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TITLE: The Impact of PERK on Posttraumatic Tauopathy in Alzheimer's Disease

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14. ABSTRACT

Risk for AD is one of the most imminent threats to military personnel sustaining TBI. A major challenge in the field of TBI/AD research is elucidation of the molecular mechanisms linking TBI with tau pathogenesis that is associated with AD. This critical and urgently needed information will identify novel therapeutic targets that will benefit both military personnel and civilian population. Our data indicate that TBI induces sustained and dramatic endoplasmic reticulum stress, and that there is a pathological relationship between AD tau species and the ER stress sensor PERK. In this proposal, we aimed to establish the impact of PERK on TBI outcomes and whether or not manipulating PERK alters tau-mediated pathogenesis following injury. Here, we aimed to directly address the role of PERK activity as a molecular mediator of TBI-induced sequelae and provide unique understanding of the association between TBI and tau. To date, our data outline a time-course of PERK activation following TBI and indicate sustained PERK activity in neurons for as long as 30 days. Chemical inhibition of PERK for 30 days following TBI resulted in successful knockdown of the PERK pathway and inflammatory markers, as well as a trending reduction in PERK-related apoptotic signaling protein CHOP. TBI in a conditional knockout mice lacking neuronal PERK demonstrated less conclusive results as global levels of PERK in the brain were unchanged, suggesting an upregulation of glial PERK after injury. Continued work will assess changes in pathological tau species in these mouse models following TBI to specifically assess the effects of PERK modulation on tau protein following TBI.

15. SUBJECT TERMS

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INTRODUCTION:
Risk for AD is one of the most imminent threats to military personnel sustaining TBI. A major challenge in the field of TBI/AD research is elucidation of the molecular mechanisms linking TBI with tau pathogenesis that is associated with AD. This critical and urgently needed information will identify novel therapeutic targets that will benefit both military personnel and civilian population. Our recent data indicate that TBI induces sustained and dramatic endoplasmic reticulum stress, and that there is a pathological relationship between AD tau species and the ER stress sensor PERK. In this proposal we aim to establish for the first time the impact of PERK on tau-mediated pathogenesis as a means by which TBI confers risk for AD. We will directly address the role PERK activity as a molecular mediator of TBI-induced *tau pathology* and provide unique understanding of the association between TBI and AD. This understanding is *critical and urgent* to develop novel therapeutic strategies. This work will further develop a novel imaging *technology* (ME-MRI) that will identify a course of functional deficits in the brain after injury and monitor the magnitude at which these phenomena persist over time. This technology will set a standard of disease course imaging from TBI to AD onset. Therapies aiming to interrupt the molecular events identified by this work will be monitored using our imaging technology. Finally, our work will test the therapeutic value of inhibiting the PERK, which is involved in several neurodegenerative disorders.

KEYWORDS:
PERK, tau, tauopathies, Alzheimer's disease, traumatic brain injury, controlled cortical impact, neurodegeneration, UPR, ER stress

ACCOMPLISHMENTS:

What were the major goals of this project?

Annual Report 1

AIM1

1. Establish mouse colony and validate anatomical and volumetric damage caused by CCI
    - *ACURO protocol approved*
    - *Wild type mouse colony established*
    - *Training to perform controlled cortical impact injury model complete*
2. Determine immunohistochemical changes in the brain (and complete all MRI analyses)
    - *Early timeline of PERK activation complete*
    - *Established which cell types show PERK activation*
3. Complete imaging analyses (this work is completed continuously as injuries are performed)

AIM2

4. Establish mouse cohorts for Aim 2
    - *rTg4510 transgenic colony established*
    - *PERK conditional knockout colony backcrossed: estimated completion date: Dec 2016*
5. Perform genetic manipulation to activate and inhibit PERK function
    - *Establishment of the PERK conditional knockout colony: estimated completion date: Dec 2016*
    - *Viral particles are continuously produced by the University of Kentucky Viral Core*
6. Perform chemical manipulations to modulate PERK
    - *Currently underway*
7. Complete data collections and analysis for all functional measurements (this work is completed continuously as injuries are performed)
    - *Cohort 1 of chemical PERK inhibition following injury data collection – MEMRI, behavioral analyses (novel object recognition, radial arm water maze)*
    - *Data collection for first four cohorts of PERK inhibition following injury (MEMRI, behavior, immunohistochemical staining) will be complete by January 1, 2017*
8. Complete data analysis (this work is completed continuously as injuries are performed)

Annual Report 2

Aim 2

1. Chemical inhibition of PERK in WT and rTg4510 mice after injury.

Annual Report 3

Aim 2

1. Complete data collection
2. Complete data analysis

What was accomplished under these goals?

Annual Report 1

During the first year, we established the mouse colony for experiments in Aim 1 and Aim 2, we successfully performed controlled cortical impact injuries to characterize PERK activation following traumatic brain injury, we performed MEMRI and analyses following injury, we established an early timeline of PERK activation using immunohistochemical staining, and we began to investigate the impact of chemical PERK inhibition following injury on cognition and neuronal function. We are continuing to complete the goals as cohorts of mice become available.

Using immunohistochemical analyses in our initial studies with a small sample group, we found that PERK is more robustly activated in the contralateral hemisphere compared to the ipsilateral hemisphere at early time points following injury. However, upon completion of the larger cohorts, we identified that early activation is even between contralateral and ipsilateral brain hemispheres (Fig. 1 and 2). We also found that PERK is active in neurons (Fig. 3) but not glia as evidenced by counterstains with GFAP (Fig. 4) or Iba1 (Fig. 5). Using the non-radioactive, puromycin-based translation assay we also determined, in a small cohort, that protein synthesis is increased at early time points in neurons (Fig. 6).

Injuries were performed as previously described in the proposal; briefly, mice were anesthetized using isoflurane and a midline incision was made. A 3mm in diameter craniotomy was performed and mice were injured using the electromagnetic CCI machine at 1.5m/s with 500msec dwell time. A cranioplasty was then placed over the injury site and the incision was sutured. Mouse brains were collected following cardiac perfusion using 0.9% saline. Tissue was sectioned using a microtome and stained using immunofluorescence.

The *major activities* were to complete Sub-Aim 2.2b (chemical inhibition) and establish the mice for Sub-Aim 2.2a (genetic inhibition). These two objectives were met. The *specific objectives* were to perform severe CCI (3.5m/s,

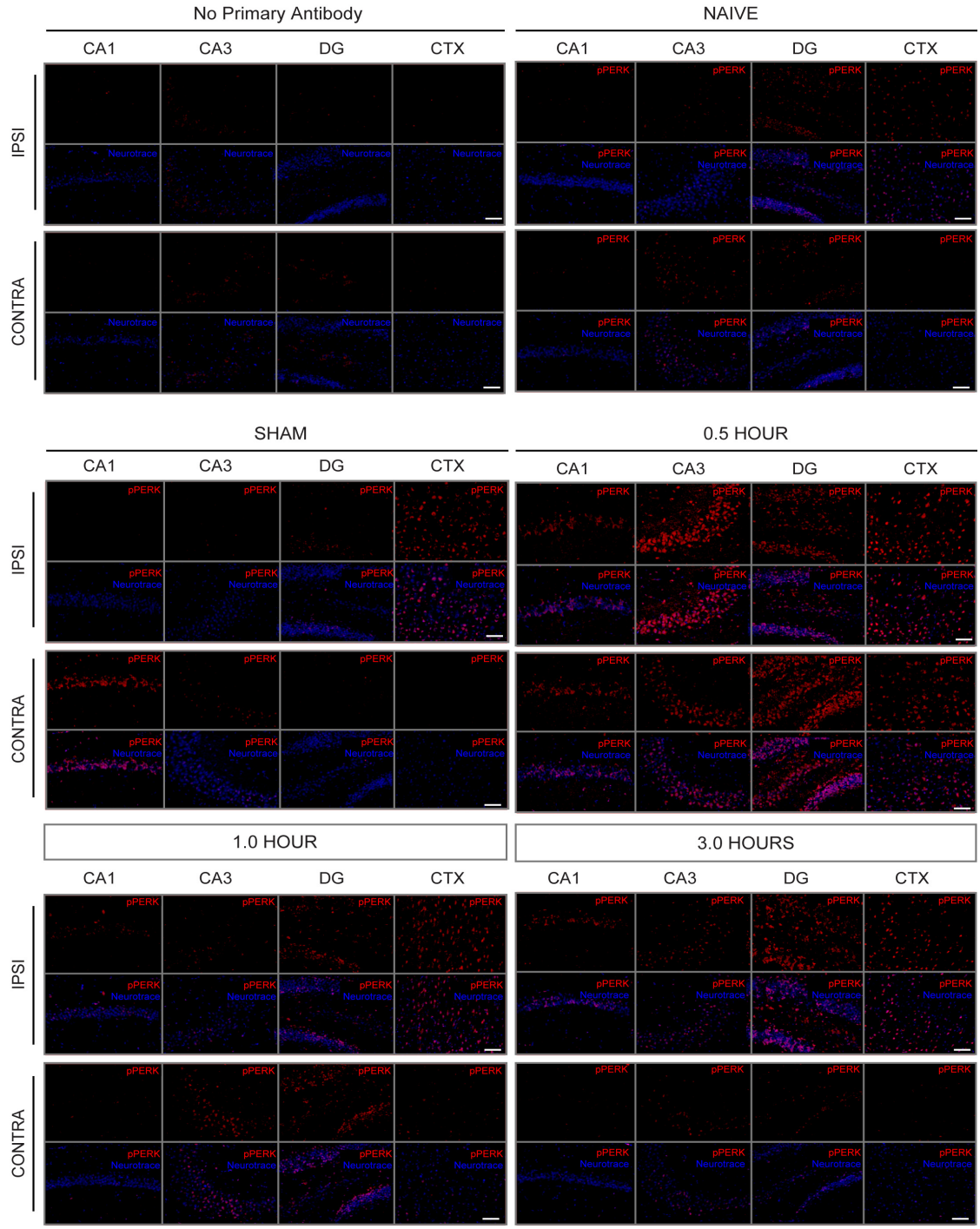

Fig. 1: Early time course of PERK activation after injury. pPERK levels (red) were measured in CA1, CA3, dentate gyrus, and cortex of ipsilateral and contralateral hemispheres to the injury.

1.0mm depth, 500ms dwell) on WT and rTg4510 animals. One hour post-injury, animals were treated with PERK inhibitor GSK2606414 (414) or vehicle (VEH). Treatment continued once a day for 30 days. Outcome measurements taken for these animals included immunohistochemical analyses of specific stains, behavioral analyses, and MRI analyses.

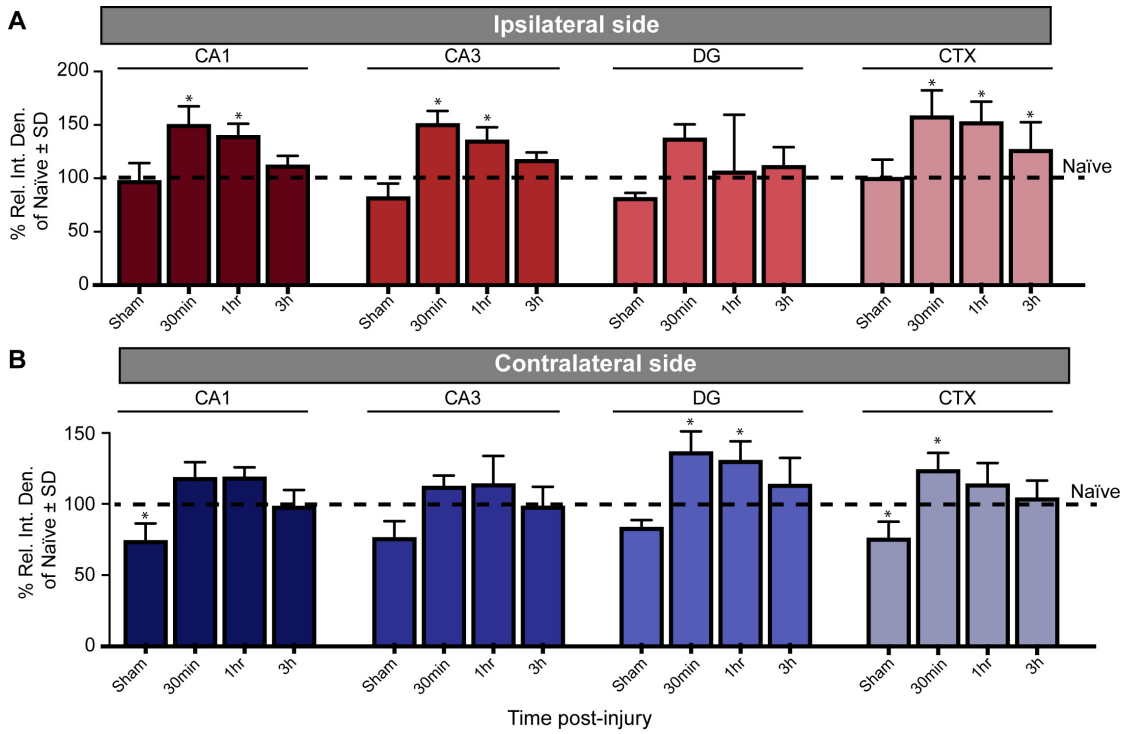

Fig. 2: Quantification of pPERK levels in different brain regions (CA1, CA3, dentate gyrus, and cortex) in ipsilateral (A) and contralateral (B) hemispheres to the injury. pPERK levels were measured at 30, 60, and 360 min after injury.

Our *significant findings* are that PERK inhibition for 30 days effectively reduced PERK activity, as expected. Moreover, its downstream target, eIF2a, was also inhibited. Surprisingly, we found that GFAP, a marker of astrocytic activation, was also decreased when treated with the PERK inhibitor. These data are surprising because, as we determined in year 1, PERK is only activated in neurons; co-localization immunofluorescence with cell markers demonstrated that PERK did not co-localize with GFAP or Iba1 (Fig. 3-5). Therefore, we suspect the compound inhibits neuronal signaling to astrocytes. This hypothesis would uncover a remarkable mechanism of intercellular communication, which we plan to explore in the future. In fact, we recently identified a PERK splice variant that lacks the amino-terminal portion containing the localization sequence, which effectively prohibits its ability to incorporate into the ER membrane. This PERK variant could be secreted to other cells. While this work is beyond the scope of this project, it is still highly thematically relevant. Future studies will evaluate the role of this PERK isoform in head injury and aging. Data to support these off-target effects were recently obtained from another study in which we treated mice with 414 and performed TMT proteomics. The data show a robust signal for highly significantly changed proteins when mice are treated

with 414 (Table 1).

Table 1: Proteins significantly changed with 414 treatment in the brains of non-transgenic mice.

414 treatment increases:	414 treatment decreases:
Arhgdia	Aldoa
Arpc5l	Atp6v1a
Bcas1	Atp6v1c1
Clta _Q6PFA2	Cacna2d1
Dnajb6	Cops4
Ermn	Crmp1 _Q6P1J1
H4c1	Cs
Hist2h2ac	Dld
Hnrnph1	Dpysl4
Hspa5	Eno2
Lgals1	Glul
Tmod2	Got2
Tpt1	Idh3a
Wasf3	Micos13
	Ndrg4
	Rcan1
	Scrn1
	Sh3glb2
	Syn1
	Uchl1
	Ywhag

Finally, and also counter to our expectations, brain volume was decreased in animals that were injured and treated with the compound. These data suggest that treatment with the inhibitor is either not beneficial (promotes atrophy post-injury) or reduces inflammation. The former would lead us to establish an earlier time course because we anticipate that inhibiting self-regulation of the UPR for 30d might improve short-term outcomes, which would be shadowed by overall tissue damage. The latter would suggest that 414 has an anti-inflammatory effect, but whether this is beneficial remains to be determined.

Other significant findings are the extent of PERK activation after injury.

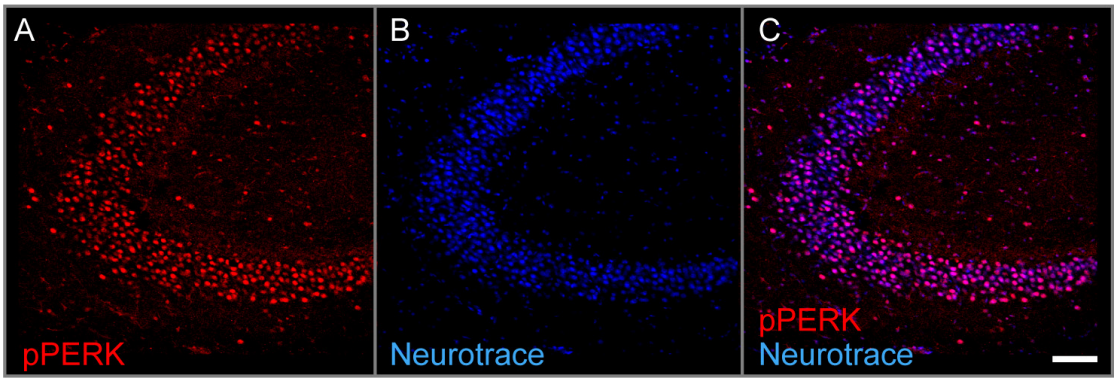

Fig. 3: pPERK signal coincides in cells positive for the neuronal marker neurotrace. Mice were injured using CCI. Brains were prepared for immunohistochemistry staining of pPERK and neurotrace 3h post injury.

Per our previously reported data, PERK activity is increased throughout the 30d of treatment. Therefore, we are hesitant to genetically activate PERK since inactive PERK levels will be depleted.

Key to these findings is the context of functional outcomes. We had proposed to perform cognitive testing (Fig. 7-8). Preliminary data showed that the injured mice did not display the cognitive defects that should have been evident. This puzzling and *negative* result was disconcerting. Similar to other concurrent studies in my lab, mice did not display cognitive alterations as predicted in the literature. We attribute this phenomenon to the construction of a new research building in a lot adjacent to where our animals are housed at the University of Kentucky. We believe construction of the foundations affected the mice such that they all perform poorly in the novel object recognition test. We are currently evaluating which would be the best strategy to obtain functional data and truly test if the compound offers benefits.

Despite having established the first successful back-crossed breeders for the PERK cKO line, moving the lab to the University of Florida interrupted the ability to successfully populate the colony. The mice we had yielded a small sample size to discern any conclusions. The small litters and cannibalism of pups forced us to re-start populating the colony. This *force majeure* interruption limits our ability to test the hypothesis that genetic inhibition of PERK has a positive outcome after TBI. We have new breeders now, and we intend to carry out the

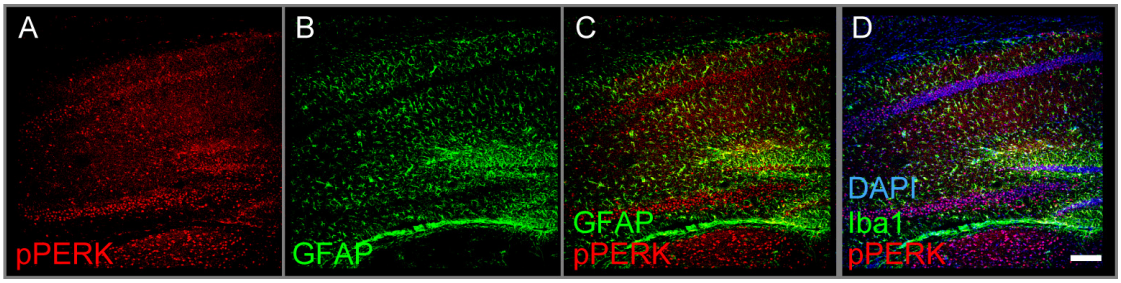

Fig. 4: pPERK signal is not in GFAP-positive cells. Mice were injured using CCI. Brains were prepared for immunohistochemistry staining of pPERK and neurotrace 3h post injury.

experiments using financial support from my startup funds. Successful completion of those experiments that may lead to any publications will acknowledge this award and the DoD will be notified.

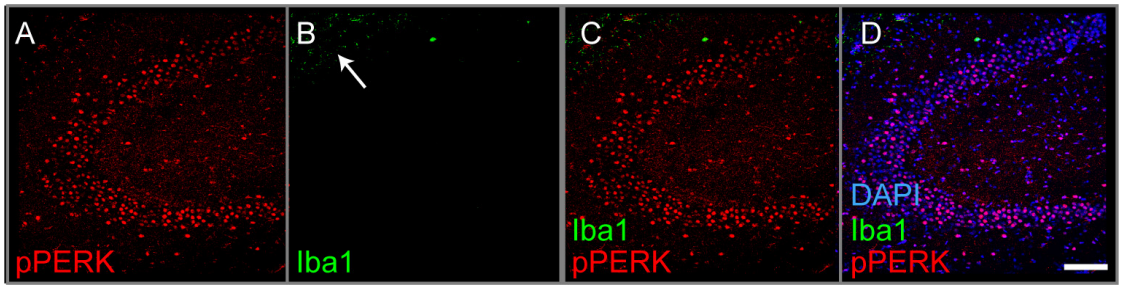

Fig. 5: pPERK signal is not in Iba1-positive cells. Mice were injured using CCI. Brains were prepared for immunohistochemistry staining of pPERK and neurotrace 3h post injury. Arrowhead posints at Iba1-positive stain

Annual Report 3:

The *major activities* in the last year were to complete further analysis under Sub-AIM 2.2b (chemical inhibition) and begin analysis of mice for Sub-Aim 2.2a (genetic inhibition). The *specific objective* was to perform CCI on WT and PERK cKO animals. Fourteen days post-injury animals were harvested and biochemical analysis was performed.

Our *significant findings* are that genetic inhibition of PERK in neurons does not significantly reduce global pPERK levels in the brain after injury, which is likely due to upregulation of pPERK in glia, where PERK is not knocked out (Fig. 9). In addition, results in the ipsilateral and contralateral

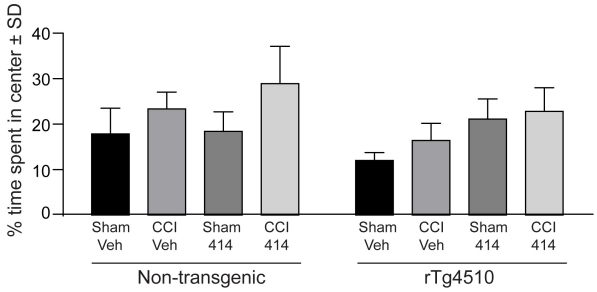

Fig. 7: Open field preliminary results. Sham: not injured. CCI: controlled cortical injury. Veh: vehicle treated. 414: PERK inhibitor GSK2606414. rTg4510: tau transgenic mice.

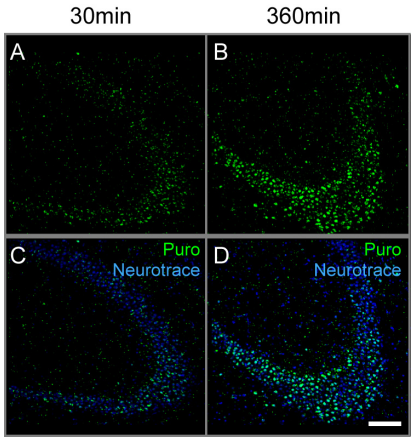

Fig. 6: Puromycinylated proteins are increased in hippocampus after CCI. Puromycin tags newly-synthesized proteins. Brains were prepared for staining 3h post-injury. Puromycin was injected 30min before harvesting brains.

hemispheres were different. In the ipsilateral hemispheres, we did not detect significant changes in the levels of Iba1 and GFAP regardless of whether PERK was knocked down or knocked out. Meanwhile, in the contralateral hemisphere, PERK knockdown mice exhibited similar levels of GFAP and Iba1. The most robust effect we observed was a significant increase in both Iba1

and GFAP in the contralateral PERK knockout hemispheres. The observation that there were no detectable changes in the ipsilateral hemisphere is likely due to the significant damage caused by injury, regardless of genetic manipulation of PERK, which would cause catastrophic events that might mask more discreet mechanistic effects. However, since the contralateral effects of the injury are milder or follow a different molecular mechanism of damage than the ipsilateral hemisphere, we propose that PERK knockout in neurons exacerbates gliosis. Whether these effects are beneficial remains unclear until after we finalize our data analysis.

Expanded IHC analysis on the animal cohort that received pharmacological PERK inhibitor GSK2606414 for 30 days after injury revealed that CHOP levels are still elevated 30 days post injury, even in GSK2606414-treated mice. CHOP is a mediator of apoptotic signaling that is thought to be activated by chronic PERK-pathway signaling. Thus, the presence of CHOP signaling 30 days post injury suggests that apoptotic pathways may still be active in cortical areas immediately peripheral to the injury site, in keeping with literature that suggests apoptosis can occur as far as a month after injury. The fact that no difference is observed in cortical CHOP levels in the GSK2602414-treated mice as compared to vehicle-treated animals suggests that CHOP activity may be independent of PERK at this prolonged timepoint.

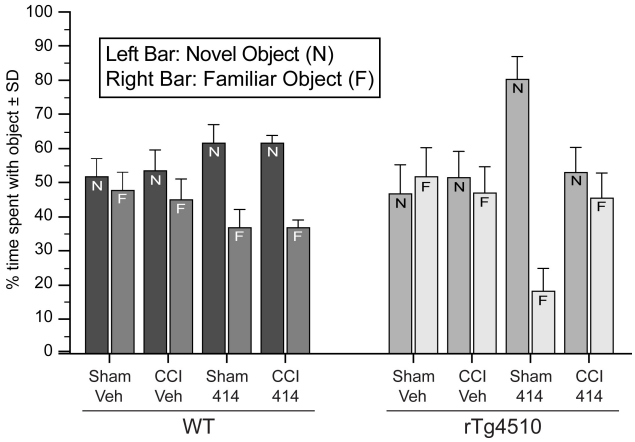

Fig. 8: Novel Object Recognition preliminary results. Sham: not injured. CCI: controlled cortical injury. Veh: vehicle treated. 414: PERK inhibitor GSK2606414. rTg4510: tau transgenic mice.

In addition, we found that the PERK inhibitor GSK2606414 alters astrocyte reactivity in both 414 and knock-down/out models (Fig. 10 and 11). Interestingly, GFAP levels were reduced after injury overall 30d following CCI. However, in sham-injured animals, 414 increased GFAP levels. This could explain a reduction in brain swelling after injury as shown by the reduction in brain volume (Fig. 12). Interestingly, these results were not observed in injured rTg4510, which is likely due to the severe brain atrophy that is characteristic of the mice. Under aggressive tauopathic conditions, the injuries did not promote brain atrophy (Fig. 13 and 14).

Recent data from other studies in our lab demonstrate that GSK2606414 confers benefits via reduction of nitroxidation. This specific process of oxidative stress is present in tau transgenic mice, and the compound we chose to inhibit PERK might confer benefits by off-target mechanisms.

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

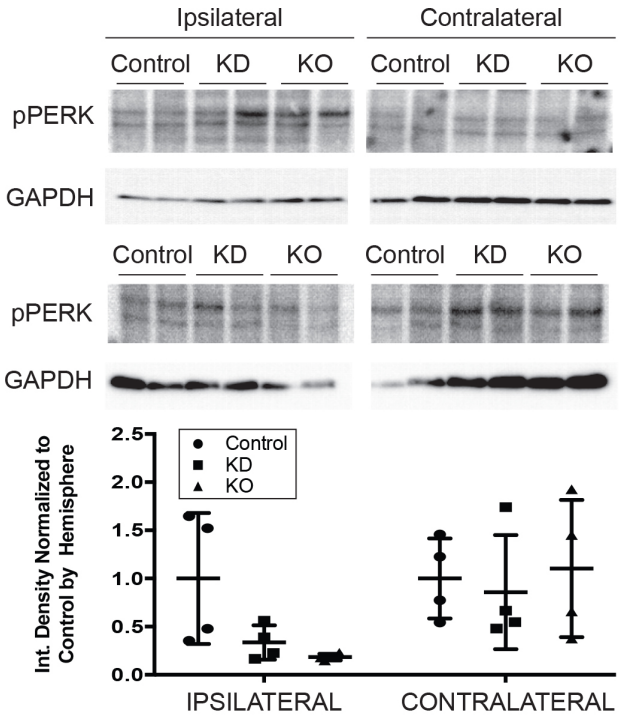

Fig. 9: Representative western blots and quantification of pPERK in ipsi and contralateral hemispheres of control, PERK knockdown, and knockout mice. Data indicate that PERK knockout in neurons significantly reduces pPERK activity in the ipsilateral hemisphere; however, there is no pPERK suppression in the contralateral hemisphere.

This project provided the opportunity to become proficient in the CCI models of injury. One graduate student successfully completed training from Dr. Kathryn Saatman, and **she is recently obtained her PhD.** This award has also allowed for professional development in allowing us to expand our knowledge and relationships with TBI experts at the National Neurotrauma Society annual meeting and the Alzheimer's Association International Conference. One graduate student presented her work at both meetings and received feedback to aid in data interpretation. These meetings greatly expanded our knowledge on the most recent findings in the TBI field.

This project also enhanced professional development by allowing work to be presented at the Alzheimer's Disease/Parkinson's Disease (ADPD), SfN, and Alzheimer's Association International Conference. These meetings greatly expanded our knowledge on the most recent findings in the TBI field. Importantly, I presented these data in the IPR Briefing where I obtained critical insight from Drs. Roderick Corriveau (NIH/NINDS), Heather Snyder (Alzheimer's Association), and Eliezer Masliah (NIA). Unfortunately, I was unable to physically attend the briefing; however, our impactful results encouraged a productive discussion via email and during ADPD.

How were the results disseminated to communities of interest?

Annual Report 1

Data collected from this project was presented at two separate meetings and in department level seminars. We anticipate submitting a manuscript within

the next few weeks to the Journal of Neurotrauma. Two other manuscripts are in preparation; they focus on the impact of PERK inhibition on tau and the impact of genetic PERK inhibition on adverse consequences of TBI.

Annual Report 2

Data collected from this project was presented at two separate meetings and has been presented at multiple department level seminars. The anticipated manuscript submission was delayed after further critical analysis of the data collected. We currently have the manuscript drafted and a preparing to send it to the Journal of Neurotrauma by the end of the month.

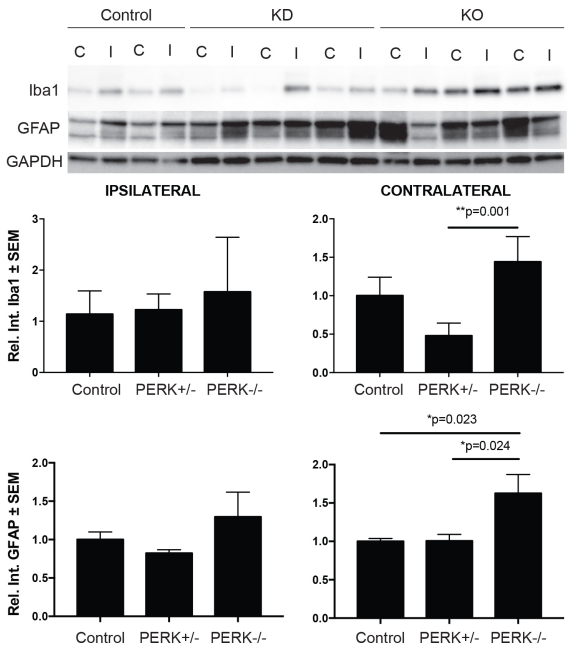

Fig. 10: Representative western blots and quantification of Iba1 and GFAP in ipsi and contralateral hemispheres of control, PERK knockdown, and knockout mice. Data indicate that PERK knockout in neurons creates an environment that is more susceptible to gliosis after injury in the contralateral hemisphere.

Annual Report 3:

Moving my lab to the University of Florida has been cause for hiring new personnel. One of these new hires is a post-doctoral associate who has a background in neurodegenerative disease work and is eagerly learning about TBI. He is now trained on methods pertinent to work in this grant, including CCI models of injury. The Center for Translational Research in Neurodegenerative Disease where I am now located fosters a tremendous environment of collaboration and we have already set up partnerships to provide TBI model training for my new post-doc.

GFAP levels in ipsilateral HC of Non

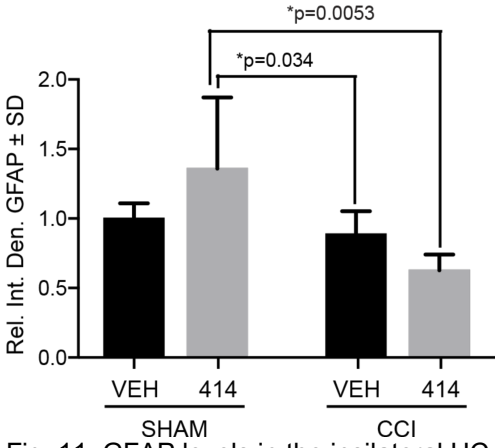

Fig. 11: GFAP levels in the ipsilateral HC of injured and non-injured non-transgenic mice treated with vehicle or 414. GFAP levels were reduced up to thirty days of daily treatment via oral gavage in injured mice. However, 414 treatment significantly increased GFAP levels in non-injured (sham) mice. These data suggest that 414 differentially modifies GFAP levels with or without injury.

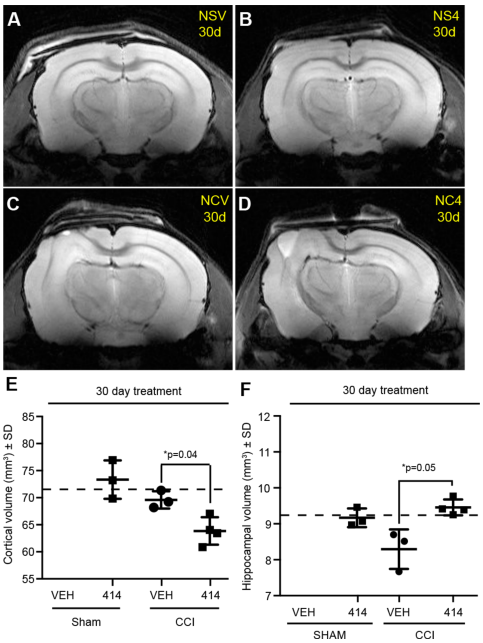

Fig. 12. 414 decreases cortical volume but rescues hippocampal volume after injury.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Annual Report 1

Although we are continuously working on increasing our sample size for each experimental group, our preliminary data suggest that CCI impacts neurons before glia. This is a surprising finding considering that previous data in related fields of neurodegeneration suggest that inflammatory responses would be more prevalent. In addition, it would explain why cognition is the first faculty to be impacted immediately after injury. Another surprising finding is that injured neurons are the primary cell type that increases protein synthesis. The identity of these proteins is unknown, and we hypothesize that they correspond to stress proteins, such as PERK, and not synaptic proteins.

Annual Report 2

So far, our data have shown that PERK plays a critical role in the brain's response to head injury, but the exact nature of that role is still unclear. Shortly after injury and despite acute PERK activation, the hippocampus increases protein synthesis as evidenced by puromycin uptake (Fig. 6). Moreover, PERK inhibition for 30d decreases brain volume. These are two examples of unexpected results that make the next steps of this project fascinating.

From a technical perspective, progress in the project has enhanced our ability to use MRI for careful and accurate measurement of brain volume (Fig. 10 and 11). These approaches are now being used in other animal studies in my lab. I have also been approach by another local lab after presenting our volumetric MRI results for a collaborative project. In addition, we used the in vivo puromycin technique for another major project in my lab. The goal of the experiment is to identify changes in the synthesis of new proteins as a consequence of tau pathology. We received our first set of results where puromycinylated proteins from tau transgenic mouse brains were identified using LC-MS/MS.

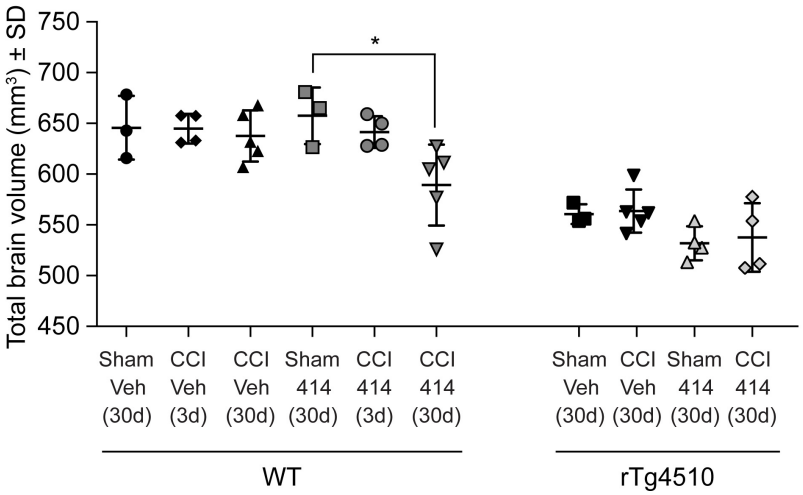

Fig. 13: T2 volumetric measurements. 414 decreased brain volume after injury. No change was detected in tau transgenic mice; this is likely because brain atrophy that is characteristic of rTg4510 mice reached the limit. Prevention of atrophy would have likely been detectable.

Annual Report 3

The role of PERK in head injury is more puzzling and complicated than expected, but our recent data from year 3 narrows the gap in our understanding of how the PERK inhibitor confers benefits, and it questions whether total PERK inhibition is beneficial. First, GSK2606414 alleviates nitroxidation, a specific measure of oxidative stress that is common in tauopathies. Second, PERK knockout (in neurons) exacerbates Iba1 and GFAP markers of gliosis. Interestingly, these effects were only observed contralaterally. In the ipsilateral cortex, there was no difference in GFAP and Iba1 markers between controls, knockdown, and knockout. Finding elevated CHOP levels peripheral to the injury site 30 days after injury in mice that have received chemical inhibition of PERK is an intriguing outcome that may merit investigation into non-PERK regulation of CHOP apoptotic signaling in the future.

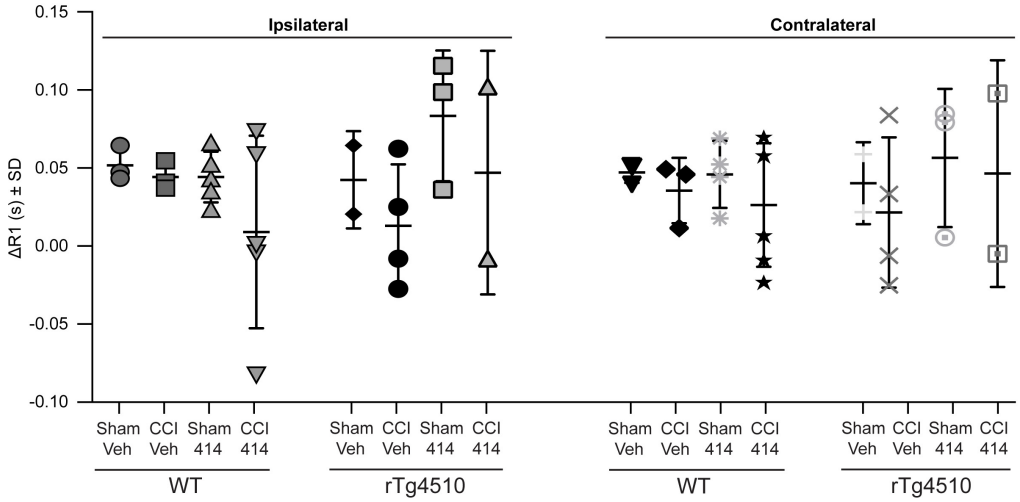

Fig. 14: MEMRI results. MEMRI did not detect defects in hippocampus as a result of injury.

What was the impact on other disciplines?

Annual Report 1

Nothing to report

Annual Report 2

Nothing to report

Annual Report 3

Nothing to report

What was the impact on technology transfer?

Annual Report 1

Nothing to report

Annual Report 2

Nothing to report

Annual Report 3

Nothing to report

What was the impact on society beyond science and technology?

Annual Report 1

Nothing to report

Annual Report 2

Nothing to report

Annual Report 3

Nothing to report

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Annual Report 1

We injured mice and analyzed PERK activation at earlier time points than originally suggested to optimize the timing of the drug delivery for chemical PERK inhibition. We wanted to make sure we were targeting an appropriate window. Now that we have a clear therapeutic window, we will continue our time points as established in the proposal.

Annual Report 2

We included experiments with altered length of chemical PERK inhibition. PERK inhibition for 30 days promotes brain atrophy, which would be considered detrimental. However, 30d inhibition abrogated tau pathology. We altered the length of treatment to investigate the effects on TBI outcomes and tau outcomes.

Annual Report 3

The Abisambra Lab moved to the University of Florida, which interrupted the final experiments requiring the use of PERKcKO mice. Breeding these mice is very difficult, and the move affected the breeders. The mice generated in Kentucky were used, but we lack sufficient sample size to generate robust data due to limited statistical power.

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

Annual Report 1

Currently, our major delay comes from establishing the PERK conditional knockout colony. The animals have been backcrossed, but now we must have the appropriate parental cross to ensure maximal usable offspring for future experiments. This requires the animals to age to appropriate breeding age before we can perform any experiments.

Annual Report 2

Two major problems we observed were in the behavioral studies and the MEMRI outcomes. For behavior, the first cohorts of animals (n=6-8 per group) showed that the tests were not sensitive enough to detect changes; we think this is due to construction occurring on campus. Additionally, our measurements on MEMRI (in multiple regions) show that this test is not sensitive enough to detect changes between sham and injured animals.

Annual Report 3

The major delay has to do with the natural set-backs of restarting and

re-staffing the lab. The biggest issue was establishment of the PERK cKO colony.

Changes that had a significant impact on expenditures
Annual Report 1
No changes that have had significant impact on expenditures

Annual Report 2
No changes that have had significant impact on expenditures

Annual Report 3
A part of the remainder of the award remained in the University of Kentucky, and the award was transferred to Dr. Bret Smith.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Annual Report 1
Nothing to report

Annual Report 2
Nothing to report

Annual Report 3
Nothing to report

Significant changes in use or care of human subjects
Annual Report 1
Not applicable

Annual Report 2
Not applicable

Annual Report 3
Not applicable

Significant changes in use or care of vertebrate animals.
Annual Report 1
Nothing to report

Annual Report 2
Nothing to report

Significant changes in use of biohazards and/or select agents

Annual Report 1
Nothing to report

Annual Report 2
Nothing to report

Annual Report 3
Nothing to report

PRODUCTS:

Publications, conference papers, and presentations *Report only the major publication(s) resulting from the work under this award.*

Journal publications.

1. Meier S, Bell M, Lyons DN, Rodriguez-Rivera J, Ingram A, Fontaine SN, Mechas E, Chen J, Wolozin B, LeVine H 3rd, Zhu H, **Abisambra JF***. Pathological Tau Promotes Neuronal Damage by Impairing Ribosomal Function and Decreasing Protein Synthesis. J Neurosci. 2016 Jan 20;36(3):1001-7. doi: 10.1523/JNEUROSCI.3029-15.2016. PubMed PMID: 26791227; PubMed Central PMCID: PMC4719006.

2. Vanderwyde T, Apicco DJ, Youmans-Kidder K, Ash PE, Cook C, da Rocha EL, Jansen-West K, Frame AA, Citro A, Leszyk JD, **Abisambra JF**, Steffen M, Li H, Petrucelli L, Wolozin B. Interaction with tau and RNA protein TIA1 regulates tau pathophysiology and toxicity. Cell Rep. 2016 May 5. pii: S2211-1247(16)30472-7. doi: 10.1016/j.celrep.2016.04.045. PubMed PMID: 27160897.

3. Fontaine SN, Lyons D, Cloyd RA, Meier S, Ingram I, Miller E, Powell DK, Vandsburger M, **Abisambra JF***. Identification of changes in neuronal function as a consequence of aging and tauopathic neurodegeneration using a novel and sensitive magnetic resonance imaging approach. Neurobiology of Aging, Available online 18 April 2017, ISSN 0197-4580, http://doi.org/10.1016/j.neurobiolaging.2017.04.007

4. Lanzillotta C, Tramutola A, Meier S, Schmitt F, Barone E, Perluigi M, Di Domenico F, **Abisambra JF*.** Premature activation and subsequent alterations to the unfolded protein response in Down Syndrome mouse models. J Alzheimers Dis. 2018;62(1):347-359.doi: 10.3233/JAD-170617. PubMed PMID: 29439332.

5. Meier S, Gilad AA, Brandon JA, Qian C, Gao E, **Abisambra** JF, Vandsburger M. Non-invasive detection of adeno-associated viral gene transfer using a genetically encoded CEST-MRI reporter gene in the

murine heart. Sci Rep. 2018 Mar 15;8(1):4638. doi: 10.1038/s41598-018-22993-4. PMID: 29545551

6. Twizere JC, Sleegers K, Dourlen P, **Abisambra JF**, Meier SM, Cloyd R, Weiss B, Dermaut B, Bessonov K, van der Lee SJ, Carrasquillo MM, Katsumata Y, Cherkaoui M, Asselbergh B, Ikram A, Mayeoux R, Farrer LA, Haines JL, Pericak-Vance MA, Schellenberg GD, Sims R, Williams J, Amouyel P, van Duij CM, Ertekin-Taner N, Van Broeckhoven C, Dequiedt F, Fardo Dw, Lambert JC, Van Steen K. Male-specific epistasis between *WWC1* and *TLN2* genes is associated to Alzheimer's Disease. Neurobiol Aging. *Accepted*

7. Lourenco MV, Frozza RL, Beckman D, Berman H, Zhang H, Staniszevski A, **Abisambra JF,** Wilcock DM, Ribeiro FC, Clarke JR, Kincheski GC, de Souza JM, Alves-Leon S, Wrann CD, Spiegelman BM[7], Arancio O, Ferreira ST, De Felice FG. FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer models. Nature Medicine. *Accepted 11/2/18*

8. Cloyd RA, Koren SA, **Abisambra JF**. Manganese-Enhanced Magnetic Resonance Imaging for neuroscience applications. Frontiers in Aging Neuroscience. *Accepted 11/26/18*

9. Bachstetter AD, Morganti JM, Bodnar CN, Webster SJ, Higgins EK, Roberts KN, Snider H, Meier SE, Nation GK, Goulding DS, Hamm M, Powell DK, Vandsburger M, Van Eldik LJ, Abisambra JF. The effects of mild closed head injuries on tauopathy and cognitive deficits in rodents: Primary results in wild type and rTg4510 mice, and a systematic review. Exp Neurol. 2020 Jan 11;326:113180. doi: 10.1016/j.expneurol.2020.113180. PMID:31930992

Books or other non-periodical, one-time publications.
Nothing to report

Other publications, conference papers, and presentations.

<u>Conferences and Symposia</u>

1. Meier, S. Abisambra, JF. PERK activation in controlled cortical impact model of TBI National Neurotrauma Society Annual Meeting. Lexington, KY. 2016. <u>Poster</u>

2. <u>Meier S</u>, Bell M, Lyons DN, Rodriguez-Rivera J, Ingram A, Fontaine SN, Mechas E, Chen J, Wolozin B, LeVine H 3rd, Zhu H, Abisambra JF. Pathological Tau Promotes Neuronal Damage by Impairing Ribosomal Function and Decreasing Protein Synthesis. Alzheimer's Association International Conference. Toronto, Canada. July 2016. <u>Podium</u>.
    a. *Received travel award from Alzheimer's Association*

3. Meier S, Boychuk J, Smith B, Saatman K, Abisambra J. Post-injury PERK inhibition in a mouse model of tauopathy. International Conference on Alzheimer's and Parkinson's Diseases (AD/PD). Vienna, Austria. March 2017. Poster.

4. Meier S, Lanzillotta, C., Galvis S., Saatman K., Boychuk J., Smith B., Abisambra J. Post-injury PERK inhibition in a mouse model of tauopathy. Alzheimer's Association International Conference. London, UK. July 2017. Poster.
    a. *Received travel award from UK COM*

5. Mechas E, Meier SM, Lyons DN, Bell M, Rodriguez-Rivera J, Ingram A, Chen J, LeVine III H, Zhu H, Abisambra JF. November 2015. Markesbery Symposium, University of Kentucky, Lexington, KY. Poster presenter Mechas E.
6. *Outstanding Poster Award*

7. Nation G., Meier S, Bell M, Lyons D, Ingram A, Chen J, Gensel J, Zhu H, Nelson P, Abisambra JF. Identification of novel tau interactions with endoplasmic reticulum proteins in Alzheimer's disease brains. Dept. of Physiology Research Retreat. Lexington, KY. July 2016. Poster.

8. Lanzillotta C, Tramutola A, Di Domenico, Perluigi M, Abisambra JF. The role of autophagy and the unfolded protein response in the development of Alzheimer's disease in a mouse model of Down Syndrome neuropathology. Dept. of Physiology Research Retreat. Lexington, KY. July 2016. Poster.

9. Weiss B, Fontaine SN, Mechas E, Lyons, D, Meier S, Miller E, Abisambra JF. Treatment with GSK2606414 rescues behavioral phenotypes in rTg4510 mice. Dept. of Physiology Research Retreat. Lexington, KY. July 2016. Poster.

10. Meier S, Diaz A, Fontaine SN, Miller E, Abisambra JF. SUnSET *in vivo*: A novel model for monitoring translation. Dept. of Physiology Research Retreat. Lexington, KY. July 2016. Poster.

11. Meier S, Lyons D, Ingram A, Bell M, Ingram A, Miller E, Mechas E, Rodriguez-Rivera J, Powell D, Vandsburger M, Abisambra JF. PERK inhibition in tau transgenic mouse model improves neuronal function in an eIF2a-independent manner. Dept. of Physiology Research Retreat. Lexington, KY. July 2016. Poster.
    a. *Outstanding Poster Award*

12. Fontaine SN, Cloyd RA, Lyons D, Ingram A, Meier SE, Bell E, Powell D, Vandsburger M, Abisambra JF. PERK inhibition improves tau-mediated neuronal dysfunction in transgenic mice. Dept. of Physiology Research Retreat. Lexington, KY. July 2016. Poster.

13. Nation G., Meier S, Bell M, Lyons D, Ingram A, Chen J, Gensel J, Zhu H, Nelson P, Abisambra JF. Identification of novel tau interactions with endoplasmic reticulum proteins in Alzheimer's disease brains. Clinical Translational Research Symposium. Lexington, KY. September 2016. Poster.

14. Lanzillotta C, Tramutola A, Di Domenico, Perluigi M, Abisambra JF. The role of autophagy and the unfolded protein response in the development of Alzheimer's

disease in a mouse model of Down Syndrome neuropathology. Clinical Translational Research Symposium. Lexington, KY. September 2016. Poster.

15. Weiss B, Fontaine SN, Mechas E, Lyons, D, Meier S, Miller E, Abisambra JF. Treatment with GSK2606414 rescues behavioral phenotypes in rTg4510 mice. Clinical Translational Research Symposium. Lexington, KY. September 2016. Poster.

16. Meier S, Diaz A, Fontaine SN, Miller E, Abisambra JF. SUnSET *in vivo*: A novel model for monitoring translation. Clinical Translational Research Symposium. Lexington, KY. September 2016. Poster.

17. Meier S, Lyons D, Ingram A, Bell M, Ingram A, Miller E, Mechas E, Rodriguez-Rivera J, Powell D, Vandsburger M, Abisambra JF. PERK inhibition in tau transgenic mouse model improves neuronal function in an eIF2a-independent manner. Clinical Translational Research Symposium. Lexington, KY. September 2016. Poster.

18. Meier S, Dealla Samadi, Miller E, Boychuk, Saatman K, Smith B, Abisambra JF. PERK inhibition improves tau-mediated neuronal dysfunction in transgenic mice. Clinical Translational Research Symposium. Lexington, KY. September 2016. Poster.

19. Fontaine SN, Cloyd RA, Lyons D, Ingram A, Meier SE, Bell E, Powell D, Vandsburger M, Abisambra JF. PERK inhibition improves tau-mediated neuronal dysfunction in transgenic mice. Clinical Translational Research Symposium. Lexington, KY. September 2016. Poster.

20. Meier S, Lyons D, Ingram A, Bell M, Miller E, Mechas E, Rodriguez-Rivera J, Powell D, Vandsburger M, Abisambra JF. PERK inhibition in rTg4510 mouse model of tauopathy. Clinical Translational Research Symposium. Lexington, KY. September 2016. Podium.

21. Meier SE, Ingram A, Poole C, Bell MC, Vandsburger M, Powell DK, Abisambra JF. PERK inhibition reverses structural and functional abnormalities in tau transgenic mice. International Conference on Alzheimer's and Parkinson's Diseases (AD/PD). Nice, France. March 2015. Podium.
    a. *I earned the Early Researcher Award*

22. Lyons DN, Ingram A, Meier SE, Bell MC, Powell DK, Vandsburger M, Abisambra JF. Manganese-enhanced magnetic resonance imaging (MEMRI) measures pre-pathological neuronal dysfunction before the appearance of tau pathology in rTg4510 mice. Alzheimer's Association International Conference. Washington, DC. July 2015. Poster.

23. Meier SE, Bell MC, Lyons DN, Lee T, Chen J, Abner E, Wilcock DM, Levine H, Zhu H, Kayed R, Abisambra JF. Association of pathological tau with the ribosomal complex impairs protein synthesis. Alzheimer's Association International Conference. Washington, DC. July 2015. Poster.
    a. *Awarded "Best Student Poster Presentation"; 4 awards out of 80 finalists*

24. Meier SE, Bell MC, Ingram A, Lyons DN, Powell DK, Vandsburger M, Abisambra JF. PERK inhibition improves structural and functional abnormalities in tau transgenic mice. Alzheimer's Association International Conference. Washington, DC. July 2015. Podium.

25. Meier S, Lyons D, Ingram A, Bell M, Miller E, Mechas E, Rodriguez-Rivera J, Powell D, Vandsburger M, Abisambra JF. PERK inhibition improves tau-mediated neuronal dysfunction in transgenic mice. Midwest Stress Response Meeting. Evanston, IL. January 2016. Podium.

26. Meier S, Bell M, Lyons DN, Rodriguez-Rivera J, Ingram A, Fontaine SN, Mechas E, Chen J, Wolozin B, LeVine H 3rd, Zhu H, Abisambra JF. Pathological Tau Promotes Neuronal Damage by Impairing Ribosomal Function and Decreasing Protein Synthesis. Alzheimer's Association International Conference. Toronto, Canada. July 2016. Podium.
    a. *Received travel award from Alzheimer's Association*

27. Abisambra JF. PERK inhibition reduces hyperphosphorylated tau and rescues neuronal function in an eIF2a-independent mechanism. 4th Global Experts Meeting on Neuropharmacology. San Antonio, TX. September 2016. Podium.
    a. *Invited to serve as Chair for this session*

28. Abisambra JF. Pathological Tau Promotes Neuronal Damage by Impairing Ribosomal Function and Decreasing Protein Synthesis. 4th RNA Metabolism in Neurological Disease. San Diego, CA. November 2016. Poster.

29. Fontaine SN, Mechas E, Chen J, Wolozin B, LeVine H 3rd, Zhu H, Abisambra JF. Manganese-enhanced magnetic resonance imaging (MEMRI) identification of prepathological neuronal dysfunction precedes significant tau pathology in rTg4510 mice. Society for Neuroscience Conference. San Diego, CA. November 2016. Podium.

30. Abisambra JF. Pathological tau associates with ribosomes and impairs the protein synthesis in tauopathic neurons and human Alzheimer's disease brains Midwest Stress Response Meeting. Evanston, IL. January 2017. Podium.

31. Meier S, Bell M, Lyons D, Rodriguez-Rivera J, Ingram A, Fontaine S, Mechas E, Chen J, Wolozin B, Levine H, Zhu H, J. Abisambra. Association of pathological tau with ribosomes impairs function and decreases protein synthesis. International Conference on Alzheimer's and Parkinson's Diseases (AD/PD). Vienna, Austria. March 2017. Poster.

32. Lanzillotta, C, DiDomenico F, Abisambra JF. The unfolded protein response is a major participant in the development of Alzheimer's disease symptomatology in a mouse model of Down Syndrome. Vienna, Austria. March 2017. Podium.

33. Meier S, Fontaine S, Ingram A, Mechas E, Bell M, Vandsburger M, Powell D, Abisambra J. PERK inhibition demonstrates a novel pathological mechanism in tauopathies. International Conference on Alzheimer's and Parkinson's Diseases (AD/PD). Vienna, Austria. March 2017. Podium.

34. Meier S, Boychuk J, Smith B, Saatman K, Abisambra J. Post-injury PERK inhibition in a mouse model of tauopathy. International Conference on Alzheimer's and Parkinson's Diseases (AD/PD). Vienna, Austria. March 2017. Poster.

35. Fontaine S., Nation G., Meier S., Abisambra J. Tau oligomers mediate ribosomal dysfunction at the synapse. Alzheimer's Association International Conference. London, UK. July 2017. Podium.
    a. *Dr. Fontaine was selected to Chair this session*

36. Meier S, Lanzillotta, C., Galvis S., Saatman K., Boychuk J., Smith B., Abisambra J. Post-injury PERK inhibition in a mouse model of tauopathy. Alzheimer's Association International Conference. London, UK. July 2017. Poster.
    a. *SM received a travel award from UK COM*

37. Cloyd R., Fontaine S., Meier S., Powell D., Vandsburger M., Abisambra J. Novel applications of MRI techniques in the detection of neuronal dysfunction before tangle pathology in tau transgenic mice. Alzheimer's Association International Conference. London, UK. July 2017. Poster.
    a. *SM received a travel award from UK COM*

38. Abisambra, JF. Identification of changes in neuronal function as a consequence of aging and tauopathic neurodegeneration using a novel and sensitive magnetic resonance imaging approach. Dementia Research 2017 Conference. Rome, Italy. September 2017. Podium.

39. Fontaine S, Nation G, Koren S, Weiss B, Cloyd R, Meier SM, Chishti E, Powell D, Vandsburger M, Abisambra, JF. A dynamic PERK-Tau complex regulated tau phosphorylation, ER stress, and treatment outcomes in rTg4510 mice. Alzheimer's Association International Conference. Chicago, IL. July 2018. Podium.

40. Koren S, Meier SM, Nation G, Chishti E, Blalock E, Zhu H, Estus S, Abisambra, JF. Tau modifies ribosomal dynamics shifting translational profiles in AD. Alzheimer's Association International Conference. Chicago, IL. July 2018. Poster.

41. Nation GK, Meier SM, Chishti E, Blalock E, Abisambra, JF. Transcriptomic profiling of tauopathy reveals gene populations responsive to tau expression and a subpopulation of therapeutically relevant genes. Alzheimer's Association International Conference. Chicago, IL. July 2018. Poster.

42. Norris C, Sompol P, Gollihure JL Cloyd R, Koren S, Nation G, Abisambra, JF, Kraner SD, Artiushin IA, Huzian O, Laszlo PG. Novel small chemical compound with NFAT inhibitory properties ameliorates synaptic deficits in a mouse model of Alzheimer's disease. Alzheimer's Association International Conference. Chicago, IL. July 2018. Poster.

43. Sompol P, Gollihue J, Kraner S, Artiushin I, Cloyd R, Koren S, Nation, G, Abisambra, JF, Huzian O, Puskas L, Norris C. Novel NFAT inhibitor Q134R ameliorates synaptic deficits in a mouse model of Alzheimer's disease. Society for Neuroscience. San Diego, CA. November 2018. Poster.

44. Koren S, Meier SM, Nation G, Chishti E, Blalock E, Zhu H, Estus S, Abisambra, JF. Pathological tau shifts translation by modifying rpS6 and 5'TOP RNA protein synthesis. Society for Neuroscience. San Diego, CA. November 2018. Podium.

45. Abisambra, JF, Fontaine S, Koren S, Nation G, Weiss B, Cloyd R, Meier SM, Powell D, Vandsburger M. PERK-tau coupling causes biphasic consequences to tau pathology and mneuronal function in vitro and in vivo. Society for Neuroscience. San Diego, CA. November 2018. Podium.

Invited talks:

11/2015	Sanders-Brown Center on Aging Seminar Series: "Lost in translation: mechanisms of tau-mediated neurotoxicity."
11/2015	Spinal Cord & Brain Injury Research Center Work in Progress Seminar: "PERK as a therapeutic target for tauopathies."
09/2016	Dept. of Physiology Seminar Series: "Lost in translation: molecular patho-mechanisms of tauopathies and acute neurodegeneration."
04/2016	Suds and Science: "Tau and diseases of Aging."
11/2016	Markesbery Symposium: "Tau and translation at the center of Alzheimer's and related dementias."
	Eastern Kentucky University
	Richmond, KY
02/2017	Seminar: "Mechanisms of neuronal dysfunction in tauopathies."
	Santa Fe College
	Gainesville, FL
09/2018	Seminar: "Lost in Translation: Science, Spanish, and Passion."
	Universidad Nacional de Colombia
	Bogota, Colombia
03/2015	Invited talk: "Mecanismos moleculares de neurodegeneración en tauopatías: tau y traducción de ARN."
	Sapienza University of Rome
	Rome, Italy
03/2015	Department of Biomedical Sciences Seminar Series: "Lost in translation: mechanisms of tau-mediated neurotoxicity."
	University of Texas Medical Branch
	Galveston, TX
03/2016	Department of Neurology Seminar Series: "Lost in translation: mechanisms of tau-mediated neurotoxicity."
	Charleston Conference on Alzheimer's Disease
	Charleston, SC

03/2016 Speaker: “The impact of tau on PERK and the unfolded protein response.”

Pontificia Universidad Javeriana
Bogota, Colombia
05/2016 Speaker: “Errores de traducción de proteinas como mecanismos de neurodegeneración en tauopatías.”

Congreso de la República de Colombia
Bogota, Colombia
05/2016 Speech on the inauguration of the Dr. Jose Francisco Socarras awards by the Colombian Congress.

University of Rochester
Rochester, NY
11/2016 Department of Pharmacology Seminar Series: “Lost in translation: mechanisms of tau-mediated neurotoxicity.”

University of Florida
Gainesville, FL
04/2017 PSP/LBD Think Tank VI: “Novel molecular mechanisms of tauopathies involving PERK and ribosomal function.”

VA Think Tank
Clearwater, FL
04/2017 “TBI, ER stress, and Tauopathies”

International Clinical Research Center (FNUSA-ICRC)
09/2017 Brno, Czech Republic
“Altered RNA translation as an essential pathogenic event in tauopathies.”

University of Florida
09/2017 Gainesville, FL
“Lost in Translation: ER stress and ribosomal damage in tauopathies.”

Society for Neuroscience
11/2017 Washington, DC
Chair Alzheimer’s Disease Social

Alzheimer’s Association International Conference Satellite Meeting
04/2018 Buenos Aires, Argentina
Session Chair

Society for Neuroscience
11/2018 San Diego, CA
Co-Chair Alzheimer’s Disease Social

Society for Neuroscience

11/2018	San Diego, CA Chair Nanosymposium: Tauopathies, Tau Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Website(s) or other Internet site(s)
Nothing to report

Technologies or techniques
Nothing to report

Inventions, patent applications, and/or licenses
Nothing to report

Other Products
Nothing to report

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."* ***Example****:*

Name:	Bret Smith
Project Role:	Co-PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Smith offered feedback and expertise in interpreting results.
Funding Support:	Collaborator

Name:	Ryan Cloyd
Project Role:	PhD Candidate
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Smith mentored Mr. Cloyd to perform the studies aligned in the documentation.

Funding Support:	T32 NIH training grant

Name:	Joe Abisambra
Project Role:	Co-PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	
Contribution to Project:	
Funding Support:	No change

Name:	Kathryn Saatman, PhD
Project Role:	Collaborator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Saatman trained Shelby Meier in the CCI model of injury
Funding Support:	No change

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

Dr. Bret Smith:

MERIT Award 1 I01 BX004542-01A1 (Co-I; PI, Slevin,J) 04/2019-03/2023 1.2 ca
VA $175,000
Optogenetics: A tool to probe mechanism and an agent to block TBI-induced epileptogenesis
Objective: Modify posttraumatic epilepsy disease progression using optogenetics
No overlap

Overlap: None

No ID 01/15-12/19 (NCE)
KSCHIRT (Co-I; PI, Saatman, K) $1
0.01 calendar
Stimulation of Posttraumatic Neurogenesis by IGF-1 Overexpression
Objective: To identify effects of IGF-1 on neurogenesis in the dentate gyrus after brain injury.

No overlap

Dr. Jose Abisambra:

1 R56 NS110384-01 (ABISAMBRA) 09/15/19-08/31/20 3 cal.mo.
NIH/NINDS $321,630
Role: Principal Investigator
Title: Tau mediated regulation of ribosomes in health and disease
Goals: To determine the role of tau in normal ribosomal function and its impact on protein synthesis in tauopathies

Overlap: None

1 R56 AG064906 (BICKFORD & ABISAMBRA) 07/01/19-06/30/20 3 cal.mo.
NIH/NIA $209,431
Role: Co-Principal Investigator
Title: Exosomes from adipose-derived stem cells modulate age-dependent progression of tauopathies
Goals: To determine the therapeutic role of exosomes derived from human adipose stem cells in normal in tauopathies

Overlap: None

1R61NS115178-01 (LEWIS, ABISAMBRA, BORCHELT) 09/17/19 - 08/30/21
0.6 cal.mo.
NIH $262,239
Role: Co-Principal Investigator
Title: Tau-head injury co-morbidity outcomes in a novel model of neurodegeneration
Goals: To develop a new mouse model of Alzheimer's disease and establish the impact of head injury on disease onset

Overlap: None

1I01BX004563-01A1 Abisambra(PI) 04/01/19-03/31/23 VA
Identification of the molecular mechanisms linking Alzheimer's disease, PERK, and mild repetitive head injury
Role: PI
Goal: Establish the role of PERK on neuronal dysfunction after closed head injury.

Overlap: None

L32MD009205-01 Abisambra(PI) 07/01/14-06/30/21 Tau as a biomarker for traumatic brain injured patients
Role: PI
Goal: Identify novel biomarkers of TBI injury severity.

Overlap: None

What other organizations were involved as partners?

Organization Name: GlaxoSmithKline
Location of Organization: Collegeville, PA
Partner's contribution to the project: GSK developed the chemical PERK inhibitor used for this project, and supplies it for us.