Concussion, Traumatic Brain Injury, and Chronic Traumatic Encephalopathy: New Insights from the Battlefield, Gridiron, and Lab Bench

Lee E. Goldstein, M.D., Ph.D., *Associate Professor of Psychiatry, Neurology, Ophthalmology, Pathology & Laboratory Medicine, Biomedical Engineering, Electrical & Computer Engineering,* Boston University School of Medicine, College of Engineering, Photonics Center, Alzheimer's Disease Center, Boston, MA.

Correspondence: lgold@bu.edu

Biography: Dr. Goldstein is Director of the Molecular Aging & Development Laboratory, Center for Biometals & Metallomics, and the Neurotrauma Laboratory at Boston University School of Medicine and College of Engineering. Dr. Goldstein received medical (MD) and doctoral degrees (PhD, Neuroscience) from Yale as an NIH MSTP Scholar. He moved to Harvard in 1994 where he completed a clinical fellowship in psychiatry at Massachusetts General Hospital and research fellowships in molecular neurobiology (with Rudolph Tanzi) and ocular biology (with Leo Chylack). He established his laboratory as an NIH-AFAR Beeson Scholar and Assistant Professor in Psychiatry at Harvard where he remained until his recruitment to Boston University in 2008. He discovered Alzheimer's disease (AD)-linked β-amyloid pathology in the lens of the eye (*Lancet*, 2003), the first evidence of the disease outside the brain. In subsequent studies, he and his team showed that AD-linked pathology in the lens precedes brain by many years, uncovered a new GWAS-significant AD risk gene (*CTNND2*, δ-catenin), and discovered identical AD-linked lens pathology in Down syndrome. Recently, he and his team uncovered mechanisms subserving blast-related neurotrauma ("shell shock") and links to chronic traumatic encephalopathy (CTE; *Science Transl Med,* 2012; *Nature*, 2015). His current research focuses on understanding the mechanisms that determine and distinguish concussion, TBI, and CTE. Dr. Goldstein is an inventor on numerous patents derived from his research, founding scientist of a laser diagnostics company (Neuroptix, now Cognoptix), and co-developer of the first FDA-approved ophthalmic drug-device combination product (for early detection of Alzheimer's disease). He has received awards from the NIH, American Federation for Aging Research, Alzheimer's Association, Optical Society of America, Harvard Medical School, and Oxford University.

Abstract: Traumatic brain injury (TBI) is a leading cause of death and long-term disability in the US and across the globe [**1**,**2**]. TBI is also the signature injury of the recent military conflicts in Iraq and Afghanistan [**3**,**4**]. Emerging research has raised concern about links between repetitive concussive and subconcussive head injuries (sustained during contact sport play, accidents, military blast exposure) and development of long-term cognitive impairment, persistent neuropsychiatric disability, and increased risk for later development of neuropathological sequelae, including chronic traumatic encephalopathy (CTE). CTE is a devastating and ultimately fatal tau protein-linked neurodegenerative disease reported in contact sport athletes with repetitive head injuries [**5**-**8**] and military veterans exposed to explosive blast [**9**,**10**]. The first part of the presentation will highlight neuropathological evidence of CTE in the first case series of postmortem brains from blast-exposed military veterans and comparison to brains from the youngest athletes with confirmed CTE studied to date [**8**,**10**]. The second part of the presentation will highlight experimental results obtained from new mouse models of blast and impact TBI developed at the Boston University Neurotrauma Laboratory. Neuropathological examination of brains from blast-exposed mice also exhibit evidence of CTE-linked neuropathology—including

phosphorylated tau proteinopathy, myelinated axonopathy, focal microvasculopathy, chronic neuroinflammation, and frank neurodegeneration--—that recapitulates core features of CTE in humans. The brains of blast-exposed mice demonstrate corresponding ultrastructural pathology, including profound changes in axonal, microvascular, blood-brain-barrier (BBB) structure. TBI-related structural changes are accompanied by persistent functional abnormalities, including impaired axonal conduction and defective synaptic plasticity in hippocampus and cortex that correlate with cognitive deficits in learning and memory tasks. Intracerebral pressure measurements and high-speed kinematic analysis showed that blast neurotrauma is not mediated by *blast wave* transit through the brain or thoracovascular mechanisms ("waterhammer effect") as previously thought. Rather, blast-induced brain injury is mediated by inertial forces associated with *blast wind* that results in traumatic acceleration of the head ("bobblehead effect") and injurious shearing forces in the brain. These forces damage fragile axons and blood vessels in the brain and induce secondary responses that trigger the distinctive pattern of neuropathology and functional deficits associated with CTE. His team has developed a mouse model of closed-head impact that produces acute concussive injury with lateralized neurological signs and CTE neuropathology that recapitulate core features of impact neurotrauma in humans. Kinematic analysis and biomechanical modeling have revealed predicted similarities and unexpected differences between blast and impact neurotrauma that inform clinical understanding of concussion, TBI, and CTE.

References: [**1**] Faul M, *et al.*, Centers for Disease Control, Atlanta, GA (2010). [**2**] Roozenbeek B, *et al., Nat Rev Neurol* 9, 231 (2013). [**3**] Hoge CW, *et al.*, *N Engl J Med* 358, 453 (2008). [**4**] Tanielian TL, Jaycox LH, *Invisible Wounds of War* RAND, Santa Monica, CA (2008). [**5**] Martland HS, *JAMA*, 91, 1103 (1928). [**6**] Critchley M, *Br Med J,* 1, 357 (1957). [**7**] Omalu B, *et al.*, *Neurosurg,* 57, 128 (2005); *Neurosurg,* 59, 1086 (2006). [**8**] McKee AC, *et al.*, *Brain* 136, 43 (2013); *Acta Neuropathol,* 131, 75 (2016). [**9**] Omalu B, *et al.*, *Neurosurg Focus,* 31, E3 (2011). [**10**] Goldstein LE, *et al.*, *Science Transl Med* **4**, 134ra60 (2012).

Continuing Medical Education (CME)

CME Needs Assessment: At the conclusion of this presentation, attendees will be better able to understand the clinical features and neuropathological hallmarks of acute and chronic effects of traumatic brain injury (TBI), including chronic traumatic encephalopathy (CTE).

CME Questions:

Q1. What is the evidence that traumatic brain injury (TBI) is a predisposing pathogenic contributor to later development of CTE?

Q2. What are the pathogenic mechanisms by which acute TBI trigger chronic neurological sequelae, including CTE?

Q3. Do acute and chronic effects of TBI differ based on the nature on the mechanism of the inciting neurotrauma?

CME Objectives:

1. Understand emerging evidence linking traumatic brain injury (TBI) to development of long-term neurological sequelae, including chronic traumatic encephalopathy (CTE).
2. Identify pathogenic mechanisms by which acute TBI triggers chronic neurological sequelae, including CTE
3. Understand and differentiate the following clinical entities: concussion, traumatic brain injury, chronic traumatic encephalopathy.