Title

Increasing Rigor of Preclinical Research to Maximize Opportunities for Translation.

Journal

Neurotherapeutics, 20(6)

Authors

Radabaugh, Hannah
Ferguson, Adam
Bramlett, Helen
et al.

Publication Date

2023-10-01

DOI

10.1007/s13311-023-01400-5

Peer reviewed

Neurotherapeutics (2023) 20:1433–1445
https://doi.org/10.1007/s13311-023-01400-5

REVIEW

Increasing Rigor of Preclinical Research to Maximize Opportunities for Translation

Hannah L. Radabaugh[1] · Adam R. Ferguson[1,2] · Helen M. Bramlett[3] · W. Dalton Dietrich[3]

Accepted: 9 June 2023 / Published online: 31 July 2023

Abstract

The use of animal models in pre-clinical research has significantly broadened our understanding of the pathologies that underlie traumatic brain injury (TBI)-induced damage and deficits. However, despite numerous pre-clinical studies reporting the identification of promising neurotherapeutics, translation of these therapies to clinical application has so far eluded the TBI research field. A concerted effort to address this lack of translatability is long overdue. Given the inherent heterogeneity of TBI and the replication crisis that continues to plague biomedical research, this is a complex task that will require a multifaceted approach centered around rigor and reproducibility. Here, we discuss the role of three primary focus areas for better aligning pre-clinical research with clinical TBI management. These focus areas are (1) reporting and standardization of protocols, (2) replication of prior knowledge including the confirmation of expected pharmacodynamics, and (3) the broad application of open science through inter-center collaboration and data sharing. We further discuss current efforts that are establishing the core framework needed for successfully addressing the translatability crisis of TBI.

Keywords Traumatic brain injury · Animal models · Data sharing · Data science

Introduction

Traumatic brain injury (TBI) poses a significant global health problem with an estimated 50% of the world's population suffering a TBI over their lifespan [1]. This vast reach positions TBI as a leading cause of death and disability across all ages, countries, and socioeconomic classes. The resulting global economic burden from acute and chronic TBI care surpasses an estimated $400 billion USD annually [2]. Despite the immense toll of TBI-induced deaths and disabilities, the identification of effective therapeutics remains elusive. Numerous pre-clinical studies have reported beneficial pharmacotherapies in animal models; however, there has yet to be a successful clinical trial based on these reports [3–6]. Understanding why the TBI research field has struggled to translate findings from bench to bedside is imperative to advance clinical management of TBI and reduce its immeasurable societal burden.

Across biomedical research, the inability to replicate a large percentage of reported findings has come to the forefront of conversation [7]. The NIH and other funding agencies have appropriately responded to these reports through numerous calls for increased rigor in animal research. Most recently, the NIH released the Jan 2023 Data Management and Sharing Policy focused on increasing reproducibility via mandated data sharing and transparency [8]. While the significance of this step cannot be overstated, there is a considerable amount of collaborative work that must be done by the field to address translation in TBI research.

TBI presents a highly variable disease in the clinic in terms of injury severity, location, type of damage, and patient comorbidities [9, 10]. These countless confounding factors make modeling the entirety of the clinical injury population in a single laboratory setting impossible. In an attempt to model relevant mechanisms of human TBI and quantify functional recovery, numerous models and endpoint metrics have been developed [11–13]. However, few attempts have been made to draw direct comparisons to the

✉ W. Dalton Dietrich
ddietrich@miami.edu

[1] Brain and Spinal Injury Center, Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA

[2] San Francisco Veterans Affairs Healthcare System, San Francisco, CA, USA

[3] Department of Neurological Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

human condition, protocol reporting and standardization remains insufficient, and there is a strong reporting bias in the literature that overvalues novel findings and undervalues negative results.

Successfully addressing the translational crisis will require targeted yet significant changes that span from daily laboratory practices to existential cultural adjustments to be adopted by the TBI research field. In the current manuscript, we explore ways that pre-clinical researchers can standardize experimental protocols, confirm prior knowledge, and increase data transparency via more extensive community-based collaboration efforts (Fig. 1). Furthermore, we discuss how adopting an open science culture will allow the TBI research field to overcome the statistical challenges inherent to animal research (i.e., limited sample size) while recognizing that this cultural adjustment will require incentives (e.g., citations and credit for data research products) to move away from the current "publish or perish" mindset [14–16].

Multifaceted Approach for Increasing Rigor and Reproducibility in Pre-Clinical Research

Capturing Clinical Heterogeneity

Human TBI is a dynamic process that is challenging to accurately recreate in non-human models [11, 12, 17]. There are several factors that contribute to this difficulty including the inherent complexity of the human brain relative to commonly used animal models, the heterogeneity of clinical TBI itself (e.g., severity, location, mechanism of injury), as well as the breadth of variability present within the patient population (e.g., age, sex, medical history). While it is unlikely that a single lab will be able to test therapeutics in a multitude of models or singlehandedly address a majority of these concerns, standardizing surgical protocols and endpoint assessments could allow for the harmonization of datasets from multiple centers [13, 15, 18–20]. Not only

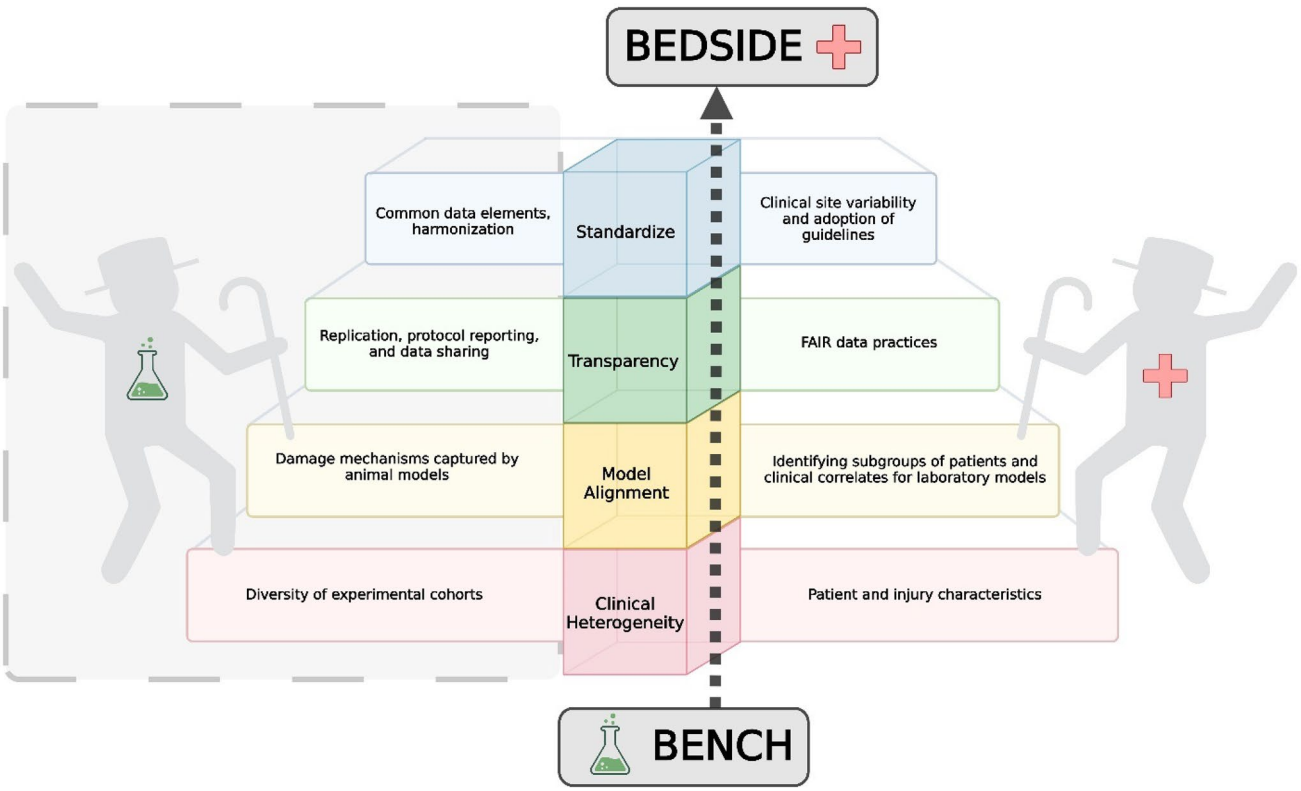

Fig. 1 Schematic describing steps that must be addressed as a TBI research community to effectively address the translation crisis. While the current manuscript focuses on the pre-clinical, animal research field (indicated by shaded, grey box), it is important to remember that clinical changes must occur simultaneously if we wish to traverse the current hurdles that exist

does this approach open the door for a broader investigation of therapeutic effectiveness across multiple types of TBI, but it will also greatly increase the statistical power of pre-clinical TBI studies [14, 21].

Anatomical Considerations

A primary factor that makes modeling TBI difficult in the laboratory is the vast complexity of the human brain. The human brain is a large, gyrencephalic structure that consists of numerous interconnected regions, each of which contributes to multiple functional networks. Rodents, the animal model most commonly found in the pre-clinical TBI literature, have lissencephalic brains that lack the same folding structure found in humans [11, 12, 22]. While the two brains do have numerous analogous regions and networks that have been detailed, the lack of anatomical folding has clear implications for the biomechanics of injury. Furthermore, structures such as the hippocampus, which play a central role in many common laboratory assessments, are differentially positioned in the rodent brain relative to the human [23–25]. This leads to difficulty in modeling human TBI given that applying the same mechanical insult to a large, gyrencephalic structure will lead to a different disturbance than would applying the same insult to a small, lissencephalic structure with dissimilar arrangement.

Although overcoming the anatomical differences between the two brains is challenging, increasing the rigor and standardization of data collection practices will allow the research field to reach the subject number necessary for the identification of promising therapeutics and the application of more advanced analytics [19, 21, 26]. By standardizing practices, more confidence can be afforded to therapeutics that show benefit across multiple models of TBI or pathophysiological endpoints. This would assist the field with identifying therapeutics worth elevating to the more resource demanding gyrencephalic models such as micropigs [22].

Severity of TBI; Clinical vs Animal Model

At the time of clinical admission, TBI patients are typically characterized by injury severity using categorization scales such as the Glasgow Coma Scale (GCS). The GCS effectively classifies injuries as [1] mild (GCS score of 13–15), [2] moderate (GCS score of 9–12), or [3] severe (GCS score of 3–8). The GCS also describes gross neurobehavioral outcomes in terms of disability in categories that range from death to full recovery. However, it is unlikely that these wide sweeping classifications will be sufficient for the development of personalized medicine [27]. Furthermore, accurately modeling something as diverse as a "mild," "moderate," or "severe" TBI in an animal model leaves significant room for interpretation and limits the feasibility of standardizing across centers while still capturing the whole of the clinical condition [11].

There is a large degree of mismatch between the clinical use of the terms mild, moderate, and severe and the pre-clinical where these terms lack any accepted field standard [12, 27]. Laboratories often rely on injury device parameters to categorize their injury severity which is in stark contrast to the symptomatic or more recent imaging-based approaches applied clinically [28–31]. This results in "severe" animal injuries where there is a great deal of tissue deformation and subsequent injury, yet the animals are still functionally adequate (e.g., walking, grooming, eating, and interacting with housing mates) 24–48 h after injury which does not accurately reflect the "severe" human TBI condition [11, 32]. However, due to anatomical differences and device limitations, these injuries are often the most severe that can be administered without leading to mortality [11]. This points to possible misalignment between the clinical and pre-clinical use of the word "severe." However, despite this misalignment, the animal models may be capturing subgroups of patients that fall within the 90% of TBIs that are discharged as "mild" yet still have persisting, and often debilitating, symptomatic burdens 1-year post-injury [33].

Identifying subgroups of patients that will assist with bettering translatability from animal models to the human condition will likely require the application of analytical methods able to explore the multivariate and multimodal space generated by TBI datasets. One potential area for alignment is harnessing previous research that has highlighted pathophysiological differences between animal models of TBI as well as a more thorough investigation of which model best captures clinical pathological subgroups. For example, extensive characterization of the controlled cortical impact (CCI) model of TBI has revealed identifiable pathological differences from other common models of TBI such as the fluid percussion injury (FPI) and penetrating ballistic-like brain injury (PBBI) in clinically relevant modalities [11, 34, 35]. However, the application of methods able to identify subgroups and provide a multivariate description of the dataset such as unsupervised machine learning clustering or principal component analyses often requires subject numbers well beyond what is feasible for a single laboratory [14, 21, 36, 37]. The application of artificial intelligence and machine learning (AI/ML) has therefore been limited to use in the few large, animal TBI datasets that exist currently (e.g., Operation Brain Trauma Therapy) [15, 21]. This is one area where data sharing and harmonization efforts that can combine multiple data sources may greatly contribute to a successful bench-to-bedside translation.

Future Considerations for Circumventing Differences

Enhancing translatability by considering pathobiologies as a potential area for bench-to-bedside alignment in TBI research presents unique challenges. The damage resulting from TBI typically occurs in two injury phases: primary and secondary injuries [38]. The primary injury encompasses the mechanical disruption at injury onset, while the secondary describes a series of pathobiological cascades initiated by the primary disruption. Researchers have identified several mechanisms that contribute to the damage caused by the primary injury, including focal necrosis, vascular and blood–brain barrier rupture, edema, hemorrhage, mechanical injury to neurons, axons, and glial cells, and the appearance of damage-associated molecular patterns responsible for signaling the initiation of subsequent injury response mechanisms [38–40]. While the primary injury is typically transient and irreversible, the secondary injury can carry on for months to years from the point of initiation leading to further cell death and dysfunctions that may be sensitive to therapeutic interventions. The secondary injury typically involves mechanisms such as inflammatory processes, excitotoxicity, oxidative stress, the generation of free radicals, demyelination, autoimmunity, neurodegeneration, and multiple types of cell death [38, 39, 41–46]. This continued stream of damage leads to injury phenotypes that change and evolve with time both in terms of physical damage observed (e.g., changes in cerebral blood flow or consequences of homeostatic disturbance) and syndromic experience reported (e.g., neurological deficits, cognitive decline, motor impairments, and/or chronic headache disorders) implying that successful treatment will require a method for understanding the damage that has yet to occur in each individual [38, 47, 48].

Intuitively, the research field has designed their animal models of TBI around the physical observation that mechanical insults often lead to human TBI. As discussed, this is wrought with biomechanical complications. However, the deep characterization of the commonly used TBI models may allow for alignment of the clinical population with animal models by investigating the secondary injury pathophysiologies that result from each type of injury. Albeit complex, predicting and grouping subjects by the current and ongoing pathophysiological mechanisms rather than severity indices could allow for precision-based approaches in translational TBI.

With regard to translation, it is important to consider that the biological processes following trauma occur on vastly different timescales for a human than they do in commonly used rodent subjects. Agoston et al. (2019) performed a detailed examination of many classic TBI pathobiologies including cerebral glucose metabolism, inflammatory processes, axonal integrity, and water homeostasis and found that there is not one "conversion rate" that can be applied to capture the differences that exist between species [49]. This group went on to suggest expanding the use of clinically relevant outcome metrics (e.g., imaging, blood-based biomarkers) in animal studies, conducting more expansive longitudinal studies, and incorporating big data approaches able to better integrate and analyze large datasets [49].

Applying approaches fielded from big data analytics typically requires subject numbers much greater than is common in animal research. Achieving increased subject number is possible through the aggregation of multi-center datasets, and this approach will allow for the inclusion of multiple injury types, clinical covariates, and TBI severities [2, 16, 18, 19, 21, 50, 51]. We envision multiple approaches for accomplishing the successful aggregation and harmonization of multi-center datasets with both retrospective (i.e., previously collected or legacy datasets) and prospective (i.e., newly collected datasets) strategies being feasible.

The harmonization of legacy datasets presents the challenge of aligning data elements that were not necessarily collected as part of the same study. One approach is to identify variables in each dataset that are [1] identical (e.g., GFAP collected 24 h post-injury), [2] similar with minor differences (e.g., Morris Watermaze conducted from days 10–14 at one site but 14–19 at another), [3] conceptually similar (e.g., ambulation-based motor assessment but different task specifics), or [4] entirely unique to one site. Each level of harmonization similarity will require different considerations and statistical approaches with the goal of removing the effect of site post-aggregation. While this approach is laden with imperfect alignment, it does provide the opportunity to generate novel insights from completed experiments, thus increasing the return on investment from previous studies, including those that never reached publication due to negative results.

From a prospective stance, multicenter consortia and field-wide commitments can design the collection of new data in a way that promotes easier alignment across centers. Many ongoing efforts are focused on the design and reporting of standard operating procedures as well as the development of common data elements (CDEs) specifically for the pre-clinical TBI field [13, 20, 52]. Adoption of these approaches and reporting standards will generate large amounts of data able to be harmonized in a more comprehensive manner. Furthermore, consortium studies focused specifically on collecting data for eventual aggregation will make important contributions to our understanding of between center model and assessment differences.

Novel insights from the application of AI/ML to analyze large TBI datasets could assist the field with detailing multimodal profiles of TBI better able to align the damage observed in subgroups of patients with that seen following the utilization of specific animal models. This approach would greatly advance our ability to design precision medicine-guided clinical trials that may have a better chance for

translation than the current studies which often rely on severity of symptoms for study enrollment rather than underlying mechanisms.

Standardization Across Centers

A primary focus for achieving the rigor and reproducibility necessary for improving confidence in pre-clinical TBI findings must be establishing standards for all experimental procedures ranging from models and surgical decisions through to endpoint testing [11–13, 53, 54]. Standardization will be crucial for both the mitigation of experimental bias and the aggregation of multi-center datasets in such a way that will increase statistical power and allow for the application of powerful analytic tools.

Model Considerations and Surgical Parameters

One of the most critical parameters in conducting translational studies is to clarify the pathophysiology and treatment of TBI using clinically relevant animal models [11, 12, 35, 55]. Over the many years of TBI research, strategies for simulating the biomechanical, pathological, and behavioral consequences of brain trauma using in vitro and in vivo models have been developed. These focal and more diffuse models of mild, moderate, and severe TBI have been evaluated by the scientific field, used to clarify novel secondary injury mechanisms, and employed to test new therapeutic interventions including manipulating physiological variables and testing pharmacological agents or cell therapies [5, 17, 56–58]. Our scientific field has emphasized the need to standardize models while making them relevant to the heterogeneous TBI population [11, 12, 55]. Nevertheless, challenges still exist regarding the clinical relevance of the models and treatment approaches for protecting and repairing the nervous system after TBI. Furthermore, the reproducibility of injury models and outcome assessments post-injury have not been fully detailed. This level of standardization will be integral to the field's ability to harmonize across data sources in such a way that site or experiment will not present as confounding factors.

Physiological Factors and Anesthesia

An important difference to highlight between animal models of TBI and the human condition is that, when using animal models, there is the need to include a variety of drugs and anesthetics in the established protocol to limit discomfort. Currently, a variety of sedatives, analgesics, and neuromuscular agents are used commonly in the laboratory to produce sedation and limit pain during surgical procedures and other necessary steps [12, 13]. Depending on the dose and routes of administration, drugs can have various effects on normal brain function and on systemic physiological variables such as blood gases, pH, systemic blood pressure, and temperature [59]. Although these anesthetics produce the desired effects under standardized protocols, they do alter the physiological state of the brain and therefore may alter the cerebral response to trauma relative to the clinical settings where patients are not under the influence of anesthesia at the time of injury.

To help standardize models and improve successful translation, the field has therefore emphasized the importance of including important details regarding the steps associated with the production of TBI that may vary between laboratories and models [13, 15, 60]. These details include the type of anesthesia used, the dosing of each pharmacotherapy, and the time frame of anesthesia relative to TBI surgery. Previous research has investigated the CNS and systemic impacts of peri-TBI anesthesia and established many of the current recommendations that are found in the literature today [61–65]. For example, isoflurane, a commonly used inhaled anesthetic, has been found to provide both histological and functional benefits following TBI in the rat model relative to other anesthetics such as fentanyl, diazepine, and ketamine [61, 63, 64]. These observations are thought to be due to the differential effects that each drug therapy exerts to either mitigate or exacerbate the secondary injury mechanisms that occur in the acute setting following primary insult. When comparing results in the literature or harmonizing data across centers, it is crucial to know how sedation and pain were managed throughout the entirety of the experiment.

It is important to note that, while human TBI patients are not typically under the influence of anesthesia at the time of injury, some are placed under anesthesia or sedation upon arrival to the clinic during the development and resolution of symptomatic emergencies [66, 67]. These cases, however, are typically more severe in nature than the animal models where subjects regain functionality within minutes after surgery. Acknowledging how this time difference of anesthetic exposure as well as the severity of injury impacts the ongoing secondary cascades is a vital piece of information for translating model observations to clinical suggestion.

Despite not being anesthetized in the same way as an animal subject, other neuroactive substances such as ethanol, caffeine or stimulants, and anti-histamines or allergy medications are commonly onboard at the time of human TBI. These substances have been found to alter the emergent pathologies following TBI and are known to interact with some administered therapeutics [68–75]. However, despite being common in clinical setting at the time of injury and persisting into the acute injury phase, these substances are rarely included in animal models of TBI investigating potential pharmacotherapies. A more thorough investigation of how commonly used

substances impact therapeutic intervention is an area where the field could make great strides.

Confirming Pharmacokinetics of Therapeutic Interventions

Although impactful research has been accomplished by clarifying the pathophysiology of TBI-induced secondary injury, pharmacologic interventions in preclinical modes have not translated well to humans [4, 76, 77]. Therapeutic responses following TBI are influenced by patient characteristics (e.g., age, sex, and genetics), co-morbidities, and other factors [77–79]. When a drug treatment is not shown to improve clinical outcomes, researchers may speculate about the strength of the preclinical findings or the clinical protocol [12, 77]. However, the pharmacokinetic and pharmacodynamic properties of the compound, as well as issues concerning optimal dose, therapeutic window, and successful target engagement are important factors that need to be investigated if the field wishes to increase the chance for a successful translation [77, 80, 81]. Specifically, the blood–brain barrier (BBB) controls the influx and efflux of nutrients and waste products and isolates the brain from compounds in the blood. Thus, the ability of a drug to show benefit in the lab and be able to treat human TBI would require the compound to successfully cross the BBB in both species and interact with its therapeutic target to impact pathological mechanisms [82, 83]. Furthermore, understanding how optimal dose, drug metabolism, and target engagement differ between animal models and human patients is not well understood for many pharmacotherapies tested in the TBI literature. To enhance scientific rigor and the potential for successful translation, these factors need to be more fully interrogated and reported for the pharmacotherapies tested [2, 20, 84].

Open Science and Data Transparency

Open science in the context of TBI animal research refers to the practice of making scientific data, publications, and other research outputs openly available to the research community following study completion. While current guidelines that focus primarily on sharing the data that contributed to findings in published manuscripts will help address reproducibility, reporting "dark data" and negative findings will also be of the utmost importance. Having a deeper knowledge of the experiments that have already been attempted will save valuable resources by avoiding unnecessary repeats. Furthermore, having access to all data collected will advance our ability to harmonize large datasets ready for secondary analyses. This may result in novel findings, thus increasing the return on investment for that particular dataset for both the funder and the researcher. That is, datasets that are published and subsequently used for secondary analyses will become citable research products just like manuscripts and be added to a researcher's list of concrete contributions they have made to the research field. This approach to dataset citation could begin to address the issues that arise from the "publish or perish" mindset by creating an avenue that allows scientists to receive credit for experiments that did not go through the publication pipeline.

In order to for data sharing to reach its full potential, there needs to be principles in place that protect scientists from having their data used inappropriately. The TBI research field should adopt and adhere to a strict set of guidelines agreed upon by the community. FAIR (Findable, Accessible, Interoperable, and Reusable) data principles are one set of guidelines that could be employed to help TBI research move towards open science in a responsible and rigorous manner (Fig. 2). The FAIR data principles provide a framework for ensuring that data generated in biomedical research is usable and valuable to other biomedical researchers interested in

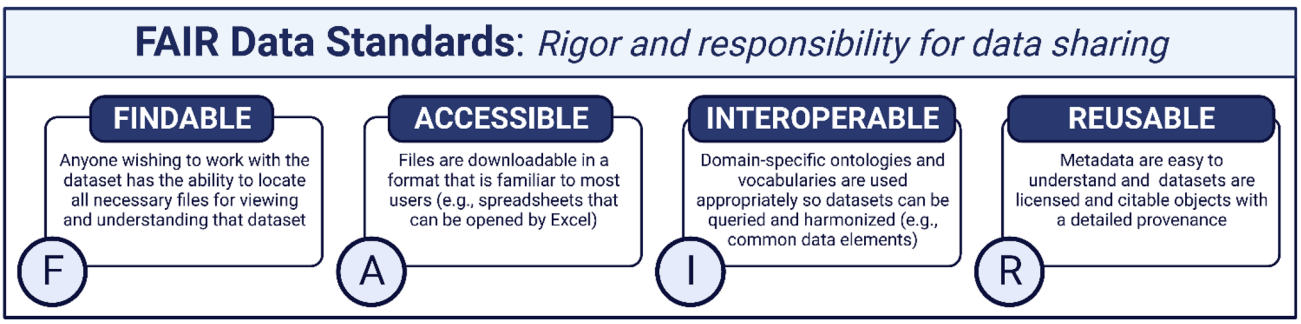

Fig. 2 Graphical summary describing the FAIR data principles as they apply to TBI research

using the data for either reproducing results or performing secondary analyses [50, 51, 53, 60]. By making data findable, accessible, interoperable, and reusable, researchers can maximize the impact of their work and facilitate data sharing and reuse, which can help to accelerate research progress.

Specifically, making data *findable* (F) involves assigning persistent and unique identifiers to datasets (i.e., one ID per subject in the dataset), using standardized metadata, and ensuring that data is indexed and discoverable through common search engines. The Open Data Commons for TBI (ODC-TBI) is a data management and sharing platform (further described in the "Efforts to address the translatability crisis" section) that addresses this first point by assigning unique digital object identifies (DOIs) to each published dataset that are searchable in any browser identical to how published journal articles can be found and referenced [15]. Furthermore, metadata, in this use case, refers to detailed descriptions about a dataset's creation and content. Metadata should provide information about who collected the data, when the data was collected, the experimental design that generated the dataset including the instruments used, as well as the structure and format of the data. This information helps to ensure that the dataset can be used appropriately and correctly interpreted by others.

Once located, making data *accessible* (A) implies that data are available in familiar file formats and that appropriate data access policies are in place. Regarding TBI research, this means that data should be made available in common file types (e.g.,.csv) that can be opened by any spreadsheet software (e.g., Excel). Furthermore, data access policies should be strictly enforced to ensure that the use and reuse of datasets is acknowledged, and citations are attributed to the scientists who generated the data.

Making data *interoperable* (I) involves using standardized terminologies, providing clear and consistent data definitions, and ensuring that data is easily integrated with other data sources. Current efforts in the TBI research field to establish pre-clinical CDEs and ontologies (see PRECISE-TBI in the "Efforts to address the translatability crisis" section) will greatly advance the harmonizability of datasets collected at different centers as well as provide a way to quickly query repositories to find datasets that align with a desired research question (e.g., datasets containing: rat, CCI, water maze). This could allow for the quick identification of experiments that have been completed regardless of whether those variables were included in a publication and potentially save valuable resources from being spent on repeated experiments.

An important distinction to make is that, for this goal to become a reality, both published data and "dark data" will need to be shared. "Dark data" refers to negative results or variables that remain unpublished following the completion of a study (e.g., reported water maze latency but swim speed, distance, etc. remained unpublished or "dark") rather than data that a researcher intends to use in a manuscript [16]. Furthermore, the investigator should have full control over when a dataset is published (often following publication of the primary results) rather than providing full access to information about ongoing research.

Finally, making data *reusable* (R) involves ensuring that data is well-documented, providing clear and concise data descriptions, and ensuring that data can be easily understood and used by others. Overall, FAIR data standards are critical for ensuring that research data is usable, valuable, and accessible to the whole of the TBI research community, which can ultimately help to accelerate the pace of TBI research and improve outcomes.

TBI researchers can best implement FAIR data standards by following a few key principles:

1. Plan for "FAIRness" from the outset of the research project. This involves planning how data will be collected, recorded, stored, and shared throughout the project. The NIH provides a list of accepted repositories with the ODC-TBI (odc-tbi.org) being both domain-specific for pre-clinical TBI research and FAIR compliant. Becoming familiar with the dataset format, variable requirements (e.g., subject ID, species, sex), and metadata expectations for the chosen repository at the beginning of a project will save significant time and limit the chance for human recall error when it comes time to make the data available to others.
2. Use standard data formats and metadata to ensure that data can be easily understood by others. This includes using standardized nomenclature, ontologies, and adhering to the application of accepted CDEs. Furthermore, data dictionaries, which define the variables in a dataset (i.e., typically the column headers) including units of measurement and other necessary information for how each variable in the raw dataset was collected, should be created alongside the data collection templates used for any given study (Fig. 3).
3. When data collection begins, researchers should assign persistent and unique identifiers to their datasets, samples, and other resources to ensure that they can be easily found and accessed. That is, each subject should have a unique ID name or number that refers only to data for that subject and is never repeated.

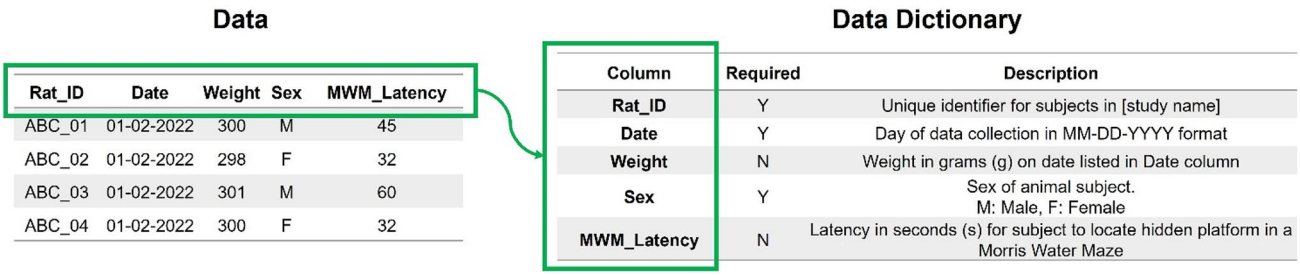

Fig. 3 Example of the type of information that could be listed in a data dictionary and shared as part of a dataset's metadata. This structure allows other users to quickly understand what the variables in a dataset are and how they were collected. Further, the "required" column could refer to the minimal, required elements required by a chosen repository or set by the community for data sharing

Efforts to Address the Translatability Crisis

Moody Project for Translational TBI Research

Funded by the Moody Endowment, the Moody Project for Translational TBI Research brought together a large number of experts in pre-clinical TBI research with the goal of better characterizing acute and chronic TBI animal models and testing therapeutics across multiple types of injuries and model systems [11, 15, 85]. In an effort to develop a standardized set of guidelines for the pre-clinical testing of therapeutics, the Moody Project hosted a symposium to discuss experimental models, endpoint selection, data analytics, and the dissemination of findings. The guidelines from this symposium were released with the intent of providing a framework of considerations for TBI pre-clinical researchers that would assist with translating findings from bench to bedside.

Recommendations from this symposium focused primarily on addressing the replication crisis and the heterogeneity of TBI. Specifically, investigators highlighted the urgent need to publish sufficiently detailed descriptions of the study design and experimental protocols including how species-dependent pharmacokinetics and timing of behavioral testing were factored into the operating procedures. Furthermore, standardizing surgical parameters and outcome metrics across centers would be a necessary step towards attaining evidence that a therapeutic may be broadly applicable to multiple types of injuries and injury severities. Lastly, symposium participants also promoted the idea of disseminating negative results noting that this would reduce the unnecessary costs of duplicating experiments.

Operation Brain Trauma Therapy (OBTT)

OBTT is a multi-center, pre-clinical drug and biomarker screening consortium for TBI which has established a framework for successfully conducting multi-center, animal research through carefully designed standards for the design and conduct of research [20, 22, 34, 57, 86, 87]. Utilizing this multicenter framework, OBTT has successfully screened numerous therapies across multiple injury types (e.g., focal, diffuse, penetrating) and animal models (i.e., rodents and micropigs). The screening battery was comprised of an extensive list of endpoints standardized across centers and designed to capture multiple aspects of the pathophysiology following TBI.

OBTT is quite mature in its publication pipeline with the primary data from multiple therapies, numerous synopsis and overview papers, biomarker-specific investigations, and secondary analyses already published [19, 21, 85–91]. In these currently published studies, three sites were tasked with testing the same therapeutics across different models of TBI. The University of Pittsburgh used the controlled cortical impact (CCI) model representing a focal type injury, the University of Miami used the fluid percussion injury (FPI) model representing a diffuse-focal type injury, and Walter Reed Army Institute for Research used the penetrating ballistic-like brain injury (PBBI) model representing a penetration type injury. OBTT screened therapies for beneficial effects across neuromotor behavioral assessments, cognition tests, histological measures, and blood-based biomarkers.

Therapies were scored for their effectiveness using a weighted statistical matrix that awarded points for beneficial findings and subtracted points for adverse [34, 55, 57]. Of all therapies tested thus far, levetiracetam (Keppra) demonstrated benefit across multiple rodent models without any findings characterized as adverse. This treatment was elevated to the micropig for screening, and future therapies that show similar promise may also follow this track [19, 22, 87].

The structured design of OBTT is also ideal for the aggregation and harmonization of some endpoints in its datasets. The resulting aggregated dataset would consist of over 1000 research subjects, a subject number not typically feasible in animal research. Due to this power, a portion of these data have been harmonized and analyzed using AI/ML methods that are typically reserved for datasets larger than your average animal study [19, 21]. These approaches

have proven successful in their ability to both confirm earlier findings and generate novel insights regarding the therapeutics tested. Harmonization strategies like the one employed in the secondary analysis papers of OBTT serve as a guide for how the TBI animal research field can begin aggregating datasets suitable for the more extensive application of powerful analytical techniques. Furthermore, OBTT has also acknowledged in multiple papers the importance of data transparency and plan to release the study data following the publication of the primary findings from all therapies.

Translational Outcomes Project in Neurotrauma (TOP-NT)

TOP-NT is an NINDS-funded initiative for a multisite consortium tasked with the development and validation of biomarkers for neurotrauma which have direct clinical correlates [52]. Developing, validating, and standardizing the data generating and reporting process for multiple clinically relevant metrics will assist with addressing the translation crisis by more closely aligning clinical TBI management with pre-clinical animal testing. Furthermore, testing injury models and endpoints across multiple centers will either confirm the reproducibility of standardized protocols or uncover challenges that need further consideration.

Laboratories at the University of California, Los Angeles (UCLA), Georgetown University, Uniformed Services University, the University of Florida, and Johns Hopkins University serve as the key data collection centers in the TOP-NT consortium. Across these sites, neuroimaging, blood-based biomarkers, and behavioral assessments are assessed for their reproducibility and utility for serving as part of multimodal, cross-domain biomarker profiles. Histology is used to better understand the pathophysiological mechanisms that underlie observed biomarker profiles at specific time points. The University of California, San Francisco (UCSF) serves as the data management, harmonization, and analytical center for the entirety of the TOP-NT initiative, and data are deposited in an NIH-approved specialist repository for preclinical data management and sharing [8, 15].

The first publications describing the data generated by the initial phase of TOP-NT have recently been published with several others in preparation [15]. The initiative requires FAIR (findable, accessible, interoperable, reusable) data sharing, reflecting early adoption of the policies that are now enforced for all NIH-funded researchers through the 2023 NIH Data Management and Sharing Policy [50, 53, 92]. That is, adhering to FAIR data standards and the full transparency of all collected data even if not all variables are discussed in the manuscript. All TOP-NT datasets will be available for other domain experts to analyze through dataset publication. For example, the first few datasets ($N = 1200$) have been published and made available through the open data commons for TBI (odc-tbi.org) [93]. It is estimated that TOP-NT will release public datasets for thousands of more subjects in the next 2 years, enabling individual subject data meta-analysis across several models in animals that mirrors the scale of clinical individual participant data meta-analysis, a tool for accumulating high-grade evidence [94].

PRE-Clinical Interagency reSearch resourcE-TraumaticBrain Injury (PRECISE-TBI)

PRECISE-TBI is an interagency consortium developed by the Department of Veterans Affairs (VA), NIH, and the Department of Defense (DoD). The mission of this consortium is to accelerate the development of therapies for TBI and bridging the translational gap. This will be done by establishing methods in sharing data to improve rigor, reproducibility, and collaboration in the pre-clinical TBI field. Several resources will be developed including a TBI model catalog, blast TBI modeling standards, data sharing standards, common data elements (CDEs), and an injury severity index. Additional information from PRECISE-TBI will provide educational and outreach and knowledge resources to TBI investigators. PRECISE-TBI will also aid investigators who use this service for their compliance with the new federal data sharing policies.

Open Data Commons for TBI (ODC-TBI)

ODC-TBI is a community-governed repository to manage, share, and publish research data for the preclinical TBI field (odc-tbi.org). ODC-TBI aims to promote transparency, rigor, and reproducibility in TBI research by providing a secure, cloud-based platform for the storage and publication of preclinical datasets in a way that fully adheres to the NIH data sharing requirements released in January 2023. ODC-TBI is the first NIH-endorsed specialist repository for preclinical TBI and, for this reason, has been adopted by TOP-NT and PRECISE-TBI as their central data sharing platform [8, 15]. In addition, portions of the Moody Project data have been uploaded to the platform [95].

ODC-TBI was conceptualized to be a collaborative effort that would create a community-based repository for TBI basic research. Currently, the repository is populated with 101 datasets from 60 labs containing basic science and de-identified human datasets which have been aggregated and harmonized to make them broadly interpretable and cross-compatible [96].

ODC-TBI also serves as a powerful data management tool for promoting rigor in lab data management protocols. Researchers can upload data into a private space and only grant access to their trusted lab members. This provides labs with a way to track datasets from each of their studies in a

version-controlled manner to ensure consistency. That is, version-controlled datasets help groups quickly understand which version of the dataset is the most updated or has been used to generate specific findings. Furthermore, each PI can generate multiple, private spaces to support ongoing collaborations that may focus on a select few datasets, thus avoiding compromising the security of other projects when granting private space access to external collaborators.

Importantly, when publishing datasets, the ODC-TBI enables the issuing of digital object identifiers (DOIs). DOIs allow the dataset to be published and citable each time it is used. This implies that researchers will be acknowledged much like a citation of their other published research products.

Conclusion

At this point in time, the TBI research field has ultimately failed to translate findings from pre-clinical animal studies to clinical application. This is especially true for the identification of effective pharmacotherapies. An effort to address this crisis in translation will require significant changes to be adopted by both the pre-clinical and clinical sides of TBI research (Fig. 3). In the current manuscript, we focused specifically on the pre-clinical realm and explored numerous avenues that must be addressed as a unified community and implemented as procedural changes. These include standardizing experimental protocols, confirming prior knowledge, and increasing data transparency via more extensive community-based collaboration efforts. We also strongly encourage the adoption of an open science culture guided by FAIR data principles. The adoption of this cultural shift will ultimately give rise to a more collaborative, transparent, and effective research ecosystem that will help researchers maximize the impact of their work, accelerate the pace of research, limit the chance of sinking resources into studies that have already been conducted, and advance our understanding of TBI.

Declarations

Conflict of Interest None.

References

1. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. The Lancet Neurology. 2017;16(12):987–1048.
2. Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. Lancet Neurol. 2022;21(11):1004–60.
3. Stein DG. Embracing failure: what the phase III progesterone studies can teach about TBI clinical trials. Brain Inj. 2015;29(11):1259–72.
4. Maas AIR, Marmarou A, Murray GD, Steyerberg EW. Clinical trials in traumatic brain injury: current problems and future solutions. Acta Neurochir Suppl. 2004;89:113–8.
5. Agoston DV, Risling M, Bellander BM. Bench-to-bedside and bedside back to the bench; coordinating clinical and experimental traumatic brain injury studies. Front Neurol. 2012;2(3):3.
6. Menon DK. Unique challenges in clinical trials in traumatic brain injury. Crit Care Med. 2009;37(1 Suppl):S129-135.
7. Rajtmajer SM, Errington TM, Hillary FG. How failure to falsify in high-volume science contributes to the replication crisis. Elife. 2022;8(11): e78830.
8. Data Management & Sharing Policy Overview | Data Sharing [Internet]. [cited 2023 Mar 28]. Available from: https://sharing.nih.gov/data-management-and-sharing-policy/about-data-management-and-sharing-policies/data-management-and-sharing-policy-overview.
9. Kline AE, Leary JB, Radabaugh HL, Cheng JP, Bondi CO. Combination therapies for neurobehavioral and cognitive recovery after experimental traumatic brain injury: is more better? Progress Neurobiol. 2016;142.
10. Nortje J, Menon DK. Traumatic brain injury: physiology, mechanisms, and outcome. Curr Opin Neurol. 2004;17(6):711–8.
11. DeWitt DS, Hawkins BE, Dixon CE, Kochanek PM, Armstead W, Bass CR, et al. Pre-clinical testing of therapies for traumatic brain injury. J Neurotrauma. 2018;35(23):2737–54.
12. Smith DH, Kochanek PM, Rosi S, Meyer R, Ferland-Beckham C, Prager EM, et al. Roadmap for advancing pre-clinical science in traumatic brain injury. J Neurotrauma. 2021;38(23):3204–21.
13. Laplaca MC, Huie JR, Alam HB, Bachstetter AD, Bayir H, Bellgowan PF, et al. Pre-Clinical common data elements for traumatic brain injury research: progress and use cases. J Neurotrauma. 2021;38(10):1399–410.
14. Huie JR, Almeida CA, Ferguson AR. Neurotrauma as a big-data problem. Curr Opin Neurol. 2018;31(6):702–8.
15. Chou A, Torres-Espín A, Huie JR, Krukowski K, Lee S, Nolan A, et al. Empowering data sharing and analytics through the Open Data Commons for traumatic brain injury research. Neurotrauma Rep. 2022;3(1):139–57.
16. Ferguson AR, Nielson JL, Cragin MH, Bandrowski AE, Martone ME. Big data from small data: data-sharing in the "long tail" of neuroscience. Nat Neurosci. 2014;17(11):1442–7.
17. Saatman KE, Duhaime AC, Bullock R, Maas AIR, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. J Neurotrauma. 2008;25(7):719–38.
18. Agoston DV, Langford D. Big data in traumatic brain injury; promise and challenges. Concussion. 2017;2(4):CNC44.
19. Radabaugh H, Bonnell J, Schwartz O, Sarkar D, Dietrich WD, Bramlett HM. Use of machine learning to re-assess patterns of multivariate functional recovery after fluid percussion injury: operation brain trauma therapy. J Neurotrauma. 2021;38(12):1670–8.
20. Kochanek PM, Dixon CE, Mondello S, Wang KKK, Lafrenaye A, Bramlett HM, et al. Multi-center pre-clinical consortia to enhance translation of therapies and biomarkers for traumatic brain injury: operation brain trauma therapy and beyond. Front Neurol. 2018;0(AUG):640.
21. Radabaugh HL, Bonnell J, Dietrich WD, Bramlett HM, Schwartz O, Sarkar D. Development and evaluation of machine learning models for recovery prediction after treatment for traumatic brain injury. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. Institute of Electrical and Electronics Engineers Inc. 2020: p. 2416–20.
22. Lafrenaye A, Mondello S, Povlishock J, Gorse K, Walker S, Hayes R, et al. Operation brain trauma therapy: an exploratory

study of levetiracetam treatment following mild traumatic brain injury in the micro pig. Front Neurol. 2021;13(11):1796.
23. Tessereau C, O'Dea R, Coombes S, Bast T. Reinforcement learning approaches to hippocampus-dependent flexible spatial navigation. Brain Neurosci Adv. 2021;5:2398212820975634.
24. Pitts MW. Barnes maze procedure for spatial learning and memory in mice. Bio Protoc. 2018;8(5): e2744.
25. Radabaugh HL, LaPorte MJ, Greene AM, Bondi CO, Lajud N, Radabaugh HL, et al. Refining environmental enrichment to advance rehabilitation based research after experimental traumatic brain injury. Exp Neurol. 2017;1(294):12–8.
26. Nielson JL, Paquette J, Liu AW, Guandique CF, Tovar CA, Inoue T, et al. Topological data analysis for discovery in preclinical spinal cord injury and traumatic brain injury. Nat Commun. 2015;6.
27. Berwick D, Bowman K, Matney C, editors. Traumatic brain injury: a roadmap for accelerating progress [internet]. Washington, D.C.: National Academies Press; 2022 [cited 2023 Mar 28]. Available from: https://www.nap.edu/catalog/25394.
28. Yuh EL, Jain S, Sun X, Pisica D, Harris MH, Taylor SR, et al. Pathological computed tomography features associated with adverse outcomes after mild traumatic brain injury: a TRACK-TBI study with external validation in CENTER-TBI. JAMA Neurol. 2021;78(9):1137–48.
29. Njoku I, Radabaugh HL, Nicholas MA, Kutash LA, O'Neil DA, Marshall IP, et al. Chronic treatment with galantamine rescues reversal learning in an attentional set-shifting test after experimental brain trauma. Exp Neurol. 2019;1(315):32–41.
30. Bondi CO, Cheng JP, Tennant HM, Monaco CM, Kline AE. Old dog, new tricks: the attentional set-shifting test as a novel cognitive behavioral task after controlled cortical impact injury. J Neurotrauma. 2014;31(10):926–37.
31. Radabaugh HL, Carlson LJ, O'Neil DA, LaPorte MJ, Monaco CM, Cheng JP, et al. Abbreviated environmental enrichment confers neurobehavioral, cognitive, and histological benefits in brain-injured female rats. Exp Neurol. 2016;286:61–8.
32. Rau CS, Kuo PJ, Chien PC, Huang CY, Hsieh HY, Hsieh CH. Mortality prediction in patients with isolated moderate and severe traumatic brain injury using machine learning models. Kou YR, editor. PLOS ONE. 2018;13(11):e0207192.
33. Machamer J, Temkin N, Dikmen S, Nelson LD, Barber J, Hwang P, et al. Symptom frequency and persistence in the first year after traumatic brain injury: a TRACK-TBI study. J Neurotrauma. 2022;39(5–6):358–70.
34. Kochanek PM, Bramlett HM, Dixon CE, Dietrich WD, Mondello S, Wang KKW, et al. Operation brain trauma therapy: 2016 update. Mil Med. 2018;183:303–12.
35. Bondi CO, Semple BD, Noble-Haeusslein LJ, Osier ND, Carlson SW, Dixon CE, et al. Found in translation: understanding the biology and behavior of experimental traumatic brain injury. Neurosci Biobehav Rev. 2015;58:123–46.
36. Jolliffe I. Principal component analysis. In: Lovric M, editor. International encyclopedia of statistical science [internet]. Berlin, Heidelberg: Springer; 2011 [cited 2023 Jan 16]. p. 1094–6. Available from: https://doi.org/10.1007/978-3-642-04898-2_455.
37. Nielson JL, Cooper SR, Yue JK, Sorani MD, Inoue T, Yuh EL, et al. Uncovering precision phenotype-biomarker associations in traumatic brain injury using topological data analysis. PloS one [Internet]. 2017 Mar 1 [cited 2022 Feb 8];12(3). Available from: https://pubmed.ncbi.nlm.nih.gov/28257413/.
38. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth. 2007;99(1):4–9.
39. Jarrahi A, Braun M, Ahluwalia M, Gupta RV, Wilson M, Munie S, et al. Revisiting traumatic brain injury: from molecular mechanisms to therapeutic interventions. Biomedicines. 2020;8(10):389.
40. Povlishock JT, Kontos HA. Continuing axonal and vascular change following experimental brain trauma. Cent Nerv Syst Trauma. 1985;2(4):285–98.
41. Nilsson P, Hillered L, Pontén U, Ungerstedt U. Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats. J Cereb Blood Flow Metab. 1990;10(5):631–7.
42. Morganti-Kossmann MC, Rancan M, Otto VI, Stahel PF, Kossmann T. Role of cerebral inflammation after traumatic brain injury: a revisited concept. Shock. 2001;16(3):165–77.
43. Javidi E, Magnus T. Autoimmunity after ischemic stroke and brain injury. Front Immunol. 2019;10:686.
44. Kerr N, Lee SW, Perez-Barcena J, Crespi C, Ibañez J, Bullock MR, et al. Inflammasome proteins as biomarkers of traumatic brain injury. PLoS ONE. 2018;13(12): e0210128.
45. Dietrich WD, Bramlett HM. Hyperthermia and central nervous system injury. Prog Brain Res. 2007;162:201–17.
46. Lee SW, de Rivero Vaccari JP, Truettner JS, Dietrich WD, Keane RW. The role of microglial inflammasome activation in pyroptotic cell death following penetrating traumatic brain injury. J Neuroinflammation. 2019;16(1):27.
47. Mckee AC, Daneshvar DH. The neuropathology of traumatic brain injury. Handb Clin Neurol. 2015;127:45–66.
48. Bramlett HM, Dietrich WD. Long-term consequences of traumatic brain injury: current status of potential mechanisms of injury and neurological outcomes. J Neurotrauma. 2015;32(23):1834–48.
49. Agoston DV, Vink R, Helmy A, Risling M, Nelson D, Prins M. How to translate time: the temporal aspects of rodent and human pathobiological processes in traumatic brain injury. J Neurotrauma. 2019;36(11):1724–37.
50. Huie JR, Chou A, Torres-Espin A, Nielson JL, Yuh EL, Gardner RC, et al. FAIR data reuse in traumatic brain injury: exploring inflammation and age as moderators of recovery in the TRACK-TBI pilot. Front Neurol. 2021;3(12): 768735.
51. Almeida CA, Torres-Espin A, Huie JR, Sun D, Noble-Haeusslein LJ, Young W, et al. Excavating FAIR data: the case of the Multicenter Animal Spinal Cord Injury Study (MASCIS), blood pressure, and neuro-recovery. Neuroinformatics. 2021.
52. Translational Outcomes Project in Neurotrauma (TOP-NT) (UG3/UH3) - Federal Grant [Internet]. [cited 2023 Mar 28]. Available from: https://www.federalgrants.com/Translational-Outcomes-Project-in-Neurotrauma-TOP-NT-UG3-UH3-64887.html.
53. Abrams MB, Bjaalie JG, Das S, Egan GF, Ghosh SS, Goscinski WJ, et al. A standards organization for open and FAIR neuroscience: the international neuroinformatics coordinating facility. Neuroinformatics. 2022;20(1):25–36.
54. Tortella FC. Challenging the paradigms of experimental TBI models: from preclinical to clinical practice. Methods Mol Biol. 2016;1462:735–40.
55. Kochanek PM, Jackson TC, Jha RM, Clark RSB, Okonkwo DO, Bayır H, et al. Paths to successful translation of new therapies for severe traumatic brain injury in the golden age of traumatic brain injury research: a Pittsburgh vision. J Neurotrauma. 2020;37(22):2353–71.
56. Agoston DV, Elsayed M. Serum-based protein biomarkers in blast-induced traumatic brain injury spectrum disorder. Front Neurol. 2012;3:107.
57. Kochanek PM, Bramlett H, Dietrich WD, Dixon CE, Hayes RL, Povlishock J, et al. A novel multicenter preclinical drug screening and biomarker consortium for experimental traumatic brain injury: operation brain trauma therapy. J Trauma. 2011;71(1 Suppl):S15-24.
58. Loane DJ, Faden AI. Neuroprotection for traumatic brain injury: translational challenges and emerging therapeutic strategies. Trends Pharmacol Sci. 2010;31(12):596–604.

59. Oddo M, Crippa IA, Mehta S, Menon D, Payen JF, Taccone FS, et al. Optimizing sedation in patients with acute brain injury. Crit Care. 2016;20(1):128.
60. Fouad K, Bixby JL, Callahan A, Grethe JS, Jakeman LB, Lemmon VP, et al. FAIR SCI ahead: the evolution of the open data commons for pre-clinical spinal cord injury research. J Neurotrauma. 2020;37(6):831–8.
61. Statler KD, Alexander H, Vagni V, Holubkov R, Dixon CE, Clark RSB, et al. Isoflurane exerts neuroprotective actions at or near the time of severe traumatic brain injury. Brain Res. 2006;1076(1):216–24.
62. Statler KD, Jenkins LW, Dixon CE, Clark RS, Marion DW, Kochanek PM. The simple model versus the super model: translating experimental traumatic brain injury research to the bedside. J Neurotrauma. 2001;18(11):1195–206.
63. Rowe RK, Harrison JL, Thomas TC, Pauly JR, Adelson PD, Lifshitz J. Using anesthetics and analgesics in experimental traumatic brain injury. Lab Anim (NY). 2013;42(8):286–91.
64. Statler KD, Kochanek PM, Dixon CE, Alexander HL, Warner DS, Clark RS, et al. Isoflurane improves long-term neurologic outcome versus fentanyl after traumatic brain injury in rats. J Neurotrauma. 2000;17(12):1179–89.
65. Tecoult E, Mesenge H, Stutzmann AM, Plotkine M, Wahl F. Influence of anesthesia protocol in experimental traumatic brain injury. J Neurosurg Anesthesiol. 2000;12(3):255–61.
66. Kayambankadzanja RK, Samwel R, Baker T. Pragmatic sedation strategies to prevent secondary brain injury in low-resource settings. Anaesthesia. 2022;77(S1):43–8.
67. Wiles MD. Management of traumatic brain injury: a narrative review of current evidence. Anaesthesia. 2022;77(S1):102–12.
68. Al Moutaery K, Al Deeb S, Ahmad Khan H, Tariq M. Caffeine impairs short-term neurological outcome after concussive head injury in rats. Neurosurgery. 2003;53(3):704–11; discussion 711–712.
69. Li W, Dai S, An J, Li P, Chen X, Xiong R, et al. Chronic but not acute treatment with caffeine attenuates traumatic brain injury in the mouse cortical impact model. Neuroscience. 2008;151(4):1198–207.
70. Sanjakdar SS, Flerlage WJ, Kang HS, Napier DA, Dougherty JR, Mountney A, et al. Differential effects of caffeine on motor and cognitive outcomes of penetrating ballistic-like brain injury. Mil Med. 2019;184(Suppl 1):291–300.
71. Lusardi TA, Lytle NK, Gebril HM, Boison D. Effects of preinjury and postinjury exposure to caffeine in a rat model of traumatic brain injury. J Caffeine Adenosine Res. 2020;10(1):12–24.
72. Katada R, Nishitani Y, Honmou O, Okazaki S, Houkin K, Matsumoto H. Prior ethanol injection promotes brain edema after traumatic brain injury. J Neurotrauma. 2009;26(11):2015–25.
73. Zink BJ, Walsh RF, Feustel PJ. Effects of ethanol in traumatic brain injury. J Neurotrauma. 1993;10(3):275–86.
74. Abdul-Muneer PM, Saikia BB, Bhowmick S. Synergistic effect of mild traumatic brain injury and alcohol aggravates neuroinflammation, amyloidogenesis, tau pathology, neurodegeneration, and blood-brain barrier alterations: impact on psychological stress. Exp Neurol. 2022;358: 114222.
75. Pan W, Cao Z, Liu D, Jiao Y. Protective effect of diphenhydramine against traumatic brain injury in rats via modulation of oxidative stress and inflammation. Pharmacology. 2020;105(1–2):47–53.
76. Marklund N, Hillered L. Animal modelling of traumatic brain injury in preclinical drug development: where do we go from here? Br J Pharmacol. 2011;164(4):1207–29.
77. Poloyac SM, Bertz RJ, McDermott LA, Marathe P. Pharmacological optimization for successful traumatic brain injury drug development. J Neurotrauma. 2020;37(22):2435–44.
78. Adams SM, Conley YP, Wagner AK, Jha RM, Clark RS, Poloyac SM, et al. The pharmacogenomics of severe traumatic brain injury. Pharmacogenomics. 2017;18(15):1413–25.
79. Bennett ER, Reuter-Rice K, Laskowitz DT. Genetic influences in traumatic brain injury. In: Laskowitz D, Grant G, editors. Translational research in traumatic brain injury [Internet]. Boca Raton (FL): CRC Press/Taylor and Francis Group; 2016 [cited 2023 Mar 28]. Front Neurosci. Available from: http://www.ncbi.nlm.nih.gov/books/NBK326717/.
80. Hutson PH, Clark JA, Cross AJ. CNS target identification and validation: avoiding the valley of death or naive optimism? Annu Rev Pharmacol Toxicol. 2017;6(57):171–87.
81. Finkbeiner S. Bridging the valley of death of therapeutics for neurodegeneration. Nat Med. 2010;16(11):1227–32.
82. Löscher W, Potschka H. Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. Prog Neurobiol. 2005;76(1):22–76.
83. Kaya M, Ahishali B. Basic physiology of the blood-brain barrier in health and disease: a brief overview. Tissue Barriers. 9(1):1840913.
84. Maas AI, Steyerberg EW, Murray GD, Bullock R, Baethmann A, Marshall LF, et al. Why have recent trials of neuroprotective agents in head injury failed to show convincing efficacy? A pragmatic analysis and theoretical considerations. Neurosurgery. 1999;44(6):1286–98.
85. Hawkins BE, Huie JR, Almeida C, Chen J, Ferguson AR. Data dissemination: shortening the long tail of traumatic brain injury dark data. J Neurotrauma. 2020;37(22):2414–23.
86. Bramlett HM, Dietrich WD, Dixon CE, Shear DA, Schmid KE, Mondello S, et al. Erythropoietin treatment in traumatic brain injury: operation brain trauma therapy. J Neurotrauma. 2016;33(6):538–52.
87. Browning M, Shear DA, Bramlett HM, Dixon CE, Mondello S, Schmid KE, et al. Levetiracetam treatment in traumatic brain injury: operation brain trauma therapy. J Neurotrauma. 2016;33(6):581–94.
88. Mondello S, Shear DA, Bramlett HM, Dixon CE, Schmid KE, Dietrich WD, et al. Insight into pre-clinical models of traumatic brain injury using circulating brain damage biomarkers: operation brain trauma therapy. J Neurotrauma. 2016;33(6):595–605.
89. Kochanek P, Dietrich WD, Shear DA, Bramlett HM, Mondello S, Lafrenaye A, et al. Exploring additional approaches to therapy ranking in operation brain trauma therapy. J Neurotrauma. 2019;36:DB9.
90. Mountney A, Bramlett HM, Dixon CE, Mondello S, Dietrich WD, Wang KKW, et al. Simvastatin treatment in traumatic brain injury: operation brain trauma therapy. J Neurotrauma. 2016;33(6):567–80.
91. Shear DA, Dixon CE, Bramlett HM, Mondello S, Dietrich WD, Deng-Bryant Y, et al. Nicotinamide treatment in traumatic brain injury: operation brain trauma therapy. J Neurotrauma. 2016;33(6):523–37.
92. Wilkinson MD, Dumontier M, Aalbersberg IjJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016;3(1):160018.
93. Chou A, Lee S, Krukowski K, Guglielmetti C, Nolan A, Hawkins BE, Chaumeil MM, Beattie MS, Bresnahan JC, Rosi S, Ferguson AR. Aggregated animal subject metadata from 11 UCSF preclinical TBI publications and 1 ODC-TBI published dataset.
94. Tudur Smith C, Marcucci M, Nolan SJ, Iorio A, Sudell M, Riley R, et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. Cochrane Database Syst Rev. 2016;2016(9):MR000007.

95. Sowers JL, Sowers ML, Zhang K, Hawkins BE. Traumatic brain injury induces region-specific glutamate metabolism changes as measured by multiple mass spectrometry methods. Open Data Commons for Traumatic Brain Injury. 2021.
96. odc-tbi | Welcome... [Internet]. [cited 2023 Mar 28]. Available from: https://odc-tbi.org/.