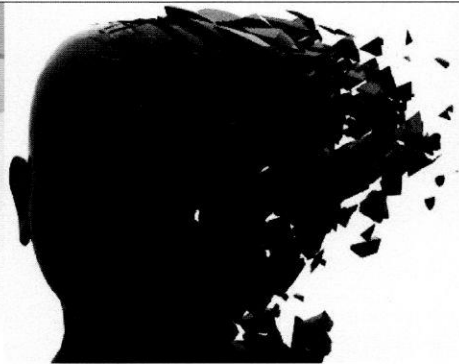




Serum Biomarkers of Concussion

Jeffrey J. Bazarian, MD, MPH

University of Rochester School of Medicine and Dentistry
Department of Emergency Medicine



MEDICINE of the HIGHEST ORDER

Disclosures

Banyan Biomarkers

- Research funding support

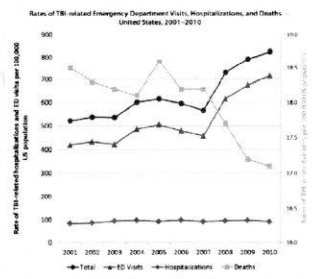
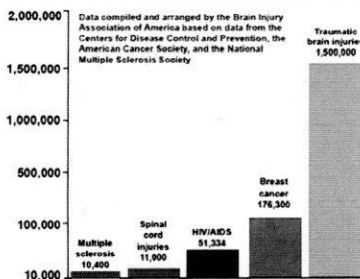
Patent

- Method for diagnosing mild TBI

CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

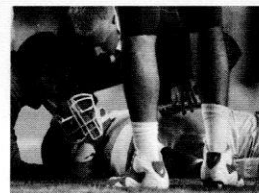
Concussion Incidence and Trends



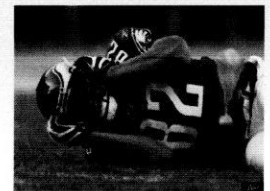
CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

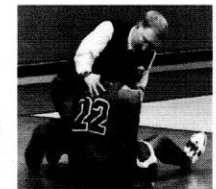
Concussion Diagnosis



Traditional
Brief LOC,
Amnesia,
Or
Confusion



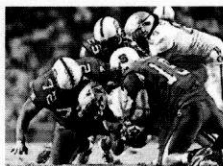
Sports
HA
Dizziness
Many Others



CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Problems with Concussion Diagnosis



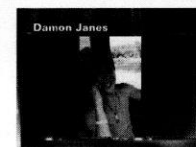
No Dx → No Rx
Current Rx: Rest
Poor outcome:
50% 3 months
25% 1 year

CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

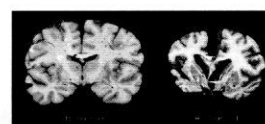
UNIVERSITY OF ROCHESTER MEDICAL CENTER

Why is it Important to Accurately Diagnose Concussion in Sports?

Second Impact Syndrome



Chronic Traumatic Encephalopathy



CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER



SPECIAL OFFER ENDS TONIGHT!
SAVE \$20
PLAY NOW

Play on the Ultimate Fantasy Football Platform. Last Chance to Save \$20! Act Today.



JON SOLOMON
National College Football Writer
39 Followers

NCAA settlement: Football players carry 3 times risk of CTE symptoms

July 30, 2014 5:39 pm ET

39 Tweets 49 8:1 9

More college football: Dennis Dodd | Jeremy Fowler | Jon Solomon | Latest news

How did the proposed NCAA concussion settlement come up with the \$70 million figure for a medical monitoring fund? The plaintiffs in the concussion lawsuit showed their math in an expert report that provides a rare look into estimated projections of long-term brain damage in contact sports.

Cellular Events

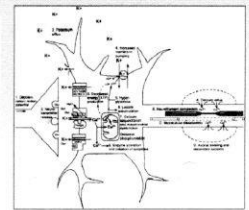
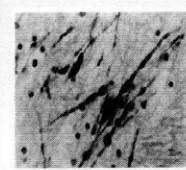
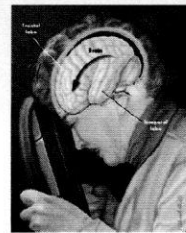
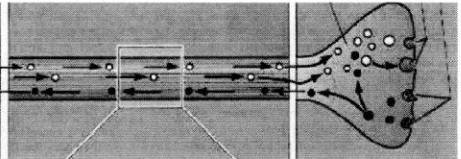
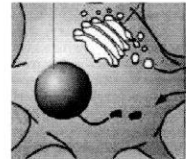
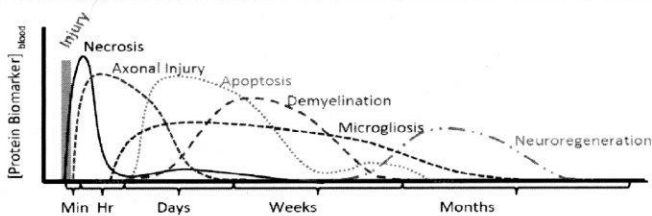


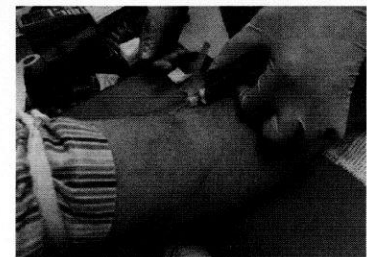
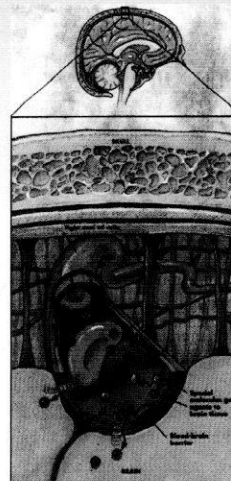
FIG. 1. APT immunopositive axonal (red) and astrocytic (green) staining among labeled axons (x400 magnification).



Cellular Events



Cellular Event Proteins Diffuse into Blood



Concussion Biomarkers Under Investigation

Biomarker	Cell Type/Matrix	Location	Function	In Vitro Experimental	Animal Clinical	Human Clinical
S100β	Glial, astrocytes, microglia	Cytoplasm, also secreted into extracellular space	Intermediate signaling, Ca ²⁺ binding, regulating PKC phosphorylation	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8}
NSE	Neurons	Neuronal cytoplasm	Cytoplasmic enzyme, regulation of intracellular chemical messengers	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
GFAP	Astroglia	Cytoplasmic	Structural filament	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
MBP	Oligodendrocytes	White matter, axon	Myelin sheath	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
Uchl-1	Neurons, neuroendocrine cells	Cytoplasmic, axon	Structural filament	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
β-actin	Neurons, neuroendocrine cells	Cytoplasmic, axon	Structural filament	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
Hsp70	Neurons, neuroendocrine cells	Nucleus, cytoplasm	Translocated upon cellular stress to protect cell	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
Secretogranin	Neurons, neuroendocrine cells	Nucleus, cytoplasm	Ca ²⁺ binding protein	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
IL-1β	Glial, immune cells	Serum, cell receptors	Released as part of inflammatory response	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
IL-6	Glial, immune cells	Serum, cell receptors	Released as part of inflammatory response	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
IL-8	Glial, immune cells	Serum, cell receptors	Released as part of inflammatory response	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
TNF-α	Activated macrophages	Serum, cell receptors	Involved in inflammatory response	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
MDA-MB-231	Neurons, neuroendocrine cells	Cytoplasmic	Ubiquitin proteasome	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
C-tau	Neurons, low level in astrocytes and oligodendrocytes	Microtubules	Axonal cytoskeleton, microtubule for intracellular transport	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
Alpha-1 Spectrin	Neurons, axon	Cytoplasmic	Structural component of neuronal plasma membrane	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
SNAP-25	Neurons, axon	Serum	Released by rupture of synaptic vesicles	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
Ceruloplasmin	Ubiquitous	Serum	Copper carrier protein involved in copper and iron metabolism	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
WVF	Many endothelial cells, other cell types	Serum, cell receptors	Cyclogenesis involved in hemostasis	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
MBP	Microglia	Serum, cell receptors	Myelin sheath	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
Claudin-5	Many endothelial cells	Cell membrane	Involved in forming tight junctions	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
AQP4	Many astrocytes	Cell membrane	Water channel	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}
MBP-10	Ubiquitous	Nucleus, cytoplasm	Involved in breaking down the extracellular matrix	Yes ^{1,2,3,4}	Yes ^{5,6}	Yes ^{7,8,9,10}

Agoston. Frontiers Neurology. 2012;3:1-10

Concussion Biomarkers Under Investigation

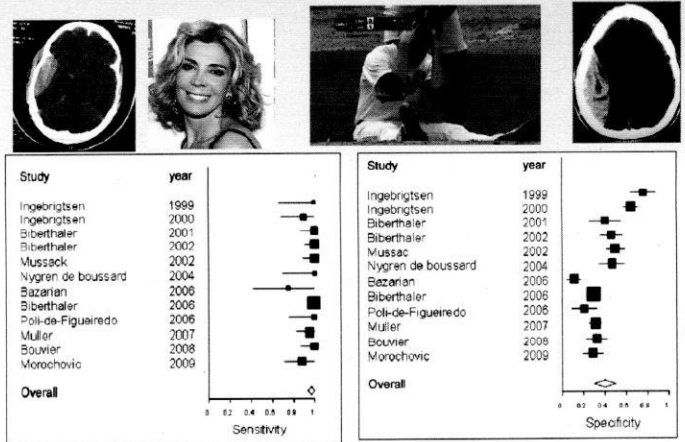
Events	Mechanism	Candidate Serum Biomarkers
Neuronal and Glial Cell Death	Activation of factors triggering necrosis and/or apoptosis	Mild TBI: Neuron: NSE, C-tau, SBP, Aβ, Spectrin
		Moderate TBI: Neuron: NSE, pNF-H, NF-H, NMDAR, Hsp70, UCH-L1, C-tau, Aβ, Spectrin, SBP, Secretogranin
Vasospasm	Dysregulation of vascular constriction and relaxation	Mild TBI: Glial: S100β, GFAP, MBP, C-tau
		Moderate TBI: Glial: S100β, GFAP, MBP, NMDAR, Hsp70, IL-1β, IL-6, IL-8, TNF-α, C-tau, AQP4
Edema	Vasogenic and cytotoxic events caused by toxic and inflammatory factors	Mild TBI: Hsp70, TNF-α, VEGF, Claudin-5, WVF
		Moderate TBI: Hsp70, IL-1β, IL-6, IL-8, VEGF, Claudin-5, WVF, AQP4, MBP
Axonal Injury	Mechanical injury, Neuronal degeneration	Mild TBI: S100β, NSE, C-tau, MBP, SBP, Aβ, Spectrin
		Moderate TBI: S100β, MBP, NSE, pNF-H, NMDAR, Hsp70, C-tau, Aβ, Spectrin, SBP
Metabolic Changes	Hypoxia; altered energy demand, ion homeostasis and neurotransmission; increased repair processes	Mild TBI: Ceruloplasmin, HIF-1α
		Moderate TBI: Ceruloplasmin, HIF-1α

Agoston. Frontiers Neurology. 2012;3:1-10

Concussion Biomarkers Under Investigation

Marker	Assay Dev	Animals	Mod-sev TBI	Mild TBI	Head CT	Clinical Use
S100B						
UCHL-1						
GFAP						
pNFH						
aII-spectrin						
Tau						
NSE					XX	
CKBB					XX	
MBP					XX	
Amyloid		XX				
APP		XX				

S100B Predicts Hemorrhage on Head CT



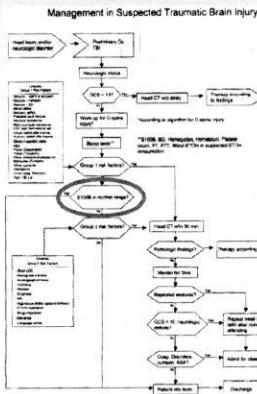
CLINICAL*TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

CLINICAL*TRANSLATIONAL SCIENCE INSTITUTE

Unden, JHTR 2010;25(4):228-240

S100B is Used in Hospitals World-wide



- Austria
- Brazil
- China
- Czech Republic
- Denmark
- Estonia
- France
- Germany
- Norway
- Romania
- Russia
- South Africa
- South Korea
- Spain
- Sweden
- Switzerland
- UK

NOT USA

CLINICAL*TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting

From the American College of Emergency Physicians (ACEP)/Centers for Disease Control and Prevention (CDC) Panel to Review the 2002 Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting.

Andy S. Jagoda, MD, Chair
Jeffrey J. Bazarian, MD, MPH
John J. Bono, Jr, MD
Stephen F. Cantrell, MD
Alex D. Cooke, MD
Patricia K. Howard, PhD, RN, CEN, EMT Representative
Natalie Schatz, MD, PhD
Shirley Rogers, MD
David W. Wright, MD
Robert L. Weaver, MD, MEd, Workforce Manager
Ari Berkus, MD
Paula Rogers, MD, MPH, Division of Injury Response, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention
Matthew H. Weist, MD, MPH, Epidemiologist, Division of Injury Response, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention
Shonda E. Whitson, MBA, Clinical Practice Manager, ACEP

Approved by the ACEP Board of Directors, August 13, 2008

Unden et al. BMC Medicine 2010, 8:100
http://www.biomedcentral.com/1745-6215/8/100

BMJ Medical

GUIDELINE Open Access

Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update

Jonas Unden^{1*}, Tor Ingebrigtsen² and Bertil Rosner³ for the Scandinavian Neurotrauma Committee (SNC)

CLINICAL*TRANSLATIONAL SCIENCE INSTITUTE

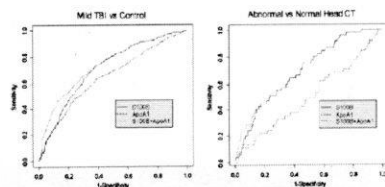
UNIVERSITY OF ROCHESTER MEDICAL CENTER

S100B to Diagnose Concussion

JOURNAL OF NEUROTRAUMA 30:1747-1754 (October 15, 2013)
© Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2013.2853

Classification Accuracy of Serum Apo A-I and S100B for the Diagnosis of Mild Traumatic Brain Injury and Prediction of Abnormal Initial Head Computed Tomography Scan

Jeffrey J. Bazarian¹, Brian J. Blyth¹, Hua He², Sohag Mookerjee³, Courtney Jones¹, Karin Kiechle⁴, Ryan Moynihan⁵, Susan M. Wojcik⁶, William D. Grant⁶, Lalaina M. Secreti⁶, Wayne Trner⁷, Ronald Moscati⁸, August Leinhardt⁹, George L. Ellis¹⁰ and Jawwad Khan¹



S100B to Diagnose Concussion

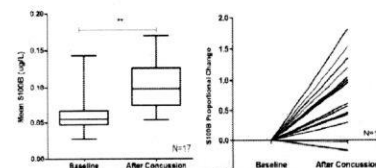
OPEN ACCESS Freely available online

PLOS ONE

Subject-Specific Increases in Serum S-100B Distinguish Sports-Related Concussion from Sports-Related Exertion

Karin Kiechle¹, Jeffrey J. Bazarian^{2*}, Kian Merchant-Borna², Veit Stoecklein³, Eric Rozen⁴, Brian Blyth⁵, Jason H. Huang⁶, Samantha Dayawansa⁶, Karl Kanzi⁷, Peter Biberthaler⁸

¹ Department of Trauma Surgery, Klinikum der Universität München, Ludwig-Maximilians-Universität, München, Germany, ² Department of Emergency Medicine, University of Rochester Medical Center, Rochester, New York, United States of America, ³ Department of Neurosurgery, Klinikum der Universität München, Ludwig-Maximilians-Universität, München, Germany, ⁴ Department of Athletics and Recreation, University of Rochester, Rochester, New York, United States of America, ⁵ Department of Neurosurgery, University of Rochester Medical Center, Rochester, New York, United States of America, ⁶ Department of Trauma Surgery, Technical University of Munich, München, Germany



CLINICAL*TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

CLINICAL*TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Total Tau

Research

Original Investigation

Blood Biomarkers for Brain Injury in Concussed Professional Ice Hockey Players

Pashtun Shahin, MD, Yehverson Tegner, MD, PhD, David H. Wilson, PhD, Jeffrey Randall, PhD, Tobias Skidback, MD, David Pazooki, MD, PhD, Birgitta Kallberg, BSc, Kaj Blennow, MD, PhD, Henrik Zetterberg, MD, PhD



Introducing the world's most sensitive, fully automated immunoassay platform with multiplexing and custom assay capability.

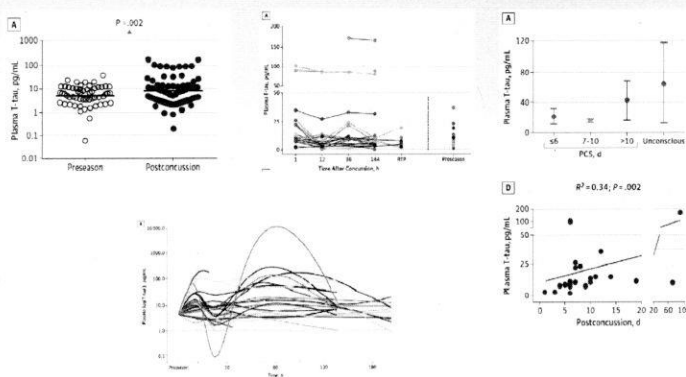
JAMA Neurol. doi:10.1001/jamaneurol.2014.367
Published online March 13, 2014.

<http://www.quantix.com/products/simoa-hd-1-analyzer>

CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Total Tau



CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Blood Test Pros and Cons

Pros

- Objective
- Potentially portable, cheap
- Patient cooperation not required

Cons

- May require BBB to be breached
 - 70% in moderate-severe TBI
 - ? % in concussion (mild TBI)
- Most are useful only acutely (<6hrs) after injury
- Requires Point of Care Test device

CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Point of Care Test Devices



CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Summary and Next Steps

Several serum proteins can help with initial diagnosis and need for head CT

- S100B
- Total Tau
- Others

These proteins must be measured within hours of injury to be useful

Correlation with objective marker of neuronal injury such as DTI?

Biomarkers that stay elevated longer and correlate with recovery

- Inflammatory markers?

Both types of markers needed to ID patients appropriate for testing putative therapeutics

CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER

Acknowledgements

Dr. Jeff Bazzarian's TBI Research Team

- Kian Merchant-Borna, MPH
- UR Trainer, Eric Rozen
- RIT Trainer, Ben Emke
- Nikita Bourque
- Kirsten Ross
- Elizabeth Saionz
- Kelley Bellinger

Research funded in part by
K24 HD 064754037

CLINICAL TRANSLATIONAL SCIENCE INSTITUTE

UNIVERSITY OF ROCHESTER MEDICAL CENTER