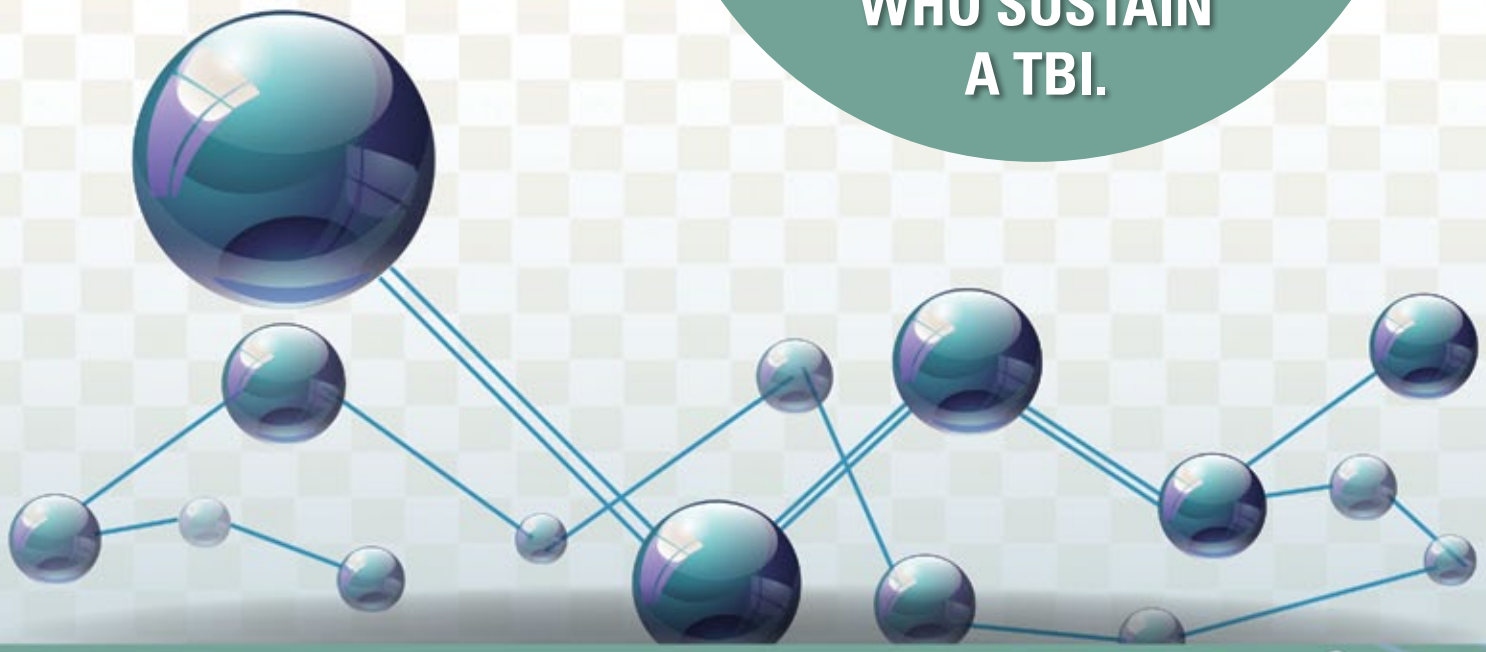
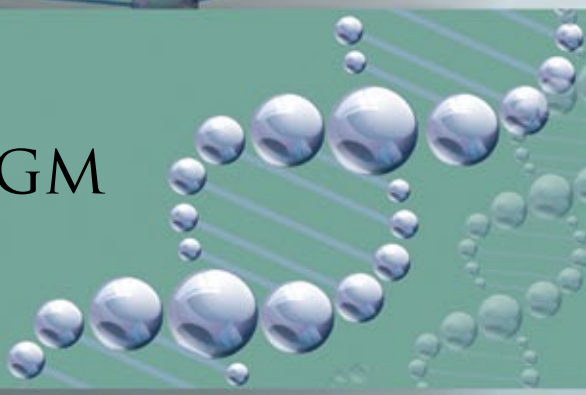
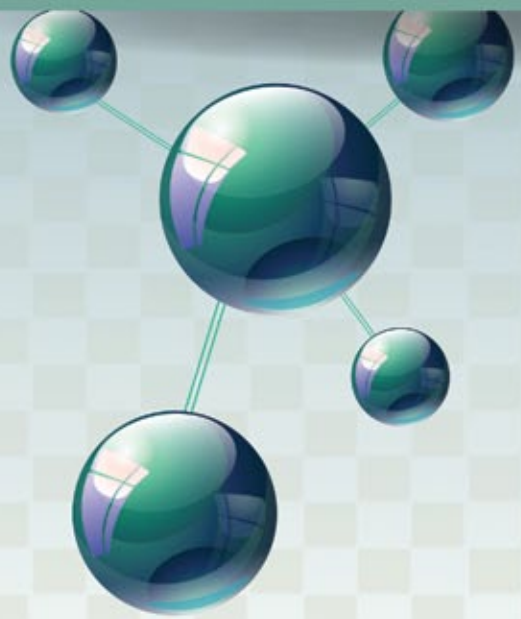
WE HOPE TO IMPROVE CARE FOR INDIVIDUALS WHO SUSTAIN A TBI.



INFLAMMATION:
A New Biological Paradigm for Understanding TBI as a Chronic Condition





By Amy K. Wagner, Shannon B. Juengst, Raj G. Kumar, Anne C. Ritter, Matthew L. Diamond, and Michelle D. Failla, University of Pittsburgh

WHILE INFLAMMATION IS NECESSARY FOR RECOVERY, TOO LITTLE OR TOO MUCH INFLAMMATION CAN BE HARMFUL

Every traumatic brain injury (TBI) is unique, so predicting immediate and long-term effects of an injury is difficult. We developed a bio-psychosocial Rehabilomics Model[1,2] to research how genetics and other biological markers explain this wide variation in the effects of TBI. One promising research area for our group is inflammation.

After a TBI, the body works to repair damage to the brain and fight infections that may be acquired while in the hospital. Much like inflammation needed to fight an infection, a well-controlled inflammatory response is vital to recovery after injury. The inflammatory response after TBI varies and can be affected by many things, such as previous illness or injury, severity of injury, or individual genetic differences. While inflammation is necessary for recovery, too little or too much inflammation can be harmful. By measuring different biological markers of inflammation, we may be able to predict risk for some adverse outcomes after injury.

To date, our published research in severe TBI suggests that those with either a very low or very high inflammatory response to stress, measured by biomarkers (cortisol) found in cerebrospinal fluid (CSF) that bathes the brain, are more likely to experience severe disability or die within six months after injury.[3] In another study, we measured different inflammation biomarkers (cytokines) in blood and found that they were elevated for up to a year after injury, well above the levels found in the blood of individuals without TBI. Importantly, individuals with TBI who had the highest inflammation biomarkers across the first three months after severe TBI were more likely to experience severe disability or die during the first year after TBI.[4]

In the absence of TBI, the body's immune system does not typically react to certain proteins that are found only in the brain. Working with Dr. Kevin Wang (University of Florida), we found that the body's immune system does react to these proteins in some individuals with TBI, resulting in an inflammatory response.[5] This is referred to as an autoimmune response, in which the body's immune system attacks the body's own molecules. We are investigating how this autoimmune response is affected by other inflammatory biomarkers,[6] by complications such as infections, and by previous injuries or illnesses. In the future we hope to learn how this autoimmune response affects risk for complications and poor long-term outcomes.

Of individuals with TBI of any severity, 15-20 percent go on to develop seizures in the brain, called post-traumatic epilepsy (PTE). To help clinicians identify those at risk, we are investigating how the likelihood of developing PTE changes based on differences in the inflammatory response early after injury and variation in the genes responsible for producing inflammatory biomarkers. To date, we have identified that a biomarker called interleukin-1β, measured through levels in CSF and blood levels early after injury and through genetic variation, contributes to increased risk for developing PTE.[7]

At some point after injury, more than half of individuals with a TBI will experience depression. In the general population, depression is associated with inflammation, but it is unclear whether inflammation that occurs after TBI contributes to the development of depression. Our recent research found that higher inflammatory protein levels in CSF early after injury were a risk factor for depression at six months after injury.[8] Related to depression, the rate of suicidal thoughts and behaviors after TBI is much higher than in the general population. Individuals who have a TBI often demonstrate disinhibition, or impulsive behavior, which may include reacting suddenly to emotions without first considering the consequences of a behavior. These individuals may be unable to suppress or cope with negative thoughts and emotions. Our work demonstrates a strong association between disinhibited behavior and suicidal thoughts. We also determined that levels of one particular inflammatory protein, TNF-α, in the blood and CSF predicted these behaviors and suicidal thoughts within the first year after injury.[9]

(continued on page 21)

INFLAMMATION: A NEW BIOLOGICAL PARADIGM FOR UNDERSTANDING TBI AS A CHRONIC CONDITION

(continued from page 11)

Through further investigation, we hope to improve care for individuals who sustain a TBI. If we can identify patterns of inflammatory genes and proteins that increase an individual's risk for poor outcomes, we will be able to generate tailored screening, prevention, and treatment protocols to improve recovery and enhance quality of life for those experiencing the life-changing effects of a TBI.

References

1. Wagner AK, Sowa G. Rehabilomics Research: A Model for Translational Rehabilitation and Comparative Effectiveness Rehabilitation Research. *Am J Phys Med Rehabil Assoc Acad Physiatr.* 2014. doi:10.1097/PHM.0000000000000114.
2. Wagner AK. A Rehabilomics framework for personalized and translational rehabilitation research and care for individuals with disabilities: Perspectives and considerations for spinal cord injury. *Spinal Cord Med.* 2014 Jul 16. [Epub ahead of print] PMID: 25029659
3. Santarsieri M, Kumar RG, Niyonkuru C, Kochanek PM, Wagner AK. Neuroendocrine-immune dysfunction in individuals with poor outcome after severe traumatic brain injury. *J Neurotrauma.* 2014;31(12):A-1-A-126.
4. Kumar RG, Boles, Jennifer A, Wagner, Amy K. Chronic inflammation after severe traumatic brain injury: Characterization and associations with outcome at 6- and 12-moths post-injury. *J Head Trauma Rehabil.* 2014 Jun 4. [Epub ahead of print]. PMID: 24901329
5. Zhang Z, Zoltewicz JS, Mondello S, et al. Human Traumatic Brain Injury Induces Autoantibody Response against Glial Fibrillary Acidic Protein and Its Breakdown Products. *PloS One.* 2014;9(3):e92698. doi:10.1371/journal.pone.0092698. PMID: 24667434
6. Ritter AC, Zhang Z, Wang KKW, Wagner AK. GFAP autoantibody developmental trajectory after TBI: characterization and associations with inflammatory markers. *J Neurotrauma.* 2014;31:A-40.
7. Diamond ML, Ritter AC, Failla MD, et al. IL-1β associations with posttraumatic epilepsy development: A genetics and biomarker cohort study. *Epilepsia.* 2014. doi:10.1111/epi.12628. PMID: 24754437
8. Juengst SB, Kumar RG, Failla MD, Goyal A, Wagner AK. Acute Inflammatory Biomarker Profiles Predict Depression Risk Following Moderate to Severe Traumatic Brain Injury. *J Head Trauma Rehabil.* 2014. 2014 Feb 28. [Epub ahead of print]PMID: 24590155.
9. Juengst SB, Kumar RG, Arenth PM, Wagner AK. Exploratory associations with Tumor Necrosis Factor-α, disinhibition and suicidal endorsement after traumatic brain injury. *Brain Behav Immun.* 2014. doi:10.1016/j.bbi.2014.05.020. PMID: 24928066.