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Exploring the Role of Biomarkers for the Diagnosis and Management of Traumatic Brain Injury Patients

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1. Introduction

There are an estimated 10 million people affected annually by traumatic brain injury (TBI) across the globe.[1] In the United States, TBI is a major cause of death and disability[2] with about 52,000 annual deaths and 5.3 million Americans impaired by its effects. TBI is a contributing factor to over 30% of all injury-related deaths in the United States and it has been referred to as the silent epidemic of our time. [3, 4] European TBI prevalence data is not consistently reported by each country but it has been estimated that 1.6 million head-injured patients are hospitalized annually in Europe with an incidence rate of about 235 per 100,000. There is an average mortality rate of about 15 per 100,000 and a case fatality rate of about 11 per 100. The TBI severity ratio of hospitalized patients is about 22:1.5:1 for mild vs. moderate vs. severe cases, respectively.[5] According to the World Health Organization, TBI will surpass many diseases as the major cause of death and disability by the year 2020.[1]

Brain injuries can be focal, diffuse or a combination of focal and diffuse. The degree of brain injury depends on the primary mechanism/magnitude of injury, secondary insults and the patient's genetic and molecular response. Following the initial injury, cellular responses and neurochemical and metabolic cascades contribute to secondary injury.[6, 7] Focal brain injuries include contusions, brain lacerations, and hemorrhage leading to the formation of hematoma in the extradural, subarachnoid, subdural, or intracerebral compartments within the head. Traumatic brain injury represents a spectrum of injury severity. The number, types, and location of lesions as well as the magnitude of overlapping injuries across this spectrum of injury severity are still not clearly described and are challenging to classify.

There are two aspects to injury caused by TBI - the damage caused by the initial impact or insult, and that which may subsequently evolve over the ensuing hours and days referred to as secondary insults. Secondary insults can be mediated through physiologic events which decrease supply of oxygen and energy to the brain tissue or through a cascade of cytotoxic events. These events are mediated by many molecular and cellular processes.

2. The importance of mild and moderate TBI

Research in the field of TBI has long been dominated by research on severe brain injury. However, of the estimated 1.8 million people in the United States who sustain a TBI each year, over 90% will have either a "moderate" (GCS 9-12) or "mild" (GCS 13-15) injury; far outnumbering severe injuries.[2, 8, 9] Moderate TBI comprises over 10% of all TBI and mild TBI over 80%.[8] The majority of these patients will present to emergency departments (ED's) around the country for assessment and treatment.[10] The direct medical costs for treatment of TBI in the United States have been estimated at more than $4 billion annually.[11] If the costs of lost productivity that result from TBI are added to this then the overall estimated cost is closer to $56.3 billion. Moreover, mild TBI is significantly under-diagnosed and the likely societal burden is therefore even greater.[12] Mild and moderate TBI are often difficult to assess and distinguish clinically during the first hours after injury because neurological examinations are of restricted value. The distinction between mild, moderate and severe TBI is initially based on a GCS score and this may be influenced by factors such as perfusion and intoxication from drugs or alcohol, sedative medications, and other distracting injuries.

The term "mild TBI" is actually a misnomer. Individuals who incur a TBI and have an initial GCS score of 13-15 are acutely at risk for intracranial bleeding and diffuse axonal injury.[13] Additionally, a significant proportion is at risk for impairment of physical, cognitive, and psychosocial functioning.[14-18] Although some patients with mild TBI may be admitted to the hospital overnight, the vast majority are treated and released from emergency departments with basic discharge instructions. Most receive little guidance with respect to follow-up care. This group of TBI patients represents the greatest challenges to accurate diagnosis and outcome prediction. With perhaps no overt signs of acute head injury and a lack of clinical tools to detect the subtle cognitive deficits the patient is considered "unimpaired" and is discharged home and typically left to deal with persisting neurocognitive deficits on their own.[19] Accordingly, a significant minority has incomplete recoveries and has outcomes disproportionately worse than would have been predicted by the objective facts of the injury.[19, 20] The lack of clinical tools to detect the deficits that affect daily function leads to a state of frustration for patients and families that arises out of a failure to understand the nature of the difficulties encountered daily. Treatment protocols for mild TBI have only slowly begun to emerge and are still experimental. The injury is often seen as "not severe" and subsequently therapies have not been aggressively sought for these individuals. Unfortunately, despite the better understanding of the anatomical, cellular and molecular mechanisms of TBI, these advances have not yet yielded significant improvements in treatment. Among the potential barriers to treatment are the heterogeneity of traumatic brain injury, difficulty with stratification of patients by injury severity and lack of early markers of injury.[21-24]

3. The problem with current assessment of TBI

Prognostic tools for risk stratification of TBI patients are limited in the early stages of injury in the emergency setting for all severities of TBI. Unlike other organ-based diseases where rapid diagnosis employing biomarkers from blood tests are clinically essential to guide diagnosis and treatment, such as for myocardial ischemia or kidney and liver dysfunction, there are no rapid, definitive diagnostic tests for traumatic brain injury. Moreover, the

reference standard for TBI is also more difficult to define than say cardiac ischemia. There is no early gold standard for stratification of patients by severity. Currently, diagnosis of TBI depends on a variety of measures including neurological examination and neuroimaging. Neuroimaging techniques such as CT scanning and MRI are used to provide objective information. However, CT scanning has low sensitivity to diffuse brain damage and confers exposure to radiation. MRI can provide information on the extent of diffuse injuries but its widespread application is restricted by cost, the limited availability of MRI in many centers, and the difficulty of performing it in physiologically unstable patients. Additionally, its role in the clinical management of TBI patients acutely has not been established.[25, 26]

While increasing CT use has reduced hospital admissions,[27] it has also raised concern over unnecessary exposure to ionizing radiation.[28-32] Although the calculation of projected cancer risk is still controversial, some studies suggest that CT scans of the head may be among the largest contributors to radiation exposure due to the frequency with which they are performed.[33] There is significant consensus that efforts should be made to prevent unnecessary radiation exposure while maintaining quality of care.[28, 29, 34, 35]

4. Challenges to the clinical application of biomarkers

There have been a number of cerebrospinal fluid (CSF) and serum biomarkers evaluated in TBI animal models and in humans. However, many of these candidate biomarkers have failed to exhibit adequate sensitivity and specificity for brain injury, and they have added minimal diagnostic and prognostic information. As a result many are skeptical about the potential of neurotrauma biomarkers to influence future clinical management and clinical trials. This reservation is based on a handful of biomarkers studied using compromised research designs and without the advantage of advancements made in the field of proteomics. Even though the application of proteomics in brain injury is still in its infancy[36, 37], neuroproteomics is penetrating the field of neurotrauma and brings great potential for improvements in research and patient care. As this technology advances and integrates other technologies such as bioinformatics and neuroimaging, characterization of CNS proteins will occur quickly and many more potential markers will be validated in a shorter timeframe.

Another important challenge in validating biomarkers for TBI will be that traditional outcome measures used to measure injury severity are, in and of themselves, limited. This is true for all severities of injury, and is particularly germane to the less severe injuries where neuroimaging, such as computed tomography (CT), may not demonstrate any obvious pathology. Traditionally, TBI has been separated into three very broad categories: mild, moderate and severe. Unfortunately, this classification scheme fails to capture the spectrum of TBI and the different types of injuries associated with it. The difficulty in classifying injury severity is one which has made clinical trials in the field of TBI challenging. Therapeutic clinical trials for TBI have met with negative results at a cost of over $200 million.[38, 39] These failures have been attributed to a multitude of factors but particularly to the heterogeneity of TBI which makes classification of the different injury types problematic. This heterogeneity, together with the lack of early definitive measures of severity opens the door for using biomarkers as early prognostic indicators. Potentially, biomarkers could provide early outcome measure for clinical trial obtainable much more reliably and economically than conventional neurological assessments, thereby significantly reducing the risks and costs of human clinical trials.

The release of substances and potential biomarkers after an injury is not a static process. Understanding the biokinetic properties of a biomarker will be essential to understanding the release pattern and "optimum" time for measurement. Clinicians and researchers will have to keep in mind that different injury types (for instance, mass lesions versus diffuse injuries) may demonstrate different kinetic parameters and, thus, may produce different quantities of a marker with different peaks and rates of decay. Moreover, secondary insults may also contribute to secondary elevations in a marker, altering its sensitivity and specificity at different time-points.

For markers measured in serum, the level of a biomarker may also reflect the extent of blood brain barrier disruption. Furthermore, extracranial sources of the biomarker may limit its specificity by creating false positives, thus compromising its clinical utility. For instance, the release of a potential CNS marker into the serum from other traumatized tissues or organs would hamper its clinical value in the setting of polytrauma. Another possible situation in which false positive marker values could occur is in the presence of a pre-existing disease state that may alter the metabolism or clearance of the marker, as with kidney or liver disease. Such factors need to be carefully assessed in rigorously designed clinical studies. Future studies should also ensure that adequate control groups are selected for comparison.

Ongoing studies by our group are currently being conducted to more fully elucidate the relationships between novel biomarkers and severity of injury and clinical outcomes in all severities of TBI patients. Before clinical application neurochemical markers will have to be rigorously evaluated and the above mentioned challenges taken into consideration.

5. Proteomic techniques in neurobiomarker discovery

Two dimensional gel electrophoresis (2D GE) and mass spectrometry has classically been the gold standard for protein identification. It is an excellent technique for discovering a multitude of proteins and is widely used. However, it requires specialized training and technical expertise. Some of the disadvantages include sample to sample variation, the inability to detect certain classes or sizes of proteins, and the need for many samples and controls.[40]

There are also non–gel-based mass spectrometry methods for identifying proteins that use high-resolution chromatography to separate complex mixtures of proteins prior to mass spectrometry. Typically the technique uses capillary chromatography for sensitivity and high-resolution mass spectrometry for identification of proteins. There is no need for two-dimensional gel electrophoresis for initial separation and it can analyze a wider range of proteins. However, the technique requires significant expertise and the cost of the materials and equipment to run this technique is much higher.[40]

Newer proteomic techniques are employing antibody-based methods such as high throughput immunoblotting and antibody panels and/or arrays (ELISA's). Antibodies are significantly more specific and selective than traditional techniques and allow the detection of proteins amid complex high-protein content biofluids such as serum or plasma.[41] Methods of amplifying the signal are under development so that only very small samples will be required for analysis. The drawback of this technique is its reliance on the sensitivity and specificity of the antibodies, and the inability to identify a wide range of proteins because the protein of interest must be pre-selected.

Examples of these techniques will be taken from studies conducted by our group. In two studies published in the Journal of Neurotrauma in 2007 by Pineda et al.[42] and in 2009 by

Brophy et al.[43] an immunoblotting technique employing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to measure alpha-spectrin. Quantitative evaluation of intact αII-spectrin and its breakdown products (SBDP150, SBDP145 and SBDP120) was performed via computer-assisted densitometric scanning.
An example of the ELISA technique is taken from a study published in Critical Care Medicine in 2010 by Papa et al.[44] that measured Ubiquitin C-terminal hydrolase. In this study samples were measured using a standard UCH-L1 sandwich ELISA where reaction wells were coated with capture antibody and detection antibody was added to wells. The wells were developed with substrate solution and read with a spectrophotometer.

6. Status of biomarker research

Although there are a number of biochemical markers that have been investigated in TBI, our discussion will include the most current and widely studied ones. The most extensively studied among these are glial protein S-100 beta(β) [45-55], neuron-specific enolase (NSE)[56-63], and myelin basic protein (MBP)[41, 59, 64-66] Although some of these published studies suggest that these biomarkers correlate with degree of injury; conflicting results exist.[67-75]
S100β is the major low affinity calcium binding protein in astrocytes [76] and it is considered a marker of astrocyte injury or death. It can also be found in non-neural cells such as adipocytes, chondrocytes, and melanoma cells.[77] Elevated serum levels have been associated with increased incidence of post concussive syndrome and impaired cognition.[78, 79] Other studies have reported that serum levels of S-100β are associated with MRI abnormalities and with neuropsychological examination disturbances after mild TBI.[80, 81] A number of studies have found significant correlations between elevated serum levels of S-100β and CT abnormalities.[82-84] It has been suggested that adding the measurement of S-100B concentration to clinical decision tools for mild TBI patients could potentially reduce the number of CT scans by 30%.[84] Other investigators have failed to detect associations between S-100β with CT abnormalities.[67, 85, 86 87] The vast majority of these clinical studies have employed ELISA to measure levels of S100B. Although S-100β continues to be actively investigated and remains promising as an adjunctive marker, its utility as a biochemical diagnostic remains controversial. Some studies have observed high serum S-100β levels in trauma patients without head injuries suggesting that it lacks CNS specificity and is released from peripheral tissues.[88-90]
Neuron specific enolase is one of the five isozymes of the gycolytic enzyme enolase found in central and peripheral neurons and it has been shown be elevated following cell injury.[91] It has a molecular weight of 78 kDa and a biological half-life of 48 hours.[92] This protein is passively released into the extracellular space only under pathological conditions during cell destruction. Several reports on serum NSE measurements of mild TBI have been published.[59, 62, 91, 93] Most of these studies employed an enzyme immunoassay for NSE detection. Many of these studies either contained inadequate control groups or concluded that serum NSE had limited utility as a marker of neuronal damage. Early levels of NSE and MBP concentrations have been correlated with outcome in children, particularly those under 4 years of age.[64, 65, 94, 95] A limitation of NSE is the occurrence of false positive results in the setting of hemolysis.[96]
A supposedly cleaved form of tau, c-tau, has also been investigated as a potential biomarker of CNS injury. Tau is preferentially localized in the axon and tau lesions are apparently related to axonal disruption.[97, 98] CSF levels of c-tau were significantly elevated in TBI

patients compared to control patients and these levels correlated with clinical outcome.[99, 100] Though levels of c-tau were also elevated in plasma from patients with severe TBI, there was no correlation between plasma levels and clinical outcome.[101] A major limitation of all of these biomarkers is the lack of specificity for defining neuropathological cascades.

Alpha-II-spectrin (280 kDa) is the major structural component of the cortical membrane cytoskeleton and is particularly abundant in axons and presynaptic terminals.[102, 103] It is also a major substrate for both calpain and caspase-3 cysteine proteases.[104, 105] A hallmark feature of apoptosis and necrosis is an early cleavage of several cellular proteins by activated caspases and calpains. A signature of caspase-3 and calpain-2 activation is cleavage of several common proteins such as cytoskeletal αII-spectrin.[106] In a rat model, mean levels of both ipsilateral cortex (IC) and cerebral spinal fluid (CSF) spectrin breakdown products (SBDP) at 2, 6, and 24 h after two levels of controlled cortical impact (1.0 mm and 1.6 mm of cortical deformation) were significantly elevated by injury using immunoblotting.[107] Using the same proteomic Western blot technique, levels of spectrin breakdown products (SBDP's) have been reported in CSF from adults with severe TBI and they have shown a significant relationship with severity of injury and clinical outcome.[42, 108-113] Following a TBI the axonally enriched cytoskeletal protein α-II-spectrin is proteolyzed by calpain and caspase-3 to signature breakdown products (SBDPs). Calpain and caspase-3 mediated SBDP levels in CSF have shown to be significantly increased in TBI patients at several time points after injury, compared to control subjects. The time course of calpain mediated SBDP150 and SBDP145 (markers of necrosis) differs from that of caspase-3 mediated SBDP120 (marker of apoptosis). Average SBDP values measured early after injury correlated with severity of injury, CT scan findings and outcome at 6 months post injury.[43]

A promising candidate biomarker for TBI currently under investigation is Ubiquitin C-terminal Hydrolase-L1 (UCH-L1). UCH-L1 was previously used as a histological marker for neurons due to its high abundance and specific expression in neurons.[114] This protein is involved in the addition and removal of ubiquitin from proteins that are destined for metabolism.[115] It has an important role in the removal of excessive, oxidized or misfolded proteins during both normal and pathological conditions in neurons.[116] In initial studies, UCH-L1 was identified as a protein with a two-fold increase in abundance in the injured cortex 48 hours after controlled cortical impact in a rat model of TBI.[117] Subsequently, a UCH-L1 sandwich enzyme-linked immunosorbent assay quantitatively showed that CSF and serum UCH-L1 levels in rats were significantly elevated as early as 2 hours following both traumatic and ischemic injury.[118] Clinical studies in humans with severe TBI confirmed, using ELISA analysis, that the UCH-L1 protein was significantly elevated in human CSF[44, 119] and was detectable very early after injury and remained significantly elevated for 168 hours post-injury.[44] Further studies in severe TBI patients have revealed a very good correlation between CSF and serum levels.[120] Most recently, UCH-L1 was detected in the serum of mild and moderate TBI (MMTBI) patients within an hour of injury.[121] Serum levels of UCH-L1 discriminated MMTBI patients from uninjured and non-head injured trauma controls and were also able to distinguish mild TBI (concussion patients) from these controls. Most notable was that levels were significantly higher in those with intracranial lesions on CT than those without lesions.[121]

Glial Fibrillary Acidic Protein (GFAP) is a monomeric intermediate protein found in astroglial skeleton that was first isolated by Eng et al. in 1971.[122] GFAP is found in white and gray brain matter and is strongly upregulated during astrogliosis.[123] Current evidence indicates that serum GFAP might be a useful marker for various types of brain damage from

neurodegenerative disorders[124, 125] and stroke[126] to severe traumatic brain injury.[127-131] Recently, Vos et al. described serum GFAP profile in severe and moderate TBI (GCS <12).[54] In a recent study by our group, GFAP was systematically assessed in human serum following mild and moderate TBI. We confirmed that the GFAP levels were significantly elevated in this population using ELISA analysis, including those with mild TBI. GFAP was able to discriminate TBI patients from uninjured controls. Additionally, serum levels were able to distinguish orthopedic and motor vehicle controls form TBI patients. GFAP was detectable in serum within a few hours of injury and was associated with measures of injury severity including the GCS score and CT lesions.[132, 133] The present work extends findings from studies in severe TBI to mild and moderate TBI.

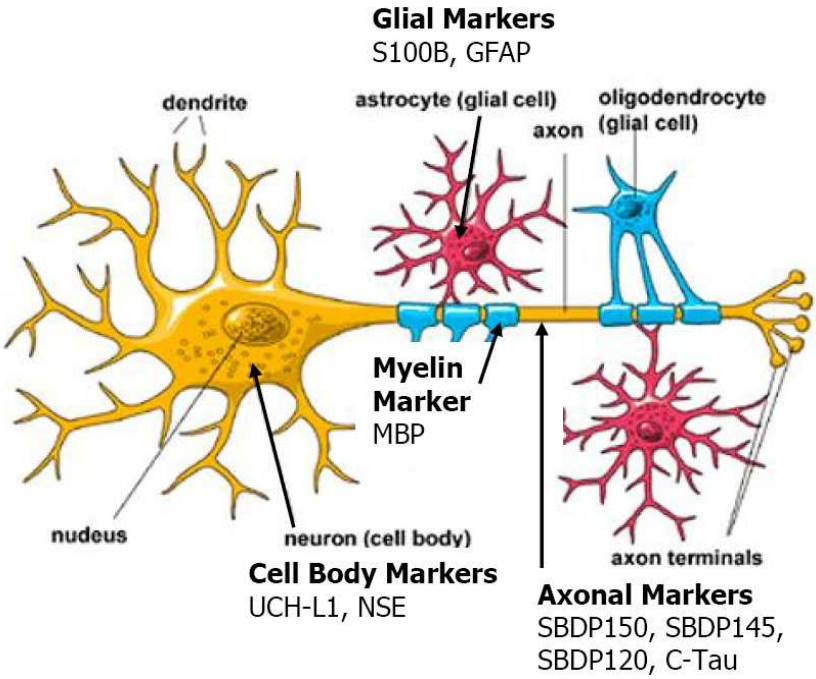

Fig. 1. The neuroanatomical locations of the above mentioned biomarkers.

7. Attributes of an ideal biomarker for TBI

Research in the field TBI biomarkers has increased exponentially over the last 20 years with most of the publications on the topic occurring in the last 10 years.[134] During the course of our work in the development of TBI biomarkers, it has become evident that there are a number of key features that a clinically useful biomarker should possess.[135] An "ideal biomarker" would: 1) demonstrate a high sensitivity and specificity for brain injury; 2) stratify patients by severity of injury; 3) have a rapid appearance in accessible biological fluid; 4) provide information on injury mechanisms; 5) have well defined biokinetc properties; 6) monitor progress of disease and response to treatment; 7) predict functional outcome; 8) be easily measured by widely available, simple techniques

Clinical researchers have developed methodological standards for developing clinical decision tools in order to ensure the validity of study results.[136, 137] As TBI biomarker research transitions from the bench to the bedside there are a number of important methodological issues that researchers will have to consider as they design their clinical protocols. Since TBI biomarkers are being designed for clinical management, the outcome or diagnosis being examined will need to be clearly defined and clinically important. In order to ensure external validity and the generalizability of the results, study patients will have to be selected without bias and represent a wide spectrum of clinical and demographic characteristics. When interpreting the data, clinical variables that potentially affect outcome will require careful consideration in the analysis. Multivariate statistical and bioinformatics models will also further improve classification of patients and help reduce systematic bias.[138] Another essential consideration will be the examination of biokinetic properties and temporal profiles of the biomarkers as well as systematic comparisons to controls.

8. The potential clinical role of biomarkers

Biochemical markers could help with clinical decision making by elucidating injury severity, injury mechanism(s), and monitoring progression of injury. Temporal profiles of changes in biomarkers could guide timing of diagnosis and treatment. Biomarkers could have a role in management decisions regarding patients at high risk of repeated injury. Accurate identification of these patients could facilitate development of guidelines for return to duty, work or sports activities and also provide opportunities for counseling of patients suffering from these deficits. Repeated mild TBI occurring within a short period (i.e. hours, days, or weeks) can be catastrophic or fatal, a phenomenon termed "second impact syndrome."[139, 140] Acute CT or MRI abnormalities are not usually found after these injuries, but levels of some neurotransmitters remain elevated, and a hypermetabolic state may persist in the brain for several days after the initial injury.[141] During this time the brain appears to be particularly vulnerable to additional TBI, which may result in severe sequelae, including greatly increased cerebral edema and even death.[139, 140]

Biomarkers could serve as prognostic indicators by providing information for patients and their families about the expected course of recovery. It opens the door to the initiation of early therapies. Identifying at-risk patients with less apparent TBI or differentiating injury pathology in those with more severe intracranial processes would be tremendously valuable in the management of these patients. For example, in a patient with a normal CT scan or MRI, a biomarker that could predict worsening neurological status or long-term disability would have great clinical utility.

There have been a large number of clinical trials studying potential therapies for traumatic brain injury (TBI) that have resulted in negative findings. Biomarkers measurable in blood would have important applications in clinical research of these injuries. Biomarkers could provide clinical trial outcome measures that are cost-effective and more readily available than conventional neurological assessments, thereby significantly reducing the risks and costs of human clinical trials. Biomarkers that represent highly sensitive and specific indicators of disease pathways have been used as substitutes for outcomes in clinical trials when evidence indicates that they predict clinical risk or benefit.

Lack of quickly accessible pathophysiologic information during the post-injury course has made pharmacologic intervention problematic. Biomarkers could provide more timely information on disease progression and the effects of interventions such as drugs and

surgery. Biomarker measurements could potentially relate the effects of interventions on molecular and cellular pathways to clinical responses. In doing so, biomarkers would provide an avenue for researchers and clinicians to gain a mechanistic understanding of the differences in clinical response that may be influenced by uncontrolled variables.

Intoxicated, unconscious, sedated, or polytraumatized patients suspected of having a TBI pose a particular challenge to emergency and trauma physicians. Biomarkers could expedite the evaluation of such patients by providing information on the degree of brain injury prior to neuroimaging. Biomarkers in this setting could also help determine the need for early neurosurgical consultation or transfer to facilities with neurosurgical capabilities.

There are potential military applications as well. Serum biomarkers could help diagnose and/or triage brain injured military servicemen and women. TBI is a leading cause of combat casualty with an estimated 15-20% of all injuries sustained in 20th century conflicts being to the head.[142-144] America's armed forces are sustaining attacks by rocket-propelled grenades, improvised explosive devices, and land mines almost daily in the recent conflicts in Iraq and Afghanistan.[145] It has been suggested that over 50% of injuries sustained in combat are the result of such explosive munitions including bombs, grenades, land mines, missiles, and mortar/artillery shells. Neuroimaging techniques to diagnose brain injury acutely and other monitoring tools that assess secondary insults are not immediately available in combat zones and such casualties have to be evacuated. Triage and management of brain injured soldiers could be significantly improved if first responders had a quick and simple means of objectively assessing severity of brain injury and of monitoring secondary insults.

There is a unique opportunity to use the insight offered by biochemical markers to shed light on the complexities of the injury process. Accordingly, certain markers could be used as indicators of damage to a particular cell type or cellular process or may be indicative of a particular type of injury. Neuroanatomically, that could include evidence of, say, primary axonal damage versus glial damage. With such heterogeneity the solution may not lie with a single biomarker but more with a complementary panel of markers that may prove useful in distinguishing different pathoanatomic processes of injury.

9. Conclusion

The exploration and validation of biomarkers for TBI using advances in proteomics, neuroimaging, genomics, and bioinformatics must continue. Biomarkers of TBI measured through a simple blood test have the potential to significantly improve the management of TBI patients by providing timely information on the pathophysiology of injury; improving stratification of patients by injury severity; monitoring of secondary insults and injury progression; monitoring response to treatment; and predicting functional outcome. Biomarkers could provide major opportunities for the conduct of clinical research including confirmation of injury mechanism(s) and drug target identification. Ultimately the goal is improve outcome in patients suffering from these injuries.

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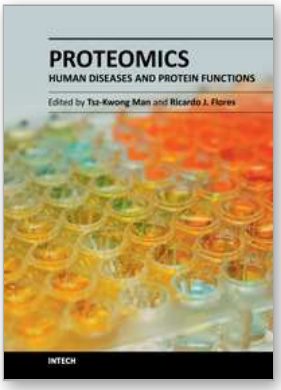

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Biomedical research has entered a new era of characterizing a disease or a protein on a global scale. In the post-genomic era, Proteomics now plays an increasingly important role in dissecting molecular functions of proteins and discovering biomarkers in human diseases. Mass spectrometry, two-dimensional gel electrophoresis, and high-density antibody and protein arrays are some of the most commonly used methods in the Proteomics field. This book covers four important and diverse areas of current proteomic research: Proteomic Discovery of Disease Biomarkers, Proteomic Analysis of Protein Functions, Proteomic Approaches to Dissecting Disease Processes, and Organelles and Secretome Proteomics. We believe that clinicians, students and laboratory researchers who are interested in Proteomics and its applications in the biomedical field will find this book useful and enlightening. The use of proteomic methods in studying proteins in various human diseases has become an essential part of biomedical research.

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