# Potential TBI Biomarkers and Therapeutics

## Developing a Framework for the Evaluation of TBI Therapeutics and Identification of New Clinical Biomarkers

The Operation Brain Trauma Therapy-Extended Studies (OBTT-ES) is an extension of the paradigm-shifting Operation Brain Trauma Therapy (OBTT), a multi-site consortium consisting of investigators from University of Miami School of Medicine (Miami, FL), Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD), Virginia Commonwealth University (Richmond, VA), Banyan Biomarkers, Inc (San Diego, CA), University of Florida (Gainesville, FL), University of Pittsburgh School of Medicine (Pittsburgh, PA) and University of Messina (Messina, ITL). OBTT uses a collaborative approach to systematically evaluate TBI therapeutics in preclinical animal models.

Ultimately, OBTT and OBTT-ES aimed to (1) identify agents that can easily transition to clinical trials or be further evaluated clinically in a precision medicine approach to explore domains of benefit (e.g., cognition, motor, lesion size) identified in preclinical models, and (2) identify cross-model assessment biomarkers that correlated with standard outcomes.

OBTT and OBTT-ES uses a two-tier system to identify candidate therapeutics. Outcomes from the evaluations were scored using a unique 22-point system that considers the differences between the models and evaluations performed. The first tier uses established models of controlled cortical impact, penetrating ballistic-like brain injury, and parasagittal fluid percussion TBI models in rodents. Agents that perform well advance to a second tier that features larger animal models and more complicated models (e.g., the inclusion of hemorrhagic shock) that mimic the battlefield experience. Of the 12 drugs that have completed testing, levetiracetam and glibenclamide have performed the best. Levetiracetam is a U.S. Food and Drug Administration (FDA) approved antiepileptic that showed the most benefit in mild TBI models. Glibenclamide, an FDA approved anti-diabetic drug, showed the most benefit in the cerebral contusion models.

The OBTT and OBTT-ES represent a research paradigm that could be used for the pragmatic evaluation of pre-clinical drugs for the treatment of neurological diseases and conditions.

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