Blasted brain

By Tim Fulmer, Senior Writer

U.S. researchers have designed a mouse model of blast-induced brain injury and shown that the animal develops chronic traumatic encephalopathy, a condition associated with concussive injuries in athletes.¹ The team plans to use the model to identify biomarkers and therapies for the condition.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by plaques and tangles of microtubule-associated protein- τ (MAPT; TAU; FTDP-17) throughout the brain, as well as widespread axonal and microvascular damage. Initial symptoms include depression, irritability and impulsivity. These primarily psychological symptoms are followed by cognitive impairment and memory loss and eventually by full dementia with speech and gait dysfunction (see Figure 1, “Brain on the battlefield”).

Over the past decade, CTE has been consistently linked to two groups of people who experience repeated concussive trauma to the head: military personnel exposed to close-range blasts on the battlefield^{2,3} and professional athletes in contact sports such as American football.^{4,5}

It is still unclear whether repeated concussive injury is the primary cause of CTE. The condition can only be diagnosed with a postmortem autopsy, and the varied medical histories of affected soldiers and athletes means a range of biological factors may underlie the disease.

Thus, a research team led by Lee Goldstein and Ann McKee set out to show that repeated concussions are necessary for the development of CTE. To do so, the group designed and characterized a mouse model of blast injury that mimicked the experience of a soldier subjected to a close-range bomb blast.

Goldstein is associate professor of psychiatry, neurology, pathology and laboratory medicine at the **Boston University School of Medicine**. McKee is professor of neurology and pathology and co-director of the Center for the Study of Traumatic Encephalopathy at BU.

The group placed anesthetized wild-type mice inside a cylindrical enclosure and exposed the animals to a single high-pressure air blast, which was comparable to detonation of 5.8 kg of trinitrotoluene (TNT) at a distance of 5.5 meters and within the reported range of conditions associated with common blast injuries in the Iraq war.⁶

The blast did not kill or cause blunt force trauma to the mice. Nor did brains isolated from mice two weeks after the

Figure 1. Brain on the battlefield. Research published in *Science Translational Medicine* by scientists at the **Boston University School of Medicine** has shown that a single concussive air blast is sufficient to generate signs of chronic traumatic encephalopathy (CTE) in mice.

The model was designed to mimic the situation of a soldier experiencing a shock wave from a nearby bomb blast on a battlefield.

Although the blast did not kill the mouse [a], it generated enough force to accelerate the mouse’s head [b] and cause phosphorylation of microtubule-associated protein- τ (MAPT; TAU; FTDP-17) as well as damage at the cellular level [c–e], including neuroinflammation and neurodegeneration [f,g]. That damage was associated with significant cognitive impairment [h,i], a hallmark of CTE.

blast show any macroscopic signs of contusion, hemorrhage, hematoma or focal tissue damage.

However, immunohistological analysis of the brains showed much greater neuropathology than brains from sham-blast control mice, including increased proliferation of proinflammatory astrocytes in response to neuronal damage throughout the cerebral cortex, hippocampus and brain stem.

Mice undergoing the blast had higher levels of phosphorylated Tau in the outer layers of the cerebral cortex than the sham-blasted mice. Electron micrographs of neurons, axons and capillaries in the hippocampus of these mice also revealed cytoskeletal and structural abnormalities, whereas the hippocampus of control mice did not.

Importantly, the tissue pathology was associated with functional impairments.

Axonal conduction velocity in the hippocampus was significantly slower than that in control mice two weeks after blast exposure ($p<0.05$), and memory-associated synaptic transmission was impaired in brain slices from blast-exposed mice ($p<0.05$). Also, based on the animals' behavior in a maze, hippocampal-dependent spatial learning and memory were significantly poorer in blast-exposed mice than in controls ($p<0.05$).

The final step was confirming that the cognitive abnormalities were the direct result of the pressure wave accelerating the mouse's head and causing a concussion. To do so, the researchers constrained the mouse's head in the blast chamber before delivering the blast to see whether they could prevent the development of cognitive impairment.

Indeed, head immobilization during blast exposure was sufficient to eliminate blast-related learning impairments and memory deficits.

In conclusion, the researchers wrote that their mouse model "is expected to open new avenues for investigation of mechanisms, biomarkers, and risk factors relevant to blast-related injury" and could facilitate the development of "diagnostics, therapeutics, and prophylactic measures for blast neurotrauma and its aftermath"

Data were published in *Science Translational Medicine*. Other principal investigators on the paper were Patric Stanton, professor of cell biology and anatomy at the **New York Medical College**, and Rudolph Tanzi, professor of child neurology and mental retardation at the **Harvard Medical School** and a researcher in the Genetics and Aging Research Unit at **Massachusetts General Hospital**.

Making use of the model

The mouse model "nicely creates a link between blast injury and the neuropathology that is seen in CTE," said Christopher Giza, associate professor of pediatric neurology and neurosurgery at the **University of California, Los Angeles David Geffen School of Medicine**. "Human pathological studies have not been able to do this directly."

He added that therapies designed to block TAU deposition and other

chronic sequelae of blast injury can now be tested and the long-term outcomes studied much more readily in the rodent model.

Giza and colleagues previously have shown that cerebral concussions and mild traumatic brain injury are sufficient to increase fear-based learning and impair brain responsiveness and neuroplasticity in rats.^{7,8}

He said the new model also could be used to look at the consequences of repeated blasts and "to look for imaging correlates of the blast injury in the mice and see how it translates to any human blast imaging studies that have been published."

Corresponding author Goldstein told *SciBX* a top priority moving forward is using the model "to study the effects of potential preventive strategies and therapies, including anti-inflammatory agents and anti-TAU compounds."

At least two companies have disclosed TAU-targeting compounds in development. Rember, a

TAU aggregation inhibitor from **TauRx Pharmaceuticals Ltd.**, is in Phase II testing to treat Alzheimer's disease (AD). ReS19-T, a small molecule that prevents neurotoxicity associated with TAU from **reMYND N.V.**, is in preclinical testing for AD. Neither company responded to requests for comment. ReS19-T is being developed in partnership with **Roche**.

Corresponding author McKee added that the model could be useful for designing a diagnostic for CTE that includes neuroimaging readouts as well as levels of circulating TAU protein in the cerebrospinal fluid.

The mouse model is not covered by patents, McKee said.

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