New Directions in Research and Therapies in Traumatic Brain Injury

Expert review:

Johannes Thome[1] and Dafin F Muresanu[2]

1. Director and Chair, Clinic and Policlinic for Psychiatry and Psychotherapy, University of Rostock, Germany;
2. Chairman, Department of Clinical Neurosciences, Iuliu Hatieganu University of Medicine and Pharmacy, Faculty for Medicine Cluj-Napoca, Romania

Abstract

Traumatic brain injury (TBI) is a significant cause of disability and death and its incidence is rising in some specific populations. TBI can result in various disabilities, cognitive problems and psychiatric disorders, depending on the location of the injury and premorbid patient conditions. Effective pharmacological and surgical treatments, however, are currently limited. Most randomised clinical trials for TBI treatments carried out to date have failed to show significant benefits. Initiatives such as the TRACK-TBI have highlighted the large variability in TBI treatment quality at different hospitals and widely differing death rates. This stimulated the establishment of the International Initiative for TBI Research (InTIBR), which aims to improve disease characterisation and patient management. The development of effective treatments for TBI and their evaluation requires an understanding of the complex neuroregenerative processes that follow an injury. In the case of haematoma in TBI, decompressive craniectomy can be a life-saving intervention but must be performed rapidly. The neurotrophic agent, Cerebrolysin®, acts by mimicking neurotrophic factors (NTFs) and by stimulating the endogenous production of NTF in brain tissue. Experimental models show that this drug increases neurogenesis following TBI but these findings need to be converted into clinical practice. The potential of Cerebrolysin in TBI was demonstrated in a large retrospective cohort trial in Romania (n=7,769 adults). Cerebrolysin significantly improved Glasgow Outcome Scores (GOS) and respiratory distress (RDS) in patients with moderate or severe TBI at 10 and 30 days compared with controls. This and other experimental treatments have potential in TBI but, in developing such therapies, the design of clinical trials should closely reflect the reality of biological processes underlying natural recovery from brain injury.

Keywords

Traumatic brain injury, research, treatment, neurogenesis, cognitive decline, cognitive recovery, behavioural aspects, Cerebrolysin®

Disclosures: Johannes Thome has obtained financial support (e.g. lecture honoraria, grants for research projects and scientific meetings, advisory board membership) from Ever Pharma, the manufacturer of Cerebrolysin whose usefulness in TBI is discussed in this text, as well as from Actelion, AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lilly, Lundbeck, Medice Arzneimittel Pütter, Merz Pharmaceuticals, Novartis Pharma, Pfizer Pharma, Roche, Servier, Shire. Dafin F Muresanu is a coordinating investigator of CARS trial and member of the CAPTAIN trial scientific advisory board.

Acknowledgements: Editorial assistance was provided by James Gilbart at Touch Medical Media, London, UK, funded by EVER Neuro Pharma.

Received: 29 January 2015 **Accepted**: 26 February 2015 **Citation**: *European Neurological Review*, 2015;10(1):56–64 *DOI: 10.17925/ENR.2015.10.01.56*

Correspondence: Dafin F Muresanu, Department of Clinical Neurosciences, Iuliu Hatieganu University of Medicine and Pharmacy, Faculty for Medicine Cluj-Napoca, Romania. E: dafinm@ssnn.ro

Support: The publication of this article was supported by EVER Neuro Pharma. The views and opinions expressed are those of the authors and not necessarily those of EVER Neuro Pharma

Traumatic brain injury (TBI) is a condition with many unmet needs in medicine and public health.[1,2] It is a major cause of death and disability and also leads to extremely high direct and indirect costs to society.[3–5] Currently the incidence of TBI among some populations such as the elderly and military personnel is increasing.[6,7] TBI populations are heterogeneous in terms of mechanism of disease, baseline prognostic risk factors, clinical severity and evolution.[8] This heterogeneity generates complex challenges. New pharmacological approaches together with more basic and clinical research are needed for better targeting TBI therapy for individual patients.[9] Monomodal drugs have substantial limitations in TBI treatment and have little efficacy. Multimodal drugs, however, have shown promising results. A key example is the neurotrophic agent Cerebrolysin®, which has shown efficacy for the treatment of TBI in various studies.[10,11] This article provides an overview of major research progress in the pathology and diagnosis of TBI and the prospects for new drug treatments that were presented and discussed at the 21st International Mondsee Medical Meeting, which was convened at Salzburg, Austria in June 2014. ■

The Changing Landscape of Traumatic Brain Injury Research

Andrew Maas

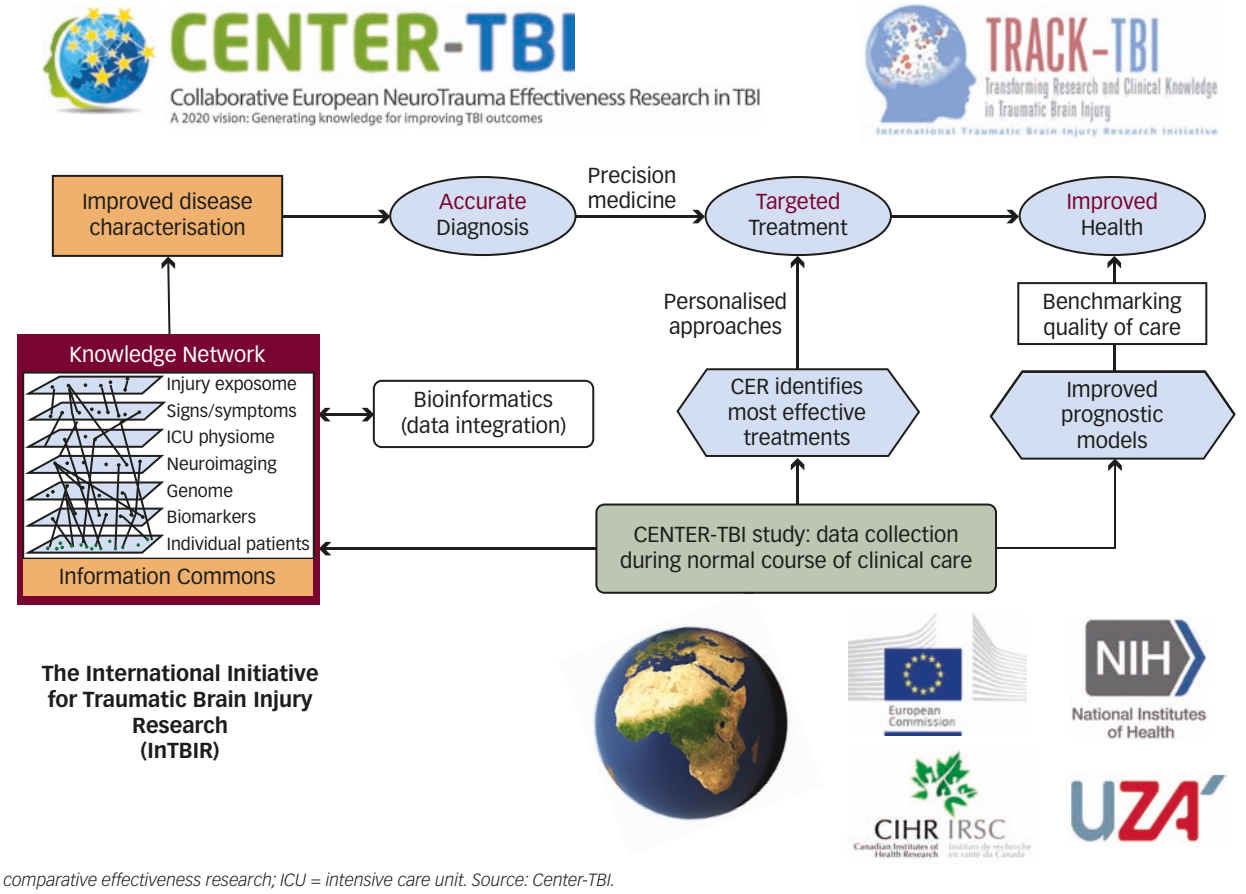
Professor and Chairman, Department of Neurosurgery University Hospital Antwerp, Belgium

A critical factor in the field of brain injuries is the development of effective therapies. In the light of the enormous impact of TBI on society and healthcare systems worldwide,[12] the failure of randomised clinical trials (RCTs) has created an urgent need for re-evaluation of the methodology used for the development of effective therapies.[13] Clinical trials are characterised by two major flaws: they single out a single factor for treatment and fail to recognise heterogeneity in pathology, treatment and outcomes. Accordingly, most RCTs in this field showed no major breakthrough. Most advances in TBI care have resulted from observational studies, meta-analyses of individual patient data and international collaboration.[9,14] Guidelines have also been of use, however, they lack individual patient perspective and therefore are not sufficient to guide effective treatments.[15]

There is a need for a broader approach encompassing the existing heterogeneity as well as for re-orientation of clinical in TBI towards a comparative effectiveness research (CER), concept[9] that includes personalised treatment requiring better characterisation of TBI in individual patients, as well as broader approaches.

Death rates in TBI are up to sixfold higher in some hospitals compared with others, which indicates large differences in treatment quality.[16] The TRACK-TBI study revealed that only one-third of all mild TBI patients will achieve full recovery.[17] These factors stimulated the establishment of the International Initiative for TBI Research (InTBIR) project.[18] InTBIR is an international project that combines the efforts of the European Commission with US institutions (National Institutes of Health [NIH]/National Institute of Neurological Disorders and Stroke [NINDS], Canadian Institutes of Health Research [CIHR]) in which CENTER-TBI is the European component. The latter is an international multidisciplinary collaboration with 38 scientific participants and six associated participants.[19] The core study (n=5,400) includes patients from three strata (emergency room, admission and intensive care unit [ICU], n=1,800 for each) and is being conducted at over 80 treatment centres in 21 countries. Patients of all ages are eligible but must have suspected TBI, indicated for computed tomography and must present <24 hours after injury. The project also includes a registry of patients (n=15,000–20,000) who were seen for TBI in participating hospitals. The registry involves simple data collection; the variables are collected during routine clinical care and outcomes are determined on hospital discharge. The analysis of data focuses on improved disease characterisation for accurate diagnosis (Precision Medicine) and CER approaches for defining effective clinical care.

Figure 1: The Rationale of the International Initiative for Traumatic Brain Injury Research as a Ground-breaking Concept in Patient Management



CER = comparative effectiveness research; ICU = intensive care unit. Source: Center-TBI.

The benefits of the InTBIR project on TBI management are expected to include: improved disease characterisation leading to accurate diagnosis, targeted treatment and improved health of a patient (see *Figure 1*). The project is open to all countries; it contributes to a new culture of data sharing and international collaboration and encourages the utilisation of knowledge resources for the benefit of TBI patients. ■

Neurogenesis and Beyond – Brain Rejuvenation in Chronic Neurodegenerative and Acute Central Nervous System Diseases

Ludwig Aigner

Paracelsus Medical University, Salzburg, Austria

Ageing populations are creating enormous challenges for healthcare providers worldwide, including large increases in age-associated diseases, such as dementias, neurodegenerative diseases and stroke. Moreover, elderly people can suffer traumatic central nervous system (CNS) injuries from simple falls. Endogenous repair mechanisms such as neurogenesis are currently the focus of intense research activities aiming to regenerate or to rejuvenate the aged and damaged brain.[20,21] In treating TBI and other neurological diseases, understanding self-repair mechanisms such as neurogenesis allows attempts to rejuvenate the aged brain and to restore function after CNS injuries. An important aim of current research is increasing the levels of neurogenesis and to lowering the inflammatory load in the aged brain.

Initial work has shown that restoring function in the ageing brain is feasible. A proof of concept study demonstrated rejuvenation of the aged brain following exposure to blood from a younger individual.[22] Current investigations aim to elucidate the role of transforming growth factor-β (TGF-β)[23] on leukotriene signalling for use as a target for brain rejuvenation. In addition, Cerebrolysin, a neurotrophic peptide drug in development, has been shown to rejuvenate the aged and diseased brain,[24] and thus offers considerable potential in the treatment of dementia, stroke and TBI. The pharmacological treatment of acute CNS lesions and spinal cord injury is also under investigation.

Several experimental treatments utilise restorative, regenerative and plasticity-enhancing approaches in the treatment of acute and neurodegenerative disorders. The usual failure of clinical trials in neurology can be attributed at least in part to their being focused solely on neuroprotection. Neuroprotection, however, is only a part of the complex rejuvenation process of the brain post-injury. The recovery from damage is based on natural, spontaneous processes leading to repair, regeneration and restoration of neurological structures and functions.[25] Lateral ventricle neurogenesis is one example of such a natural process that can be further stimulated by pharmacological intervention.

In the experimental models of brain and spinal cord injuries, the leukotriene receptor antagonists (such as montelukast, an asthma treatment agent) reduce neuroinflammation, stimulate neurogenesis and improve functional outcomes in the aged brain as well as in models of spinal cord injury.[26] Other experimental models show that Cerebrolysin induces structural plasticity in ageing brain and also restores synaptic density, neurogenesis, learning and memory in Alzheimer's disease models in mice.[27–29]

Clinical data available to date suggest that Cerebrolysin is effective in the treatment of acute and neurodegenerative disorders.[11,30,31] Further clinical investigations are warranted for Cerebrolysin in order to optimise already existing treatment protocols. The significance of treatment regimen optimisation is well illustrated by a granulocyte colony-stimulating factor trial, which failed to show efficacy due to the poor understanding of the biology of recovery processes with the resulting inadequate treatment protocol employed in the trial.[32] ■

Neuroregeneration in Both Experimental Brain Injuries and Clinical Trials

Wai Poon

Professor and Chief in Neurosurgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

Clinical management of brain injuries has focused on the prevention of secondary insults and once disabling deficits are established, treatments have proved disappointing. Cell therapies have proved effective in animal models of brain injuries, both in molecular and behavioural terms.[33,34] However, clinical trial data are needed to confirm these findings. In order to achieve meaningful clinical effects, improvements are needed in the quality of the cells and associated molecular factors.

TBI treatment developed by Dr Wai Poon's team at the Prince of Wales Hospital in Hong Kong is based on mesenchymal stem cell (MSC) therapy at both preclinical and pilot clinical research stages. The assessment of therapy efficacy includes: behaviour (motor rod, water maze, gait analysis); pathological examination (haematoxylin and eosin stain, immuno-histochemistry); physiological factors (spikes, electrocardiogram [ECG]) and biochemical factors (biomarkers, gene expression). Several biomarkers are currently in clinical development.[35–37]

Experimental stem cell therapies currently use various cell types: embryonic, foetal, adult bone marrow, adipose tissue and induced pluripotent stem cells (iPS cells). Proposed mechanisms of action of adult stem cells in CNS injuries are: engraftment and cell differentiation

or cell fusion, suppression of apoptosis, modulation of inflammation, paracrine/endocrine effects and enhancement of angiogenesis. Possible routes of administration include: systemic infusion, direct implantation and topical application. Stem cells therapies, however, are in early phase development and safety concerns must be addressed in clinical investigations.

An example of cell therapy for brain injury is the use of green fluorescent protein-mesenchymal cells (GFP-MSCs) in a rat model.[38] The GFP-MSC cells migrate to the place of injury and impact on recovery at molecular and cellular level. Most importantly, this therapy achieved improvements in functional outcome assessed as performance in the Morris Water Maze experiment. MSC therefore holds considerable potential in the treatment of neurological disorders.[39,40]

There is a place for MSC-based therapies in axonal regeneration. However, experimental advances and better understanding have not yet converted into clinical practice. There is a need to develop better stem cell technology and to use this approach in combination with other agents, such as small molecules, which can enhance viability of the transplants as well as work in synergy with MSC for stimulation of endogenous repair mechanisms. ■

Standards and Recent Developments for the Treatment of Brain Injury – A Neurosurgical Procedure

Peter A Winkler

Department of Neurosurgery, Paracelsus Medical University Salzburg, Austria

Recent findings emphasise that patients with severe TBI require analogue sedation and intubation, need to be relaxed and must undergo controlled respiration. Hypotension with a systolic pressure <90 mmHg and hypoxia (paO_2 under 60 mmHg and saO_2 under 90 %) must be avoided or treated urgently. In addition, an adequate cerebral perfusion pressure (CPP) must be maintained. Refractory intracranial hypotension should be treated with forced hyperventilation with a paO_2 below 30 mmHg, high-dosage barbiturates and decompressive craniectomy (a life-saving emergency surgical intervention). The therapeutic effect, if any, of hypothermia is currently being investigated in the ongoing Edinburgh Eurotherm Study. More recently, prospective, RCTs have been initiated with the clear statement of exact target values for intracranial pressure. Therefore, continuous multimodal measurement of cerebral perfusion and oxygenation of the brain is of great importance in the monitoring of therapeutic procedures in patients with severe brain trauma.

A complete decompressive craniectomy and venous drainage is important when a haematoma expands. Recent findings indicate that as soon as oedema subsides following a craniectomy, there is a need for rapid cranioplasty.[41] The beneficial effects of cranioplasty on brain metabolism are related to: regulation of postural blood flow, cerebrovascular reserve capacity (CVR),[41–43] cerebral glucose metabolism[44] and improvement in cognitive functions.[45]

A compelling need to optimally use time in surgical patients exists. Without fast intervention a patient's health can rapidly deteriorate and additionally the financial burden of the TBI management rises. 'Save the brain – not the bone!' therefore, is one of the main messages for TBI emergency surgery. ■

The Glasgow Coma Scale Training Tool and Results of a Validation Study

Christian Matula

Neurosurgical Department, Medical University of Vienna, Austria

One of the most important challenges of using neurological assessments such as the Glasgow Coma Scale (GCS) is to reduce the inter-rater variability to an absolute minimum thus maximising the reliability of the measure. A review of the use of the GCS in an injury assessment[46,47] clearly showed that this is a matter that can make results of any trial obsolete. However, reduction of inter-rater variability is possible through planned training of the raters.[48] There is, however, a chronic lack of clear operational rules and GCS training in TBI studies. For these reasons, a GCS Training Tool has been developed to achieve this goal. The tool is now available as a standalone version but also via Internet in different languages.[49]

Preliminary trends from the study show clear difference between groups with and without training, with a trend towards an increase in the accuracy of GCS assessment after standardised training. As expected, there are notable differences between the different disciplines (neurosurgeon, neurologist, intensivist, traumatologist), different hospitals and countries. Neurosurgeons tend to overestimate bad situations and underestimate good ones. Intensive care personnel seem to achieve the highest benefit. Overall, benefits manifest quickly and appear stable, reliable and, above all, effective. ■

Cerebrolysin Enhances Cognitive Recovery of Mild Traumatic Brain Injury Patients

Chun-Chung Chen

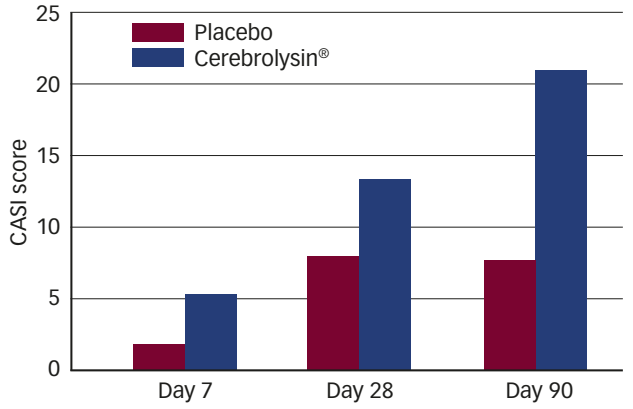
Department of Neurosurgery, China Medical University Hospital,Taichung, Taiwan

Among TBIs, approximately 80 % are mild (MTBI), and up to 15 % of these patients have persisting clinical symptoms (poor memory, poor attention, headache, dizziness).[50,51] Evidence suggests that about 50 % of young adults with MTBI experienced moderate to severe disability at 1-year post-injury.[52] In adults, MTBI frequently results in impairments of cognitive functions, emotions and brain mechanisms of behavioural control. All these symptoms often lead to problems with learning, social adaptation and unfavourable social and psychological consequences.[53]

MTBI is defined by: conscious alertness, GCS ≥13, brain concussion or brain contusion. Patients with brain contusions have significantly poorer cognitive functions than patients with concussions. Consequently, the safety and efficacy of Cerebrolysin, a multimodal and neurotrophic agent with both neuroprotective and neuroregenerative properties, has been evaluated in patients with MTBI related to contusions.[11] Cerebrolysin is effective in the treatment of cognitive complications after stroke and in neurodegenerative disorders, such as Alzheimer's disease and vascular dementia.[54]

The 'Cognitive effects of Cerebrolysin on MTBI patients presented with brain contusion: A preliminary study' is an investigator-driven, double-blind, RCT that enrolled 32 MTBI patients within 24 hours after the onset of TBI.[54] The inclusion criteria were: adults between 18 and 70 years old, to be alert and conscious, a GCS of ≥13 and having abnormal imaging results (brain contusion). Patients were randomised to Cerebrolysin (30 ml once daily [OD] intravenous [iv] infusion for 5 days) or placebo (normal saline iv infusion OD). Results showed a strong trend towards improvement of cognitive functions in the Cerebrolysin-treated group in comparison with the placebo group. This included a statistically significant clinical benefit at 12 weeks as measured with the Cognitive Abilities Screening Instrument (CASI) (see *Figure 2*). Cerebrolysin therapy, therefore, can improve CASI scores and enhance cognitive recovery. The most significant impact was observed on improvement of MTBI patients' long-term memory and drawing functions, an encouraging finding since many TBI patients suffer from long-term cognitive problems. ■

Figure 2: Cognitive Functions Assessment with the Cognitive Abilities Screening Instrument



CASI = Cognitive Abilities Screening Instrument. Source: Chen et al., 2013.[11]

Can Cognitive Decline in Intubated Patients be Prevented? A Potential New Treatment Option

Ignacio Previgliano

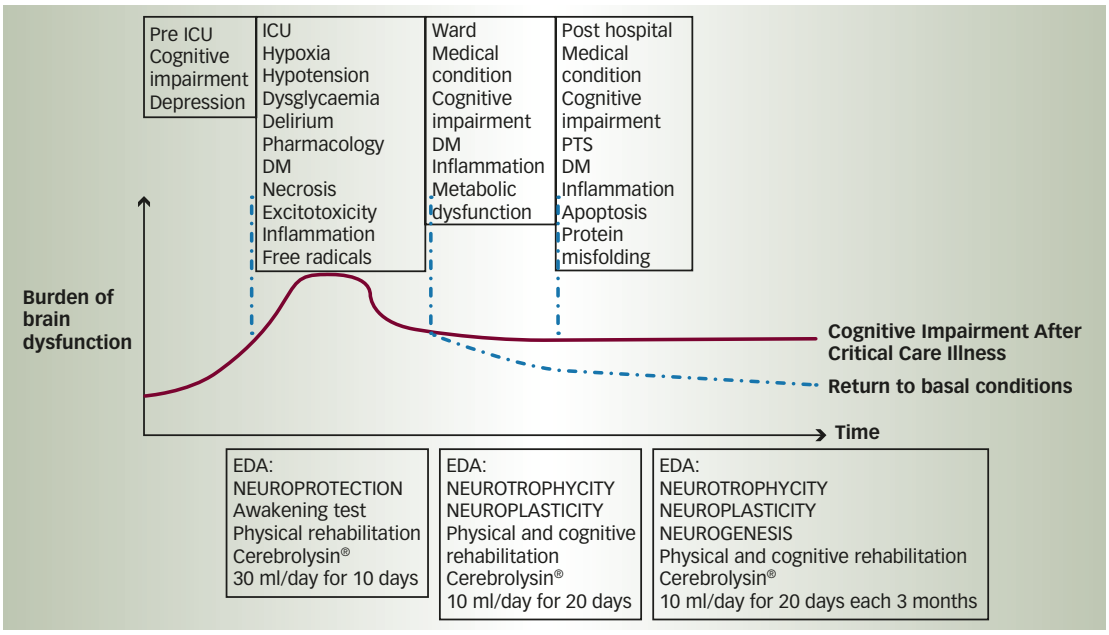
Hospital Fernandez, Buenos Aires, Argentina

Long-term cognitive impairment after critical illness (CIACI) is an increasingly recognised problem that affects patients 1 year after ICU discharge and is probably lifelong. The largest CIACI study, to date, included 821 patients; 40 % had global cognition scores that were 1.5 standard deviations below the population means (similar to scores for moderate TBI or mild cognitive impairment).[55] A further 26 % had scores 2 standard deviations below the population means (similar to scores mild Alzheimer's disease [AD]) after 3 months. These scores persisted in 34 % and 24 %, respectively, after 1 year. Deficits occurred in both older and younger patients, and a longer duration of delirium was independently associated with worse global cognition at 3 and 12 months.

Dementia prevention in ICU patients has enormous scope.[56–58] A recent literature search found that 67 papers were published between 1999 and 2013 mainly by Hopkins (17 publications), Ely (14 publications) and Herridge (12 publications), and concluded that ICU patients are at high risk of developing long-term cognitive impairment or dementia. Imaging data from ICU survivors[59,60] indicated that a longer duration of delirium was significantly associated with greater brain atrophy at hospital discharge (p=0.03) and at 3-month follow-up (p=0.05). Longer duration of delirium was also associated with significantly smaller superior frontal lobe (p=0.03) and hippocampal volumes at discharge (p<0.001). Larger brain atrophy at 3 months was associated with worse cognitive performances at 12 months and delirium duration in the ICU was associated with white matter disruption at both discharge and 3 months. Delirium, therefore, appears to be a major clinical variable connected with CIACI.[55,61]

Cerebrolysin is currently the only neurotrophic agent in clinical use and acts by mimicking neurotrophic factors (NTFs) and by stimulating the endogenous production of NTF in brain tissue. Experimental studies

Figure 3: Treatment with Cerebrolysin for the prevention of CIACI



Model based on published and unpublished clinical data. CIACI = cognitive impairment after critical illness; DM = damage mechanisms; EDA = endogenous defense activities; ICU = intensive care unit; PTS = post traumatic stress. Source: modified from Wilcox et al., 2013.[58]

revealed neuroprotection and neuroregeneration properties. Results of clinical trials in stroke, TBI and dementia suggest the clinical efficacy of Cerebrolysin in these indications.[54,62] The treatment of CIACI data associated with Alzheimer's disease is of major clinical interest.[55]

The efficacy of Cerebrolysin persists for up to several months after treatment, suggesting not only symptomatic benefits, but also a disease-delaying potential. In TBI, acute Cerebrolysin treatment of mild TBI patients prevents development of cognitive decline 3 months post-injury. Clinical trials in stroke show a strong implication for CIACI prevention as a result of Cerebrolysin treatment.[11] Cerebrolysin also induces early and accelerated recovery in motor, activities of daily living and cognitive functions.[63]

These data suggest that Cerebrolysin can support early mobilisation of patients, an important outcome for the majority of injured patients. Combined data from clinical and preclinical studies, suggest that Cerebrolysin is a good candidate for the preventive treatment of CIACI and have provided the rationale for a clinical investigation entitled: 'Changes in brain haemodynamics after neurotrophic factors compound Cerebrolysin treatment in severe traumatic brain injury survivors'. Initial unpublished results show that compared with untreated TBI patients, Cerebrolysin significantly improved hemodynamic parameters at 3 months and 1 year following treatment and showed a favourable safety profile in this group of patients.

Treating patients in the ICU with a Cerebrolysin regimen appears to be justified based on the experience of the author and on published clinical data (see *Figure 3*). The findings need verification in appropriately designed RCTs but, if positive, will support a major therapeutic breakthrough in the management of ICU patients. ■

Pharmacological Support with Multimodal Drugs in Traumatic Brain Injury Treatment – Results from a Large Retrospective Cohort Trial with Cerebrolysin

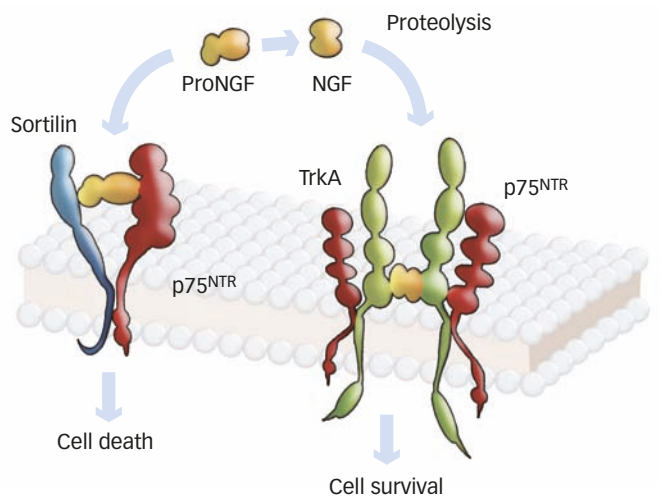
Dafin F Muresanu

Chairman, Department of Clinical Neurosciences, University of Medicine and Pharmacy Faculty for Medicine Cluj-Napoca, Romania

The interplay between mechanisms of damage/cellular death and natural processes of neurorepair was hardly considered when designing single-target chemical treatments in neurology, resulting in the failure of clinical development programmes in recent years. Endogenous neuromodulation is a better therapeutic target since it more accurately reflects biological reality of neurological disorders. Pathophysiological mechanisms represent imbalances in normal neurobiological processes, and endogenous molecules (e.g. NTFs) are vital components of brain protection and recovery that alter DNA expression, generate post-lesional patterns of molecular synergism and rebalance major neurobiological processes.[64] The concept of endogenous neuromodulation is essential to understanding the mechanisms of brain protection and recovery and in developing treatments. This concept can be illustrated by the example of nerve growth factor as potential natural enhancer or potential natural inhibitor of cellular death (see *Figure 4*). Cerebrolysin has similar actions to NTFs and therefore can stimulate natural defence activities within the injured nervous tissue.[11,65]

The 'Early Cerebrolysin Treatment in TBI – a Multicenter, Cohort Trial' included 7,769 adult patients with TBI (TBI), who were admitted at 10 departments of neurosurgery in Romania.[66] Cerebrolysin-treated patients were assigned to two different drug regimens (20 ml or 30 ml/day), or to control treatment. In mild TBI, treatment with both Cerebrolysin regimens significantly improved Glasgow Outcome Scores (GOS) and respiratory distress (RDS) scores at 10 days compared with controls. However, no difference was seen in GOS and RDS scores at 30 days between Cerebrolysin and control patients, probably due to the generally good progress of mild TBI patients (so-called 'ceiling effect'). In moderate and severe TBI, treatment with Cerebrolysin, both 20 ml and 30 ml/day regimens, significantly improved GOS and RDS scores at both 10 and 30 days compared with controls. Moreover, a significant dose-dependent effect was seen for Cerebrolysin on GOS score at 10 and 30 days. The results of this large retrospective study show significant beneficial effects of early Cerebrolysin treatment in TBI patients and justify a large prospective study to further support the use of Cerebrolysin in this indication. ■

Figure 4: Neurotrophic Factors in Brain Protection and Recovery



NGF = nerve growth factor. Adapted from Nykjaer et al. 2004.[76]

Behavioural and Psychiatric Aspects of Traumatic Brain Injury

Johannes Thome

Director and Chair, Clinic and Policlinic for Psychiatry and Psychotherapy, University of Rostock, Germany

The most frequent TBI-related conditions with psychiatric relevance are affective alterations (e.g. depression, mania) and changes of personality.[67–69] In addition, psychotic symptoms are reported relatively frequently.[70] TBI patients are also often diagnosed with post-traumatic stress disorder (PTSD) and have an increased risk of substance-use disorders, such as alcoholism.[71] This patient group greatly benefits from multi-professional support that is not only restricted to addressing physical but also mental health problems. The exact nature of the behavioural alterations and psychiatric symptoms is largely dependent on the type and localisation of the injury and also on premorbid patient characteristics (e.g. vulnerability, resilience). Thus, the inter-individual variability as well as the prognosis of each patient varies widely, so an individualised treatment approach is mandatory.

In recent years, diagnostic and therapeutic options for TBI have considerably improved and understanding of the pathophysiological mechanisms leading to the psychiatric symptoms is increasing.[72] As improvements over time due to neuroplastic processes are often observed in this patient group, treatment options supporting such neuroregeneration and neuroplasticity are of considerable interest and are urgently needed. Nevertheless, psychiatric symptoms in TBI are often chronic;[73] patients and their families require long-term support by an expert team.

Possible psychiatric consequences of TBI can be diverse, including combinations of: post-traumatic personality change, mood changes, anxiety, attentional deficits, thought and executive function disturbances, behavioural changes (e.g. impulsivity) and alteration of language. These changes have been further characterised in terms of gender, age and the milieu in which the recovery from trauma takes place. The variability of symptoms is related to many factors among which the site and the extent of injury as well as personal characteristics of each patient are probably the most prominent variables.

The development of pharmacological therapies that could aid recovery from the psychiatric consequences of TBI necessitates studying animal models that reflect as closely as possible the complex reality of challenges faced by TBI survivors. Imaging modalities such as diffusion tensor imaging (DTI) are increasingly employed in animal models[74] and as surrogate analysis tools in clinical trials. Notable recent studies in this field include neuro-immune modulation experiments (with Ibudilast – inhibitor of glial cell activation); and modulation of neural plasticity (with Cerebrolysin).[54,74,75]

Discussion and Conclusions

Approaches to TBI are advancing on several different levels. Improved techniques are becoming available for ensuring consistent patient assessment and managing behavioural problems; more successful treatments are in development and better clinical trial methodologies are becoming established. TBI is a heterogeneous condition that requires improved characterisation in order to aid understanding of the condition. The pathology of TBI is complex and much further studies are needed to adequately map the processes involved and develop means of manipulating them. In patients, improved use of assessment scales and multimodal monitoring is necessary to ensure more reliable and complete documentation in trials and in clinical practice.

Many experimental treatments for TBI arising from a reductionist approach have failed to rectify damage to brain tissue and address the long-term consequences of injury. More recent developments, however, using cell-based therapies or NTFs have produced more promising results. It is clear that to achieve successful restoration of nerve tissue and function requires a multimodal approach in which many genetic and biochemical pathways are activated to promote recovery. However, experimental cell-based neurotherapies have enabled structural recovery of the spinal cord but have not yet shown the same level of functional restoration. Further work using these cells in combination with pharmacological agents is needed.

The large multicentre cohort trial conducted in Romania showed that Cerebrolysin is effective in the treatment of mild to severe TBI and provided significant improvements in GOS and RDS scores after 10 and 30 days compared with controls. This result is encouraging and justifies further development of Cerebrolysin in this indication. In addition, other studies show that Cerebrolysin can be successfully used to treat CIACI, which is often an additional long-term problem following neurological injury.

The design of clinical trials to investigate this and other therapies should closely reflect the reality of biological processes underlying natural recovery from brain injury. In addition, investigators must ensure that all medical personnel assessing patients in trials are well trained to provide correct and consistent results when using instruments such as the GCS to avoid higher inter-rater variability. Clinical trials should also address cognitive decline and the behavioural effects of TBI, which can severely affect the social and professional lives of patients for many years after the injury or permanently disable them.

Effective treatment of TBI is likely to remain a serious medical challenge and its incidence is likely to remain high, especially among military personnel and the older population. An enhanced understanding of the underlying process of brain tissue repair, better short- and long-term management of patients and the development of effective multimodal therapies are likely to reduce the effects of this often devastating condition. ■

1. Pickelsimer EE, Selassie AW, Sample PL, et al., Unmet service needs of persons with traumatic brain injury, *J Head Trauma Rehabil*, 2007;22:1–13.
2. Ragnarsson KT, Traumatic brain injury research since the 1998 NIH Consensus Conference: accomplishments and unmet goals, *J Head Trauma Rehabil*, 2006;21:379–87.
3. Garcia-Altes A, Perez K, Novoa A, et al., Spinal cord injury and traumatic brain injury: a cost-of-illness study, *Neuroepidemiology*, 2012;39:103–8.
4. Sut N, Memis D, Intensive care cost and survival analyses of traumatic brain injury, *Ulus Travma Acil Cerrahi Derg*, 2010;16:149–54.
5. Whitmore RG, Thawani JP, Grady MS, et al., Is aggressive treatment of traumatic brain injury cost-effective?, *J Neurosurg*, 2012;116:1106–13.
6. Cameron KL, Marshall SW, Sturdivant RX, et al., Trends in the incidence of physician-diagnosed mild traumatic brain injury among active duty U.S. military personnel between 1997 and 2007, *J Neurotrauma*, 2012;29:1313–21.
7. Perez K, Novoa AM, Santamarina-Rubio E, et al., Incidence trends of traumatic spinal cord injury and traumatic brain injury in Spain, 2000–2009, *Accid Anal Prev*, 2012;46:37–44.
8. Faden AI, Neuroprotection and traumatic brain injury: the search continues, *Arch Neurol*, 2001;58:1553-5.
9. Maas AI, Menon DK, Lingsma HF, et al., Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research, *J Neurotrauma*, 2012;29:32–46.
10. Alvarez XA, Sampedro C, Perez P, et al., Positive effects of cerebrolysin on electroencephalogram slowing, cognition and clinical outcome in patients with postacute traumatic brain injury: an exploratory study, *Int Clin Psychopharmacol*, 2003;18:271–8.
11. Chen CC, Wei ST, Tsaia SC, et al., Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients: double-blind, placebo-controlled, randomized study, *Br J Neurosurg*, 2013;27:803–7.
12. Langlois JA, Rutland-Brown W, Wald MM, The epidemiology and impact of traumatic brain injury: a brief overview, *J Head Trauma Rehabil*, 2006;21:375–8.
13. Stein DG, A clinical/translational perspective: can a developmental hormone play a role in the treatment of traumatic brain injury?, *Horm Behav*, 2013;63:291–300.
14. Hung R, Carroll LJ, Cancelliere C, et al., Systematic review of the clinical course, natural history, and prognosis for pediatric mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis, *Arch Phys Med Rehabil*, 2014;95:S174–91.
15. Gianino JW, Afuwape LO, Evidence-based guidelines for the management of traumatic brain injury, *Mo Med*, 2012;109:384–7.
16. Lingsma HF, Roozenbeek B, Li B, et al., Large between-center differences in outcome after moderate and severe traumatic brain injury in the international mission on prognosis and clinical trial design in traumatic brain injury (IMPACT) study, *Neurosurgery*, 2011;68:601–7; discussion 7–8.
17. McMahon P, Hricik A, Yue JK, et al., Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study, *J Neurotrauma*, 2014;31:26–33.
18. Tosetti P, Hicks RR, Theriault E, et al., Toward an international initiative for traumatic brain injury research, *J Neurotrauma*, 2013;30:1211–22.
19. CENTRE-TBI, 2014; Project Overview. Available at: https://www.center-tbi.eu/project/overview (accessed 16 December 2014).
20. Christie KJ, Turnley AM, Regulation of endogenous neural stem/progenitor cells for neural repair-factors that promote neurogenesis and gliogenesis in the normal and damaged brain, *Front Cell Neurosci*, 2012;6:70.
21. Sun D, The potential of endogenous neurogenesis for brain repair and regeneration following traumatic brain injury, *Neural Regen Res*, 2014;9:688–92.
22. Conboy IM, Conboy MJ, Wagers AJ, et al., Rejuvenation of aged progenitor cells by exposure to a young systemic environment, *Nature*, 2005;433:760–4.
23. Mendelsohn AR, Larrick JW, Overcoming the aging systemic milieu to restore neural stem cell function, *Rejuvenation Res*, 2011;14:681–4.
24. Masliah E, Diez-Tejedor E, The pharmacology of neurotrophic treatment with Cerebrolysin: brain protection and repair to counteract pathologies of acute and chronic neurological disorders, *Drugs Today (Barc)*, 2012;48(Suppl. A):3–24.
25. Richardson RM, Singh A, Sun D, et al., Stem cell biology in traumatic brain injury: effects of injury and strategies for repair, *J Neurosurg*, 2010;112:1125–38.
26. Genovese T, Rossi A, Mazzon E, et al., Effects of zileuton and montelukast in mouse experimental spinal cord injury, *Br J Pharmacol*, 2008;153:568–82.
27. Alcantara-Gonzalez F, Mendoza-Perez CR, Zaragoza N, et al., Combined administration of cerebrolysin and donepezil induces plastic changes in prefrontal cortex in aged mice, *Synapse*, 2012;66:938–49.
28. Rockenstein E, Mante M, Adame A, et al., Effects of Cerebrolysin on neurogenesis in an APP transgenic model of Alzheimer's disease, *Acta Neuropathol*, 2007;113:265–75.
29. Rockenstein E, Ubhi K, Pham E, et al., Beneficial effects of a neurotrophic peptidergic mixture persist for a prolonged period following treatment interruption in a transgenic model of Alzheimer's disease, *J Neurosci Res*, 2011;89:1812–21.
30. Alvarez XA, Cacabelos R, Sampedro C, et al., Efficacy and safety of Cerebrolysin in moderate to moderately severe Alzheimer's disease: results of a randomized, double-blind, controlled trial investigating three dosages of Cerebrolysin, *Eur J Neurol*, 2011;18:59–68.
31. Bornstein N, Poon WS, Accelerated recovery from acute brain injuries: clinical efficacy of neurotrophic treatment in stroke and traumatic brain injuries, *Drugs Today (Barc)*, 2012;48(Suppl. A):43–61.
32. Ringelstein EB, Thijs V, Norrving B, et al., Granulocyte colony-stimulating factor in patients with acute ischemic stroke: results of the AX200 for Ischemic Stroke trial, *Stroke*, 2013;44:2681–7.
33. Bedi SS, Hetz R, Thomas C, et al., Intravenous multipotent adult progenitor cell therapy attenuates activated microglial/macrophage response and improves spatial learning after traumatic brain injury, *Stem Cells Transl Med*, 2013;2:953–60.
34. Imura T, Matsumoto M, Fukazawa T, et al., Interactive effects of cell therapy and rehabilitation realize the full potential of neurogenesis in brain injury model, *Neurosci Lett*, 2013;555:73–8.
35. Wang KKW, Moghieb A, Yang Z, Zhang Z, Systems biomarkers as acute diagnostics and chronic monitoring tools for traumatic brain injury, SPIE Proceedings (Sensing Technologies for Global Health, Military Medicine, and Environmental Monitoring), 2013;8723. Available at: http://proceedings.spiedigitallibrary.org/proceeding.aspx?articleid=1692457 (accessed 14 February 2015).
36. Mondello S, Muller U, Jeromin A, et al., Blood-based diagnostics of traumatic brain injuries, *Expert Rev Mol Diagn*, 2011;11:65–78.
37. Zhang Z, Mondello S, Kobeissy F, et al., Protein biomarkers for traumatic and ischemic brain injury: from bench to bedside, *Transl Stroke Res*, 2011;2:455–62.
38. Lam PK, Lo AW, Wang KK, et al., Transplantation of mesenchymal stem cells to the brain by topical application in an experimental traumatic brain injury model, *J Clin Neurosci*, 2013;20:306–9.
39. Liu AM, Lu G, Tsang KS, et al., Umbilical cord-derived mesenchymal stem cells with forced expression of hepatocyte growth factor enhance remyelination and functional recovery in a rat intracerebral hemorrhage model, *Neurosurgery*, 2010;67:357–65; discussion 65–6.
40. Liu Y, Ao LJ, Lu G, et al., Quantitative gait analysis of long-term locomotion deficits in classical unilateral striatal intracerebral hemorrhage rat model, *Behav Brain Res*, 2013;257:166–77.
41. Winkler PA, Stummer W, Linke R, et al., Influence of cranioplasty on postural blood flow regulation, cerebrovascular reserve capacity, and cerebral glucose metabolism, *J Neurosurg*, 2000;93:53–61.
42. Kuo JR, Wang CC, Chio CC, et al., Neurological improvement after cranioplasty - analysis by transcranial doppler ultrasonography, *J Clin Neurosci*, 2004;11:486–9.
43. Sakamoto S, Ohba S, Eguchi K, et al., Churg-Strauss syndrome presenting with subarachnoid hemorrhage from ruptured dissecting aneurysm of the intracranial vertebral artery, *Clin Neurol Neurosurg*, 2005;107:428–31.
44. Winkler PA, Stummer W, Linke R, et al., The influence of cranioplasty on postural blood flow regulation, cerebrovascular reserve capacity, and cerebral glucose metabolism, *Neurosurg Focus*, 2000;8:e9.
45. Agner C, Dujovny M, Gaviria M, Neurocognitive assessment before and after cranioplasty, *Acta Neurochir (Wien)*, 2002;144:1033–40; discussion 40.
46. Rowley G, Fielding K, Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users, *Lancet*, 1991;337:535–8.
47. Zuercher M, Ummenhofer W, Baltussen A, et al., The use of Glasgow Coma Scale in injury assessment: a critical review, *Brain Inj*, 2009;23:371–84.
48. Tuijn S, Janssens F, Robben P, et al., Reducing interrater variability and improving health care: a meta-analytical review, *J Eval Clin Pract*, 2012;18:887–95.
49. Matula C, 2013; AO Neuro Webcast 'Meet the Experts' How to classify a neurotrauma patient: Methods and solutions, https://www.aofoundation.org/Structure/AONeuro/news/Pages/AONeuro-Webcast %20new.aspx (accessed 8 January 2015).
50. Ruff RM, Weyer JC, Myths and mild traumatic brain injury, *Psychological Injury and Law*, 2005;2:34–42.
51. Silver JM, McAllister TM, Yudofsky SC, *Textbook of traumatic brain injury*, Washington DC: American Psychiatric Publishing, 2005.
52. Thornhill S, Teasdale GM, Murray GD, et al., Disability in young people and adults one year after head injury: prospective cohort study, *BMJ*, 2000;320:1631–5.
53. Carroll LJ, Cassidy JD, Cancelliere C, et al., Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis, *Arch Phys Med Rehabil*, 2014;95:S152–73.
54. Cerebrolysin: a review of a neurotrophic treatment strategy in acute and chronic neurological disorders, *Drugs Today (Barc)*, 2012;4 (Suppl. A):1–69.
55. Pandharipande PP, Girard TD, Jackson JC, et al., Long-term cognitive impairment after critical illness, *N Engl J Med*, 2013;369:1306–16.
56. Herridge MS, Cheung AM, Tansey CM, et al., One-year outcomes in survivors of the acute respiratory distress syndrome, *N Engl J Med*, 2003;348:683–93.
57. Hopkins RO, Weaver LK, Pope D, et al., Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome, *Am J Respir Crit Care Med*, 1999;160:50–6.
58. Wilcox ME, Brummel NE, Archer K, et al., Cognitive dysfunction in ICU patients: risk factors, predictors, and rehabilitation interventions, *Crit Care Med*, 2013;41:S81–98.
59. Gunther ML, Morandi A, Krauskopf E, et al., The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study*, *Crit Care Med*, 2012;40:2022–32.
60. Morandi A, Rogers BP, Gunther ML, et al., The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study*, *Crit Care Med*, 2012;40:2182–9.
61. Engel GL, Romano J, Delirium, a syndrome of cerebral insufficiency, *J Chronic Dis*, 1959;9:260–77.
62. Chen N, Yang M, Guo J, et al., Cerebrolysin for vascular dementia, *Cochrane Database Syst Rev*, 2013;1:CD008900.
63. Ladurner G, Kalvach P, Moessler H, et al., Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial, *J Neural Transm*, 2005; 112:415–28.
64. Muresanu DF, Buzoianu A, Florian SI, et al., Towards a roadmap in brain protection and recovery, *J Cell Mol Med*, 2012;16:2861–71.
65. Álvarez XA, Figueroa J, Muresanu D, Peptidergic drugs for the treatment of traumatic brain injury, *Future Neurology*, 2013;8:175-92.

66. Popescu BO, Onose G, Chendreanu CD, et al.,2011, Early Cerebrolysin treatment in traumatic brain injury – A large retrospective national multicenter cohort study 7th Congress of the Society for the Study of Neuroprotection and Neuroplasticity, Krakow, Poland,.
67. Bowen A, Neumann V, Conner M, et al., Mood disorders following traumatic brain injury: identifying the extent of the problem and the people at risk, *Brain Inj*, 1998; 12:177–90.
68. Jorge RE, Neuropsychiatric consequences of traumatic brain injury: a review of recent findings, *Curr Opin Psychiatry*, 2005;18:289–99.
69. Jorge RE, Arciniegas DB, Mood disorders after TBI, *Psychiatr Clin North Am*, 2014;37:13–29.
70. Arciniegas DB, Harris SN, Brousseau KM, Psychosis following traumatic brain injury, *Int Rev Psychiatry*, 2003;15:328–40.
71. Bryant R, Post-traumatic stress disorder vs traumatic brain injury, *Dialogues Clin Neurosci*, 2011;13:251–62.
72. Bondi CO, Semple BD, Noble-Haeusslein LJ, et al., Found in translation: Understanding the biology and behavior of experimental traumatic brain injury, *Neurosci Biobehav Rev*, 2014;S0149-7634(14)00335-2.
73. Whelan-Goodinson R, Ponsford J, Johnston L, et al., Psychiatric disorders following traumatic brain injury: their nature and frequency, *J Head Trauma Rehabil*, 2009;24:324–32.
74. Budde MD, Shah A, McCrea M, et al., Primary blast traumatic brain injury in the rat: relating diffusion tensor imaging and behavior, *Front Neurol*, 2013;4:154.
75. Rodgers KM, Bercum FM, McCallum DL, et al., Acute neuroimmune modulation attenuates the development of anxiety-like freezing behavior in an animal model of traumatic brain injury, *J Neurotrauma*, 2012;29:1886–97.
76. Nykjaer A, Lee R, Teng KK, et al., Sortilin is essential for proNGF-induced neuronal cell death, *Nature*, 2004 26;427(6977):843–8.