Treatment Strategies

Operation Brain Trauma Therapy (OBTT)-Extended Studies

OBTT (http://safar.pitt.edu/obtt) is a consortium of top experimental traumatic brain injury (TBI) centers in the world to rapidly screen potential TBI therapies and evaluate TBI biomarkers in preclinical experimental models and translate them ultimately for use in combat casualty care. Member institutions include military and civilian academic centers in partnership with industry. This group brings together unprecedented expertise in experimental TBI research including all of the necessary tools for preclinical drug screening and biomarker development. OBTT uses a two-tier screening process to rapidly evaluate potential new drugs. In Tier A, OBTT uses established models of TBI in rats to screen the potential new therapies, using a standard battery of tests. Those agents that perform well advance to Tier B, in which more advanced tests are performed in rat models of TBI. In each tier, biomarkers of TBI are also evaluated. The most promising agent each year from Tier B advances to secondary screening in models of TBI in micropigs. To date, OBTT has tested nine therapies across three rodent models, with over 5,000 individual biomarker assessments. Two of these potential new drugs, levetiracetam and glibenclamide, have shown promising effects in one or more of the TBI rat models. Levetiracetam was identified as the most promising therapy to date, and was advanced to testing in micropigs. Glibenclamide has shown promise specifically in contusions and might represent an excellent candidate for a precision medicine approach to treating cerebral contusions. In addition, data from rigorous preclinical testing across three experimental models on two biomarkers, glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1, were very favorably reviewed by the US Food and Drug Administration (FDA) in the applications for ultimate clinical use of these markers as TBI drug development tools. Finally, promising data are being observed by OBTT in exploratory studies with the more novel serum biomarker phospho-neurofilament-heavy. OBTT's efforts have garnered national and international acclaim and exposure. In March 2016, a total of seven manuscripts[1-7] were published together as a special issue of the *Journal of Neurotrauma* describing the results of the first five therapies tested by OBTT with an introduction by the Director of the Combat Casualty Care Research Program (CCCRP) and Neurotrauma Portfolio Manager.[8] The current lack of an effective therapy for TBI is a critical problem facing Service Members, and the work of OBTT in developing new treatment options is of considerable importance for those who are injured. Agents tested have favorable safety profiles and most have been used clinically; therefore, a seamless transition to human clinical trials is anticipated.

1. Kochanek, P. M., Bramlett, H. M., Shear, D. A., Dixon, C. E., Mondello, S., Dietrich, W. D., … Tortella, F. C. (2016). Synthesis of Findings, Current Investigations, and Future Directions: Operation Brain Trauma Therapy. Journal of Neurotrauma, 33(6), 606–614. https://doi.org/10.1089/neu.2015.413
2. Shear, D. A., Dixon, C. E., Bramlett, H. M., Mondello, S., Dietrich, W. D., Deng-Bryant, Y., … Tortella, F. C. (2016). Nicotinamide Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. Journal of Neurotrauma, 33(6), 523–537. https://doi.org/10.1089/neu.2015.4115
3. Bramlett, H. M., Dietrich, W. D., Dixon, C. E., Shear, D. A., Schmid, K. E., Mondello, S., … Kochanek, P. M. (2016). Erythropoietin Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. Journal of Neurotrauma, 33(6), 538–552. https://doi.org/10.1089/neu.2015.4116

4. Dixon, C. E., Bramlett, H. M., Dietrich, W. D., Shear, D. A., Yan, H. Q., Deng-Bryant, Y., … Kochanek, P. M. (2016). Cyclosporine Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. Journal of Neurotrauma, 33(6), 553–566. https://doi.org/10.1089/neu.2015.4122
5. Mountney, A., Bramlett, H. M., Dixon, C. E., Mondello, S., Dietrich, W. D., Wang, K. K. W., … Shear, D. A. (2016). Simvastatin Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. Journal of Neurotrauma, 33(6), 567–580. https://doi.org/10.1089/neu.2015.4130
6. Browning, M., Shear, D. A., Bramlett, H. M., Dixon, C. E., Mondello, S., Schmid, K. E., … Kochanek, P. M. (2016). Levetiracetam Treatment in Traumatic Brain Injury: Operation Brain Trauma Therapy. Journal of Neurotrauma, 33(6), 581–594. https://doi.org/10.1089/neu.2015.4131
7. Mondello, S., Shear, D. A., Bramlett, H. M., Dixon, C. E., Schmid, K. E., Dietrich, W. D., … Kochanek, P. M. (2016). Insight into Pre-Clinical Models of Traumatic Brain Injury Using Circulating Brain Damage Biomarkers: Operation Brain Trauma Therapy. Journal of Neurotrauma, 33(6), 595–605. https://doi.org/10.1089/neu.2015.4132
8. Rasmussen, T. E., & Crowder, A. T. (2016). Synergy in Science and Resources. Journal of Neurotrauma, 33(6), 511–512. https://doi.org/10.1089/neu.2016.29007.ter