Editorial

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Biomarkers in Medicine

# Developing a molecular taxonomy for traumatic brain injury: a perspective to enable the development of diagnostics and therapeutics

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"Prodigious advances in genomics, proteomics and biomarker development provide unparalleled opportunities for unraveling TBI heterogeneity and complexity… in addition to refining disease characterization, holding promise for precision medicine to enhance patient care and outcomes."

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Traumatic brain injury (TBI) is a major cause of death and disability and one of the greatest unmet needs in medicine and public health [1,2]. It is considered "the most complex disease of our most complex organ", strikingly heterogeneous in terms of mechanisms, pathology, severity and treatment, with widely varying outcomes [3]. To date, traditional, unidimensional and insensitive methods discretely categorize TBI as mild/moderate/severe giving little insight into the disease phenotype and individual specific molecular pathophysiology behind the injury. On the other hand, characterization and classification of TBI would require multidimensional approaches able to encompass the clinical reality of TBI consisting of a continuum of severity and a spectrum of pathobiological processes. Thus, there is a glaring need for more objective and informative criteria to support 'softer' clinical criteria and enhance the pathophysiological specificity of the diagnosis and treatment. Prodigious advances in genomics, proteomics and biomarker development provide unparalleled opportunities for unraveling TBI heterogeneity and complexity, in addition to refining disease characterization, holding promise for precision medicine to enhance patient care and outcomes (National Research Council 2011).

Drug development in TBI has also faced challenges due to the heterogeneity of the target population, inappropriateness of conventional clinically based classification of TBI, lack of mechanistic measures of efficiency and safety of the treatment, limited translational value of preclinical data to human studies and the use of variable and insensitive outcomes measures [4]. Consequently, developing a molecular taxonomy for TBI might have a substantial value in drug development setting as well as in clinical trials, which include:

- Indicating whether a TBI patient is likely to benefit from a treatment and monitoring the biochemical effects of the therapeutic interventions ('theragnostic' biomarkers);
- Reducing diagnostic uncertainty and screening for discrete and specific disease mechanisms, enabling enrollment in clinical trials of more homogeneous patient cohorts;
- Being used as a surrogate end point in a clinical trial;
- Generating data regarding the pathophysiological mechanisms and describing novel molecular patterns that can represent an innovative approach for drug discovery.

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Markers for reliable diagnosis, accurate classification and to track disease course are indispensable for research development and patient care.

## The current status of biomarkers toward an improved taxonomy for TBI

Biochemical markers have been proposed to offer additional value for better characterization and categorization of TBI in individuals, potentially leading to more targeted pathways for clinical management and care by tailoring intervention to patient-specific pathophysiology and phenotype [3]. Three main directions of clinical research on biomarkers in TBI can be recognized in the acute and sub-acute phases. In the more chronic phases, biomarkers may indicate ongoing progressive damage with neuronal and glial cell loss.

Biomarkers can potentially be used to differentiate between neuronal and glial damage [5], thus reflecting the central pathogenic processes in TBI, but also extend to inflammatory, neurodegenerative and regenerative processes and alterations of the blood–brain barrier.

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Discoveries and progress in the evaluation of multimodal biomarkers in TBI have been previously described [6] and are not the subject of this article. Based on the specific clinical utilities and applications, different technologies and modalities (imaging and blood-based biomarkers) serve complementary roles and their comparative value will have to be established in prospective studies. An integrated multidisciplinary approach using biomarkers and imaging-based assessments to improve diagnosis and classification is required. This vision is now being realized within the International Initiative for Traumatic Brain Injury Research (InTBIR), a collaboration of funding agencies [7]. For example, in the USA, the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot Study, a NINDS-funded multicenter, prospective, collaboration has tested and refined Common Data Elements and explored neuro-imaging standards, and best practices for genetics and biomarkers in TBI studies [8,9]. Several international collaborative efforts are starting or ongoing in Europe such as CENTER-TBI [17,10] and TBICARE [18].

Biomarker panels are providing new insights into the biology of disease. Broader definitions include general laboratory values, genetic disposition, metabolomic data and results of neuroimaging studies (CT, MR, DTI, etc). To date, a variety of putative markers with potential clinical utility in TBI and which provide opportunities for the development of a classification scheme based on molecular profiles have been discovered [11–14]. Ideally, biochemical biomarkers for TBI should be brain-specific and also appear early after injury. Nevertheless, many general lab assessments, which are routinely performed, may provide important therapeutic and prognostic information. Some laboratory parameters may mainly reflect the degree of injuries, but others may be related to progressive damage and delayed recovery processes. For example, coagulopathy can cause more rapid increase of contusional lesions, hyperglycemia may aggravate pathophysiological pathways and hyponatremia may enhance cerebral edema. Despite a large number of biomarker studies in TBI, there is no hard high level evidence that biomarkers can make the key transition from technically demanding research tools to robust clinical management tools that can be used in everyday practice. Besides relatively small patient numbers in studies, other specific issues confound an easy and simple transition. These include heterogeneous characteristics of patient population, brain specificity, transport from brain to blood, influence of sample handling and requirements for analytical standardization. Different transport mechanisms (resorption into capillaries versus drainage into the CSF) will influence time profiles and biomarker levels may not only depend on the extent of cellular damage but also in particular on the degree of edema formation, which may be indirectly related to blood pressure.

## Initiatives in other CNS disorders to develop molecular taxonomies & their relevance to TBI

Similar strategies are being developed in other CNS diseases such as neurodegeneration (AD, PD), oncology and other therapeutic areas. CSF biomarkers which track the key elements of Alzheimer's pathology, have been developed [15] to the point that revised diagnostic criteria for AD incorporating biomarker information as diagnostic adjuncts in predementia stages have been published by the Alzheimer's Association and the National Institute of Aging of the NIH [19]. Importantly, such efforts demonstrated a substantial biological variability for biomarkers in addition to intercenter and interlaboratory variation (due to preanalytical, analytical and postanalytical factors) across studies, highlighting the need for extensive standardization at different levels. To overcome this situation, several standardization efforts have been initiated and an international quality control (QC) program by

the Alzheimer's Association was launched in 2009 [16] to monitor analytical variability for CSF biomarkers and to provide a network where sources of variation could be identified. The TBI community should learn these lessons and use as a foundation to guide further biomarker development and improvement.

## Future perspective & Conclusion

The current unidimensional approach to TBI classification has caused us to be like the prisoners chained in Plato's cave watching shadows projected on the wall. A multimodal biomarker profile offers opportunities to characterize and refine categorization and risk stratification of patients with TBI by informing on the pathological characteristics of the injury, and pathophysiological response of the brain.

However, only an integrated approach combining use of biochemical and genetic markers and advanced imaging with clinical examination will determine the release from the cave and allow us to perceive the true form of TBI. This improved multidisciplinary approach has potential to revolutionize our understanding of TBI and offer a real knowledge that may be translated into new therapeutic strategies, ultimately optimizing patient outcomes and decreasing healthcare costs.

### Financial & competing interests disclosure

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## References

1 Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol.* 7(8), 728–741 (2008).

2 Mondello S, Muller U, Jeromin A, Streeter J, Hayes RL, Wang KKW. Blood-based diagnostics of traumatic brain injuries. *Exp. Rev. Mol. Diagn.* 11(1), 65–78 (2011).

3 Saatman KE, Duhaime AC, Bullock R *et al.* Classification of traumatic brain injury for targeted therapies. *J. Neurotrauma* 25(7), 719–738 (2008).

4 Maas AI, Murray GD, Roozenbeek B *et al.* Advancing care for traumatic brain injury: findings from the IMPACT studies and perspectives on future research. *Lancet Neurol.* 12(12), 1200–1210 (2013).

5 Mondello S, Jeromin A, Buki A *et al.* Glial neuronal ratio: a novel index for differentiating injury type in patients with severe traumatic brain injury. *J. Neurotrauma* 29(6), 1096–1104 (2012).

6 Mondello S, Schmid K, Berger RP *et al.* The challenge of mild traumatic brain injury: role of biochemical markers in diagnosis of brain damage. *Med. Res. Rev.* 34(3), 503–531 (2014).

7 Tosetti P, Hicks RR, Theriault E *et al.* Toward an international initiative for traumatic brain injury research. *J. Neurotrauma* 30(14), 1211–1222 (2013).

8 Yue JK, Vassar MJ, Lingsma H *et al.* Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Pilot: Multicenter Implementation of the Common Data Elements for Traumatic Brain Injury. *J. Neurotrauma* 30(22), 1831–1844 (2013).

9 Yue JK, Vassar MJ, Lingsma HF *et al.* Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury. *J. Neurotrauma* 30(22), 1831–1844 (2013).

10 Maas AI, Menon DK, Steyerberg EW *et al.* Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 76(1), 67–80 (2015).

11 Zetterberg H, Smith DH, Blennow K. Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. *Nat. Rev. Neurol.* 9(4), 201–210 (2013).

12 Shahim P, Tegner Y, Wilson DH *et al.* Blood biomarkers for brain injury in concussed professional ice hockey players. *JAMA Neurol.* 71(6), 684–692 (2014).

13 Mondello S, Papa L, Buki A *et al.* Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study. *Crit. Care* 15(3), R156 (2011).

14 Diaz-Arrastia R, Wang KK, Papa L *et al.* Acute biomarkers of traumatic brain injury: relationship between plasma levels of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein. *J. Neurotrauma* 31(1), 19–25 (2014).

15 Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nat. Rev. Neurol.* 6(3), 131–144 (2010).

16 Reiman EM, Mckhann GM, Albert MS, Sperling RA, Petersen RC, Blacker D. Alzheimer's disease: implications of the updated diagnostic and research criteria. *J. Clin. Psychiatry* 72(9), 1190–1196 (2011).

17 Center TBI.
www.center-tbi.eu

18 TBicare.
www.tbicare.eu

19 Alzhiemer's and Dementia.
www.alzheimersanddementia.org/content/ncg