hippocampus).

SPECIFIC AIM 2. Inflammatory correlates of childhood and adolescent/young adult epilepsy.
It is our hypothesis that the period of sPLA2 elevation (relative to stable patients) represents the period of maximum vulnerability to seizure-induced inflammatory destruction of central nervous system (CNS) tissue, presumably instigated by inflammatory mediators and the cellular participants in the immune response. We therefore will measure plasma and urinary sPLA2 activity and levels of selected phospholipids in young epileptic patients and compare to seizure history. The relationship of systemic inflammation to other epidemiological and clinical parameters such as age, duration of epilepsy, type of epilepsy and medication will also be determined.

Summary of Research Completed

SPECIFIC AIM 1 - Inflammation, sPLA2 inhibition and seizure control. - COMPLETED
We screened active peptide inhibitors of sPLA2 called CHEC-9 in a kainic acid seizure model

applied to young adult rats. A wealth of data exists that demonstrates the anti-inflammatory and survival promoting activity of these compounds, and studied their influence of excitability and synaptic functions. Our experiments demonstrate that oral CHEC-9 peptide inhibits kainic acid-induced seizures and abnormal firing of hippocampal neurons. The results also show clearly that CHEC peptides protect neurons that would usually degenerate following seizures. See below for details of subjects and graphical presentation of results.

Seizures in humans produce high levels of sPLA2 making these enzymes a worthwhile therapeutic target for controlling hyperexcitability and subsequent inflammatory pathology. These studies show that the enzymes are involved in human epilepsy and the CHEC peptides, which are sPLA2 inhibitors, are ideally suited for this therapy, since they are effective orally and operate on an "as needed" basis. There is increased interest in the contribution of secreted phospholipase A2 (sPLA2) enzymes to neurodegenerative diseases. Systemic treatment with the nonapeptide CHEC-9, a broad spectrum uncompetitive inhibitor of sPLA2, has been shown previously to inhibit neuron death and aspects of the inflammatory response in several models of neurodegeneration. A persistent question in studies of sPLA2 inhibitors, as for several other anti-inflammatory and neuroprotective compounds, is whether the cell protection is direct or due to slowing of the toxic aspects of the inflammatory response. To further explore this issue, we developed assays using SY5Y (neuronal cells) and HL-60 (monocytes) cell lines and examined the effects of sPLA2 inhibition on these homogeneous cell types *in vitro*. In order to mimic the response to an inflammatory event *in vivo*, the inhibitor was introduced to stressed neuronal cells after they had differentiated, while the monocyte/macrophage line was treated during differentiation (activation) of the cells.

Methods: SY5Y cells were differentiated with retinoic acid and then exposed to oxidative stress (medium change, serum deprivation) and to medium conditioned by activated HL-60 cells. Cell and process survival were quantified by a MTT assay and TUJ1 immunostaining respectively. HL-60 cells were differentiated into macrophages using phorbol 12-myristate 13-acetate (PMA) in the presence or absence of sPLA2 inhibition. We examined morphological (process formation) and biochemical differentiation (expression of cytokines TNF-α, IL-6, and activation marker CD36) as well as measured phagocytic activity using fluorescent beads. sPLA2 enzyme activity was also tested in those cultures.

Results: sPLA2 inhibition with CHEC-9 peptide provided direct protection to SY5Y cells and their processes in response to several forms of stress including exposure to conditioned medium from HL-60 cells. In cultures of HL-60 cells, sPLA2 inhibition had no effect on survival of the cells but attenuated their differentiation into macrophages, with regard to process development, phagocytic ability, and the expression of differentiation marker CD36, as well as the secretion of proinflammatory cytokines TNF-α and IL-6.

Conclusion: These results suggest that sPLA2 enzyme activity organizes a cascade of changes comprising both cell degeneration and inflammation -- processes that could theoretically operate independently during neurodegenerative conditions. The effectiveness of sPLA2 inhibitor CHEC-9 may be due to its ability to affect both processes in isolation. Testing potential anti-inflammatory/neuroprotective compounds with these human cell lines and their conditioned media may provide a useful screening tool prior to *in vivo* therapeutic applications.

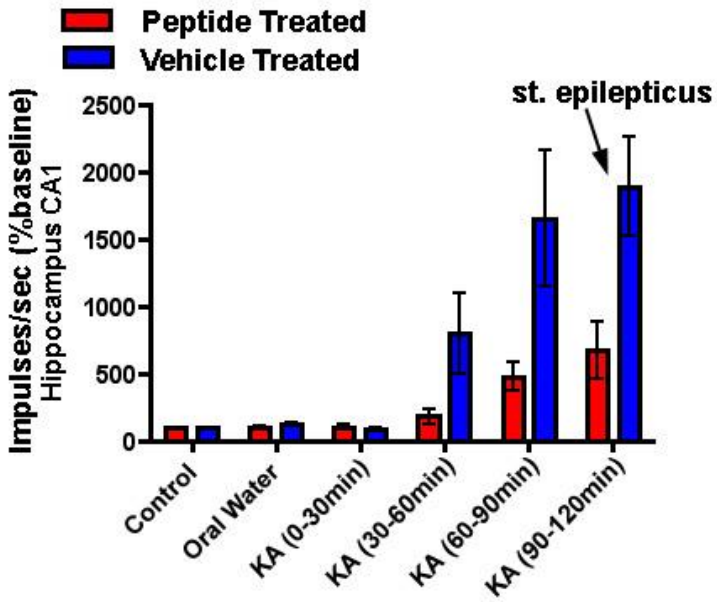

Fig. 1. Multiunit activity in the hippocampus of awake, freely-moving kainic acid (KA)-treated rats with and without pretreatment with CHEC-9 or vehicle. The rats were implanted with a multichannel electrode bundle one week earlier. Baseline activity (mean firing rate, expressed in Hz) was collected during a 30min control period, followed by oral CHEC-9 (1mg/kg) or Vehicle for 40 min prior to IP kainic acid (10mg/kg). The response to the eleptogen is robust. CHEC-9 pre-treatment (n=3) significantly attenuates the kainic acid-induced increase in neuronal and seizure activities. (Vehicle treated rats (n=3) reached status epilepticus after ~1 hr.; peptide treated rats showed no obvious symptoms. See also Table 1.)

Table 1- CHEC-9 (C9) and Vehicle (V) pre-treatment of KA-induced seizures. The behavioral results from 14 rats demonstrate that the CHEC-9 peptide inhibits kainic acid-induced status epilepticus, including via oral delivery. ** Severity is graded by a classical scale: 1, hypoactivity, mouth and facial automatism; 2, head nodding and mastication; 3, forelimb clonus without rearing; 4, bilateral forelimb clonus and rearing; and 5, rearing and loss of posture. We define *Status epilepticus* (Stat EP) as stages 3-5 appearing continuously for 30 min. [s.c. –subcutaneous; po-oral]

Gender	C9 Dose mg/kg route	KA mg/kg ip	Max Seizure Stage**
F	V sc	5	Stat Ep
F	V po	10	Stat Ep
F	V po	10	4
M	V po	5	Stat Ep
M	V sc	6	Died
M	V sc	5	1
M	V po	10	Stat Ep
M	0.5 sc	6	2
M	1.0 po	10	1
M	1.0 po	5	1
F	1.0 po	10	3
F	0.5 sc	5	1
M	0.5 sc	5	1

Histological/Immunocytochemical Studies:

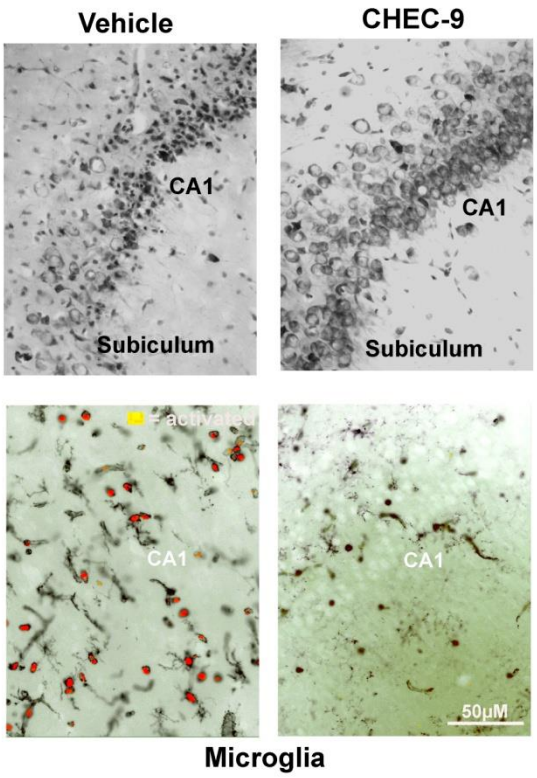

Fig. 2. Inhibition of seizure activity by CHEC-9 prevents microglia activation (inflammation) and neuron death in CA1 of hippocampus. The border between CA1 and the subiculum is shown in horizontal sections. Top: Cresyl violet-stained sections showing pyramidal cells 24hrs. after kainic acid-induced status epilepticus (SE). In the vehicle treated rats the cells were degenerated. CHEC-9 inhibits SE and preserves the cells. Bottom: Adjacent double-stained with lectin IB4 (all microglia, black) and ED- (activated microglia, red). The number and activation of microglia is inhibited by CHEC-9 consistent with the neuron rescue shown above.

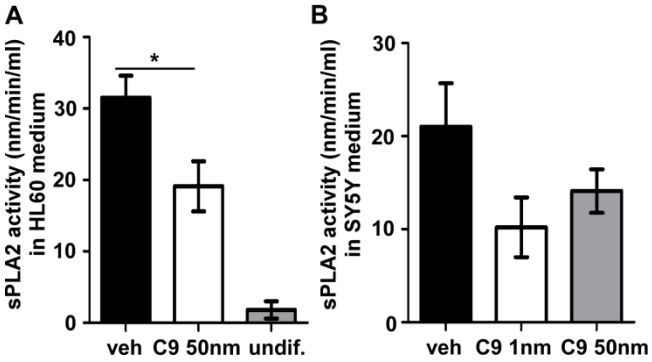

Fig. 3. Measurement of sPLA2 activity. **(A)** HL-60 cells were treated with 50nM CHEC-9 or TBS vehicle for 4 days with stimulation b PMA. The large increase of sPLA2 activity after differentiation was significantly attenuated by CHEC-9 treatment. **(B)** Differentiated SY5Y neuronal cells were subjected to medium change and serum deprivation for 2 days. Compared with vehicle group, CHEC-9 treatments at 1 and 50nM both reduced sPLA2 activity, but this change just missed significance (p=0.07).

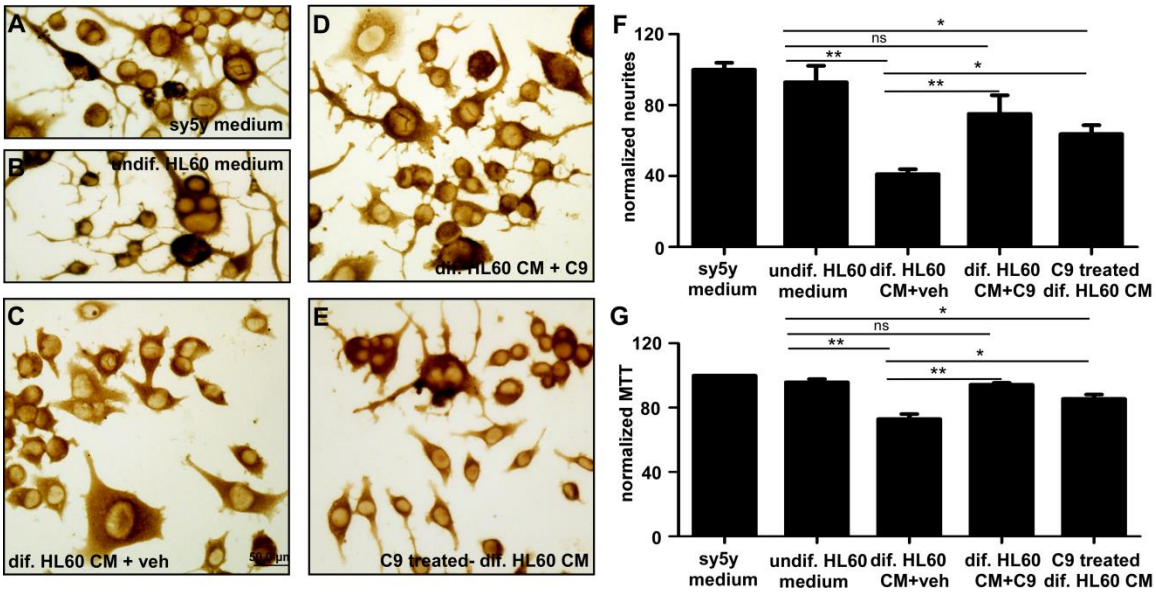

Fig. 4. Protective effects of CHEC-9 on SY5Y cells. Retinoic acid differentiated SY5Y neuronal cells were subjected to different conditioned media for 72 hrs**. Cell process survival (A-F).** Long and elaborated processes were seen in cultures that were subjected to control media either from SY5Y cultures or undifferentiated HL-60 cultures **(A, B)**. Dramatic degeneration of neuritic processes was found when SY5Y cells were subjected to medium from differentiated HL-60 cultures **(C)**. These degenerative changes were reversed by CHEC-9 (50nM, **D)**. Medium from HL-60 cultures, which were pretreated with 50nM CHEC-9 during differentiation, also preserved processes **(E)**. **(F)** Quantification of the results. **Cell body survival (G)**. Both SY5Y conditioned medium and undifferentiated HL-60 did not affect SY5Y survival, whereas the medium from differentiated HL-60 cells significantly decreased viability. 50nM CHEC-9 significantly restored the cell number to control level. Medium from HL-60 cultures-pretreated with 50nM CHEC-9 during differentiation, also promoted cell survival. (* $p<0.05$, ** $p<0.005$)

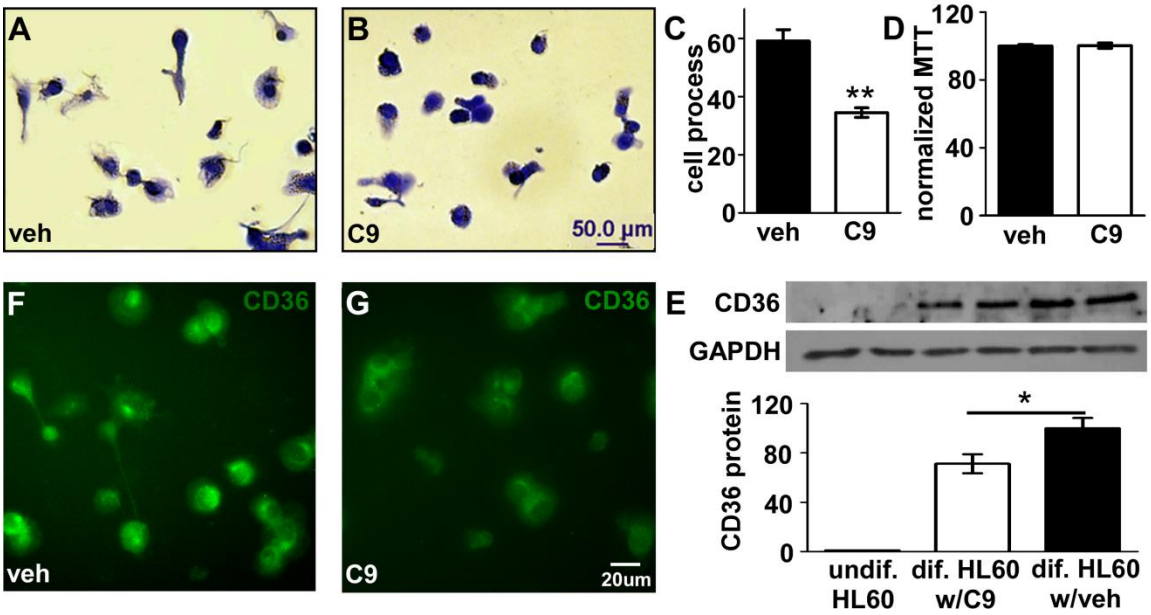

Fig. 5. Inhibition of differentiation of HL-60 cells by CHEC-9. HL-60 cells were treated with 50nM CHEC-9 or TBS vehicle for 4 days with stimulation by PMA. HL-60 cells adhere to plate surface, flatten out and grow processes **(A)**. CHEC-9 treatment decreased the number of cells with process **(B)**. Quantification of Coommassie blue staining **(C).** CHEC-9 did not affect viability of the cells **(D)**. Immunostaining for CD36 showed that the fluorescent intensity of CHEC-9 group was decreased compared with vehicle group **(E, F)**. This observation was supported by western analysis **(G)**. Quantification was by normalization to GAPDH bands. (* $p<0.05$, ** $p<0.005$).

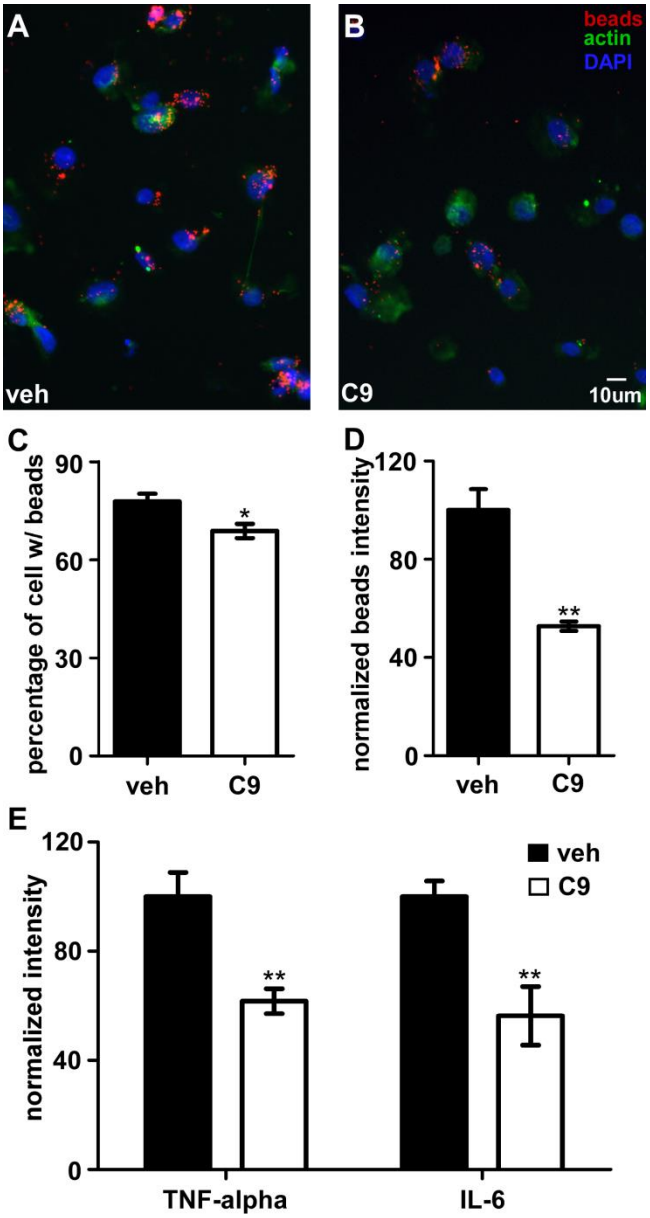

Fig. 6. Phagocytosis activity and cytokine levels of macrophages differentiated from HL-60 cells. Most macrophages in vehicle group were labeled with red beads and the intensity of beads was high **(A).** Macrophages treated with CHEC-9 engulfed significantly fewer beads after 4 days differentiation and resulted in a lower percentage of cells containing beads. Quantification of the results **(C, D)**. Decreased expression of TNF and IL-6 by 50-60% was found in the cell medium of CHEC-9 treated group **(E)**. (** $p<0.005$)

SPECIFIC AIM 2. Inflammatory correlates of childhood and adolescent/young adult epilepsy.

No progress was made on this Aim due to the inability to procure patient samples.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X__No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X_ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04),

the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Secreted phospholipase A2 involvement in neurodegeneration: differential testing of prosurvival and anti-inflammatory effects of enzyme inhibition.	Chen, S., Yao, L. and Cunningham TJ	PLoS One	February, 2012	☐Submitted ☐Accepted ☒Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No__X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The research added to the efficacy demonstrations of a previously discovered therapeutic peptide.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No____X
no new inventions.

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number: Use patent for epilepsy is under consideration by Drexel Tech Transfer

Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No___X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Timothy J. Cunningham, Ph.D.	POSITION TITLE Professor
eRA COMMONS USER NAME (credential, e.g., agency login):CUNNINGHAM1	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Whitman College, Walla Walla, WA	A.B.	06/68	Chemistry
University of Washington, Seattle, WA	Ph.D.	11/72	Biological Structure

A. PERSONAL STATEMENT

I have investigated neuron death, neurodegenerative disorders and brain injury for more than four decades. My Laboratory has studied strategies to overcome these injuries, including the identification, isolation, and mechanisms of novel therapeutic peptides that rescue neurons and their processes after systemic administration. We have also studied the mechanisms of inflammation and neuron death, most recently demonstrating the importance of secreted phospholipase A2 enzymes and their products in these processes through a series of experiments in models of neurodegenerative disorders, and in patients afflicted with these disorders,

B. POSITIONS AND HONORS

1972–1974 Postdoctoral Fellow, National Eye Institute, Department of Psychology, Vanderbilt University, Nashville, Tennessee.

1973 Visiting Assistant Professor, Program in Medical Sciences and Department of Psychology, Florida State University.

1974–1979 Assistant Professor, Department of Anatomy, The Medical College of Pennsylvania, Philadelphia, PA.

1979–1989 Associate Professor, Department of Anatomy, The Medical College of Pennsylvania, Philadelphia, PA.

1989–present Professor, Department of Neurobiology and Anatomy, Drexel University College of Medicine (formerly MCP/Hahnemann University), Philadelphia, PA.

Institutional

2006- present Chair, Institutional Animal Care and Use Committee

2012 Chair Drexel University College of Medicine 5-year Strategic Planning Committee

Advisory

1989-1993 Regular Member, Neurology BII Study Section, National Institutes of Health

B. POSITIONS AND HONORS (continued)

Editorial

1999-2004 American Journal of Alzheimer's Disease and Other Dementias
2007-present The Open Enzyme Inhibition Journal

Corporate

2011-present Chief Scientific Officer Pultis Biotechnology, INC

C. SELECTED PEER REVIEW PUBLICATIONS (Emphasis on most recent)

Cunningham, T.J. Naturally Occurring Neuron Death and Its Regulation by Developing Neural Pathways. *In*: International Review of Cytology, Vol. 74, Academic Press, New York, pp. 163–186,1982.

Milligan, C.E., T.J. Cunningham and P. Levitt. Differential immunochemical markers reveal the normal distribution of brain macrophages and microglia in the developing rat brain. J. Comp. Neurol. *314*:125–135, 1991.

Cunningham, T.J., L. Hodge, D. Speicher, D. Reim, C. Tyler, P. Levitt, K. Eagleson, S. Kennedy and T. Wang. Identification of a survival-promoting peptide in medium conditioned by oxidatively stressed cell lines of nervous system origin. J. Neurosci. *18*:7047-7060 , 1998.

Cunningham, T.J., H. Jing, Y. Wang and L. Hodge. Calreticulin binding and other biological activities of survival peptide Y-P30 including effects of systemic treatment of rats. Exp. Neurol. *163*:457-468, 2000.

Cunningham TJ, H. Jing, I. Akerblom, R. Morgan, T. S. Fischer and M. Neveu. (2002). Identification of the human cDNA for new survival/evasion peptide (DSEP): Studies *in vitro* and *in vivo* of overexpression by neural cells. Exp. Neurol. *177*:32-39.

Cunningham, T.J., Jameson, B., Mitchell, J., Souayah, N, and Yao, L. (2004). Systemic treatment of cerebral cortex lesions in rats with a new secreted phospholipase A2 inhibitor. J. Neurotrauma, 21:1683-1691. PMID:15684658.

Cunningham TJ, Yao L, Oetinger M, Cort L, Blankenhorn EP, Greenstein JI. Secreted phospholipase A2 activity in experimental autoimmune encephalomyelitis and multiple sclerosis. J Neuroinflammation. 2006 Sep 11;3:26. PMID:16965627 PMCID: PMC1592473

Cunningham TJ, Maciejewski J, Yao L.Inhibition of secreted phospholipase A2 by neuron survival and anti-inflammatory peptide CHEC-9.J Neuroinflammation. 2006 Sep 11;3(1):25. PMID:16965626 PMCID: PMC1624820.

Cunningham, TJ, Yao, L, Lucena, A (2008) Product inhibition of secreted phospholipase A2 may explain lysophosphatidylcholine's unexpected therapeutic properties, Journal of Inflammation 5:17. PMID:18945345 PMCID: PMC2580763.

Cunningham TJ, Yao L, Lucena A, Greenstein JI (2009) Uncompetitive Phospholipase A2 Inhibition by CHEC Sequences including Oral Treatment of Experimental Autoimmune Myeloencephalitis, The Open Enzyme Inhibition Journal 2:1

Chen, S, Yao,L, and TJ Cunningham (2012) Secreted phospholipase A2 (sPLA2) involvement in neurodegeneration: Differential testing of prosurvival and anti-inflammatory effects of sPLA2 inhibition. PLos One, in press