Traumatic brain injury biomarkers

April 2023—Pradip Datta, PhD, D(ABCC), senior staff technical team leader, Siemens Healthineers, Newark, Del., highlighted the list of traumatic brain injury biomarkers—what they are, what's available, what's promising.

- *S100B*—S100B, the oldest and most-published biomarker for TBI, is an acidic, cytoplasmic, calcium-binding glial (astrocytes) protein, Dr. Datta said. Its half-life is 97 minutes. In one trial of S100B for glial injury and blood-brain barrier damage, the authors found 80 to 100 percent sensitivity and 30 to 65 percent specificity (Rodríguez A, et al. Neuronal and glial biomarkers research for traumatic brain injury. In: Zhou Y, ed. *Traumatic Brain Injury—Neurobiology, Diagnosis and Treatment*. IntechOpen; 2019). Its alpha subunit is found in the heart, which explains its low specificity. S100B is not FDA approved as a TBI biomarker and is used mainly in Europe. "All the European TBI guidelines use S100B as one of the primary diagnostic measures," he said.
- *GFAP*—Glial fibrillary acidic protein is a cytoskeleton component and indicates blood-brain barrier damage and glial injury, Dr. Datta said. Its serum level is proportional to the amount of TBI, and it has a half-life between 16 and 144 hours. Basal concentration is <0.03 μg/L, and the cutoff concentration is 0.29 μg/L. In one trial, GFAP's sensitivity was 97 percent, and its specificity was 55 percent, "much better than S100B," he said (Thelin EP, et al. *Acta Neurochir [Wien]*. 2017;159[2]:209–225). In a study of sports-related concussion, athletes with concussion with loss of consciousness or post-traumatic amnesia had much higher levels of GFAP than athletes with concussion but no loss of consciousness or amnesia (McCrea M, et al. *JAMA Netw Open.* 2020;3[1]:e1919771). GFAP meets the "good marker criteria," Dr. Datta said.
- *UCH-L1*—Ubiquitin carboxy-terminal hydrolase-L1 is a ubiquitination enzyme with a small molecular weight and a 20-minute half-life, Dr. Datta said. At a cutoff concentration of 0.09 μg/L, UCH-L1's sensitivity and

negative predictive value are 100 percent, but its specificity is 21 percent.

GFAP and UCH-L1 in combination is called the brain trauma indicator, Dr. Datta said, and is the only FDA-approved biomarker for concussion, "to rule out CT." It is 98.6 percent sensitive, and the negative predictive value is 99.6 percent.

- *P-tau, T-tau*—The axonal structural tau proteins are phosphorylated tau and total tau. "When tau proteins are released from the cell, it has about 85 phosphorylation points," Dr. Datta said, and P-tau mainly forms when the cell is damaged. In a cohort study using TRACK-TBI data from three TBI groups, T-tau could distinguish patients with TBI from the controls (AUC = 0.919), and P-tau levels were much higher for TBI patients, both mild and moderate (Rubenstein R, et al. *JAMA Neurol.* 2017;74[9]:1063–1072). "This one is a good marker," Dr. Datta said.
- *NSE*—Neuron-specific enolase has five isozymes. "We'll measure only the gamma isoform" released with neuronal damage, Dr. Datta said. NSE has a half-life of two days, a high molecular weight, and a cutoff concentration of 18.9 μg/L. High serum NSE at 48 hours indicates a worse outcome (and high cell death probability) than for 24 hours, he said, "and in 72 hours it is very bad." Serum NSE remains elevated two months after injury.

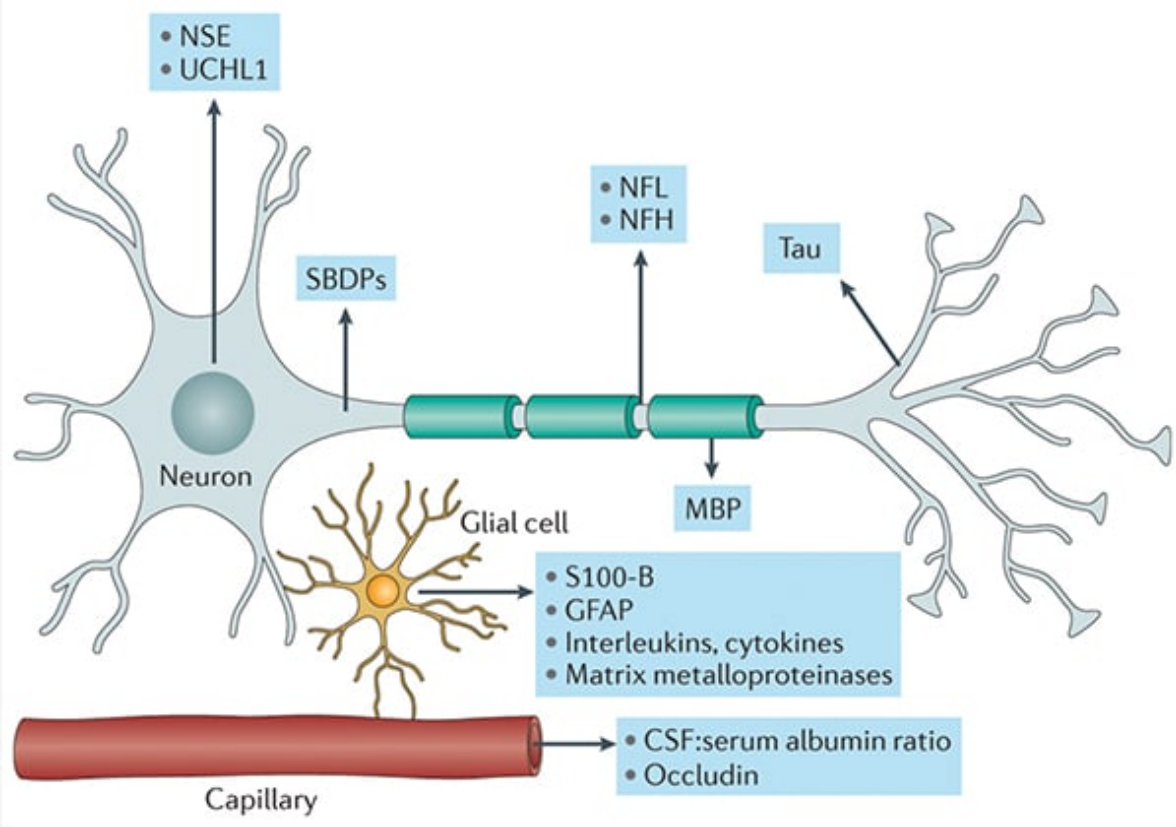
Dr. Datta

Dr. Datta spoke briefly of these four upcoming TBI markers:

- *MBP*—Myelin basic protein is a glial from the neuron's myelin sheath. Its molecular weight is 18.5 kDa, and it's quickly cleared, he said.
- *SBDP*—α-II spectrin breakdown products come from the neuron

cytoskeleton. SBDP has a molecular weight of 120 to 150 kDa and is a long-term marker, Dr. Datta said. “If there is a problem, SBDP will remain elevated for weeks and months.”

- *NF-L*—Neurofilament light has an axonal subskeleton component and a molecular weight of 68 kDa. It too is a longer-term marker—one study reported elevated serum NF-L concentration in patients with TBI five years after injury compared with controls, he said (Shahim P, et al. *Neurology.* 2020;95[6]:e623-e636).
- *Amyloid*-β—Amyloid-β is a long-term injury marker. It and NF-L have also been used as markers for dementia.



Henrik Zetterberg, et al. Fluid biomarkers for mild traumatic brain injury and related conditions. *Nature Reviews Neurology*, 2016 Oct;12(10):563–574, Springer Nature.

Point-of-care TBI assays can be useful in sports, the military, ambulances, or the emergency room, Dr. Datta noted. One study reported that GFAP, measured on a POC platform prototype assay, “has high discriminative ability to predict intracranial abnormalities on CT scan in patients with TBI across the full injury spectrum of GCS 3–15 through 24 hours post-injury,” and outperforms S100B (Okonkwo DO, et al. *J Neurotrauma.* 2020;37[23]:2460–2467).

—*Amy Carpenter Aquino*