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TITLE: TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies

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14. ABSTRACT TRACK-TBI Precision Medicine utilizes the rich TRACK-TBI dataset to validate biomarkers of diffuse axonal injury (DAI), microvascular injury (MVI), and neuro-inflammation using advanced blood-based assay platforms and MRI sequences. The project will validate early and ultra-early blood-based and imaging biomarkers of DAI, MVI, and neuro-inflammation and will conduct a multicenter, double-blind, placebo-controlled exploratory clinical trial comparing the impact of cyclosporine A on blood-based and imaging biomarkers of DAI and neuro-inflammation in moderate/severe TBI patients.					
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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

TRACK-TBI Precision Medicine utilizes the rich TRACK-TBI dataset to validate biomarkers of diffuse axonal injury (DAI), microvascular injury (MVI), and neuro-inflammation using advanced blood-based assay platforms and MRI sequences. The project will validate early and ultra-early blood-based and imaging biomarkers of DAI, MVI, and neuro-inflammation and will conduct a multicenter, double-blind, placebo-controlled exploratory clinical trial comparing the impact of cyclosporine A on blood-based and imaging biomarkers of DAI and neuro-inflammation in moderate/severe TBI patients.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

traumatic brain injury, concussion, blood-based biomarker, biofluid biomarker, neuroimaging biomarker, clinical outcome assessment (COA), Glial Fibrillary Acidic Protein (GFAP), clinical trial, diffuse axonal Injury, microvascular Injury, Neuroinflammation, brain magnetic resonance imaging (MRI), brain computed tomography (CT), precision medicine

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Overview of Research Plan

- Phase 1-Base: Validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and MR imaging sequences in prospectively-collected data from existing TRACK-TBI subjects.
- Phase 2-Option I: Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate-severe TBI subjects.
- Phase 3-Option II: Conduct a multicenter double-blind, placebo-controlled exploratory clinical trial comparing the impact of Cyclosporine A (CsA) on imaging and blood-based biomarkers of DAI, MVI, and neuroinflammation in moderate-severe TBI patients admitted to the ICU.

Phase I-Base (09/30/2018 – 09/29/2019)

In Phase 1 (Aims 1.A-C), blood-based protein biomarkers will be measured in **existing** biospecimen samples; 2 sets of **existing** MRI scans on these same subjects will be analyzed in concert with serially collected multivariate outcome measures. These will be used to characterize specific mechanistic endophenotypes in individual patients, DAI, MVI, and neuroinflammation, chosen for: (i) their importance to TBI outcome across the severity spectrum; (ii) existing pre-clinical and clinical data supporting the biomarkers' ability to identify these mechanistic endophenotypes; and (iii) the opportunity to translate candidate therapeutics against these mechanisms into targeted clinical trials.

Phase II-Option 1 (09/30/2019 – 09/29/2020)

Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate-severe subjects.

In the existing TRACK-TBI study, MRIs were first obtained at 2-weeks after injury, and the initial blood sample was obtained within 24 hours after injury. Since it is likely that many effective TBI therapies will have to be started within hours or days post-injury, to obtain the necessary precision to design future clinical trials, we must have more granular information about the early evolution of the imaging and molecular biomarkers identified in Phase 1. In Aim 2 we will recruit a new cohort of subjects (n=75) with moderate to severe TBI stratified according to VA/DoD criteria through the existing TRACK-TBI Network sites and at WRNMMC. In this cohort, we will validate blood-based biomarkers at early (<24h) and ultra-early time periods (~3h), and neuroimaging biomarkers at early (1w) and ultra-early (<24h) time periods, the selection of which will be informed by Phase 1 (Aim 1) findings.

Phase III-Option 2 (09/30/2020 – 09/29/2021)

Conduct a multicenter double-blind, placebo controlled exploratory clinical trial comparing the impact of e.g., Cyclosporine A (CsA) on blood-based and imaging biomarkers of DAI, MVI, and neuroinflammation in moderate-severe TBI patients admitted to the ICU.

This early Phase IIa pilot will use biomarkers to select subjects with specific injury endophenotypes, as well as to assess whether the drug is engaging its molecular target and impacting the pathobiology of injury.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

IRB and HRPO Approval (09/30/2018 - 04/09/2019 (COMPLETED))

UCSF has received local IRB approval as well as HRPO approval for the “TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies” protocol. This IRB approval encompasses biospecimen and imaging analyses and was shared with the University of Pennsylvania and University of Florida to use as a template. The IRBs at both the University of Pennsylvania and University of Florida determined that the study was not human subjects’ research and issued a review status of *exempt*. HRPO reviewed the protocols from UPenn and UF and issued determinations of “Research Not Involving Human Subjects.”

TOTAL PROTOCOLS:

Protocol (1 of 1 total):

Protocol [HRPO Assigned Number]: E00485.1a

Title: TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IRB in addition to HRPO).

- Protocol developed and submitted to UCSF IRB on 11/30/2018
- UCSF IRB approval received on 01/04/2019
- University of Florida IRB decision of “exempt” received on 12/6/2018. HRPO determination of “research not involving human subjects” returned on 03/15/2019
- University of Pennsylvania IRB decision of “exempt” received on 01/11/2019. HRPO determination of “research not involving human subjects” returned on 03/18/2019
- UCSF submitted its IRB approved protocol and supporting documentation to the Human Research Protections Office on 01/14/2019
- Protocol was assigned a Human Subjects Protection Scientist (HSPS) from the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) on 02/14/2019
- UCSF received HRPO approval on 04/09/2019

Status:

- IRB and HRPO approval obtained for the TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies at the University of Pennsylvania, University of Florida, and University of California, San Francisco

Biofluid Biomarker Accomplishments (09/30/2018 - 09/29/2019 ONGOING)

We are validating blood-based biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using standard (Abbott architect and Roche cobas) and advanced assay platforms (Mesoscale Discovery (MSD) and Quanterix).

Biofluid specimens (plasma and serum) were shipped to our contract analytic laboratory at Dublin College where biomarker analyses for NF-L, Tau, IL-6, TNF, IL-10, NSE, S100, and CRP analyses of >3,000 biospecimens from TRACK-TBI brain-injured (Days 1, 3, 5, 90, and 180), Ortho Control,

Friend Control, and Healthy Control cohorts with 2-week and 6-month MRI scans are planned. Assays for NF-L, Tau, IL-6, TNF α , and IL-10 are now underway after some delay (see Changes/Problems Section) on these 3000 biospecimens and we anticipate completion of the assay runs in early 2020. NF-L and Tau are candidates for our Diffuse Axonal Injury endophenotype panel and IL-6, TNF α and IL-10 are candidate pro-inflammatory and cytokine markers for our Neuroinflammatory panel.

Researchers at the University of Florida received 2,213 biospecimens that were collected from TRACK-TBI subjects with 2-week and 6-month MRI scans. These is the same cohort that was sent to our contract lab partner in Dublin. We are currently analyzing Tau and p-Tau using the SOPHIA platform. We anticipate results by the end of the year (2019). These assays will determine the utility of Tau and p-Tau as biomarkers for characterizing the DAI endophenotype.

We have also sent biospecimens from the TRACK-TBI Pilot Study cohort to the University of Florida for exploratory analyses of a wide range of new biomarkers to characterize Microvascular Injury, and Neuroinflammation endophenotypes. Using the Meso Scale Discovery method with a V-PLEX Human Biomarker 40-Plex Kit, biomarkers have been assessed.

The Meso Scale Discovery (MSD) V-PLEX Human Biomarker 40-Plex Kit contains a range of inflammatory markers, cytokine, chemokines, and angiogenesis and vascular markers. This broad panel will cover our exploratory work for MVI and Neuroinflammatory endophenotypes (Table 1 below), They are largely Proinflammatory, Chemokine, and Cytokine markers and they include: GM-CSF, ICAM-1, IFN- γ , IL-10, IL-17A, IL-1 α , IL-1 β , IL-6, IL-7, IL-8, MCP-1, MIP-1 α , MIP-1 β , PIGF, TARC, TNF- α , VCAM-1, and VEGF-A.

Table 1. V-PLEX Human Biomarker 40-Plex Kit

V-PLEX Human Biomarker 40-Plex Kit	Proinflammatory Panel 1	Cytokine Panel 1	Chemokine Panel 1	Angiogenesis Panel 1	Vascular Injury Panel 2
CRP					✓
Eotaxin			✓		
Eotaxin-3			✓		
FGF (basic)				✓	
GM-CSF		✓			
ICAM-1					✓
IFN- γ	✓				
IL-10	✓				
IL-12/IL-23p40		✓			
IL-12p70	✓				

IL-13	✓				
IL-15		✓			
IL-16		✓			
IL-17A		✓			
IL-1 α		✓			
IL-1 β	✓				
IL-2	✓				
IL-4	✓				
IL-5		✓			
IL-6	✓				
IL-7		✓			
IL-8	✓		✓		
IL-8 (HA)			✓		
IP-10			✓		
MCP-1			✓		
MCP-4			✓		
MDC			✓		
MIP-1 α			✓		
MIP-1 β			✓		
PIGF				✓	
SAA	✓				
TARC			✓		
Tie-2				✓	
TNF- α		✓			
TNF- β		✓			
VCAM-1					✓
VEGF-A		✓		✓	
VEGF-C				✓	
VEGF-D				✓	
VEGFR-1/Flt-1				✓	

During the last quarter of Year 1, Dr. Wang and team began to assess TBI endophenotypes with targeted blood-based protein biomarkers on the MSD platform using acute and chronic TBI subjects, friend controls, and orthopedic controls. These markers are categorized as TBI Precision Medicine Biomarker Panel #1 – Brain-systemic cross-talk biomarkers (Table 2) and TBI Precision Medicine Biomarker Panel #2 - CNS/brain origin biomarkers (Table 3).

Table 2. TBI Precision Biomarker Panel #1 – Brain-systemic cross-talk biomarkers				
Biomarkers	# Markers Screened / Platform	Key Markers	TBI Endophenotype	Mechanism of Biomarker Production / Release
Inflammatory Cytokines	20 -MSD /	IL-1b, IL-4, IL-6, IL-7, IL-8, IL-10 IL-16, IL-17A, IFN- γ TNF-a*, IL-1b*, IL-6*	Neuroinflammation	Immune-cells released
Chemotactic Cytokines	MSD	MCP-1, MCP4, MIP-1b, MDC Exotaxin, Exotaxin-3	Neuroinflammation / Vascular injury	Chemotaxis of immune cells to brain vasculature
Acute-phase Proteins / Alarmin	MSD	HMGB1 / C-RP / SAA (Serum amyloid A)	Post-TBI acute phase response	Liver-released
Vascular Injury/ Modulation Panel	MSD	VGEF-A, VGEF-C, sFLT-1 ICAM-1, VCAM-1 C-Fibronectin	Vascular injury	Vascular damage and BBB modification
Autoantibodies	UF Assay	anti-GFAP; anti-MOG (IgM, IgG)	Autoimmunity response	T-cell /B-cell mediated autoimmune response

Table 3. TBI Precision Medicine Biomarker Panel #2 – CNS/Brain Origin			
Biomarkers	Assay Platform	TBI Endophenotypes	Mechanism of Biomarker Production / Release
UCH-L1 / GFAP [*FDA-approved TBI biomarker benchmark]	Abbott i-STAT /Abbott architect	Contusion	Necrosis of neuron/ Astroglia
NF-L/pNF-H	Quanterix	Diffuse axonal injury	Axonal injury
Tau, P-Tau	Quanterix / SOFIA	Neurodegeneration (CTE, AD)	Tauopathy

Figure 1 shows patterns of six representative markers with distinct profiles in Acute and Chronic TBI subjects, Friend Controls, and Ortho Controls (Baseline and 6 months).

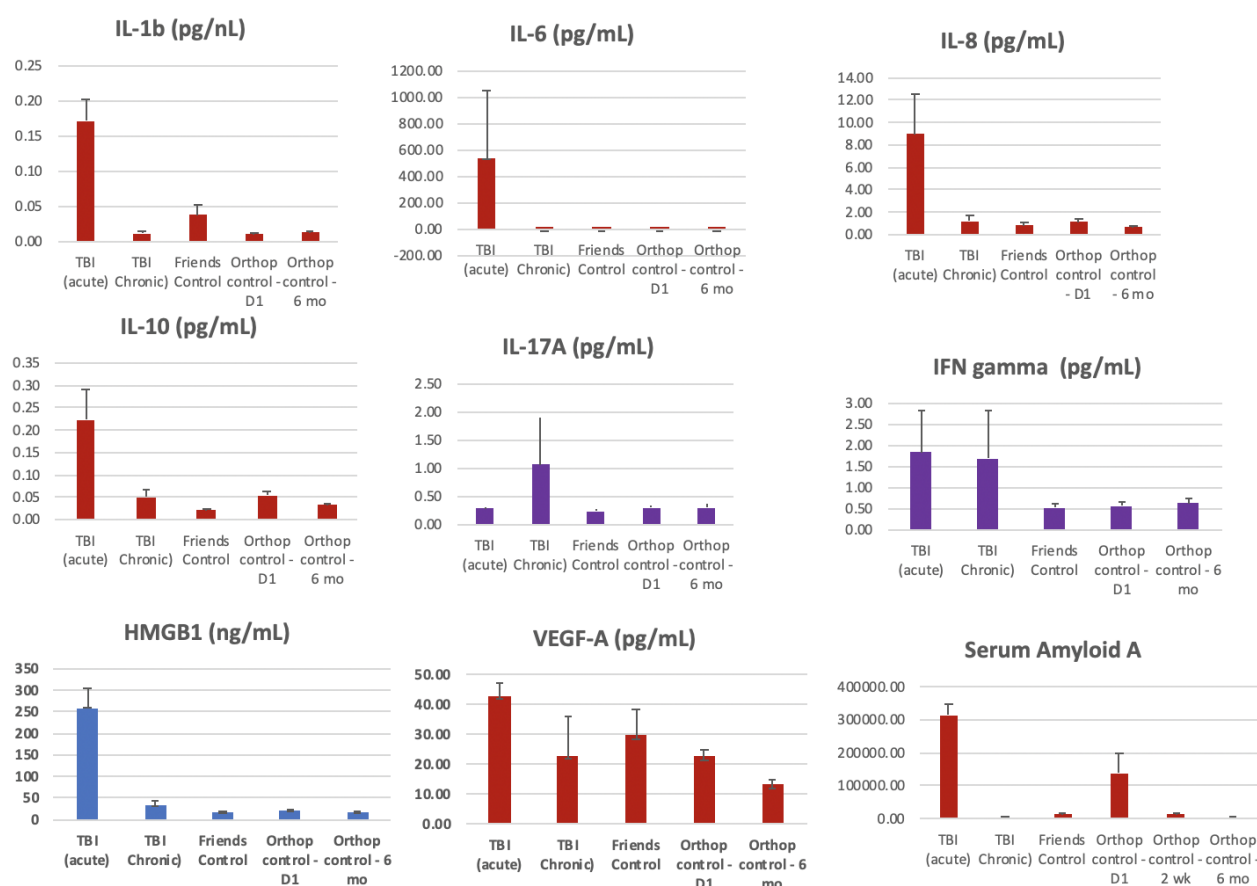


Fig. 1. Patterns of biomarkers with distinct profiles in acute and chronic TBI subjects

IL-1, IL-6, IL-8, and IL-10 are elevated in Acute TBI and not in Chronic TBI or Controls. While this has been reported by several groups, our addition of Ortho Controls supports the utility of these biomarkers in subjects with polytrauma. We also find that the anti-inflammatory cytokine IL-10 is also elevated. It is of significant interest that IL-17a is elevated in Chronic TBI, but not Acute TBI. High levels of this cytokine are associated with several chronic inflammatory diseases. Interferon gamma (IFN gamma) was elevated in both Acute and Chronic TBI, but not Controls. The elevation of HMGB1, a ubiquitous nuclear protein released by glia and neurons upon inflammasome activation, is also very promising as it is a key initiator of neuroinflammation.

Together these markers support the development of a neuroinflammatory endophenotype panel. Initial results were also seen with the vascular biomarkers VEGF-A and Serum Amyloid A, in support of the development of a MVI endophenotype panel. Additional vascular markers will be evaluated by Dr. Diaz-Arrastia and MSD as described below.

Under Dr. Diaz-Arrastia's direction, Dr. Margalit Haber at the University of Pennsylvania conducted preliminary assays for IL-6, IL-10 and TNF on ~50 TRACK-TBI Pilot samples. Her results were presented at the NNS meeting in Toronto in 2018 (Appendix 1). These results formed the rationale for running the Quanterix cytokine 3-plex in the TRACK-TBI U01 samples, which is currently underway in Dublin, as reported in the Q3 submission. The University of Pennsylvania analytic site has begun direct collaboration with MSD (PI- Dr. Chris Campbell) using the MSD multi-plex platform and targeting vascular injury that will derive data on potentially 19 different proteins. Thereafter, with the allocation of TRACK-TBI Pilot (n~160 participants, identical to the subjects analyzed at the University of Florida) biospecimens under the direction of the University of Pennsylvania analytic site, and using aliquots of 100 uL, the MSD platform will run assays as indicated in the table below (**Table 4**). A DUA/MTA between University of Pennsylvania and MSD has just been executed and biospecimens will be transferred.

Table 4. MSD Multi-plex Kit	Recommended Dilution
Ang-1	2x
Ang-2	2x
Angiogenesis Panel: FGF (basic), PlGF, Tie-2, VEGF-A, VEGF-C, VEGF-D, VEGFR-1/Flt-1	2x
Vascular Injury Panel 1: E-Selectin, ICAM-3, P-Selectin, Thrombomodulin	5x
Vascular Injury Panel 2: CRP, ICAM-1, SAA, VCAM-1	1,000x
PDGFR- β	2x
vWF	1,000x

Overlap, which is designed to be minimal, between the 2 custom MSD Multi-plex panels (e.g., VEGF-A) will serve as internal controls for comparison between the 2 MSD chips in the same subjects.

Neuroimaging Biomarkers (09/30/2018 - 09/29/2019 ONGOING)

Continued progress is being made in coding Common Data Elements (CDE) findings on TRACK-TBI head CT scans (~2600 participants) and Tesla (3T) MRI scans (>700 TBI patients now completed), and incorporating these results into studies linking pathoanatomic lesions with outcomes and blood-based biomarkers. Structural CT is best suited for identification of MVI/vascular injuries (e.g., contusion, subdural hematoma). We have coded Common Data Elements (CDE) findings on the 2-week post-injury TRACK-TBI 3 Tesla (3T) MRI scans on >700 TBI patients, including assessment of microbleeds on 3D T2* weighted susceptibility imaging sequences that represent **MVI**. We have also completed pre-processing and post-processing of the diffusion tensor imaging (DTI) sequences from the entire TRACK-TBI Phase 1 MRI TBI patient cohort (n=549 participants) that have both 2-week and 6-month post-injury scans. The data are undergoing statistical analysis to generate definitive results on how brain white matter microstructure evolves after TBI, which is considered to be the most sensitive standard imaging biomarker of **DAI**. An interim analysis of 387 mild TBI patients ages 17 years and up from this cohort shows that global white matter fractional anisotropy (FA), the most commonly used measure of microstructural integrity, declined from 2-weeks to 6-months post-injury with a Cohen's d effect size of 0.1 (p=0.002). Regional white matter FA in 12 candidate tracts also showed longitudinal reductions in all tracts with effect sizes ranging from 0.05 to 0.12 (p<0.05 for all 12 tracts). This is the first definitive demonstration of long-term white matter degeneration due to **DAI** from mild TBI that is reproducible across 13 MRI scanners at 11 different patient enrollment sites, with standardized DTI acquisition, postprocessing and analysis procedures. This result provides clarity to the DTI of mTBI literature which has shown different and often conflicting results across many single-center studies using non-standardized methodology. We are now completing the final longitudinal DTI analysis of the full Phase 1 MRI TBI cohort with comprehensive quality control (QC), including exclusions for patient motion and for anatomic deformations due to focal TBI lesions. Together, these results support the utility of neuroimaging biomarkers to identify MVI and DAI endophenotypes.

Advanced diffusion MRI processing using the Neurite Orientation Dispersion and Density Imaging (NODDI) has been completed for the 2-week and 6-month scans of a pilot group of n=40 Phase 1 mild TBI patients, showing evidence of white matter vasogenic edema suggesting **neuroinflammation** that evolves over time. The results also show loss of white matter axonal density over time that is more sensitive than DTI metrics and is thought to represent the sequela of **DAI**. These preliminary results have been published in bioRxiv and the definitive manuscript is currently under review for publication in a peer-reviewed journal.

We have also completed longitudinal Freesurfer 6.0 analysis of global and regional brain volume changes from 2 weeks to 6 months after injury in the 3D T1-weighted structural sequence of the TRACK-TBI Phase 1 MRI TBI cohort (n=549 participants) and this is currently undergoing statistical analysis to generate definitive results on how brain volume changes after TBI. The expectation is that there would be both regional and global volume loss in TBI patients with significant **DAI**.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Nothing to report

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Dr. Wang gave multiple presentations to the scientific community that served to disseminate results of this biofluid biomarker work:

Invited Speaker: The 10th Arrowhead TBI Conference, Washington, DC. *Copenhagen Head Injury Ciclosporin (CHIC) study: A phase IIa safety, pharmacokinetics and biomarker study of ciclosporin in severe head injury patients.* May 2019.

Invited Speaker: NeuroTrauma2019. *Utilities of Precision Biomarkers in preclinical TBI model research.* June 2019.

Speaker: 2019 Military Health Science Research Symposium. *Reverse translational approach on using neuroimaging and blood-based precision biomarkers as endpoint assessments for TBI subphenotyping in three different rat TBI model.* August 2019.

Dr. Diaz-Arrastia gave multiple presentations to the scientific community that served to disseminate results of this biofluid biomarker work:

Invited Keynote Speaker: Traumatic Brain Injury and Protection Research Symposium, Temple University. *Traumatic Microvascular Injury: A Potentially Treatable Endophenotype of TBI.* October 2018.

Invited Speaker: International Traumatic Brain Injury Research (IntBIR) Consortium, Brussels, Belgium. *Report of IntBIR Biomarkers Working Group.* October 2018.

Invited Speaker: Neurology Grand Rounds, New York Hospital-Weil Cornell Medical Center. *Endophenotypes of traumatic brain injury: What we need to know for the next generation of clinical trials in TBI.* October 2018.

Invited Speaker: Department of Defense State of the Science of Blood Based Biomarkers in Traumatic Brain Injury. *Future use of Blood-Based Biomarkers for the Clinical Management of Traumatic Brain Injury.* November 2018.

Invited Speaker: 9th Annual Arrowhead Traumatic Brain Injury Conference, Arlington, VA, *Towards Precision Medicine for Traumatic Brain Injury: Lessons from TRACK-TBI*. May 2019.

Invited Speaker: Brain Injury Association of Pennsylvania. *Endophenotypes of traumatic brain injury: Biomarkers will guide the therapy*. June 2019.

Dr. Manley gave multiple presentations to the neurotrauma community that served to disseminate the goals of TRACK-TBI Precision Medicine:

Invited Speaker: University of Rochester Grand Rounds. *Paving the Way for a New Era in Brain Injury Research and Clinical Care*. September 2019.

Invited Speaker: Massey TBI Regional Conference. *TRACK-TBI: Transforming Research & Clinical Knowledge in Traumatic Brain Injury*. October 2018.

Invited Speaker: Craig Hospital - Mark P. Cilo Memorial Lecture. *Paving the Way for a New Era in Brain Injury Research and Clinical Care*. January 2019.

Invited Speaker: UCSF Weill Institute for Neurosciences. *Precision Neuroscience for Personalized Care*. February 2019.

Invited Speaker: Johns Hopkins University Grand Rounds. *Paving the Way for a New Era in Brain Injury Research and Clinical Care*. May 2019.

Invited Speaker: University of Kentucky Grand Rounds. *Paving the Way for a New Era in Brain Injury Research and Clinical Care*. May 2019.

Invited Speaker: The White House - President's Roadmap to Empower Veterans and End a National Tragedy of Suicide (PREVENTS). *Coordinating Research Efforts: TRACK-TBI and Team Science*. September 2019.

In conjunction with NeuroTrauma2018 in Pittsburgh, PA, a combined TRACK-TBI / TED Initiative Investigators meeting was held with approximately 60 participants from around the country. This meeting was open to TRACK-TBI investigators and also interested members of the neurotrauma community. Drs. Mukherjee and Wang presented the Aims of TRACK-TBI Precision Medicine to attendees.

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

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

In the next reporting period, the Blood-based/Biofluid Biomarker team plans to complete the following analyses:

- The pNF-H and c-fibronectin assay are scheduled to be conducted. Overall data and correlation analysis of TBI endophenotypes on the Phase 1 subjects will then be conducted.
- Autoantibodies have been initiated (anti-GFAP, anti-MOG) IgM and IgG assays on a subset of TRACK-TBI cohort (977 subjects) with serial plasma samples (977 baseline, 652 2-week, 528 6-mo. samples), orthopedic injury controls (117 baseline, 157 2-week samples) and Friend Controls (baseline 91, and 6 mo. 72 samples) that will be part of the validation study
- The same set of samples will be analyzed with the high sensitivity p-Tau (Thr-231) and Tau RCA-SOFIA platform, also as part of the Phase 2 validation study
- A subset of approximately 15 biomarkers will then be down selected to be assayed in a multiplex manner for TRACK-TBI cohort-based validation.
- Blood-based biomarkers will be correlated with imaging biomarkers to refine DAI, MVI and Neuroinflammatory endophenotypes

In the next reporting period, the Neuroimaging team plans to complete the following analyses in order to achieve the stated goals of the project:

- Complete statistical analysis of Longitudinal Freesurfer 6.0 analysis to generate definitive results on how brain volume changes after TBI and how it is related to clinical and cognitive recovery.
- Complete longitudinal Freesurfer 6.0 analysis of orthopedic trauma control subjects (n=110) for the Phase 1 MRI cohort of TBI patients
- Prepare for Freesurfer, DTI and resting state fMRI pre-processing the 3T MRI scans of the friend control subjects (n=366) who are demographically matched to the Phase 1 MRI cohort of TBI patients
- 3T MRI scans of the Phase 2 (HDFT: High-Definition Fiber Tractography) MRI cohort of TBI patients (n=471) have undergone directory reorganization, full de-identification, cleaning and curation. Prepared the 3T MRI scans of the Phase 2 HDFT MRI cohort of TBI patients (n=471) for Freesurfer, DTI and resting state fMRI pre-processing
- Complete pre-processing and post-processing of the resting state functional MRI scans from the entire TRACK- TBI Phase 1 MRI TBI cohort (n=549 participants) cross-sectional and longitudinal studies of functional connectivity after TBI

Additionally, the Neuroimaging team intends to submit the following manuscripts:

1. Longitudinal Freesurfer volumes in TBI
2. Inter-rater reliability of 3T MRI CDEs
3. Inter-rater reliability of CT CDEs
4. Longitudinal DTI changes of white matter microstructure in mTBI

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

We intend to deliver on critical military and public health knowledge gaps and needs: objective classification of TBI based on what we term mechanistic endophenotypes, e.g., diffuse axonal injury (DAI), microvascular injury (MVI), and neuroinflammation. An endophenotype is an internal phenotype discoverable by biochemical, physiological, radiological, pathological, or other techniques. Endophenotypes are quantitative, continuous variables, unlike a phenotype which is usually a binary, categorical variable. These mechanistic endophenotypes, defined by imaging and blood-based biomarkers, will direct targeted treatments based on mechanism, providing the tools needed for successful execution of precision medicine clinical trials. To achieve the goal of precision medicine in TBI, it is necessary to identify subgroups of TBI patients that will respond to a targeted therapy. To achieve this, our propose approach is the combined use of MR neuroimaging sequences and biofluid biomarker panels to aid in the identification and monitoring of major TBI subphenotypes.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

NOTHING TO REPORT

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

NOTHING TO REPORT

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

NOTHING TO REPORT

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:*

NOTHING TO REPORT

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

The analyses of NSE, S100, and CRP that are being performed on the standard Abbott and Roche platforms are anticipated to be completed by December 2019. The analyses for NF-L, Tau, IL-6, TNF, IL-10 have been delayed for over 3 months due to technical issues with the Quanterix Simoa Analyzer purchased by our contract laboratory partner. We have worked closely with this contract lab for the past 3 years and they have a very rigorous QA process. They uncovered a hardware performance issue with the latest production run of the Simoa HD-1 analyzers. Three different HD-1 analyzers have been installed over the past 5 months and subjected to their QA process. The first 2 analyzers failed QA and were returned to Quanterix. The third unit performed reasonably well and required onsite repair on one of the components to meet performance standards.

Having resolved the hardware issue, the contract lab quickly calibrated and validated the assays for NF-L, IL-6, TNFa, and IL-10. Unfortunately, calibration issues were encountered with the Tau biomarker assay. A new calibrator was released with updated calibrator concentration values (Tau calibrator lot# 501903). Up until we received this new information, 4 separate Tau plates had been run as part of the QC precision study. The cumulative QC values produced using the original calibration values were perfect. However, when inputting the updated calibrator values from the amended calibration (lot# 501903) into the previous runs, there was a significant shift in concentration in the negative bias range for both level 1 and level 2 control in values. A 31% mean difference in Level 1 results and a 17% mean difference in Level 2 were observed. These results were shared with Quanterix and it was agreed to use a new Tau reference calibrator. This has now been validated and passed QC.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

NOTHING TO REPORT

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting

period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

N/A

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications.

NOTHING TO REPORT

Books or other non-periodical, one-time publications. Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

NOTHING TO REPORT

Other publications, conference papers and presentations. Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

N/A

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

A dedicated page to TRACK-TBI Precision Medicine is located on the main TRACK-TBI NET Website: <https://tracktbinet.ucsf.edu/precision-medicine>

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

N/A

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

N/A

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

N/A

7. Participants and Other Collaborating Organizations

Personnel Name	Institution	Role	Person month worked during 9/30/18-9/29/19 (cal. mos)	Contribution
Manley, Geoffrey	UCSF	Principal Investigator	1.48	PI
Mukherjee, Pratik	UCSF	Co-Investigator	0.13	Dr. Mukherjee oversees all aspects of the neuroimaging for the Specific Aims.
Palacios, Eva	UCSF	Specialist	5.03	Eva Palacios performs the advanced neuroimaging analyses in support of accomplishing the Specific Aims and reports to Dr. Mukherjee.
Raptentsetsang, Sky	UCSF	Clinical Research Coordinator	5.89	Sky assisted in imaging data management for the neuroimaging analyses.
Fecho,	UCSF	Staff Research Associate	1.20	Cassandra Fecho performs data and metadata entry for the neuroimaging analyses.
Nguyen, NhuNhu	UCSF	Clinical Research Coordinator	1.28	NhuNhu Nguyen coordinates the work of the other Clinical Research Coordinators (CRCs) and Staff Research Associates (SRAs) for accomplishing the neuroimaging aspects of the Specific Aims and reports to Dr. Mukherjee.
Bourla, Ioanna	UCSF	Clinical Research Coordinator	0.75	Ioanna Bourla performs data and metadata cleaning, curation and other forms of data management for the neuroimaging analyses.
Zargham, Sina	UCSF	Staff Research Associate	11.50	Sina Zargham performs data and metadata entry for the neuroimaging analyses.
Wang, Kevin	UF	Co-Investigator	1.44	Project coordination (internal, external with UCSF overall PI Dr. G. Manley and other project members), data interpretation
Yang, Zhihui	UF	Co-Investigator	0.80	Biomarker assay, data graphing, presentation, interpretation, and report preparation
McCrea, Michael	MCW	Co-Investigator	0.57	Dr. McCrea serves on as clinical outcome assessment expert.
Okonkwo, David	UPMC	Co-Investigator	0.25	Dr. Okonkwo advises on biofluid biomarker analysis.
Giacino, Joseph	SRH	Co-Investigator	1.20	In collaboration with the TRACK/TED Executive Committee, Dr. Giacino participated in protocol refinement activities and provided expertise on clinical outcome assessment measures that will be used to identify, validate, and test the blood-based biomarkers in this study.
Temkin, Nancy	UW	Co-Investigator	1.80	Dr. Temkin has worked on analyzing data relevant to the study and participating in calls/meetings
Robertson, Claudia	BCM	Co-Investigator	3.00	Dr. Robertson advises on clinical protocol development

OTHER SUPPORT PAGES

PREVIOUS, CURRENT, AND PENDING SUPPORT

Joseph Giacino

ACTIVE

TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies (W81XWH-18-2-0042 DOD (Prime PI: Manley))

U.S. Department of Defense

Contracting/Grants Officer: Mirlene Andou, Grants Specialist, 301-619-7733

Performance Period: 10/01/2018 – 09/30/2021

Annual Funding: \$36,075

Level of effort: 1.2 Calendar Months

The goals of this 3-year project are to validate blood-based and imaging biomarkers to improve the characterization of TBI and elucidate factors to influence design of future precision medicine clinical trials and inform patient responsiveness to targeted therapeutics.

- Aims: 1. Validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and MR imaging sequences in prospectively collected data from existing TRACK-TBI subjects.
2. Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate severe TRACK-TBI subjects.
3. Conduct a multicenter double-blind, placebo-controlled exploratory clinical trial comparing the impact of Cyclosporine A on blood-based and imaging biomarkers of DAI and neuroinflammation in moderate-severe TBI patients admitted to the ICU.

Overlap: There is no overlap.

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Longitudinal (TRACK-TBI LONG) (Prime PI: Manley)

National Football League

Contracting/Grants Officer: Joshua Keidan, Finance Manager, 212-450-2309

Performance Period: 09/30/2018 – 09/29/2021

Annual Funding: \$87,500

Level of effort: 0.6 Calendar Months

This project will extend TRACK-TBI's current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury depending on participants' original enrollment date. These data will validate endpoints for acute and chronic diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.

- Aims: 1. Extend examination of existing injured and control TRACK-TBI participants with 3 annual telephonic and Web-based follow-ups: capturing neuropsychological and cognitive symptoms and life function/quality and screening for neurodegenerative and post-traumatic disorders;
2. Characterize long-term trajectory of imaging biomarkers in brain-injured and control subjects ("MRI Cohort") using DTI, rs-fMRI, and high-resolution structural studies;
3. Characterize long-term trajectories of neurocognitive/psychological function and their relationship to e.g., plasma-CSF proteomic markers related to inflammation and neurodegeneration, and imaging;
4. Apply PET imaging to characterize prevalence and extent of A β plaques and neurofibrillary tangles in a subset of the MRI Cohort age >50y;

5. Apply traditional and novel neuroimaging-guided and quantitative neuropathologic approaches to donated brains to interrogate TBI-associated structural and biological changes correlated with antemortem phenotyping.

Overlap: There is no overlap.

Multimodal network connectivity architecture (MOCA) of the brain and its role in the recovery of consciousness of comatose cardiac arrest patients (1R01NS102574-01A1 (Prime PI: Wu))

National Institutes of Neurological Disorders and Stroke

Performance Period: 09/15/2018 – 06/30/2023

Annual Funding: \$17,701

Level of effort: 0.43 Calendar Months

The primary aim of this study is to determine whether neuroimaging, electrophysiology, clinical markers, and biochemical markers collected less than 7 days following cardiac arrest can identify which patients that are comatose for more than 24 hours are most likely to regain arousal. The secondary aim is to determine whether improvements on serial imaging or electrophysiology are associated with arousal recovery by discharge or favorable neurologic outcome between 6 and 12 months after injury.

Overlap: There is no overlap.

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)

U.S. Department of Defense- Medical Technology Enterprise Consortium

Contracting/Grants Officer: Rebecca Harmon, Advance Technology International, 315 Sigma Drive, Summerville, SC 29483, 843-760-3358

Performance Period: 08/10/2018 – 08/09/2023

Annual Funding: \$75,000

Level of effort: 2.4 Calendar Months

This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.

Aims: 1. Adapt the current TRACK-TBI study network into a Phase 2 clinical trial network and work with DoD, FDA, and industry partners to identify key drug candidates for randomized controlled trials.
2. Enroll 504 participants into a Phase 2 multi-arm, multi-stage (MAMS) adaptive platform design for randomized, controlled clinical trial(s).
3. Complete study close-out, analyses, dissemination of findings, and meet with MTEC, FDA, and industry partners to begin plans for Phase 3 clinical trials.

Overlap: There is no overlap.

Spaulding-Harvard Traumatic Brain Injury Model System

National Institute on Disability, Independent Living, and Rehabilitation Research

Contracting/Grants Officer: Leslie Caplan, PhD, 400 Maryland Ave., S.W., Washington, DC

Performance Period: 10/1/17-9/30/22

Annual Funding: \$441,500

Level of effort: 2.4 Calendar Months

The aims of this 5-year program grant are to contribute prospective demographic, clinical and outcome data acquired from patients with moderate to severe TBI to the TBI National Data and Statistical

Center, develop and validate an abbreviated version of the Coma Recovery Scale-Revised for use in the ICU and participate in multi-site collaborative projects in concert with other funded TBI model systems.

Overlap: There is no overlap.

Central thalamic stimulation for traumatic brain injury

National Institutes of Health

Contracting/Grants Officer: Amy Lane, Asst. Director, Office of Sponsored Research, 1300 York Avenue Box 89, New York, NY 100654805

Performance Period: 9/30/2015 - 8/31/2020

Annual Funding: \$71,820

Level of effort: 1.0 Calendar Months

The goal of the research is to develop a deep brain stimulation system that will recover cognitive capacity following brain injury sufficient to improve daily function and vocational or academic reentry.

Aims: 1. To establish the safety of CT-DBS in patients with severe-to-moderate brain injuries and outcomes of GOSE 6-7.

2. To establish measures of efficacy of CT-DBS stimulation in patients with severe-to moderate brain injuries and outcomes of GOSE 6-7.

3. To obtain and analyze critical human subject data to guide device design enabling effective and robust modulation of the DTTm in the human central thalamus.

Overlap: There is no overlap.

Traumatic Brain Injury Endpoints Development Award (TED)

Dept. of the Army - United States Army Medical Research Acquisition Activity

Contracting/Grants Officer: Janet P Kuhns, 820 Chandler St., Fort Detrick, MD 21702-5014

Performance Period: 9/30/2014 - 9/29/2020 (NCE)

Annual Funding: \$108,958

Level of effort: 1.84 Calendar Months

The objective of this study is to identify (Stage I) and validate (Stage II) candidate clinical outcome assessments and biomarkers that could be qualified by the Food and Drug Administration as drug development tools for future TBI trials to benefit military and civilian populations.

Aims: 1. To establish a collaborative, multidisciplinary team to advance the identification and validation of clinical outcome assessments (COAs) and biomarkers for use as potential FDA qualified drug development tools (DDTs), and initiate development of CDISC data standards for trials involving diagnosis and treatment of mTBI to modTBI.

2: To validate candidate COAs and biomarkers selected in Stage I, leveraging the existing research infrastructure and clinical study networks of TRACK-TBI, CENC, and CRC for potential qualification as DDTs.

3: Continue FDA qualification process for validated COAs and biomarkers, and develop an Implementation and Dissemination Transition Plan.

Overlap: There is no overlap.

Multicenter evaluation of memory remediation after traumatic brain injury with donepezil National Institute on Disability and Rehabilitation (MEMRI-TBI-D)

National Institute on Disability, Independent Living, and Rehabilitation Research

Contracting/Grants Officer: Leslie Caplan, PhD, 400 Maryland Ave., S.W., Washington, DC

Performance Period: 10/1/13-9/30/19 (NCE)

Annual Funding: \$101,377

Level of effort: 0.96 Calendar Months

The objective of this 5-year, four-site, randomized, placebo-controlled trial is to test the effectiveness of donepezil for treatment of declarative memory problems experienced by individuals who have sustained mild to severe traumatic brain injury.

Aims: 1. To evaluate the effects of donepezil on neuropsychologically identified, clinically important, verbal memory impairments among persons with complicated mild, moderate, or severe non-penetrating TBI in the subacute to chronic recovery period.
2: To evaluate the effects of donepezil on everyday memory functioning among persons with clinically important declarative memory impairments in the subacute or chronic recovery period following complicated mild, moderate, or severe non-penetrating TBI.
3: To acquire data that inform on the effects of donepezil on attention, processing speed, executive function, neuropsychiatric symptoms, community participation, quality of life, and caregiver burden among persons with complicated mild, moderate, or severe non-penetrating TBI in the subacute to chronic recovery period.

Overlap: There is no overlap.

Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI II)

National Institute of Neurological Disorders and Stroke

Contracting/Grants Officer: Aaron Kinchen, 6001 Executive Blvd MSC 9525, Bethesda, MD 20892-9525

Performance Period: 9/30/2013-8/31/19 (NCE)

Annual Funding: \$72,800

Level of effort: 0.4 Calendar Months

The overall goal of TRACK-TBI II is to determine the relationships among the clinical, neuroimaging, cognitive, genetic and proteomic biomarker characteristics for the entire spectrum of TBI from concussion to coma, across the entire age spectrum and to validate biomarkers and outcome measures for use in clinical trials.

Aims: 1. To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research.
2. To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI.
3. To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity.
4. To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Overlap: There is no overlap.

PENDING

None

PREVIOUS (within the last 5-years)

Spaulding-Harvard Traumatic Brain Injury Model System

National Institute on Disability, Independent Living, and Rehabilitation Research

Contracting/Grants Officer: Cate Miller, PhD, 400 Maryland Ave., S.W., Washington, DC

Performance Period: 10/1/12-9/30/18 (NCE)

Annual Funding: \$430,100

Level of effort: 1 Calendar Months

The aims of this 5-year center grant are to contribute prospective demographic, clinical and outcome data acquired from patients with moderate to severe TBI to the TBI National Data and Statistical Center, complete a site-specific functional neuroimaging study entitled, "Looking for Consciousness: A Novel Functional Neuroimaging Approach for Detection of Visual Cognition in Patients with Severe TBI and Disorders of Consciousness" and participate in collaborative "module" projects in concert with other funded TBI model systems.

Overlap: There is no overlap.

Huperzine A for the Treatment of Cognitive, Mood and Functional Deficits After Moderate and Severe TBI

US Department of Defense

Contracting/Grants Officer: Jennifer Shankie, US Army Medical Research and Materiel Command, 820 Chandler Street Fort Detrick, MD 21702

Performance Period: 9/1/11-8/31/18 (NCE)

Annual Funding: \$409,000

Level of effort: 1.08 Calendar Month

The primary objective of this study is to conduct a phase II, randomized, double-blind, placebo-controlled clinical trial to investigate the effects of Huperzine A on memory function, TMS-induced neurophysiologic markers, EEG event related potentials (P50 and p300), seizure frequency and incidence of adverse effects in civilian and military personnel who sustain moderate to severe traumatic brain injury.

- Aims:
1. To determine whether Huperzine A, as compared to placebo, has a differential effect on learning and memory functions after moderate to severe TBI.
 2. To determine whether administration of Huperzine A produces significant differences in neurophysiologic markers (as indexed by EEG event related potentials (P50 and P300) and TMS-indexed cortical excitability (cholinergic activity)) associated with cognition relative to a placebo.
 3. To determine whether Huperzine A reduces the prevalence/frequency of post-traumatic seizures after moderate and severe TBI as compared to placebo.
 4. To evaluate the safety and tolerability of Huperzine A in this patient population as compared to placebo. Safety and tolerability will be assessed by a comparison of the frequency and intensity of adverse effects.

Overlap: There is no overlap.

An Evidence-Based Clinical Outcome Assessment Platform to Advance the Identification and Validation of Clinical Outcome Assessment Measures for Use as FDA-Qualified Drug Development Tools: A Traumatic Brain Injury Endpoints Development (TED) SEED Award

Dept. of the Army - United States Army Medical Research Acquisition Activity

Contracting/Grants Officer: Susan Dellinger, 820 Chandler St., Fort Detrick, MD 21702-5014

Performance Period: 02/01/2016- 01/31/2017

Annual Funding: \$274,981

Level of effort: 1 Calendar Month

The objective of this study is to design, build and pilot test an evidence-based platform for assessment of COAs, placing particular emphasis on the validity of the COA as it pertains to a specific concept of interest within a given context of use.

Aims: 1. Facilitate completion of Stage 1 of TED by designing and building an evidence-based clinical outcome assessment platform that will enable efficient, transparent and systematic grading of COAs to aid selection of suitable candidates for regulatory acceptance or FDA qualification.
2: Pilot test the EB-COP platform on the Glasgow Outcome Scale- Extended (GOSE), the only COA designated as a “core” CDE for TBI, and the only measure currently accepted by the FDA for use in clinical trials.

Overlap: There is no overlap.

The INjury and TRaumatic STress (INTRuST) Consortium Neuroimaging Acquisition and Archival

US Department of Defense

Contracting/Grants Officer: Pamela Fisher, USA MED Research Acq Activity, 820 Chandler Street
Fort Detrick, MD 21702

Performance Period: 3/31/2013-9/30/2014

Annual Funding: \$315,230

Level of effort: 1 Calendar Month

The primary goal of this project is to acquire and archive neuroimages representing a diverse population (civilian and military) and a spectrum of traumatic brain injuries (e.g., blast vs. impact in the military population).

Overlap: There is no overlap.

CURRENT/PENDING SUPPORT

Name of PI or Key Person: **Levin, Harvey, PhD**

Current Support

Title: <i>MPI: SALIVA BIOMARKERS FOR MTBI DIAGNOSTICS IN CHILDREN</i>	Time Commitments: 10% (percent effort)
Supporting Agency: National Institute of Health Prime: Gaia Medical Institue <i>R43-HD097039</i>	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Sarka Southern, Ph.D. CEO www.gaiamedical.com 505 Coast Blvd. South Ste 104 La Jolla, CA 92037 Office: 858-459-1703 Cell: 760-871-5141
Performance Period: 5/01/2018-6/30/2020 Role: Site Principal Investigator	Level of Funding: \$76,643 (total)
<u>Brief Description of the Project's Goals:</u> The major goals of this project are to (1)Collect serial saliva samples from school children with medically diagnosed mild traumatic brain injury (mTBI, n=40), controls with orthopedic injury (OI, n=30) who are evaluated in Emergency Medicine, Texas Children's Hospital (TCH) and from uninjured, healthy controls (HC, n=15) to measure salivary biomarkers for brain injury; and (2)Determine diagnostic accuracy of saliva mTBI biomarkers in classifying the mTBI and OI groups. Saliva samples will be obtained on three occasions (within 48 hours after injury, 7 to 14 days, and 30 days); postconcussion symptoms will also be measured on each visit. As a secondary goal, we will evaluate the accuracy of the biomarkers measured within 48 hours in predicting persistent postconcussion symptoms (PPCS) based on the day 30 outcome assessment; functional status on day 30 of the children with mTBI will also be analyzed in relation to the biomarkers measured within 48 hours . The ultimate goal is to develop a new point-of-care (POC) test for diagnostics of mTBI) in children. Salivary samples from healthy children and existing baseline samples from pre-season high school athletes will define normal range and daily/diurnal variability in biomarker concentrations.	

Pending Support

None

Previous Support

Title: <i>Chronic Effects of Neurotrauma Consortium (CENC): Project 1: Longitudinal Cohort Study</i>	Time Commitments: 5% (percent effort)
Supporting Agency: US Department of Veterans Affairs, Rehabilitation Research and Development Service Identifying number: SPLF-001-13F (Scheibel, Michael E. DeBakey VA Medical Center)	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Stuart W. Hoffman, Ph.D., Scientific Program Manager for Brain Injury, Rehabilitation Research and Development Service U.S. Department of Veterans Affairs 810 Vermont Avenue (10P9R) Washington, DC 20240
Performance Period: 10/01/2013 – 09/30/2018	Level of Funding: \$1,188,700
<u>Brief Description of the Project's Goals:</u> To establish a large longitudinal case-control cohort Veterans to comprehensively evaluate for the late effects of combat related mTBI, describe the late outcomes and change over time of Veterans with single and repeated mTBI, and establish whether, and to what extent, mTBI(s) is associated with poorer outcome among combat-exposed Veterans. Role: Co-Investigator	
List of Specific Aims: <u>Specific Aim 1:</u> Establish a large longitudinal mTBI exposed vs. unexposed cohort of former OEF/OIF/OND combatants to comprehensively evaluate for the late effects of combat-related mTBI including evidence of neurodegeneration. <u>Specific Aim 2:</u> Determine whether the mTBI exposed group differs from the non-TBI control group and the effects of single versus multiple mTBIs either on baseline post-acute outcomes or longitudinally across time (adjusting for potential moderators including personal factors, environmental factors, and comorbidities). <u>Specific Aim 3:</u> Identify subgroups with different levels or patterns of decline over time inferring neurodegeneration. Subgroups will be potentially defined by moderating factors and a variety of clinical variables (baseline neurocognitive, neurological signs and symptoms). The a priori patterns of main interest are purported behavioral pattern(s) of CTE; that is: Stage 1: poor concentration and headaches; Stage 2: memory problems, depression, poor impulse control, and emotional instability ; Stage 3: executive dysfunction, cognitive impairment and Stage 4: language difficulties, aggression, and dementia <u>Specific Aim 4:</u> Identify biologic variables (for example: APO E4 carrier, other genotype, cortical thickness changes, disrupted white matter integrity, white matter hyperintensities, altered cerebral blood flow, disrupted functional connectivity, neuroendocrine abnormality, presence or absence of pathology) associated with Aim 3 patterns to provide converging evidence for neurodegeneration. Specific Aim 5 (Exploratory, Richmond only): Measure ERPs (specifically multimodal working memory, long-term memory access, & auditory cortical potentials) to: a) seek additional physiologic evidence of neurodegeneration via association to Aim 3 patterns, b) clarify functional significance of changes in neurobiological variables through real-time measure of neural coordination; and c) characterize the neurocognitive mechanisms of impairments shown on cognitive performance tests.	
Title: <i>Diffusion Tensor Imaging Standardization using Novel MR Diffusion Phantoms</i>	Time Commitments: 20% (percent effort)

Supporting Agency: US Department of Veterans Affairs, Rehabilitation Research and Development Service Identifying number: F1880I (Wilde, Michael E. DeBakey VA Medical Center)	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Stuart W. Hoffman, Ph.D., Scientific Program Manager for Brain Injury, Rehabilitation Research and Development Service U.S. Department of Veterans Affairs 810 Vermont Avenue (10P9R) Washington, DC 20240
Performance Period: 01/01/15-6/30/2017	Level of Funding: \$892,500
<u>Brief Description of the Project's Goals:</u> In this proposal, we use diffusion imaging phantoms to evaluate differences between scanners with the goal of providing acquisition techniques that will data to be compared across different patient groups and combined into large data collections. Role: Principal Investigator	
<u>List of Specific Aims:</u> <u>Aim 1.</u> Using the four 3T MRI scanners and infrastructure of the Chronic Effects of Neurotrauma Consortium, we will examine sources of inter- and intra-scanner variability utilizing two diffusion phantoms. <u>Aim 2.</u> Once data is collected from the phantoms, information from the phantoms and normal volunteers will be applied to adjust and optimize diffusion sequence parameters that will allow for greater consistency in diffusion imaging measurement between scanners at different sites and across time points.	

Title: <i>CT and MRI Prognostic Biomarkers for Mild to Moderate TBI (TBI Endpoints Development seed grant</i>	Time Commitments: 7 % (percent effort)
Supporting Agency: US Army Medical Research and Materiel Command (USAMRMC), Office of the Congressionally Directed Medical Research Programs (CDMRP) Identifying number: W81XWH-14-2-0176	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: B. Christie Vu, Ph.D. Health Science Program Manager Congressionally Directed Medical Research Programs, USAMRDC 1077 Patchel Street Fort Detrick, MD 21702-5024 E-Mail: bao-han.c.vu.civ@mail.mil Telephone: 301-619-4227
Performance Period: 02/01/2016-09/29/2017	Level of Funding: \$98,911
Brief Description of the Project's Goals: The goal of the grant is to determine whether CT and MRI may provide useful biomarkers for FDA approval. Role: Co-Investigator <u>List of Specific Aims:</u> <u>Specific Aim 1:</u> Interrater reliability of TBI imaging Common Data Elements (CDE). The TBI imaging CDEs are highly promising imaging biomarkers that were designed based on principles consistent with the FDA biomarker qualification process. <u>However, the FDA qualification process requires proof that a biomarker can be measured reliably.</u> We will identify 200 subjects through random selection of subjects from each of 5 studies in the TED metadataset. Three expert readers will review brain MRI and head CT exams for these 200 subjects. Kappa statistics, measures of interrater agreement for multiple raters, and 95% confidence intervals around them, will be calculated for each CDE. <u>Specific Aim 2:</u> Prognostic validity of CT and MRI CDEs. We aim to enhance the power of therapeutic clinical trials by validating CDE imaging biomarkers for stratification of mild to moderate TBI patients according to risk for persistent post-concussive symptoms and disability. CT/MRI biomarkers that can be reliably measured, and that have been proven to bear prognostic significance, would reduce the heterogeneity in pathophysiology that is not currently considered when randomizing patients based exclusively on GCS scores. For each of 5 studies in the TED metadataset, we will analyze 3-, 6- and 12-month outcome measures in relation to each imaging CDE, using nonparametric statistical tests for multicategory CDEs and linear regression for continuous CDEs. Next, we will repeat these univariable analyses after pooling patients who satisfy the same or very similar inclusion and exclusion criteria across studies. Finally, we will construct multivariable models of outcome using statistically significant univariable imaging predictors as determined above. We will construct 2 types of models. One will apply to the Context of Use (COU) in which mild or moderate TBI patients ≥ 18 years of age with nonpenetrating head trauma have undergone acute head CT (e.g., as part of standard clinical care according to American College of Emergency Physicians/Centers for Disease Control criteria), with or without subsequent brain MRI in the subacute time frame (within 1 month of TBI). The other will apply to a COU in which patients have undergone subacute brain MRI only. Our study design allows for replication of analyses, and confirmation of reproducibility of results, across 5 independent cohorts.	

Title: <i>Objective Brain Function Assessment of MTBI from Initial Injury to Rehabilitation and Treatment Goals: Optimization-(Collegiate Study and High School Study</i>	Time Commitments: 10% (percent effort)
Supporting Agency: Department of the Navy/BrainScope Identifying Number: N6311614MPX083	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Leslie S. Prichep, Ph.D. Chief Scientific Officer BrainScope Company, Inc. 4330 East West Highway Suite 1000 Bethesda, MD 20814 leslie.prichep@brainscope.com
Performance Period: 07/01/2016 – 06/30/2017	Level of Funding: \$463,671
Brief Description of the Project's Goals: This multi-site project seeks to examine the validity and efficacy of portable EEG measures in collegiate athletes sustaining sports-related concussion. Role: Co-Director of Imaging Core	
<u>List of Specific Aims:</u> The purpose is to evaluate a portable encephalography (EEG) device that is designed to detect a mild traumatic brain injury (mTBI) or concussion. The study will evaluate the sensitivity of the EEG device to concussion and its measurement of the recovery. The study will recruit 750 collegiate football players at 8 sites who will undergo pre-season cognitive and symptom assessments, and EEG. EEG will be repeated within 24 hours after sustaining a concussion, MRI/DTI and cognitive and symptom assessment within 72 hours after injury. A post-season follow-up assessment involving MRI/DTI, EEG, and cognitive assessment will also be performed. Sensors placed within the players' helmets will detect the impacts which will be correlated with the EEG. For the estimated 8 to 10% of the athletes who sustain a concussion, an athletic trainer or physician will diagnose the concussion. Comparison of the EEG findings with the MRI/DTI and cognitive assessments will address the validity of the EEG device as will analysis of the EEG findings in relation to the impacts detected by the sensors. A subgroup of the non-concussed contact sport players and the players engaged in a non-contact sport will also undergo the above assessments for comparison with the concussed group and to contribute data toward refinement of the BrainScope algorithm for detecting a concussion.	
Title: <i>TBI Biological Diagnosis via High Definition Tractography Asymmetry Screening</i>	Time Commitments: 5% (percent effort)
Supporting Agency: US Army Medical Research and Materiel Command (USAMRMC), Office of the Congressionally Directed Medical Research Programs (CDMRP) Identifying number: PT110773, W81XWH-12-2-0140 (Schneider, University of Pittsburgh)	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: B. Christie Vu, Ph.D. Health Science Program Manager Congressionally Directed Medical Research Programs, USAMRDC 1077 Patchel Street Fort Detrick, MD 21702-5024 E-Mail: bao-han.c.vu.civ@mail.mil Telephone: 301-619-4227
Performance Period: 09/30/12 – 09/29/17	Level of Funding: \$ 241,692 (Baylor only)
<u>Brief Description of the Project's Goals:</u> Develop new diffusion methodology to better detect TBI-related injury. Role: Co-Investigator	

List of Specific Aims: This comprehensive proposal includes acquisition, methods development, and scientific assessment and results. The three clusters, methods development, data acquisition, and scientific results, are executed by nine specific objectives as summarized in the technical abstract.

Development of Methods:

Specific Aim 1: Reduce scanning time while preserving fiber tracking quality via development of optimized sampling.

Specific Aim 2: Increase fiber tracking anatomical accuracy to 90% on reference tracts.

Specific Aim 3: Develop automatic tract segmentation to match human segmentation quality.

Specific Aim 4: Develop computational tract anomaly detection, and visualization.

Specific Aim 5: Build a HDTAS TBI query database of cases and related literature relating tract damage to function outcomes.

Data Acquisition:

Specific Aim 6: Collect normative human fiber tract data on 50 healthy controls and provide normative data on 40 tracts.

Specific Aim 7: Obtain HDFT scans in 250 military and civilian TBI patients to develop HDTAS measuring cortical area volumes and neuropsychological deficits in 250 chronic TBI individuals with stable, combat-related TBI of varying initial severity: mild (N=50), moderate (N=50) and severe (N=150) using both HDTAS and standard MRI/DTI methods.

Scientific Results:

Specific Aim 8: Test the hypothesis of can HDTAS find otherwise neuroimaging "silent" TBI damage when DTI and MRI methods cannot

Specific Aim 9: Provide an anatomically accurate and comprehensive atlas of fiber tracks based on the subject population representative of DoD personnel and provides quantification of the major tracts in healthy and TBI damaged individuals.

Title: *Does Graph Theory Analysis of DTI Identify New Brain Networks*

Time Commitments:
(percent effort)

Supporting Agency:
Mission Connect of the TIRR Foundation

Name and Address of Funding Agency's
Procuring Contracting/Grants Officer:
Cynthia Adkins
TIRR Foundation
4605 Post Oak Place
Suite 222
Houston, Texas 77027
adkinsc@tirrfoundation.org
(713)877-0489

Identifying number: N/A (Levin, Baylor College of Medicine)

Performance Period: 6/1/2015-05/31/2016

Level of Funding: \$60,000

Brief Description of the Project's Goals: Utilize a novel form of graph theory in diffusion data analysis in subjects with TBI.

Role: Co-Investigator

List of Specific Aims: The overarching aim is to investigate the overall local and global network abnormalities that characterize brain dysfunction after mild traumatic brain injury (mTBI), through comparison with a control group of patients who sustained orthopedic injury using diffusion tensor imaging (DTI) data acquired by the Mission Connect Consortium at 24 hours and 3 months post-injury. We will investigate the nature of these abnormalities using graph theoretical methods, with the aim of identifying measures that are most indicative of network abnormalities and may act as biomarkers of mTBI diagnosis, as well as prognosis for cognitive recovery.

Title: <i>Mission Connect Mild TBI Translational Research Consortium</i>	Time Commitments: 30% (percent effort)
Supporting Agency: US Army Medical Research and Materiel Command (USAMRMC), Office of the Congressionally Directed Medical Research Programs (CDMRP) Identifying number: W81XWH-08-2-0133; PT074693P2 (Levin, Baylor College of Medicine)	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Dwayne Tagliaferro, Ph.D. Health Science Program Manager Congressionally Directed Medical Research Programs, USAMRDC 1077 Patchel Street Fort Detrick, MD 21702-5024
Performance Period: 8/1/2008 – 7/31/2014	Level of Funding: \$770,042
<u>Brief Description of the Project's Goals:</u> The major goals of this consortium project are to develop and evaluate methods for diagnosis and treatment of mild TBI. Project 2 involved Specific Aims 2-3, which are detailed below. Role: Co-Investigator	
List of Specific Aims: <u>Specific Aim 2:</u> To improve the diagnosis of MTBI, developing more objective criteria in the early post-injury period as well as in the chronic condition. <u>Specific Aim 2.1:</u> To study early (<24 hr) diagnosis of MTBI and differentiation of its sequelae related to brain injury from PTSD symptoms present in MTBI and in orthopedic injury (OI) groups studied over a six-month follow-up interval. <u>Specific Aim 3:</u> To develop new and innovative treatment strategies for MTBI and provide the preclinical and phase 1-2 testing of treatments found to improve outcome. Five specific aims (3.1-3.5) will investigate neuroprotection strategies. <u>Specific Aim 3.1:</u> To study neuroprotection and enhanced neurological recovery with atorvastatin after MTBI. This study has both laboratory (<i>Specific aim #3.1.1</i>) and clinical (<i>Specific aims #3.1.2-3.1.7</i>) parts.	

Title: <i>Neurobehavioral Outcome of Head Injury in Children</i>	Time Commitments: 12% (percent effort)
Supporting Agency: National Institutes of Health/ Eunice Kennedy Shriver National Institute of Child Health and Human Development (NIH/NICHHD) Identifying number: R01 NS21899 (Levin, Baylor College of Medicine)	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Mary Ellen Michel, PhD, Program Director, Repair and Plasticity 6001 Executive Boulevard Suite 3309 Bethesda, MD 20892- 9531
Performance Period: 02/15/10-01/31/14	Level of Funding: \$459,673
<u>Brief Description of the Project's Goals:</u> The major goals of this project are studying changes in cognitive control, motivation, and social cognition in relation to brain regional volumes, DTI, fMRI, and other forms of advanced imaging analysis. Role: Co-Investigator	
List of Specific Aims: <u>Specific Aim 1</u> (Executive Functions, Behavioral Regulation and Social Cognition): Investigate the contribution of executive functions to social cognition in youth at 12 months following moderate to severe TBI (MSTBI). <u>Specific Aim 2</u> (Neural Mechanisms): Investigate neural mechanisms mediating poor executive functions and social cognition in youth at 12 months following MSTBI.	

Title: <i>Neurorehabilitation: Neurons to Networks (N:N2N) Center of Excellence</i>	Time Commitments: 22% (percent effort)
Supporting Agency: US Department of Veterans Affairs, Rehabilitation Research and Development Service Identifying number: B6812C	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Stuart W. Hoffman, Ph.D., Scientific Program Manager for Brain Injury, Rehabilitation Research and Development Service U.S. Department of Veterans Affairs 810 Vermont Avenue (10P9R) Washington, DC 20240
Performance Period: 07/01/09-06/30-14	Level of Funding: \$5,000,000
<u>Brief Description of the Project's Goals:</u> The major goal of this project is to improve the diagnosis of mild traumatic brain injury through investigation of advanced brain imaging and neurocognitive testing. Other goals of the COE include investigation of genetic factors related to recovery from mild TBI. The COE will also provide clinical services and vocational rehabilitation. Role: Co-Investigator	
<u>List of Specific Aims:</u> <u>Specific Aim 1:</u> Investigate brain activation during phases of encoding, maintenance, and retrieval on a working memory task in OEF/OIF veterans who sustained MTBI due to blast 12 to 48 months prior to imaging. <u>Specific Aim 2:</u> In veterans who sustained MTBI due to blast at least 12 months prior to imaging evaluate the integrity of cerebral white matter using diffusion tensor imaging (DTI) and measure brain region volumes of gray and white matter on anatomic magnetic resonance imaging (MRI). <u>Specific Aim 3:</u> Investigate the relation of brain activation to acute injury variables, preinjury cognitive reserve, brain volumes, and outcome measures given in the Assessment Core	
Title: <i>A Psychiatric and Imaging Study of Pediatric Mild Traumatic Brain</i>	Time Commitments: 10% (percent effort)
Supporting Agency: National Institutes of Health/ Eunice Kennedy Shriver National Institute of Child Health and Human Development (NIH/NICHHD) Identifying number: R01HD068432	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Theresa Cruz, Program Director, 6001 Executive Boulevard Suite 3309 Bethesda, MD 20892- 9531 cruzth@mail.nih.gov
Performance Period: 09/01/11-10/31/16	Level of Funding: \$481,426
<u>Brief Description of the Project's Goals:</u> The proposed study involved a 1-year, 4-assessment, prospective longitudinal study of consecutively treated injured children with mild TBI (n=220) and a control group of children with mild orthopedic injuries not involving the brain (n=110). Assessments will include validated structured interviews to identify psychiatric disorders, adaptive behavior skills, academic achievement, family psychiatric history, and family function. Lesion identification, lesion localization, lesion volumetrics, regional volumetrics, and measures of white matter integrity, will be defined using high-resolution structural magnetic resonance imaging (MRI). MRI analyses will include diffusion tensor imaging, susceptibility weighted imaging, T2-weighted imaging, and fluid attenuated inversion recovery imaging. Role: Site Principal Investigator	

List of Specific Aims:

Specific Aim 1: Examine the occurrence and phenomenology of new-onset psychiatric disorders in children after mTBI.

Specific Aim 2: Assess predictors and mechanisms for the development of new-onset psychiatric disorders in children after mTBI and orthopedic injury. Predictors and mechanisms will be investigated by examining child, family, and injury risk factors.

Title: *Imaging and Biomarkers in Adolescents Cleared for Return to Play after Concussion*

Time Commitments: 5%
(percent effort)

Supporting Agency: National Institutes of Health, National Institute of Neurologic Disease and Stroke (NIH/NINDS)

Name and Address of Funding Agency's
Procuring Contracting/Grants Officer:
Patrick Bellgowan
National Institute of Disorders and Stroke
6001 Executive Blvd. Rm 3250
Bethesda, MD 20892-9605

Identifying number: R21NS086714 (Levin, Baylor College of Medicine)

Performance Period: 1/1/14-12/31/17

Level of Funding: \$214,023 (annual)

Brief Description of the Project's Goals: The goal of this project is to investigate advanced neuroimaging findings which may be evident even after subjects are cleared to return to play.

Role: Co-Investigator

List of Specific Aims:

Specific Aim 1: Investigate effects of sports concussion on brain function and structure in adolescent athletes who meet clinical guidelines for return to play.

Specific Aim 2: Evaluate prognostic usefulness of specific miRNA biomarker levels in plasma of acutely concussed and non-concussed adolescent athletes.

Specific Aim 3: Investigate differential effects of sports concussion according to neurodevelopmental stage across the adolescent age range.

SUPPORT**MANLEY, GEOFFREY T.****CURRENT**

Title:	Hypothermia for Patients Requiring Evacuation of Subdural Hematoma: Effect on Spreading Depolarizations (PI: Hartings, A133799)
Time Commitment:	0.1 calendar months
Support Agency:	University of Cincinnati (Subaward)
Grants Officer:	S. Theresa Yockey, Senior Grant Administrator Sponsored Research Service, 51 Goodman Ave, Suite 530, Cincinnati, Ohio 45221 Telephone: 513-556-4390 Email: Confint@ucmail.uc.edu
Performance Period:	02/01/2019 – 09/29/2021
Total Costs of the Project:	\$50,000
Project Goals:	UCSF will oversee the analysis of therapies and physiologic monitoring data during intensive care, as well as facilitate study management and coordination of aims with TRACK-TBI.
Overlap:	None

Title:	Assay Cartridge Development for Traumatic Brain Injury (TBI) Diagnostic Device (A133407)
Time Commitment:	1.20 calendar months
Support Agency:	Abbott Point of Care Inc.
Grants Officer:	Dr. Hongwei Zhang 613-688-5949 x 2935 Hongwei.zhang@abbott.com
Performance Period:	03/15/2019 – 09/30/2022
Total Costs of the Project:	\$19,693,781
Project Goals:	The primary objective of this study is to determine the clinical performance of the i-STAT TBI test when it is used for the proposed intended use. The secondary objective of this study is the collection of data and specimens from subjects with a wider range of GCS scores, that may support other purposes related to the understanding of TBI.
Specific Aims:	1) To analyze the clinical sensitivity, clinical specificity, negative predictive value [NPV] and positive predictive value [PPV] of the i-STAT TBI test when it is used in determining the need for a CT scan in patients presenting with suspected mild traumatic brain injury (TBI) who are 18 years of age or older, have a Glasgow Coma Scale (GCS) score of 13-15 and present within 12 hours of injury (intended use). The clinical performance will be determined in both whole blood and plasma. 2) To determine the potential ability of the i-STAT to assist in possible genetic testing, the development of future in vitro diagnostic tests, and other potential intended uses for the i-STAT TBI test such as the assessment of the need for

	magnetic resonance imaging (MRI), prognostic claims, or severity stratification.
Overlap:	None

Title:	W81XWH-18-2-0042 / TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies (A132436)
Time Commitment:	1.20 calendar months
Support Agency:	DOD US Army Med. Res. Acq. Activity
Grants Officer:	Mirlene Andou 301-619-7733 Mirlene.d.andou.civ@mail.mil
Performance Period:	09/30/2018 – 09/29/2019
Total Costs of the Project:	\$1,500,000
Project Goals:	Validate blood-based and imaging biomarkers to improve the characterization of TBI, and elucidate factors to influence design of future precision medicine clinical trials and inform patient responsiveness to targeted therapeutics.
Specific Aims:	1) Validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and MR imaging sequences in prospectively collected data from existing TRACK-TBI subjects. 2) Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate severe TRACK-TBI subjects. 3) Conduct a multicenter double-blind, placebo controlled exploratory clinical trial comparing the impact of Cyclosporine A on blood-based and imaging biomarkers of DAI and neuroinflammation in moderate-severe TBI patients admitted to the ICU.
Overlap:	None

Title:	Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET) (A131954)
Time Commitment:	3.60 calendar months
Support Agency:	Medical Technology Enterprise Consortium
Grants Officer:	Rebecca Harmon Advanced Technology International 315 Sigma Drive, Summerville, SC 29483 Telephone: 843-760-3358 Email: mtec-contracts@ati.org
Performance Period:	10/01/2018 – 11/30/2023
Total Costs of the Project:	\$24,999,999
Project Goals:	This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to

	characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.
Specific Aims:	1) Adapt the current TRACK-TBI study network into a Phase 2 clinical trial network and work with DoD, FDA, and industry partners to identify key drug candidates for randomized controlled trials. 2) Enroll 504 participants into a Phase 2 multi-arm, multi-stage (MAMS) adaptive platform design for randomized, controlled clinical trial(s). 3) Complete study close-out, analyses, dissemination of findings, and meet with MTEC, FDA, and industry partners to begin plans for Phase 3 clinical trials.
Overlap:	None

Title:	Transforming Research and Clinical Knowledge in Traumatic Brain Injury Longitudinal (TRACK-TBI LONG) (A131769)
Time Commitment:	Effort as needed
Support Agency:	National Football League
Grants Officer:	Joshua Keidan, Finance Manager Telephone: 212-450-2309 Email: Joshua.Keidan@nfl.com
Performance Period:	07/01/2018 – 06/30/2021
Total Costs of the Project:	\$3,454,080
Project Goals:	This project will extend TRACK-TBI's current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury depending on participants' original enrollment date. These data will validate endpoints for acute and chronic diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.
Specific Aims:	1) Extend examination of existing injured and control TRACK-TBI participants with 3 annual telephonic and Web-based follow-ups: capturing neuropsychological and cognitive symptoms and life function/quality and screening for neurodegenerative and post-traumatic disorders; 2) Characterize long-term trajectory of imaging biomarkers in brain-injured and control subjects ("MRI Cohort") using DTI, rs-fMRI, and high-resolution structural studies; 3) Characterize long-term trajectories of neurocognitive/psychological function and their relationship to e.g., plasma-CSF proteomic markers related to inflammation and neurodegeneration, and imaging; 4) Apply PET imaging to characterize prevalence and extent of Aβ plaques and neurofibrillary tangles in a subset of the MRI Cohort age >50y; 5) Apply traditional and novel neuroimaging-guided and quantitative neuropathologic approaches to donated brains to interrogate TBI-associated structural and biological changes correlated with antemortem phenotyping.
Overlap:	None

Title:	Co-Design for Artificial Intelligence Coupled with Computing at Scale for Extremely Large, Complex Datasets (A131066)
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Time Commitment:	0.60 calendar months
Support Agency:	Lawrence Livermore National Laboratory
Grants Officer:	Gary M. Ward, LLNS Contract Analyst Telephone: (925)-423-5952 Email: ward31@llnl.gov
Performance Period:	05/01/2018 – 09/30/2020
Total Costs of the Project:	\$730,000
Project Goals:	The overall objective of this collaborative project is to develop and demonstrate a “cognitive simulation” approach that tightly couples artificial intelligence, simulations, and computing at scale with extremely large datasets and pilot it to the specific challenge of learning actionable insights from growing complex Traumatic Brain Injury (TBI) datasets. Longer term, this will serve as a premier platform and test bed to develop and demonstrate scalable scientific machine learning approaches and tools suited for the analysis of extremely large, highly complex and uncertain datasets, including other TBI, VA and UCSF data.
Specific Aims:	1) establish enclaves capable of securely handling sensitive data and to perform data management. 2) to develop and perform new classes of scalable analytics on provided pilot TRACK-TBI data 3) to run analysis experiments at multiple DOE sites and generation of actionable insights for TBI.
Overlap:	None

Title:	Subrecipient PI: 010376-002 / W81XWH-16-2-0020 Development and Validation of Spreading Depolarization Monitoring for TBI Management (SDII) (A129063)
Time Commitment:	0.12 calendar months
Support Agency:	University of Cincinnati (Subaward)
Grants Officer:	Katherine Carey, Senior Accountant Telephone: (513)-558-3915 Email: careyk@ucmail.uc.edu
Performance Period:	09/15/2016 – 09/14/2019
Total Costs of the Project:	\$509,075
Project Goals:	The objective of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Research Collaboration Policy is to establish a framework to support the conduct of collaborative research projects involving the TRACK-TBI Investigators, the TRACK-TBI Dataset, and external parties
Specific Aims:	1) Permit more accurate disease / condition diagnosis 2) Identify patient subpopulations likely to benefit from therapy / intervention, and 3) Provide refined outcome assessments to confirm efficacy
Overlap:	None

Title:	Co-Investigator: Clinical Center of Excellence in Spinal Cord Injury: TRACK-SCI (A128168)
Time Commitment:	0.06 calendar months
Support Agency:	Craig H. Neilsen Foundation
Grants Officer:	Tracey Wheeler Telephone: 517-281-3018 Email: tracey@chnfoundation.org
Performance Period:	09/30/2016 – 09/29/2021
Total Costs of the Project:	\$1,000,000
Project Goals:	This project will provide new data for driving evidence-based recommendations and guidelines for the treatment of acute SCI. The ultimate aim is to provide a sustainable, coordinated network of trauma centers with shared SCI treatment guidelines capable of providing high quality data on SCI patients from admission through rehab and community integration.
Specific Aims:	1) To prepare practice guidelines based on our retrospective and prospective datasets and evolving best practices and submit application for certification. 2) To expand and solidify our clinical research effort and infrastructure at the Brain and Spinal Injury Center at ZSFG 3) To disseminate Joint Commission approved ZSFG practice guidelines to our affiliates trauma centers 4) Begin enrolling patients at these additional network centers in the TRACK SCI database/ registry. 5) Improve our ability to track SCI patients to and through discharge, rehabilitation and community placements by strengthening our collaborations with Laguna Honda Hospital and Santa Clara Valley Medical Center.
Overlap:	None

Title:	PI: U01NS086090 Transforming Research and Clinical Knowledge in Traumatic Brain Injury (A127834)
Time Commitment:	0.60 calendar months
Support Agency:	NIH National Institution Neurological Disord and Stroke
Grants Officer:	Aaron Kinchen, Grants Management Officer P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-451-7966 Email: aaronkinchen@ninds.nih
Performance Period:	05/16/2016 – 08/31/2020
Total Costs of the Project:	\$7,657,982
Project Goals:	TRACK-TBI is built from the foundational NINDS-funded TRACK-TBI Pilot study, which collected clinical data from 3 sites and 600 subjects. With over a dozen publications and growing, the TRACK-TBI Pilot dataset is the first to populate the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository and with

	the current TRACK-TBI data, is compatible with the International Initiative for Traumatic Brain Injury Research (InTBIR), a collaborative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR) and the National Institutes of Health (NIH). TRACK-TBI also forms one of the core datasets of the Department of Defense-funded TBI Endpoints Development (TED) Initiative, which has established an interrogatable Metadataset of high quality studies across civilian, sports, and military populations. TED's goals, aligned with TRACK-TBI, are to identify and validate the FDA regulatory readiness of candidate clinical outcome assessments and proteomic and neuroimaging biomarkers and technologies that may serve as endpoints in the design of precision clinical trials.
Specific Aims:	1) Improve TBI classification/taxonomy for targeted clinical treatment trials 2) Improve TBI outcome assessments, such that the size and costs of clinical trials can be reduced 3) Identify the health and economic impact of Mild TBI patient disposition 4) Create a legacy database with analytic tools and resources to support TBI research
Overlap:	None

Title:	PI: TRACK-TBI biospecimen collection and transfer (A124817)
Time Commitment:	Effort as needed
Support Agency:	Abbott Laboratories
Grants Officer:	Beth A. Schodin, PhD., Manger, Global Scientific Affairs Abbott Diagnostics 100 Abbott Park Road Dept 09AA/CPI-5 Abbott Park, IL 60064 Telephone: (224)-668-1020 Email: Beth.Schodin@abbott.com
Performance Period:	12/18/2014 – 12/18/2021
Total Costs of the Project:	\$2,656,000
Project Goals:	The TRACK-TBI Investigators will add an additional blood collection as well as tubes to the study and provide them to Abbott for use in the TBI Biomarker program
Specific Aims:	1) Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) is an ongoing study that aims to create a large, high quality database that integrates clinical, imaging, proteomic, genomic and outcome biomarkers to establish more precise methods for TBI diagnosis and prognosis, refine outcome assessment, and compare the effectiveness and costs of TBI care.
Overlap:	None

Title:	PI: W81XWH-14-2-0176 TBI Endpoints Development (TED) (A124306)
Time Commitment:	1.20 calendar month

Support Agency:	U.S. Department of Defense
Grants Officer:	Susan Dellinger, Grant Officer USA Med Research ACQ Activity 820 Chandler Street, Fort Detrick, MD 21702-5014 Telephone: (301)-619-2090 Email: susan.m.dellinger.civ@mail.mil
Performance Period:	09/30/2014 – 09/29/2020
Total Costs of the Project:	\$17,109,805
Project Goals:	To identify and validate candidate COAs and biomarkers for future DDT qualification.
Specific Aims:	1) AIMS: Stage I (Years 1-2) Technical 2) Objective 1: Establish a collaborative, multidisciplinary team to advance the identification and validation of clinical outcome assessments (COAs) and biomarkers for use as potential FDA-qualified drug development tools (DDTs), and initiate development of CDISC data standards for trials involving diagnosis and treatment of mTBI to modTBI. 3) Stage II (Years 3-5) Technical Objective 2: Validate candidate COAs and biomarkers selected in Stage I, leveraging the existing research infrastructure and clinical study networks of TRACK-TBI, CENC and CRC for potential qualification as DDTs.
Overlap:	None

Title:	PI: Supplemental Funding for TRACK TBI (A123381)
Time Commitment:	Effort as needed
Support Agency:	One Mind for Research, Inc.
Grants Officer:	Joan Demetriades One Mind for Research Inc. 120 Lakeside Avenue, Suite 100 Seattle, WA 95122 Telephone: (206)-457-8400 Email: joan.demetriades@onemind.org
Total Costs of the Project:	03/01/2014 – 08/31/2019
Level of Funding:	\$421,049
Project Goals:	This grant is designed to supplement the research of the TRACK-TBI U01 NS086090 study
Specific Aims:	1) To supplement the TRACK TBI study by providing funds for patient stipend payments and travel reimbursements 2) To accelerate the data curation for FDA submission
Overlap:	None

Title:	Subrecipient PI: Center-TBI: Collaborative European NeuroTrauma Effectiveness Research in TBI (A122281)
Time Commitment:	0.12 calendar months

Support Agency:	Antwerp University Hospital subcontract (PI: Andrew Maas) European Commission 7th Framework Programme (PI: Maas)
Grants Officer:	Annina Sorgner, International Projects Management CABO; milliarium mbH & Co. KG Oskar-von-Miller-Ring 29, D-80333 Munich Telephone: (49)-89-288-104-22 Email: annina.sorgner@gabo-mi.com
Performance Period:	10/01/2013 – 03/31/2020
Total Costs of the Project:	\$161,375
Project Goals:	UCSF will contribute to this international effort through participation in the management committee, harmonizing data collection forms, and by facilitating collaboration with TRACK-TBI. CENTER-TBI aims to advance the care for patients with traumatic brain injury (TBI), a field in medicine with one of the greatest unmet needs. The project will be based upon a prospective longitudinal data collection in 60 centres from 20 countries including approximately 6000 patients (CENTER-TBI Core Study). Data will be collected from ictus up to 2 years after injury, thus bridging the acute and post-acute care phases. The core study cohort will include detailed data on the entire clinical course on injury details, treatment, outcome and health costs.
Specific Aims:	1) Moreover, information on provider profiles will be captured. These data sets will be subjected to extensive analyses aimed at improving characterization of injury and outcome and 2) 2) identify the most effective (and cost-efficient) clinical interventions taking into consideration the type of brain injury and the history of the TBI patient (comparative effectiveness research, CER).
Overlap:	None

PENDING

Title:	Co-design of Advanced Artificial Intelligence (AI) Systems for Predicting and Understanding Perturbations to Complex Systems (PI: Manley)
Time Commitment:	0.60 calendar months
Support Agency:	Lawrence Livermore National Laboratory
Grants Officer:	Gary M. Ward, LLNS Contract Analyst Telephone: (925)-423-5952 Email: ward31@llnl.gov
Performance Period:	10/1/2019 – 09/30/2022
Total Costs of the Project:	\$600,000
Project Goals:	UCSF investigators will provide access to TRACK-TBI Pilot and TRACK-TBI U01 database including clinical, imaging and outcome data along with supporting documentation, neurotrauma/TBI subject matter expertise, guidance on standard analysis methods, as well as current knowledge and collaborative research activities to carry out as necessary, analyze and interpret data.
Overlap:	None

Title:	Transforming Research And Clinical Knowledge in Geriatric Traumatic Brain Injury (TRACK-GERI) (PI: Gardner)
Time Commitment:	0.30 calendar months
Support Agency:	NIH/NINDS
Grants Officer:	TBD
Performance Period:	07/01/2019 – 06/30/2024
Total Costs of the Project:	\$3,859,042
Project Goals:	The goals of this project are to launch a new prospective geriatric TBI cohort in order to identify age-appropriate TBI predictors, outcomes, and blood biomarkers in order to inform evidence-based clinical care and clinical trials in this population.
Overlap:	None

Title:	A translational evaluation of Sur1-Trpm4 imaging endophenotypes and genetics to direct precision medicine for cerebral edema after traumatic brain injury (PI: Jha)
Time Commitment:	0.24 calendar months
Support Agency:	University of Pittsburgh (NIH Prime)
Grants Officer:	TBD
Performance Period:	04/04/2020 – 03/31/2025
Total Costs of the Project:	\$311,625
Project Goals:	To explore the genetic variability in the SUR1 pathway on metrics of cerebral edema, contusion expansion, intracranial hypertension and outcome.
Overlap:	None

Title:	Biomarkers in the Hyperbaric Oxygen in Brain Injury Trial (PI: Korley)
Time Commitment:	0.5 calendar months
Support Agency:	University of Michigan (NIH prime)
Grants Officer:	TBD
Performance Period:	07/01/2020 – 06/30/2025
Total Costs of the Project:	\$148,450
Project Goals:	UCSF investigator will provide access to data from severe TBI subjects enrolled in TRACK-TBI for the purposes of creating prognostic models for predicting outcomes in TBI; direct the harmonization of data from TRACK-TBI, Bio-BOOST and Bio-HOBIT, and guide the interpretation and analysis of data obtained from the TRACK-TBI cohort.
Overlap:	None

Title:	TRACK-TBI Epileptogenesis Project (PI: Diaz-Arrastia)
Time Commitment:	0.27 calendar months
Support Agency:	University of Pennsylvania (DOD USAMRAA prime)
Grants Officer:	TBD

Performance Period:	04/01/2019 – 03/31/2023
Total Costs of the Project:	\$201,896
Project Goals:	To efficiently integrate extended follow-up evaluation and study of existing and prospective subjects in the TRACK-TBI study
Overlap:	None

Title:	Analytical Validation of Tau and P-Tau as acute and subacute prognostic biomarkers for complicated mild TBI (PI: Wang)
Time Commitment:	1.20 calendar months
Support Agency:	NIH
Grants Officer:	TBD
Performance Period:	04/01/2020 – 03/31/2025
Total Costs of the Project:	\$350,000
Project Goals:	UCSF investigators will collect and organize a subset of archived clinical subjects and biosamples from TRACK-TBI study and provide clinical data, including data on CT and MRI.
Overlap:	None

Title:	CONNECT-TBI (PI: Smith/Steward)
Time Commitment:	0.45 calendar months
Support Agency:	University of Pennsylvania (NIH prime)
Grants Officer:	TBD
Performance Period:	09/01/2019 – 08/31/2024
Total Costs of the Project:	\$188,410
Project Goals:	UCSF investigators will collaborate with Drs. Smith, Stewart, and the rest of the CONNECT-TBI team and contribute to the project by providing access to data from severe TBI subjects enrolled in TRACK-TBI, as well as examining the clinical information in the database for potential correlations with the neuropathology findings, and participating in further comparisons as additional cases are added and the diagnostic criteria (e.g., CTE vs. AD) are clarified.
Overlap:	None

PREVIOUS (within the last 5 years)

Title:	Subrecipient PI: 0043845-1 / W911QY-14-C-0070 Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) - High Definition Fiber Tracking Neuroimaging, Biospecimen and Data Informatics Repositories (A124574)
Time Commitment:	0.12 calendar months
Support Agency:	The University of Pittsburgh
Grants Officer:	Heather Bragg Office of Research

	123 University Place R21 UCLUB / Lower Lobby Pittsburgh, PA 15213-2303 Telephone: (412)-624-7009 E-mail: hmb30@pitt.edu
Performance Period:	09/05/2014 – 09/04/2019
Total Costs of the Project:	\$787,065
Project Goals:	To build a legacy database with analytic tools and resources to support the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) initiative. This will be accomplished by the creation of a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research. The Bioinformatics Core will submit TRACKTBI data into the Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR). Utilizing TBI-Common Data Elements (CDEs), along with uniform standards for acquiring multi-site MRI data, the TRACK Information Commons will serve as a resource for current and future TBI research and international collaborations.
Specific Aims:	1) Deliverable 1: Develop Data Management Plan for TRACK Repository. We will develop an integrated data management plan across the Cores for data quality control and quality assurance. This will involve convening Core leaders via conference calls and in-person meetings to determine priorities and resources for harmonization of data across Cores. 2) Deliverable 2: Implementation of Data Management Plan. As subject enrollment is ongoing during the 4-year project period, there will be extensive ongoing efforts to 3) clean and curate the datasets across the Cores at baseline enrollment and again at each milestone. 4) Deliverable 3: Submission of Baseline Data to FITBIR. Data will be prepared for end users, and ultimate mapping and migration of TRACK-TBI data into the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system. Core and Basic data will be submitted on a quarterly schedule for a total of 3,000 subjects. 5) Deliverable 4: Provide Technical Support to Users. As an "Information Commons" a goal of TRACK-TBI is to promote the sharing of data among investigators and to all qualified and approved researchers as determined by the Data Access and Quality Committee. The Informatics Repository will manage requests associated with Data Use Agreements to provide access to and training on the tranS MART platform for conducting analysis. The Informatics Repository team will also serves as a "help desk" for the collaborators and clinical study sites to address technical problems and other requests.
Overlap:	None

Title:	Co-Investigator: Early Critical Care Decisions and Outcomes after SCI: Track-SCI (A127941)
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Time Commitment:	0.24 calendar months
Support Agency:	DoD US Army Med. Res.
Grants Officer:	Christopher Meinberg Telephone: 301-619-2657 Email: christopher.l.meinberg.civ@mail.mil
Performance Period:	08/15/2016 – 08/14/2019
Total Costs of the Project:	\$2,376,474
Project Goals:	The objective of this proposal is to understand the critical care practices and outcomes for SCI patients and to build a knowledge network for acute SCI.
Specific Aims:	1) Diagnosis: Building a knowledge network for acute SCI 2) Prognosis: Predictive models and biomarkers 3) Data analysis and sharing
Overlap:	None

Title:	Co-Investigator: U10NS058931 SF-NETT: San Francisco Neurological Emergencies Trials Network (A127796)
Time Commitment:	0.12 calendar month
Support Agency:	NIH National Institution Neurological Disord and Stroke
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/01/2012 – 07/31/2017
Total Costs of the Project:	\$305,651
Project Goals:	National Institute of Neurological Disorders cooperative grant to create a hub-spoke hospital network from which to conduct streamlined phase III clinical trials testing new treatments for neurological emergencies such as status epilepticus, traumatic brain or spinal injury, and stroke.
Specific Aims:	1) To continue high-volume enrollment of research subjects in multiple acute phase III neurological emergency clinical trials using a scalable hub-spoke hospital system and a multidisciplinary group of acute care investigators; 2) 2) To utilize SF-NETT as a platform for junior emergency medicine physicians to participate in neurological emergency clinical trials as part of an academic career development pathway; 3) 3) To enhance the participation of underserved minorities in clinical trials of new treatments for neurological emergencies
Overlap:	None

Title:	Co-Investigator: R01NS067092 Bioinformatics for Translational Spinal Cord Injury (SCI) (A114558)
Time Commitment:	0.12 calendar month
Support Agency:	National Institute of Health

Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	05/01/2010 – 04/30/2017
Total Costs of the Project:	\$1,644,785
Project Goals:	The major goal of this project is to pool data from several laboratories and make cross-species comparisons to identify common metrics of SCI that can be used for evaluating mechanisms of SCI that translate across species.
Specific Aims:	1) Build a pooled database of existing experimental rodent and primate SCI research data to provide a platform for knowledge discovery and multivariate quantification of translational features across diverse outcomes and experimental models. We will start with data from 5 major SCI research centers to provide a framework for later contributions from other research groups. 2) Identify syndrome measures in rodent SCI models, using the same multivariate techniques often used by clinical researchers to define and measure complex disease states. 3) Identify which multivariate outcome patterns in rodent models are most sensitive to the effects of graded injury and which are most sensitive to change over time, with the goal of improving sensitivity and streamlining testing of therapeutic interventions. 4) Identify which multivariate outcome patterns in non-human primates are most sensitive to the effects of SCI and recovery over time, providing important information about the most sensitive outcomes for therapeutic testing in this valuable preclinical model. 5) Make translational multivariate comparisons of rodent and primate SCI data to identify which outcome patterns best translate across experimental models and which are species- and model-specific, setting the stage for future multivariate comparisons to human data.
Overlap:	None

Title:	CO-Investigator: R21NS087458 Contribution of infiltrating macrophages on synaptic function after TBI (A123947)
Time Commitment:	0.12 calendar month
Support Agency:	National Institute of Health
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/01/2014 – 08/31/2016
Total Costs of the Project:	\$435,250

Project Goals:	We will gain critical and novel information in regard to the contribution of peripheral macrophage accumulation in the pathogenicity of TBI-induced neuroinflammation and potentially a novel therapeutic target and optimal time point for its treatment
Specific Aims:	1) Will examine if genetic and pharmacological deletion of CCR2 signaling ameliorates TBI-induced synaptic and cognitive dysfunction. TBI will be induced using controlled cortical impact on both wild type and CCR2RFP/RFP mice. We will examine hippocampal-dependent cognitive function as well as homeostatic synaptic function, 28 days after injury. Preliminary studies indicate that CCR2 deletion abrogates TBI-induced hippocampal cognitive dysfunction compared to WT mice. 2) Will determine the temporal kinetics and inflammatory profile of TBI-induced Ly6ChiCCR2+ monocytes/macrophages into the brain parenchyma. TBI will be induced as in Aim 1 except using CX3CR1+/GFPCCR2+/RFP mice. Multiple time points following injury will be examined to include acute, subacute, and chronic phases. Preliminary data shows that 48 hours after injury, TBI-treated mice had a significant increase in macrophage infiltration and that a specific subset of those resembled resident microglia.
Overlap:	None

Title:	PI: Manley, Geoffrey Codman Neuro Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) (A126352)
Time Commitment:	Effort as needed
Support Agency:	Codman Neuro
Grants Officer:	Worldwide Director of Clinical Research Codman Neuro, a division of DePuy Orthopaedics, Inc. Clinical Research Department, MS34 325 Raynham, MA 02767 Telephone: (508)-880-8274 Email: RA-DPYUS-ClinRsrCod@its.jnj.com
Performance Period:	10/16/2015 – 02/16/2016
Total Costs of the Project:	\$64,400
Project Goals:	TRACK-TBI is built from the foundational NINDS-funded TRACK-TBI Pilot study, which collected clinical data from 3 sites and 600 subjects. With over a dozen publications and growing, the TRACK-TBI Pilot dataset is the first to populate the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository and with the current TRACK-TBI data, is compatible with the International Initiative for Traumatic Brain Injury Research (InTBIR), a collaborative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR) and the National Institutes of Health (NIH). TRACK-TBI also forms one of the core datasets of the Department of Defense-funded TBI Endpoints Development (TED) Initiative, which has established an interrogatable Metadataset of high quality studies across civilian, sports, and military populations. TED's goals, aligned with TRACK-TBI, are to identify and validate the FDA regulatory readiness of candidate clinical outcome assessments and proteomic and

	neuroimaging biomarkers and technologies that may serve as endpoints in the design of precision clinical trials.
Specific Aims:	1) Improve TBI classification/taxonomy for targeted clinical treatment trials 2) Improve TBI outcome assessments, such that the size and costs of clinical trials can be reduced 3) Identify the health and economic impact of Mild TBI patient disposition 4) Create a legacy database with analytic tools and resources to support TBI research
Overlap:	None

Title:	PI: W81XWH-13-1-0441 Transforming Research and Clinical Knowledge in Traumatic Brain Injury (A122361)
Time Commitment:	0.84 calendar month
Support Agency:	U.S. Department of Defense
Grants Officer:	Dana Herndon, Contracting Officer USA MED Research MAT CMD 1077 Patchel Street Bldg 1056 Fort Detrick, MD 21702 Telephone: (301)-619-7140 Email: dana.l.herndon.civ@mail.mil
Performance Period:	09/26/2013 – 09/25/2016
Total Costs of the Project:	\$1,463,453
Project Goals:	The major goals of this project are to determine an imaging phenotype for TBI; validate and develop prognostic and diagnostic models using the TBI Common Data Elements; and identify proteomic and genomic associations with TBI phenotypes from the patients enrolled into the TRACK TBI study at UCSF, University of Pittsburg, Mt. Sinai and University of Texas, Austin
Specific Aims:	1) To develop improved prognostic, diagnostic and outcome models for TBI; 2) To identify neuroimaging biomarkers for diagnosis and prognosis in TBI; 3. To identify proteomic and genomic associations with TBI phenotypes
Overlap:	None

Title:	PI: U01NS086090 Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI) (A122283)
Time Commitment:	2.26 calendar month
Support Agency:	NIH National Institution Neurological Disord and Stroke
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/30/2013 – 08/31/2016

Total Costs of the Project:	\$9,687,014
Project Goals:	The goal of this multicenter study is to create a high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers for 3,000 patients that will be enrolled across the spectrum of mild to severe TBI. Analytic tools will be developed to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services.
Specific Aims:	1) To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research; 2) To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI; 3) To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity; 4) To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.
Overlap:	None

Title:	Subreceipt PI: T062576 ProTECT III (A113421)
Time Commitment:	1.20 calendar month
Support Agency:	Emory University NIH (U01NS062778) (PI: David Wright)
Grants Officer:	Claire French, Office of Sponsored Programs 1599 Clifton Road NE, 4 th Floor 1599-001-1BA Atlanta, GA 30322 Telephone: (404)-727-4054 Email: cvfrenc@emory.edu
Performance Period:	07/01/2009 – 06/30/2014
Total Costs of the Project:	\$157,449
Project Goals:	The major goal of this multicenter Phase III clinical trial is to determine the efficacy of administering intravenous (IV) progesterone (initiated within 4 hours of injury and administered for 72 hours, followed by an additional 24 hour taper) versus placebo for treating victims of moderate to severe acute traumatic brain injury.
Specific Aims:	1) The Clinical Standardization Team will examine and refine the goal directed therapy protocols for ProTECT III at all the NETT sites; 2) Oversee the implementation of these protocols; 3) Monitor compliance with the protocols and 4) Resolve any issues related to real or perceived variability in neurological treatment.

Overlap:	None
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Title:	Co-PI: R21AG042016-01A1 Effects of traumatic brain injury on hippocampal network activity: age difference (A121632)
Time Commitment:	0.14 calendar months
Support Agency:	National Institute of Health
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/01/2012 – 08/31/2014
Total Costs of the Project:	\$432,834
Project Goals:	From these studies we will establish the role and the effect of age on the progression of TBI-related cognitive impairments from a behavioral, cellular and network prospective.
Specific Aims:	1) Identify the dynamics of the post transcriptional infrastructure of gene expression involved in synaptic plasticity and memory after TBI in behaviorally characterized young and old mice; 2) 2) determine how age at the time of TBI affects hippocampal networks mediating contextual and spatial information processing
Overlap:	None

Title:	Co-Investigator R01 NS060776 Macrostructural and Microstructural Imaging Biomarkers of Traumatic Brain Injury (A112322)
Time Commitment:	0.24 calendar months
Support Agency:	National Institutes of Health
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	07/15/2009 – 06/30/2014
Total Costs of the Project:	\$1,761,547
Project Goals:	The major goals of this project are to establish quantitative macrostructural and microstructural imaging biomarkers for predicting patient outcome after TBI.
Specific Aims:	1) The hypothesis will be tested that increasing spatial extent of progressive focal atrophy detected by DBM of serial MRI and/or progressive white matter microstructural injury on serial DTI is correlated with worse neurocognitive and functional outcomes at one year after injury, after controlling for clinical measures of injury severity including Glasgow Coma Scale, duration of unconsciousness, and duration of post-traumatic amnesia. These macrostructural and microstructural imaging biomarkers will also be correlated with functional and metabolic imaging data using fMRI and 3D MR

	spectroscopic imaging, respectively. If the proposed investigation is successful in establishing these quantitative macrostructural and microstructural imaging biomarkers of long-term outcome in TBI, then they could potentially serve as surrogate endpoints for clinical intervention trials. They might also yield endophenotypes for studies of genetic susceptibility factors that worsen outcome after TBI. Towards this purpose, DNA will be banked from patients in this study for genotype analysis. Specifically, we will examine whether ApoE genotype influences the degree of regional brain atrophy and microstructural white matter injury. The allelic variants of ApoE are already known to modulate clinical outcome after TBI, and this study will determine if DBM and DTI can provide "intermediate phenotypes" for the effect of ApoE genotype on TBI outcome.
Overlap:	None

Title:	Co-Investigator: Sanofi-Aventis Collaboration with UCSF on Traumatic Brain Injury (TBI) (A119072)
Time Commitment:	0.12 calendar months
Support Agency:	Sanofi-Aventis
Grants Officer:	Marie-Noelle Castel 185 Berry Street, San Francisco, CA 94107 Telephone: (415)-856-5000 Email: Marie-Noelle.Castel@sanofi.com
Performance Period:	11/28/2011 – 06/30/2014
Total Costs of the Project:	\$171,662
Project Goals:	The major goal of this project is to study effects of SAR127963 on proNGF versus LPS-induced Tumor Necrosis Factor production in whole blood and peripheral blood monocytes in healthy volunteers and TBI patients.
Specific Aims:	1) Ex-vivo human assay to test the effects of SAR127963 on proNGF versus LPS-induced TNF production in the whole blood and by Peripheral Blood Monocytes from healthy volunteers and Trauma brain injury patients.
Overlap:	None

Title:	Co-Investigator: W81XWH-13-1-0297 Effects of Early Acute Care on Autonomic Outcomes in SCI: Bedside to Bench and Back (A122126)
Time Commitment:	0.12 calendar month
Support Agency:	U.S. Department of Defense
Grants Officer:	Susan Dellinger, Grant Officer USA Med Research ACQ Activity 820 Chandler Street, Fort Detrick, MD 21702-5014 Telephone: (301)-619-2090 Email: susan.m.dellinger.civ@mail.mil
Performance Period:	09/30/2013 – 09/29/2016

Total Costs of the Project:	\$1,108,987
Project Goals:	The objective of this proposal is to understand the role of cardiovascular variables in the recovery process after acute spinal cord injury using clinical data to model the range of variations, then testing methods to determine the how to achieve the best outcome
Specific Aims:	1) Examine the available evidence for a correlation between early BP management and vasopressor use, and later outcomes, including outcomes on autonomic, bladder and bowel function; 2) Provide detailed reports and physiological monitoring in the ED and ICU to identify cardiovascular parameters and (events) during early management of SCI that may be associated with poor outcome, including bowel and bladder function; 3) Determine the effects of episodes of hypotension and hypertension on the recovery of locomotor, bladder and bowel function in our rat model of high thoracic contusion SCI.
Overlap:	None

Title:	PCORI: ME-1306-02735 Semiparametric Causal Inference Methods for Adaptive Statistical Learning in Trauma Patient-Centered Outcomes Research (A123709)
Time Commitment:	0.12 calendar month
Support Agency:	University of California, Berkeley/PCORI
Grants Officer:	Deborah Howard University of California, Berkeley Berkeley, CA 94720 Telephone: (510)-642-6000 Email: subcontracts@berkeley.edu
Performance Period:	04/01/2014 – 08/31/2016
Total Costs of the Project:	\$266,396
Project Goals:	Combine the expertise physicians/surgeons in critical care facilities, along with computational biostatistics to develop methods for targeting patient-centered parameter estimation.
Specific Aims:	1) To leverage new advances in statistical theory for creating real-time decision-tools calibrated for individual patients based on their characteristics, which can provide continuously updated prognosis information along with estimated outcomes of potential treatment decisions.
Overlap:	None

MCCREA, MICHAEL**ACTIVE**

W81XWH-14-2-0176 (Manley) 10/1/14-9/30/20 0.60 calendar months
 CDMRP \$665,955
 TBI Endpoints Development (TED)

The goal of this project is to validate candidate endpoints and improve clinical trial design to inform and accelerate FDA approval of diagnostic tools and therapeutic agents for TBI.

W81XWH-18-DMRDP-PTCRA (Manley) 9/30/18-9/29/20 0.60 calendar months
 CDMRP \$88,165
 TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies

This project will utilize the existing TRACK-TBI infrastructure to develop and validate imaging and biofluid-based protein markers that can serve as (i) prognostic biomarkers (to identify patients at risk of poor outcome), (ii) predictive biomarkers (to identify patients likely to respond to particular therapies), or (iii) pharmacodynamic biomarkers (to demonstrate that a biologic response has occurred following therapeutic intervention).

GRANT12443726 (McCrea, Wang) 4/1/19-3/31/24 0.24 calendar months
 NIH/NINDS \$483,597
 Longitudinal Evaluation of Changes in Brain Structure & Function after Exposure to Subconcussive Impacts
 The goal of this research is to combine biomechanical and neuroimaging metrics to identify key pathophysiological processes underlying brain alterations due to repetitive subconcussive impacts, and develop in vivo measurements of the effects of recurrent impacts during contact sports.

BA170608 (Broglio, McAllister, McCrea) 2 years 4.80 calendar months
 USAMRMC and NCAA (Subcontract with IU-CARE 2.0) \$7,737,972
 Cumulative and Persistent Intermediate Effects of Concussion and Head Impact Exposure in CARE Consortium Military Service Academy Members and NCAA Athletes
 The goal of this proposal is to answer three critical questions related to the intermediate-term effects of concussion and/or repetitive head impact exposure in MSA cadets and NCAA student-athletes.
 Specific Aims

GRANT12407777 (Thomas) 4/1/18-3/31/22 0.12 calendar months
 Center for Disease Control (CDC) \$388,043
 Active Injury Management (AIM) after Pediatric Concussion in Adolescents

The objective of the current proposal is to determine the benefit of prescribed low intensity physical activity, behavioral management, or both, versus standard initial (24-48 hrs) rest in acute mTBI patients presenting to the pediatric Emergency Department.

--- Manley (McCrea Site PI) 07/01/2017 – 08/31/2019 0.6 cal. Months
 National Football League Foundation
 Title: TRACK LONG
 Goal: This clinical trial is being conducted to further elucidate TBI's natural history, identify those individuals most at risk for unfavorable outcomes, and lead to the development of diagnostic, prognostic, and therapeutic/management tools for this heterogeneous condition.

--- (Meehan) 10/31/17-10/30/19 1.8 months
 National Football League (Subcontract with BCH – NFL LONG) \$4,035,768
 Neurologic Function across the Lifespan: A Prospective, LONGitudinal, and Translational Study for Former National Football League Players: NFL-LONG

--- Manley (McCrea Site PI) 09/14/2018 – 08/31/2019 0.6 cal. Months
Medical Technology Enterprise Consortium \$197,953
Title: Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)
Goal: This project is to analyze patient phenotyping and outcome assessment.

--- (Register-Mihalik, Guskiewicz, McCrea) 5/1/16-4/30/20 0.24 calendar months
National Football League (UNC) \$787,865
Role of Rehabilitation in Concussion Management: A Randomized, Controlled Trial

The goal of this project is to conduct a randomized clinical trial to yield preliminary data on the added benefits of active rehabilitation during recovery after SRC in professional and amateur athletes.

W81XWH-17-1-0019 Stemper (McCrea Investigator) 11/01/2018 – 10/31/2019 0.12 cal. months
DOD Department of Defense
Title: Human Head Impact Dose Concussion Risk Functions and Sensor-Based Military-Specific Environmental Monitoring System (Prevent)
Goal: to expand on data from the Head Impact Measurement Core of the CARE Consortium collection for other contact sports and military training activities, perform additional repetitive head impact exposure (RHIE) characterization in concussed football athletes, and perform repeated clinical assessments in non-concussed military personnel, cadets, and civilian athletes to characterize the dose relationship for clinical changes in non-concussed individuals and injury risk functions for the onset of concussion.

Previous

--- (McCrea, Guskiewicz) 7/1/13-6/30/19 (NCE)
National Collegiate Athletic Association (NCAA) \$74,331
A Prospective, Longitudinal Study of Head Impact Exposure, Neurologic Health and Brain Imaging Biomarkers in Former NCAA Athletes: 15 Year Follow-Up of the Original NCAA Concussion Study

This prospective, longitudinal study will answer the critical question of whether participation in collegiate contact sports or prior concussion exposure is associated with the risk of developing poor health outcomes in former college athletes.

5R44HD090763-02 Stemper (McCrea Co-I) 03/01/2018 – 10/31/2019
NIH Child Health and Human Development - Advanced Medical Electronics Corp. \$258,023.00
Title: Correlation of Head Impact Exposure in High School Athletics with Clinical Changes and Concussion
Goal: The goal is to show that repetitive head impact exposure (RHIE) may be a second mechanism of concussion for athletes in contact sports.

----- McCrea (PI) 4/1/14-8/6/19
NFL-GE Head Health Challenge
A Prospective Study of Advanced MRI Biomarkers to Determine Acute Physiological Effects and Longitudinal Recovery after Sport-Related Concussion

This project aims to further characterize and validate noninvasive, quantitative neuroimaging biomarkers of acute physiological effects and longitudinal physiological recovery after sport related concussion.
Role: Principal Investigator

U0-1NS086090 (Manley) 9/1/16-8/31/19
NIH/NINDS \$125,000
Transforming Research and Clinical Knowledge in TBI (TRACK TBI-UCSF)

TRACK-TBI will create a large, high quality database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers to establish more precise methods for TBI diagnosis and prognosis, refine outcome assessment, and compare the effectiveness and costs of TBI care.

W81XWH-14-1-0561 (McCrea)

9/30/14-9/29/19

U.S. Army MRMC (Head to Head) \$6,158,636

Comprehensive Study of Acute Effects and Recovery after Concussion: An Integrated Investigation of Head Impact Sensor Technology, Blood Biomarkers, Advanced Neuroimaging, Genetic Testing and Clinical Outcome Metrics

This goal of this study is to conduct a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as pre-injury function (e.g. cognitive, behavioral, and psychosocial function, genotype), injury biomechanics and dynamics (e.g. mechanism, severity, frequency, associated injury), immediate post-injury characteristics (e.g. acute biological, structural and functional markers), and longitudinal follow-up (e.g. true natural history of biological, physiological and clinical recovery).

-- (McCrea, Klein)

11/30/15-1/20/19

GE Healthcare & Abbott Laboratories (Clinical Trial) \$408,005

Advanced MRI Applications for Mild Traumatic Brain Injury (mTBI) & Blood Biomarker Candidate Study for Mild Traumatic Brain Injury

This clinical trial is being conducted for hypothesis generation in population of mild traumatic brain injury (mTBI) patients using advanced applications for magnetic resonance imaging (MRI) and corresponding clinical neuropsychological assessments. The purpose of the companion blood biomarkers trial is to measure potential blood-based biomarkers of mild traumatic brain injury and evaluate associations with clinical data, neurocognitive testing, and magnetic resonance imaging data.

--- (Wang)

2/1/17-1/31/19

Advancing a Healthier Wisconsin – Research and Education Program \$100,000

Assessing Cerebrovascular Alterations During Recovery After Sports-Related Concussions (SRC)

The overarching goal of this proposal is to advance our knowledge of the window of cerebral vulnerability by identifying key neurophysiological mechanisms underlying brain recovery after SRC and develop objective imaging assessments to accurately assess these changes over time.

PENDING

None

OVERLAP

No overlap with any of the listed grants

UPDATED EXISTING AND PENDING SUPPORT

OKONKWO, D.O.

EXISTING

R44-HD090817 (Southern/Griffin/Peacock/Puccio) 08/15/17 – 07/31/20 0.12 calendar (1.00%)
GAIA Medical Institute via NIH PRIME \$200,000 (No Cost Extension)

Rapid Saliva Test for Diagnostics of Neuro-Cognitive Disorder Due to TBI (NCDT)

The ultimate goal of this project is to develop a rapid saliva test for diagnostics of post-concussive disorder (PCD).

Agency Point of Contact Name/Address

Griffen C Stapp
GAIA Medical Institute, LLC
505 Coast Blvd. South
La Jolla, CA 92037-4616

List of the specific aims:

1. Specific Aim 1 will collect N=2,610 longitudinal saliva samples from N=500 patients (N=120 NCDT, N=230 mTBI without NCDT, N=130 orthopedic injury controls and N=20 healthy controls) at 3 clinical sites: Baylor College of Medicine, University of Pittsburgh Medical Center and University of California San Diego.
2. Specific Aim 2 will measure 15 candidate NCDT biomarkers in saliva samples from SA1 using 3 orthogonal assays. Results will cross-validate the molecular specificity and diagnostic accuracy of the candidate biomarkers, and down select 3-4 best biomarkers for the commercial NCDT test.
3. Specific Aim 3 will develop a prototype device using proven commercial platform based on a lateral-flow immunoassay with onboard digital reader. The proposed mTBI test has potential to radically change standard practice in TBI care, reduce healthcare costs and improve mechanistic understanding of mTBI and NCDT.

Proposed Project Overlap: None

W81XWH-15-9-0001 (Manley/Okonkwo) The Regents of the University of California, San Francisco via Medical Technology Enterprise Consortium	09/14/18 – 08/31/20 \$507,819	2.40 calendar (20.00%)
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Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)

Brief description of the project's goals: This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.

Agency Point of Contact Name/Address

Regnier Jurado, Associate Director
Research Management Services
UCSF Office of Sponsored Research
3333 California Street, Suite 315
San Francisco, CA 94143-0962

List of the specific aims:

1. N/A

Proposed Project Overlap: None

UFRA-144 (Manley/Okonkwo)	09/01/18 – 08/31/20	0.06 calendar (0.50%)
The Regents of the University of California, San Francisco via National Football League	\$395,200	
Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK II)		
Brief description of the project's goals: We will enroll patients into TRACK II, a large, high quality, TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services.		
<u>Agency Point of Contact Name/Address</u>		
Regnier Jurado, Associate Director Research Management Services UCSF Office of Sponsored Research 3333 California Street, Suite 315 San Francisco, CA 94143-0962		
List of the specific aims:		
1. Screen and enroll TBI patients, complete CRF's for demographics, interview, presentation, hospital components & transmission of clinical CT's and MRIs.		
Proposed Project Overlap: None		

U01-NS086090 (Manley/Okonkwo)	09/30/13 – 08/31/20	0.06 calendar (0.50%)
The Regents of the University of California, San Francisco via NIH PRIME	\$595,518 (No Cost Extension)	
Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK II)		
Brief description of the project's goals: We will enroll patients into TRACK II, a large, high quality, TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services.		
<u>Agency Point of Contact Name/Address</u>		
Regnier Jurado, Associate Director Research Management Services UCSF Office of Sponsored Research 3333 California Street, Suite 315 San Francisco, CA 94143-0962		
List of the specific aims:		
1. Screen and enroll TBI patients, complete CRF's for demographics, interview, presentation, hospital components & transmission of clinical CT's and MRIs.		
Proposed Project Overlap: None		

RFA67-49 (Okonkwo/Munin)	09/28/16 – 09/27/20	0.01 calendar (0.10%)
SanBio, Incorporated	\$1,218,797	
A Double-Blind, Controlled Phase 2 Study of the Safety and Efficacy of Modified Stem Cells (SB623) in Patients with Chronic Motor Deficit from Traumatic Brain Injury (TBI)		
Brief description of the project's goals: The primary objective of this study is to evaluate the clinical efficacy of intracranial administration of SB623 cells.		
<u>Agency Point of Contact Name/Address</u>		
Damien Bates, MD Sanbio, Incorporated 231 S. Whisman Road Mountain View, CA 94041		
List of the specific aims:		

1. Enroll subjects according to inclusion/exclusion criteria.

Proposed Project Overlap: None

W81XWH-14-2-0176 (Manley/Okonkwo)
The Regents of the University of California, San
Francisco via USAMRAA

09/30/14 – 09/29/20
\$441,002

0.60 calendar (5.00%)

TBI Endpoints Development (TED)

Brief description of the project's goals: The ultimate goal of this study is to identify and validate candidate COAs and biomarkers for future DDT qualification leading to effective treatments for traumatic brain injury (TBI).

Agency Point of Contact Name/Address

Regnier Jurado, Associate Director
Research Management Services
UCSF Office of Sponsored Research
3333 California Street, Suite 315
San Francisco, CA 94143-0962

List of the specific aims:

1. Validate candidate COAs and biomarkers selected in Stage I, leveraging the existing research infrastructure and clinical study networks of TRACK-TBI, CENC and CRC for potential qualification as DDTs.

Proposed Project Overlap: None

W81XWH-18-D2-0042 (Manley/Okonkwo)
The Regents of the University of California, San
Francisco via USAMRAA

09/30/18 – 09/29/20
\$15,827

0.60 calendar (5.00%)

TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies

Brief description of the project's goals: TRACK-TBI, through this proposal, is now primed to deliver on critical military and public health knowledge gaps and needs: objective classification of TBI based on what we term "mechanistic" phenotypes, e.g., diffuse axonal injury (DAI), microvascular injury (MVI), and neuroinflammation. These mechanistic phenotypes as defined by imaging and blood-based biomarkers, will direct targeted treatments based on mechanism, providing the tools needed for successful execution of precision medicine clinical trials.

Agency Point of Contact Name/Address

Regnier Jurado, Associate Director
Research Management Services
UCSF Office of Sponsored Research
3333 California Street, Suite 315
San Francisco, CA 94143-0962

List of the specific aims:

1. Specific Aim 1.A. Validate biomarkers of Diffuse Axonal Injury (DAI), with existing TRACK-TBI biospecimens and neuroimaging.
2. Specific Aim 1.B. Validate biomarkers of Microvascular Injury (MVI)
3. Specific Aim 1.C. Validate biomarkers of Neuroinflammation
4. Specific Aim 2.A. Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate-severe TRACK-TBI subjects.
5. Specific Aim 3. Conduct a multicenter double-blind, placebo-controlled exploratory clinical trial comparing the impact of Cyclosporin A on biomarker and clinical endpoints in moderate-severe TBI patients admitted to the ICU.

Proposed Project Overlap: None

R43-CE003070 (Southern/Puccio)	09/30/18 – 12/31/19	0.01 calendar (0.10%)
GAIA Medical Institute via Centers for Disease Control and Prevention	\$69,594	

Saliva Biomarkers for Predicting Outcome in Pediatric and Adult TBI Patients

Brief description of the project's goals: The proposed project will provide proof-of-concept for the core technology: saliva biomarkers for predicting neurological outcome at 6 months after moderate or severe TBI in pediatric and adult patients.

Agency Point of Contact Name/Address

Griffen C Stapp
GAIA Medical Institute, LLC
505 Coast Blvd. South
La Jolla, CA 92037-4616

List of the specific aims:

1. Enroll subjects according to inclusion/exclusion criteria.

Proposed Project Overlap: None

W81XWH-16-2-0020 (Hartings)	07/01/16 – 07/14/20	0.01 calendar (0.10%)
University of Cincinnati via USAMRAA	\$386,496	

Development and Validation of Spreading Depolarization Monitoring for TBI Management (SDII)

Brief description of the project's goals: To develop quantitative data processing algorithms for automated bedside detection of SD in non-invasive EEG recordings that can be applied to all TBI patients and to characterize SD across the spectrum of mild-moderate-severe TBI patients, both surgical and non-surgical, and determine its relevance to neurologic outcomes.

Agency Point of Contact Name/Address

S. Theresa Yockey
Senior Grant Administrator
University of Cincinnati
Sponsored Research Services
51 Goodman Ave. Suite 530
Cincinnati, OH 45221

List of the specific aims:

1. Develop signal processing methods for automated bedside detection of spreading depolarizations in both ECoG and non-invasive EEG recordings.
2. Determine the incidence of spreading depolarizations in TBI patients requiring intensive care.
3. Determine whether spreading depolarizations are independently associated with worse neurologic outcomes across the continuum of moderate-severe TBI.

Proposed Project Overlap: None

W81XWH-17-C-0006 (Pierro)	01/10/19 – 08/31/20	0.01 calendar (0.10%)
Vivonics Inc. via USAMRMC	\$74,178 (No Cost Extension)	

Non-Invasive Intracranial Pressure Assessment Using a Compact, Portable Monitor

Brief description of the project's goals: The subcontractor shall apply the Intracranial Pressure Assessment and Screening System (IPASS) to patients that meet the inclusion criteria. The subcontractor shall then use the methodology described in the protocol approved by the local Institutional Review Board (IRB).

Agency Point of Contact Name/Address

Michelle M. Burke
Manager, Contracts and Grants Administrator
Vivonics, Inc.
175 Great Road, Suite 110
Bedford, MA 01730-2730

List of the specific aims:

1. Enroll subjects according to inclusion/exclusion criteria.

Proposed Project Overlap: None

W81XWH-16-1-0748 (Treggiari)

09/30/17 – 09/29/20

0.01 calendar (0.10%)

Oregon Health & Science University via USAMRAA

\$22,066

Randomized Trial of Early Hemodynamic Management of Patients following Acute Spinal Cord Injury (TEMPLE)

Brief description of the project's goals: This is a multicenter, randomized, controlled study to assess the efficacy and safety of early blood pressure manipulation in an ICU setting in patients with acute SCI with blunt injury. We will determine whether targeted blood pressure manipulation will improve long-term neurological and functional outcomes in patients with SCI, presumably by maintaining adequate spinal cord perfusion pressure.

Agency Point of Contact Name/Address

Jen Michaud

Oregon Health & Science University

Subout Grants & Contracts Administrator

3181 SW Sam Jackson Park Road

Mail Code: L106OPAM

Portland, Oregon 97239-3098

List of the specific aims:

1. To determine if compared to a mean atrial pressure (MAP) between 65 and 70 mm Hg (conventional group), a MAP between 85 and 90 mm Hg (augmented group) for seven days after injury differently affects long-term outcomes.

Proposed Project Overlap: None

No Contract Number (Puccio)

12/12/16 – 12/11/20

0.01 calendar (0.10%)

Abbott Laboratories

\$400,000

Blood Biomarker Candidate Study for mTBI

Brief description of the project's goals: The purpose of this study is to measure potential blood-based biomarkers of mild traumatic brain injury and evaluate associations with clinical data, neurocognitive testing, and magnetic resonance imaging data.

Agency Point of Contact Name/Address

Abbott Laboratories

100 Abbott Park Road

Abbott Park, IL 60064

List of the specific aims:

1. Enroll subjects according to inclusion/exclusion criteria.

Proposed Project Overlap: None

W81XWH-16-C-0161 (Hartings)

09/30/16 – 09/30/2021

0.14 calendar (1.20%)

University of Cincinnati via USAMRAA

\$136,497

Hypothermia for Patients Requiring Evacuation of Subdural Hematoma: Effect on Spreading Depolarizations

Brief description of the project's goals: The goal is to determine the effect of hypothermia on cortical spreading depolarizations and the relationship of hypothermia and cortical spreading depolarizations to outcome in this severe TBI subpopulation. *Preparatory work is completed, and we are in the state of readiness while awaiting approval to conduct the study.

Agency Point of Contact Name/Address

S. Theresa Yockey

Senior Grant Administrator

University of Cincinnati
Sponsored Research Services
51 Goodman Ave. Suite 530
Cincinnati, OH 45221

List of the specific aims:

1. To determine whether hypothermia (35°C) induced in TBI patients before surgical evacuation of traumatic intracranial hematomas and maintained for at least 48 hours post-operatively (33°C) leads to improved outcomes at 6 months when compared to normothermia.
2. To determine whether hypothermia (35°C) induced in TBI patients before surgical evacuation of traumatic intracranial hematomas and maintained for at least 48 hours post-operatively (33°C) reduces the incidence of cortical spreading depolarizations in the injured brain.

Proposed Project Overlap: None

4100077085 (Okonkwo/Taylor/LeDuc)	01/01/17 – 12/31/20	1.80 calendar (15.00%)
Commonwealth of PA; DOH	\$4,116,177	

Biomarkers and Drug Discovery Pipeline of TBI-Related Neurodegeneration

Brief description of the project's goals: Using a multi-disciplinary, global team that is based in Pennsylvania, the goal of this project is to identify neuroimaging and biomarker correlates of TBI-related neurodegeneration and to pinpoint therapeutic targets through an innovative drug discovery pipeline that will lead to new approaches to TBI prevention, diagnosis and treatment.

Agency Point of Contact Name/Address

Susan Guy
PA Department of Health
Bureau of Administrative and Financial Services
Division of Contracts
Room 824, Health & Welfare Building
625 Forster Street
Harrisburg, PA 17120

List of the specific aims:

1. Establish a comprehensive neuroimaging and biomarker panel for the diagnosis of neurodegeneration following TBI.
2. Employ a Quantitative Systems Pharmacology (QSP) approach together with a neuronal stretch model and a Nerve-Integrated Tissue on a Chip (NITC) platform for drug discovery to target trauma-related neurodegeneration.
3. Establish the Pennsylvania CURE TBI Scholars program to train underrepresented minority students.

Proposed Project Overlap: None

CSA 06092016 (Okonkwo/Neal)	01/01/18 – 12/31/20	0.12 calendar (1.00%)
Accriva Diagnostics, Inc.	\$12,720	

Testing for Platelet Inhibition before and after Platelet Transfusion in Traumatic Brain Injury (TPI-TBI)

Brief description of the project's goals: This project will be testing for platelet inhibition before and after platelet transfusion in traumatic brain injury (TPI-TBI).

Agency Point of Contact Name/Address

Marc Rubinstein, MD
Director, Medical Affairs
Accriva Diagnostics, Inc.
6260 Sequence Drive
San Diego, CA 92121

List of the specific aims:

1. Enroll subjects according to inclusion/exclusion criteria.

Proposed Project Overlap: None

R01-AR0069543 (Anderst)	04/20/16 – 03/31/21	0.21 calendar (1.75%)
NIH – NIAMS	\$68,142	

Adjacent Segment Mechanisms in Cervical Arthrodesis Patients

Brief description of the project's goals: To determine to what extent patient-specific factors, iatrogenic factors, and biomechanical factors influence cervical spine mechanics after single-level and two-level arthrodesis.

Agency Point of Contact Name/Address

Gail Hamilton
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872

List of the specific aims:

1. Determine the independent effect patient-specific factors have on adjacent segment kinematics and arthrokinematics.
2. Determine the independent effect iatrogenic factors have on adjacent segment kinematics and arthrokinematics.
3. Determine the independent effect of increased stress on adjacent segment kinematics and arthrokinematics over time.

Proposed Project Overlap: None

W81XWH-16-D-0024 (Sperry)	09/23/16 – 09/22/21	0.30 calendar (2.50%)
USAMRC / USAMRAA	\$30,751	

Linking Investigators in Trauma and Emergency Services (LITES) Network

Brief description of the project's goals: To adequately execute robust and well-designed clinical trials, this project proposes the resources of an operational LITES network that is currently capable of conducting prospective, multicenter, injury care and outcomes research of relevance to the Department of Defense (DOD) while minimizing time, cost and regulatory barriers and exploring innovative strategies to improve recruitment, consent rates and data acquisition for multicenter clinical trials in trauma.

Agency Point of Contact Name/Address

Erika K. Smith
Defense Finance and Accounting Service
DFAS-INDY VP GFEBS
889 E 56th Street
Indianapolis, IN 46249-3800

List of the specific aims:

1. To characterize the epidemiology of moderate and severe physical injury in the U.S. and across the LITES network and investigate regional variations of presenting characteristics, management practices and attributable outcomes.
2. To determine and characterize injury related factors, management practices and trauma system factors resulting in or associated with preventable mortality.
3. To Determine the ability of early injury characteristics, laboratory measurements and biomarker levels obtained within the first 3 hours of injury to predict the development of multiple organ failure following moderate or severe traumatic injury.

Proposed Project Overlap: None

W81XWH-16-D-0024 (Sperry)	09/25/17 – 09/24/21	0.30 calendar (2.50%)
USAMRC / USAMRAA	\$20,170	

Linking Investigations in Trauma and Emergency Services (LITES) Task Order #2: Shock, Whole Blood, and Traumatic Brain Injury Trial (SWAT Trial)

Brief description of the project's goals: The LITES network will determine the impact of whole blood resuscitation in trauma patients with hemorrhagic shock at risk of large volume resuscitation with and without TBI.

Agency Point of Contact Name/Address

Erika K. Smith
Defense Finance and Accounting Service
DFAS-INDY VP GFEBS
889 E 56th Street
Indianapolis, IN 46249-3800

List of the specific aims:

1. Evaluate patient centered outcomes associated with early whole blood resuscitation practice as compared to component resuscitation in poly-trauma patients with hemorrhagic shock and further characterize outcome benefits in those with traumatic brain injury
2. Characterize blood pressure and resuscitation targets during the acute resuscitation phase of care and the associated/attribution outcomes for traumatic brain injury in patients with hemorrhagic shock.

Proposed Project Overlap: None

W81XWH-18-1-0739 (Okonkwo)	09/30/18 – 09/14/21	0.12 calendar (1.00%)
USAMRAA	\$1,300,000	

Comprehensive Biomarker Panel for Trauma-Related Dementia: Mechanistic Links Among Axonal Injury, Neuroinflammation, and Neurodegeneration

Brief description of the project's goals: The project goal is to explore and establish the clinical applicability of a comprehensive biomarker panel as an indicator of trauma-related dementia.

Agency Point of Contact Name/Address

Karen L. Petrone
Congressionally Directed Medical Research Program Office
US Army Medical Research ACQ Activity
820 Chandler St.
Fort Detrick, MD 21702-5014

List of the specific aims:

1. Use MR imaging to detect and characterize the extent of white matter axonal injury and use PET imaging to detect and characterize Ab ([11C]PiB), tau ([18F]AV-1451), and neuroinflammatory ([11C]PBR-28) pathology in (a) chronic TBI subjects aged 35-55 with cognitive impairment based on clinical neuropsychologic assessments and (b) age-matched cognitively normal subjects. The relationships between white matter injury and markers of neurodegeneration and neuroinflammation will be analyzed.
2. Compare levels of serum and CSF biomarkers of axonal injury, neuroinflammation, and neurodegeneration between chronic TBI subjects with cognitive impairments and age-matched cognitively normal subjects.
3. Correlate quantitative analyses of neuroimaging and biofluid biomarkers of traumatic axonal injury, neuroinflammation, and neurodegeneration with neuropsychological test performance in controls versus chronic TBI subjects

Proposed Project Overlap: None

W81XWH-18-2-0051 (Billiar)	09/30/18 – 09/29/21	0.30 calendar (2.50%)
USAMRAA	\$61,661	

A Precision Medicine Approach Based on Discrete Time Windows for Predicting Outcomes of Polytrauma Patients

Brief description of the project's goals: The overarching goal of this proposal is to develop a Precision Medicine methodology that will optimize outcomes in multiply injured patients by leveraging patient-specific metrics that quantify genetic and demographic signatures combined with individualized injury and injury response signals to accurately stratify expected clinical trajectories and be used to direct timing and choices of interventions.

Agency Point of Contact Name/Address

Jennifer Shankle
Congressionally Directed Medical Research Program Office
US Army Medical Research ACQ Activity
820 Chandler St.
Fort Detrick, MD 21702-5014

List of the specific aims:

1. Phase 1 Aim 1: Optimization of a narrow window-based patient stratification platform formulated using patient-specific genomic, clinical, and inflammation biomarkers obtained upon hospital admission to stratify expected clinical trajectories based on meaningful in-hospital outcomes.
2. Phase 1 Aim 2: Adaptive design re-analysis of previous interventional and observational studies in both military and civilian blunt trauma based on the narrow-window platform.
3. Phase 2 Aim 1: Optimization of a wide window-based patient stratification platform formulated using genomic, clinical, and inflammation biomarkers obtained at multiple time points post-admission to stratify expected clinical trajectories based on meaningful in-hospital outcomes.
4. Phase 2 Aim 2: Adaptive design re-analysis of previous interventional and observational studies in both military and civilian blunt trauma based on the wide-window platform.
5. Phase 3 Aim 1: Optimization of a window-based patient stratification platform based on data obtained in Phases 1 and 2.
6. Phase 3 Aim 2: A prospective, observational clinical study of polytrauma $\pm$ TBI aimed at validating a streamlined set of variables, obtained at key time points post-injury, with respect to prognosticating adverse outcomes of patients with polytrauma $\pm$ TBI.
7. Phase 3 Aim 3: Extend the observational period to 1 year to understand how early stratification and selection of in-hospital outcome variable correlates with long-term outcomes. These aims will be carried out by collaborative team at the Univ. of Pittsburgh, Uniformed Services University of the Health Sciences / Surgical Critical Care Initiative, and Indiana Univ., which bring expertise in trauma care, inflammation biomarker analysis, statistical and computational modeling, and adaptive trial design.

Proposed Project Overlap: None

No Contract Number (Manley/Puccio)	02/21/15 – 12/18/21	0.01 calendar (0.10%)
The Regents of the University of California, San Francisco via Abbott Laboratories	\$521,340	

TBI Biomarker Program Under Background Ongoing Study TRACK-TBI

Brief description of the project's goals: The objective of this study is for the TRACK-TBI investigators to collect additional serum samples for use in the TBI Biomarker program.

Agency Point of Contact Name/Address

Michael O'Rourke
Industry Contracts Division
The Regents of the University of California
3333 California Street, S-11
San Francisco, CA 94143-1209

List of the specific aims:

1. To enroll subjects according to the Inclusion/exclusion criteria to create a large, high quality database that integrates clinical, imaging, proteomic, genomic and outcome biomarkers to establish more precise methods to TBI diagnosis and prognosis, refine outcome assessment and compare the effectiveness and costs of TBI care.¹

Proposed Project Overlap: None

No Grant Number (Okonkwo)	04/01/18 – 03/31/22	1.20 calendar (10.00%)
National Football League	\$6,070,384	

Prevalence of Brain Health Versus Neurodegeneration in Professional Football Retirees

Brief description of the project's goals: Our hypothesis is that rates of brain health and neurodegeneration will be similar in former professional football players to rates in matched controls. Based on our power analysis, we will randomly sample 150 professional football retirees and 150 controls over four years. This study will establish, for the first time, the true prevalence of neurodegeneration in a sample of living, former professional football players.

Agency Point of Contact Name/Address

Jeff Miller
National Football League
345 Park Avenue
New York, NY 10154

List of the specific aims:

1. Establish prevalence of brain health and neurodegeneration through blinded review of a comprehensive assessment of clinical, neuroimaging, and biomarker measures in a random sample of professional football retirees from NFL franchises.
2. Compare prevalence and characteristics of neurodegeneration in professional football retirees to unexposed controls using the comprehensive assessment.
3. Analyze risk factors for neurodegeneration in professional football retirees and unexposed controls.

Proposed Project Overlap: None

R01-NS076511 (Bayir/Kagan/Winograd)

07/01/18 – 06/30/23

0.49 calendar (4.08%)

NIH – NINDS

\$29,881

Lipid Imaging in Traumatic Brain Injury by High Resolution GCIB-Secondary Ion Mass Spectrometry

Brief description of the project's goals: The study will initiate the first exploratory phase of the numerous detailed future studies decoding specific features of topography of individual types of lipid molecules in cells and tissues and their role in signaling functions in health and disease.

Agency Point of Contact Name/Address

Elizabeth E Conklin
Grants Management Officer
National Institutes of Neurological Disorders and Stroke
6001 Executive Boulevard, Suite 3290, MSC 9537
Rockville, MD 20852 (Express Mail)
Bethesda, MD 20892-9537 (Regular Mail)

List of the specific aims:

1. Will employ high-resolution GCIB-SIMS to explore molecular speciation and construct cell-specific maps of CL and PE in all major types of brain cells – neurons, glia, microglia, astrocytes, oligodendrocytes – in different anatomical regions of normal brain.
2. Will identify TBI induced molecular alterations in CL and PE in these major types of brain cells as well as in inflammatory cells recruited during the inflammatory response invoked by CCI.
3. Will determine the effectiveness of select anti-apoptotic and anti-ferroptotic small molecule regulators to prevent cell-specific changes of CL and PE molecular speciation induced by TBI in affected areas of the brain.

Proposed Project Overlap: None

U01-NS099046 (Barsan/Shutter/Diaz-Arrastia)

07/01/18 – 06/30/23

0.84 calendar (7.00%)

University of Michigan via NIH PRIME

\$113,477

Brain Oxygen Optimization in Severe Traumatic Brain Injury-Phase 3 (BOOST-3)

Brief description of the project's goals: This study is a two-arm, single-blind, randomized, controlled, phase III, multi-center trial of the efficacy of PbtO2 monitoring, and is designed to obtain data regarding the efficacy of physiologic maneuvers aimed at normalizing PbtO2.

Agency Point of Contact Name/Address

Khaled J. Eid

Contract Administrator Lead
University of Michigan
Sponsored Programs – Office of Contract Administration
5065 Wolverine Tower, 3003 S. State St.
Ann Arbor, MI 48109-1287

List of the specific aims:

1. Combined brain tissue oxygen (PbtO₂) and intracranial pressure (ICP) directed care for patients with traumatic brain injury (TBI) will result in improved neurologic outcome compared to treatment based on ICP directed care only.
2. Adverse events, particularly pulmonary-related, associated with PbtO₂ directed care are low.
3. PbtO₂ + ICP directed care will result in improved survival at discharge from the hospital.
4. PbtO₂ directed care will result in reduction of total hypoxia exposure, and total hypoxia exposure is positively correlated with neurological outcome.

Proposed Project Overlap: None

R01-NS102725 (Michael/Puccio)	08/15/18 – 07/31/23	0.48 calendar (4.00%)
NIH – NINDS	\$78,153	

Enhanced Bedside Microdialysis for TBI

Brief description of the project's goals: This project will deliver enhanced microdialysis as a bedside technology for monitoring interstitial brain glucose and K⁺ in patients under intensive care following neurosurgery for severe Traumatic Brain Injury (sTBI).

Agency Point of Contact Name/Address

Jeannette Gordon
Grants Management Officer
National Institutes of Neurological Disorders and Stroke
6001 Executive Boulevard, Suite 3290, MSC 9537
Rockville, MD 20852 (Express Mail)
Bethesda, MD 20892-9537 (Regular Mail)

List of the specific aims:

1. Clinical translation of enhanced microdialysis of glucose and K⁺ to patients under intensive care after neurosurgery for sTBI.
2. Expand our fundamental knowledge of strategies for mitigating the detrimental consequences on microdialysis performance of the localized tissue damage that occurs when probes are inserted into brain tissue.

Proposed Project Overlap: None

PENDING

Pending R01-NS110944 (Gardner)	07/01/19 – 06/30/24	0.24 calendar (2.00%)
The Regents of the University of California, San Francisco via NIH PRIME	\$645,972	

Transforming Research and Clinical Knowledge in Geriatric Traumatic Brain Injury

Brief description of the project's goals: This project will support establishing a new prospective cohort of older adults with traumatic brain injury (TBI) and developing and validating improved geriatric-appropriate TBI predictors, outcomes, and diagnostic/prognostic blood biomarkers.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. Enroll subjects according to inclusion/exclusion criteria.

Proposed Project Overlap: None

Pending U54 (Stewart/Kofler) 09/01/19 – 08/31/24 0.12 calendar (1.00%)
The Trustees of the University of Pennsylvania via NIH \$60,000

Collaborative Neuropathology Network Characterizing Outcomes of Traumatic Brain Injury (CONNECT-TBI)

Brief description of the project's goals: This project is a multi-institutional submission to establish an autopsy brain donation network and centralized database focused on cases with a history of acute or chronic traumatic brain injury (TBI).

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. To establish a multi-center, autopsy brain donation network underpinned by a centralized database and access arrangements to support international research programs, with case accrual from: a) former athletes across multiple global sports b) former military personnel exposed to blast and non-blast TBI c) multiple field leading, international, prospective studies in TBI.
2. To convene an expert consensus group to interrogate autopsy case material from those surviving TBI of all severities and exposure circumstances and to define standardized criteria for tissue banking, assessment and reporting of outcomes in TBI.

Proposed Project Overlap: None

Pending W81XWH-19-S-CCC1 (Charalambides) 01/01/20 – 12/31/21 0.30 calendar (2.5%)
Carnegie Mellon University via JWMP \$1,019,309

Advanced Technology Development for Transitioning a Secure Wireless Disposable Physiological Monitoring Patch for Benefiting Service Members

Brief description of the project's goals: The goal of this work is to accelerate the development of Lifeware's Wireless Sensing, Processing and Recording (WiSPR) patch toward Technology Readiness Level (TRL) 8 through development, testing and our work with the Food and Drug Administration (FDA).

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. Demonstrating device safety and developing clinical safety and effectiveness trials, including testing and analysis supporting an initial CDRH assessment
2. Developing scalable manufacturing approaches and capability for WiSPR. This includes Design for Manufacturability (DFM) and development of a Device Master Record (DMR).
3. Demonstrate operation within relevant military environments and quantify capability and performance within battlefield scenarios
4. Extend existing signal processing, data fusion and machine learning approaches supporting sensor auto-calibration and enhanced accuracy
5. Obtain 510 (k) certification. Disseminate analysis, results and suggested modifications for future implementations.

Proposed Project Overlap: None

Pending U01-NS111680 (Wang) 02/01/20 – 01/31/25 0.06 calendar (0.50%)
University of Florida via NIH PRIME \$75,000

Analytical Validation of Tau and P-Tau as New Diagnostic and Prognostic Markers for TBI-linked Neurodegeneration

Brief description of the project's goals: This project will serve as TRACK-TBI biorepository to organize and pull out serial biofluid samples to from a subset of TRACK-TBI clinical subjects.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. Establish authenticated and qualified Tau/P-Tau gold standards solutions and conduct standardization

across multiple assay platforms.

2. Optimize Tau/P-Tau assays in multiple platforms and conduct multi-site assay performance validation.
3. Complete the assay quality authentication of these Tau/P-Tau assays using biosamples from TBI subjects, normal healthy controls and other controls groups and verify their utilities in the stated COU.
4. Assemble Tau/P-Tau TBI biomarker qualification plan for submission to FDA's Center for Drug Evaluation & Research's Biomarker Qualification Program.

Proposed Project Overlap: None

Pending R01 (Jha)	04/01/20 – 03/31/25	0.12 calendar (1.00%)
National Institutes of Health	\$196,806	

A Translational Evaluation of Sur1-Trpm4 Imaging Endophenotypes and Genetics to Direct Precision Medicine for Cerebral Edema After Traumatic Brain Injury

The objective of this translational R01 is to define the impact of Sur1-Trpm4 related genetic and protein variability on different edema endophenotypes, contusion growth and response to inhibition in preclinical and human TBI.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. To test the correlation between Sur1-Trpm4 expression and edema endophenotypes in mouse TBI.
2. To test effects of Sur1 inhibition on edema endophenotypes, contusion and outcome in mouse TBI.
3. To test effects of genetic variation in the Sur1 pathway on edema and contusion in human TBI.

Proposed Project Overlap: None

Pending R01-NR018781 (Conley)	04/01/20 – 03/31/25	1.20 calendar (10.00%)
National Institutes of Health	\$189,450	

Multi-omics of patient outcomes after Traumatic Brain Injury

Brief description of the project's goals: The proposed project will use an integrative, multi-omic approach that allows the strengths of epigenomic approaches (ability to capture the interaction of genetic and environmental risk factors on patient outcomes), the strengths of polymorphism based approaches (that polymorphisms do not change over time) and the strengths of integrative analyses (better understanding of the dynamic complex nature of biological factors post-TBI that are related to patient outcomes and improve causal inferences) to elucidate novel genes and biological pathways as well as provide evidence related to biological causality.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. Identify genes and biological pathways associated with variability in patient outcomes after TBI using an EWAS approach.
2. Identify genes and biological pathways associated with variability in patient outcomes after TBI using multi-omic (genomic and epigenomic) data and integrative analyses.
3. Conduct a replication study.

Proposed Project Overlap: None

Pending R01 (Kochanek/Jackson/Jackson)	07/01/20 - 06/30/25	0.24 calendar (2.00%)
National Institutes of Health	\$260,524	

PNPase Bottleneck in TBI

Brief description of the project's goals: The present proposal provides a sound, valid and logical strategy for developing a novel treatment for TBI, i.e., a recombinant form of PNPase that can be given systemically yet restores PNPase activity in the brain.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. Determining in vitro whether injury alters PNPase in neurons and glial cells
2. Determining in vitro whether neurons are protected against different modes of injury by cell membrane permeable forms of PNPase that we have engineered in our labs using recombinant technology;
3. Determining in vivo whether TBI reduces PNPase expression and activity in the brain
4. Determining in vivo whether inhibition of PNPase worsens TBI outcomes
5. Determining in vivo whether intravenous administration of a PNPase construct designed to enter the brain improves TBI outcomes
6. Determining in patients the relationships between CSF levels of PNPase, CSF purines and TBI outcomes.

Proposed Project Overlap: None

Annotation:

The following grants were previously listed as active and are now closed: W81XWH-12-0139; W911QY-14-C-0070

The following grants were previously pending and are now active: W81XWH-15-9-0001; W81XWH-18-D2-0042; R43-CE003070

The following grants were not previously listed and are now active: W81XWH-17-C-0006; UFRA-144; W81XWH-16-1-0748.

PREVIOUS, CURRENT, AND PENDING SUPPORT

ROBERTSON, CLAUDIA

PREVIOUS (ending within the last 5-years)

1U01NS077964-01 (Robertson) 4/01/2012-1/31/2016 2.4 CM
NIH NINDS \$2,344,548 total costs
Patrick Bellgowan, PhD, Program Director, Repair and Plasticity
Neuroscience Center, Room 2206, 6001 Executive Blvd MSC 9525, Bethesda, MD 20892-9525
An Erythropoietin-Mimetic Peptide for Treatment of TBI

Goals: The goal of this project is to develop the preclinical data to translate pyroglutamate Helix B surface peptide from the laboratory to a phase II clinical trial for treatment of severe TBI.

Specific aims:

- 1: To determine the optimal dose level, effective time window, and optimal dose regimen for acute dosing of pHBSP for treatment of severe TBI
- 2: To confirm efficacy of optimal dosing regimen of pHBSP in a spectrum of injury severities
- 3: To confirm efficacy of optimal dosing regimen of pHBSP in a second TBI injury model
- 4: To study gender and age differences in response to optimal dosing regimen of pHBSP
- 5: To begin discussions with FDA, and plan IND application as well as grant application for phase II clinical trial

Role: PI

2R44NS076167-02A1 (Das) 9/1/2014-8/31/2016 0.6 CM
NIH \$218,377 total costs
Patrick Bellgowan, PhD, Program Director, Repair and Plasticity
Neuroscience Center, Room 2206, 6001 Executive Blvd MSC 9525, Bethesda, MD 20892-9525

Phase II: Portable brain injury biomarker detection system with integrated microdialysis probe

Goals: The goal of this project is to develop a fully integrated near-patient microdialysis instrument that automatically collects, analyzes and reports relevant biomarker levels in cerebral interstitial fluid at desired intervals without user intervention, so as to enable clinically meaningful decisions on TBI sequelae. In year 2 and 3 of the project, we will validate the instrument by comparing values obtained with the instrument to those measured using standard assays.

Specific Aim: To develop a fully integrated near-patient microdialysis instrument that automatically collects, analyzes and reports relevant biomarker levels in cerebral interstitial fluid at desired intervals without user intervention, so as to enable clinically meaningful decisions on TBI sequelae.

Task 1: Modify the existing prototype to accommodate following improvement

- a. Add feedback control system (integrated with pressure and flow sensor) with push and pull mechanism for microdialysis flow. Push 'n pull mechanism will improve the collection efficiency for protein biomarkers (Phase I result). Feedback control system will ensure that the flow rate variation is less than 1% and the pressure sensor will continuously monitor the performance of the microdialysis probe. Any increase in

- back pressure and change in flow rate coupled with urea levels will trigger an alarm to replace the microdialysis probe.
- There will be option of varying the flow rate from 0.25 uL/min to 5 uL/min. This will allow initial optimization of device performance during animal studies.
 - Automatic Inline calibration once every 8 hrs. The system will perform self-calibration with stored reagents to make sure the reporting parameters are correct. There will be an option to perform user (nurse) initiated calibration protocol at any point in time.
 - Small molecules detected directly by electrochemical sensor will be lactate, pyruvate, glucose, glutamate, NO and urea. Urea will be used for in vivo calibration and to indicate probe fouling. Estimated temporal response will be 5 minutes for these small molecules. The LOD and dynamic range for each molecule is provided later.
 - Based on Phase I results, S100B assay will be improved by optimization of push pull mechanism and optionally with an additive such as dextran. A microcolumn-based flow injection immunoassay will be implemented with appropriate detection system to achieve reliable assay of S100B in clinically relevant levels.
 - Software running the system will be improved with password protection, inbuilt redundancy checking and user friendly GUI
- Task 2: Extensive testing of the instrument for system reliability, accuracy and precision
- Accuracy level:?
 - Precision level:?
 - Work with external electrode supplier to improve their electrode self-life and reliability and quantitative way of characterizing the electrode life remaining.
 - Development of fail safe and robust software
- Task 3: Animal study and limited clinical trials
- Identification of critical optimization parameters in animal and human studies
 - Subsequent instrument modifications and iterations.

Role: CoPI

P01-NS38660 and P01-NS38660-10S1 (Robertson) 3/15/2006– 1/31/2014 5.4 CM
NIH NINDS \$1,947,271 total costs

Ramona Hicks, PhD, Program Director, Repair and Plasticity
Neuroscience Center, Room 2206, 6001 Executive Blvd MSC 9525, Bethesda, MD 20892-9525

Vascular Mechanisms of Secondary Insults after TBI

Goals: The major goals of this project are to study the vascular changes that occur after TBI.

Specific Aims:

- Project 1: 1. To study the natural history of Epo and Epo receptor (EpoR) expression by the injured brain.
2. To study the acute effects of rhEpo administration on cerebral hemodynamics
3. To study the chronic effects of rhEpo administration on the brain's response to injury
- Project 2: 1. To study the role of anemia of critical illness on brain oxygenation and cerebral hemodynamics (including ICP) after traumatic brain injury (TBI).

2. To study the complications associated with transfusion of blood products in patients with TBI.
 3. To study the role of rhEpo administration on reducing the need for blood transfusion after TBI.
- Project 3:
1. Determine if the mechanism of EDHF-mediated dilations following traumatic brain injury involves the metabolism of arachidonic acid through the P450 epoxygenase pathway.
 2. Determine if the mechanism of EDHF-mediated dilations following traumatic brain injury involves an increased production of hydrogen peroxide (H₂O₂).
 3. Measure Ca²⁺ and membrane potential in endothelium and vascular smooth muscle during EDHF dilations following traumatic brain injury.
 4. Study EDHF dilations *in vivo* during normal conditions and following traumatic brain injury.
- Project 4:
1. To study the expression of Epo and Epo receptor (EpoR) by the injured brain.
 2. To study the acute effects of augmented Epo signaling on cerebral hemodynamics and the resulting effects on long-term neurological outcome
 3. To study the chronic effects of augmented Epo signaling on the brain's response to injury.
 4. To study the synergistic effects of Epo and SMEPO-A administration on the brain's response to injury.

Role: Program Director and PI of Projects 1 and 4

R13NS084681-01 (Robertson) 8/1/2013 – 7/31/2014 .25 calendar
NIH-NINDS \$25,000 total costs
Ramona Hicks, PhD, Program Director, Repair and Plasticity
Neuroscience Center, Room 2206, 6001 Executive Blvd MSC 9525, Bethesda, MD 20892-9525

31st Annual National Neurotrauma Society (NNS) Symposium

Goals: The goal of this project is to support student travel to the Annual NNS scientific meeting.
Specific Aims:

1. To disseminate knowledge about new advances in the field of neurotrauma, both basic science advances in the understanding of pathological processes that cause injury, and in translational clinical topics.
2. To facilitate trainees (PhD trainees and MD students/residents) as well as nurses and other allied health professionals to attend the meeting by subsidizing their symposium costs.
3. To encourage all early career investigators, but especially women and minorities, to enter and remain in the field of neurotrauma research.
4. To enhance public awareness of neurotrauma through a public educational event.

Role: PI

W81XWH-08-2-0132 (McCarthy) 8/01/08-8/31/15 3.6 CM
Department of Defense \$900,000

Dwayne L. Taliaferro, PhD, Science Officer, Congressionally Directed Medical Research Programs

Attn: MCMR-CD, 1077 Patchel Street, Fort Detrick MD 21702-5024

Mission Connect Mild TBI Translational Research Consortium

Goals: To develop and evaluate methods for diagnosis and treatment of mild TBI

Specific Aims:

1. To standardize animal models of MTBI utilizing clinically important neurobehavioral endpoints.
- 2: To improve the diagnosis of MTBI, developing more objective criteria in the early post-injury period as well as in the chronic condition.
- 3: To develop new and innovative treatment strategies for MTBI and provide the preclinical and phase 1-2 testing of treatments found to improve outcome.

Role: CoDirector of consortium, and Partnering PI

1R03-NS087989-01 (Robertson) 9/30/2014 – 3/31/2016 0.6 CM

Department of Defense \$163,314 total costs

Legacy Clinical Data from the EPO TBI Trial

Dwayne L. Taliaferro, PhD, Science Officer, Congressionally Directed Medical Research Programs

Attn: MCMR-CD, 1077 Patchel Street, Fort Detrick MD 21702-5024

Goals: The goal of this proposal is to format clinical/research data from 200 patients enrolled in our Epo clinical trial so that the data can be submitted to FITBIR for sharing with other investigators.

Specific Aim:

1. To format clinical/research data from 200 patients enrolled in our Epo clinical trial so that the data can be submitted to FITBIR for sharing with other investigators.

Role: PI

W911QY-14-C-0070 (PI: Robertson) 9/31/16 – 9/30/17 0.6CM

Department of Defense \$307,402

Kimberly Pope, PhD, Science Officer, Congressionally Directed Medical Research Programs

Attn: MCMR-CD, 1077 Patchel Street, Fort Detrick MD 21702-5024

Legacy Clinical Data from the Mission Connect Mild TBI Translational Research Consortium

Goals: The goal of this project is to submit clinical data from the Mission Connect project to FITBIR.

Role: PI

W81XWH-14-2-0176 (PI: Manley) 9/1/2014 – 8/31/2019 0.6CM

Department of Defense \$94,695

Catherine Henry, Grants Specialist. US Army Medical Research Acquisition Activity

TBI Endpoints Development (TED)

Goals: This proposal will establish a collaborative multidisciplinary research team to develop and validate endpoints for use in trials involving the diagnosis and treatment of mild to moderate traumatic brain injury (TBI). While a number of potentially useful endpoints for mild-moderate

TBI exist, a majority of them have not been validated and qualified for use as a reference measure of diagnostic or therapeutic effectiveness. The research team will address a critical need within the TBI research community by developing clinical relevant endpoints that can support regulatory approvals and be applicable for use in research tests and clinical trials.

Role: CoPI

W911QY-14-C-0070 (PI: Okonkwo) 9/5/14 – 9/4/18 0CM
US Navy \$63,000

Victor Hernandez, Contracting Office Representative, DCMA Philadelphia

Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) – High Definition Fiber Tracking Neuroimaging, Biospecimen and Data Informatics Repositories

Goals: The goal of this project is to provide supplemental funds to the TRACK-TBI study for specialized high definition fiber tracking MRI imaging.

Role: site PI

5R44HD090817-02 (PI: Southern) 10/1/17 – 9/30/19 .84CM
NIH/NINDS \$69,164

Rapid Saliva Test for Diagnostics of Mild TBI

Goals: The proposal is to develop a test that will have key advantages over standard practice: objective metrics (biomarkers), accurate result (not confounded by LOC and CT scan), noninvasive (saliva), rapid (5 min), simple (disposable) and convenient (point-of-care or sideline).

Role: CoPI

W81WH-6-2-0020 (PI:Gopinath) 07/01/17-6/30/20 .30CM
DoD CDMRP \$37,600

Development and Validation of Spreading Depolarization Monitoring for TBI Management (SDII)

Dwayne L. Taliaferro, PhD, Science Officer, Congressionally Directed Medical Research Programs

Goals: The goal of this study is to extend SD monitoring to all TBI patients (surgical and non-surgical, mild through severe) admitted to intensive care, by applying minimally invasive and non-invasive techniques, and to determine SD incidence and the clinical value of monitoring in this broader population. Development of automated techniques for data processing is a further objective that will facilitate future implementation of real-time monitoring.

Role: CoPI

W81XWH-17-C-0006 (Vivonics, Inc.) 8/1/16-8/31/19
DoD \$69,420

Non-invasive Intracranial Pressure Assessment Using a Compact, Portable Monitor

Goals: To develop a noninvasive method for measuring intracranial pressure

Role: Site PI

CURRENT

1U01NS086090-01 (Robertson, MPI) 09/30/2013 – 08/31/20 2.4 CM
NIH/NINDS \$249,807

Yvonne Talley, Grants Management Specialist

6001 Executive Boulevard, Suite 3262, Bethesda, MD 20892-9537

Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TBI)

Goals: To create a large, high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers, and provides analytic tools and resources to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services

Aims:

1. To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research.
2. To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI.
3. To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity.
4. To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Role: PI (multiple PI grant)

5R01NS094535-03 (Thomas Kent PI) 7/1/17-6/30/20 0CM
NIH/NINDS \$41,773

Novel carbon nanoparticle superoxide dismutation pathways

Goals: To develop novel therapeutic nanoparticles to provide neuroprotection following traumatic brain injury.

Role: Site PI

(Manley PI) 10/1/2018-9/30/2023 3.42CM
MTEC \$500,000

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)

Goals: A phase 2 clinical trials network that will conduct clinical trials of neuroprotective agents for traumatic brain injury

Role: Site PI

(Rubenstein PI) 3/19/19-2/28/2025 1.2CM

NIH

\$594,375

Validation of Precision Medicine-based Biomarkers Approach to Traumatic Brain Injury Subphenotypes.

Goals: To develop a panel of biofluid-based biomarkers that will identify major TBI subphenotypes in the acute (days 1-3 postinjury), subacute (days 4-14 postinjury), and chronic (1mo to years postinjury) phases.

Role: site PI

PENDING

None.

OVERLAP:

None

Nancy Temkin, PhD**ACTIVE**

R01 NS080648 (Chesnut) 9/30/12 – 7/31/19 1.2 calendar
NIH/NINDS \$420,000

Managing severe TBI without ICP monitoring- guidelines development and testing

The objective of this project is to create guidelines for the treatment of severe TBI in the absence of ICP monitoring and test them.

W81XWH-14-2-0176 (Manley, Temkin Site PI) 9/30/14-9/29/19 1.2 calendar
DOD US Army Med. Res. Acq. Activity \$123,212

Traumatic Brain Injury Endpoints Development (TED)

The goals are to harmonize and curate data from military, civilian and sports-related TBI studies to create the TED Metadataset in order to identify endpoints to validate as measures for diagnostic and therapeutic trials for TBI. Existing research networks will be leveraged to validate endpoints and once validated will be submitted for the FDA qualification process for Drug Development Tools for TBI trials.

R01 NS091618 (Mac Donald) 4/1/15-3/31/20 0.6 calendar
NIH/NINDS \$499,900

EValuation Of Longitudinal outcomes in mild TBI in Active-Duty Military and Veterans (EVOLVE)

The goal of this study is to evaluate the long term impact of blast and non-blast concussive TBI on US military service members and leverage existing early clinical and imaging data in these subjects along with data from both blast and non-blast exposed control subjects to develop complex models of predictive outcome.

No number (Manley, Temkin Site PI) 7/1/2018 – 6/30/21 Effort as needed
National Football League \$46,922

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Longitudinal (TRACK-TBI LONG)

This project will extend TRACK-TBI's current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury depending on participants' original enrollment date. These data will validate endpoints for acute and chronic diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.

U01 NS099084-01 (Barsan; Chesnut, Site PI:) 3/01/18-2/28/23 1.8 calendar
NIH/NINDS \$32,532,017 (UW: \$1,760,014)

Brain Oxygen Optimization in Severe Traumatic Brain Injury—Phase 3 (BOOST-3)

This is a Phase 3 clinical trial comparing management of severe TBI based on brain tissue oxygen levels as well as intracranial pressure vs. intracranial pressure alone.

No number yet (Manley, Temkin Site PI) 9/14/18 – 9/13/20 3.60 calendar
Medical Technology Enterprise Consortium \$1,631,270 (total study),

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)

This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.

OVERLAP: None

OTHER SUPPORT

Yuh, Esther

ACTIVE

W81XWH-14-2-0176 (Manley)	09/30/14-09/29/20 (NCE)	0.65 calendar
DOD US Army Med. Res. Acq. Activity	\$3,672,707	

TBI Endpoints Development (TED)

To improve diagnosis, treatment, and rehabilitation strategies for mTBI to mod TBI.

Role: Co-Investigator

W81XWH-18-2-0042 (Manley)	09/30/2018-09/29/2021	0.6 calendar
Dept of Defense (DoD)	\$1,059,807	

TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies

We hypothesize that particular blood-based biomarkers will correlate with select MRI biomarkers (Phase 1) that can be validated as predictive and pharmacodynamic biomarkers of DAI, MVI, and neuroinflammation (Phase 2); as a "use-case" we propose that cyclosporine A (CsA) (Phase 3) will affect these biomarkers, directing treatment for TBI based on well-defined mechanistic endophenotypes.

Role: Co-Investigator

2018-674 (Manley)	09/14/18 – 11/30/23	0.96 calendar
MTEC	\$1,631,270	

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)

This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.

Role: Co-Investigator

R01AG056326 (Mac Donald)	08/01/18-04/30/23	2.51 calendar
NIH	\$132,735 (Subcontact)	

Reclaiming and Revitalizing ACT Neuroimaging Records

1) To test the hypothesis that ACT participants with higher cumulative prescription and over-the counter anticholinergic use will show greater change on longitudinal neuroimaging measures, specifically greater rate of change in ventricular enlargement and overall atrophy over time coinciding with Alzheimer's Disease (AD) and dementia risk. 2) To test the hypothesis that ACT participants with higher glucose levels will show greater changes on longitudinal imaging measures, specifically greater rate of change in white matter hyperintensities (also known as leukoaraiosis) over time coinciding with the risk of dementia and AD.

Role: Co-Investigator

A133407 (Manley)	03/15/19-09/30/22	0.6 calendar
Abbott Point of Care INC	\$14,856,119	

Assay Cartridge Development for Traumatic Brain Injury (TBI) Diagnostic Device

The primary objective of this study is to determine the clinical performance of the i-STAT TBI test when it is used for the proposed intended use. The secondary objective of this study is the collection of data and specimens from subjects with a wider range of GCS scores, that may support other purposes related to the understanding of TBI.

Role: Co-Investigator

PENDING

R01 NS110944-01A1 (Gardner)	07/01/2019-06/30/2024	0.6 calendar
NIH	\$536,742	

Transforming Research and Clinical Knowledge in Geriatric Traumatic Brain Injury (TRACK-GERI)

Goal: To assemble a new prospective longitudinal cohort study of acute geriatric traumatic brain injury (TBI) that will establish the natural history and neuropathology, identify age-appropriate blood-based biomarkers, and develop an optimized set of tools for capturing geriatric TBI predictors and outcomes for use in large-scale geriatric TBI clinical trials.

Role: Co-Investigator

OVERLAP

None.

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*

- 9. APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*



Appendix 1

TRACK-TBI/TED Initiative Investigators' Meeting

June 29, 2019 | Pittsburgh, PA | Brigade Room

Saturday, June 29 | Closed Morning Session

7:30am – 8:00am | Continental Breakfast

8:00am – 8:20am | TRACK-TBI U01 close out deliverables

8:20am – 8:40am | TED update/Year 5 NCE plans

8:40am – 9:00am | TRACK Precision Medicine/ Year 2 plans

9:00am – 9:20am | TRACK-TBI NET update/launch

9:20am - 9:30am | Abbott IV

9:30am – 10:00am | Manuscript status/work flow

10:00am – 10:15am | Coffee Break + Site PIs/Key Personnel arrive

Zoom Link

<https://ucsf.zoom.us/j/491665682>

Meeting ID: 491 665 682



TRACK-TBI/TED Initiative Investigators' Meeting

June 29, 2019 | Pittsburgh, PA | Brigade Room

Open Meeting

10:00am – 10:15am | Coffee Break + Site PIs/Key Personnel/Industry Partners arrive

10:15am – 10:30am | Welcome/Objectives of Open Investigators' Meeting

10:30am – 12:15pm | Where We Are/Where We're Going Part 1

- Status of Enrolling Studies and Future Planning
 - U01/Post-U01: Aims Completion Status & Synergies by Core
 - Outcomes (Joe)
 - Imaging (Pratik)
 - Biospecimens (Ava/Ramon/Kevin)
 - Statistical/Curation (Mary/Nancy/Sonia)
 - High Definition Fiber Tracking (David)
 - Spreading Depolarization II (Laura N)
 - TRACK-TBI LONG (Mike)
 - Friend Controls (Sabrina)
- Pathology Core/Brain Bank Discussion (Dirk/Ramon/Christine)
- Status of Analytic Studies and New Grants
 - TED Initiative: Aims Completion Status & Synergies by Core (Mike/Joe)
 - Lin Nelson RO1
 - Raquel Gardner RO1

12:15pm – 1:15pm | Lunch

1:15pm – 3:00pm | Where We Are/Where We're Going Part 2

- Status of Studies Planning to Enroll
 - Abbott IV (Geoff)
 - TRACK-TBI EPI (Ramon)
 - TRACK-TBI Precision Medicine (Pratik/Kevin)
 - TRACK-TBI NET (Geoff)

3:00-3:15pm | Coffee break

3:15pm – 4:00pm | Data Access and Collaboration Requests (Adam) / Big Data Analytics (Adam)/ Future Manuscripts

4:00 - 4:20pm | Q&A

6:30pm | Cocktail Reception & Team Dinner / Grand Concourse Seafood Restaurant



TRACK-TBI/TED Initiative Investigators' Meeting

June 30, 2019 | Pittsburgh, PA | Brigade Room

Sunday, June 30 | Closed Session

10:00am | Start

Updates

- Imaging
 - Esther on CTs and MRIs
- Biorepository
 - Ava - planning to report the metrics on inventory
 - Ramon – GAIN
- Curation Processes and Priorities Across Cores
 - Outcomes
 - Clinical Core
 - Biorepository
 - Imaging
- TRACK-TBI LONG (Nancy)

Zoom link

<https://ucsf.zoom.us/j/577272338>

Meeting ID: 577 272 338