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Advanced Traumatic Brain Injury Research

Validated Models and Research Services for Drug Development

Traumatic brain injury (TBI) is a major cause of mortality and morbidity. Delayed pathogenic events can exacerbate the injury and TBI survivors frequently endure long-term cognitive and sensory-motor deficits. To investigate the pathological features of TBI and evaluate potential treatments, researchers utilize translational models that mimic various aspects of TBI. Inotiv offers contract research services that utilize our established mouse model of TBI to test the efficacy of new therapeutics.

WEIGHT DROP MODEL

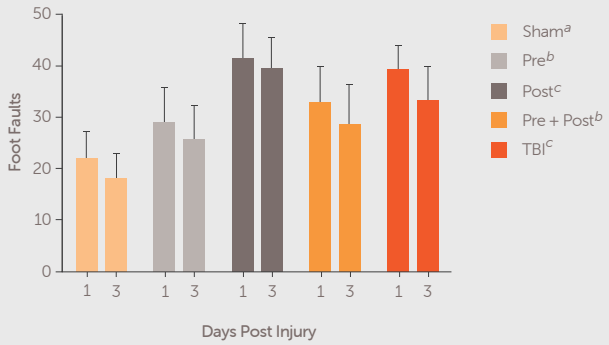
Inotiv utilizes the weight drop model, first developed by Marmarou *et al.*, to mimic diffuse TBI. The model involves delivering a blunt force to the intact skull of an animal laying prone on a foam pad, and is meant to replicate the injuries seen in humans following a fall or motor vehicle accident. Our clients can pair this model with a large portfolio of endpoints, including behavioral testing and histopathological analysis, to assess their novel treatment.

BEHAVIORAL TESTING

TBI induces multiple functional impairments including cognitive deficiencies, motor dysfunction, pain, emotional disorders, and social abnormalities. Inotiv offers a full range of assays that monitors behaviors associated with TBI for drug validation.

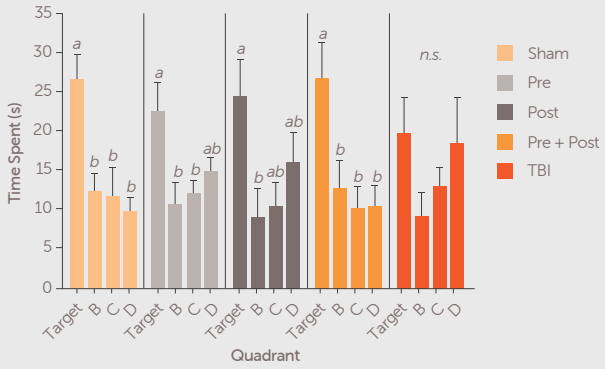
- Barnes maze
- Beam walk
- Contextual/Cue fear conditioning
- Cylinder test
- Elevated plus maze
- Forced swim test
- Hargreaves test
- Home cage activity
- Morris water maze (MWM)
- Light-dark box
- Open field arena
- Rotarod
- Sucrose preference test
- Three chamber social task
- Von Frey test

Figure 1 BCAAs Reduce Motor Dysfunction in TBI Mice



Acute motor recovery was tested on the beam walk 1- and 3-days post injury. Untreated TBI mice (TBI, red bars) had significantly more foot faults than sham injured animals (Sham, light orange bars) and more than mice that received branched-chain amino acids (BCAAs) either before (Pre, light grey bars) or both before and after (Pre + Post, orange bars) TBI induction. Administrating BCAAs only after TBI induction (Post, dark grey bars) did not reduce motor dysfunction in TBI mice. *Data sets that do not share any letters differed significantly. The data were generated by Inotiv scientists and reported in Dickerman, R.D. et al. (2022) Neurotrauma Rep. 3:321.*

Figure 2 BCAAs Preserve Spatial Memory in TBI Mice



Mice were trained in the MWM on days 4-11 after TBI induction. Memory for the task was probed 24 hours after the last acquisition trial. Mice administered BCAAs both before and after TBI (Pre + Post, orange bars) remembered the task as well as the sham injured animals (Sham, light orange bars). Conversely, untreated TBI mice (TBI, red bars) could not differentiate the target quadrant from the other non-target quadrants. *Data sets that do not share any letters differed significantly. The data were generated by Inotiv scientists and reported in Dickerman, R.D. et al. (2022) Neurotrauma Rep. 3:321.*

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Histopathological Analysis

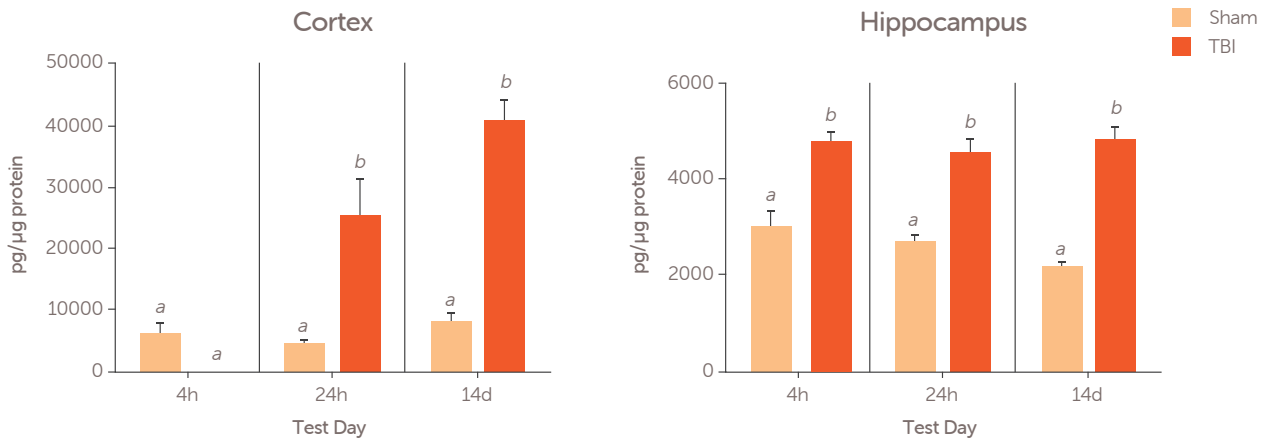
Depending on severity, TBI can cause neuropathological damage including neuroinflammation, astrogliosis, axonal injury, neuronal cell death, and cytotoxic cerebral edema. Inotiv offers a full range of immunohistochemistry, histopathology, and image analysis/digital pathology services to analyze neural tissue from your TBI models.

Additional Services for TBI Research

Inotiv's capabilities extend beyond models and behavioral testing and includes additional GLP and non-GLP *in vivo* and *in vitro* services and assays that can be customized to provide solutions for your TBI research program.

- Stereotaxic surgery
- Tissue harvesting
- Oxidative stress enzymology
- Biomarker analysis with ELISA and Luminex® Assays
- CSC/clinical chemistry analysis
- Mass spectrometry proteomics
- Primary neural cell culturing
- Human stem cell and brain organoid culturing
- Confocal and electron microscopy

Figure 3 Tissue Levels of UCH-L1 Increase in a Mouse Model of TBI



Levels of the tissue damage marker UCH-L1 in the cortex and hippocampus of mice subjected to TBI were measured by ELISA. Significant increases in UCH-L1 were observed in TBI mice (TBI, red bars) compared to sham operated mice (Sham, orange bars) at most time points after injury induction. *Data sets that do not share any letters differed significantly.*

Contact us at inotivco.com/contact to discuss how our models and services can support your TBI research

References

Marmarou, A. *et al.* (1994) J. Neurosurg. **80**:291.
Dickerman, R.D. *et al.* (2022) Neurotrauma Rep. **3**:321.

Inotiv's capabilities for TBI research are powered by its legacy companies, which include:
Envigo *– research models and related services |* ***Bolder BioPATH*** *– preclinical pharmacology and pathology CRO |* ***Histotox Labs*** *– routine and specialized histology, immunohistochemistry, histopathology, image analysis/digital pathology |* ***Protypia*** *– protein/peptide bioanalysis*