Brain Injury Biomarkers and Their Utilities in Personalized Medicine

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According to the Cochran Library, there have been more than 200 unsuccessful clinical trials assessing potential therapies for traumatic brain injury (TBI) [Maas et al., 2008], and there are currently no FDA approved therapies. As early as 2002, an NIH workshop recognized the need for development of more refined surrogate measures to improve design and execution of clinical trials in head injury (Narayan et al., 2002).

There are a number of areas in which incorporation of biomarkers could significantly improve clinical trial design and execution. Injury magnitude is an important criterion for determining patient eligibility for TBI clinical trials. Obviously, it is important to have patients with similar magnitudes of injury in different treatment groups. At present, the Glasgow Coma Scale (GCS) is the primary, if not the exclusive, entry criterion assessment tool for injury magnitude. Given the difficulties associated with accurate GCS assessment outlined above, biomarkers could provide an objective, quantitative assessment of injury magnitudes.

Secondary brain insults worsen neurologic outcome after TBI (Stein et al., 2011; Hellewell et al., 2010). In an effort to prevent occurrences of these insults, physiologic vital signs (e.g. intracranial pressure, mean arterial blood pressure, tissue oxygenation) are routinely assessed in intensive care environments, although usually recorded only intermittently in the medical record. Conventional manual recording of vital signs can underestimate the total number of secondary insults (Hemphill et al., 2006). Undetected occurrence of secondary insults and increased neurologic damage in different treatment groups can significantly enhance variability in clinical trials. Detection of increases in biomarker levels, in conjunction with physiological assessment and management, could provide critical information to reduce the number of undetected secondary insults and allow for stratification of patients by occurrence of these insults.

As mentioned previously, management of severe TBI patients can importantly influence outcome (Celso et al., 2006; Faul et al., 2007), potentially by altering the number of secondary insults. In spite of vigorous educational programs, the American Association of Neurological Surgeon Guidelines for Management of Severe TBI Patients is not uniformly followed. Moreover, even when efforts are made, failure to rigorously standardize clinical management in different centers could contribute to outcome variability in severe TBI clinical trials. For example, in a recent trial assessing the effects of moderate hypothermia on severe TBI (Clifton et al., 2001), treatment effects for the 5 largest centers varied between 14% positive and 20% negative. Although there were significant differences in cerebral perfusion pressure management among centers, investigators did not detect a correlation with treatment effect and attributed center differences to other baseline variables. In any case, systematic assessment of biomarkers on admission and during the course of management could provide critical insights into potential differences between patient cohorts among centers (Maas et al., 2007).

Accurate prediction of outcome is a critical component of design of clinical trials for TBI. In severe TBI, the GCS (Jennet et al., 1976) or an extended version of this scale (Hellewell and Signorini, 1997) is typically used. These scales provide broad distinctions and include categories such as "good outcome," "severely disabled," "vegetative" or "dead". New more powerful clinical trial designs for Phase III trials in TBI and stroke employ statistical techniques based on outcome predictions as better as or worse than expected, taking into account each individual patient's baseline prognosis.
Thus, the use of biomarkers to enhance the accuracy of early predictions of outcome could importantly improve the power of Phase III trial designs.

The recent Workshop on Classification of TBI (Saatman et al., 2008) emphasized the need for surrogate markers based on pathophysiological mechanisms of TBI in humans in clinical trials assessing targeted TBI therapies. For example, recent work by us has confirmed the potential utility of biochemical markers to assess pathophysiological mechanisms of necrosis and apoptosis, specific forms of cell death occurring after severe TBI (Pineda et al 2007; Lewis et al 2008; Mondello et al., 2010). The biochemical markers identify the activity of specific destructive proteases (e.g. calpain and caspases) related to these pathological processes. Appropriate drug therapies targeting proteolytic destruction could use these biochemical markers as indices of therapeutic efficacy. This therapeutic marker would be available to investigators during the acute phase of injury well in advance of six month outcome assessments typically used in such studies. Obviously, these biochemical markers are more closely linked to therapeutic effects on brain tissue than neurological outcome measures such as the Glasgow Outcome Score (GOS) or GOS-extended (GOS-E).

### Biomarkers for Drug Discovery, Drug Development and Personalized Medicine

Recently, there has been broad recognition that biomarkers can play a critical role in drug discovery and development. This close linkage between diagnostic biomarkers and therapy development has been termed theranostics (Therapy + Diagnostics) (Warner 2004). There are several areas in which biomarkers can facilitate TBI drug development and eventually personalized medicine (Zhang et al., 2010):

- Biomarkers now provide proof of principle target inhibition in in vitro and in vivo models.
- Biomarkers can be used to optimize dosing regimens to obtain maximal target inhibition.
- Biomarkers can facilitate assessments of potential drug neurotoxicity.
- Biomarkers can assist in providing patients with individualized treatment/medication choices or regime (personalized medicine).

Biomarkers can assist in translation of data from preclinical models into clinical studies employing timely go-no go decisions (Papa et al, 2008). For example, the demonstration that the same biochemical markers are present both in preclinical animal models as well as in target patient populations can allow comparisons of preclinical and clinical data with far greater assurance. Banyan scientists have recently demonstrated that markers of necrotic and apoptotic cell death processes can be tracked both in preclinical animal models of TBI as well as in severe TBI patients (Pineda et al 2007; Ringger et al 2005).

Thus, demonstration of drug efficacy by biomarker reduction in preclinical models can be more confidently expected to be observed in human patients. In addition, there have been significant challenges in translating therapeutic windows for drug

### Table 1. Candidate biomarkers for traumatic brain injury

<table>
<thead>
<tr>
<th>Putative biomarker</th>
<th>Key characteristics</th>
<th>Animal TBI model evidence</th>
<th>Human TBI evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100B</td>
<td>Glial and BBB dysfunction marker</td>
<td>CSF, serum</td>
<td>CSF, serum</td>
</tr>
<tr>
<td>MBP</td>
<td>Axonelation marker</td>
<td>[Not available]</td>
<td>Serum</td>
</tr>
<tr>
<td>NSE</td>
<td>Neural damage-marker</td>
<td>[Not available]</td>
<td>Serum</td>
</tr>
<tr>
<td>GFAP</td>
<td>Gliosis</td>
<td>[Not available]</td>
<td>Serum</td>
</tr>
<tr>
<td>all-Spectrin-BDP1 (SBP150, SBP145, SBP120)</td>
<td>Neural Necrosis/apoptosis (calpain/caspase), axonal injury</td>
<td>CSF</td>
<td>CSF, serum</td>
</tr>
<tr>
<td>C-tau</td>
<td>Axonal injury marker</td>
<td>CSF, serum</td>
<td>CSF</td>
</tr>
<tr>
<td>IL-6, B, TNF-α</td>
<td>Neuroinflammation</td>
<td>[Not available]</td>
<td>CSF, Serum</td>
</tr>
<tr>
<td>NMDA-R-fragment</td>
<td>Postsynaptic receptor marker</td>
<td>CSF, serum (?)</td>
<td>Serum</td>
</tr>
<tr>
<td>FABPs (brain, heart types)</td>
<td>Neural protein</td>
<td>[Not available]</td>
<td>Serum</td>
</tr>
<tr>
<td>Neurofilament proteins (NF-H,M,L)</td>
<td>Axonal injury markers</td>
<td>CSF, serum</td>
<td>CSF, serum</td>
</tr>
<tr>
<td>UCH-L1</td>
<td>Neural cell body marker</td>
<td>CSF, serum</td>
<td>CSF, serum</td>
</tr>
<tr>
<td>PARK7-NDKA</td>
<td>Unknown</td>
<td>[Not available]</td>
<td>Plasma (Stroke)</td>
</tr>
<tr>
<td>EMAP-II</td>
<td>Microgliosis / inflammation</td>
<td>CSF, plasma</td>
<td>[Not available]</td>
</tr>
</tbody>
</table>
effects on TBI from preclinical to clinical models (Narayan et al., 2002; Wang et al., 2006). Direct confirmation of the temporal profile of biomarker changes in human TBI patients allows characterization of temporal profiles of pathological changes with far greater accuracy in human populations. For example, proteolytic mechanisms underlying apoptosis may have a more prolonged therapeutic window than proteolytic mechanisms underlying necrosis following TBI (Brophy et al, in press; Pineda et al 2007; Papa et al., 2010). Table 1 lists the current candidate biomarkers for TBI (Mondello et al., 2011). Singular or combination use of these markers might be unique utilities in a theranostic or personalized medicine setting, as they could represent distinct TBI-relevant pathobiocchemical pathways that the medicinal intervention is targeting (Figure 1).

**Figure 1.**
Biomarkers for monitoring various temporally and patho-biochemically distinct events following TBI.

**References**


About the Authors

Authors Dr. Kevin K.W. Wang is Founder, Chief Scientific and Operations Officer, and Ronald L Hayes is Founder and President at Banyan Biomarkers, Inc. (Alachua, Florida, USA), a biotechnology company that is working towards commercialization of FDA-approved diagnostic tests for TBI.