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EDITORIAL

Pharmacotherapy for Traumatic Brain Injury: The Next Generation of Clinical Trials

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Traumatic brain injury (TBI) is one of the most common maladies affecting humanity and, until the late twentieth century, was largely considered beyond the reach of medical science. This view started to change in the 1980s, with the realization that secondary injury (distinguished from primary injury, which occurred at the time of mechanical impact) contributed significantly to a poor outcome after TBI, and that interventions in animal models designed to block the effects of excitatory amino acids, free radicals, inflammatory mediators, or injury activated proteases (for review, see [1]) could produce significant cytoprotection and improve neurological outcomes. This new paradigm led to the creation of the American and European Brain Injury Consortia (ABIC and EBIC) and the first generation of clinical trials for TBI, which enrolled thousands of participants in multiple trials of novel and repurposed compounds. Unfortunately, none of these trials demonstrated clinical efficacy, prompting the National Institute of Neurological Disorders and Stroke (NINDS) to convene a workshop in May 2000 to review the key lessons from these failures and design strategies to improve clinical trial design [2]. Important issues included the need to conduct studies which were adequately powered to detect realistic but clinically meaningful effects, the importance of standardizing clinical management across multiple hospitals involved in multicenter trials, refinement of outcome measures, and improving the quality and translational relevance of the preclinical studies. This advice was followed by investigators who launched the second generation of TBI clinical trials, which incorporated these suggestions in high-quality trials run by the Neurologic Emergencies Treatment Trials Network (NETT), the NCMRR TBI Clinical Trials Network, and the Australia-New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, among others, but unfortunately were no more successful [3–7]. A subsequent NINDS workshop convened in 2007 [8] to readdress these failures concluded that much more knowledge was needed regarding the heterogeneous mechanisms of secondary injury after TBI, and that imaging and molecular biomarkers were needed to identify and measure specific injury mechanisms, to allow the selection of participants for clinical trials who prominently manifested the pathology targeted by the therapy, to confirm target engagement of the compound under investigation, and to allow fine-tuning of critical issues such as dose, timing, and duration of therapy. While there has been a pause in new Phase III clinical trials of pharmacotherapies for TBI over the past decade, the successful completion of carefully conducted large-scale observational studies such as TRACK-TBI (in the USA), the CENTER-TBI study (in Europe), among others [9, 10], have put us on the cusp of launching the third generation of TBI clinical trials, which will incorporate imaging and molecular biomarkers, begin to address issues such as target engagement, and focus in the Phase II space. This issue of *Neurotherapeutics* highlights many of the leading pharmacologic candidates for this third generation of studies. We asked contributors to incorporate new insights and the latest thinking on how third-generation trials will incorporate the lessons from the past 35 years, to get us closer to the promise of neuroprotective therapies to meaningfully advance current guidelines and algorithms of care across the spectrum of injury severity and sequelae [11–13]. The articles in this special issue include preclinical and clinical investigations, feature studies addressing adult and pediatric patients, span the spectrum of injury severity, and include work examining acute and/or delayed therapy administration.

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The first contribution, from Dietrich and colleagues [14], describes recent work on improving the rigor of preclinical research, with the goal of maximizing the ability to translate therapies proven to be effective in preclinical models to the bedside. To the embarrassment of biomedical science extending well beyond neuroscience, it became evident that many beneficial effects demonstrated in pre-clinical and early-phase studies were not as robust as expected and/or showed model dependence when tested in rigorous multicenter studies, and that there was a vast need to improve the rigor and robustness of pre-clinical studies. The lead manuscript addresses the efforts over the past 10 years to set high standards for pre-clinical studies, providing confidence in the biologic efficacy of candidate compounds and potential guidance for precision clinical investigation moving forward. This includes the value of multi-center preclinical consortia.

Dr. Borlongan's team [15] next brings our attention to an important problem that confounds much of TBI clinical research, namely the important role that psychosocial stressors have on TBI outcomes. With his collaborators, he has developed a rodent model of homelessness and demonstrates that psychosocial stressors impact motor function after moderate controlled cortical impact and are associated with white matter degeneration in the corpus callosum. This work in the pre-clinical space highlights the potential challenges for therapy translation that are imposed by the many confounders linked to psychosocial stressors, whether the stressors occur at the time of injury or during acute or chronic recovery. And that stressors can impact not only behavioral outcomes but also neuropathology.

The contribution from Dr. Christos Lazaridis and his colleagues [16], while not focused on pharmacotherapy, updates the current state-of-the-art on multi-modality neuromonitoring of patients with severe TBI, as is practiced in leading neurocritical care units. Multi-modality neuromonitoring is designed to identify episodes of secondary brain injury resulting from intracranial hypertension, brain tissue hypoxia, or metabolic crisis so that the right therapy can be delivered at the right time, treating secondary brain injury while it is still reversible. This can include not only pharmacotherapy (such as vasopressors, osmotic agents, anti-epileptic drugs) but also management strategies such as fluids, ventilator adjustments, and surgical interventions. Beyond guidelines-based care, novel therapies targeting these secondary insults in the intensive care unit are also needed, and it will be important to discern how new therapies might mitigate the evolution of secondary injury and be used as additional tools to respond to these secondary insults. The development of new therapies targeting cerebral edema and/or cerebrovascular failure represents perfect examples in this regard [17, 18], and other therapies presented in this issue may also serve in this manner.

The remaining manuscripts in this volume focus on some of the leading candidate drugs, with a strong scientific rationale based on rigorous and reproducible studies in preclinical models, and in most cases experience with neurological disorders that share some pathophysiologic features with TBI. Dr. Simard and his collaborators [19] summarize their work over several decades with glibenclamide, a sulfonylurea receptor blocker that is widely used to treat diabetes mellitus, as a promising treatment for cerebral edema in patients with brain contusions. This approach, which is currently being tested in human clinical trials, is an excellent example of precision medicine, by targeting patients with a specific endotype of TBI and using an imaging biomarker as evidence of target engagement and physiologic efficacy. Dr. Magnus Hansson [20] next summarizes the experience of his team and others with NeuroStat, a novel formulation of cyclosporine, another repurposed compound, that targets mitochondrial permeability transition pore opening—a mechanism distinct from the traditional use of cyclosporine in immunosuppression. The potential value of this agent is supported by a large body of rigorous preclinical data in TBI, including work in large animal models, and in early-phase clinical trials. Dr. Daniel Laskowitz and his team [21], taking a clue from the strong genetic evidence that apolipoprotein E variants modify multiple pathophysiologic mechanisms relevant to acute and chronic neurodegenerative processes, developed a small peptide derivative which readily penetrates the CNS, has potent neuroprotective effects in multiple brain injury pre-clinical models, and is currently in early-phase clinical trials for intracranial hemorrhage. This report and others in this issue highlight the surprisingly recent concept of targeting mechanisms involved in chronic neurodegeneration after TBI—a concept that was greatly advanced across the entire TBI field by the recognition of the long-term sequelae of mild repetitive TBI. Dr. Adel Helmy [22] and his team's contribution summarizes the pre-clinical and clinical experience with anakinra, a recombinant interleukin-1 receptor antagonist (rHuIL-1ra) which is widely used to treat rheumatoid arthritis, as a repurposed compound in severe TBI. A particularly elegant feature of Dr. Helmy's work is the use of cytokines, chemokines, and inflammatory mediators as putative pharmacodynamic response biomarkers to document target engagement and physiologic efficacy. Dr. Clark and his collaborators [23] summarize their work with N-acetylcysteine, a potent antioxidant molecule that has a long track record of research in TBI. His team pioneered the combination of N-acetylcysteine with probenecid, to optimize entry into the central nervous system and present pharmacokinetic and pharmacodynamic data, including cutting-edge cerebrospinal fluid metabolomics, from a small Phase I clinical trial in pediatric severe TBI. This work represents one of the first approaches to combination therapy development in a clinical trial for severe TBI.

The next three contributions focus on repurposed oral drugs which show much promise as neuroprotective agents in TBI, based on a compelling biological mechanism, extensive preclinical work, and early clinical trial data. HMG-CoA reductase inhibitors (statins) are widely used in clinical medicine, have potent vasoprotective and anti-inflammatory effects, and have been extensively studied in pre-clinical models of TBI. Early clinical studies by Dr. Robertson and her colleagues [24] provide hints of efficacy in humans. Minocycline is a tetracyclic antibiotic which has potent anti-inflammatory properties and has been widely studied in preclinical models. Dr. Bergold and his team [25] have led much of that work over the past 15 years, and his studies point out that combination therapy has much promise, particularly the potential to combine minocycline with N-acetylcysteine, which is the topic of the earlier manuscript by Clark et al. [23]. While combination therapy can present challenges for early-phase clinical trials, the experience from other areas of medicine such as oncology and infectious disease and the well-recognized multi-faceted pathobiology involved in secondary injury after TBI suggest that this is an issue the neurotrauma field will have to grapple with. Finally, angiotensin receptor blockers (ARBs), which are widely used to treat hypertension, also show promise as neuroprotective agents in TBI. Drs. Villapol, Symes, and colleagues [26] have been among the leaders studying ARBs in preclinical TBI models, providing the rationale for early-phase clinical trials.

The next two contributions highlight compounds at earlier stages of clinical development. Dr. Michel Baudry and his team [27] have studied the role of the protease calpain, which has been implicated for decades in neurodegeneration including TBI. He and his colleagues have shown that different calpain isoforms have distinct effects on the tissue response to injury, that calpain-1 has a predominantly adaptive role promoting synaptic plasticity, while calpain-2 plays a predominantly maladaptive role promoting neurodegeneration. A specific calpain-2 inhibitor developed by his team shows promise in pre-clinical models and is in the early stages of development for clinical use. Dr. Verdoorn and his colleagues [28] summarize a large volume of data on the neuroprotective effects of neurosteroids, including pregnenolone, allopregnanolone, ganaxolone, estrogen, and progesterone. Although the initial TBI clinical trials with progesterone were not successful, these investigators highlight both the development of novel progesterone formulations and/or analogs, and the potential value of other neurosteroids given their pleiotropic effects.

The final two contributions represent work addressing therapies targeting neurodegeneration and/or neurological dysfunction in pre-clinical models or patients with therapies administered in the delayed phase (months or years) after injury—an extremely hot topic in our field [29–32]. Dr. Pieper and his colleagues [31] provide an update on their work on P7C3 and derivatives, discovered through an unbiased, target-agnostic screen of a large chemical library, which were subsequently found to stabilize nicotinamide adenine dinucleotide (NAD^+)/NADH, resulting in neuroprotective and pro-neurogenic effects. This strategy shows promise in pre-clinical models relevant to a broad spectrum of neurodegenerative disorders, including TBI, and although early studies supported benefit with acute treatment, more recent evidence suggests efficacy even after delayed administration—as long as a year after injury. Dr. Kenney and her collaborators [32] present work targeting neurologic dysfunction in the chronic stage after TBI, specifically using the phosphodiesterase-5 inhibitor sildenafil to ameliorate cerebrovascular dysfunction. They have focused on a particular endophenotype of chronic TBI, cerebral microvascular injury, using imaging measures of cerebrovascular reactivity (CVR) as a biomarker, and show that phosphodiesterase-5 inhibitors, drugs widely used in medicine to treat erectile dysfunction and primary pulmonary hypertension, show promise to mitigate some of the deficits in CVR after TBI—anticipating that they will produce beneficial effects on cognition and other facets of functional outcome.

We hope that the manuscripts in this volume convey the enthusiasm in the neurotrauma field for improving outcomes after TBI with novel therapies, and that several exciting compounds are advancing through the drug development pipeline, including novel chemical entities as well as repurposed compounds. Although we featured many therapies, we recognize that there are numerous other therapies and/or mechanisms that are emerging as exciting and possible opportunities to treat TBI. This includes therapies targeting spreading depolarization [33], ferroptosis [34], microglial senescence [29, 30], coagulation disturbances [35], the microbiome [36], exosomes [37], nanoparticles with anti-inflammatory cargo [38], therapies targeting p-tau [39], cellular therapies [40–42].

In conclusion, we agree with Sir Winston Churchill that "success requires the ability to go from failure to failure with undiminished enthusiasm." If we continue to learn from our mistakes, elucidate the molecular mechanisms underlying secondary brain injury, discover new biomarkers that allow us to monitor these mechanisms, strengthen the link between pre-clinical and clinical investigation, and design innovative clinical trials of exciting therapeutics, the elusive goal of disease-modifying therapies for TBI is within reach.

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Declarations

Conflict of Interest None.

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