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14. ABSTRACT The Traumatic Brain Injury Endpoints Development (TED) Initiative is a 5-year, Department of Defense (DoD) funded project that is working toward the ultimate goal of developing better designed clinical trials leading to effective treatments for traumatic brain injury (TBI). TED is comprised of leading academic clinician-scientists, along with innovative industry leaders in biotechnology and imaging technology, patient advocacy organizations, and philanthropies, working collaboratively with regulators, specifically the US Food and Drug Administration. The TED Initiative Contact Principal Investigator is Geoffrey T. Manley, MD PhD of the University of California, San Francisco.					
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INTRODUCTION

The Traumatic Brain Injury Endpoints Development (TED) Initiative is a 5-year, Department of Defense (DoD) funded project that is working toward the ultimate goal of developing better designed clinical trials leading to more precise diagnosis and effective treatments for traumatic brain injury (TBI). Our aims are to gain consensus as to TBI outcomes and biomarkers that presently signify the strongest evidence of regulatory readiness, and ultimately begin to validate their use for FDA and other regulatory agencies to accelerate drug and device development processes. TED is comprised of leading academic clinician-scientists, along with innovative industry leaders in biotechnology and imaging technology, patient advocacy organizations, and philanthropies, working collaboratively with regulators, specifically, the US Food and Drug Administration. The TED Initiative Contact Principal Investigator is Geoffrey T. Manley, MD PhD of the University of California, San Francisco.

KEYWORDS

traumatic brain injury, concussion, biofluid biomarker, neuroimaging biomarker, clinical outcome assessment (COA), Glial Fibrillary Acidic Protein (GFAP), pathoanatomic lesion, clinical trial, regulatory readiness, brain magnetic resonance imaging (MRI), brain computed tomography (CT), Food and Drug Administration (FDA)

ACCOMPLISHMENTS

What were the major goals of the project?

Technical Objective I (Stage I | Years 1-2): 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.

YEAR 4 PROGRESS TOWARD COMPLETION OF AIMS:

(Ongoing Aims are bolded)

AIM 1.1. Organize and host a multi-stakeholder consensus conference (CC1) in Year 1 to assess the current landscape of COAs and biomarkers for potential qualification as DDTs. COMPLETED YEAR 1

AIM 1.2. Engage in information exchange and collaboration with FDA and regulatory experts to ensure that the consensus process, workstreams, and intended deliverables are consistent with established FDA guidelines. COMPLETED AND ONGOING

AIM 1.3. Curate and harmonize data on candidate clinical outcome assessments and biomarkers from existing military, civilian, and sports mTBI and modTBI databases with well-characterized samples (The TED Metadataset). COMPLETED AND ONGOING

AIM 1.4. Establish Expert Working Groups (EWGs) to organize the analyses of individual studies and the TED Metadataset, and review existing TBI COA and biomarker literatures. COMPLETED AND ONGOING

AIM 1.5. Collaborate with the Clinical Data Interchange Standards Consortium (CDISC) to conform TBI Common Data Elements (TBI-CDEs v.2) to CDISC standards for FDA regulatory submission. COMPLETED YEAR 1

AIM 1.6. Solicit, evaluate, and collaboratively develop “Seed Projects” to further the TED goals of identification and validation of endpoints for diagnostic and therapeutic trials. COMPLETED YEAR 3

AIM 1.7. Organize and host Consensus Conference 2 (CC2). COMPLETED YEAR 3

New AIM Continued into Stage II

- **Develop and implement TED Friend Control Study**
 - **Develop protocol, obtain IRB and HRPO approval. COMPLETED YEAR 5**
 - **Enroll 300 friend controls utilizing existing TRACK-TBI infrastructure. COMPLETED YEAR 5**

New Subtasks Continued into Stage II

- **Initiate Letter of Support Pathway with FDA CDER for Neuroimaging Biomarkers. COMPLETED**
- **Collaborate with FDA CDER to obtain Letter of Support for Neuroimaging Biomarkers. COMPLETED**
- **Initiate Letter of Support Pathway with FDA CDER for Biofluid Biomarkers. COMPLETED**
- **Collaborate with FDA CDER to obtain Letter of Support for Biofluid Biomarkers. COMPLETED**

Technical Objective II (Stage II | Years 3-5): 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.

AIM 2.1 Validate COA endpoints. ONGOING

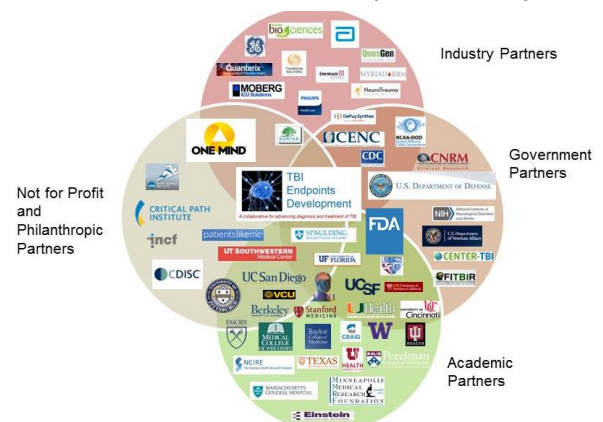
AIM 2.2 Validate biomarkers with diagnostic, prognostic, predictive, and pharmacodynamic endpoints. ONGOING

Development of a Unique Collaborative to Accelerate TBI Regulatory and Clinical Research

No drug or device has been approved by the U.S. Food and Drug Administration (FDA) to treat acute TBI, with decades of well-designed clinical trials failing. The TED Initiative was launched to address these shortcomings and develop a new model to take on this multi-faceted condition. This has required multisite, multi-institutional research collaboration that also leverages the expertise and experience of philanthropies, patient advocacy organizations, and a committed cadre of pharmaceutical, imaging, and emerging technology industry members. (Fig .1) TED is disrupting the traditional model of siloed TBI research with its creation of a collaborative model in the precompetitive space, which stretches across domains, institutions, and industry.

Fig. 1. The Collaborative – A Precompetitive Ecosystem

Expertise from across domains is evidenced by Co-Investigators representing over 30 academic institutions (and growing) in the fields of neurotrauma surgery, neuropsychology, neuroradiology, psychiatry, neurology, sports medicine, pediatrics, geriatrics, health economics, biostatistics, and informatics who all play key roles in advancing TED's goals. Investigators have also engaged with FDA, as described elsewhere in this report. Over the course of the grant, expert guidance in the regulatory arena has been provided by C-PATH, CDISC, and One Mind, also outlined elsewhere in this report.



Industry partners are showing great interest in the TED model of an “end-to-end” research enterprise, and have provided both monetary and in-kind support to test and/or validate new proteomic, neuroimaging, and genomic biomarkers, as well as to develop advanced analytic methodologies and novel platforms for executing them. A significant monetary contribution has been made by an industry partner that has supported Stage II imaging curation of the TED Metadataset, outlined later in this report. This type of cross-cutting collaboration is essential to overcome the myriad challenges of TBI research.

Continuing into Year 5 has brought an exciting collaboration between TED investigators and data scientists and neuroscientists from the Department of Energy's National Laboratories at Lawrence Livermore, Berkeley, and Argonne. This collaboration has already proved fruitful and is further described in the *New Initiatives* section of this report.

1. Engagement with FDA; Advances in Regulatory Efforts toward Endpoint Validation

Early and consistent communication and collaboration with FDA has been an integral goal of the TED Initiative. We demonstrated our commitment to regulatory science beginning with the first Consensus

Conference, with active participation from key members from multiple FDA divisions.

Center for Devices and Radiological Health (CDRH). Members of the TED Neuroimaging Core initiated contact with representatives from CDRH in March 2016. Close collaboration has continued with CDRH and has resulted in Qualification of TED's Neuroimaging Medical Device Development Tool (MDDT).

The Qualified MDDT consists of a software module that facilitates identification and measurement of the number of brain contusions seen on MRI, in conjunction with validation of the prognostic utility of this biomarker for the purpose of identifying patients at higher risk for poor outcome for participation in clinical trials of therapies for mild TBI. The FDA Context of Use is articulated as: *Contusions, as assessed by an expert rater from MRI using OsiriX CDE Software Module MDDT, may be used for enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3 months for patients aged between 18-65 years with acute non-penetrating head trauma and Glasgow Coma Scale (GCS) 13-15 who have undergone acute head CT (e.g., as part of standard clinical care) at a U.S. Level 1 trauma center.*

CDRH Medical Device Development Tool (MDDT) QUALIFIED. Following two years of engagement with FDA CDRH through the MDDT program, the MDDT submitted by Dr. Esther Yuh and team, with oversight by TED leadership, received qualification on March 12, 2019. The OsiriX CDE Software Module (Fig. 2.), is only the third qualification of a medical device development tool by the FDA, the first of a biomarker test tool of any type, and the first such tool for TBI. This qualification provides a tool for more efficient development of devices in TBI.

The MDDT program enables the FDA to qualify tools that medical device developers can use in the development of medical devices and the evaluation of their safety and effectiveness. Qualification means that the FDA has evaluated the tool and concurs with available supporting evidence that the tool produces scientifically and clinically meaningful measurements of data that can be used to help inform medical product development within the specified context of use. The OsiriX CDE is qualified to be used to better identify eligible patients for enrollment in clinical trials. Qualification of Dr. Yuh's MDDT is a significant step forward for the TBI field and represents an extremely robust return on investment for the TED Seed Project grants, which provided initial startup funding for Dr. Yuh and team.

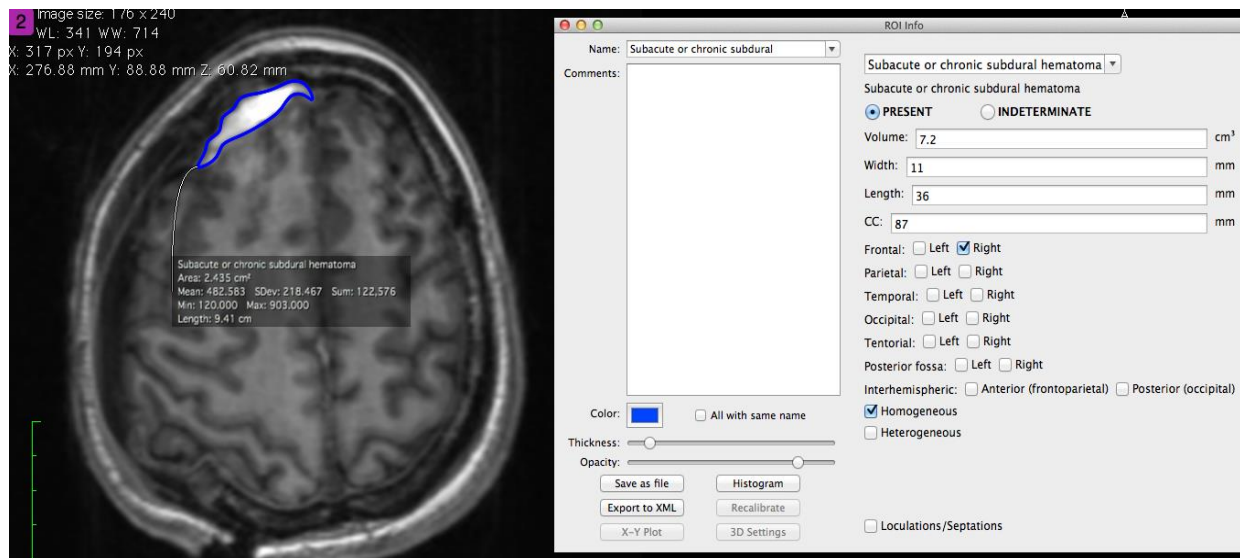


Fig 2. OsiriX CDE Software Module

The OsiriX CDE Software Module on the FDA MDDT website at: <https://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/default.htm> and FDA's summary document can be downloaded by the public at: <https://www.fda.gov/media/120973/download>. A summary of the MDDT is provided in Appendix 1.

Follow-on MDDT Submission

After receiving MDDT Qualification for the OsiriX CDE software module, Dr. Esther Yuh and team have continued to collaborate with FDA CDRH. In an advisory conference call on June 19, 2019 facilitated by Dr. Brandon Gallas of FDA CDRH Division of Imaging, Diagnostics, and Software Reliability, Dr. Yuh's team discussed planning and submission of a new data MDDT for qualification. This submission would consist of the curated imaging and clinical data set (including 517 MRI scans interpreted independently by three highly experienced board-certified academic neuroradiologists at UCSF and Massachusetts General Hospital) used for FDA MDDT qualification of the OsiriX CDE Software module. This is motivated by FDA's increasing need for high-quality imaging datasets for use as gold-standard references for the benchmarking of deep learning and other advanced machine learning algorithms in the neuroimaging space. This qualified MDDT will facilitate the validation of a new generation of analytic tools for MRI for clinical care and FDA clinical trials. Dr. Yuh obtained the necessary guidance from Dr. Gallas regarding appropriate context of use and other content, and plans to submit a successful data MDDT proposal during the no-cost extension year.

2. Progress by Expert Working Groups (EWGs)

Expert Working Groups in the domains of Clinical Outcome Assessments, Blood-Based Biomarkers, and Neuroimaging Biomarkers have been continuously refining work streams to move our research forward. During Year 5, the EWGs (previously merged with their corresponding Core Teams from the NIH-funded TRACK-TBI study) have held bi-monthly conference calls and in-person meetings at the joint TED Initiative/TRACK-TBI Investigator Meeting held in conjunction with the National Neurotrauma Society annual meeting in Pittsburgh, PA on June 29, 2019 (Appendix 2), and at other professional events, including the annual MHSRS convening in Florida in August 2019.

A. Clinical Outcome Assessments (COAs) EWG.

The COA EWG is charged with identifying a multidimensional set of clinical outcome assessments to be validated for use in therapeutic clinical trials for TBI. The ultimate goal of this EWG is the development of a complex, multi-dimensional modeling of TBI outcome measurement that moves us closer to a neurobiopsychosocial understanding of TBI effects and recovery. Now merged with the TRACK-TBI Outcomes Core, these two groups continue to meet bi-monthly to develop workstreams to reach research goals stipulated in the grant. This group has diligently worked over the past year to refine protocols for the TED Friend Control Study, described in more detail later in the report. The COA EWG leads have mapped out key COA deliverables with corresponding priorities and approach that will extend in to the no cost extension year.

Table 1. COA EWG Deliverables No Cost Extension Year

TED COA EWG Deliverable	COA EWG Priorities & Approach (leads)
Application of EB-COP to selected COAs	• Application of EB-COP to Rivermead Post-concussion Questionnaire using multiple validation approaches – In Process (Stein, Giacino) • An evidence-based methodology to systematically and transparently evaluate performance of TBI COAs for specific purposes of use (ie, diagnosis, detection of sequelae, stratification of subpopulations, prognosis, natural history, detection of treatment effects) • Paper outline complete; draft started; Submission targeted to PLOS Med
Compare performance of COA's measuring same COI (e.g., memory)	• Validity of the Brief Test of Adult Cognition by Telephone (BTACT) in Level 1 Trauma Center Patients 6 Months Post-Traumatic Brain Injury: A TRACK-TBI Study • Construct validity of BTACT for assessing TBI-related dysfunction
GOSE 2 ways—Moderate/Severe TBI	• To determine the extent to which scores differ if disability from only the brain injury is considered compared with disability arising from both brain and peripheral injuries occurring in the same event and to determine the effect on power and sample size
Prediction of recovery of orientation based on performance on measures of arousal and basic cognition	• Similar to the approach used in the National Traumatic Coma Databank in which the ability to complete neuropsychological testing predicted subsequent functional outcome.³
TRACK-TBI COA Crosswalk Project	• TED Postdoctoral Fellows will collaborate with the DoE team to perform crosswalk analyses on selected measures from the TRACK-TBI Comprehensive Assessment Battery to streamline the existing battery • Analyses will include comparison of performance-based cognitive measures (eg, BTACT executive function items v. TMT), self-reported psychological health measures (eg, PHQ-9 v. BSI-18) and participation measures (ie, QoLIBRI-OS v. SWLS).

The COA EWG has also worked extensively with collaborators from the Department of Energy National Labs (Lawrence Livermore, Berkeley, and Argonne) to create novel exploratory analyses of our COA data. This collaboration began with bi-monthly conference calls that have now developed into more specialized calls with COA EWG members providing targeted expertise to the Machine Learning and Rapid Response groups. These more targeted working groups are meeting monthly to leverage the high-throughput computing capabilities of the Labs to create an Outcomes landscape analysis. Expertise of the COA EWG has been essential to provide DOE data scientists with guidance on domain-specific variables in the dataset, as well as expected results (directionality, magnitude, trend) for core outcome variables.

More detail on this collaboration is found in the *New Initiatives* section of this report.

B. Neuroimaging EWG. The Neuroimaging EWG has set an overarching goal to identify the requirements and expectations necessary for validation of an imaging method for utilization as a diagnostic, prognostic or predictive modality for TBI. A secondary objective is to review current TBI imaging methodologies and make recommendations as to further validation that may be required and/or if new imaging modalities are needed.

The Neuroimaging EWG was instrumental in advancing two different regulatory pathways: 1) securing the first FDA CDER Letter of Support focusing on TBI and 2) receiving MDDT Qualification for the OsiriX CDE software module. (See, *Engagement with FDA section, above*)

Year 5 activities have included work to complete Common Data Element Interpretation and recording of CT scans collected as part of the TED Metadataset. To date, CT data has been extracted from 4,264 scans in the TED Metadataset (Fig. 3.) A priority in the no-cost extension year is to complete the reads of all CT scans contained in the TRACK-TBI U01 dataset.

Members of the EWG, spearheaded by Dr. Yuh, have also been working with Rancho Biosciences to harmonize the CT Annotation Tool with TBI Common Data Elements and map it to NINDS Common Data Elements. Described later in the report, the revamped tool has been hosted on a Rancho server as these new modifications are being tested by TED neuroradiologists. A key question for the GSC is where this tool may be hosted as a DOD instance.

Members of the Neuroimaging EWG have also been actively collaborating with the National Laboratories. Detailed later in the report, work to accelerate and standardize the Connectome Analysis Pipeline has resulted in MRI patient scan run times to be decreased from 10 hours to 20 minutes. The EWG has also been working with DOE collaborators on deep learning MRI segmentation, as segmentation is the bottleneck of the Connectome. They have trained a model on MRIs and anatomical atlases that will accelerate faster processing to enable downstream diagnosis/prognosis.

Finally, the team has multiple manuscripts in process (and see *Next Reporting Period* section of this report).

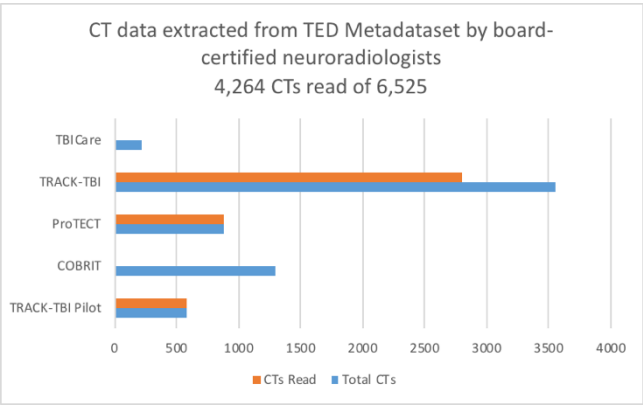


Fig 3. Metadataset CT extraction

Table 2. Imaging EWG Deliverables

TED Neuroimaging EWG Deliverable	Neuroimaging EWG Priorities & Approach (leads)
Metadataset imaging curation	- Complete NIH CDE pathoanatomic classification for the CT and MRI scans of the large multicenter studies of the TED Metadataset, including TRACK-TBI U01, ProTECT and COBRIT. - Utilize new imaging annotation and management tool designed by Rancho Bioscience - Complete quantitative imaging biomarker extraction from the standardized multicenter longitudinal TRACK-TBI research scans
Manuscript preparation and submission	- Interrater reliability of Traumatic Brain Injury CT Common Data Elements (Yuh) - Interrater reliability of Traumatic Brain Injury MRI Common Data Elements (Yuh) - Regulatory Science of Neuroimaging-based TBI Biomarkers as Drug Development Tools (companion piece with Biofluid Biomarker EWG) (Mukherjee, Mac Donald, Yuh) - MRI/Outcomes manuscript (Yuh) - DTI vs NODDI manuscript (Re-Submitted to <i>Science Advances</i>)

C. Biofluid Biomarker EWG

The Blood-based Biomarker EWG is tasked with the following goals: 1) coordinate biosample collection and data collection among TED-linked major clinical TBI studies such as TRACK-TBI, CENTER-TBI, and MISSION CONNECT; 2) standardize the sample request form for biomarker studies; and 3) collaborate with FDA toward use of biomarkers as tools for therapeutic development and clinical trials, including potential submission of one or more blood-based biomarkers to the FDA biomarker qualification program. To facilitate

achievement of these goals, the Biofluid Biomarker EWG holds monthly conference calls facilitated by leads Drs. Ramon Diaz-Arrastia and Kevin Wang, along with European counterparts at InTBIR to align strategies of both efforts.

Members of the Biofluid Biomarkers EWG participated in multiple high visibility national conferences during Year 5. Dr. David Okonkwo was the Keynote Speaker at the JPC-6/CCCRP sponsored State of Science meeting for Blood-based TBI Biomarkers held at Ft. Detrick, MD on November 27-28, 2018. He gave a presentation entitled, *Biomarkers for TBI: An empowering moment in the history of TBI care and research*. EWG leads Drs. Kevin Wang and Ramon Diaz-Arrastia gave presentations respectively titled, *Temporal Biomarkers for Traumatic Brain Injury* and *Qualification of Biomarkers for Clinical Investigations in Traumatic Brain Injury*. Dr. Manley also presented, *Biomarkers for TBI: Lessons learned from TRACK-TBI and TED*.

Members of the working group have continued analyses of a number of studies on the validation of molecular biomarkers of diffuse axonal injury (tau, p-tau, neurofilament light (NF-L)) and inflammation (IL-6, TNF, IL-10) as prognostic biomarkers of TBI. The working group is also assessing the relationship between these molecular biomarkers and neuroimaging biomarkers of diffuse axonal injury (diffusion tensor imaging, tractography) and neuroimaging biomarkers of inflammation (free water fraction). A high-profile publication in *The Lancet Neurology* reported our analysis of blood GFAP concentrations using the Abbott I-Stat prototype assays on a point-of-care platform. We showed that within 24 h of injury, levels of GFAP might improve detection of TBI and identify patients who might need subsequent MRI and follow-up.

Dr. Wang's team also completed ability tests of the Quanterix high sensitivity GFAP, UCH-L1 and Tau assay formats in detecting native biomarker targets in human TBI CSF versus healthy control CSF. The Quanterix neurology four-plex platform was capable of simultaneously detecting native TBI biomarker targets (GFAP, UCH-L1 and Tau) in 5 pooled TBI CSF samples over three pooled control CSF samples (5 µL loading).

These tests have provided Dr. Wang and his team the requisite data to write his final Seed Project results manuscript, which has been submitted to *Clinical Chemistry*. The manuscript is currently under review.

Table 3. Biofluid Biomarker EWG

TED Biofluid Biomarker EWG Deliverable	Biofluid Biomarker Priorities & Approach (leads)
Manuscripts Submitted/Published	• <i>Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study</i>. Published <i>The Lancet Neurology</i> • <i>Point-of-Care Blood Biomarker Testing of GFAP versus S100B for prediction of intracranial injuries on head CT: a TRACK-TBI study</i> (Okonkwo). Submitted to <i>JAMA Neurology</i>
Manuscripts in-preparation	• Regulatory Science of Biofluid-based TBI Biomarkers as Drug Development Tools (companion piece with Neuroimaging Biomarker EWG) (Diaz-Arrastia, Wang) • Enhancing the 'Regulatory Readiness' of Top TBI Biomarkers Toward FDA Drug Development 'Biomarker Qualification Program'. – Submitted to <i>Clinical Chemistry</i> • Validation of GFAP as a diagnostic biomarker for TBI (compared to CT as FDA standard for diagnosis) To definitively determine the prognostic accuracy of day-of-injury GFAP and UCHL1 and their combination for identifying TBI patients with a high probability of having delayed functional recovery. (Diaz-Arrastia) • Validation of GFAP as a diagnostic biomarker for TBI in CT-negative subjects (subgroup MRI+ and MRI- TBI subjects) vs Orthopedic Controls and Healthy Volunteer Controls (Manley, Korley)

3. Seed Projects

The TED Initiative awarded four Seed Projects with a period of performance from February 1, 2016 to January 31, 2017. All four were completed, and two, the Giacino and Yuh projects, have continued to

progress. Dr. Giacino's *Evidence-Based Clinical Outcome Assessment Platform (EB-COP)* is currently being hosted by the American Academy of Neurology. Dr. Yuh's Seed Project resulted in MDDT Qualification.

3.A. Joseph Giacino, PhD – Harvard Medical School – \$218,239

An Evidence-Based Clinical Outcome Assessment Platform (EB-COP) to Advance the Identification and Validation of COAs for use as FDA-qualified Drug Development Tools

Objective

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.

Activities over the past year have focused on the optimization of the EB-COP Web-Based Data Entry Tool and accompanying Manual of Operating Procedures. Progress toward this objective and plans for upcoming dissemination activities are described below:

1) EB-COP Web-Based Data Entry Tool: As previously reported, in collaboration with the Guideline Development Office of the American Academy of Neurology (AAN), Dr. Giacino's team has continued to refine and test the Qualtrics Web-based Data Entry tool, which the team developed to steer and semi-automate the EB-COP Review Process. The team worked on completing the workflow for Step V (Data Synthesis) and the Web-based back-end logic for Step VI (COA Grading and Recommendation), so that the appropriate grade and recommendation for future research is produced on the basis of the evidence that the user identifies and subsequently enters into the web-based tool.

The Qualtrics Web-based Data Entry tool has been cross-checked against the EB-COP Manual of Operating Procedures to ensure that terms instructions are consistent across formats. Beta-testing has begun to identify back-end logic and software glitches. A number of issues were identified and reported to programming personnel at AAN responsible for revision and error correction. The team completed the last round of software revisions and a new instance of the Qualtrics platform was delivered in the Spring of 2019.

In June 2019, Dr. Giacino was advised by the AAN Guideline Development Office that the Qualtrics Web-based Data Entry Tool for the EB-COP was fully built and ready for beta testing. The Qualtrics Data Entry Tool guides the user through the evidence review process through semi-automated prompts. Back-end (e.g., display and looping programming) and front-end (e.g., editing appearance) changes were implemented during the last round of edits to improve usefulness of the platform. The team has also finalized the EB-COP Manual of Operating Procedures and have confirmed that it is consistent with the instructions in the on-line Data Entry Tool.

Beta testing of the EB-COP software platform was scheduled to commence in July 2019, however, a programming error was detected that interrupted the data entry flow. This error was corrected by staff at the AAN. Beta testing has been re-scheduled to begin in October 2019 and is expected to take approximately 4-6 weeks to complete.

2) Dissemination Activities: With the EB-COP Web-Based Data Entry Tool in beta testing, dissemination activities will now focus on the completing the manuscript describing the development of the EB-COP model, the accompanying Web-Based Data Entry Tool, and its application to the GOSE. This tool can also be used to evaluate other COAs in a highly structured and reproducible manner. Dr. Giacino believes the partnership with the American Academy of Neurology will provide broad access to the EB-COP tool and a pathway for sustainability.

If no additional refinements to the EB-COP are required, a meeting will be arranged with the TED Administrative PI, Dr. Manley, and administrative personnel at the AAN to discuss transfer of the EB-COP platform to AAN for long-term operational management.

3.B. Esther Yuh, MD PhD – UCSF – \$ 236,655

CT and MRI Prognostic Biomarkers for Mild to Moderate Traumatic Brain Injury

Objective:

Demonstrate interrater reliability of TBI imaging Common Data Elements (CDE) and prognostic validity of CT and MRI CDEs

Key Milestones:

- MDDT is Qualified by FDA CDRH (see MDDT report, above)

4. Creation and Curation of the TED Metadataset

The TED Metadataset contains granular data on over 6,000 mild-moderate and severe TBI study participants. The originally conceived constituent studies included TRACK-TBI, TRACK-TBI Pilot, COBRIT, TBICare, Concussion Research Consortium, ProTECT III, Mission Connect, and an NIH-funded neuroimaging study led by TED Neuroimaging EWG Lead Dr. Pratik Mukherjee. In the intervening years, the TED Initiative has executed data sharing agreements with Neuren Pharmaceuticals for the INTREPID study. While it is unlikely that additional studies will be added, we will be open to consideration of relevant, high quality, studies.

The backbone of the TED Metadataset is the TRACK-TBI study dataset that has reached its NINDS-mandated target of enrolling 3,000 TBI patients and control subjects. To date, TRACK-TBI has enrolled approximately 3,000 subjects with TBIs across the age and injury spectrum and over 350 orthopedic trauma controls. Additionally, 300 'Friend Controls' have been enrolled under the TED Friend Control Study protocol.

The data quality assurance team at University of Washington has taken the lead in curating TRACK-TBI GOS-E scores. The GOS-E at 6 months is the primary outcome for the study and over 3,500 assessments have been audited. Auditing of other entered subjects is ongoing, with the plan to have manual audits of all TRACK/TED cases and controls. Automatic checks have also been built into QuesGen to aid in data curation covering over 137,000 CRFs, with over 6,000 rule checks.

During the last quarter curation efforts have continued to focus on the GOS-E and sections of the Patient/Surrogate Interview. To date, all GOS-Es within the TRACK-TBI U01 Cohort have been reviewed and all but a few queries closed. Data from the Orthopedic and TED Friend Controls has also been reviewed and queries sent. The team at University of Washington has now reviewed over 7,000 GOS-Es from the TRACK-TBI U01 cohort. Of the 537 TRACK-TBI LONG participants entered into the system, data from 420 have been reviewed and necessary queries sent.

Further strengthening the Metadataset is the neuroimaging inventory that now contains over 6,500 CT scans, of which, over 4,264 have been read with CDEs catalogued by TED Neuroradiologists. (Fig. 3) Quantitative interpretation has been completed on more than 200 scans. Board-certified Neuroradiologists at UCSF and Massachusetts General Hospital are now reading CT scans from the ProTECT III and COBRIT studies to extract Imaging CDEs with expected completion by early 2020. These neuroradiologists are using the imaging annotation tool developed by TED investigators and built by Rancho Biosciences to remotely log the CDE data, thus expanding the Metadataset.

The imaging annotation tool continues to undergo significant refinement to improve its utility and increase its

value. These refinements allow for mapping to FITBIR variables and permissible values. Pop-up windows have been added with FITBIR definitions for each variable. In addition, interface modifications have been made to make the tool more user friendly. (Fig. 4) These modifications have been completed with TED neuroradiologists using the updated version of the tool.

Fig 4. Imaging annotation tool modifications

The screenshot shows a web-based form for imaging annotation. The form is divided into several sections:
1. **Subdural hematoma type***: Radio buttons for Acute (selected), Chronic, Lengthy, Prolonged, and Subacute.
2. **Acute SDH status***: Radio buttons for Indeterminate, Premorbid, and Present (selected).
3. **probSAH** and **probEDH**: Checkboxes.
4. **Anatomic site**: Two buttons, "Occipital - L" and "Parietal - R".
5. **Type**: A dropdown menu showing "Heterogeneous (i.e. mixed density)".
6. **Volume**: Radio buttons for N/A (selected), Dimensions, and Volume. Below this are input fields for Length (2), Width (3), Thickness (1), and Volume(cm3) (6).
7. **Buttons**: "Create New" (blue), "Update Selected" (green), and "Clear Form" (red).
8. **Summary**: A section with "Delete SDH" and "Summary" tabs. The "Summary" tab shows a text summary: "SDH 1: Acute / Present / Occipital - L, Parietal - R / Heterogeneous (i.e. mixed density) / Volume: 6 /".
9. **Footer**: A section with "Status*" (No, Yes), "Subdural hematoma type*", "probSAH", "probEDH", and "Volume" (N/A, Dimensions, Volume).

Next Level Metadataset Harmonization

In the second half of Year 5, data scientists working out of the UCSF Admin. Core have been performing advanced data-driven analytics on the TED Metadataset, readying these data for harmonization with other data assets including the TRACK-TBI U01 comparative effectiveness research (CER) cohort. This has involved cross-walking the data elements across studies back to the NINDS CDEs and FITBIR CDEs, correcting incompatibilities/inconsistencies across data, and performing advanced missing

TED harmonization workflow

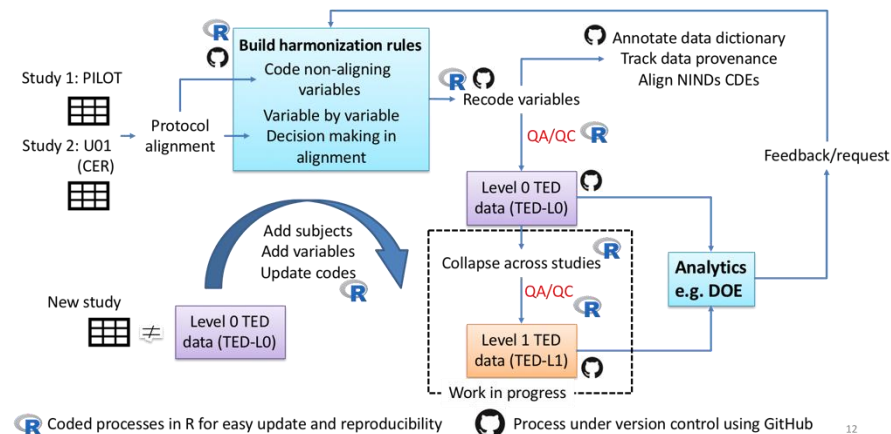


Fig 5. TED Harmonization Workflow

values analysis (MVA) across studies. This computational workflow revealed that despite CDE application there has been subtle drift in variable names as datasets have been repurposed for analysis. This stems from issues related to the final stages of 'curation for analysis' where variable names are reformatted and variables are transformed for compatibility with specific analytical workflows. For example, some of the advanced latent variable models and non-negative matrix factorization approaches championed by our analytic team require that variables be mean centered, normalized, or rescaled. These transformations result in derivative variables that then must be re-harmonized with the TED Metadataset. With thousands of variables collected as part of TED Metadataset, this becomes an intractable problem for human-curation necessitating the development of a combined human-machine workflow. (Fig. 5.)

The main strategy of this next level of TED harmonization has been to harmonize the TRACK-TBI PILOT dataset and the CER cohort of TRACK-TBI with the maximal granularity possible to then be able to incorporate other datasets. This strategy and sequence include:

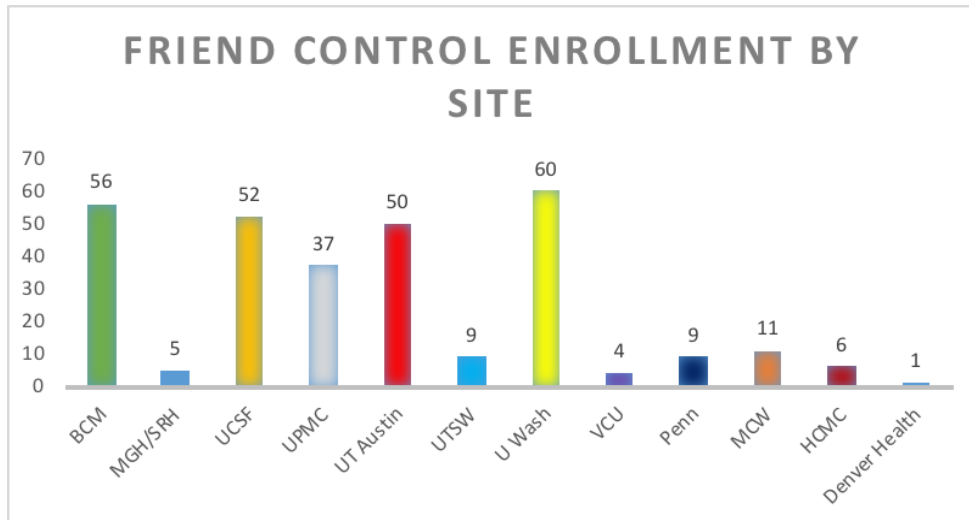
1. Code the process in R and follow a non-destructive process so that the original raw datasets do not change.
2. Align TRACK-TBI PILOT and TRACK-TBI protocols to determine the compatibility between data collection.
3. Choose variables and instruments that were compatible as starting point for aligning them.
4. The alignment was done for each potential variable by systematically:
 1. Align the variable names using the data dictionaries from both studies. In case of doubt, check the CRF and/or the instrument instructions for outcomes.
 2. Check the permitted values and levels for each variable in each original dataset. When codes and levels matched, no action is taken
 3. If the codes did not match but the levels matched, recode the TED variable
 4. If levels did not match, find the minimal common denominator creating a new version of the variable for TED with different levels than the original variables.
 5. If the variable was continuous, check that were in the same scale on the original datasets and that the distributions look similar (to detect potential errors).
 6. Reconcile across variable codes: 888 as unknown, 999 as other, N/A as not applicable, 666 as not collected.
 7. Check for potential inconsistencies within and between variables
 8. Annotate code with decisions made.
 9. Annotate data dictionary.
5. QA/QC per variable: plot distribution and levels for TED variable to check that only permitted values are present
6. QA/QC global: custom TED missing data plot looking for patterns that might indicate problems in harmonization

These harmonization efforts will continue into the no-cost extension year.

4. TED Friend Control Study

Utilizing and leveraging the existing study infrastructure of TRACK-TBI, we have reached the target goal of 300 enrollments. Twelve TRACK-TBI sites enrolled these 300 controls; 280 of the 300 Friend Controls had a 2-week MRI and 217 of these 280 also have a 6-month MRI. About 90% of the Friend Controls had a baseline blood draw as well. As the final Friend Control was enrolled in early October 2019, the cohort is still moving through the milestone cycle with the final 12-month assessments to be completed in October 2020.

Table 4. Friend Control enrollment by site



A new TED Friend Control repository has been established in FITBIR with an initial submission completed for 262 controls. This submission included outcome assessment visits for 2-wk, 3-mo, 6-mo, and 12-mo. An updated dataset is planned for submission in the first quarter of the no-cost extension year.

Table 5. Friend Control forms submitted to FITBIR

FORM	GUID	# of Records
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/AUDIT_FITBIR	261	826
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/BSI18	261	826
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/BTACT	178	178
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/DemogrFITBIR	263	263
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/GOAT_FITBIR	260	276
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/GOSE_Standard	262	834
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/InjHx_FITBIR	263	263
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/InsomniaSeverityIndex_FIT	261	824
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/MedHx_FITBIR	260	3663
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/PHQ9	261	824
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/PROMISPainInterference	261	824
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/Rivermead	261	826
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/SF12	262	832
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/SWLS_CDISC_FITBIR	262	827
http://ninds.nih.gov/dictionary/ibis/1.0/FormStructure/TMT_Standard	262	573
		12659

5. New Initiatives

Collaborative Partnership with U.S. Department of Energy (DOE) National Laboratories

Harnessing High Through-put Computing in a Precision Medicine Approach to TBI

A collaborative partnership has developed with the DoE National Labs: Lawrence Livermore National Laboratory (LLNL), Lawrence Berkeley National Laboratory (LBNL), and Argonne National Laboratory (ANL). The three laboratories have executed Data Use and Human Material Transfer Agreements for the TRACK-TBI Pilot, TRACK-TBI (U) studies, and the TED Metadataset. This collaboration seeks to enhance, extend, and expand our ability to both objectively stratify and develop effective treatments for patients with TBI. Building on expertise in high performance computing and data analytics/artificial intelligence, the National Labs will develop scalable algorithms, tools and capabilities for use on multi-scalar data collected from brain injured and control study subjects, which feature several challenges commonly found in DoE mission data i.e., extremely large, complex, heterogeneous, and with missing and variable quality elements. Early feasibility and utility of such an approach is being demonstrated using the TRACK-TBI Pilot dataset and will be extended to the TRACK-TBI U dataset.

Over the course of Year 5, this partnership has been streamlined into three main working groups: Imaging (Connectome and CT Registration), Outcomes Machine Learning, and Rapid Response.

IMAGING

Connectome Working Group

The Connectome Working Group continues to meet on a monthly basis to streamline and scale up the Edge Density Imaging pipeline protocol created by the UCSF team. The pipeline was successfully used to generate 570 connectomes from the TRACK-TBI projects across LLNL and ANL compute clusters. Efforts are underway to generate an additional 1500 connectomes with parallelization across the three DoE sites (ANL, LLNL, LBL) without changing the pipeline.

The segmentation step of the pipeline is a computational bottleneck for the connectome pipeline. Thus, the team has worked on replacing the freesurfer-based segmentation with a Deep Learning approach using a model that is trained on 1200 T1 MRIs and 82 anatomical regions of interest for 72 hours. This has resulted in strong initial results that generalize to TRACK-TBI subjects. We are exploring ways to quantify the accuracy and improve it. This approach, after validation, would substantially improve the speed of generating of connectomes as the time taken for segmentation would drop from 6-7 hours to 1 minute.

CT Registration Build-out

There exists no public reference anatomical atlas for CT. Newer methods employing deep-learning techniques have shown successful improvements in both accuracy and processing, but also rely on atlases or the manually segmented volumes the atlases are generated from. While there have been efforts to manually segment CT volumes, the data is not public and communication with the developing groups has been as of yet unforthcoming.

Therefore, the team will utilize the atlases and labeled volumes in the MR domain. For patients with MR volumes available, MRs will be registered to an Atlas, and the MR will be registered to the CT. Doing this for roughly 250 patients with both imaging modalities will provide two useful datasets:

1. Volumetrically aligned cross-modality imaging pairs
2. Anatomical segmentation labels for CT volumes

The labeled CT volumes may be sufficient to compute an atlas for intersubject registration (patient -> atlas). The pairs can further be used to learn the mapping between the imaging domains using generative deep learning techniques. From this, an end-to-end approach to CT anatomical segmentation using scalable, non-rigid, non-linear deep learning models may be employed. The synthesis of MR from CT may be useful for the connectome work, as well as for conditionally synthesizing patient images to improve diagnosis/prognosis accuracy of classification models, and publishing models/data that protects patient privacy.

During Year 5, the team made significant projects in the CT Registration project Milestone Completion

- Registered the ~250 pairs of MR & CT scans in the TRACK-TBI Pilot dataset
- Investigated efficacy of derived “CT Atlas”
- Developed model trained on pairs to synthesize MR from CT and vice versa
- Developed end-to-end DL approach for anatomical segmentation using pilot pairs (~250)
- Obtained as many as possible manually labeled CT images for validation

In the coming year, the team will work on the following tasks to complete the registration:

- Use existing lesion segmentation (non-localizing) methods and patient scan-level CT annotations to broadly validate and quantify accuracy.
- Investigate disparities between CT and MR annotations, with minimum goal to predict when an MR may be necessary.

OUTCOMES

Machine Learning Working Group

The outcome landscape of TRACK data is highly complex. There are a diverse range of outcome metrics recorded at 3-, 6-, and 12-months post-injury. These are categorized into the following domains: neuropsychological impairment, psychological status, TBI-related symptoms, perceived health-related quality of life, and physical function [Nelson 2017]. Individual item-level responses comprise these domains, resulting in hundreds of individual variables. These items can be statistically weak, biased, or unreliable for prediction. In addition, there is a large level of (intended) redundancy across these variables.

Careful combination of these variables, however, can lead to robust and predictable categorization of TBI patients. The goal of the Machine Working Group is two-fold: to develop a computational approach to characterize the landscape of the outcome variables, and to develop an interactive tool that can query item-level responses. This landscape is a compression of the large array of variables into statistically similar groups, which result in repeatable and robust combinations of individual outcome metrics. This will result in the identification of distinct TBI phenotypes that could lead to more precise treatment. In addition, we can use this analysis to search for biomarker combinations that most reliably predict outcome groups.

The interactive tool allows the user to input an arbitrary set of known individual values and predicts distributions of outcomes. Instead of predicting the single most likely outcome, the outcome distribution allows for a quantitative evaluation of the likelihood of various scenarios. This can be used to compute, for example, an odds ratio for elevated depression using biomarker data.

The working group has developed several methods to address these problems and develop the tools described above, using TRACK-TBI data. Challenges from a data modeling and analysis perspective include: (1) incorporating heterogeneous data types such as continuous, discrete measures and imaging; (2) leveraging all patient data given the large amounts of missing data; and (3) differing levels of uncertainty associated with each item. The team’s methods attempt to tackle the problem of learning associations between the space of input (or biomarker) measures and outcome measures in spite of these challenges.

One method is based on factorization of a patient similarity matrix and is used for delineating TBI phenotypes. We decompose an estimated patient-patient similarity matrix into latent factors which results in grouping of patients with similar measures. In one analysis of this approach on 6-month outcome summary scores, we find 4 patient groups. Examination of the poor outcome group shows many mild GCS cases in this group, indicating that GCS is not a reliable predictor of outcome. Using the associated variable distributions for each group, a structure of 5 high-level outcome sets can be delineated, for which each of the 4 patient groups have varying levels of outcome. These 5 sets are: Anxiety/Depression, Memory, Global Function, Life Satisfaction, and Processing Speed.

The team's item-level modeling uses a latent variable Bayesian network that constructs a model across all variables. This method handles heterogeneity in the data by using appropriate probability distributions for each variable. We use all patient data, including missing values in the probabilistic framework. This model can be used for prediction, imputation of missing values, and uncertainty estimation. The associated interactive tool can be used to interrogate the model using any arbitrary combination of known values, producing distributions for unknown values. This tool works inside any modern web browser.

Rapid Response Group

The TRACK-TBI Rapid Response group is a transdisciplinary team that was brought together to provide agile solutions to the big data problems that we are tackling with the TRACK-TBI and TED datasets. The team consists of Dept. of Energy data scientists from Argonne, Lawrence Livermore, and Lawrence Berkeley National labs, neuroscientist/bioinformaticians at UCSF, and clinicians with backgrounds in psychometrics from Harvard and the Medical College of Wisconsin. Meetings are held monthly, with each meeting typically centered around discussion and refinement of recent data-driven insights and approaches. The National Labs teams employ sophisticated machine learning analytics to TBI data problems, while the neuroscientists help to guide the interpretation and impact of the findings. These meetings also provide the team with an opportunity to develop further data cleaning and curation workflows to better serve all TRACK-TBI researchers.

The Rapid Response team members are developing a number of advanced analytic approaches to TBI data, including data-driven patient classification, analyses of outcome trajectories, as well as intensive connectome mapping with high-volume imaging data. To keep all of this work streamlined and organized, the team has created a github repository to track and update the computer code that underlies each analytical process, in order to provide clarity, transparency, and reproducibility of this work.

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

Dr. Fred Korley has been taking leading role in the Biofluid Biomarker EWG. His K Award is supported as part of the TRACK-TBI study, and includes mentors drawn from the TED/TRACK-TBI lead, Ramon Diaz-Arrastia. The TED COA and Imaging EWGs continue to mentor Dr. Raquel Gardner, whose work using latent class growth to identify outcome trajectories in TBI uses the TED Metadataset. COA EWG Lead, Dr. Michael McCrea has mentored Dr. Lindsay Nelson, who has published manuscripts using with TRACK-TBI data. Two TED Post-Doctoral Fellows have been working under the tutelage of Drs. Giacino and McCrea focused on the DOE collaboration.

How were the results disseminated to communities of interest?

Combined TED/TRACK-TBI Investigators Meeting | Pittsburgh, PS

Taking advantage of NeuroTrauma 2019, a combined TED Initiative/TRACK-TBI investigators meeting was held in Pittsburgh, PA. Key personnel from both programs met to discuss programmatic issues that included progress of the Friend Control Study, data management and curation, and synergies between TRACK-TBI and TED Initiative working groups. (Appendix 2)

2019 Military Health System Research Symposium Presentations

Multiple TED Initiative investigators attended the 2019 Military Health System Research Symposium, where they were able to hold offline meetings to further aims of the project. Dr. Nancy Temkin of University of Washington presented a poster entitled, “Functional Status Examination vs GOS-E as Outcome Measure in Traumatic Brain Injuries: How Do They Compare?” (Appendix 3)

Neuroimaging Biomarker EWG Manuscripts

The evolution of white matter changes after mild traumatic brain injury: A DTI and NODDI study.

Palacios EM, Owen J, Yuh EL, Wang M, Vassar MJ, Ferguson AR, Diaz-Arrastia R, Giacino J, Okonkwo DO, Robertson CS, Stein MB, Temkin NR, Jain S, McCrea M, Mac Donald C, Levin HS, Manley GT, Mukherjee P. Re-Submitted to *Science Advances*.

Blood-based Biomarker EWG Manuscripts

Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study.

Yue JK, Yuh EL, Korley FK, Winkler EA, Sun X, Puffer RC, Hansen D, Choy Wm, Taylor SR, Ferguson AR, Huie R, Rabinowitz M, Puccio AM, Mukherjee PM, Vassar MJ, Wang KKW, Diaz-Arrastia R, Okonkwo DO, Jain S, Manley GT, and the TRACK-TBI Investigators. *The Lancet Neurology*. 2019 Oct;18(10):953-961.

Clinical Outcome Assessment EWG Manuscripts

Recovery After Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study.

Nelson LD, Temkin NR, Dikmen D, Barber J, Giacino JT, Yuh E, Levin HS, McCrea MA, Stein MB, Mukherjee P, Okonkwo DO, Diaz-Arrastia R, Manley GT; and the TRACK-TBI Investigators. *JAMA Neurol*. 2019 June 3. Epub ahead of print.

Diagnosing the GOSE: Structural & psychometric properties using item response theory, A TRACK-TBI Pilot Study.

Ranson J, Magnus BE, Temkin N, Dikmen S, Giacino J, Okonkwo DO, Valadka A, Manley GT, Nelson LD; TRACK-TBI Investigators. *J Neurotrauma*. 2019 Sep 1;36(17):2493-2505.

Functional status examination versus Glasgow Outcome Scale Extended as outcome measures in traumatic brain injuries: How do they compare?

Dikmen S, Machamer J, Manley GT, Yuh EL, Nelson LD, Temkin NR; TRACK-TBI Investigators. *J Neurotrauma*. 2019 Aug 15;36(16):2423-2429.

Risk of posttraumatic stress disorder and major depression in civilian patients after mild traumatic brain injury: A TRACK-TBI study.

Stein MB, Jain S, Giacino JT, Levin HS, Dikmen SS, Nelson LD, Vassar MJ, Okonkwo DO, Diaz-Arrastia R, Robertson CS, Mukherjee P, McCrea M, Mac Donald CL, Yue JK, Yuh EL, Sun X, Campbell-Sills L, Temkin NR, Manley GT; TRACK-TBI Investigators. *JAMA Psychiatry*. 2019 Mar 1;76(3):249-258.

The functional status examination in mild traumatic brain injury: A TRACK-TBI Sub-Study.

Zahniser E, Temkin NR, Machamer J, Barber J, Manley GT, Markowitz AJ, Dikmen SS; TRACK-TBI Investigators. *Arch Clin Neuropsychol*. 2019 Jan 4. Epub ahead of print.

The Temporal Relationship of Mental Health Problems and Functional Limitations following mTBI: A TRACK-TBI and TED Study

Zahniser E, Nelson LD, Dikmen S, Machamer J, Stein M, Yuh E, Manley GT, Temkin N, and the TRACK-TBI Investigators. *J Neurotrauma*. 2019 Jun;36(11):1786-1793.

A comparison of satisfaction with life and the Glasgow Outcome Scale-Extended after traumatic brain injury: An analysis of the TRACK-TBI Pilot study.

Kreitzer NP, Hart KW, Lindsell CJ, Manley GT, Dikmen SS, Ratcliff JJ, Yue JK, Adeoye OM. *J Head Tr Rehabil*. 2019 May/Jun;34(3):E10-E17.

TED Initiative Website

The TED website is hosted on the UCSF Drupal platform, which is free for UCSF programs and departments. (<https://tbiendpoints.ucsf.edu>) The site provides an overview of the goals and objectives of program, highlights the leadership and key investigators, announces key news items and events, publicizes recent publications, and provides resources for TBI patients and researchers. From October 1, 2018 to September 30, 2019, the website has garnered over 6,500 page views with over 2,000 users.

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

The project has been granted a No-Cost Extension, from 30 September 2019 to 29 September 2020, amendment No: P00005 during which the following goals will be accomplished:

1. Continued collaboration with FDA CDRH to submit a new MDDT Qualification Package by Dr. Esther Yuh consisting of a curated imaging and clinical data set
2. Comprehensive harmonization of studies in the TED Metadataset under the data management team at UCSF with a focus on reading/cataloging neuroimaging features of remaining CT scans
3. Quantitative imaging biomarker extraction from standardized multicenter TRACK-TBI research scans
4. Continued follow-up of the 300 enrolled Friend Controls to close out the study by October 2020
5. Targeted Clinical Outcomes Assessment EWG Interrogations
 1. Submitting Trail Making Test and PTSD Checklist to EB-COP process
 2. Longitudinal performance of multidimensional COAs in TBI over time
 - Manuscript in progress
 3. Utility of multidimensional COAs to stratify TBI patients into clinical phenotypes for targeted intervention trials
 - Pending completion of TRACK-TBI dataset
6. COA EWG will collaborate with DoE team to perform crosswalk analyses on selected measures from the TRACK-TBI Comprehensive Assessment Battery to streamline the existing battery
7. COA EWG to complete and submit following manuscripts:
 1. EB-COP process
 2. Feasibility of a Flexible Outcome Assessment Battery for use in Longitudinal Traumatic Brain Injury Research
 3. Identifying and mitigating common threats to the validity of outcome assessment in TBI

- research: perspectives from TRACK TBI
4. Glasgow Outcome Scale Extended — Differences Counting Disability from Only Brain Injury Versus Including Peripheral Injuries
 5. Risk factors for suicidal ideation following mild traumatic brain injury: A TRACK-TBI study
8. Metadataset planned analyses
1. Co-Linearity and Redundancy Analysis: conduct analysis of TRACK PILOT/TED Metadata outcome measures to determine the degree of co-linearity/redundancy across the measure set, and determine each measure's contribution to overall variance in outcome with core functional domains.
 2. Cluster/Subtype Analysis: apply multiple approaches (cluster analysis, LCM, etc.) to determine subtypes/clusters of TBI outcomes at 6 months; first conduct analysis on all TBI patients (GCS 3-15), followed by focused analysis of mTBI cohort (GCS 13-15).
 3. Outcome Prediction Analysis: apply multiple approaches to determine predictors of outcome at 6 months; include pre-injury, acute injury and post injury variables in prediction models. The dependent (outcome) variable in these analyses may be, depending on the results of Analysis #2, cluster or subtype group membership.
9. Neuroimaging EWG to complete and submit following manuscripts:
1. Inter-Rater Reliability for TBI Common Data Elements (CDEs) on MRI Scans
 2. Inter-Rater Reliability for TBI Common Data Elements (CDEs) on CT Scans
 3. Regulatory Science of Neuroimaging-based TBI Biomarkers as Drug Development Tools
 4. MRI/TBI Outcomes manuscript
10. Biofluid Biomarker EWG to complete and submit following manuscripts:
1. Validation of GFAP as a diagnostic biomarker for TBI (compared to CT as FDA standard for diagnosis)
 2. To definitively determine the prognostic accuracy of day-of-injury GFAP and UCHL1 and their combination for identifying TBI patients with a high probability of having delayed functional recovery.
 3. Validation of GFAP as a diagnostic biomarker for TBI in CT-negative subjects (subgroup MRI+ and MRI- TBI subjects). Submitted to *JAMA Neurology*.
11. Biofluid Biomarker Core will assess the relationship between molecular biomarkers and neuroimaging biomarkers of diffuse axonal injury and inflammation
12. Blood-based biomarker validation studies looking at GFAP and UCHL-1 that will utilize data collected from approximately 1,500 TBI patients, 100 trauma controls, 50 healthy controls, and newly enrolled friend controls

Impact

The importance of the TED collaborative as a paradigm for “a new way of doing business” has taken hold. We continue to expand our pre-competitive research ecosystem in which academic collaboration is advanced by synergistic contribution by historically siloed private industry competitors, and guided by key scientific and community stakeholders. Our essential goal is to effectively and efficiently design TBI clinical trials that will lead to diagnostics and treatments that will receive approval by FDA. In the five years since our launch, we have brought together over 40 academic institutions, more than 20 private industry partners, and key departments within FDA. The TED Initiative was certainly instrumental in the TRACK-TBI/TED Team being awarded DoD funding to stand up the TRACK-TBI NETWORK Phase 2 Drug Trial initiative, which will

utilize TED-supported evidence and tools to conduct Phase 2 trials in TBI beginning in 2020. We intend to utilize imaging and blood-based biomarkers for patient enrichment and stratification. Biomarkers will also be used as the primary outcome measure and to determine whether the candidate drug is on target, both fundamental aims of the TED Initiative. Secondary Clinical Outcome Assessments will also be selected based on evidence reported by TED-supported investigators.

FDA continues to elevate TBI to a higher priority status for therapeutic standards development; in addition to improved regulatory review, standards will reduce variability of data mapping, and enable reviewers to combine data from multiple sources in a consistent format for analysis. Collecting prospective clinical trial data with CDISC standards will streamline clinical research data flow across the life of a study. By way of the TED Metadataset, we have created an informatics platform that contains harmonized data on thousands of subjects from multiple studies of mild, moderate, and severe TBI. With the progression of the TRACK-TBI study, the Metadataset continues to grow in size and richness. The ability to study the natural history of the disease over time, and conduct analyses that are powered to test hypotheses regarding the trajectories of recovery or decline are essential to the validation of biomarkers and outcome assessments that will advance the field of TBI toward effective diagnostics and treatments.

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

The building of the Metadataset will leave a lasting imprint on the field of TBI research. The last large-scale effort to create a harmonized database was the IMPACT study, which concluded a decade ago. While IMPACT was a major achievement, the studies upon which this metadataset was built were conducted in 1980's and 1990's. The TED Metadataset includes ongoing observational studies and recent interventional studies that are likely more generalizable to future clinical trials. We are beginning to test its promise as a widely interrogatable dataset to which forthcoming studies can add their data and provide the investigation platform not only for the current TED investigators, but the wider scientific community. At the conclusion of this initiative, the TED Metadataset will be publically accessible via FITBIR.

In the field of neuroimaging, FDA Qualification of the Yuh et al OsiriX CDE software module provides a standardized way to locate, count, measure, and record imaging biomarkers that we can show provide a prognostic correlation to negative outcomes. The software will assist expert raters e.g., neuroradiologists, to classify pathoanatomic lesions using CDE criteria and label abnormalities on the appropriate MR images to enhance and standardize clinical assessment of contusions and hemorrhagic axonal injury on MRI. By targeting patients with these biomarkers, medical product developers will have a more enriched patient population in which to study therapeutic effectiveness. Identification of these imaging biomarkers will lead to reliable enrichment of therapeutic clinical trials through association of those biomarkers to negative patient outcomes at 3 months. As a result of Qualification, the field now has greater certainty that patients have presented with definitive identification of pathoanatomic lesions, with reduced subjectivity toward interpretations of imaging results, and that the therapy being evaluated will be able to make specific claims towards the improvement in outcomes.

Designed in collaboration with Rancho Biosciences, the imaging annotation tool designed to streamline the process of reading, annotating, and cataloging Metadataset images will possess great utility for TED investigators as they work their way through the roughly 56,000 CT scans in the Metadataset. This web-based platform is currently being utilized by multiple neuroradiologists in different geographic locations. Recent updates during Year 5 has bolstered its utility by allowing for mapping to FITBIR variables and permissible values. To be determined is how the tool may be hosted on a DOD-approved instance, for use by DOD-embedded clinicians and investigators.

The development of the Giacino et al EB-COP Platform will provide the field with 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. EB-COP, as a semi-automated tool, is designed to enable an efficient, transparent, and systematic process for selection and validation of clinical outcome assessment measures. Its research impact will be to identify which COAs are best equipped to address specific types of research questions (ie, COU-specific); its clinical impact will serve to evaluate COA performance separately for different clinical applications (eg, diagnosis, prognosis), and its regulatory impact will be to provide a pipeline for vetting COAs (including CDEs) nominated for use in drug and device trials. As the near-completed tool is in beta testing, Dr. Giacino will soon enter into discussion with TED Initiative and AAN leadership to discuss transfer of the EB-COP platform to AAN for long-term operational management.

The Wang et al work to produce quantified high-purity antigen protein gold standard solution (0.50 mg/mL) for a set of identified blood-based biomarker (UCH-L1, S100 β , GFAP, NFL, and Tau) will permit assay cross-referencing, a first in the field. Testing of serum samples in all assay formats for each of the 4 biomarkers to establish a cross-referencing capacity and obtaining a complete assay performance and reproducibility profile for the four biomarkers across all assay platforms will be an ongoing contribution to the field.

The partnership with DOE National Labs has the potential to significantly impact clinical practice in the TBI field. The demonstrated ability to speed up the imaging pipeline by a factor of 1000 shows the immense potential of this collaboration, making MRIs clinically actionable and creating the first-ever CT registration tool.

What was the impact on other disciplines?

The pre-competitive collaborative model that TED has built is directly applicable to other neurocognitive and neurodegenerative diseases that similarly rely on the combination of outcome assessments to measure recovery or decline over time, and the validation of biomarkers to assess disease progression and to test drug targets and regimens. The model is extensible to psychiatric conditions that share these same attributes of multi-dimensional assessment via outcome measures and biomarkers. Dr. Manley has presented to the White House Office of Science and Technology's PREVENTS initiative as a model of collaborative Team Science.

What was the impact on technology transfer?

The collaborative model of data and analytics sharing is the foundation of precision medicine and personalized medicine. We are creating the necessary components of both the research and analytic pipelines that allow us to confidently step onto and across the bridge, even as we are building it, because we are attending most carefully to the quality of the data curation and harmonization as the Metadataset is expanded, and utilizing both traditional and novel approaches, in sync, to test our methods.

Our efforts appear to have been embraced by FDA, with the contribution of senior FDA officers at our conferences and to our MDDT submission. We are at an inflection point in regulatory collaboration, as FDA has signaled its intentions to utilize all of its available regulatory pathways, Qualification of Drug and Device Development Tools, Guidance Documents, and Letters of Support to propel our efforts.

What was the impact on society beyond science and technology?

TBI remains a major public health issue that impacts patients and their families. The lifetime incidence of TBI is 40% and nearly every family has been touched by this injury. With the annual cost to Americans estimated to be over \$70 billion a year, TBI has an economic impact on everyone. TED is providing new

tools for clinical trials such as the new CDISC TBI data standards that will improve the efficiency and costs of all future clinical trial in TBI. It is anticipated that as we identify and validate better tools for patient stratification and enrichment along with improved clinical outcome assessment tools, we usher in a new era in clinical trials. Given the recent flurry of activity in the drug and device clinical trial space by our public-private partners, lessons learned from TED are contributing to the design of these studies that will likely lead to improved diagnostic tools and new therapeutics for TBI.

CHANGES/PROBLEMS:

Nothing to report

PRODUCTS

1. Qualified Medical Device Development Tool: The OsiriX CDE Software Module

Publications

The evolution of white matter changes after mild traumatic brain injury: A DTI and NODDI study.

Palacios EM, Owen J, Yuh EL, Wang M, Vassar MJ, Ferguson AR, Diaz-Arrastia R, Giacino J, Okonkwo DO, Robertson CS, Stein MB, Temkin NR, Jain S, McCrea M, Mac Donald C, Levin HS, Manley GT, Mukherjee P. Submitted to *BRAIN*. Preprint published on bioRxiv: <https://doi.org/10.1101/345629>

Temporal lobe contusions on computed tomography are associated with impaired 6-month functional recovery after mild traumatic brain injury: A TRACK-TBI study.

Yue JK, Winkler EA, Puffer RC, Deng H, Phelps RRL, Wagle S, Morrissey MR, Rivera EJ, Runyon SJ, Vassar MJ, Taylor SR, Crossen MC, Lingsma HF, Yuh EL, Mukherjee P, Schnyer DM, Puccio AM, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. *Neurol Res*. 2018 Sep 3:1-10. PMID 30175944.

Optimizing outcome assessment in multicenter TBI trials: Perspectives from TRACK TBI and the TBI Endpoints Development Initiative.

Bodien Y, McCrea M, Dikmen S, Temkin N, Boase K, Machamer J, Taylor S, Sherer M, Levin H, Kramer J, Corrigan J, McAllister T, Whyte J, Manley G, Giacino J; and the TRACK-TBI Investigators. *The Journal of Head Trauma Rehabilitation*. 2018 May/Jun;33(3):147-157. PMID 29385010

Performance evaluation of a multiplex assay for simultaneous detection of four clinically relevant TBI biomarkers.

Korley FK, Yue JK, Wilson D, Hrusovsky K, Diaz-Arrastia R, Ferguson AR, Yuh EL, Mukherjee P, Wang KKW, Valadka A, Puccio A, Okonkwo DO, Manley GT. *J Neurotrauma*. 2018 Jul 23. PMID 29690824.

Age-related differences in diagnostic accuracy of plasma GFAP and Tau for identifying acute intracranial trauma on CT: A TRACK-TBI study.

Gardner RC, Rubenstein R, Wang KKW, Korley FK, Yue JK, Yuh EL, Mukherjee P, Valadka AB, Okonkwo DO, Diaz-Arrastia R, Manley GT; TRACK-TBI Investigators. *J Neurotrauma*. 2018 Jun 29. PMID 29717620.

Functional status examination in patients with moderate-to-severe traumatic brain injuries.

Machamer J, Temkin NR, Manley GT, Dikmen S. *J Neurotrauma*. 2018 May 15;35(10):1132-1137. PMID 29415608.

An update on diagnostic and prognostic biomarkers for traumatic brain injury.

Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, Manley GT. Expert Rev Mol Diagn. 2018 Feb;18(2):165-180. PMID 29338452

Temporal profile of care following mild traumatic brain injury: Predictors of hospital admission, follow-up referral and six-month outcome.

Yue JK, Winkler EA, Sharma S, Vassar MJ, Ratcliff JJ, Korley FK, Seabury SA, Ferguson AR, Lingsma HF, Deng H, Meeuws S, Adeoye OM, Rick JW, Robinson CK, Duarte SM, Yuh EL, Mukherjee P, Dikmen SS, McAllister TW, Diaz-Arrastia R, Gordon WA, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. Brain Inj. 2017;31(13-14):1820-1829. PMID 29166203.

Validating Multi-Dimensional Outcome Assessment: Using the Traumatic Brain Injury Common Data Elements: An Analysis of the TRACK-TBI Pilot Study Sample.

Nelson LD, Ranson J, Ferguson AR, Giacino J, Okonkwo DO, Valadka AB, Manley GT, McCrea MA, and the TRACK-TBI Investigators. J Neurotrauma. 2017 Nov 34:3158–3172

Apolipoprotein E epsilon 4 (APOE-ε4) genotype is associated with decreased six-month verbal memory performance after mild traumatic brain injury.

Yue JK, Robinson CK, Burke JF, Winkler EA, Deng H, Cnossen MC, Lingsma HF, Ferguson AR, McAllister TW, Rosand J, Burchard EG, Sorani MD, Sharma S, Nielson JL, Satris GG, Talbott JF, Tarapore PE, Korley FK, Wang KKW, Yuh EL, Mukherjee P, Diaz-Arrastia R, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. Brain Behav. 2017 Aug 9;7(9):e00791. PMID 28948085.

Emergency department blood alcohol level associates with injury factors and six-month outcome after uncomplicated mild traumatic brain injury.

Yue JK, Ngwenya LB, Upadhyayula PS, Deng H, Winkler EA, Burke JF, Lee YM, Robinson CK, Ferguson AR, Lingsma HF, Cnossen MC, Pirracchio R, Korley FK, Vassar MJ, Yuh EL, Mukherjee P, Gordon WA, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. J Clin Neurosci. 2017 Nov;45:293-298. PMID 28789959.

Website

<https://tbiendpoints.ucsf.edu>

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Personnel Name	Institution	Role	Person's month worked during 9/30/18-9/29/19 (cal. mos)	Contribution
Manley, Geoffrey	UCSF	Principal Investigator	1.20	PI (5% cost-sharing support from departmental funds)
Mukherjee, Pratik	UCSF	Co-Investigator	1.07	Dr. Mukherjee will extract CT and MRI common data elements from the metadataset for both Specific Aims 1 and 2.
Yuh, Esther	UCSF	Co-Investigator	2.25	Dr. Yuh will extract CT and MRI common data elements from the metadataset for both Specific Aims 1 and 2.
Tosun-Turgut, Duygu	UCSF	Co-Investigator	4.20	Dr. Tosun provides technical and analytical expertise for the proposed high-resolution MRIs and the Tau and amyloid PET scans.
Palacios, Eva	UCSF	Specialist	5.52	Eva Palacios focuses on supporting data management and analysis of the finding from the advanced neuroimaging and emerging technology studies.
Torres Espin, Abel	UCSF	Post-Doc	10.59	Dr. Torres Espin is a data scientist who has been working on harmonization efforts for the TED Metadataset.
Fabian, Jeffrey Brian	UCSF	Research Administrator	3.80	Mr. Fabian support the efforts among the six Core Leaders to implement and manage the tasks and deliverables and aim to assure that milestones are achieved in accordance with the study timelines. He serves as a liaison between Dr. Manley and other Core Leaders, Co-PIs, DOD, industry, public-private partners.
Taylor, Sabrina	UCSF	Clinical Project Manager	2.50	Dr. Taylor oversees the day-to-day project operations. She provides support to study personnel at all sites regarding implementation of the Core protocols. She supervises all aspects of the project at UCSF including enrollment, follow-up, and the meeting of all milestones for the TED Validation Stage II studies.
Ma, Man Ho Herman	UCSF	Finance Manager	3.45	Mr. Ma supports the financial operations of the project. He is responsible for managing reimbursement for subcontracts, developing and managing budgets, and approving purchase orders, travel and research subject reimbursements.
Coss, Nathan	UCSF	Clinical Research Coordinator	6.00	Mr. Coss is responsible for subject screening and enrollment; completion of the electronic case report forms; subject retention efforts; scheduling of the TED supplemental neuroimaging and follow-up for outcome assessment; processing of subject stipends.
Fecho, Cassandra	UCSF	Staff Research Associate	5.93	Cassandra Fecho performs data and metadata entry for the neuroimaging analysis of the metadataset.
Hwang, Anna	UCSF	Research Data Analyst	3.65	Anna Hwang performs neuroimaging data analysis for the metadataset.
Nguyen, NhuNhu	UCSF	Clinical Research Coordinator	0.75	NhuNhu Nguyen administers a variety of CDE-recommended assessments, including those that measure global outcome, neurocognitive function, and psychological status.
Robertson, Claudia	BCM	Site PI	3.00	Dr. Robertson participates in the Consensus and Implementation Conferences. She provides the infrastructure and oversee the clinical enrollment.
Levin, Harvey	BCM	Co-Investigator	1.20	Dr. Levin is involved in all phases of the project in support of the Outcomes Core for the Consensus and Implementation Conferences and Validation studies.
Brennan, Jeffrey	BCM	Research Coordinator	7.00	Mr. Brennan helps with statistical analysis of demographic/injury characteristics, CT and MRI imaging findings, genetics, blood-based biomarkers, and neurological outcome assessments.
Gonzalez, Luis	TIRR	Research Assistant	12.00	Dr. Sherer served as site PI overseeing the RA effort and IRB as well as consulting with other site PIs and the project PI.
Stein, Murray	UCSD	Co-PI and Subaward PI	1.40	Dr. Stein continues to provide expert input into planning for biomarker validation. He regularly attends planning calls and meetings, with an emphasis on mental health input.
Agtarap, Stephanie	UCSD	Post Doc	9.70	Dr. Agtarap participated in analyses pertaining to the goals of TED.
Sweet, Alison	UCSD	SRA	1.10	Ms. Sweet is assisting Dr. Stein with organizational aspects of this project at UCSD.
Sharpless, Jane	UPMC	HRPO Coordinator	3.00	Ms. Sharpless is responsible for securing site-specific IRB and HRPO approval to initiate human-subject recruitment at each participating military site. Additionally, she works with the FITBIR team to upload data collected under this protocol into FITBIR compliant form structures.
Hahner, Thomas	UPMC	NPSYCH Technician	2.40	Mr. Hahner is responsible for subject screening, enrollment and for conducting neuropsychological testing and follow-up on enrolled study participants at scheduled time points.
McCrea, Michael	MCW	Co-Investigator	0.90	Serves on the TED Executive and Steering Committees and Outcomes Core providing expertise in neuropsychology and long term effects on sports related brain injuries
Kramer, Mark	MCW	Statistician	3.37	Dr. Kramer has conducted statistical analysis and advanced modeling analyses on the project.
Brett, Benjamin	MCW	Post Doc	4.03	Dr. Brett has contributed analyses and writing to the publication.
Hsiao-Ping Han	MCW	Post Doc	4.34	Dr. Han has contributed analyses and writing to the publication.
Wilmoth, Kristen	MCW	Post Doc	2.97	Dr. Wilmoth has contributed analyses and writing to the publication.
Ristow, Georgia	MCW	Tech	1.88	Friend control enrollment.
Giacino, Joseph T.	SRH	Co-Investigator	1.84	Dr. Giacino continues to oversee all outcome core activities, including development of new TED Metadataset studies, collaboration with the DoE National Laboratories on approaches to TRACK data analytics, and review of all clinical outcome assessment (COA) manuscripts and deliverables.
Bodien, Yelena	SRH	Research Scientist	3.00	Dr. Bodien serves as a member of the TED/TRACK-TBI Outcomes Core. She continues to perform data curation activities (ie, data extraction, site queries, data repair) for the TRACK-TBI severe TBI cohort.
Malone, Christopher	SRH	Postdoctoral Fellow	8.00	Dr. Malone worked closely with American Academy of Neurology staff to refine and test the EB-COP web-based data entry tool to identify bugs that interrupted data entry flow and to ensure consistency with the Manual of Operating Procedures, identified and implemented back-end (e.g., display and looping programming) and front-end (e.g., editing appearance) changes to optimize the platform, and prepared for beta testing of the EB-COP. He also served as a member of the TED-DoE Rapid Response Team.
Bergin, Michael	SRH	Postdoctoral Fellow	2.40	Dr. Bergin served as a member of the TED-DoE Rapid Response Team, which supports the collaboration between the TRACK/TED and DoE National Laboratory teams through development of scalable scientific machine learning approaches and tools suited for the analysis of extremely large, highly complex and uncertain datasets.
Temkin, Nancy	UW	Principal Investigator	1.20	Dr. Temkin has worked on data analyses and papers

Dikmen, Sureyya	UW	Co-Investigator	2.40	Dr. Dikmen has worked on papers
Mac Donald, Christine	UW	Co-Investigator	1.10	Dr. Mac Donald has worked in the area of neuroimaging
Machamer, Joanie	UW	Research Scientist	4.40	Ms. Machamer has worked on data curation and papers
Boase, Kimberly	UW	Research Scientist	6.00	Ms. Boase has worked on data curation and papers
Barber, Jason	UW	Research Scientist	1.40	Mr. Barber has worked on data management and data analyses
Toga, Arthur	USC	Co-Investigator	0.91	Dr. Toga was involved in the project in support of the Consensus and Implementation Conferences and Validation studies.
Samadani, Uzma	HCMA	Site PI	0.60	Oversight for all study activities
Rafter, Daniel	HCMA	Coordinator	3.00	Oversaw and participated in all study activities
Chettupally, Tabitha	HCMA	Research Assistant	6.00	Participated in all study activities
Wang, Kevin	UF	Sub PI	1.58	Project coordination (internal, external with UCSF overall PI Dr. G. Manley and other project members), data interpretation
Yang, Zhihui	UF	Co-Investigator	1.52	Project coordination (internal, external with UCSF overall PI Dr. G. Manley and other project members), data interpretation
Whyte, John	AEHN	Sub PI	1.2	Dr. Whyte attends all scheduled teleconferences and reviews and advises on all outcomes measurement strategies.
Snyder, Corey	UTA	Research Assistant	3.5	Corey Snyder was a research assistant to the project and helped with follow up visits.
Lewis, Sara	UTA	Assistant Research Coordinator	6	Ms. Lewis was responsible for recruiting and conducting follow-up visits/assessments. Additionally, responsible for data entry and error checking.
Duhaime, Ann-Christine	MGH	Site PI	1.15	Dr. Duhaime served as Site Principal Investigator for the Massachusetts General Hospital. Her duties included overseeing both the adult and the pediatric patient enrollment and acute data collection as well as the outcomes arm for pediatric subjects.
Fortes-Montiero, Carla	MGH	Clinical Research Coordinator	3.14	Carla was responsible for subject screening and enrollment; completion of the electronic case report forms; subject retention efforts; scheduling of the TED supplemental neuroimaging and scheduling outcome assessments with our partners at Spaulding Rehabilitation Hospital; and coordinating the processing of patient stipends and travel reimbursements.
Post, Ryan	UTSW	Research Coordinator	4.2	Regulatory, patient interactions, MRI scans Data entry
Silva, Valeria	UTSW	Research Coordinator	1.2	Regulatory, patient interactions

CURRENT SUPPORT

CURRENT SUPPORT

1R01NS080648 (CPI Chesnut) 9/30/12/12-7/31/20 0.3 cal mos
 NIH/NINDS and Fogarty \$2,516,005
 Grants Officer: Patrick Bellgowan, 9000 Rockville Pike, Bethesda, MD 20892
 Project Title: **Managing severe TBI without ICP monitoring - guidelines development and testing**
 Brief Description of the Project's Goals: The objective of this project is to create guidelines for the treatment of severe TBI in the absence of ICP monitoring and test them.
 Role: Investigator

R01 NS091618 (Mac Donald) 4/1/15-3/31/20 0.6 cal mos
 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.

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.

U01 NS099084 (Barsan; Site PI: Chesnut) 4/1/18 – 3/31/23 2.4 cal mos
 NIH/NINDS \$32,532,017 (UW: \$1,760,014)
 Grants Officer: Scott Janis, 9000 Rockville Pike, Bethesda, MD 20892
 Project Title: **Brain Oxygen Optimization in Severe Traumatic Brain Injury—Phase 3 (BOOST-3)**
 Brief Description of the Project's Goals: 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.
 Role: Investigator

OVERLAP

There is no scientific, budgetary or commitment overlap. If all pending applications are funded, the effort on funded projects will be adjusted to maintain support at or below 12 calendar months."

KEY PERSONNEL OTHER SUPPORT

PREVIOUS, CURRENT, AND PENDING SUPPORT

JOSEPH GIACINO, PHD

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 neuroinflammation using advanced blood-based assay platforms and MR imaging sequences in Aims: prospectively collected data from existing TRACK-TBI subjects. ocular injury (MVI), and

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 Institute <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.

OTHER SUPPORT

CHRISTINE L. MAC DONALD, PhD

ACTIVE

R01HD083126 (Mac Donald) 4/1/2015–3/31/2020 2.4 cal mos
NIH/NINDS \$416,649 (annual direct cost, YR 5)

***E*valuation ***O*f** *L*ongitudinal Outcomes in Mild TBI Active-Duty Military and Veterans – The *E*volve Study**

The goal of this study is to evaluate the long term impact of concussive TBI in four distinct groups of US Military service members, blast-TBI, non-blast TBI, blast-exposed control, and non-blast-exposed control and leverage existing early clinical and imaging data in these subjects to develop complex models of predictive outcome.

W81XWH-14-2-0176 (PI: Temkin) 9/30/14–9/29/20 0.96 cal mos
DOD US Army Med. Res. Acq. Activity \$123,526

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.

Department of Defense/Henry Jackson Foundation 07/01/17 –07/31/2020 1.2 cal mos
PI: Christine Mac Donald \$310,000

Evaluation Of Longitudinal outcomes in mild TBI Active-Duty Military and Veterans-Supplement
We propose to characterize four cohorts of individuals who have been prospectively followed since the point of concussion injury in combat to dramatically increase what is known about the long-term implications of head injury among people who have served in the military. We seek at this time to expand the EVOLVE study to include brain donation and autopsy consent in these service members. Sadly, the death rate in this study is currently sitting at just over 1:100 and the suicide rate is 833/100,000 in stark contrast to the CDC reported suicide rate in the US population at large of 18-20/100,000.

AZ160022 (PI: Dams-O'Connor) 9/30/17–9/29/21 0.90 cal mos
DOD US Army Med. Res. Acq. Activity \$180,547 (subaward)

Late Life Consequences of TBI and Military Service: A Population-Based Study

The project will collaborate with researchers at the Icahn School of Medicine at Mount Sinai to use the extensive clinical research and data resources available through the ongoing Adult Changes in Thought (ACT) study to the late life outcomes of veterans who were exposed to military service and traumatic brain injury.

2R01AG029672-06A1 (PI: Crane) 04/15/17–03/31/22 1.80 Cal mos
ADNI Psychometrics Y3 DC: \$547,737

This project proposes to analyze extensive cognitive, neuroimaging, and fluid biomarker data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and from the Australian Imaging Biomarkers and Lifestyles of Ageing (AIBL) studies to optimize psychometric strategies to address substantively important questions on Alzheimer's disease and the aging brain.

1RF1AG056326-01A1

08/01/2018 – 06/30/2023

3.0 Cal mos

\$2,809,114 Direct Costs yr 1

(CPI: MacDonald, Christine) (MPI: Mac Donald C, Crane P, Larson E)

Reclaiming and Revitalizing Act Neuroimaging Records

The overarching goals of this R01 proposal are to leverage extensive existing clinical imaging data from a well-characterized cohort of older adults to improve scientific understanding of potential mechanisms by which anticholinergic medications (Aim 1) and glucose metabolism (Aim 2) lead to dementia and Alzheimer's disease risk, and to provide a valuable resource that characterizes longitudinal changes in brain structure over time for this cohort of older adults (Aim 3). The proposal builds on the resources of the Adult Changes in Thought (ACT) study

PENDING

R01 NS091618 (Mac Donald)

4/1/2020-3/31/2025

0.6 cal mos

Competing Renewal

NIH/NINDS

\$470,148 (annual direct cost, YR 6)

EValuation Of Longitudinal outcomes in mild TBI in Active-Duty Military and Veterans 10-Year (EVOLVE10)

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.

Role: PI

OVERLAP

There is no scientific overlap.

If pending proposals are funded, effort will be re-budgeted to ensure total effort does not exceed 12 calendar months.

For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED**PHS 398 OTHER SUPPORT**

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether federal, non-federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for reporting Other Support. Information on Other Support should be provided in the *format* shown below.

For information pertaining to the use of and policy for other support, see [NIH Grants Policy Statement, Section 2.5.1: Just-in-Time Procedures](#). Neither the application under consideration nor the current PHS award for this project should be listed as Other Support.

Effort devoted to projects must be measured using "person months." NIH and other PHS agencies use the concept of "person months" as a metric for determining percent of effort. For more information about calculating person months, see NIH's [Frequently Asked Questions on Person Months](#).

Format**NAME OF INDIVIDUAL****ACTIVE/PENDING**

Project Number (Contact Principal Investigator) Source Title of Project (or Subproject)	Dates of Approved/Proposed Project Annual Direct Costs	Person Months (Cal/Academic/ Summer)
The major goals of this project are...		
<u>OVERLAP</u> (summarized for each individual)		

Christopher Madden, MDOngoing Research Support

1U01 NS086090 (Madden)

09/01/2013-08/31/2018

0.4 cal. months

NIH/NINDS

\$131,986

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

The goal of this project are to establish a platform for conducting clinical research in traumatic brain injury patients.

Specific Aim 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. Specific Aim 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. Specific Aim 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. Specific Aim 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.

1D43TW01046301 (Nwariaku) (NEW)

09/20/2016-08/31/2021

0.36 cal. months

NIH-FOGARTY INTERNATIONAL CENTER

\$204,692

Partnerships to Develop Injury Research Capacity in the Sub-Saharan Africa

The goals of this project are to develop collaborations with UT Southwestern Medical Center and institutions in sub-Saharan Africa to provide resources and expertise to develop the injury research programs in those countries.

Specific Aims; (i) To train high-quality candidates in modern methods and principles of clinical and translational research, and (ii) To support trained candidates to develop productive and sustainable institutional research programs focused on injury in sub-Saharan Africa. We will train candidates from Ethiopia and Nigeria for up to 12 months in the U.S. and/or their home country.

Pending Research Support

None.

Overlap

None.

If any of the pending grants are awarded, effort will be reduced accordingly.

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

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)
Commonwealth of PA; DOH

01/01/17 – 12/31/20
\$4,116,177

1.80 calendar (15.00%)

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)
Accriva Diagnostics, Inc.

01/01/18 – 12/31/20
\$12,720

0.12 calendar (1.00%)

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.

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

\$645,972

Francisco via NIH PRIME

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.

UPDATED EXISTING AND PENDING SUPPORT

PUCCIO, Ava M.

EXISTING

W81XWH-15-9-0001 (Manley/Okonkwo) 09/14/18 – 08/31/20 2.40 calendar (20.00%)
The Regents of the University of California, San Francisco \$378,496
via Medical Technology Enterprise Consortium

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 0.03 calendar (0.25%)
The Regents of the University of California, San Francisco \$7,513
via National Football League

Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI Post U0-1)

Brief description of the project's goals: We will continue to 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.

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. 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

W81XWH-14-2-0176 (Manley/Okonkwo) 09/30/14 – 09/29/20 0.24 calendar (2.00%)
The Regents of the University of California, San Francisco \$102,633
via USAMRAA

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

R43-CE003070 (Southern/Puccio)	09/30/18 – 12/31/19	0.12 calendar (1.00%)
GAIA Medical Institute via Centers for Disease Control and Prevention	\$67,729	

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

005 (Puccio)	03/01/18 – 02/28/20	0.12 calendar (1.00%)
Chuck Noll Foundation	\$100,000	

Biomarker Panel for Inflammation and Tau in Concussed Athletes

Brief description of the project's goals: To generate pilot data to identify and provide a temporal timeline of biological pathways implicated in concussion, (ie. tau and inflammatory pathways) using novel sweat patch analyses and correlation to objective symptomology.

Agency Point of Contact Name/Address

John Denny
Executive Director
Chuck Noll Foundation for Brain Injury Research
3400 South Water Street
Pittsburgh, PA 15213

List of the specific aims:

1. Collect novel sweat patch samples of participants from 2 established, enrolling research studies of mild TBI (NCAACARE Consortium and University of Pittsburgh Medical Center) following acute concussion and 1-week follow-up.
2. Analyze blood biomarker and explore sweat biomarker of tau protein and inflammatory markers in concussed athletes and patients and correlate with acute symptomology and outcomes.
3. Compare blood and sweat biomarker data with concussive history to determine pilot data on repetitive, potential accumulative concussive pathology and outcomes.

Proposed Project Overlap: None

W81XWH-16-2-0020 (Hartings) 07/01/16 – 07/14/20 0.06 calendar (0.50%)
University of Cincinnati via USAMRAA \$40,750

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

R44-HD090817 (Southern/Griffin/Peacock/Puccio) 08/15/17 – 07/31/20 0.24 calendar (2.00%)
GAIA Medical Institute via NIH PRIME \$200,000 (No Cost Extension)

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

Brief description of the project's goals: 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-17-C-0006 (Pierro/Puccio)	01/10/19 – 08/31/20	0.03 calendar (0.25%)
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Vivonics Inc. via USAMRMC

\$71,010 (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

No Contract Number (Puccio)

09/22/16 – 08/31/20

0.01 calendar (0.10%)

ArcheOptix Biomedical, Inc.

\$138,083

Near-Infrared Spectroscopy (NIRS) Device for the Detection of Intra-Cranial Hematoma in TBI

Brief description of the project's goals: This study has been designed to determine the effectiveness of a new technology for detecting intracranial hematomas.

Agency Point of Contact Name/Address

Sav Stratis

ArcheOptix Biomedical, Inc.

3B-745 Development Drive

Kingston, Ontario, K7M-4W6 Canada

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	0.03 calendar (0.25%)
Abbott Laboratories	\$261,293	

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 – 09/30/21	1.00 calendar (8.40%)
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	0.24 calendar (2.00%)
Commonwealth of PA; DOH	\$285,756	

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

W81XWH-18-2-0051 (Billiar)
USAMRAA

09/30/18 – 09/29/21
\$21,052

0.30 calendar (2.50%)

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

W81XWH-18-1-0739 (Okonkwo/Mountz)
USAMRAA

09/30/18 – 09/29/21
\$7,275

0.12 calendar (1.00%)

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. Petrore

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

No Contract Number (Manley/Puccio)

02/21/15 – 12/18/21

0.06 calendar (0.50%)

The Regents of the University of California, San Francisco
via Abbott Laboratories

\$272,940

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.

Proposed Project Overlap: None

I# 0061071 (Okonkwo)

04/01/18 – 03/31/22

0.12 calendar (1.00%)

National Football League

\$11,512

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

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

07/01/18 – 06/30/23

3.00 calendar (25.00%)

University of Michigan via NIH

\$88,786

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
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

1.20 calendar (10.00%)

National Institutes of Health -NINDS

\$58,915

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. The 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

R01-NS110944 (Gardner)	07/01/19 – 06/30/24	0.18 calendar (1.50%)
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. Facilitate appropriate biospecimen banking in the University of Pittsburgh TBI Biospecimen Repository and ensure subsequent safe delivery of collected biospecimens to TBD laboratory for analysis.

Proposed Project Overlap: None

PENDING

JIT; Pending EP180013 (Diaz-Arrastia)	04/01/19 – 03/31/23	0.60 calendar (5.00%)
The Trustees of the University of Pennsylvania via USAMRAA	\$216,914	

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

Brief description of the project's goals: This program proposes to address the clinical and societal need for assessing the demographic and neurological outcomes of a new prospective cohort of adults with traumatic brain injury (TBI) and post-traumatic epilepsy (PTE). This includes the development and validation of improved epileptogenesis appropriate TBI predictors and outcomes.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. Extend follow-up period of TRACK-TBI participants from 1 to 5 years.
2. Extend follow-up period of the TRACK-TBI affiliated studies, SD-II, from 6 months to 2 years.
3. To conduct specialist epileptologist evaluation for all TBI patients who screen positive for PTE.
4. To measure candidate blood biomarkers to determine if they are prognostic for epileptogenesis.

Proposed Project Overlap: None

JIT; Pending BA170613 (Diaz-Arrastia/Puccio)	06/01/19 – 05/31/24	0.30 calendar (2.50%)
The Trustees of the University of Pennsylvania via USAMRMC PRIME	\$379,075	

Biorepository for the Biomarkers in Brain Oxygen Optimization in Severe TBI Trial (Bio-BOOST)

Brief description of the project's goals: The Bio-BOOST study will collect blood and, where feasible, cerebrospinal fluid (CSF), in a subset of 300 participants in BOOST-3 (both randomized groups), at ten BOOST-3 sites, selected based on their proven ability to enroll patients with severe TBI and to collect biological fluids efficiently.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. Prepare a study specific Manual of Procedures for biospecimen collection, processing, storage and shipping. Instruction for sample documentation will be provided.
2. Provide remote site training via a Webinar.
3. Prepare and send to each enrolling site (10 sites) biospecimen collection kits.
4. Arrange with the enrolling sites the shipment of the frozen samples and electronic specimen logs (estimated 1 shipment/site/year).
5. Upon receipt of a shipment, the TBI Biorepository will inventory the received samples and upload a verified specimen file to the Biorepository database and arrange for their long-term storage.
6. Sample processing: DNA extraction/QC and sub-aliquoting of 1 sample/subject.
7. Upon completion of the study, the TBI Biorepository will arrange shipments, via World Courier, to the long-term storage or the biomarker analyses company/site for final batch processing.

Proposed Project Overlap: None

JIT; W81XWH-18-2-0042 (Manley)	09/30/19 – 09/29/21	0.60 calendar (5.00%)
The Regents of the University of California, San Francisco via USAMRAA	\$566,386	(effort starts in yr02)

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. Validate biomarkers of Diffuse Axonal Injury (DAI), with existing TRACK-TBI biospecimens and neuroimaging.
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 Cyclosporin A on biomarker and clinical endpoints in moderate-severe TBI patients admitted to the ICU.

Proposed Project Overlap: None

JIT; U01-NS114140-01 (Puccio/Diaz-Arrastia)	12/01/19 – 11/30/24	0.60 calendar (5.00%)
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The Trustees of the University of Pennsylvania via NIH \$181,042

PRIME

Clinical Validation of Serum Neurofilament Light as a Biomarker of Traumatic Axonal Injury

Brief description of the project's goals: This project aims to clinically validate Neurofilament Light as a biomarker of traumatic axonal injury, with the goal of facilitating future clinical trials of axono-protective therapies.

Agency Point of Contact Name/Address

Unknown/Pending Grant Application

List of the specific aims:

1. We will determine reference intervals (RIs) for NF-L using Clinical and Laboratory Standards Institute (CLSI) guidelines using assays provided from our industry partner (Quanterix, LLC, Lexington, MA). CLSI guidelines recommend using 120 subjects per partition calculated by the non-parametric rank method with 90% confidence intervals (CI) around each RI calculated using ranked observations²⁷. The only published RI data for NF-L is based on a small number of subjects (n=254) age 18-70y without multiple sclerosis collected from a single center in Switzerland,²² which is insufficient for clinical validation. Plasma samples will be drawn from the CHMS Niobank, , as well as the Omni cohort from FHS.
2. We will measure NF-L in existing plasma samples (obtained on the day of injury and 2 weeks later) from TRACK-TBI participants who also have MRIs at 2 weeks and 6 months after injury (n=1100). The relationship between NF-L elevations and neuroimaging measures of TAI (DTI measure of FA at the 2-week scan) and Wallerian degeneration (white matter volume at 6 months after injury) will be assessed.
3. We will extend the follow-up period of a subset of TRACK-TBI participants(n=300) from one year to 5 years after injury. TRACK-TBI has enrolled 2800 subjects with TBI from 2/2014 – 10/2018, with the last follow-up assessment scheduled at 1 year after injury. We propose extending the follow-up period for a subset of TRACK-TBI (n=400) to 5 years, which will allow assessment of the long-term trajectory of NF-L after TBI. The extensive clinical, imaging, and biomarker data that has already been collected in these subjects will be leveraged to identify risk factors, co-morbidities, and prognostic biomarkers of TBI-associated axonal degeneration.

Proposed Project Overlap: None

Pending W81XWH-19-S-CCC1 (Charalambides)

01/01/20 – 12/31/22

0.60 calendar (5.00%)

Carnegie Mellon University via USAMRMC

\$416,197

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 0.48 calendar (4.00%)
University of Florida via NIH PRIME \$70,000

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)
National Institutes of Health

07/01/20 - 06/30/25
\$260,524

0.60 calendar (5.00%)

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**; **R43-CE003070**; **I#0061071**; **R01-NS110944**

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.

- b. 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.
- c. 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.
- d. 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.
- e. 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.
- f. 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

- a. Accuracy level:?
- b. Precision level:?
- c. Work with external electrode supplier to improve their electrode self-life and reliability and quantitative way of characterizing the electrode life remaining.
- d. Development of fail safe and robust software

Task 3: Animal study and limited clinical trials

- a. Identification of critical optimization parameters in animal and human studies
- b. 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

CURRENT

1U01NS086090-01 (Robertson, MPI)

09/30/2013 – 08/31/18

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)

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

5R01NS094535-03 (Thomas Kent PI) 7/1/17-6/30/19 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

PENDING

(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

OVERLAP:

None

**For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED
For Non-competing Progress Reports (PHS 2590) – Submit only Active Support for Key Personnel**

PHS 398/2590 OTHER SUPPORT

Provide active support for all key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. **Include the principal investigator's name at the top and number consecutively with the rest of the application.** The sample below is intended to provide guidance regarding the type and extent of information requested.

For instructions and information pertaining to the use of and policy for other support, see Other Support in the PHS 398 Part III, Policies, Assurances, Definitions, and Other Information.

Note effort devoted to projects must now be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

Format

NAME OF INDIVIDUAL

ACTIVE/PENDING

Project Number (Principal Investigator) Source Title of Project (or Subproject) The major goals of this project are...	Dates of Approved/Proposed Project Annual Direct Costs	Person Months (Cal/Academic/ Summer)
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Schnyer, David M.

ACTIVE

National Football League - Manley (PI), Schnyer (Site PI) 07/01/2018 – 06/30/2021
Title: 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.

R01AG043425 Schnyer & Worthy (Co-PIs) – NIA 01/2014-12/2019. Total - \$1,727,640.
Title: A computational neuroscience approach to frontal compensation in decision making.
Effort: Cost shared 1 calendar month

This proposal examines neurocognitive changes in functioning associated with normal aging using a computational neuroscience approach.

R33MH109600-01 Beevers & Schnyer (Co-PIs). 04/01/2016 – 03/31/2020. Total - \$1,754,833.
Title: Development of Attention Bias Modification for Depression.
Effort: 1.5 calendar months

This proposal aims to test the efficacy of attention bias modification in altering the neurocognitive basis of attention control and improving mood symptoms in individuals suffering from MDD.

CDMRP - Manley, et. al., (Co-PIs), Schnyer (UT Site PI) 09/01/2014 08/31/2020 Site PI
Subcontract to UT - \$201,516
Title: TBI Endpoints Development (TED)
Effort: 0.5 calendar month

The overall objective of validating endpoints and improving clinical trial design to inform and accelerate FDA approval of diagnostic tools and therapeutic agents for TBI.

PENDING

None

OVERLAP

There is no scientific overlap.

Murray B. Stein, MD, MPH: Current/Pending Research Support

Current Research Support

Title: San Diego Clinical and Translational Research Institute

Role: Co-Investigator (PI: Gary Firestein MD, UCSD)

Time commitment: 2.4 cal months

Supporting Agency: NIH/NCATS; Type: UL1 TR001442

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: NCATS Grants Management Specialist, National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Boulevard, Bethesda MD 20892-4874

Performance period: 08/31/2015 – 03/31/2020

Level of funding: ~\$5,000,000 DC current year

Project Goals/Specific Aims: The major goals of this grant are to foster innovative research and research partnerships and advance the science of collaborative research.

Title: TBI Endpoints Development (TED)

Role: Consortium PI (PI: Manley)

Time commitment: 1.37 cal months

Supporting Agency: Department of Defense (DoD) Type: W81XWH-13-PHTBI-TED

Performance period: 09/30/2014 – 09/29/2020 (NCE)

Level of funding: \$112,356 DC current year

Project Goals/Specific Aims: The major goal of this award is the support of the Consensus and Implementation Conferences and validation studies pertinent to TBI endpoints and outcomes.

Title: Army Study to Assess Risk and Resilience in Service Members-Longitudinal Survey (STARRS-LS)

Role: Co Investigator (with Ursano, HJF)

Time commitment: 3.19 cal months

Supporting Agency: US Department of Defense

Performance period: 07/01/2015 – 11/30/2019

Level of funding: ~\$343,080 DC current year

Project Goals/Specific Aims: The major goals of this award are to develop models and report actionable findings pertinent to suicide and related mental health problems and resilience in the military. This iteration of the project focuses on longitudinal follow-up of the inception cohort.

Title: Enhancing Fear Extinction via Angiotensin Type 1 Receptor Inhibition: A Randomized Controlled Trial in Posttraumatic Stress Disorder

Role: PI

Time commitment: 1.06 cal months

Supporting Agency: Department of Defense (DoD) Type: W81XWH-15-2-0090

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Allison Milutinovich, U.S. Army Medical Research Acquisition Activity, 820 Chandler St., Fort Detrick, MD 21702-5014

Performance period: 09/30/2015 – 09/29/2019

Level of funding: \$6,973,352.00 Total Costs for Entire Project Period

Project Goals/Specific Aims: The goal of this project is to conduct a multi-site randomized controlled trial to determine the efficacy of losartan for symptoms of PTSD.

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

Role: Co-Investigator (Manley, UCSF)

Time commitment: 1.06 cal months

Supporting Agency: DOD/MTEC; Type: W81XWH-15-9-0001

Performance period: 09/14/2018 – 11/30/2023

Level of funding: \$26,254,760 Total Costs for Entire Project Period

Project Goals/Specific Aims: The goal of this project is to establish the TRACK-TBI NETWORK (TRACK-TBI NET), an innovative Phase 2 TBI adaptive clinical trials network in traumatic brain injury.

Title: Investigation Flotation- REST as a novel technique for reducing anxiety and depression

Role: Co-Investigator (Paulus, LIBR)

Time commitment: 0.46 cal months

Supporting Agency: NIH via Laureate Institute for Brain Research; Type: R34AT009889

Performance period: 09/25/2018 – 07/31/2021

Level of funding: \$74,642 Total Costs for Entire Project Period at UC San Diego

Project Goals/Specific Aims: The goal of this project is to [...].

Title: Study to Assess Risk and Resilience in Servicemembers (Army STARRS) Continuation

Role: Co Investigator (with Ursano, HJF)

Time commitment: 1.2 cal months

Supporting Agency: USU via Henry M. Jackson Foundation; Type: HU00011920025

Performance period: 07/01/2019 – 06/30/2020

Level of funding: \$300,429 Total Costs for Entire Project Period at UC San Diego

Project Goals/Specific Aims: The goal of this project is to investigate the use of flotation to reduce anxiety and depression.

Title: Psychiatric Genomics Consortium for PTSD

Role: Multi-PI (Nievergelt, UCSD)

Time commitment: 0.91 cal months

Supporting Agency: NIH / NIMH; Type: R01MH106595

Performance period: 09/01/2019 – 06/30/2024

Level of funding: \$3,667,586 Total Costs for Entire Project Period at UC San Diego

Project Goals/Specific Aims: The goal of this project is to investigate the genetic basis of posttraumatic stress disorder.

Pending:

Title: TRACK-TBI Brain Recovery After Injury vs. Neurodegeneration (TRACK-TBI BRAIN)

Role: Co Investigator (with Manley, UCSF)

Time commitment: 0.6 cal months

Supporting Agency: NIH / NINDS;

Performance period: 12/01/2019 – 11/30/2024

Level of funding: \$ 271,746 Total Costs for Entire Project Period at UC San Diego

Project Goals/Specific Aims: The goal of this project is to determine the efficacy of losartan for treating PTSD.

Completed:

Title: The impact of traumatic stress on the methylome: implications for PTSD

Role: Co-Investigator (Smith)

Time commitment: 0.48 cal months

Supporting Agency: NIH/NIMH Type: R01MH108826

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Maggie Paolini, NIMH Grants Management Specialist, 6001 Executive Boulevard Rockville, MD 20852

Performance period: 08/18/2016 – 05/31/2020

Level of funding: \$2,222,029.00 Total Costs for Entire Project Period

Project Goals/Specific Aims: The goal of this project is to facilitate a multi-site, epigenome-wide analysis of PTSD, with the long-term goal of developing an epigenetic panel that informs the prediction or treatment of PTSD.

Title: Novel Behavioral Intervention to Target Social Reward Sensitivity and Attachment

Role: Co-Investigator (Taylor)

Time commitment: 1.8 cal months

Supporting Agency: NIH/NIMH Type: R61MH113769

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: James Pugh, NIMH Grants Management Specialist, 6001 Executive Boulevard Rockville, MD 20852

Performance period: 08/05/2017 – 05/31/2019

Level of funding: \$485,715 annual direct costs

Project Goals/Specific Aims: The goal of this project is to test the hypothesis that social approach training can up-regulate social reward sensitivity, investigate optimal dosing of social

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

Role: Consortium PI (PI: Manley)

Time commitment: 0.5 cal months

Supporting Agency: National Institute of Health (NIH) Type: U01 NS086090

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Krista Roznovsky, UC San Francisco, 3333 California St, San Francisco, CA 94118

Performance period: 09/30/2013 – 08/31/2018

Level of funding: \$12,415 DC current year

Project Goals/Specific Aims: The goal of this project is to test and refine data elements by conducting clinical studies on victims of traumatic brain injury.

Title: PTSD-TBI Clinical Consortium (INTRuST)

Role: Director of Biostatistics (PI: Stein)

Time commitment: 3.0 cal months

Supporting Agency: Department of Defense (DoD); Type: W81XWH08-2-0159

Performance period: 09/15/2008 – 10/14/2016

Level of funding: \$1,829,370 DC

Project Goals/Specific Aims: The major goal of this 10-Site Clinical Consortium was to conduct clinical research that will advance therapeutics in posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI).

Title: A GEWIS Study of Smoking, Hazardous Drinking, and Other Health Risk Behaviors

Role: MPI (Kaufman/Stein MPI)

Time commitment: 0.9 cal months

Supporting Agency: NIH/NIAAA Type: R21 AA024404

Performance period: 04/01/2015 – 03/31/2017

Level of funding: ~\$25,000 DC current year

Project Goals/Specific Aims: The major goal of this award is to conduct genome-wide gene-environment interaction analyses in a large, population-based extant dataset on risks for smoking, hazardous drinking and other health risk behaviors.

Title: Latent Constructs: Negative-Positive Valence Domains in Anxiety and Depression

Role: Co-Investigator (PI: Martin P. Paulus)

Time commitment: 0.9 cal months

Supporting Agency: National Institute of Mental Health (NIH); Type: R01 MH101453

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Joel Sherrill, PhD; 6001 Executive Boulevard, Room 7145, MSC 9633, Bethesda, MD 20892-9633

Performance period: 09/09/2013 – 05/31/2017

Level of funding: \$373,768 DC current year

Project Goals/Specific Aims: The major goal of this award is to develop constructs that connect across units of analysis to gain a deeper understanding of psychiatric conditions.

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.

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.

W81XWH-18-2-0042 (Manley, Temkin Site PI)	9/30/2018-9/29/21	1.20 calendar
DOD US Army Med. Res. Acq. Activity	\$1,059,807 (total study), \$ 411,707 (UW)	

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.

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

PREVIOUS, CURRENT, AND PENDING SUPPORT

WHYTE, JOHN

PREVIOUS (within the last 5-years)

ME-1403-14083 (Whyte) 01/01/2015-10/01/2018 2.40 calendar
PCORI

Valerie Clark

1828 L Street NW, Suite 900, Washington, DC 20036

Better Rehabilitation through Better Characterization of Treatments: Development of the Manual for Rehabilitation Treatment Specification

Goal: Develop the conceptual framework of the RTT into standardized operational procedures by which clinicians, educators, and researchers across all rehabilitation disciplines may define and specify rehabilitation treatments according to their targeted effects, mechanisms of action, and hypothesized active ingredients.

Aims: 1. Develop a reliable and useful Manual for Rehabilitation Treatment Specification describing a standardized procedure to guide researchers, clinical educators, and clinicians in applying the tripartite structure of treatment theory

2. Provide training based on the Manual, to a multidisciplinary cohort of rehabilitation professionals, and use this training to assess the reliability and utility of the method for treatment definition and specification

3. Use 50 well-defined treatment examples produced in the first phase of the project to make recommendations for further development of a Rehabilitation Treatment Taxonomy.

Role: PI

H133A120037 (Hart) 10/01/2013-09/29/2019 2.40 calendar
NIDRR \$2,295,000

Pimjai Sudsawad, Program Specialist

US Dept of Education, 400 Maryland Ave, SW, Mailstop 2700, Washington, DC 20202

The Moss Traumatic Brain Injury Model System

Goal: characterize the long-term outcomes following rehabilitation from moderate and severe traumatic brain injury, and to conduct specific research projects related to attention, spasticity, and electronic memory aides.

Aims: **Aim 1:** To develop, using consumer input, a manual for a 2-hour intervention session, integrating principles of brief BA with the implementation intention development protocol previously piloted by our group.

Aim 2: To conduct a randomized controlled pilot trial (N=60) that examines the effects of this intervention session accompanied by daily individually tailored *implementation intentions* for 8 weeks (Intention- experimental condition), compared to an initial session devoted to education on goals and motivation accompanied by receipt of self-selected motivational messages for 8 weeks (Motivation- comparison condition). A range of outcomes relevant to emotional well-being and societal participation after TBI will be examined.

Aim 3: To examine the trajectory of observed treatment effects, if any, by comparing change in the 1st 4 weeks of treatment to change in the 2nd 4 weeks of treatment on all measures. No hypotheses are proposed, as the purpose of this Aim is to explore the time course of treatment, if it is effective, to inform the design of a more comprehensive trial.

Aim 4: To examine the relationships between changes indicative of treatment response, and participant characteristics, including: gender and racial/ ethnic status; severity and chronicity of TBI; baseline intellectual, memory, and executive function; severity of pre-treatment emotional dysfunction; involvement/ absence of an SO; and discrepancies between self- and SO report of participant status. Formal hypotheses are not proposed for this Aim, as we recognize that the power for examining treatment response in sub-groups of participants will be relatively low. We will pursue this Aim to help develop hypotheses to inform the design of a larger trial comparing the treatment groups, should the primary hypothesis be supported.

Role: Co-Investigator

CURRENT

5K12HD001097 (Boninger) 03/01/2013-02/28/2023 0.60 calendar
NIH/NICHD thru Univ of Pittsburgh \$144,527

Barbara J. Aul, Office of Research
123 University Place, Pittsburgh, Pa 15213

Rehabilitation Medicine Scientist Training (RMST) Program

Goal: train psychiatrists who wish to pursue a career as independent researchers.

Aims: 1. Pre-application phase seeks to enroll PGY-2 and PGY-3 residents, and junior faculty with research interest and potential, in a career development process, culminating in a well-formed funding application. A special emphasis will be placed on recruitment of pediatric psychiatrists and psychiatrists from under-represented minorities.

2. During Phase I, trainees will work for 3 years with a productive senior scientist to learn skills relevant to psychiatric research.

3. In Phase II, the trainee will seek to transition to a career as an independent investigator, with a minimum of 50% protected research time for a 2-year period, with a goal of 75% research time.

4. The net result of the program will be a cadre of faculty for departments of PM&R who can compete successfully for extramural funds and be productive independent investigators, ultimately fulfilling a vision of psychiatric research.

Role: Program Co-Director

T32HD071844 (Whyte) 05/13/2013-04/30/2023 0.60 calendar
NIH/NICHD

Saiyda Khan, Grants Management Specialist
31 Center Drive, Building 31, Room 2A32, Bethesda, MD 20892-2425

Postdoctoral Training in Translational Neurorehabilitation Research

Goal: train postdoctoral fellows, recruited from basic science and clinical disciplines using a mixture of didactic and hands-on training methods.

Aims: 1. Candidate selection based on applicant qualifications and available mentor support

2. Implementation of the training curriculum, including didactic content, and opportunities for peer-to-peer interactions within and across the training sites

3. Annual review of the candidate selection process to evaluate the balance of trainees in more basic and applied areas, ways to streamline the selection process, satisfaction with the selection process by mentors and trainees Annual review of the training curriculum with modifications based on individualized trainee and mentor feedback

4. Annual review of trainee progress reports and productivity of prior trainees and identification of needs for additional training and supports

Role: PI

90DPTB0004-01-00 (Rabinowitz)

09/30/2017-09/29/2022

2.40 calendar

NIDILRR

\$2,237,500

Dr. Cate Miller, Project Officer

Switzer Building, 330 C Street, SW, Washington, DC 20201

The Moss Traumatic Brain Injury Model System

Goal: characterize the long-term outcomes following rehabilitation from moderate and severe traumatic brain injury, and to conduct specific research projects related to attention, spasticity, and electronic memory aides.

Aims: **Aim 1:** To develop, using consumer input, a manual for a 2-hour intervention session, integrating principles of brief BA with the implementation intention development protocol previously piloted by our group.

Aim 2: To conduct a randomized controlled pilot trial (N=60) that examines the effects of this intervention session accompanied by daily individually tailored *implementation intentions* for 8 weeks (Intention- experimental condition), compared to an initial session devoted to education on goals and motivation accompanied by receipt of self-selected motivational messages for 8 weeks (Motivation- comparison condition). A range of outcomes relevant to emotional well-being and societal participation after TBI will be examined.

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Aim 4: To examine the relationships between changes indicative of treatment response, and participant characteristics, including: gender and racial/ ethnic status; severity and chronicity of TBI; baseline intellectual, memory, and executive function; severity of pre-treatment emotional dysfunction; involvement/ absence of an SO; and discrepancies between self- and SO report of participant status. Formal hypotheses are not proposed for this Aim, as we recognize that the power for examining treatment response in sub-groups of participants will be relatively low. We will pursue this Aim to help develop hypotheses to inform the design of a larger trial comparing the treatment groups, should the primary hypothesis be supported.

Role: Co-Investigator

PENDING

None

OVERLAP

None

OTHER SUPPORT

Wright, David W.

U01CE002939-01-00 (Wright, Ratcliff, Simon) 09/30/18 – 09/29/22 1.35 calendar months
CDC \$444,321

Promoting Recovery in Children Who Sustain a Mild Traumatic Brain Injury: The TBI Evaluation and Management (TEaM) Toolkit

This four-year trial is designed to determine whether the TEaM Toolkit with PCP training and tools, integrated within a Neighborhood of Care model will enhance detection, provide a more streamlined assessment, improve documentation, clinical management, injury prevention messaging and return to activity information, and provide a link between Emergency Care, Urgent Care, Primary Care, Parents and Schools that has the potential to improve the outcome of the child suffering from mTBI.

Role: Co-PI

Foundation Award (Sevransky) 01/01/18 – 12/31/19 0.57 calendar months
Marcus Foundation \$9,266,929

Vitamin C, Corticosteroids and Thiamine in Sepsis Study (VICTAS Study)

This multi-center trial is designed to study the clinical impact of the addition of Vitamin C, Thiamine, and Hydrocortisone to the usual therapy for sepsis.

Role: Co-I

1U24NS100673 (Wright) 07/15/17 – 05/31/22 0.18 calendar months
NIH \$116,794

Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN) – Network Clinical Center

SIREN will enable conduct of high-quality, multi-site clinical trials to improve the outcomes for patients with neurologic, cardiac, respiratory, and hematologic and trauma emergency events. Hubs will actively enroll patients into every clinical trial performed in SIREN, regardless of disease focus. A hub will additionally provide scientific leadership and administrative oversight to its multiple satellite sites, together providing access to a large and varying patient population for clinical trials.

Role: PI

DTNH2217D00068 (Rupp, Wright) 09/29/17 – 09/28/22 0.12 calendar months
NHTSA \$617,193

Crash Injury Research and Engineering Network (CIREN)

CIREN is a sponsor-led multi-center research and data collection program involving a collaboration of clinicians and engineers in academia, industry, and government pursuing in-depth studies of crashes, and the resultant injuries and treatment, to improve processes and outcomes. CIREN centers are based at Level One Trauma Centers and biomechanics research laboratories. CIREN's mission is to improve the prevention, treatment, and rehabilitation of motor vehicle crash injuries to reduce deaths, disabilities, and human and economic costs.

Role: Co-PI

U24NS107234 (Frankel, Wolf, Wright) 09/01/18 – 07/31/23 0.12 calendar months
NIH / NINDS \$200,000

Stroke Trials Network - Regional Coordinating Stroke Centers

The major goal of this project is to build a research network of investigators at metro-Atlanta hospitals for clinical trials to develop effective treatments for patients with stroke.

Role: Co-PI

CSS-CNV-17-001 (Nogueira, Wright)

11/01/18 – 10/31/28

0.12 calendar months

Cerenovus

\$4,936,623

ENDOLOW Multi-Center Clinical Trial

This award is for a multi-center clinical trial with sites in US, Canada, and Europe, designed to compare outcome of low NIHSS patients that undergo thrombectomy procedure using the EmboTrap device within 8 hours to those receiving medical management only.

Role: PI of Clinical Coordinating Center

What other organizations were involved as partners?

One Mind

One Mind is an independent, non-profit organization dedicated to benefiting all affected by brain illness and injury through fostering fundamental changes to radically accelerate the development and implementation of improved diagnostics, treatments, and cures — while eliminating the stigma that comes with mental illness. Located in Seattle, WA, One Mind has provided direct salary support for the TED Administrative Core working out of UCSF. One Mind has also proved to be a valuable collaborative partner as demonstrated by their work to support conversion of the TBI CDEs to CDISC standards.

Clinical Data Interchange Standards Consortium (CDISC)

Located in Austin, TX, CDISC is a global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata. TED investigators have been collaborating with CDISC to conform TBI Common Data Elements to CDISC standards for FDA regulatory submission.

Rancho Biosciences

Rancho Biosciences is a data curation company located in San Diego, CA. Through a donation from a private partner, the TED Initiative has contracted with Rancho Biosciences to design and build a custom an imaging annotation and management tool designed to streamline the process of reading, annotating, and cataloging Metadataset images.

Department of Energy

As previously reported to the TED Government Steering Committee, we have established a collaboration with the Department of Energy to bring their expertise in artificial intelligence, machine learning, and their high-performance computing infrastructure to analyze data from the TED Metadataset.



March 12, 2019

The TBI Endpoints Development (TED) Initiative
Esther Yuh, MD PhD
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Zuckerberg San Francisco General Hospital and Trauma Center
Department of Neurosurgery
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San Francisco, CA 94110

Re: Q-Submission Number: Q161252
MDDT Name: OsiriX CDE Software Module
MDDT Type: Biomarker Test
Dated: July 30, 2018
Received: August 01, 2018

Dear Esther Yuh and Geoff T. Manley:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of Medical Device Development Tool (MDDT) Qualification Package for the OsiriX CDE Software Module. We are pleased to inform you that the MDDT is qualified for the following context of use (COU):

Contusions, as assessed by an expert rater from MRI using OsiriX CDE Software Module MDDT, may be used for enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3 months for patients aged between 18-65 years with acute non-penetrating head trauma and Glasgow Coma Scale (GCS) 13-15 who have undergone acute head CT (e.g., as part of standard clinical care) at a U.S. Level 1 trauma center.

This qualification determination does not constitute marketing clearance or approval of this product as a medical device, and does not affect a previous clearance or approval of a device.

Once an MDDT is qualified for a specific COU, CDRH intends to accept its use by any medical device sponsor for that COU. When used within the above COU, the results of an assessment that uses this MDDT can be relied upon in medical device evaluation in a regulatory submission without the need to reconfirm with CDRH the suitability and utility of the MDDT. CDRH maintains the

responsibility for evaluating regulatory submissions using information obtained from a qualified MDDT.

MDDT qualification does not obviate the need for a medical device sponsor to meet existing regulatory requirements, nor does it alter the benefit-risk threshold for regulatory decision-making related to a medical device; rather, it can facilitate the development and regulatory evaluation of a medical device by providing a more efficient and predictable means for collecting the necessary information to make regulatory assessments.

The use of an MDDT in a medical device clinical study does not change the IDE requirements for a given investigation.

CDRH will notify the public of its decision to qualify your MDDT. You have provided consent for FDA to make public certain information regarding this qualified MDDT.

Nothing about the MDDT program is intended to place limitations or requirements on MDDT licensing or fees, or the degree of access to intellectual property associated with an MDDT that a tool developer may give to a device sponsor.

You may request that CDRH incrementally expand or otherwise modify the qualified COU in response to new data or changing science by submitting a new qualification package. CDRH also intends to reconsider qualification decisions as appropriate. For example, if the bases upon which an MDDT was qualified have changed, CDRH may re-evaluate the qualification decision.

If you have any questions concerning this qualification decision letter, please contact Eriko Yoshimaru at (301) 796-4180 or Eriko.Yoshimaru@fda.hhs.gov.

Sincerely yours,

Robert A. Ochs, Ph.D.
Deputy Director for Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

***MDDT SUMMARY OF EVIDENCE AND BASIS OF QUALIFICATION DECISION FOR
OSIRIX CDE SOFTWARE MODULE***

BACKGROUND

MDDT NAME: OSIRIX CDE SOFTWARE MODULE

SUBMISSION NUMBER: Q161252

DATE OF SUBMISSION: AUGUST 01 2018

CONTACT:

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TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

The OsiriX CDE consists of a software module that assists expert raters, e.g., neuroradiologists, by providing a standardized way to demarcate and classify brain contusions using Common Data Element (CDE) criteria and to label abnormalities on MR images. Brain contusions measured by expert readers using the OsiriX CDE Software Module may be used as an enrichment tool for enrollment in clinical trials of therapeutic medical devices intended to improve outcomes of mild traumatic brain injury (TBI) patients.

In this summary, the term enrichment means the prospective use of any patient characteristic to select a study population in which detection of a medical device effect (if one is in fact present) is more likely than it would be in an unselected population.

MR acquisition protocols intended for evaluation include:

- T2*-weighted gradient echo or susceptibility-weighted images (T2*)
- T2-weighted spin-echo (T2)
- T2-weighted Fluid Attenuation Inversion Recovery (FLAIR)
- 3D T1-weighted gradient echo (3D T1)

From the NINDS Common Data Elements¹:

Contusion is defined as a focal area of brain parenchymal disruption due to acute mechanical deformation. Contusions typically occur in the cortex and may extend into subcortical region. Contusions may show grossly visible hemorrhage or minimal/absent hemorrhage. Acute contusions typically have a mottled, inhomogeneous appearance due to stippling of blood along the brain surface. As such, their size is difficult to measure. In addition, CT streak artifact limits visualization of the cortical surface, so contusions are best seen with MRI, particularly on the Fluid Attenuation Inversion Recovery (FLAIR) sequence. For purposes of categorization, contusions are differentiated from “intracerebral hematomas” by containing a *mixture* of hemorrhagic and non-hemorrhagic tissue, or by having no grossly visible hemorrhage (“bland contusion”), while an “intracerebral hematoma” is predominantly a uniform collection of blood alone. The term “contusion” should not be used for hemorrhagic lesions which fit better in other categories, such as small hemorrhages associated with the pattern of diffuse axonal injury, lesions which in context are more likely to represent infarction or other primary vascular lesion, or isolated subarachnoid hemorrhage (SAH). Contusions can, however, be associated with other lesions which commonly co-occur, such as brain laceration, adjacent SAH, and depressed skull fractures. Contusions which are questionable, such as those in an area of beam hardening on CT scan, should be noted as “indeterminate”. Note: areas of delayed hypodensity or signal change around a traumatic lesion should not necessarily be classified as contusions. Contusions in which the hemorrhagic component enlarges over time should not be re-classified on subsequent images as “intraparenchymal hemorrhage”.

While there are possible advantages for using the OsiriX CDE Software Module MDDT for enrichment of a clinical trial, it is important to understand the possible disadvantages and limitations as well. The user of this MDDT should refer to the sections *Summary of Evidence to Support Qualification* and *Assessment of Advantages/Disadvantages of Qualification* to evaluate the totality of the information provided to determine the appropriate use of the MDDT for their application.

QUALIFIED CONTEXT OF USE

Contusions, as assessed by an expert rater from MRI using OsiriX CDE Software Module MDDT, may be used for enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3 months for patients aged between 18-65 years with acute non-penetrating head trauma and Glasgow Coma Scale (GCS) 13-15 who have undergone acute head CT (e.g., as part of standard clinical care) at a U.S. Level 1 trauma center.

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

To support the qualification of the MDDT, the requestor provided a two part clinical study as described in the section below. In addition to the clinical study, previous investigations and pilot studies^{2,3}, level of risk associated with the use of the MDDT, and the possible advantages/disadvantages were used as evidence to support qualification for enrichment in clinical trials.

Biomarker-Outcome Association Study Overview

Extended Glasgow Outcome Scale (GOS-E) at three months was analyzed in relation to the presence vs absence of 1) ≥ 1 brain contusion and/or 2) ≥ 4 diffuse axonal injury (DAI). The presence of these radiologic findings was determined independently by three (3) board-certified neuroradiologists and annotated using OsiriX CDE software module. MR images were acquired on 3T systems from multiple vendors.

Study population and Inclusion Criteria

The study included 517 patients between the ages of 18-65 who presented to the emergency department (ED) at one of 11 U.S. Level 1 trauma centers. The patients had acute non-penetrating head trauma that prompted the physician to order a head CT scan within 24 hours of injury and a Glasgow Coma Scale (GCS) ED arrival scores of 13-15, and completion of both 2-week MRI exam and 3-month GOS-E score.

Protocol violation

One of the 11 original study sites was excluded from the MDDT study population due to concerns that GOS-E was not administered according to standard study protocols.

Study Objective

The objective of the study was to evaluate the association between contusions and DAI with 3-month GOS-E outcomes.

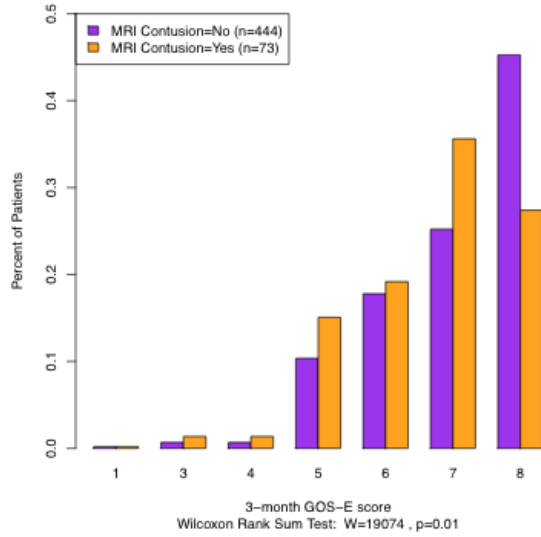
Results

The study compared the 3-month GOS-E outcomes with the biomarker outcome using the Wilcoxon Rank Sum test for each neuroradiologist and biomarker (See Figures below). The Wilcoxon Rank Sum Test can be rescaled by dividing the number of patients with a contusion and by the number of patients without a contusion. This rescaling yields a number that is equivalent to AUC, the area under the ROC curve, (a probability) such that 0.5 indicates no relationship.

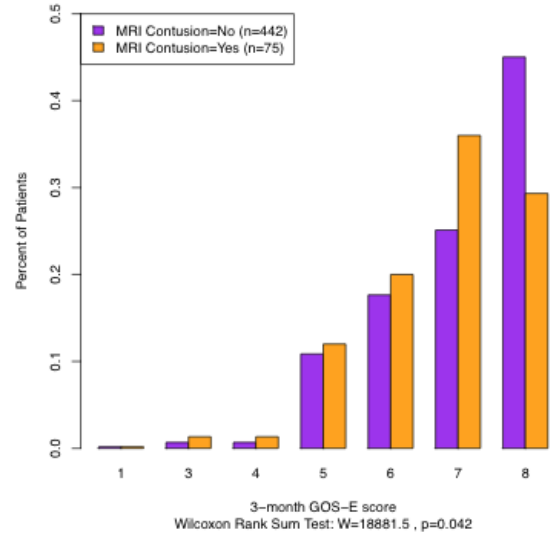
	MRI Contusion Biomarker			
	Positive	Negative	Wilcoxon	AUC (Rescaled Wilcoxon)
Reader 1	73	444	19074.0	0.588
Reader 2	75	442	18881.5	0.570
Reader 3	75	442	19282.0	0.582

	MRI DAI Biomarker			
	Positive	Negative	Wilcoxon	AUC (Rescaled Wilcoxon)
Reader 1	67	450	15586.5	0.517
Reader 2	72	445	15935.3	0.497
Reader 3	50	467	11675.0	0.500

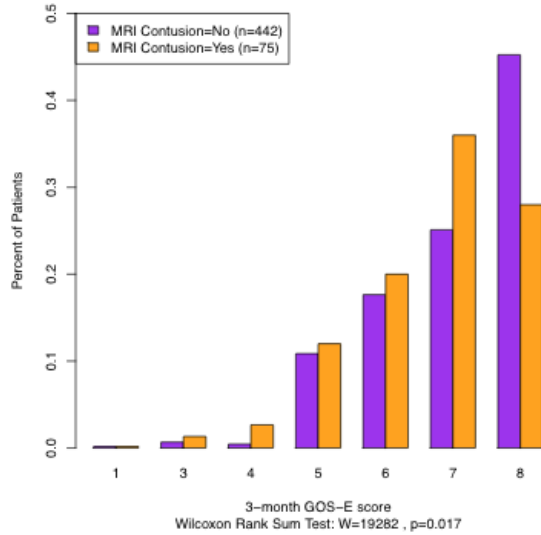
TRACK-TBI, 18–65yrs, GCS 13–15, by MRI Contusion (Neuroradiologist 1)

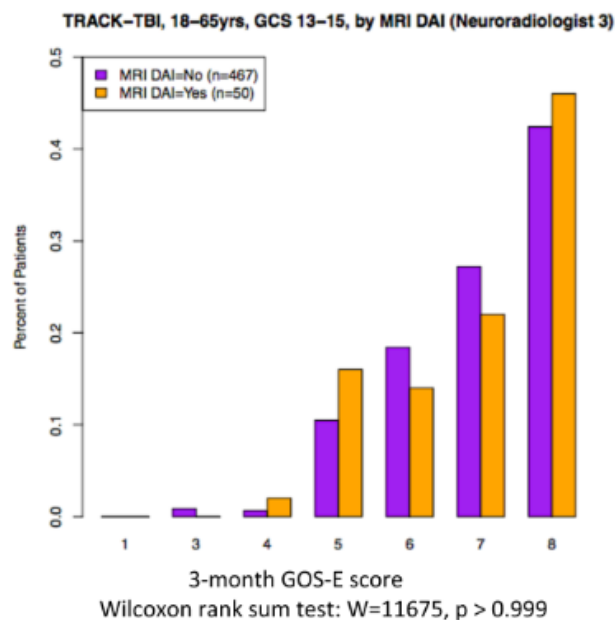
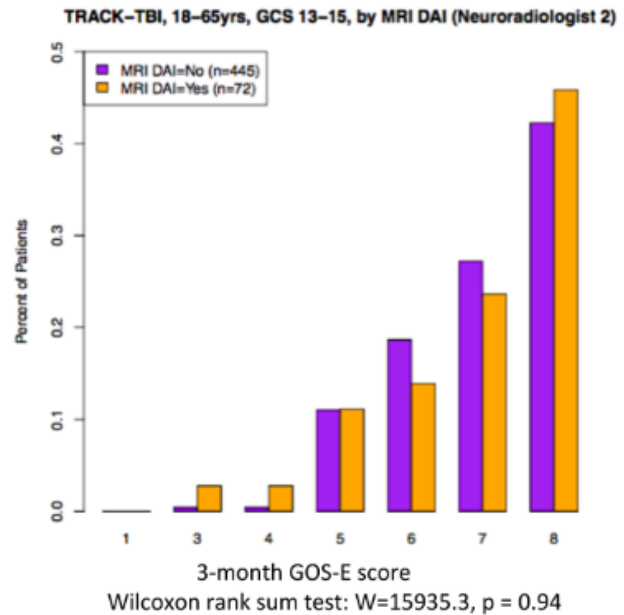
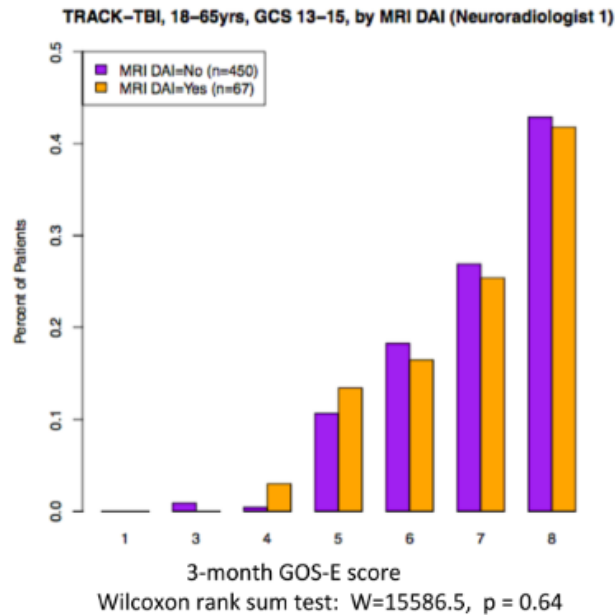


TRACK-TBI, 18–65yrs, GCS 13–15, by MRI Contusion (Neuroradiologist 2)



TRACK-TBI, 18–65yrs, GCS 13–15, by MRI Contusion (Neuroradiologist 3)





Interrater reliability (IRR) Study Overview

The percent agreement (PA), positive percent agreement (PPA), and negative percent agreement (NPA) were determined for each pair of board certified neuroradiologists who participated in the IRR study. The average of the pairwise measure over the three readers were calculated (APA = Average Percent Agreement, ANA = Average Negative Agreement). In addition, the 95% confidence intervals for each measure were calculated using a bootstrap procedure. Based on the results of the biomarker-outcome association study, only the IRR results for contusions are provided.

Study population

The study patient population is the same as the biomarker-outcome association study. All readers were U.S. board-certified neuroradiologists.

Results of IRR for contusion

	Reader 1 vs Reader 2	Reader 2 vs Reader 3	Reader 1 vs Reader 3
PPA [95% CI]	86.7% [76.8-93.4%]	86.7% [76.8-93.4%]	88.0% [78.4-94.4%]
NPA [95% CI]	98.2% [96.5-99.2%]	97.7% [95.9-98.9%]	98.4% [96.8-99.4%]
PA [95% CI]	96.5% [95.0-98.15%]	96.1% [94.4-97.7%]	96.9% [95.4-98.3%]

	Reader 2 vs Reader 1	Reader 3 vs Reader 2	Reader 3 vs Reader 1
PPA [95% CI]	89.0% [79.5-95.1%]	86.7% [76.8-93.4%]	90.4% [81.2-96.1%]
NPA [95% CI]	97.7% [95.9-98.9 %]	97.7% [95.9-98.9%]	98.0% [96.2-99.1%]
PA [95% CI]	96.5% [95.0-98.15%]	96.9% [95.4-98.3%]	96.1% [94.4-97.7%]

	Reader 1 vs Reader 2	Reader 2 vs Reader 3	Reader 1 vs Reader 3
APA [95% CI]	87.8% [81.5-92.6%]	86.7% [80.2-91.7%]	89.2% [83.0-93.7%]
ANA [95% CI]	98.0% [96.8-98.8%]	97.7% [96.5-98.6%]	98.2% [97.1-99.0%]

ADDITIONAL EVIDENCE TO SUPPORT QUALIFICATION

In a previous investigation², the requestor studied the relationship between TBI-CDE defined pathoanatomic injuries identified on MRI and the outcomes of mild TBI (mTBI) patients at 3 months post injury. The results showed that one or more brain contusions and ≥ 4 foci of hemorrhagic axonal injuries were independently correlated with poorer 3-month patient outcome when demographic/socioeconomic, clinical and CT findings were controlled. As part of this MDDT submission, the requestors carried out a prospective study with three neuroradiologists to independently validate the initial results. This prospective study, as described under the *Summary of Evidence to Support Qualification*, was reviewed as part of the qualification package for this MDDT.

ASSESSMENT OF ADVANTAGES/DISADVANTAGES OF QUALIFICATION

Assessments of Advantages of Using the MDDT

Use of this tool may serve as an option in the design of clinical trials which help advance the study of mTBI. While researchers may choose to select other criteria to enrich a clinical trial, the tool proposed here may serve as a convenient methodology for patient selection to enrich the patient population to either (1) decrease the overall number of subjects needed in the trial or (2) increase the likelihood of observing a statistically significant treatment effect in a trial of similar number of patients.

Below is a hypothetical example of how the MDDT can be used as part of the evaluation of a medical device. The values used in this example are based on the results of the clinical study reviewed as part of the qualification. The company name, “CureForPCS” is fictional.

CureForPCS has developed a therapy for postconcussive syndrome (PCS), and has an estimated effect size for its therapy based on early-phase clinical trials. It plans to conduct a clinical trial to demonstrate the therapy’s effectiveness in mild traumatic brain injury (GCS 13-15).

To boost the power for detecting a statistically significant treatment effect, the company decides to enrich their study population with patients expected to have poorer functional outcome, and thus for whom therapy could be shown to have a benefit. Based on biomarker-outcome association study data, patients with brain contusion on MRI are more likely (71.8%) than those without (54.8%) to have poor outcome, defined as a Glasgow Outcome Scale – Extended (GOS-E) of ≤ 7 at 3 months postinjury. Given that 14.4% of mild TBI patients in the biomarker-outcome association study demonstrated brain contusion on MRI, the percent of patients expected to have a poor outcome without regard to the presence of a brain contusion is 57.3%.

	Biomarker Positive Only (at 3 months)		Biomarker Negative Only (at 3 months)		Intended Population (All Patients at 3 months)	
	GOS-E ≤ 7	GOS-E = 8	GOS-E ≤ 7	GOS-E = 8	GOS-E ≤ 7	GOS-E = 8
Reader 1	72.6% (53/73)	27.4% (20/73)	54.7% (243/444)	45.3% (201/444)	57.3% (296/517)	42.7% (221/517)
Reader 2	70.7% (53/75)	29.3% (22/75)	55.0% (243/442)	45.0% (199/442)	57.3% (296/517)	42.7% (221/517)
Reader 3	72.0% (54/75)	28.0% (21/75)	54.8% (242/442)	45.2% (200/442)	57.3% (296/517)	42.7% (221/517)

- Proportion of biomarker-positive patients who have GOS-E ≤ 7 at 3 months, averaged across all 3 readers: 71.8%
- Proportion of biomarker-negative patients who have GOS-E ≤ 7 at 3 months, averaged across all 3 readers: 54.8%
- Proportion of all patients (regardless of biomarker) who have GOS-E ≤ 7 at 3 months, averaged across all 3 readers: 57.3%
- Prevalence of contusion on brain MRI, averaged across all 3 readers: 14.4%

Applying this information, the company uses the MDDT to enroll a study population in which 50% of the subjects have brain contusion on MRI, and 50% do not. We would expect 63.3% (average of 54.8% and 71.8%) of this “enriched” population, without treatment, to have a GOS-E ≤ 7 at 3 months postinjury. The company decides to enroll 100 patients in its control arm, and

100 patients in its therapy arm. In this case, 63 patients of the 100-patient control group, and 63 of the 100-patient treatment group, would be expected, without treatment, to have a GOS-E ≤ 7 at 3 months postinjury.

Had the study population **not** been enriched for those with brain contusion on MRI, only 57 of the 100-patient control group, and 57 of the 100-patient treatment group would be expected, without treatment, to have a GOS-E of ≤ 7 at 3 months (based on prevalence).

Using the MDDT, the company tests its therapy in an “enriched” population – that is, a study population with a greater proportion of patients in whom the therapy could be proven to have a benefit. If the therapy were tested in a population with too few patients who could be shown to benefit from the treatment, this would reduce the power of the trial to prove a statistically significant treatment effect, or require a larger sample size.

Assessments of Disadvantages of Using the MDDT

The use of this tool requires participants in a study to have an MR exam which may require additional resources and potentially increase the number of screen failures for a future trial (individuals who might otherwise meet the eligibility for the trial but are not included based on the results of the biomarker test). This may mean that there will be added costs to the clinical trials through the requirement of a brain MRI and through the additional patients who would need to be screened due to some potential participants being excluded due to MRI contraindications.

Individuals using this tool should clearly understand the statistical limitations of the data provided to support this qualification and the uncertainty associated with the use of the MDDT. The users should carefully review the results presented in under *The Summary of Evidence to Support Qualification* and use this tool within its qualified Context of Use.

CONCLUSION

Prior investigations, possible advantages and disadvantages, as well as the prospective clinical trial information were all taken into considerations in the decision to qualify the MDDT as an enrichment tool.

REFERENCE

1. NINDS COMMON DATA ELEMENTS.
https://commondataelements.ninds.nih.gov/TBI.aspx#tab=DATA_STANDARDS
2. Yuh, Esther L., et al. "Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury." *Annals of neurology* 73.2 (2013): 224-235.
3. Yue, John K., et al. "Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury." *Journal of neurotrauma* 30.22 (2013): 1831-1844.

CONTACT INFORMATION FOR ACCESS TO TOOL

FOR ACCESS TO OSIRIX CDE SOFTWARE MODULE, PLEASE CONTACT:

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Co-PI, THE TBI ENDPOINTS DEVELOPMENT (TED) INITIATIVE

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Appendix 2

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



TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI



TRACK-TBI

Transforming Research and Clinical Knowledge
in Traumatic Brain Injury

International Traumatic Brain Injury Research Initiative

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

1861

Nancy R. Temkin , Sureyya Dikmen , Joan Machamer , Geoffrey Marney , Esther Tull , Lindsay Nelson

1. University of Washington, Neurological Surgery & Rehabilitation, Seattle, USA

2. UCSF, Neurosurgery & Radiology, San Francisco, USA

3. Medical College of Wisconsin, Neurosurgery & Neurology, Milwaukee, USA

INTRODUCTION

- Everyday functioning is an important outcome of TBI
- GOS-E is most commonly used measure
- Functional Status Examination (FSE) is an alternative
 - More detailed, structured administration rules
 - Wider scoring range

METHODS

- 533 TBI survivors from Magnesium Sulfate study and TRACK-TBI (University of Washington site)
- TBI severity defined by initial post-resuscitation GCS and intracranial CT abnormalities
- Both measures given at 3 and 6 months in both studies; and in TRACK-TBI at 2 weeks and 12 months
- GOS-E — 8 category ordinal scale
- FSE — 7 domains each scored 0 (no change from pre-injury) to 3 (not doing activities or completely dependent)
 - Sum categories scores to get total score 0 to 21 with deaths scored as 22
- Data analysis: Correlation with severity, effect size of change

MAIN FINDING

FSE was more sensitive to change and more closely related to severity than the GOS-E. It might be worth considering as a functional outcome for TBI studies.

Research Supported by: W81XWH-14-2-0176, R01 NS19643, U01NS086090

Appendix 3

RESULTS – Table 1: Correlation with Severity

3 Months Post-Injury	Total FSE ALL Score			GOS-E Overall	
	N	Median	r	Median	r
GCS Total			-0.48		0.51
3-8	193	15		4	
9-12	96	11		5	
13-15	132	5		6	
CT Abnormal			0.40		-0.39
No	77	3		6	
Yes	350	13		5	

No significant differences in correlation.

6 Months Post-Injury	Total FSE ALL Score		
	N	Median	r
GCS Total			-0.3
3-8	202	12	
9-12	101	8	
13-15	131	2	
CT Abnormal			0.3
No	74	1	
Yes	372	11	

FSE more closely related to GCS (p=.001) CT abnormal (p=.014)

RESULTS – Table 2: Sensitivity to Recovery

Change from 2 Weeks to 3 Months Post-Injury—TRACK-TBI study

N (%)	Improve	No Change	Worsened	
FSE	79 (86%)	6 (7%)	6 (7%)	
GOS-E	61 (67%)	25 (28%)	5 (5%)	

FSE detects recovery better (P<.001)TRACK study only

Change from 3 to 6 Months Post-Injury—TRACK-TBI and Magnesium studies

N (%)	Improve	No Change	Worsened	
FSE	263 (63%)	86 (21%)	67 (16%)	
GOS-E	156 (38%)	204 (49%)	56 (13%)	

FSE detects recovery better (P<.001)

Change from 6 to 12 Months Post-Injury—TRACK-TBI study

N (%)	Improve	No Change	Worsened	
FSE	33 (32%)	48 (47%)	21 (21%)	
GOS-E	36 (35%)	54 (53%)	12 (12%)	

GOSE detects recovery better (P<.001) in TRACK study only

CONCLUSIONS

- FSE holds promise for assessing functional outcome after TBI
- FSE is more detailed, more clearly structured, and better worded than GOS-E
- FSE has a broader range of scores
- FSE is more sensitive to severity at 6 months
- FSE reflects recovery better through 6 months after injury