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Authors

Wang, Kevin K
Yang, Zhihui
Zhu, Tian
[et al.](#)

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An update on diagnostic and prognostic biomarkers for traumatic brain injury

Kevin K. Wang¹, Zihui Yang¹, Tian Zhu¹, Yuan Shi², Richard Rubenstein³, J. Adrian Tyndall⁴, and Geoff T. Manley^{5,6}

¹Departments of Emergency Medicine, Program for Neurotrauma, Neuroproteomics & Biomarkers Research, Psychiatry, Neuroscience and Chemistry, University of Florida, Gainesville, Florida, USA

²Department Of Pediatrics, Daping Hospital, Chongqing, Third Military Medical University, No. 10 Changjigang Zhilu, Chongqing 400042, China

³Departments of Neurology and Physiology/Pharmacology, Laboratory of Neurodegenerative Diseases and CNS Biomarker Discovery, SUNY Downstate Medical Center, Brooklyn, NY, USA

⁴Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA

⁵Brain and Spine al Injury Center, San Francisco General Hospital, San Francisco, CA, USA

⁶Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA

Abstract

Introduction: Traumatic brain injury (TBI) is a major worldwide neurological disorder of epidemic proportions. To date, there are still no FDA-approved therapies to treat any forms of TBI. Encouragingly, there are emerging data showing that biofluid-based TBI biomarker tests have the potential to diagnose the presence of TBI of different severities including concussion, and to predict outcome.

Area covered: The authors provide an update on the current knowledge of TBI biomarkers, including protein biomarkers for neuronal cell body injury (UCH-L1, NSE), astroglial injury (GFAP, S100B), neuronal cell death (α II-spectrin breakdown products), axonal injury (NF proteins), white matter injury (MBP), post-injury neurodegeneration (total Tau and phospho-Tau), post-injury autoimmune response (brain antigen-targeting autoantibodies), and other emerging non-protein biomarkers. The authors discuss biomarker evidence in TBI diagnosis, outcome prognosis and possible identification of post-TBI neurodegenerative diseases (e.g. chronic traumatic encephalopathy and Alzheimer's disease), and as theranostic tools in pre-clinical and clinical settings.

Correspondence to: Kevin K. Wang.

Declaration of Interest

KK Wang is a stockholder of Banyan Biomarkers, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Expert Commentary: A spectrum of biomarkers is now at or near the stage of formal clinical validation of their diagnostic and prognostic utilities in the management of TBI of varied severities including concussions. TBI biomarkers could serve as a theranostic tool in facilitating drug development and treatment monitoring.

Keywords

biomarkers; traumatic brain injury; diagnostics; theranostics; neurotrauma

1. INTRODUCTION:

Traumatic brain injury (TBI), often referred to as a silent epidemic [1], is defined as a neurotrauma caused by a mechanical force that is applied to the head. In the United States, there are approximately 1.7–2.0 million incidents of TBI annually [2] (Table 1). In addition, CDC reported that approximately 5.3 million Americans live with the effects of TBI. About half of the Americans who experience TBI each year incur at least some short-term disability [2–7]. The Armed Forces Health Surveillance Center has reported that 375,230 US service members sustained TBI between 2000 and 2016 [3] (Table 1). TBI is a heterogeneous neurological disorder – it ranges from penetrating injury, focal contusion, different forms of hematoma (subdural, epidural) to diffuse injury to single or repetitive concussion /mild TBI. Currently, TBI can also be classified by Glasgow Coma Scale (GCS) score: severe (GCS 3–8), moderate (GCS 9–12) and mild (GCS 13–15) as well as cranial computer tomography (CT) abnormality (CT positive vs. CT negative) [6,7]. Mild TBI (mTBI, CT negative) accounts for over 85% of all cases of TBI. In the U.S., TBI accounts for 1.3% of all emergency department visits [8]. The direct medical costs for treatment of TBI in the U.S. have been estimated to be \$4 billion annually. In addition to concussions that occur in the general populace in everyday activities, professional as well as recreational collegiate and scholastic athletes and high school athletes who participate in contact sports (e.g. American football, wrestling, hockey, boxing, soccer, lacrosse, rugby) are particularly vulnerable to experiencing concussions [9]. Between 1.6–3.8 million sports or recreational activities-related concussions occur annually in the United States and approximately half of these involve children and adolescents [10]. On average, 25% of athletes will report more than one concussion in their lifetime [11,12].

2. The need for TBI biomarkers

Significant scientific advances in the last decade have increased our understanding of the complex and heterogeneous pathophysiological processes associated with TBI. During the same period, numerous experimental drugs have been shown to be neuroprotective in animal models of brain injury. Unfortunately, none of these strategies have proven to be efficacious in TBI clinical trials [13–15]. The failure of clinical therapy trials has been attributed to the lack of therapeutic intervention-tracking CNS biomarkers complicated by the heterogeneity of TBI and poor translatability of preclinical TBI models. For example, it is now recognized that the pathophysiology of TBI is not only acute event, but is also a progressive and delayed neurodegenerative process made up of multiple, parallel, interacting, and interdependent cascades of biological reactions at the tissue, cellular, and subcellular levels. Due to the

extended length of axonal fiber tracks, axons are particularly vulnerable to physical trauma to the brain. Thus, axonal injury is a common occurrence in both focal as well as diffuse brain trauma and can be found in TBI of all severities [16,17]. But in addition, neuronal body, dendrites, and synapses are also subjected to TBI-induced damage [18,19]. Similarly, not only are neurons at risk for injury, but also astroglia cells and the myelin-forming oligodendrocytes. For these reasons, a comprehensive understanding of these pathobiological processes at every cellular and subcellular level in greater detail is critical to bridging the knowledge gap that will allow new therapy development. Many agree that there is an unmet medical need for a rapid, simple biofluid-based diagnostic testing for the management of TBI patients, whether it is for monitoring severe TBI patients in the intensive care unit, or triaging mild and moderate TBI patients in the emergency room. Due to the multi-component pathobiology in brain injury, it would be ideal to have a panel of neuroinjury biomarkers that closely match with the various pathological processes we described above. There are emerging data from many recent studies from multiple research teams showing that biofluid-based TBI biomarker tests have the potential to assess the extent of TBI severity and determine a patient prognosis even at times when correlation with other neurological measures (neuroimaging) may not always be informative such as for mild TBI.

3. TBI biomarker attributes

In order for a biofluid-based TBI protein biomarker to be clinically useful, ideally it should have as many of the following attributes as possible (Table 2): **(1)** The protein biomarker levels should be readily measured in accessible biofluid such as cerebrospinal fluid (CSF), serum, plasma and/or whole blood in TBI patients. [For severe TBI (i.e. those TBI patients in neurointensive care unit), the biofluid type where the biomarker can be detected should be biofluids such as cerebrospinal fluid, serum, plasma and/or whole blood. For moderate and mild TBI (e.g. those patients managed in Emergency Departments or admitted to non ICU settings), the biofluid type should be serum, plasma and/or whole blood for rapid accessibility and convenience. **(2)** The biomarker levels must be elevated in various forms and/or severities of human TBI in the acute phase (3 h to 24 h post-injury), when compared to normal control counterparts, **(3)** the biomarker must have low background or basal biofluid levels in general non-injured healthy control population. **(4)** The biomarker detected in biofluid after TBI should be derived from or originated from the injured brain as the major source. **(5)** The biomarker levels in the above stated biofluids should be readily determined and quantified using sandwich ELISA or similar immunoassays with at least two assay formats or platforms. **(6)** There should be one or more available assay platform for such biomarker with test-retest reliability and reproducibility assay that meet assay analytical performance requirements acceptable to FDA. **(7)** The biomarker should be translational in nature with demonstrated evidence that there are similar to biofluid profiles in at least two different animal models of TBI (e.g. rodent control cortical impact (CCI), fluid percussion injury (FPI), close head injury (CHI), penetrating ballistic brain injury (PBBi) or blast overpressure-wave brain injury (OBI)). **(8)** The biomarker should be sensitive to severity of TBI as defined by GCS, CT abnormality. **(9)** The biomarker should allow for repeated detections in one of the above-mentioned biofluids within a 48 h window following brain injury. **(10)** The biomarker should have initial acute levels (within first 48 h

postinjury) that correlate with currently available and commonly accepted TBI patient outcome indices (such as Glasgow outcome scale (GOS) or GOS-extended (GOS-E)), and (11) the post-TBI biofluid levels of the biomarker are responsive to therapeutic treatments. Based on cumulative evidence on a number of existing neuroinjury biomarkers and the discovery of additional biomarkers, we derived a TBI biofluid-based biomarker panel (Table 3).

4. Current biomarker candidates

Mirroring the different pathophysiologic processes occurring in TBI, a panel of TBI biofluid-based protein biomarkers has now been identified. The processes covered by these biomarkers thus far include axonal injury, dendritic injury, neuronal cell body injury, demyelination, synaptic injury and astroglia injury and microglia responses (Figure 1) [20–22] [23].

4.1 Neuronal cell body injury markers:

4.1.1. Neuron specific enolase (NSE): NSE is also known as gamma-enolase or enolase 2 (encoded by ENO2 gene) (Figure 1). NSE exists as a homodimer in mature neurons and neuroendocrine cells. NSE elevations in blood compartment has been documented in severe TBI [24–26]. NSE elevation in mTBI has also been documented [27–29]. NSE elevations were also reported in animal model of overpressure blast wave-induced brain injury in rodents [24–30] (Table 3). One major drawback of using NSE as specific marker for TBI is that it is also abundantly expressed in red blood cells, which prompted researchers to use a hemolysis correction when measuring NSE in blood [31].

4.1.2. Ubiquitin C-terminal hydrolase-L1 (UCH-L1): UCH-L1 is a protein that mainly resides in the neuronal cell body cytoplasm. It was one of the few TBI biomarker candidates identified based on recent proteomic studies [32,33] (Figure 1). We reason that UCH-L1 is a functional biomarker and serves as a barometer of neuronal cell body injury (Table 3). UCH-L1 was first found to be released into CSF and serum among severe TBI patients [34–36]. The use of CSF UCH-L1 levels also appears to improve clinical outcome predictors of mortality following non-penetrating TBI. A new study also found UCH-L1 has utilities in long-term prognosis of severe TBI [37]. In addition, two independent studies demonstrated that UCH-L1 was released into serum/plasma in mTBI subjects [38]. It has been suggested that UCH-L1 together with GFAP form the foundation of a biomarker panel representing the two dominant cell types in the brain [39]. Interestingly, serum levels of both UCH-L1 and GFAP also appear elevated in professional breacher trainees who were exposed to repeated explosive discharges [40]. Lastly, Puvenna et al. (2014) also found significant UCH-L1 elevations in serum among athletes after concussions [41].

4.2 Astroglial biomarkers

4.2.1 S100B protein: S100B is an astroglial 11 kDa calcium-binding protein. It is perhaps the most investigated brain injury biomarker to date [42,43] (Figure 1). Preclinical animal TBI model data is present [30,44] (Table 3). S100B has been studied in TBI of various severities [45–47]. However, since it has been noted that S100B can also be released

from adipose tissue and cardiac/skeletal muscles, its levels are also elevated in orthopedic trauma without head injury [48]. Despite these confounders, S100B is actually a sensitive biomarker for predicting CT abnormality and post-concussive syndrome development among mTBI patients [49–51].

4.2.2 Glial fibrillary acidic protein (GFAP): astroglial GFAP is emerging as the most robust TBI biomarker (Figure 1). GFAP biomarker levels are elevated within 3 to 34 h in CSF and serum/plasma following severe TBI [46,52–55] and in serum and plasma samples after moderate to mTBI [56]. GFAP as a biomarker, in the form of either the GFAP intact protein (50 kDa) or as breakdown products (GFAP-BDPs; 44–38 kDa) are predominantly released from injured brain tissue into biofluid such as cerebrospinal fluid and serum/plasma shortly following TBI [46,52,57]. In parallel with human TBI studies, GFAP elevations in CSF have been identified in several rat models of severe TBI (CCI, PBBI, OBI) [58,59] and as well as in serum /plasma samples in mTBI models [30,60–62]. There is additional evidence that the post-TBI elevation of GFAP is severity-dependent [59]. Lastly, GFAP levels are also linked to CT pathological alterations and patient outcomes [56,63,64] (Table 3).

4.3 α -II-spectrin breakdown products/fragments as cell death markers:

More recently, C-terminal BDPs of axonal protein α II-spectrin (SBDP150 and SBDP145) produced by calpain during necrosis, and SBDP120 produced by caspase-3 during apoptosis) have been identified as potential cell death biomarkers in both animal models of TBI and human CSF samples [65–70] [71] (Figure 1). In parallel to SBDP150, the N-terminal spectrin fragment (SNTF) (~140 kDa) was also produced [65,66,72,73]. SNTF was shown to be elevated in circulation after concussion. One potential confound is that the α II-spectrin protein, although enriched in the CNS, is also expressed in other organs as well as peripheral blood mononuclear cells (PBMC). Thus, SBDP or SNTF elevations in blood alone may not be conclusively interpreted as the presence of brain trauma or concussion (Table 3).

4.4 Delayed axonal injury and demyelination markers:

4.4.1 Neurofilament proteins (NF): NF belong to the so-called “class IV” intermediate filaments (10 nm diameter). They are found exclusively in neurons. NF exist as bundles known as neurofibrils and are a major cytoskeleton component that functions primarily to provide structural support for the axon and to regulate axon diameter. NF are composed of three polypeptide subunits of different molecular weight: neurofilament-light protein (NF-L; 68K) neurofilament-medium protein (NF-M, 150K) and neurofilament-heavy protein (NF-H; 200K) (Figure 1). NF-H is subjected to phosphorylation. Phospho-NF-H (pNF-H) is enriched in axons – making it a good immunohistochemical biomarker for staining fiber track. All three NF subunits are vulnerable to proteases such as calpain and cathepsin-B/D [74,75]. Following proteolysis, they can be dissociated from the cytoskeleton into cytosol or possibly extracellular fluid, especially if cell membrane integrity is compromised. pNF-H was found released in blood following experimental TBI [76]. Li et al. (2015) also showed that serum pNF-H elevations were correlated to mechanical impact responses elevated in serum following a weight drop closed head injury model [77].

Martínez-Morillo and colleagues showed that (NF-M) protein concentrations were increased in CSF and serum samples from patients with severe TBI [78]. Neselius et al. (2013) found increased CSF levels of pNF-H following bouts among amateur boxers [79], while pNF-H also appears to be a predictor of mortality after brain injury in children [80]. In addition, serum NF-L also appears elevated in American football players over the course of a season [81] and in TBI subjects [82],[79]. Importantly, NF protein release into biofluid is a delayed process with respect to the initial insult (days following insults) (Table 3). Thus, it could reflect on-going axonal degeneration and might be linked to cognitive decline and development in chronic TBI subjects. It is worth-noting that another axonally-located microtubule associated protein Tau is also an emerging TBI biomarker – it will be covered further in a later section.

4.4.2 Myelin basic protein (MBP): MBP is an oligodendrocyte protein and a key structural component of the multi-layered myelin sheath covering nerve fibers (Figure 1). The myelin sheath found in the nervous system serves as an insulator to increase the velocity of axonal impulse conduction [3]. MBP maintains the correct structure of myelin, interacting with the lipids in the myelin membrane [83]. In myelinated fiber tracks of the white matter, MBP degradation by proteases, such as calpain, results in degradation of axons and the myelin sheath (demyelination) [84,85]. Thus, under these conditions, MBP or its fragmented forms might be released into biofluid after TBI. For example, MBP are shown to be released into CSF after rat CCI [44], while MBP is also found to be elevated in serum after severe TBI in children [20,44] and mTBI in adults [20] (Table 3).

4.5 Subacute, chronic TBI biomarkers:

Evidence show that biofluid (CSF, blood) levels of most acute TBI markers will return to baseline levels within a matter of days following TBI, especially for those who suffered from mild brain injury (Table 3). Yet subacute and chronic effects of TBI can persist for months following the initial injury event. These effects might include CNS and systemic sequelae such as cognitive impairment (memory and executive dysfunction), neurological symptoms (headache, sleep disturbance and pain), neuro-endocrine dysfunction and mental health impairment (depression, anxiety, apathy and suicidality) and, as yet, unclear processes leading to the development of neurodegenerative diseases such as chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD) [86–90]. Thus, it might be appropriate to consider a continuum of TBI biomarkers that might be released at different time points following the initial brain injury event (Figure 2). These biomarkers could represent different but parallel pathways active at various time points after the initial injury. Some of the emerging subacute and chronic TBI biomarkers might include neurodegeneration markers such as total Tau (T-Tau) protein and phosphorylated Tau (P-Tau) and amyloid beta peptides ($A\beta_{1-40}$, $A\beta_{1-42}$), autoantibody response to neuroproteins [91,92] and inflammatory markers. Proinflammatory cytokines such as IL-1 β , IL-6 IL-8 and TNF- α are released into brain tissue or biofluids (CSF, blood) in human and rat likely by reactive microglia or glia after TBI [93–99]. However this last group of markers is not specific to TBI.

4.5.1 Postinjury Neurodegeneration/Tauopathy biomarkers: Increasing evidence has suggested that TBI may also be a risk factor for the development of age-associated

neurodegenerative disorders including AD, Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis and Multiple Sclerosis [100–103]. The increased relative risk is in the modest range (1.5 – 3-fold). The exact mechanism of this has not been elucidated. It is possible the TBI (either single or multiple impacts of varying severities) can cause initiation of a protein aggregation-related seeding event that, over time, leads to neurodegeneration-linked protein aggregate accumulation. Moderate to severe TBI has been shown in autopsy studies to result in increased amyloid deposition in the brain. As we are unable to perform brain biopsies on participants, $A\beta_{1-40}$ and $A\beta_{1-42}$ are proxies for altered amyloid metabolism and easily followed over time. Tau is a neuronal protein, which helps stabilize microtubules in the axon. Since axonal injury is a key feature of TBI, tauopathy and amyloidopathy could be chronic manifestations of TBI. Moreover, Smith and colleagues (1999) have shown deposition of P-Tau following TBI [104]. CTE is another emerging neurodegenerative condition believed to be induced by the repeated concussions. CTE is characterized clinically by changes in personality, increased in anxiety or aggression and other related psychiatric symptoms [105]. Neuropathologically, CTE is characterized by the presence of Tau and TAR DNA binding protein-43 kDa (TDP-43) deposits in the cerebral cortex [106]. Such Tau deposits are mostly readily detected by P-Tau specific antibodies [105,107]. Tau is phosphorylated at many sites potentially by kinases such as casein kinase II, tau tubulin kinases, GSK3 β , and cdk5 [108] [109,110]. Tau hyperphosphorylation has also been reproduced in animal models of TBI [111].

Elevated levels of P-Tau are seen in the brain in CTE years following mTBI or repeated concussions as a significant tauopathic neurodegenerative disease likely occurring as a result of repeated concussions [105,107] (Figure 1, 2). Using the high sensitivity SIMOA platform (Quanterix), Tau can be observed in the acute to subacute/chronic stage following mTBI (hockey players and military veterans) [112,113]. In parallel, we recently developed an ultrasensitive rolling cycle amplification (RCA) based ELISA format platform for both T-Tau and P-Tau (T231 and S202) assays and found elevations of serum P-Tau and T-Tau from severe human TBI and in rodent repetitive mTBI in both acute and subacute period [109,110]. In human cohort of mostly moderate-severe TBI (n=21 subjects), we detected plasma T-Tau and P-Tau elevations not only in the acute phase (< 24 h), but also in the chronic phase (average 6 mo. post-injury) [114]. The availability of such ultrasensitive tests of T-Tau and P-Tau holds promise on tracking the possible development of post-TBI CTE and AD (Table 3). TDP-43 and its breakdown product were also found elevated in human CSF 24–48 h following severe TBI [115].

4.5.2. Autoantibodies as autoimmune response biomarkers: Reports have documented brain-directed autoimmunity in neurological and neurodegenerative diseases such as AD, stroke, epilepsy, spinal cord injury and paraneoplastic syndromes [116–121]. In human TBI and stroke, however, autoimmunity has only been examined in a limited manner, and current studies focused on autoantibodies against preselected antigens such as MBP, S100B, and glutamate receptors [91,122–125]. Recently, Marchi et al. demonstrated that anti-gliial protein S100B antibodies are elevated in football players with repeated concussions [126]. In parallel, we have gathered evidence that unexpectedly shows an immunodominant autoantibody response to GFAP and its BDPs in a subset of subacute and

chronic TBI patients (day 5 to 6 mo. post injury) [52,127] (Figure 1, 2). Our hypothesis is that TBI-induced release of GFAP-BDPs is in substantive quantity through the compromised brain-blood-barrier into circulation and becomes accessible to and recognized by the immune systems as a non-self protein, triggering autoantibody response in these vulnerable individuals. As autoantibody specifically targeting a major brain protein (GFAP) might trigger a persistent autoimmune attack of the CNS, it might negatively affect TBI patient long-term outcome (Table 3). Also, Tanriverdi et al. showed the presence of anti-pituitary antibodies in patient serum 3 years after TBI [128,129]. This could be linked to hypopituitarism observed in the chronic phase of TBI [130]. Growth hormone deficiency was also found by Tanriverdi et al. (2013) in amateur boxers and kick boxers [131]. Additional neuroantigen targets capable of triggering TBI autoimmunity response are likely to be identified and verified in the future [132].

5. Other emerging biomarkers:

5.1 New protein biomarker candidates:

There are other TBI biomarker candidates with biofluid evidence from animal models of TBI from severe to mTBI in human. These include dendritic protein microtubule-associated protein-2 (MAP2) [133], [134], brain derived nerve growth factor (BDNF) [135], and postsynaptic protein neurogranin [136] (Table 3). Further evaluation of the utility and TBI specificity of these biomarkers are needed. Post-TBI vascular injury is also an emerging pathological mechanism under investigation [137,138]. Thus, it has been suggested that it might be possible to use vascular dysfunction/markers to track such events. They include fibrinogen, D-dimer and von Willebrand factor [139], [140], [141].

5.2. MicroRNA (miRNA)

miRNA are a class of small (19–28 nt) endogenous RNA molecules that regulate gene expression at post transcriptional level. Circulating miRNAs have been shown to be associated with several human diseases and disorders. A number of candidate miRNAs have in fact been reported to be elevated in biofluid (CSF, serum or plasma) in several rodent models of TBI with different severities. These include miR-Let-7i in acute CSF and serum using a rat overpressure blast brain injury model [142], miRNA (MiR-376a, MiR-214, MiR-199a-3p) candidates in acute serum samples using a mild close head injury model {Sharma:2014ig}. For human data, recently, Redell, et al. were the first to identify elevations of three miRNA (MiR-16, MiR-92a, MiR-765) in acute plasma samples after severe TBI [143]. Bhomia and our group also identified a total of ten candidate miRNAs (miR-151–5p, miR-195, miR-20a, miR328, miR-362–3p, miR30d, miR-451, miR-486, miR-505 and miR-92a) using acute CSF, and/or serum samples from human TBI that ranging from mild, moderate to severe TBI [144]. These miRNAs in fact can distinguish mTBI from healthy volunteers and orthopedic injury control samples. Another recent study showed that two miRNAs (miR-142–3p and miR-423–3p) can identify mild TBI patients who are likely to post-concussive syndrome [145]. Pietrao et al. also showed that miR-425–5p and miR-502 were elevated in mTBI in the early time points, while the latter also predicted the 6-month outcome [146].

5.3. Circulating nucleic acids

Circulating nucleic acids have been considered as diagnostic tools in trauma patients [147], [148]. Most researchers focused on DNA rather than mRNA, as unlike miRNA, DNA are highly labile and subjected to degradation by RNase found in biofluids. Total plasma cell-free DNA levels were found to be an independent mortality predictor for severe TBI subjects in several studies [148] [149] [150] [151]. However, since total plasma DNA is not brain-specific, it is unlikely DNA-based test will become a specific TBI diagnostic tool.

5.4. Exosome / Microvesicles

Another emerging field is the study of circulating microvesicles and exosomes (MV/E) in CSF and/or blood after TBI [152]. Exosomes and microvesicles are lipid-bilayer encapsulated particles (10–100 nm in diameter) that are released from cells (healthy or injured) into biofluids including extracellular fluid, CSF and blood. Often they contain distinct protein or miRNA content when released under a disease or disorder state. For example, plasma of TBI patients has a distinct set of proteins, as revealed by mass spectrometry-based method [153]. In addition, Manek et al. showed that MV/E released into CSF in TBI patients contains elevated levels of several protein biomarkers (SBDPs, synaptophysin, UCH-L1 and GFAP) [154]. Nekludov et al. (2017) also found that microvesicles isolated from TBI subject plasma (n=15) contains brain-derived GFAP and aquaporin-4 [155]. Circulating exosomes embedded with tau might be a better diagnostic tool for chronic TBI subjects at risk of developing chronic traumatic encephalopathy (CTE) [156].

6. Utilities of TBI biomarkers

As brain protein biomarkers detected in biofluid originated from the brain, they offer an organic measure of the pathophysiological processes at various time points following TBI. Since they can be readily measured in accessible biofluids, they can be referred to as a “liquid brain biopsy”. Such TBI biomarker tests can be used in acute, subacute and chronic patient care and management (Table 4).

6.1 TBI diagnostics:

6.1.1. Neurointensive Care: Severe TBI patients (about 10–15% of all TBI, GCS 3–8) are often managed in neurointensive care units (neuro-ICU) in major hospitals. Monitoring of patient’s brain and systemic status (including intracranial pressure) is critical in enhancing patient’s survival rate and long-term outcome. Here, ventriculostomy procedure is often performed as a means of cranial decompression. Thus, the availability of both blood samples and CSF samples can be obtained for possible “real time” biomarker monitoring. For example, the biomarker load (e.g. biomarker levels over a period time, or area under the curve) for UCH-L1 in both CSF and serum can distinguish injury severity and mortality [35]. Thus, we envision repeated monitoring of TBI biomarker levels over time in a neuro-ICU setting might provide useful and actionable information in the management of patients with severe TBI.

6.1.2. Emergency Department: In the civilian setting the majority of TBI cases are mild-moderate TBI (about 80–85%, GCS 13–15 for mild, GCS 9–12 for moderate). Most of these patients would arrive at Emergency Departments for treatment and care. Currently, the cranial CT is the primary diagnostic tool for assessing injury severity. However, while CT can detect blood hemorrhage, it is not particularly sensitive in detecting DAI (Diffuse Axonal Injury) or other more subtle forms of brain injuries. In addition, repeated CT scanning can present high radiation exposure to at risk population such as children. Thus we envision a rapid POC device being developing as a screening prior to the use of CT. It is possible that repeated measurement of biomarkers over time could potentially be used to access evolving lesion, worsening of injury or the course of brain recovery.

6.1.3. Sports-related concussions/ mTBI: On the opposite end of the TBI spectrum, a common form of everyday mild is sometimes referred to concussion. Sports-related single or repeated concussions are especially common among professional, recreational and collegiate athletes. In this setting, it is very important to access (a) if a concussion indeed occurred, and (ii) the degree of injury. If a biomarker is present in circulation within 30 min post-impact, its detection might be useful in making decision for return to play (RTP) in real time. Alternatively, with repeated testing of the same biomarkers within the days following concussion, in conjunction with other measures such as sports concussion assessment tools (SCAT3), they are useful in RTP decision. Another important feature of sports-related mTBI, the athletes who take part in such impact-prone sports activity often experience not only a single concussion, but also repeated concussion over time, both in recreational or professional sport setting. There is another potential life-threatening but rare condition – “second impact syndrome” – it occurs if an athlete who has not fully recovered from a recent concussion suffers another concussion, resulting in a greatly increase risk of severe disability or mortality [157] [158] [159].

6.1.4 Military mTBI: Mild TBI also commonly occurs in military operations – including in the theater of operations as well as during training. Similar to sports concussion, triaging decisions rely on having accurate information on the severity of the impact in individual subjects. It is possible to use a POC diagnostic test to monitor biomarker levels over time. Biomarker testing might also be useful in assisting the decision of return to duty when blood levels of a biomarker return to below a preset cutoff value.

6.2 TBI prognostics:

TBI biomarkers can also be used as a prognostic tool in the ED setting, in neurointensive care unit for the more severely injured patients or even in an out-of-hospital setting. For mTBI cases, similar biomarkers might predict the possible development of persistent post-concussive syndrome (PCS). Several protein biomarkers have shown some promise in this emerging area.

6.2.1. S100B—One of the most powerful uses of biomarkers is to utilize acute phase levels of such biomarkers to inform on the outcome of patients. For example, serum levels of S100B within 12–36 h from TBI in neurointensive care units correlate with patient outcomes. [160]. These studies have been confirmed by a German research group showing a

significant correlation of S100B concentrations in serum and Glasgow Outcome Score (GOS) score at 6 months. In addition, they also find that serum levels of S100B > 0.7 ng/mL correlate with 100% mortality [161]. Di Battista et al. (2015) reported that unfavorable neurological outcomes are associated with elevation in serum levels of S100B and GFAP [162]. Combined admission concentrations of these three markers are able to discriminate favorable versus unfavorable outcome and survival versus death. S100B can also detect brain death development or mortality after severe TBI [163], [164]. In another study, GFAP and S100B were found to be strong predictors of unfavorable outcome among severe TBI patients [46]. Another study also confirmed that acute S100B, GFAP, and UCH-L1 in severe TBI correlated significantly with the injury severity and clinical outcome [165]. One review analyzed how S100B may be utilized in TBI patients and pointed out S100B appears to be an important and useful predictor of functional outcome in moderate-to-severe TBI [166].

6.2.2 GFAP: Acute plasma GFAP levels also modestly correlate with patient with poor outcomes (GOSE 4) (AUC, 0.74) or with good outcome (GOSE 7) (AUC, 0.65) [38]. Similar results were obtained in early studies that demonstrated the relationship of increased serum-GFAP in patients with severe TBI and clinical outcomes [53] [167]. Serum GFAP levels were also significantly higher in patients who died or had an unfavorable outcome and have predicted neurological outcome at 6 months [168]. These findings were confirmed by Czeiter and colleagues (2012) when evaluating the correlation between serum values of GFAP and the 6-month mortality [169]. Another study confirmed that serum concentration of GFAP and UCH-L1 proteins also strongly predicted poor outcomes and performed better than S100B [170]. In addition, as far as TBI in children, serum GFAP measured on day 1 of injury correlated with functional outcomes at 6 months as determined with Pediatric Cerebral Performance Category scores [171]. Taken together, GFAP and S100B levels in serum may enhance prognostication when combined with clinical variables [46].

6.2.3 UCH-L1: Similarly, serum UCH-L1 can distinguish mild-moderate TBI subjects that require neurosurgical intervention from those that do not [172]. Both serum UCH-L1 and GFAP concentrations on the second day predicate the recovery and unfavorable outcome by distinguishing patients with GOS score 1–3 from patients with GOS score 4–5 [173]. Besides, in a pediatric TBI serum biomarker study, UCH-L1 was correlated with GOS, which was used to predict outcome [82].

6.2.4. NF proteins: A study in Sweden involving 182 TBI patients reported that serum NF-L independently predicted TBI outcomes assessed at 6 to 12 months after injury using GOS [82]. Another study by Shahim et al. (2016) reported that initial serum levels of NF-L correlated with clinical outcome as assessed by the GOS scale at 12 months follow-up [174]. Similarly, the usefulness of NF-H (in addition to S100B and GFAP) as predictive biomarker of outcome in children with TBI has been also reported [175].

6.2.5. Tau protein: Tau protein in serum is found to predict outcomes after severe TBI with a significantly higher concentration in the poor outcome group than that in the good outcome group. Both GCS score and Tau protein levels are independent prognostic factors for poor outcome which is determined by abnormal pupil light reflex and basal cistern

compression on CT [176]. An early study showed that serum “cleaved Tau protein” levels (c-tau) in CSF is a predictor of clinical outcomes in severe TBI subjects [177]. Another recent study also revealed that serum “c-tau” levels in good outcome group (74.26 pg/ml) is lower than the poor outcome group (127.32 pg/mL) at 6 months follow up [178]. But the exact protein characterization of c-Tau remains elusive.

6.2.6. Other markers: There are new biomarkers showing predictive value in TBI outcome. Early levels (within 24 h of injury) of MAP-2 in ventricular CSF MAP-2 provide enhanced prognostic capabilities for mortality at 6 months [72]. A TRACK-TBI pilot study revealed that day-of-injury serum BDNF provides 6-month prognostic information regarding recovery from TBI [160]. They found that BDNF has a higher prognostic value among mTBI subjects than moderate/severe TBI subjects. In addition, plasma A β 42 levels at day 30 after the TBI correlate with clinical outcome assessed at 6 months after injury [179].

6.2.7. Opposing results: However, others have reported opposite results, possibly due to the current lack of standardization of biomarker assays. Some studies found that serum S100B concentrations neither correlate with clinical outcome using GOS, GOS-E nor with imaging studies [49] [174]. In another study, while serum S100 β levels increased in patients with minor to moderate TBI, S100B serum levels did not predict one-month neuropsychological outcomes [180]. Similarly, in multivariate analysis, GFAP was not predictive for outcome determined by GOS-E and return to work (RTW) time line. Lastly, for c-tau, an earlier study shows that its serum level is a poor predictor after mTBI [181].

7. TBI biomarkers as drug development Tools

7.1 Preclinical animal experimental therapeutic studies supporting the use of TBI biomarkers as therapeutic development tools:

As pointed out above, TBI biomarkers such as GFAP levels in CSF have been found to be elevated in several rodent models of severe TBI (CCI, PBBI, OBI) [58,59] and as well as in serum /plasma samples in mTBI models [30,60–62]. There is additional evidence that the post-TBI elevation of GFAP is severity–dependent [59]. In terms of using biomarkers to track therapeutic intervention in animal models of TBI, the best example is perhaps the Operation Brain Trauma Therapy (OBTT) study, which is a DoD–sponsored multi-center consortium study [182]. This study employed three rat models: CCI, PBBI and FPI to screen for more than 10 drugs with existing promising preclinical data in TBI already [182,183]. A composite scoring system was used to assess drug effects involving histopathology score, neurobehavioral /functional outcome and blood-based biomarkers (GFAP and UCH-L1 levels). Interestingly, it was shown that 4 h and 24 h GFAP levels significantly correlated with lesion volume as well as functional outcome [184]. Most importantly, one experimental drug, Simvastatin, was found to suppress the levels of serum GFAP at 24 h in FPI and PBBI models [185]. Another experimental drug, nicotinamide, also attenuated serum GFAP levels at 24 h in PBBI and CCI models [186].

7.2 Human clinical trials involving the use of biomarkers:

Large-scale therapeutic clinical trials are also beginning to incorporate blood-based biomarkers as a secondary endpoint (Table 4). The following are two examples: (1) INTREPID-2566 study; ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00805818) Identifier: NCT00805818), The purpose of this randomized, double-blind, placebo-controlled, dose-escalation study of NNZ-2566 is to assess the effect of an experimental drug, NNZ-2566 which is being developed as a treatment to decrease neuronal damage/death to the brain following moderate to severe TBI [187]. Among the secondary outcomes is examination of the modification of the acute physiological processes in TBI by evaluating electroencephalographic (EEG) determinants in patients with moderate to severe TBI (defined as GCS 4–12) and biomarker levels (GFAP, UCH-L1). (2) Blood Biomarkers of Injury and Outcome in Traumatic Brain Injury (Bio-ProTECT) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01730443) Identifier: NCT01730443) and the parent ProTECT III study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00822900) Identifier: NCT00822900) [188], [189]. The Bio-ProTECT study examines serum biomarkers of structural brain injury in subjects with severe TBI (S100B, GFAP, UCH-L1, SBDP150) with and without progesterone treatment.

The use of blood-based biomarkers for mTBI is particularly appealing. Currently most of the FDA-approval seeking therapeutic clinical trials target the severe to moderate TBI. Yet, the majority (>80%) or all TBI patients are in the mild category. One of the key factors is that over 80–85% of all mTBI subjects will recover spontaneously. Therefore, large numbers of patients would need to be recruited to adequately power a clinical trial designed to show therapeutic benefit in subjects with long-term neurological deficits. In addition, therapeutic effects might be difficult to detect in mTBI as the majority of mTBI subjects who get better without treatment. This makes achieving clinical efficacy much more challenging. As indicated above, acute biomarkers have the potential to inform on those subjects who are more likely to have poor outcome and experience persistent post-concussive syndrome (PCS). Thus it follows that in a therapeutic trial setting, one could administrate such a blood test in the acute phase to potential subjects and then only enroll subjects who are more likely to have poor outcome or develop PCS, based on the biomarker test results. This approach might enhance the probability of demonstrating therapeutic efficacy (Table 4).

8. Expert Commentary

Collective evidence shows that TBI protein biomarkers are a promising diagnostic and prognostic tool, which may ultimately improve patient treatment and management. Some biomarkers might facilitate the development of guidelines for management of mTBI or concussion including decisions regarding returning to work, duty or sports / athletic events while providing opportunities for other short and long term interventions for patients suffering the sequelae of TBI [14,66,88,190]. TBI biomarkers could also provide major opportunities for the conduct of clinical research including confirmation of injury mechanism(s) and drug target identification. A temporal profile of changes in biomarkers would guide timing of treatment. In addition, biomarkers can be used in clinical trials of new therapeutic interventions as an early outcome predictor thus potentially reducing the risks and costs of clinical trials. Potential gender and developmentally related differences in biomarker profiles [191–194], as well as sensitivity to therapeutic interventions can be

further examined in future studies. With the accelerated development of biofluid-based protein biomarker assays, there is a strong future promise for significant advances in TBI management and treatment.

9. Five-year view:

The full validation of the diagnostic and prognostic utilities of a TBI biomarker has been a slow process. This is in part due to the lack of clinically compatible platforms that can run such TBI biomarker assays (with the exception of S100B being available on the Roche Elecsys platform), and the lack of formal regulatory agency approval (e.g. FDA). Within the next five years – we anticipate that at least one major diagnostic company (e.g. Abbott i-STAT platform) will overcome these hurdles and make newer markers (e.g. UCH-L1 and GFAP) available for clinical uses. Another trend we are seeing is that increasing number of large and smaller diagnostic companies are entering the race by adding new POC or automated/semi-automated clinical lab-based assay platforms to TBI -based diagnostics (e.g., including BioMerieux, Phillips, Sysmex, BioDirection and Banyan Biomarkers). We also anticipate that the clinical utilities of additional new markers will be independently validated in this period.

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Key issues:

- Assay platforms: Challenges remain in developing robust TBI assay - devices that can be used in POC environment with a rapid turnaround time and simple to use are on the horizon but the usefulness will need to be verified.
- Assay standardization: Standardized assays format and qualified protein antigen standard and reference materials for the top TBI protein biomarkers candidates should be established. Assays may also undergo further analytical validation in accordance with good manufacturing practice (GMP) and good laboratory practice (GLP) guidance and Clinical & Laboratory Standards Institute (CLSI) guidelines.
- Potential Confounds: The effects of age (e.g. age range from newborn to 80-year-old) on baseline (normal control) and post- TBI CSF, serum, plasma and whole blood values for the top biomarker candidates should be established. The ability of the candidate biomarkers to distinguish mTBI from non-TBI trauma patients (e.g. orthopedic injuries), and post-traumatic stress syndrome (PTSD) need to be firmly demonstrated.
- Clinical usefulness validation of new biomarkers: As more researchers report on the discovery of “new” TBI biomarkers, many of them use a very small sample size, and they often show simple group comparison as evidence (e.g. showing statistically significant difference in the mean or median values between TBI group and control group, or between CT normal vs. CT abnormal groups, or outcome prediction). However, this exercise does not indicate any real-life practical clinical utilities of a given marker as a biomarker. For that, a larger study cohort is needed, and positive predictive (rate of true positive) and negative predictive values (rate of true negative) and a receiver operating characteristic curve (ROC) should be used in order to evaluate the clinical usefulness any new biomarker candidate.
- Better classification of TBI: TBI is heterogeneous neurological disorder – it ranges from penetrating injury, focal contusion, and different forms of hematoma to diffuse injury to repetitive concussion. GCS is originally developed to assess functional responses after TBI (i.e. eye, muscle and verbal responses), but it informs very little about the size, location and type of brain injury. Thus, It is possible that a biomarker does not correlate well with GCS. In fact, one could argue that in the future, a more complete classification of TBI might include the use of one or more TBI biofluid-biomarkers.
- Neurodegeneration monitoring: A direct link between elevated and sustained blood levels of P-Tau, T-Tau or related markers and risk of development of post-traumatic CTE and/or AD needs to be further studied.

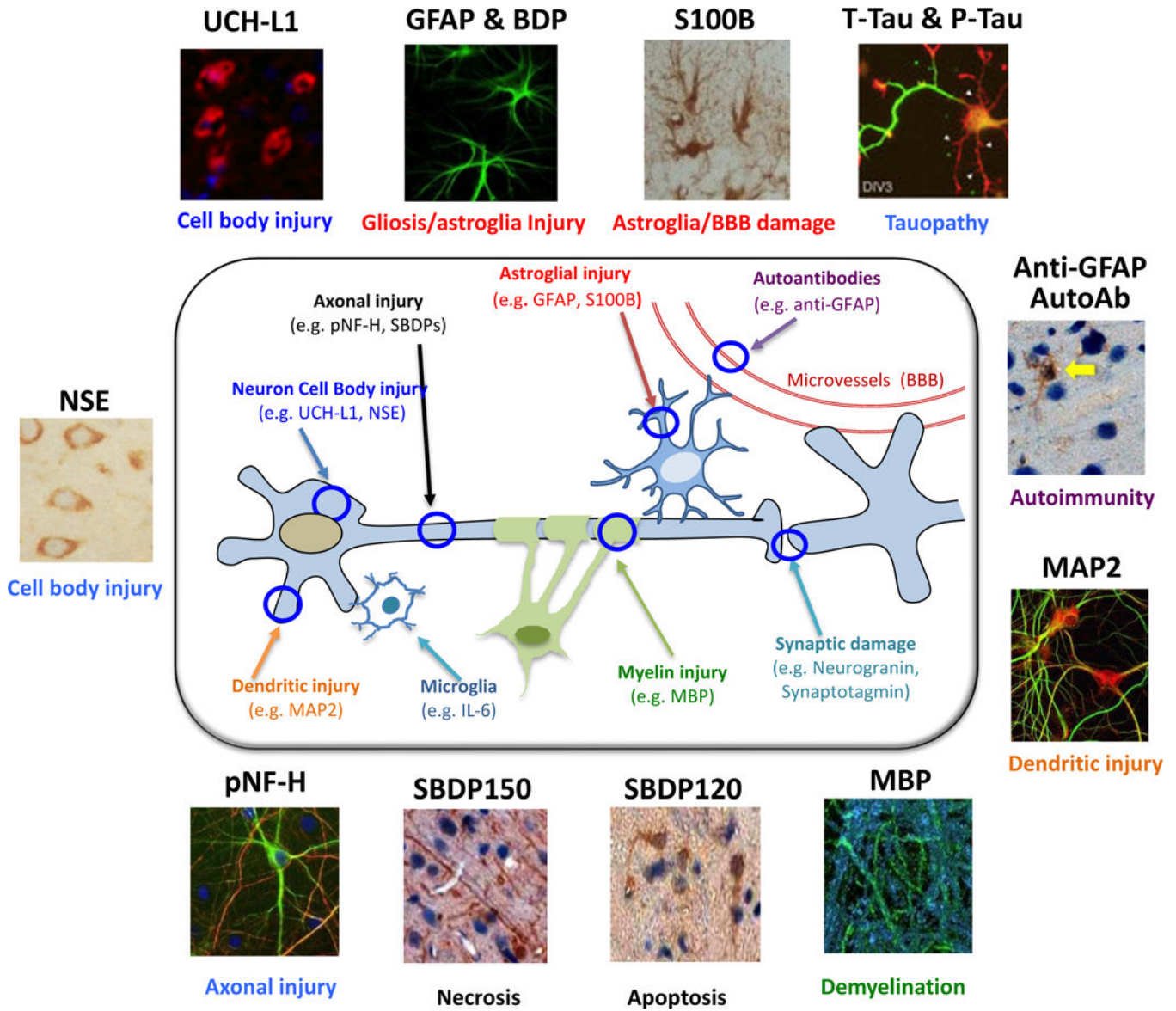


Figure 1. Graphic representation of major TBI protein biomarkers linked to different pathophysiologic processes in TBI. These processes thus far include axonal injury, dendritic injury, neuronal cell body injury, demyelination, synaptic injury and astroglia injury and microglia responses. Cellular and subcellular localization of representative TBI biomarkers are also shown with immunocytochemical staining images (based on mouse brain data).

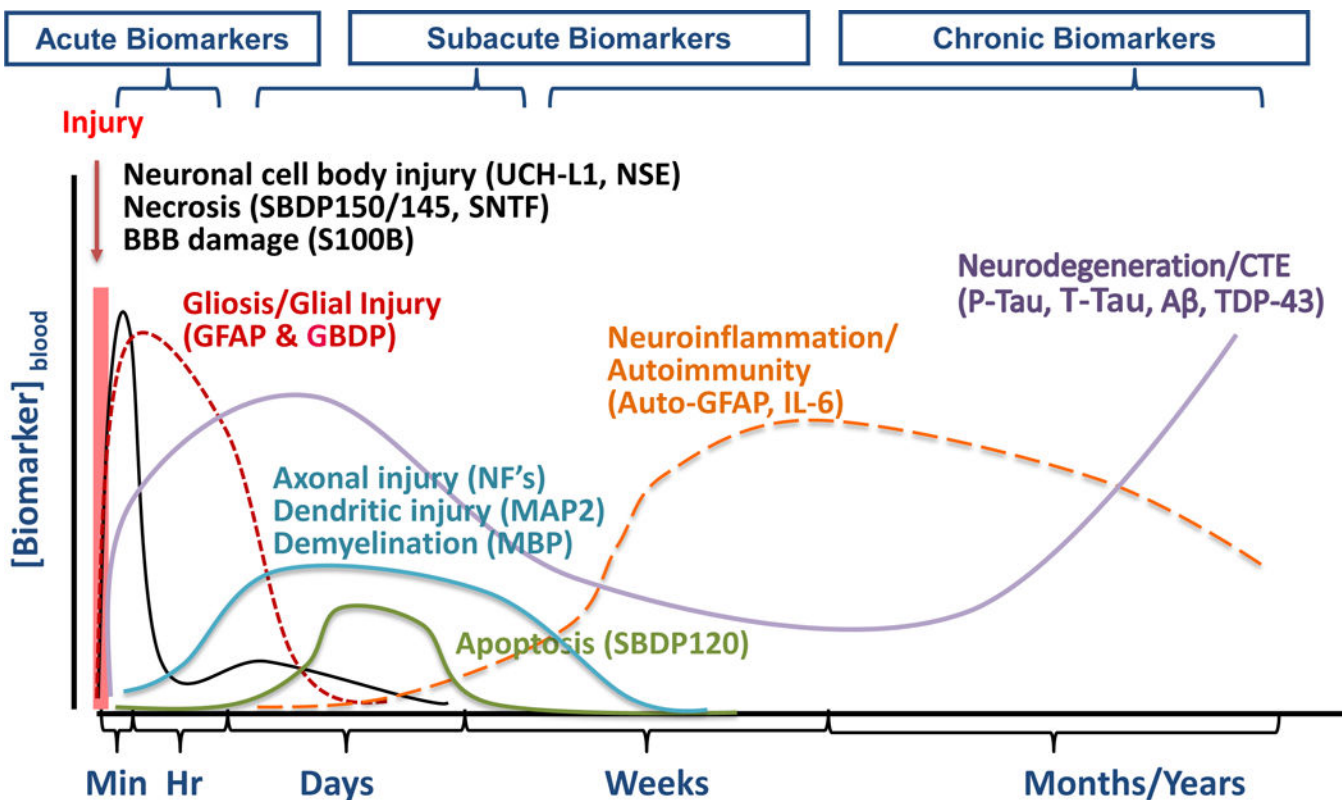


Figure 2. A continuum of protein biomarkers in tracking different phases of TBI. Acute neuronal cell body injury markers UCH-L1 (ubiquitin C-terminal hydrolase-L1), NSE (neuronal specific enolase), necrosis markers SBDP150/145 (α II-spectrin breakdown product 150 kDa & 145 kDa), SNTF (α II-spectrin N-terminal fragment), S100B (glial calcium-binding protein S100B), GFAP & BDP (glial fibrillary acidic protein & breakdown product), delayed axonal injury NF-H, M, L (neurofilament-heavy, medium & light), demyelination marker MBP (myelin basic protein), apoptosis marker SBDP120 (α II-spectrin breakdown product 120 kDa), autoimmunity markers auto[GFAP] (autoantibodies to GFAP), neurodegeneration markers Tau (tau protein), P-Tau (phosphorylated tau), A β (amyloid β -peptides) and TDP-43.

Table 1.

Spectrum of TBI in the USA.

TBI Spectrum	Incidents	Point of Care	Glasgow Coma Scale
Severe TBI	~ 170,000/per yr. US	Neuro-intensive care unit	3–8
Moderate TBI	~ 85,000 / per yr. US	Hospital in-patient	9–12
Mild TBI	~ 1.4 million/per yr. US	Emergency Dept.;Ambulance;	13–15
Military TBI(including blast brain injury)	~375,000 cases (2000–2017)	In Theater, CSH	3–15
Sports-related Concussions	1.6– 3.8 million/per year (CDC)	Sport-field, Athletic facility	(13–15)

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Table 2.

Attributes of an ideal biofluid-based biomarker for TBI.

1	The TBI biomarker levels can be readily measured in accessible biofluid. The biofluids will likely include whole blood, serum and/or plasma for moderate and mild TBI patients with the inclusion of CSF in cases of severe TBI patients.
2	The biomarkers are elevated in native and/or modified various forms which directly correlates to the degree of severity of human TBI in the acute phase (3 h to 24 h post-injury)
3	The biomarker has low background or basal biofluid levels in >95% of general non-injured healthy control population.
4	The biomarker detected in biofluid after TBI is the direct result of brain trauma.
5	The biomarker levels in the above-stated biofluids can be readily determined and quantified using at least two independent assay formats or platforms.
6	There are one or more available assays for such biomarker with test-retest reliability and reproducibility that meet analytical performance requirements acceptable to FDA.
7	The biomarker is translationally relevant relative to the model systems with demonstrated evidence that there are parallel biofluid-based biomarker profile patterns in at least two different animal models of TBI (e.g. rodent control cortical impact, fluid percussion injury, close head injury, penetrating brain injury or blast overpressure-wave brain injury)
8	The TBI protein biomarker should be qualitatively and quantitatively related to severity of TBI as defined by GCS, cranial CT and/or MRI abnormality.
9	The TBI protein biomarker should allow for repeated detections in one of the above mentioned biofluids within a 24–48 h window following brain injury.
10	The TBI protein biomarker should have initial acute levels (within first 24 h post-injury) that correlate with currently available and commonly accepted TBI patient outcome indices (such as Glasgow outcome scale-extended (GOS-E)).
11	The post-TBI biofluid levels of the TBI biomarker is responsive to therapeutic treatments (i.e. Therapeutic treatment following TBI might reduce biomarker loads).

Table 3.

TBI protein biomarker candidates that could have in vitro diagnostic, prognostic and therapeutic development / monitoring utilities.

Origin/ Pathobiological mechanisms	TBI Biomarker Candidates	Evidence for Animal TBI detection	Evidence for Human severe/moderate TBI detection	Evidence for mild TBI detection (including concussion)
Neuronal cell body injury	UCH-L1	Liu et al. 2010	Brophy et al. 2011	Diaz-Arrastia 2014 Papa 2010, Papa 2012a Tate et al. 2013; Puvenna et al. 2014
	NSE	Agoston et al. 2012 Svetlov et a. 2012 Liu et al., 2015	Bohmer et al., 2011; Berger et al., 2012;	Topolovec-Vranic et al., 2011; Buonora et al., 2015
Astrogliosis, astroglial injury	GFAP	Zoltewicz et al. 2013; Agoston et al.2012; Yan et al., 2015 Svetlov et al. 2012	Mondello et al., 2010 Vos et al. 2010	Papa et al. 2012, Okonkwo et al. 2013 Tate et al. 2013
	S100B	Agoston et al. 2012; Liu et al., 2015	Vos et al. 2010	Cervellin:2012 Kiechle et al. 2014
Axonal injury; Brain cell Necrosis- Apoptosis	SBDPs (SBDP150, SBDP145, SBDP120,SNTF)	<u>SBDP150,145,1120</u> : Pike et al, 2001	<u>SBDP150, 145, 120</u> : Mondello et al., 2010; <u>SBDP150, 145, 120</u> : Papa et al., 2014 <u>SNTF</u> : Siman et al., 2009	<u>SNTF</u> : Siman et al., 2013, 2015
Axonal injury	NF-L, NF-M, NF-H (pNF-H)	Anderson et al., 2008; Yan et al., 2015 Rostmi et al., 2012	Blyth et al., 2011 Zurek et al. 2011	NF-L: Gaston et al., 2014s; Shahim et al., 2016 <u>NF-H</u> : Oliver et al., 2015
Axonal injury, CTE	Tau, ,P-Tau	Yang et al., 2015	Rubenstein et al., 2015	Shahim et al., 2014 Olivera et al., 2016 Rubenstein et al., 2017
Demyelination	MBP	Ringger et al. 2004 Liu et al. 2015	Berger et al., 2012; Zhang, et al. 2014	Berger et al., 2012
Postsynaptic injury	Neurogranin	-	Yang et al., 2015	Yang et al., 2015
Autoimmunity	AutoAb[GFAP] Auto[S100b]	-	Zhang et al., 2014; Wang et al. 2015	Wang et al. 2015 Marchi et al., 2013

Footnote: The above list of markers is not exhaustive but reflects the current state-of the art. Other possible markers include neurofilament proteins MAP2 (microtubule associated protein 2A, 2B), H-FABP (heart-type fatty acid binding protein) and BDNF (brain derived neurotrophic factor) and TDP-43 (TAR DNA-binding protein 43). But further studies are required for further clinical utility verification and biomarker characterization.

Table 4.

Potential Utilities of TBI biomarkers.

	As diagnostic tools	As patient stratification tools in therapeutic clinical trials	As disease prognosticator	As monitor for chronic TBI
Setting	Acute (up to first 24 h post-injury)	Acute (within hours post-injury)	Acute to subacute (hours to days)	Weeks, months, years
Clinical utilities	<ul style="list-style-type: none"> To reduce usage of CT To triage patients for hospitalization 	<ul style="list-style-type: none"> To screen and enroll mild TBI subjects who are likely to have poor outcome or develop post-concussive syndrome To screen and enroll subjects who are likely to respond to a certain therapy 	<ul style="list-style-type: none"> To inform patient and/or family of likelihood of mid- and long-term prognosis 	<ul style="list-style-type: none"> Monitor development of CTE, AD or PD Monitor autoimmune response
Examples	GFAP, UCH-L1, S100b or β , SBDP150/145/SNTF, T-Tau/P-Tau, pNF-H, NF-L	GFAP, pNF-H	GFAP, P-Tau, S100B, NF-L	T-Tau, P-Tau, A β peptides, AutoAb[GFAP]

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