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Animal models of traumatic brain injury

Ye Xiong[1], **Asim Mahmood**[1], and **Michael Chopp**[2,3]

[1]Department of Neurosurgery, E&R Building, Room 3096, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, 48202, USA

[2]Department of Neurology, E&R Building, Room 3096, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, 48202, USA

[3]Department of Physics, Oakland University, Rochester, MI 48309, USA

Abstract

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity in both civilian life and the battlefield worldwide. Survivors of TBI frequently experience long-term disabling changes in cognition, sensorimotor function and personality. Over the past three decades, animal models have been developed to replicate the various aspects of human TBI, to better understand the underlying pathophysiology and to explore potential treatments. Nevertheless, promising neuroprotective drugs, which were identified to be effective in animal TBI models, have all failed in phase II or phase III clinical trials. This failure in clinical translation of preclinical studies highlights a compelling need to revisit the current status of animal models of TBI and therapeutic strategies.

Traumatic brain injury (TBI) is defined as damage to the brain resulting from an external mechanical force, such as that caused by rapid acceleration or deceleration, blast waves, crush, impact, or penetration by a projectile, and can lead to temporary or permanent impairment of cognitive, physical and psychosocial functions[1]. TBI is the leading cause of death and disability for people under the age of 45 years[2]. Indeed, worldwide, 10 million deaths and/or hospitalizations annually are directly attributable to TBI and an estimated 57 million people have experienced such brain injury[2].

TBI is not a single pathophysiological event but a complex disease process[3] (BOX 1), and causes structural damage and functional deficits that are due to both primary and secondary injury mechanisms[12]. The primary injury is the result of the immediate mechanical disruption of brain tissue that occurs at the time of exposure to the external force and includes contusion, damage to blood vessels (hemorrhage), and axonal shearing, in which the axons of neurons are stretched and torn[13,14]. Secondary injury evolves over minutes to months after the primary injury, and is the result of cascades of metabolic, cellular and molecular events that ultimately lead to brain cell death, tissue damage and atrophy[15-17].

Many biochemical derangements responsible for secondary injury have been identified, including glutamate excitotoxicity, perturbation of cellular calcium homeostasis, increased free radical generation and lipid peroxidation, mitochondrial dysfunction, inflammation, apoptosis, and diffuse axonal injury (DAI)[18]. As highlighted above, collectively, the cascade of secondary injury events culminates in neuronal, endothelial and glial cell death and white matter degeneration[15,19]. Cell death occurs within minutes after injury and extends over a period of days to months[19,20]. Necrotic and apoptotic cell death have been identified in

Correspondence to Y.X. yxiong1@hfhs.org.

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contused areas, the injury boundary zone and subcortical regions[20,21], and apoptosis coincides with progressive atrophy of gray and white matter following TBI[15].

The relative contributions of cell death and sublethal neurobiological derangements to posttraumatic morbidities remain to be determined. Many sublethal cellular events and systemic insults, including hypoxia and hypotension, may in concert ultimately lead to cell death without timely intervention. Both acute cell death and delayed apoptosis have an important role in mediating functional deficits after TBI. However, even mild TBI without notable cell death can lead to cognitive deficits, which are probably associated with TBI-induced DAI, as indicated by studies in humans[22,23], rodents[24] and swine[25]. These findings suggest that multifocal axonal and myelin abnormalities also contribute to posttraumatic cognitive impairments.

Since primary injury occurs immediately after the moment of trauma, it can only be preventable (for example, through use of a seat belt or helmet). By contrast, the elongated nature of secondary injury development provides a window of opportunity for therapeutic intervention, which may prevent and/or reduce secondary brain damage and improve long-term patient outcome. To date, however, promising results from preclinical studies of potential TBI treatments have not been translated into successful outcomes in clinical trials. The pathophysiological heterogeneity observed in patients with TBI, the lack of sufficient pharmacokinetic analysis for determination of optimal dose, and the compounds given outside of the therapeutic window may have led to the clinical trial failures[26].

The pathophysiological heterogeneity observed in patients with TBI may arise from the location, nature and severity of the primary injury and preexisting factors and conditions, including but not restricted to age, health, gender, medication, alcohol and drug use, and genetics[27]. Animal models of TBI are each designed to produce a relatively homogeneous type of injury, with age, gender, genetic background and the injury parameters all well controlled. Thus, any one animal model may not be able to fully recapitulate all aspects of secondary injury development observed in human TBI, and this may explain in part why drugs that showed promise in preclinical studies failed in clinical studies [17]. Undoubtedly, however, animal models are essential for studying the biomechanical, cellular and molecular aspects of human TBI that cannot be addressed in the clinical setting, as well as for developing and characterizing novel therapeutic interventions. To develop new therapeutic strategies, new and existing animal models of TBI need to be developed and modified, respectively, to traverse the therapeutic gap between preclinical studies and patient medical care.

This review aims to provide a broad overview of current knowledge of animal models of TBI, to identify the issues and challenges of therapeutic strategies in preclinical studies, and to highlight research strategies for improving animal models and therapeutic efficacy.

Animal models of TBI

In view of the heterogeneous nature of the clinical situation in TBI, numerous animal models of such injury have been developed. Although larger animals are closer in size and physiology to humans, rodents are mostly used in TBI research due to their modest cost, small size and standardized outcome measurements, among other reasons (BOX 2). Whereas early models of TBI addressed the biomechanical aspects of brain injury[45-47], more-recent models have been targeted at improving our understanding of the detrimental, complex molecular cascades that are initiated by head trauma. Among them, four specific models are widely used in research: fluid percussion injury (FPI)[48], cortical impact injury (CCI)[49,50], weight drop–impact acceleration injury[51], and blast injury[52,53] (FIG 1; TABLE 1,2).

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This review will cover the main types of animal models of TBI and will not discuss cerebellar injury models. Direct cerebellar injury is a relatively uncommon phenomenon[79]. For animal models of traumatic cerebellar injury, please see the review by Potts et al[79].

Fluid percussion injury models

In FPI models, the insult is inflicted by a pendulum striking the piston of a reservoir of fluid to generate a fluid pressure pulse to the intact dura through a craniotomy, which is made either centrally around the midline[65], or laterally over the parietal bone[68], between bregma and lambda. The percussion produces brief displacement and deformation of brain tissue, and the severity of injury depends on the strength of the pressure pulse[68].

FPI models replicate clinical TBI without skull fracture[16]. Moderate to severe TBI in humans is often associated with skull fracture and contusions across multiple gyri[80], features that cannot be replicated in this model. FPI can replicate, however, intracranial hemorrhage, brain swelling and progressive gray matter damage — all pathophysiological hallmarks of human TBI[81].

Based on the position of the craniotomy away from the sagittal suture, FPI models can be divided into midline (centered on the sagittal suture), parasagittal (<3.5 mm lateral to midline) and lateral models (>3.5 mm lateral to midline; LFPI)[68,82-84]. The midline FPI model of TBI was initially developed for use in cats and rabbits[63,64,85], subsequently adapted for use in rats[48,65] and then modified to produce the LFPI model in rodents[68,69]. FPI has also been used for studying TBI pathophysiology and pharmacology in cats[86], rabbit[64], dogs and sheep[66], rats[87], mice[69,88], and pigs[67,89].

The LFPI model is one of the most widely used TBI animal models[16]. In rats, LFPI produces a combination of focal cortical contusion and diffuse subcortical (such as hippocampus and thalamus) neuronal injury, which occurs within minutes of the impact, progresses to a loss of neurons by 12 h, and does not markedly expand into other brain regions by 7 days post injury[90] The contused cortex beneath the injury site enlarges over weeks to become a cavity lined with glia and continues to expand up to one year post-injury due to ongoing cell death[91]. Over days to months, progressive degenerative cascades persist in selectively vulnerable brain regions, including the ipsilateral hippocampus, thalamus, medial septum, striatum and amygdala[16,90,92]. LFPI produces neurobehavioural and cognitive deficits such as difficulties with movement and memory that are commonly seen in patients with TBI[93,94]. Cognitive dysfunction and neurological impairments persist for more than a year following severe LFPI[95]. However, FPI models have high mortality compared with other models, probably due to the brainstem-compromised prolonged apnea[13].

The site of craniotomy is crucial in determining the extent and location of tissue injury produced by LFPI in rats[83]. Indeed, careful attention should be paid to where the craniotomy is conducted to increase the reliability and reproducibility of this model. The LFPI model inflicts primarily unilateral cortical damage, rarely involving the contralateral cortices and brainstem, whereas midline and parasagittal FPI causes bilateral cortical alterations associated with direct axial movement of the lower brainstem[13]. The degree of cortical damage highly depends on both craniotomy position and injury severity[84].

The FPI model allows minimal biomechanical control of the insult, with the height of pendulum as the only adjustable mechanical parameter. To improve reproducibility, Kabadi and colleagues developed a microprocessor-controlled, pneumatically driven instrument to address operational concerns associated with the use of the standard FPI device in rats[96]. With this new device, the impact pressure and dwell time can be precisely controlled, thus

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reducing variation between trials. This approach produced acute and chronic TBI features similar to that observed in the LFPI literature, as quantified by histological changes, structural changes seen on MRI and chronic behavioural sequelae. One final point to note is that although the LFPI model has been popular for studying neuronal cell death mechanisms in TBI, there is a recent resurgence of interest in midline FPI because of the increased interest in diffuse brain injury associated with sport and blasts[97,98].

Controlled cortical impact injury model

The CCI model uses a pneumatic or electromagnetic impact device to drive a rigid impactor onto the exposed intact dura, and mimics cortical tissue loss, acute subdural hematoma, axonal injury, concussion, blood–brain barrier (BBB) dysfunction and even coma[49,50,56,93,99]. It has been applied to ferrets[50], rats[49], mice[56], swine[57] and monkeys[58]. The controlled impact is delivered to the intact dura through a unilateral craniotomy most often between bregma and lambda, causing deformation of the underlying cortex[49]. Hall *et al*. performed a comprehensive neuropathological evaluation of the CCI TBI model and reported that the associated damage can be widespread, including acute cortical, hippocampal and thalamic degeneration[100].

The advantage of this injury model over other TBI models is the ease at which mechanical factors, such as time, velocity and depth of impact, can be controlled; thus, it may be more useful than the FPI model for biomechanical studies of TBI[13,101,102]. An additional strength of the CCI model, when compared with models involving gravity-driven devices, is the lack of risk of a rebound injury. The histopathological severity of CCI rises with increasing cortical deformation and impact velocity, permitting adjustment of the injury severity appropriate for specific experimental requirements[103,104]. The functional deficits such as cognitive impairments measured in the Morris water maze test are highly related to both the depth of deformation and the velocity of the impact in mice and rats[38,105,106]. The cognitive deficits persist up to a year post CCI and may be associated with brain atrophy[107,108] and progressive decline in cerebral blood flow[109]. CCI also caused deficits in emotional behavior as quantified in the forced swim test, elevated-plus maze, and prepulse inhibition of acoustic startle in mice[109]. Cognitive deficits increase in relation to injury severity, but emotional deficits do not, suggesting that the threshold for emotional changes after experimental TBI is low[38]. The swine CCI model generates a reproducible injury with pathological features similar to human TBI[57,110]. Despite its cost and complexity, this large animal model offers the opportunity to collect physiological data following brain injury in an environment similar to the intensive care unit and thus may facilitate translation of animal data into clinical practice.

Penetrating ballistic-like brain injury models

Penetrating ballistic-like brain injury (PBBI) is caused by transmission of projectiles with high energy and a leading shockwave, which produces a temporary cavity in the brain that is many times the size of the projectile itself[111]. Outcome in this model is directly related to the projectile's anatomical path and degree of energy transfer[76,111,112]. In the past, the experimental PBBI studies most relevant to gunshot were done in cats using a penetrating missile model[75,113]. A rat model of penetrating brain injury has been characterized and shown to produce cognitive impairment[111,114]. It induces marked white and grey matter damage, brain swelling, seizures, cortical spreading depression and neuroinflammation with a resulting sensorimotor impairment[112,115]. Therapeutic treatments including dextromethorphan and human amnion-derived multipotent progenitor cells have been recently evaluated in this model[116,117].

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Recently, several new PBBI rodent models have been developed[37,55,118]. A novel non-fatal model for low velocity PBBI has been established, involving a modified air rifle that accelerates a pellet[55]. This PBBI rat model causes cavity formation, white matter degeneration, hemorrhage, oedema, and gliosis. Bullets or shrapnel that penetrate the brain with high energy produce a temporary cavity in the brain[126]. To mimic the ballistic effect of PBBI, a PBBI rat model has been established to characterize immediate and subacute (out to 7 days) changes in intracranial pressure (ICP)[118]. BBB permeability, brain oedema formation, enduring motor and cognitive deficits have been identified in a unilateral frontal PBBI in rats[37,119]. Neurofunctional assessments revealed that motor (balance beam and rotarod tasks) and cognitive deficits (spatial learning in the MWM test) correlated with the degree of injury severity.

Several pathophysiological characteristics of PBBI are similar to those reported in other brain trauma models, including the presence of hemispheric swelling, increased ICP, remote white matter injury, and neuroinflammation[76,115]. However, compared with other TBI models, PBBI causes extensive intracerebral hemorrhage throughout the primary lesion, due to the penetrating nature of the injury and the temporary cavity that it forms. The PBBI model captures several unique temporal aspects of a ballistic brain injury and may serve as a highly relevant model of moderate-to-severe brain trauma for mechanistic studies and for evaluation of therapeutic intervention.

Weight drop TBI models

In weight drop models, the skull is exposed (with or without a craniotomy) to a free falling, guided weight[93]. Injury severity in these models can be altered by adjusting the mass of the weight and the height from which it falls.

In Feeney's weight-drop model, the weight is delivered to the intact dura through a craniotomy and causes a cortical contusion[59]. Morphologically, these injuries progress from hemorrhages in white matter directly under the contused cortex during the first hours after injury to the development of a necrotic cavity by 24 hours. The cavitation appears to expand over the subsequent two weeks[59,120]. Although most functional recovery occurs in the first two weeks after trauma in rats, with severe contusions, deficits can persist beyond 90 days[59,121].

Shohami's group later introduced a rodent model for closed head injury (CHI) using a weight-drop impact delivered to one side of the unprotected skull in rat[30,60] and mouse[29,122,123], with the head being placed on a hard surface. A mouse CHI model was described in detail, with a standardized weight-drop device inducing a focal blunt injury over the unprotected skull[123]. The resulting impact caused neurological impairment and breakdown of the BBB. Neurological severity score (NSS) was performed to evaluate the neurological impairment in motor function, alertness, and seeking behavior. The neurological impairment highly correlates with the severity of brain injury. Recently, neurobehavioral deficits, activation of microglia and astrocytes, neurodegeneration, and morphological changes assessed by MRI were demonstrated in this mouse CHI model[71], indicating this model resembles the clinical conditions of human CHI[61].

Marmarou *et al.*[51] developed a model of DAI — Marmarou's impact acceleration model — to mimic human diffuse TBI caused by falls or motor vehicle accidents[51]. DAI is common in humans and experimental animals[124,125], and in this model, the trauma device consists of a sectioned brass weight set that falls freely from a designated height through a Plexiglas tube. In anaesthetized rats with skull exposure made by a midline incision, a stainless steel disc is mounted with glue to the skull midline between lambda and bregma to prevent skull fracture. The rats are then placed on a foam bed and subjected to the impact by dropping the

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brass weight onto the stainless steel disc. Death is primarily caused by respiratory depression, and mechanical ventilation after the impact greatly reduces the mortality rate after severe injury[51,126]. The Marmarou model causes widespread and bilateral damage of neurons, axons, dendrites, and microvasculature as well as extensive DAI, particularly in the corpus callosum, internal capsule, optic tracts, cerebral and cerebellar peduncules, and the long tracts in the brainstem[126]. It also induces motor and cognitive deficits such as difficulties with beam walking and memory[127,128], similar to those observed after FPI and CCI, and these deficits correlate with injury severity[30,51,129]. One disadvantage of the weight-drop models is the relatively high variability in injury severity. However, it is inexpensive, easy to perform, and capable of producing graded DAI that closely mimics that seen in human TBI.

Previously available rodent models of CHI do not reproduce the frontal impact commonly encountered in motor vehicle and sports accidents[62]. A new rat model of CHI has been developed, by modification of the Marmarou impact-acceleration model, to investigate these scenarios[62]. In the new model (called the Maryland model), the impact force is applied to the anterior part of the cranium and produces TBI by causing anterior–posterior plus sagittal rotational acceleration of the brain inside the intact cranium[62]. The animals are characterized by an absence of cortical contusions, skull fractures, prolonged apnea, and an absence of mortality, but demonstrate petechial hemorrhages and DAI. Neurobehavioural dysfunction, manifesting as reduced spontaneous exploration, persists for more than 1 week. Additional study will be needed to further characterize this model.

Models of blast TBI

Many military personnel exposed to a blast but without external injuries have been diagnosed with TBI[130,131]. To elucidate the effects of primary blast waves on the central nervous system, various animal models of blast TBI have been established, mainly in rodents[52,74,132-134] and swine[72,135]. Using a compression-driven shock tube to simulate blast effects, Long and colleagues assessed the physiological, neuropathological, and neurobehavioural consequences of blast exposure, and also evaluated the effect of a Kevlar thoracic protective vest on acute mortality in rats and on the frequency of TBI and DAI in those that survived[134]. The Kevlar vest, which encased the thorax and part of the abdomen, greatly reduced air blast mortality, and also ameliorated the widespread axonal fiber degeneration, indicating that shock tube-generated blast causes TBI in rats, in part through systemic effects, including hypotension and hypoxemia, possibly evoked by blast-induced lung injury and/or hemorrhage[136].

Reneer and colleagues developed a blast-induced TBI rat model to mimic real blast mild TBI seen in recent military conflicts[137]. Non-impact blast injury exhibits an interesting pathophysiology that is characterized by diffuse cerebral brain oedema, extreme hyperemia and a delayed vasospasm seen in animal and human blast brain injury[138]. DAI was the most prominent feature during the initial 2 weeks following blast exposure in rats with body shielding[139]. Kuehn *et al*. found that exposure of the head alone to severe explosive blast predisposes to causes significant neurological dysfunction[140]. Importantly, even exposure of rats to low level blast increases ICP and causes cognitive deficits[141].

Although functional deficits due to blast exposure represent the principal health problem in modern warfare, the majority of available blast models focus on tissue destruction rather than functional deficits[136,137,139,142]. A recent report indicates that even mild blast brain injury caused prolonged behavioural and motor abnormalities in mice, including deficits in social recognition, spatial memory and motor coordination, and shielding of the torso ameliorated axonal injury and behavioural deficits[143]. Clearly, further research is necessary

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to address whether and how blast TBI, in particular multiple exposures to low-level blast, can lead to long-term functional deficits.

Goldstein *et al*.[71] demonstrated that blast-exposed mice show phosphorylated tauopathy, myelinated axonopathy, microvasculopathy, chronic neuroinflammation and neurodegeneration in the absence of macroscopic tissue damage or hemorrhage. Head immobilization during blast exposure prevented blast-induced learning and memory deficits, indicating that head rotation may play an important role in generating these deficits. It has become increasingly clear that brain pathology, the underlying mechanisms and potential biomarkers associated with primary blast exposures may be different from those imposed by focal mechanical head trauma[144]. It should be noted that animal placement locations along the length of the shock tube (that is, inside, outside or near the exit) have an important role in the biomechanical loading on the animal and thereby alter the injury type, its severity and the probability of lethality[145]. Considering the variations in the current blast injury models, comparison of the results between different laboratories is virtually impossible. Thus, the further design, characterization, and implementation of relevant standard experimental blast models is of particular importance for the elucidation of the mechanisms of blast injury, the identification of biomarkers and, eventually, the development of strategies for mitigating blast-induced brain injury.

Mild TBI models

Mild TBI constitutes most of the 1.7 million TBIs reported in the US annually[146]. Repeated mild TBI, a form of CHI, commonly occurs in contact sports (for example, boxing, hockey, soccer and American football), child abuse victims, and modern military personnel[147,148]. Growing evidence indicates that repeated brain concussion can result in cumulative and long-term behavioural symptoms, neuropathological changes and neurodegeneration[146,149]. Several models have been developed to mimic the clinical consequences of repeated mild TBI[148], including the weight drop model[150,151], blast TBI model in mouse[74], the FPI model in rat[73], and the CHI model in swine[152].

Kane and colleagues modified Marmarou's impact acceleration model to allow repeated head impacts in lightly anaesthetized mice[153]. This method does not require scalp incision and protective skull helmets. Mice spontaneously recover the righting reflex without evidence of seizures and paralysis, and skull fractures and intracranial bleeding are rare. Minor deficits in motor coordination and locomotor hyperactivity recover over time. Mild astrocytic reactivity and increased phospho-tau levels occur without BBB disruption, oedema and microglial activation. This new animal model is suitable for screening of new therapies for mild concussive injuries.

A single mild LFPI induces short-term behavioural and neuropathological changes in the rat[154], whereas repeated mild LFPI in rats causes cumulative long-term behavioural impairments, neuroinflammation and cortical neuron loss[155]. Interestingly, sub-concussive brain injury induces acute neuroinflammation in the absence of behavioural impairments in the rat after TBI[156]. In an immature large animal model of TBI in neonatal piglets, two head rotations following injury led to poorer outcomes, as assessed by neuropathology and neurobehavioral functional outcomes, than did a single rotation[43]. White matter injury increased in the repeat rotation group compared with the single injury group. More importantly, an increase in injury severity and mortality was observed when the head rotations occur 24 hours apart compared with 7 days apart. Worsening performance on cognitive composite score was associated with increasing severity of white matter axonal injury.

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These findings in animal models suggest that repeated mild TBI occurring within a short period can be catastrophic or fatal, and are consistent with findings in human patients who have experienced repeated brain concussions. These models will provide further insight into sports- and combat-related repeated concussions to help healthcare providers to make better decisions about allowing individuals with TBI to return to their duties and to identify people who may be at enhanced risk for TBI.

Limitations of current animal models

Physiological differences

Although there is substantial similarity in the physiology between non-human mammals (in particular rodents) and human brains, it is clear that notable differences exist between these groups in terms of brain structure and function, including brain geometry, craniospinal angle, gyral complexity, and white to gray matter ratio[93,157]. These structural characteristics may lead to substantially different responses to trauma of comparable severity or type from species to species[158]. This situation becomes even more complex, as a number of investigations have described profound differences between behavioural and histopathological responses to TBI among different rat strains[159,160] and mouse strains[161].

There is also evidence for sex differences in outcome after TBI in animals and humans[162,163]. Female sex is often associated with a lower rate of comorbidities and complications after TBI than male sex [163], and experimental animal studies suggest that female sex hormones may have a neuroprotective effect[163,164]. Current clinical evidence indicates that the female hormone progesterone improves the neurological outcome of patients with TBI[165]. However, controversy exists regarding the sex differences in clinical TBI outcome[163,166]. In addition to sex hormones, many other differences between sexes, including preinjury comorbidities, brain function and metabolism, may affect outcome[166]. As most experimental TBI studies have been conducted in male animals, further studies on sex differences in response to TBI and treatment are clearly warranted.

Many investigators studying TBI models do not rigorously measure physiological variables before and after TBI including PCO2, PO2, pH, blood pressure and brain temperature. These variables are extremely important in determining pathophysiological responses to injury and therapy. Indeed, this is one of the shortcomings of the TBI field and should be strengthened because of the importance of these variables on acute and long-term outcomes.

Injury severity measurement

Acute assessment of injury severity is critical for diagnosis, management and prognosis of TBI. Currently in TBI clinical trials, the Glasgow Coma Scale (GCS) is the primary means for patient selection, and the Glasgow Outcome Scale (GOS), or its eight point extended version (GOSe), remains a primary method for assessing outcome[167,168]. Although the severity of injury can be determined by the neurological severity score (NSS) evaluated at 1 h after CHI in mice and rats[123,169], there has been no common scoring system for injury severity that has been widely adopted for animals based on a brief neurological examination like the GCS in patients with TBI. Thus, the mechanical injury parameters in combination with histological evidence and functional tests are the most reliable measurements for classification of experimental TBI into mild, moderate and severe levels[16,38,123,170]. Scoring systems based on mechanical parameters may be specific only for a particular laboratory since most injury devices are custom-made and show subtle differences in design and operation. Additionally, small shifts in craniotomy position produce differences in cognitive performance, hippocampal cell loss and reactive astrogliosis in rats after LFPI[84], and this variability makes the comparison of experimental findings from different laboratories challenging. Moreover, the posttraumatic sequelae after mild TBI without overt

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morphological damage and severe TBI with high mortality have not been comprehensively studied in animal models.

MRI is especially useful for non-invasively detecting white matter reorganization after brain injury[171,172]. Advanced MRI can detect subtle changes in brain activity and morphology related to impairment in cognitive or emotional function even in mild clinical TBI[173,174] and in animal models of TBI[171,175,176]. Despite notable advances in diagnostic neuroimaging, accurate and early evaluation of the severity of TBI and prediction of long-term outcome are difficult. This calls for a concerted effort to search for sensitive and reliable biomarkers of TBI. Unique biochemical, neuroimaging and genetic biomarkers may be identified in response to different injury severities and different types of injuries. To ensure biomarkers in animal models of TBI genuinely reflect those associated with TBI in humans, the biomarkers measured in humans with TBI should also be measured in TBI animals and vice versa, so that clinically relevant biomarkers can be identified. A common biomarker if identified will facilitate translation of findings from the laboratory (for example, evaluation of the efficacy of preclinical therapeutic treatments) to the clinic.

Improving translation from animals to the clinic

Rigorous testing of therapeutic approaches in animal TBI models

To improve the translation of preclinical findings into successful clinical treatments, various factors need to be considered in future preclinical studies. Prior to the translation of a preclinical therapy into TBI clinical trials, ideally, sufficient preclinical data should be obtained from multiple experiments, preferably in several TBI models (in small and large animals) with different injury severities, on optimal administration routes, dose-response, therapeutic windows, single dose versus multiple dose, bolus dose versus continuous infusion.

In addition, the effective progression of strategies into clinical trials may require multifunctional agents and/or combination therapies. These potential combinations could include single pharmaceutical agents together either with cells (for example, somatic or stem cells, or genetically modified derivatives) or with other approaches (biomaterial materials, physical or electrical stimulation) for reduction of secondary damage and increase in neuroplasticity. Of note, the interaction of agents used in a combination therapy should be fully addressed in preclinical studies prior to their assessment in clinical trials. The importance of this point is illustrated by erythropoietin (EPO), which showed promise as a treatment for ischemic stroke in small clinical trials[177] but failed in a recent stroke clinical trial where it was combined with the thromobolytic drug tissue plasminogen activator (tPA)[178]. Recent preclinical data demonstrated that there is a previously unknown interaction of tPA with EPO, suggesting that EPO may not be suitable as a stroke treatment after tPA induces thrombolysis[179,180]. Multiple drugs are often used to treat the TBI patients with polytrauma or complications such as higher ICP, infection and seizure. This may increase risks of potential interactions of those drugs with a drug tested in the clinical trial. Thus, preclinical studies are needed to rigorously address drug safety and efficacy to guide subsequent clinical trials, especially of combination therapies for TBI. One other point is that many agents entered into clinical trials for TBI were rarely assessed in pharmacokinetic and pharmacodynamic studies or in terms of brain penetration and distribution (for systemically administered drugs) in TBI models[27]. Extensive studies on these issues are warranted in preclinical studies.

The therapeutic approach tested in preclinical studies has to reflect the clinical scenario. Neuroprotection approaches have historically been dominated by targeting neuron-based injury mechanisms, either as the primary or even exclusive focus of the therapeutic

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strategy[181]. In the vast majority of animal models of TBI, the prospective neuroprotective compounds have been administered either early after TBI or, frequently, before the injury is delivered[106], which is not clinically relevant. The early administration of a compound by prehospital care personnel may be problematic because of the difficulty in obtaining informed consent[182]. Thus, it is eminently reasonable to test compounds that can be administered late after onset of TBI, which have neurorestorative effects. The essential difference between neuroprotective and neurorestorative treatments is that the former mainly target the lesion and the latter treat the intact tissue[183]. Thus, neurorestorative treatments can be made available for targeting a larger portion of patients with TBI. It is essential to rigorously test neurorestorative therapies in addition to neuroprotective therapies in animal models of TBI (Box 3).

Long-term versus short-term studies

To date, most of studies in animal models of TBI have focused primarily on short-term survival times, in the range of hours to days and rarely extend beyond one month after injury[106]. These short-term studies have provided abundant information on the pathophysiology and functional outcomes during the acute stage after TBI. The histological and behavioural data obtained at the early time points post injury may not provide a valid assessment of long-term outcome and cannot be used to assess clinical therapies for long-lasting efficacy. To verify whether early changes can predict long-term outcome, more studies evaluating injury response and functional deficits over longer time periods (3 months up to 1 year after TBI) are warranted. A small number of experimental TBI studies have followed outcomes of animals beyond 1 month after injury[28,108,109,197-199]. However, several studies have demonstrated that long-term functional and structural changes take place up to 1 year after TBI[28,91,109,198]. These findings suggest that therapeutic window may not be limited to the first few hours after TBI and may extend far beyond this period. In addition, the delayed progression of brain damage over periods of months and even years suggests that to reduce brain damage, early treatment is necessary but may not be sufficient to promote long-term recovery; continued treatment may be needed for long-term functional recovery. Delayed treatment may benefit patients with TBI who miss the early window of neuroprotection therapy. Previous studies in animals have provided a proof of principle for improvement of functional recovery with delayed neurorestorative treatments initiated 24 hr [195,200] or beyond[201] after TBI.

Although long-term behavioural deficits can be detected in rodent models of TBI, it seems that cognitive deficits are more robust and persistent than sensorimotor deficits, and different focal impact sites produce dissociable patterns of cognitive deficits in rats[108,202,203], consistent with the observations that cognitive deficits are the most common disabling sequelae of human TBI[106,204]. These findings suggest that rodents can be used to model different subgroups of patients with TBI. Given that the therapeutic potential of novel treatments may be limited to specific injury types, and even to specific behavioural deficits[205], the use of a variety of injury types and a comprehensive battery of long-term behavioural tests is highly recommended for future preclinical studies.

TBI models with comorbidities

Despite modern intensive care, death and disability in polytrauma patients with concomitant TBI remain unacceptably high[206]. TBI in the clinical setting is a heterogeneous injury with a combination of hematomas, contusion, DAI, subarachnoid hemorrhage, hypoxia, and ischemia and is often accompanied by medication or substance use[13]. To better mimic clinical situations, some of these factors have been integrated into the animal TBI models. The CCI and impact acceleration models have been combined with hypoxia[207], hypoxia and hypotension[208,209] and the LFPI model has been combined with hypoxia[210] and/or

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hypotension[211]. These systemic insults were shown to exacerbate histological and behavioural outcomes in these models[212]. However, these factors are understudied in animal models of TBI. Further development of more clinically relevant animal models of TBI is necessary to incorporate hypoxia, ischemia, and other potentially relevant factors that influence clinical head injury to reproduce the complete pathobiology of human TBI and to test potential therapies targeting these factors.

Multiple injuries can result in a complex pathophysiological and immunological response[213]. Indeed, LFPI combined with a tibial fracture initiates a robust systemic inflammatory response in rats[214]. Pharmacological treatment should be evaluated in TBI models with multiple injuries because injury to other organs may significantly change drug biodistribution, bioavailability and metabolism, which together may affect drug efficacy and toxicity. In addition, identification of unique neurochemical mediators and mechanisms following multiple injuries will help determine effective therapeutic interventions in individual patients with TBI.

Age is another important comorbidity factor affecting outcomes of TBI. TBI is the leading cause of death in children. Survivors of childhood TBI are at risk for developing and sustaining behavioural impairments[54]. Clinical and experimental studies demonstrate that the developing brain may be more vulnerable to traumatic injury than the adult brain[215]. Animal models have shown that developmental TBI results in different acute injury responses and recovery[54,216]. Among the developmental animal models of TBI, CCI, FPI and Marmarou weight drop models are most commonly used in immature rodents and pigs[54] while rapid non-impact inertial head injury are used in immature pigs[152,217]. Relative to adult TBI, our understanding and management of pediatric TBI is still in its infancy. More comprehensive studies in this area will strengthen our understanding of the complex interactions between brain maturation and recovery from injury and will provide critical ground work for addressing unique responses of this specific age group to TBI.

With increasing age comes an increased risk for sustaining TBI[218]. Elderly individuals with TBI differ from younger adults with TBI in several ways, including their incidence rates, aetiology of injury, nature of complications, lengths of hospitalization, functional outcomes, and mortality[219]. Adults older than 75 have the highest rates of TBI-related hospitalization and death, with falls as the leading cause of TBI[220]. Older age is known to negatively affect outcome after TBI[221]. However, the effect of age is rarely studied in animal models. To address this important public health issue, age is an important factor to consider in pre-clinical efficacy studies[218,220]. In addition, therapeutic doses of a treatment identified to be effective in young animals with TBI may have no effect even worsen outcome in aged TBI rats[218]. This finding suggests that it is not sufficient to simply study the effects of age on TBI and novel therapies must be evaluated in aged populations of animals with TBI. Given the high incidence of TBI in the aged population, much more preclinical research is needed in this area.

Conclusions and perspective

Overcoming the lack of drugs with proven clinical efficacy in TBI is a major challenge for the neuroscience research community and the pharmaceutical industry. Studies employing various animal models, *in vitro* models and computational modeling of TBI have contributed to the current understanding of the posttraumatic sequelae. Among these approaches, the animal models remain necessary to address complex physiological and pathophysiological mechanisms associated with this condition, test new therapeutic agents, and ensure that clinical trials are safe and, ultimately, successful. A variety of rodent models of TBI have been developed to model different injury mechanisms associated with human TBI. The

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rodent models by Marmarou[51] and Shohami[29] are widely used for CHI and they reproduce predominantly diffuse and focal brain injury, respectively. Probably due to the excellent reproducibility, LFPI and CCI are the most widely used rodent models for TBI. There is an increasing research in blast TBI and sports-related concussions, especially repeated mild TBI.

Although small animal models have been used in TBI research to investigate the basic mechanisms and pathology of TBI and to test therapeutic efficacy, successful TBI investigations in small animal models have not resulted in marked improvements in clinical outcomes of patients with such injury. One of the major barriers to crossing the translational gap is that, due to ethical and financial issues, researchers rarely use clinically meaningful large animal models of TBI to monitor clinically relevant physiological parameters and long-term functional and/or cognitive outcomes, and to test the efficacy of new treatments. Thus, it is extremely important to further develop and increasingly use higher species with brains that are more anatomically and functionally closer to man. At least, before initiation of clinical trials, an effective treatment in rodents should be tested, with its efficacy confirmed, in large animal models that closely mimic the complex pathogenesis of TBI in humans.

Numerous promising treatment options have emerged in recent years, including neuroprotective, neurorestorative and anti-inflammatory agents[186] These drugs should be subjected to a rigorous preclinical dose–response analysis of their efficacy on the target mechanism and the ability to reduce posttraumatic neurodegeneration and to improve behavioural and neurological recovery. This endeavor would facilitate the transition of TBI therapies from the bench to the bedside.

The failure to achieve a therapeutic breakthrough in TBI may not result only from limitations of the animal models per se. Poor clinical study design is also a factor in why therapeutic translation has not occurred. For example, early therapeutic hypothermia is beneficial in many experimental models of TBI. Hypothermia appears to improve outcome in TBI patients undergoing craniotomy for hematoma only when it is applied before or within 1.5 hours after craniotomy, but does not improve the outcome of patients with diffuse brain injury[222]. This implies that optimal timing of combined treatments has a critical role in beneficial outcome in a specific population of patients with TBI. Thus, the continued translation of new findings from the bench to the bedside and then back to the bench will ultimately teach us a lot about the relevance of our animal models. Most importantly, these types of back and forth exchange of observations and ideas will help us determine which pathophysiological mechanisms are most important to target in specific patient populations. The lack of success of translating preclinical effective treatments to clinical TBI is complex and may result both from the multifaceted issues of suboptimal animal models and inadequate design and implementation of clinical trials, as described by us in this review and by others[22,35,36,192]. In addition, as we have discussed, the pathophysiological heterogeneity of patients with TBI, the lack of sufficient pharmacokinetic analysis for determination of optimal dose, the compounds given outside of the therapeutic window, and insensitive outcome measures may limit proof of clinical efficacy[223-226]. The ongoing international effort to develop an improved classification system for individuals with TBI may enable selection of more homogenous patient cohorts in future clinical trials to facilitate multicentre comparisons[225].

In conclusion, current animal models mimic some but not all types of human brain injury. To achieve a therapeutic breakthrough in TBI will probably require a multifaceted approach, combining innovations in clinical trial design, the development of new clinically relevant models, refinements of established models and functional tests, consideration of systemic

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insults and multimodality monitoring, searching for specific and sensitive biomarkers, and optimization of therapeutic dosing and timing of single and combination treatment. In addition, more research into the effect of age, sex and species or strain on the outcome of TBI is necessary. One final important issue is that the majority of drugs tested to date cannot cross the BBB to effectively target the injured brain. Additional studies in improving brain drug delivery systems and monitoring of target drug levels and drug effects are warranted in both animal models and the clinical setting.

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Glossary

Diffuse axonal injury (DAI)	DAI is characterized by impaired axoplasmic flow that progresses to axotomy, and is typically identified by immunohistochemical staining of amyloid-β precursor protein
Erythropoietin (EPO)	EPO is a glycoprotein hormone secreted by the kidney in the adult and by the liver in the fetus, which acts on stem cells of the bone marrow to stimulate red blood cell production (that is, erythropoiesis)
Tissue plasminogen activator (tPA)	tPA is an enzyme that catalyzes the conversion of plasminogen to plasmin, used to dissolve blood clots rapidly and selectively, especially in the treatment of heart attacks and ischaemic stroke
Phosphorylated tauopathy	This is the accumulation of hyperphosphorylated tau protein (a highly soluble microtubule-associated protein), which causes the formation of neurofibrillary tangles, a pathological hallmark of tauopathies, a group of diseases including Alzheimer's disease, frontal temporal dementia with Parkinsonism and corticobasal degeneration
Glasgow coma scale (GCS)	The GCS is a standardized scale used to measure level of consciousness, to assess the degree of brain impairment and to identify the seriousness of injury in relation to outcome after TBI. Scoring is determined by summing the ratings assigned to three factors depending on whether and how the patient responds to certain standard stimuli by opening the eyes, giving a verbal response, and giving a motor response. A high score of 13 to 15 indicates a mild brain injury. A score of 9 to 12 reflects a moderate brain injury and a score of 3 to 8 reflects a severe brain injury
Glasgow outcome scale (GOS)	The GOS is a 5-point score given to victims of TBI for classifying the outcome that rates patient status into one of five categories: Dead, Vegetative State, Severe Disability, Moderate Disability or Good Recovery. The Extended GOS (GOSe) provides more detailed categorization into eight categories by subdividing the categories of severe disability, moderate disability and good recovery into a lower and upper category
Neurological severity score (NSS)	The NSS is a reliable tool for evaluating neurological damage in closed head trauma in mice and rats and assess both motor function and behavior
Modified neurological	The mNSS is a composite of motor, sensory, reflex, and balance tests in rats. It is graded on a scale of 0 to 18 (normal score, 0; maximal deficit score, 18). One point is awarded for inability to

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severity score (mNSS)	perform the tasks or for lack of a tested reflex: 13–18, severe injury; 7–12, moderate injury; 1–6, mild injury
Biomarker	A specific biochemical, molecular, anatomic and physiologic characteristic that is used to measure or indicate the presence or progress of disease or the effects of treatment

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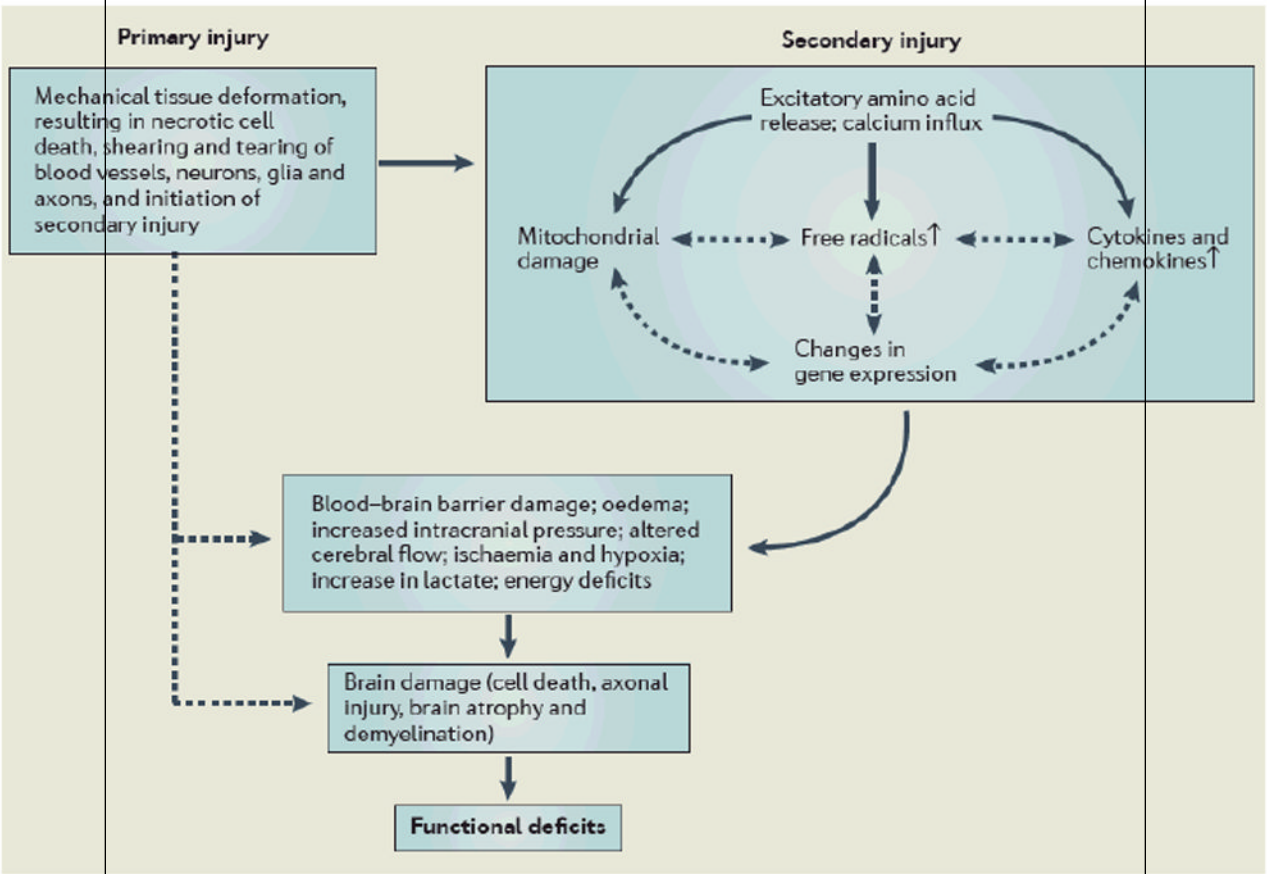
Box 1

Simplified pathophysiology of traumatic brain injury

In traumatic brain injury, the primary injury, which is the direct result of the external force, involves mechanical tissue deformation and causes diffuse neuronal depolarization and release of excitatory neurotransmitters including glutamate and aspartate[4,5], which bind to glutamate receptors and induce a massive influx of calcium[6]. Calcium activates calcium-dependent phospholipases, proteases and endonucleases that degrade lipids, proteins and nucleic acids (not shown). Calcium sequestration in mitochondria leads to calcium disturbance, energy deficits, free radical formation, and initiation of apoptosis[7,8]. Increased formation of oxygen and nitrogen reactive species oxidizes lipids, proteins and nuclei acids after TBI[9]. TBI up-regulates many transcription factors, inflammatory mediators, and neuroprotective genes but down-regulates neurotransmitter receptors and release mechanisms[10]. Increased expression of detrimental cytokines and chemokines induces brain oedema, blood–brain barrier damage, and cell death[11]. The result of these complex cascades after TBI eventually leads to cell damage and death, which causes functional deficits. Substantial experimental and clinical data have accumulated over the past decade indicating that the adult brain is capable of substantial structural and functional reorganization after injury, which may contribute to spontaneous functional recovery. Interventions targeting secondary injury mechanisms and modulating neuroplasticity promote functional recovery in animal models of TBI. Red line: Main effects; dotted black line: possible effects; black line with arrows: possible interactions.



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Box 2

Functional outcome testing in animal models of traumatic brain injury

Motor function is mediated by a complex system of neural networks originating in the brain cortex and terminating in skeletal muscles[28]. The association cortex, sensorimotor cortex, subcortical nuclei, cerebellum, and brainstem all communicate with each other to send a signal through the spinal cord to coordinate movement[28]. Brain injury-induced disruption in any or all parts of these pathways will cause motor deficits. Few, if any, purely motor behavioural tasks exist. Deficits caused by traumatic brain injury (TBI) result from disruption of complex motor pathways and sensorimotor integration, and therefore most of the described tests for assessing the outcome of such injury in animal models are sensorimotor in nature[28]. Widely used sensorimotor function tests include the cylinder test, Rotarod test, grip strength tests, skilled forelimb reach and staircase tests[28]. The neurological severity score (NSS) composed of motor functions and behavior is widely used for closed head injury in rodents[29,30]. In addition, the modified neurological severity score (mNSS) is a very useful tool to evaluate neurological functional deficits in rodents after unilateral brain injury[31,32].

TBI in humans often leads to cognitive dysfunction, the degree of which often depends on the injury severity[33]. Cognitive dysfunction has been described in the CCI, lateral and midline FPI, blast, and impact acceleration animal models of TBI2[4,29,34-37]. Commonly used tests of cognition in rodents include the Morris water maze, freezing response test, memory task and object recognition test[28]. Some more complex behavioural tests have also been developed in experimental TBI research to mimic the complex personality and psychological disturbances in patients with TBI. Anxiety-like tests include the elevated plus maze, emotional and exploratory activity, and the open field tests[38-41]. Depression, a common clinical problem after TBI, has not been fully studied in animal models, although there are a few reports using the forced swimming test to assess depression-like behaviour[41,42].

Functional tests have been rarely developed or performed in large animals after TBI. Recently, a wide range of neurobehavioural functions including open field testing (executive function), glass barrier task (visual-based problem solving), food cover task (olfactory-based problem solving), and balance beam (motor) has been performed in the neonatal pig following closed head injury[43,44]. Further development or use of functional tests in large animals is warranted to verify the safety and efficacy of promising treatments that are effective in small animal models of TBI before clinical trials are initiated.

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Box 3

Neuroprotection and neurorestoration

Acute neuroprotective therapies aim to block the molecular cascade of injury following traumatic brain injury (TBI). Although neuroprotection is an important strategy for the treatment of such injury[184], to date, no effective neuroprotective agents have been identified from TBI clinical trials. The disappointing clinical trials may be due to variability in both treatment approaches and heterogeneity of the population of TBI patients[184-187]. Another important aspect is that most clinical trial strategies have used drugs that target a single pathophysiological mechanism, despite the fact that many mechanisms are involved in secondary injury after TBI[185]. Testing multiple functional agents or combination therapy targeting complex mechanisms is an important research direction in animal models of TBI. A major limitation of neuroprotection strategies is the short time window. As such, an efficacy of therapies can be expected only within several minutes to hours after TBI onset.

Subacute neurorestoration therapies enhance neuroplasticity and brain reorganization following TBI. Recent preclinical studies from us and others have revealed that TBI induces many neurorestorative processes including neurogenesis, axonal sprouting, synaptogenesis, oligodendrogenesis and angiogenesis, which may contribute to spontaneous functional recovery[188-193]. In addition, agents and treatments that promote these neurorestorative processes have been demonstrated to improve functional recovery after brain injury[183,194]. However, clinical trials in TBI have primarily targeted neuroprotection, and trials directed specifically at neurorestoration have not been fully investigated in animal models and are rarely conducted in TBI patients. Unlike neuroprotection, restorative therapies are aimed at remodeling brain tissue rather than solely against cell death or lesion volume. The extended 24 hour window for treatment which improves neurological recovery, without altering cortical lesion volume, is a major benefit of this novel neurorestorative therapy in TBI animals[195,196]. Thus, neurorestorative therapy potentially will have a high clinical impact. Further investigation of neurorestorative agents in animal models is warranted to increase the therapeutic window and target an expanded population of patients with TBI.

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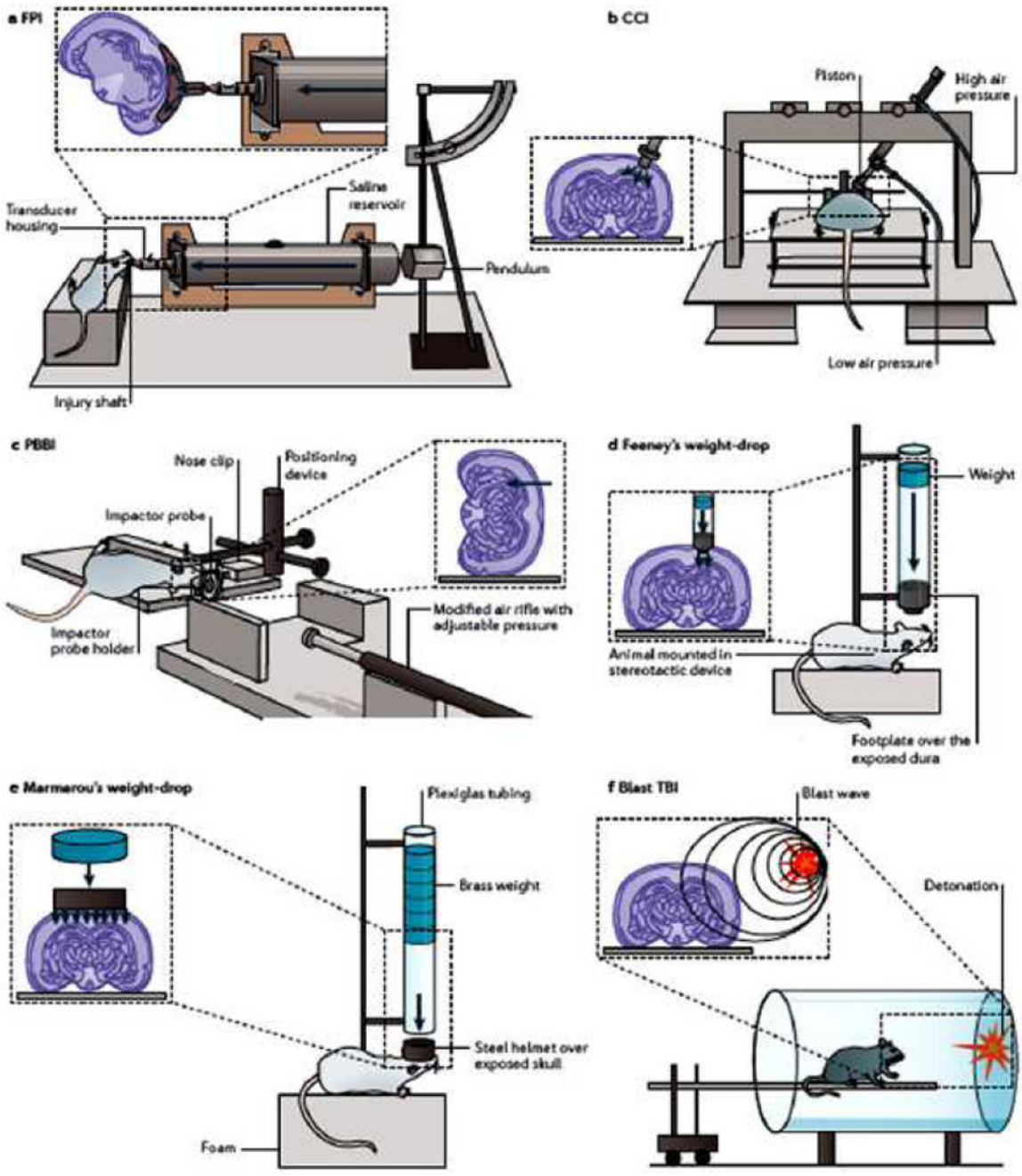

Figure 1. Experimental set ups for the animal models of traumatic brain injury

a | The fluid percussion injury (FPI) device uses rapid injection of a fluid pulse into the epidural space. **b** | The controlled cortical impact (CCI) model uses an air or electromagnetic driven piston to penetrate the brain at a known distance and velocity. **c** | The penetrating ballistic-like brain injury (PBBI) involves the transmission of projectiles with high energy of a metal rod or expansion of the probe's elastic balloon. **d** | In the Feeney weight-drop model, a free weight is released directly onto the exposed dura. **e** | In the Marmarou weight-drop model, a metal disk is placed over the skull to prevent bone fracture. **f** | The blast brain injury caused by primary injury of blast or other mechanisms, e.g., thoracic effect. Panels a,b,d,e are modified, with permission, from REF[54]. [54]© 2003 Mary

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Table 1

Commonly used animal models of TBI

Model	Type of injury	Strengths	Weaknesses	Species
CCI	Mainly focal	Highly reproducible	Need for craniotomy	Ferret[50], mouse[56], rat[49], swine[57], monkey[58]
Weight drop				
Feeney	Mainly focal	Injury mechanism close to human TBI	Need for craniotomy; high mortality rate	Rat[59]
Shohami	Mainly focal	Easy operation, with immediate neurological severity scoring at 1h	Not highly reproducible	Rat[60], mouse[29]
Marmarou	Mainly diffuse	Injury mechanism close to human TBI; well characterized	Not highly reproducible, high mortality without ventilation	Rat[51], mouse[61]
Maryland model	Mainly diffuse	Injury mechanism close to human TBI	Needs further characterization	Rat[62]
FPI				
Middle	Mixed	Highly reproducible with fine-tuning	Need for craniotomy, high mortality	Cat[63], rabbit[64], rat[65], dog and sheep[66], swine[67]
Lateral	Mixed	Highly reproducible with fine-tuning	Need for caniotomy, high mortality	Rat[68], mouse[69], swine[70]
Blast	Mainly diffuse	Injury mechanism close to military TBI	Need standardization	Rat[52], mouse[71], swine[72]
Repeated mild	Mainly diffuse	Injury mechanism close to sports TBI	Need further characterization	Rat[73], mouse[74], swine[43]
PBBI	Mainly focal	Injury mechanism close to human TBI	Need standardization	Cat[75], rat[76]

CCI, controlled cortical impact; FPI, fluid percussion injury; PBBI, penetrating ballistic-like brain injury; TBI, traumatic brain injury. The Table is modified, with permission, from REF[77]. [77] © 2010 BioMed Central.

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Table 2

Major pathological features of animal models that are seen in human TBI

TBI model	Concussion	Contusion	Traumatic axonal injury	Hemorrhage	Skull fracture	References
Shohami's and Marmarou's weight drop models	++	+	++	+	+/-	29, 51, 60, 126, 212
Feeney's weight drop model	+	++	+	+	-	59
Maryland's model	+	-	+	+	-	62
Fluid percussion injury	+	++	+	+	-	16, 45, 63-70, 83, 84, 88, 154, 155
Controlled cortical impact	+	++	+	++	-	38, 49, 50, 56-58, 93, 99, 103-110
Blast	++	+	++	+	+/-	52, 71, 72,74, 132-145
Penetrating ballistic-like brain injury	+	++	+	++	+/-	37, 55, 75, 76, 111-119

-, does not duplicate the condition observed in humans; +/- may duplicate the condition observed in humans; + duplicates the human condition to some degree; ++ shows high fidelity to the human condition.