EDITORIAL

Traumatic Brain Injury: Therapeutic Challenges and New Directions

The realization of a successful pharmacological treatment for use in severe clinical traumatic brain injury (TBI) has eluded researchers for at least 3 decades in spite of the fact that several excellent candidate compounds have been identified in preclinical studies. As with developing therapies for stroke, in which more than 140 trials have been negative, there is a perception in the pharmaceutical industry, as well as in the biotechnology investment sector, that TBI represents an indication that is unattractive for further investment and development. Some have coined the term "valley of death" to describe the dichotomy that separates robustly successful, preclinical TBI science from the failures of clinical trials. Yet, now more than ever, substantial changes in the field have made successful translation of pharmacological neuroprotection in traumatic brain injury a strong, tangible reality for the next few years.

The need to develop new therapies in TBI has never been stronger, even though its incidence has fallen in Europe, Japan, Australia, and North America. TBI remains the most significant cause of mortality and morbidity in persons less than 45 years of age throughout the world, and there has been a massive increase in its incidence in the "powerhouse developing nations" of Brazil, China, and India, especially, where increasing motorization has led to an epidemic increase in TBI. The future socioeconomic impact of head injury survivors in these countries may be even more profound than in the United States and Europe, where 1 in 200 families supports a TBI survivor.

How can such therapies be implemented? All who are involved in the bench-to-bedside translation of TBI therapies need to learn lessons from the failures of the past; in 2009, many factors are interacting to make the likelihood of successful translation increasingly probable. For example, translation of therapies from theoretical concepts to a "clinic-ready" drug is now much more rapid than ever previously, thanks to such novel pharmacological techniques as structure-affinity relationship analysis, high throughput screening, more rapid information sharing, and far more efficient safety testing. New mechanisms, such as apoptotic cell death and the importance of neurotrophins in sustaining neuronal preservation in the face of injury, have now been shown to be robust in TBI, both in animal models and in humans, and moreover, new drugs aimed at both these mechanisms have already entered clinical phase IIA trials as rapidly as within 5 years of discovery of the mechanism.

In recent years there has been growing concern among preclinical scientists who evaluated therapies in rodent models of TBI, as well as among funding agencies, that these models may be fundamentally incapable of effectively reproducing the complexity of severe human TBI, which is characterized by multiple interacting pathomechanisms within the same patient at the same or different times. For example, diffuse axonal injury, ischemic/hypoxic neuronal damage, increased intracranial pressure, and contusions are present in the majority of severe TBI patients, yet have not been combined in any single, small animal model. This has led to the important insight that multiple concurrent or sequential therapies are likely to be needed to influence these processes, and the National Institutes of Health National Institute of Neurological Disorders and Stroke have taken steps to pursue that aim. Nevertheless, despite this limitation, rodent models have produced a wealth of new molecular and biochemical results that have demonstrated homology in human TBI. For example, the realization of the importance of specific mitochondrial damage and the increasing importance of neurogenic inflammation have led to human phase III trials (cyclosporin A) without the intermediate step of using large animal gyrencephalic models.

Thus, the concept of the "magic silver bullet," which dominated thinking 2 decades ago, has been replaced with the view that the most likely successful interventions in TBI will be simultaneous multiple treatments, so-called "multipotential therapies" or alternatively, multifunctional drugs that target different harmful pathomechanisms. In this issue, several of these multipotential therapies are reviewed—hypothermia, statins, magnesium, progesterone, and others.

As with preclinical drug development, clinical trial design has recently been critically examined, and the landmark studies of the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) group have led to critical reanalysis of previous trials with formulation of new recommendations which offer the tangible prospect of improving clinical phase III and phase II trial design, not only in terms of number of

patients entered, but also in term of overall duration of the study through the use of novel outcome comparisons and statistical methods, such as the "sliding dichotomy technique," which are reviewed in this issue of the journal.

More funding is available at present than ever before for translational TBI research, in spite of the global economic difficulties we all face. For example, the U.S. Department of Defense has injected funding amounts of $150 to $200 million during each of the last 3 years, which has massively increased the scope of both preclinical and clinical studies for TBI. The benefit of these investments in TBI research will be experienced incrementally within the next 5 years. One tangible example is the emergence of consortia. Currently, there are at least six major TBI clinical trials of consortia in Europe and North America that are harnessing the power of more than 200 hospitals to standardize treatment of severe TBI with the purpose of conducting clinical trials. In many of these centers, Consortium funding establishes the necessary infrastructure (e.g., regulatory specialists and clinical trial nurses) to facilitate translation-neuroprotection studies. Against this background, several large pharmaceutical companies are deploying new therapies for this TBI indication.

Perhaps the most important lesson to be learned by those of us who are involved in translational neuroprotection studies for TBI, however, is to gain from the experience of researchers in HIV/AIDS therapy development and cancer chemotherapy. Both HIV/AIDS and cancer were previously considered incurable, but for both of these disorders, survival is now common. Funding on a scale of almost two orders of magnitude greater than that for TBI (e.g., $2.6 *billion* in HIV/AIDS research funding in 2007 in North America alone) has led to an exponential activity increase in clinical trials. Thus, in HIV/AIDS drug development, there have been more than 600 clinical trials performed, leading to the current generation of highly successful, potent, multi-drug antiretroviral therapy HAART (highly active antiretroviral therapy). This is in stark contrast to TBI, which has a higher incidence and prevalence than HIV/AIDS, and for which annual funding is around $70 million in North America, in which only approximately 30 phase III neuroprotection trials have been performed. An important tool in the development of clinical trials in both HIV/AIDS and cancer chemotherapy has been the emergence of biomarkers. Therapy for acute myocardial infarction has also been revolutionized by biomarkers, and the progress toward biomarker development for TBI is presented within this issue of the journal.

Thus, the enormous complexity of translational neuroprotection for TBI becomes increasingly apparent as basic research advances and with the availability of new tools, greater research funding, and the steady increase in the awareness of TBI importance worldwide has led to a sense of enormous optimism for the future. It is no longer a question of if but when neuroprotective therapy will develop in TBI, and this issue of the journal seeks to outline the state of progress toward this goal.

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