AWARD NUMBER: W81XWH-15-1-0550

TITLE: TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains

PRINCIPAL INVESTIGATOR: Ottavio Arancio

CONTRACTING ORGANIZATION: Columbia University, 630 West 168th Street, New York NY 10032

REPORT DATE: Sept 2019

TYPE OF REPORT: Final

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
Sept 2019	Final	**15 SEP 15 – 30 Jun 2019**

4. TITLE AND SUBTITLE

TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains

5a. CONTRACT NUMBER
W81XWH-15-1-0550

5b. GRANT NUMBER
AZ140095

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Ottavio Arancio

E-Mail: oa1@columbia.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

COLUMBIA UNIVERSITY
630 West 168th Street
New York, NY 10032

8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Materiel Command
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

The goal of the current study is to demonstrate that blast-induced traumatic brain injury (TBI) and Alzheimer's disease (AD) lead to similar biochemical changes in tau that increase its toxicity and contribute to cognitive and electrophysiological impairments. Specifically we will test the hypothesis that 1) blast-induced TBI leads to the production of a toxic form of tau that contributes to cognitive and electrophysiological impairments; 2) the formation of soluble tau aggregates contributes to cognitive impairments associated with both blast-exposure and AD; 3) an increase in tau phosphorylation contributes to cognitive impairments associated with both blast-exposure and AD. During the last year we have completed experiments related to the first point of the hypothesis, and started working on the second point. Specifically, we have found that the presence of tau is necessary for a preparation from shockwave-exposed mice to reduce 1) memory including contextual fear memory and spatial memory, and 2) long-term potentiation, a type of synaptic plasticity thought to underlie learning. We have also performed a dose response curve for the toxic effect of blasted tau onto memory and LTP.

15. SUBJECT TERMS

Tau, contextual fear memory, spatial memory, synaptic plasticity, traumatic brain injury, Alzheimer's disease

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	21	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

Although epidemiological studies find a strong link between traumatic brain injury (TBI) and an increased risk for dementia (i.e. Alzheimer's Disease - AD), the molecular mechanisms responsible remain unclear. Evidence continues to accumulate highlighting the similarities between AD and post-TBI pathologies. A similarity between TBI and AD-related neurodegeneration exists at the histological level where both are characterized by the presence of aggregates of hyperphosphorylated forms of the microtubule associated protein, tau (DeKosky et al., 2010; Johnson et al., 2012). Tau abnormalities and neurofibrillary tangles (NFTs), the classical histopathological hallmark of AD consisting of insoluble aggregated tau, have been reported in multiple animal models of TBI (Cui et al., 2004; Redmond et al., 2002; Smith et al., 1999; Yoshiyama et al., 2005a). NFTs like those in AD have been reported after a single TBI in humans (Ikonomovic et al., 2004; Uryu et al., 2007). Evidence also exists in favor of a link between TBI and amyloid-β (Aβ), the amyloid precursor protein (APP) proteolytic fragment thought to act upstream of tau in AD (Shipton et al., 2011) that deposits in amyloid plaques. After experimental TBI in animal models, Aβ accumulated in injured neurons and axons both acutely (Cui et al., 2004; Redmond et al., 2002; Uryu et al., 2002; Yoshiyama et al., 2005b) and chronically (Iwata et al., 2002). Similar deposits of Aβ have been observed after a single TBI in humans (Ikonomovic et al., 2004; Smith et al., 2003; Uryu et al., 2007). Here we seek to define the toxic molecular mechanism leading to TBI and AD.

2. KEYWORDS

Tau, contextual fear memory, spatial memory, synaptic plasticity, traumatic brain injury, Alzheimer's disease

3 ACCOMPLISHMENTS

a. What were the major goals?

1) **Test the hypothesis that blast-induced TBI leads to the production of a toxic form of tau that contributes to cognitive and electrophysiological impairments.**
2) **Test the hypothesis that the formation of soluble tau aggregates contributes to cognitive impairments associated with both blast-exposure and AD.**
3) **Test the hypothesis that a similar increase in tau phosphorylation contributes to cognitive impairments associated with both blast-exposure and AD.**

b. What was accomplished under these goals?

All questions at point (a) above have been addressed during these years as detailed below.

Blast produces toxic forms of tau that cause behavioral/ electrophysiological impairments

At the beginning of work proposed for the project, we found that administration of tau purified from shockwave-exposed mice onto wild-type mice markedly reduces a) associative memory assessed through contextual fear conditioning (Fig. 1), b) spatial memory assessed through the 2-day radial arm water maze (RAWM) (Fig. 2), and c) long-term potentiation (LTP), a type of synaptic plasticity thought to underlie learning and memory (Fig. 3).

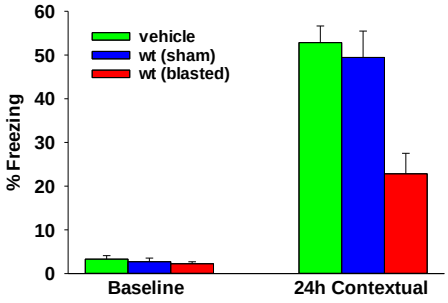

Fig. 1: Contextual fear memory is impaired following injection of tau from shockwave-exposed mice onto hippocampus. The percent freezing time in the group injected with tau from shockwave exposed mice was significantly lower than in the vehicle and sham tau groups in the contextual fear conditioning (10 mice per group; $p<0.05$, Two way ANOVA, Bonferroni post hoc).

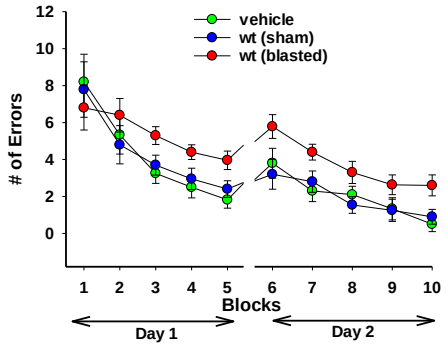

Fig. 2: Spatial memory is impaired following injection of tau from shockwave-exposed mice onto hippocampus. Performance in the 2-day radial arm water maze was significantly lowered in the group of mice injected with tau from shockwave exposed mice compared to vehicle and sham tau groups (10 mice per group; $p<0.05$, Two way ANOVA, Bonferroni post hoc).

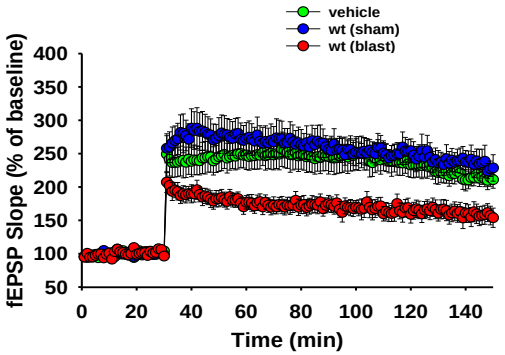

Fig. 3: Long-term potentiation (LTP) is impaired following hippocampal slice perfusion with of tau from shockwave-exposed mice. Tetanus induced long-lasting enhancement of synaptic strength was significantly lowered in slices perfused with tau from shockwave exposed mice compared to vehicle and sham tau slices 9/13 slices per group, ($p<0.05$, Two way ANOVA).

Experiments shown on Figs 1-3 are consistent with the hypothesis that shockwave produces toxic forms of tau. However, the preparation isolated from the brain of blasted animals is tau-enriched but does not contain only tau protein. Thus, other molecules triggered by the blast might be responsible for the observed effect onto LTP and memory. To conclusively demonstrate that tau is necessary for blasted specimens to impair memory and LTP, we used extracts from tau-KO mice (Jackson Lab: Stock #007251), and found that shockwave-exposed preparations from these animals do not impair associative and spatial memory (Fig 4A-B). We obtained similar results when we examined LTP using tau preparation from C57Bl6 mice compared with a preparation extracted from tau-KO mice (Fig. 4C).

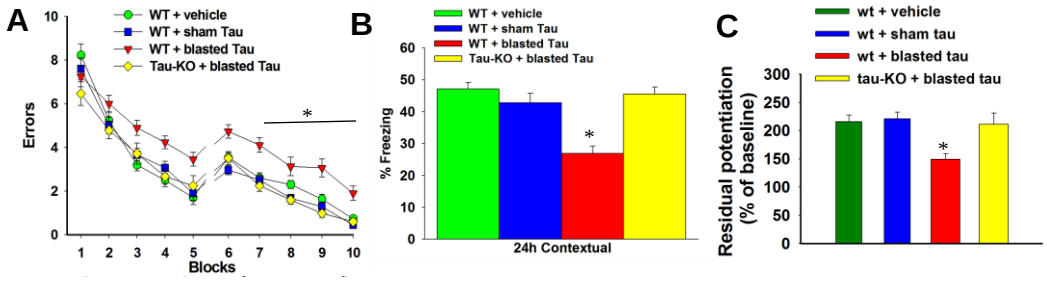

Fig. 4 Shockwave-exposure leads to the production of toxic tau in mouse brain impairing memory and LTP. A) 2-day RAWM performance in mice infused with 4.59 µg/ml tau purified from shockwave-exposed, tau-KO mice or sham animals (*p<0.05, RM-ANOVA, n= 7/10 animals per group). **B)** Percent of freezing during contextual FC test in mice infused with 4.59 µg/ml tau purified from shockwave-exposed, tau-KO or sham control animals (*p<0.05, Bonferroni post-hoc comparisons, n= 10/12 animals/group). **C)** Amounts of LTP in slices perfused for 20 min with 110 ng/ml shockwave exposed tau, extract from tau-KO or sham tau, prior to eliciting LTP (*p<0.05, Tukey's post-hoc test, n= 7/10 slices/group).

Altogether, these data suggest that shockwave-exposed tau undergoes changes capable of altering memory and synaptic plasticity. Interestingly, these results were similar to the effect of tau extracted with similar techniques from the brain of AD patients which impaired both memory and LTP (Fa et al., 2016), suggesting the possibility that molecular similarities between tau prepared from shockwave-exposed mouse brains and human AD brains may underlie a common ability to produce cognitive impairment when infused into normal mice.

The last subaim of Aim1 included establishing the dose-dependence of tau-induced behavioral and electrophysiological impairments. This was achieved through analysis of the 2-day RAWM and contextual fear conditioning performance on animals infused with purified tau from either shockwave or sham-exposed mice at concentrations of 0.18, 0.92, 4.58 and 114.5 µg/ml. We also compared the ability of tau to interfere with LTP when bath applied to acute hippocampal slice preparations at 0.92, 22.9, 110 and 573.5 ng/ml. These experiments were necessary to establish parameters of concentrations for future studies described in the last aim of the current studies.

Soluble tau aggregates contribute to cognitive impairments associated with both blast-exposure and AD.

What is the nature of the toxic forms of tau that are responsible for reduction in synaptic plasticity and memory after shockwave exposure? In a series of experiments, we purified tau from the forebrains of mice subjected to shockwave or sham exposure 24 hrs prior to harvesting the brains as described previously. This method produces high quantities of protein (0.1-1.5mg tau from 1.5g of frozen tissue), preserves tau phosphorylation, and removes the vast majority of other proteins and DNA (Fa et al., 2016). When we analyzed the purified samples using non-reducing SDS-PAGE, we observed the presence of tau in the fractions obtained during chromatography. Interestingly, we obtained similar results when we used similar techniques to analyze tau extracted from human Alzheimer's Disease (AD) subjects (Fa et al., 2016). These findings confirm the possibility that molecular similarities between tau prepared from shockwave-exposed mouse brains and human AD brains may underlie a common ability to produce cognitive and plasticity impairments when infused into normal mice.

The protocol to produce tau from the animal brain included a step consisting of treating the preparation with H_2O_2. To understand the implication of such a manipulation, we performed another series of experiments in which we purified tau from sham and shockwave exposed C57Bl6 mice, but did not treat this material with H_2O_2. Fear conditioning and 2-day RAWM did not show any significant changes both in the percent freezing time and number of errors in mice treated with shockwave tau compared to mice treated with vehicle and sham tau (Fig. 5). Consisting with these results LTP was not affected in the blast-tau preparation compared to sham-tau preparation and vehicle treated slices (Fig. 6).

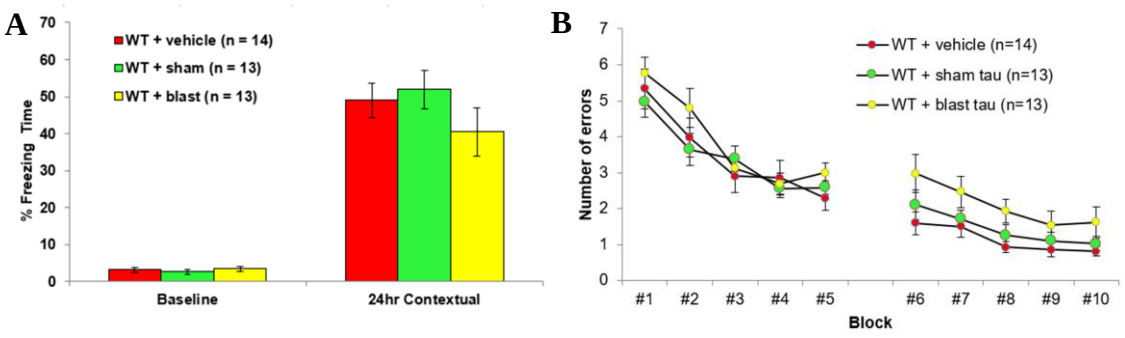

Fig 5. Naïve C57Bl6 mice treated with tau extracted from blasted mice did not show any significant change in percent freezing time in contextual fear conditioning **(A)** and number of errors in 2-day RAWM ($p>0.05$). **(B).** Similarly, tau extracted from sham-exposed mice exhibited no changes in behavior in either behavioral experiment compared to vehicle treated mice ($p>0.05$). The number of animals used per each group is shown in parenthesis on the figure.

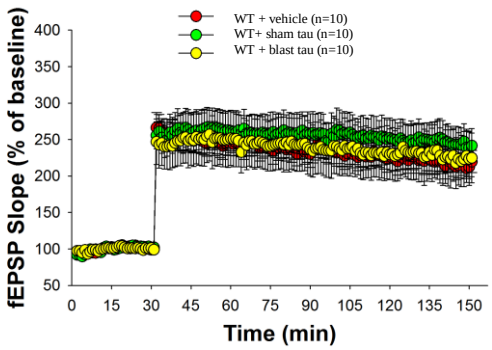

Fig. 6: Hippocampal slices perfusion with blast-tau that did not go for treatment with H_2O_2 failed to produce CA3-CA1 LTP impairment, similar to sham-tau or vehicle ($p>0.05$). The number of slices per each group is shown in parenthesis on the figure.

Findings shown at Figs 5 and 6 delineate the relevance of the treatment with H_2O_2 which might highlight the propensity of the shockwave exposed tau preparation to form oligomers. To confirm this possibility, we performed an in depth analysis of the effect of tau oligomerization onto cognition and LTP. The preparation was de-oligomerized through DTT and re-oligomerized with H_2O_2 prior to examining the effect of both de-oligomerized and re-oligomerized tau onto memory and LTP. Behavioral analysis onto C57Bl7 mice infused with sham/blast (de-oligomerized/re-oligomerized) tau revealed that re-oligomerized blast tau impairs associative memory as well as spatial reference memory whereas the de-oligomerized preparation does not impair associative and spatial memory (Figs. 7-8). In interleaved experiments in which we used sham tau associative and spatial memory were not affected regardless of the oligomerization status of tau (Figs 7-8). Consistent with these results, electrophysiological analysis onto slices from C57Bl7 mice perfused with sham/blast (de-oligomerized/re-oligomerized) tau revealed that re-oligomerized blast tau impairs LTP whereas the de-oligomerized preparation does not impair LTP (Fig. 9). In interleaved experiments in which we used sham tau, LTP was not affected regardless of the oligomerization status of tau (Fig. 9).

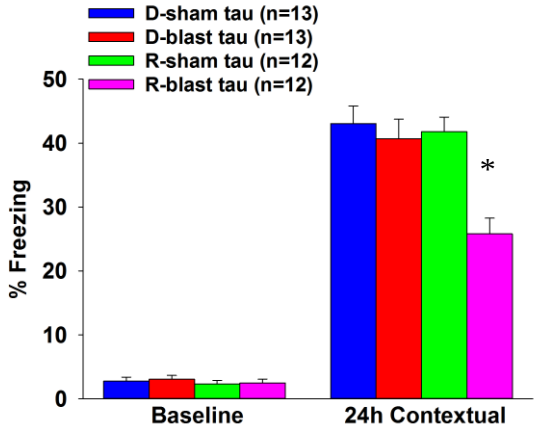

Fig. 7: Hippocampal infusion with re-oligomerized tau obtained from blast mice reduced contextual fear memory in mice, whereas the de-oligomerized blast tau preparation and both re-oligomerized and de-oligomerized sham tau preparations did not affect fear memory (*p,0.05).

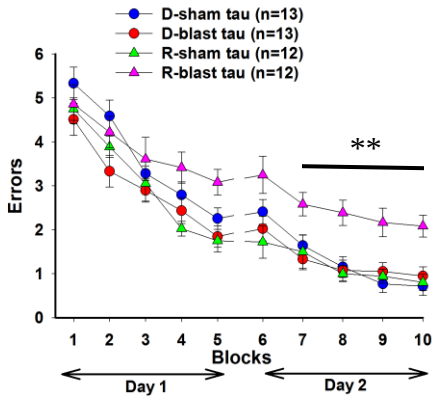

Fig. 8: Hippocampal infusion with re-oligomerized tau obtained from blast mice reduced spatial reference memory in mice, whereas the de-oligomerized blast tau preparation and both re-oligomerized and de-oligomerized sham tau preparations did not affect spatial memory (**p<0.01).

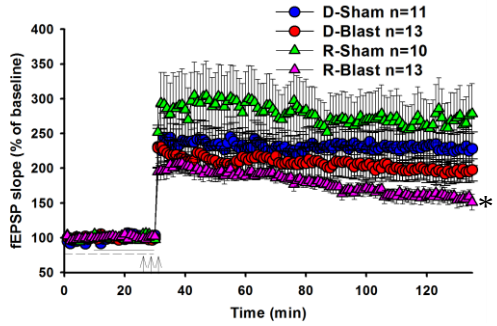

Fig. 9: Hippocampal slices perfusion with re-oligomerized tau obtained from blast mice reduced CA3-CA1 LTP, whereas the de-oligomerized blast tau preparation and both re-oligomerized and de-oligomerized sham tau preparations did not affect LTP (p<0.05).

Taken all together, findings shown at Figs 5-9 indicate that shockwave increased propensity to oligomerize of tau. Interestingly, these results were similar to the effect of tau extracted with similar techniques from the brain of AD patients which impaired both memory and LTP when the preparation was oligomerized (but not de-oligomerized) (Fa et al., 2016), confirming the possibility that molecular similarities between tau prepared from shockwave-exposed mouse brains and human AD brains may underlie a common ability to produce cognitive impairment when infused into normal mice.

Encouraged by these results, we directly examined whether, similar to humans affected by AD, tau oligomers were present in the preparation by blasted mice. This was achieved through the mouse monoclonal antibody specific for tau oligomers, TOC1, as the “capture” antibody in a sandwich ELISA (detection with R1, a rabbit polyclonal pan-tau antibody). TOC1 exhibited reactivity to blast- but not to sham-tau (Fig. 10). The specificity of this result for tau oligomers was demonstrated by the control ELISA using capture antibody Tau7, a pan-tau antibody for total tau (detection with R1) that showed similar levels of tau in both sets of samples (Fig. 10A). Moreover, similar to sham preparations, brain tissue extracted from shockwave-exposed mice that were not treated with H_2O_2 did not exhibit any difference in oligomerization in comparison to tau extracted from sham-exposed mice (Fig. 10B).

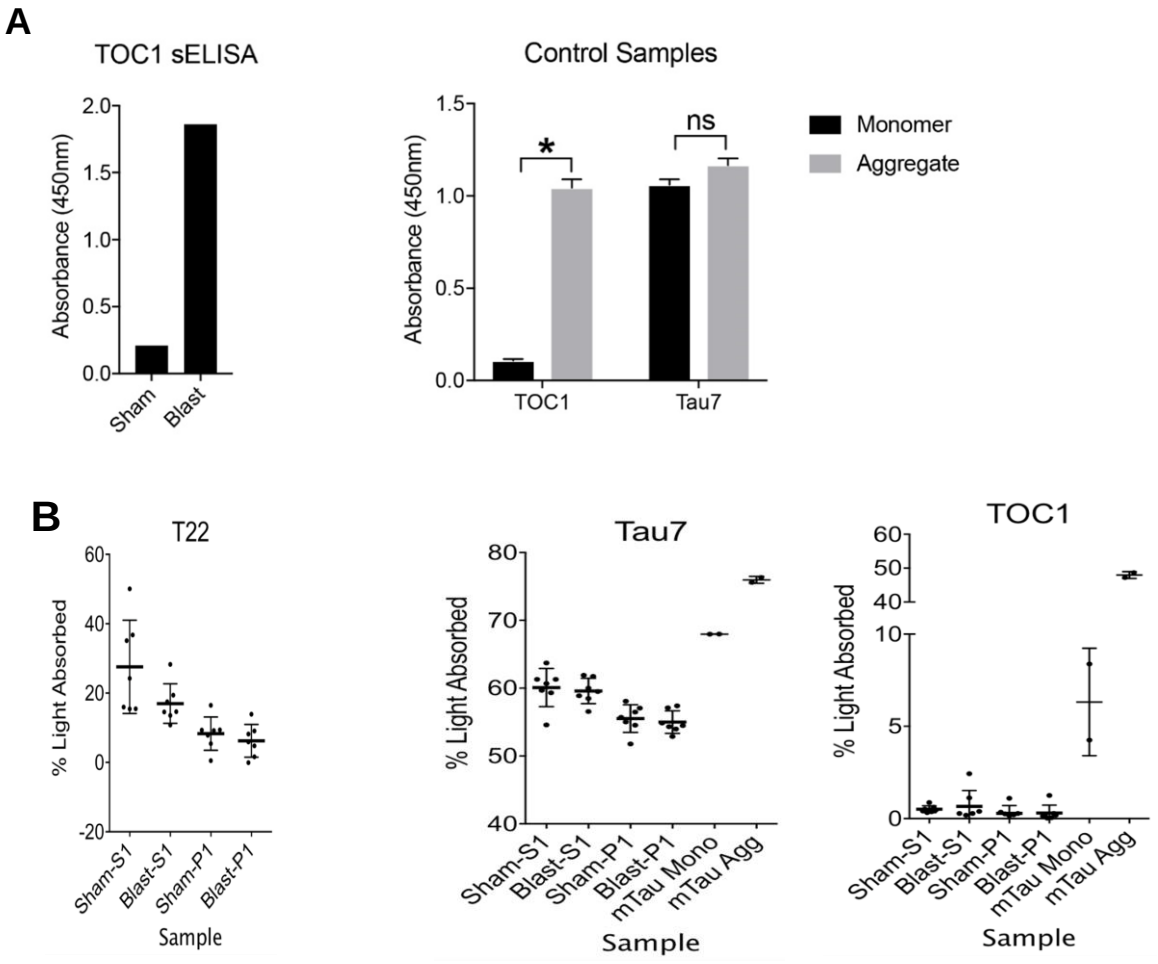

Fig. 10: Level of tau oligomers in sham and blast samples using sandwich ELISAs. **A)** Oligomer specific TOC1 antibody shows strong signal in blast, but not in sham samples. Total tau antibody measuring level of total tau shows substantial amounts of total tau protein both in sham and blast samples. **B)** Brain tissue that was not treated with H_2O_2 and extracted from shockwave-exposed mice did not exhibit any difference in oligomerization in comparison to tau extracted from sham-exposed mice in ELISA assessments with oligomer tau antibodies, TOC1 and T22, similar to Tau7 antibodies detecting tau species.

Thus, <u>these experiments show that, similar to AD subjects, TOC1-positive tau oligomers are present in the shockwave-exposed preparations used in the experiments that showed synaptic and cognitive impairments.</u>

<u>A similar increase in tau phosphorylation contributes to cognitive impairments associated with both blast-exposure and AD.</u>

What does increase the propensity to oligomerize of tau from shockwave-exposed animals? Aim 3 of the parent project proposed testing the hypothesis that a similar increase in tau phosphorylation contributes to plasticity/cognitive impairments associated with both blast-exposure and AD. This was

accomplished through biochemical, electrophysiological and behavioral approaches.

Biochemical approaches included proteomic analysis and Western blotting. Proteomic analysis showed a significant increase in phosphorylation for the SPVVSGDTpSPR site (a.k.a. as S404 site), the IGpSTENLK site, the SGYSSPGpSPGTPGSR site (a.k.a. as S202 site), the TTPSPKpTPPGSGEPPK site, the TPPKpSPSASK site, the TPpSLPTPPTR site, and the pTPPGSGEPPK site, associated with a decrease at the IGpSLDNITHVPGGGNK site. Western blotting analysis demonstrated an increase in phospho-tau at sites CP13:S202, AT8: pS202/pT205, S396, and S404 both at 1 hr and 24 hrs after the blast in the absence of changes in total tau levels.

Electrophysiological and behavioral approaches utilized mice overexpressing the PP2A methylesterase, PME, and the PP2A methyltransferase LCMT. We tested the effect of PME and LCMT overexpression on sensitivity to cognitive and electrophysiological impairments caused by tau purified from shockwave-exposed mice. We found that overexpression of PME impairs associative and spatial memory in mice infused with subtoxic (4.59 µg/ml) doses of tau oligomers extracted from blast injured mice (Fig. 11A-B). We also found that PME overexpression impairs LTP in slices exposed to subtoxic (28.7 ng/ml) doses of tau oligomers extracted from blast injured brains (Fig. 11C). Taken all together, these data demonstrate that overexpression of the PP2A methylesterase, PME, alters sensitivity to exposure to tau oligomers extracted from blast-injured brains.

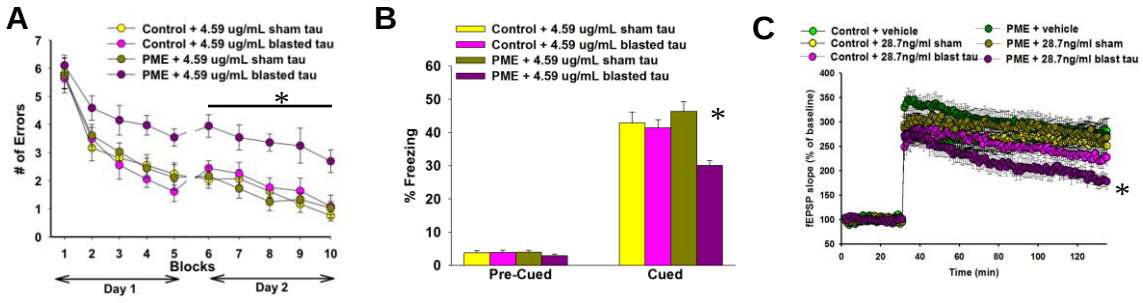

Fig. 11: PME overexpression enhances shockwave-exposed tau ability to lead to the impairing of memory and LTP. **A)** 2-day radial-arm water maze performance in PME transgenic mice infused with 4.59 µg/ml tau purified from shockwave-exposed or sham animals (*p<0.05, RM-ANOVA,). **B)** Percent of freezing during contextual Fear Conditioning test in PME transgenic mice infused with 4.59 µg/ml tau purified from shockwave-exposed, or sham control animals (*p<0.05, Bonferroni post-hoc comparisons). **C)** Amounts of LTP in slices from PME transgenic mice perfused for 20 min with 28.7 ng/ml shockwave exposed tau, or sham tau, prior to eliciting LTP (*p<0.05, Tukey's post-hoc test).

In another series of experiments, we tested the ability of LCMT overexpression to protect against the impairment of memory and LTP produced by blasted tau. Analysis of the 2-day RAWM and contextual fear conditioning performance on LCMT transgenic animals infused with purified tau from either

shockwave or sham-exposed mice at concentrations of 22.9 µg/ml showed that

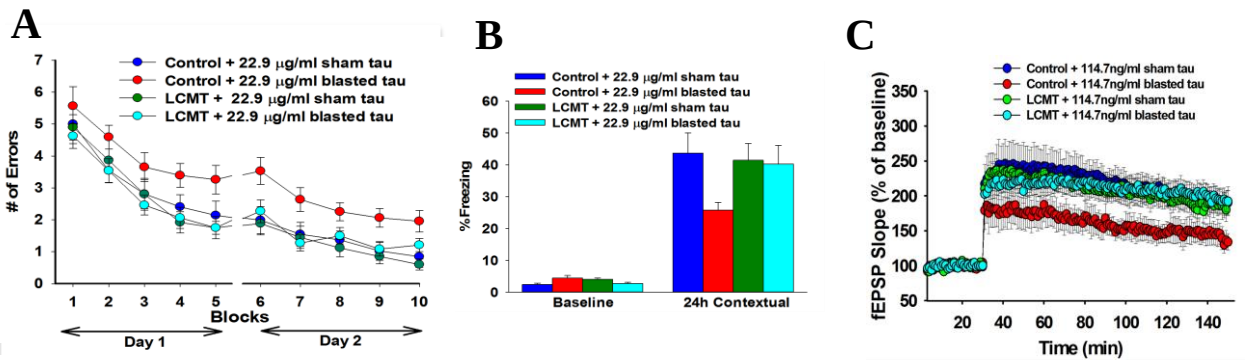

Fig. 12: LCMT overexpression protects against shockwave-exposed tau ability to lead to the impairing of memory and LTP. **A)** 2-day radial arm water maze performance in LCMT transgenic mice infused with 22.9 µg/ml tau purified from shockwave-exposed or sham animals (*p<0.01, RM-ANOVA,). **B)** Percent of freezing during contextual fear conditioning test in LCMT transgenic mice infused with 22.9 µg/ml tau purified from shockwave-exposed, or sham control animals (*p<0.05, Bonferroni post-hoc comparisons). **C)** Amounts of LTP in slices from LCMT transgenic mice perfused for 20 min with 14.7 0 ng/ml shockwave exposed tau, or sham tau, prior to eliciting LTP (*p<0.01, Tukey's post-hoc test).

toxic doses of blast tau were no longer capable of impairing memory tested both with the RAWM and the contextual fear conditioning in the LCMT transgenic mice, whereas memory was impaired in the non-transgenic littermates (Fig. 12A-B). We have also compared the ability of tau to interfere with LTP when bath applied to acute hippocampal slice preparations from LCMT transgenic mice at 114.7 ng/ml. We found no impairment of LTP in slices from LCMT transgenic mice treated with blasted tau, whereas slices from non-transgenic littermates showed an impairment (Fig 12C). Taken all together, these data demonstrate that overexpression of the PP2A methyltransferase, LCMT, alters sensitivity to exposure to tau oligomers extracted from blast-injured brains.

In summary, these experiments demonstrate that regulation of phosphorylation by PP2A plays a key role in the cognitive damage induced by TBI.

CONCLUSIONS:

- Shockwave-exposed tau undergoes changes capable of altering memory and synaptic plasticity
- Shockwave increases tau propensity to oligomerize, thereby impairing synaptic plasticty and memory.
- Similar to AD subjects, TOC1-positive tau oligomers are present in the shockwave-exposed preparation, thereby causing synaptic and cognitive impairments.

- Shockwave exposure causes an increase in phospho-tau at sites CP13:S202, AT8: pS202/pT205, S396, and S404 both at 1 hr and 24 hrs after the blast in the absence of changes in total tau levels.
- Overexpression of the PP2A methylesterase, PME, sensitizes towards exposure to tau oligomers extracted from blast-injured brains.
- Overexpression of the PP2A methyltransferase, LCMT, protects against exposure to tau oligomers extracted from blast-injured brains

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

Nothing to Report.

d. How were the results disseminated to communities of interest?

Nothing to Report.

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

Nothing to Report.

4 IMPACT

a. What was the impact on the development of the principal discipline

Our studies have provided depth to the identification of tau as a culprit in TBI.

b. What was the impact on other disciplines?

Our studies indicate a very interesting similarity between TBI and Alzheimer's disease with tau being similarly affected in the two conditions and being held responsible for the cognitive problems linked with them.

c. What was the impact on technology transfer?

Nothing to Report

d. What was the impact on society beyond science and technology?

Our studies are important as they are likely to impact the development of therapies against TBI and Alzheimer's disease.

5 CHANGES/PROBLEMS

No changes, nor problems

6 PRODUCTS

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project

Dr. Ottavio Arancio (Principal Investigator) – no change

Dr. Russell Nicholls (Co-Principal Investigator) – no change

Dr. Barclay Morrison (Co-Principal Investigator) - no change

Dr. Lewis Brown (Co-Investigator) – no change

Dr. Nicholas Kanaan (Co-Investigator/Subaward PI) – no change

Sowmya Sundaresh – no change

Collin Richards – no change

Chelsea Hamel – no change

b. Has there been a change in the active or other support of the PD or key personnel during the last reporting period?

Dr. Ottavio Arancio

W81XWH-15-1-0550 (Arancio)	09/15/2015 - 09/14/2019 (NCE)	1.00 Calendar
DoD	$136,883	

TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains
This project seeks to determine changes in tau status that are evoked by traumatic brain injury.

R01 NS092045 (Arancio/Nicholls) 02/15/2015 - 12/31/2019 1.20 Calendar
NIH/NINDS $196,875
The regulation of beta-amyloid sensitivity and Alzheimer's related impairments by PP2A
This project seeks to examine the ability of the serine/threonine protein phosphatase, PP2A, to control sensitivity to the pathological actions of beta-amyloid, a protein that accumulates in the brain of Alzheimer's disease patients.

R01 AG049402 (Arancio) 09/01/2015 - 03/31/2020 2.40 Calendar
NIH/NINDS $184,500
Extracellular tau oligomers and Alzheimer disease
This project seeks to establish extracellular soluble species of tau as major toxic species responsible for reduction of synaptic plasticity and memory in Alzheimer's disease.

R01 AG050658 (Bartolini) 09/01/2016 – 05/31/2021 0.17 Calendar
NIH/NIA
Pathogenic role for formin mediated microtubule stabilization pathways in Alzheimer's disease
Test a unifying theory for the pathogenesis of Alzheimer's disease and examine the role for formins as potential targets in drug therapies aimed at rescuing Aβ and phospho--tau toxicity in Alzheimer's disease.
Role: Co-I

A2018816S (Arancio/Nicholls) 07/01/2018 – 06/30/2021 0.24 calendar
Brightfocus $100,000
Tau-induced impairments at hippocampal tripartite synapses
The goal of this project is understand how tau's pathological actions in the presynaptic, postsynaptic, and astrocytic constituents of hippocampal synapses contribute to synaptic dysfunction.

RF1 AG055125 (Arancio/Nicholls) 08/01/2018 – 07/31/2023 1.20 calendar
NIH/NIA $250,000
The role of methylation-sensitive PP2A isoforms in regulating the pathological response to tau
The goal of this project is to understand how PP2A regulates pathological responses to toxic forms of tau.

(Requested No-Cost Extension)
R56 AG058449 (Gosh/Arancio) 09/30/2018 – 08/31/2020 1.59 calendar
NIH/NIA $120,442
ECSIT protects against neurodegeneration and Alzheimer's disease through the regulation of mitochondrial function and oxidative stress
The goal of this project is to investigate the contribution of the mitochondrial protein ECSIT to the regulation of mitochondrial function, mitochondrial reactive oxygen species production, and mitophagy, in the context of AD pathogenesis and progression.

R01 NS104390 (Tang) 09/01/2018 – 06/30/2023 0.48 calendar

NIH $42,066 (Arancio portion)
Cellular and Molecular basis for cognitive impairment associated with Glucocerebrosidase (GBA1) mutation
The goal of this project is to define how GBA1 plays a role in the reduction of memory in Parkinson's disease
Role: Co-I

R01 AG059854 (Teich) 09/15/2018 – 05/31/2023 0.01 calendar
NIH $11,987 (Arancio portion) Years 4-5 only
A Translational Bioinformatics Approach to Rescuing Synaptic and Neurophysiologic Dysfunction in Alzheimer's Disease
The goal of this project is to use bioinformatics tools to defines genes and molecules that negatively influence synaptic function in Alzheimer's disease
Role: Co-I

R01CA222931 (Amengual) 09/21/2018 – 08/31/2023 0.60 calendar
NIH $40,000 (Arancio's portion)
Development of first-in-class Histone Acetyltransferase (HAT) Activators for Precision targeting of Epigenetic Derangements in Lymphoma
The goal of this project is to determine whether and how the novel HAT activator, YF2, can be used to in the therapy diffuse large B-cell lymphoma (DLCBL)
Role: Co-I

(This grant has ended)
R56 AG056108 (Arancio/Verderio) 09/15/2017 – 08/31/2019 (NCE) 0.48 calendar
NIH/NIA $335,036
On the role of microglia-derived extracellular vesicles in amyloid-beta induced changes in synaptic function and network activity in Alzheimer's disease
The goal of this project is to determine whether Aβ-containing extracellular vesicles originating from microglia may result in synaptic and network activity dysfunction in AD, and whether the cellular prion PrPc protein mediates trans-synaptic propagation of these vesicles.

Dr. Russell Nicholls

W81XWH-15-1-0550 (Arancio) 09/15/2015 – 06/30/2019 (NCE) 0.01 calendar
DoD $136,883
TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains
This project seeks to determine changes in tau status that are evoked by traumatic brain injury.

R01 NS092045 (Arancio/Nicholls) 02/15/2015 - 12/31/2019 3.60 Calendar
NIH/NINDS $196,875
The regulation of beta-amyloid sensitivity and Alzheimer's related impairments by PP2A
This project seeks to examine the ability of the serine/threonine protein phosphatase, PP2A, to control sensitivity to the pathological actions of beta-amyloid, a protein that accumulates in the brain of Alzheimer's disease patients.

R01 NS101134 (Mouradian/Nicholls) 05/01/2017 – 04/30/2022 1.20 Calendar
NIH/NINDS $67,909 (Subaward – Rutgers)
PP2A Dysregulation in the Pathogenesis of alpha-Synucleinopathies
The goal of this project is to understand how PP2A activity and synuclein phosphorylation affect pathological actions of alpha-synuclein.

A2018816S (Arancio/Nicholls) 07/01/2018 – 06/30/2021 1.20 calendar
Brightfocus $100,000
Tau-induced impairments at hippocampal tripartite synapses
The goal of this project is understand how tau's pathological actions in the presynaptic, postsynaptic, and astrocytic constituents of hippocampal synapses contribute to synaptic dysfunction.

R01 AG055125 (Arancio/Nicholls) 08/01/2018 – 07/31/2023 3.00 calendar
NIH/NIA $250,000
The role of methylation-sensitive PP2A isoforms in regulating the pathological response to tau
The goal of this project is to understand how PP2A regulates pathological responses to toxic forms of tau.

(New Grant Awarded)
R21 NS113063 (Nicholls/Wylie) 06/01/2019 – 05/31/2021 1.20 calendar
NIH/NINDS $150,000
Exploring the contribution of viral PP2A inhibition to tau pathology in Alzheimer's disease.
The goal of this project is to test whether infection with viruses that inhibit the serine/threonine protein phosphatase, PP2A, contributes to the development of Alzheimer's disease.

Dr. Barclay Morrison

W81XWH-15-1-0550 (Arancio/Morrison) 09/15/2015 - 09/14/2019 (NCE) 1.00 Calendar
DoD $136,883
TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains
This project seeks to determine changes in tau status that are evoked by traumatic brain injury.

PI: Meaney/Morrison 07/2017 – 06/2022 1.92 calendar
Paul Allen Family Foundation $2,065,000
Reconstructing Concussion
The purpose of this grant is to uncover mechanisms and principles of concussive injury, repair and recovery at multiple scales from single cells to whole animals.

PI: Morrison 09/2017 – 07/2020 0.48 calendar
Department of Army $270,000
Long term potentiation deficits after repetitive primary blast
The purpose of this grant is to determine tolerance criteria to repetitive primary blast in organotypic brain slice cultures.

5R01EB009041 (Konofagou) 09/2014 – 08/2019 0.48 calendar

NIBIB $85,000
Optimization of ultrasound-facilitated blood-brain barrier opening
The purpose of this competitive renewal grant is to optimize ultrasound parameters for non-invasive opening of the BBB.
Role: Co-I

R44NS086118 (Graudejus) 09/2018 – 08/2020 1.20 calendar
NIH/NINDS $128,416
Lab-To-Marketplace: Commercialization of a stretchable microelectrode array
The purpose of this Phase II SBIR grant is to develop a commercially viable system for studying neurotrauma with stretchable microelectrode arrays for commercial sales for research purposes
Role: Co-I

(New Grant Awarded)
PGXXXXX (Morrison) 12/2018 – 09/2019 1.0 calendar
Honda R&D $156,000
Bridging vein and superior sagittal sinus population variability
The purpose of this grant is to measure the geometry of cerebral bridging veins and the superior sagittal sinus from MRI scans to quantify population variation in their geometry.

(New Grant Awarded)
PGXXXXX (Morrison) 01/2018 – 09/2019 1.0 calendar
Honda R&D $363,088
Edema simulations with FEBio
The purpose of this grant is to numerically model cerebral edema after TBI using triphasic biomechanics and FEBio.

Dr. Lewis Brown
No changes

Dr. Nicholas M. Kanaan
R01 AG044372 (Kanaan) 9/30/14 – 4/30/19 2.4 calendar
NIA (NIH) $232,000
Tau-induced axonal degeneration in Alzheimer's disease and tauopathies
The main goal of this proposal is to identify the molecular mechanisms underlying axonal degeneration induced by AT8 phosphorylated tau using a viral vector rat model and a rat primary neuron model.

R01 NS082730 (Kanaan, Brady) 4/01/14-3/31/19 2.4 calendar
NINDS (NIH) $239,350
Tau Conformation in Tauopathies and Neuronal Function
This R01 is aimed at studying how tau conformation in various oligomeric forms affects its toxicity through axonal transport impairment and how tau conformation is regulated under normal biological conditions.

P01 AG14449 (Counts) 7/01/97-6/30/19 1.2 calendar
NIA (NIH) $285,000

Neurobiology of Mild Cognitive Impairment in the Elderly
This PPG contains multiple projects that investigate the neurobiological substrates of cognitive decline in the elderly using the cholinergic basal forebrain as a model system for selective vulnerability.
Role: Co-Investigator

W81XWH-15-1-0550 (Arancio) 9/1/15-8/30/2018 1.2 calendar
DoD $148,914
TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains
The purpose of this grant is to explore the molecular mechanisms that underlie the cognitive decline and mental health problems resulting from repetitive traumatic brain injuries

Gibby vs Parky Parkinson's Disease Research (Kanaan/Moore) 7/1/2018 – 06/30/2020 0.24 calendar
LRRK2 and Tau in Parkinson's Disease
Goal: The aim of this project is to study the role of LRRK2 mutations in the spread of tau in the brain in the context of animal and cell models of Parkinson's disease.

c. What other organizations were involved as partners?

None to Report

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES

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