Technology Licensing Opportunity

BIOMARKER FOR TRAUMATIC BRAIN INJURY

Soluble cellular prion protein (PrP\textsubscript{C}) is a blood-based biomarker for traumatic brain injury (TBI). Researchers at the University of Saskatchewan identified PrP\textsubscript{C} as a blood-based biomarker corresponding to TBI severity (mild concussion to severe TBI) in sophisticated models provided by the Canadian National Department of Defense. Additional clinical studies confirmed the potential of PrP\textsubscript{C} as a TBI biomarker (UofS Husky athletics, Banyan Biomarkers). PrP\textsubscript{C} in blood plasma is measured through an ELISA test developed by the UofS researchers. Clinical validation of this TBI biomarker is ongoing through a collaboration with the Centre for Drug Research and Development in Vancouver, Canada.

**TBI – Need for a new test:** Traumatic brain injury (TBI) is a major burden to public health and the leading cause of mortality and neurological disabilities in individuals under the age of 45, and is estimated to occur in 600/100,000 people. In Canada, between 2009 and 2010, 99,000 individuals needed medical attention for concussion or other brain injuries. Moreover, the Economic Burden of Injury in Canada was estimated at $19.8 billion annually, including $10.7 billion for direct health costs and $9.1 billion associated with reduced productivity related to hospitalization, disability and premature deaths. A vast majority of TBI patients suffer mild, non-penetrating closed head injuries, which often go untreated due to the subjective nature of the diagnostic process. A meaningful, non-biased, and easy to use diagnostic tool is therefore urgently needed not only for mild TBI, but also to guide treatment strategies in moderate and severe TBI where current methods have weak prognostic power.

**PrP\textsubscript{C} – A novel TBI biomarker:** Significant changes in the concentration of certain proteins in biological fluids following TBI can be used as biomarkers for diagnosis and prognosis and to guide therapy, however there is a lack of clinically validated markers currently available. Although various proteins have been investigated (S100B, C-tau, GFAP) they remain inconclusive for having clinically practical screening qualities. As such, investigation towards establishing both a highly predictive and reliable protein biomarker continues.

In addressing this issue, Dr. Taghibiglou hypothesized that a significant external force to the head could potentially release cell surface localized cellular prion protein (PrP\textsubscript{C}) to the extracellular compartment and eventually pool within the circulation (Fig.1), serving as a biomarker for TBI. Various physiological functions are attributed to PrP\textsubscript{C} in the central nervous system including cellular adhesion, cell signaling, ion homeostasis and neuroprotection. Because of PrP\textsubscript{C}'s extracellular orientation, a concussive event may cause the release of PrP\textsubscript{C} to the extracellular compartment and eventually to the systemic circulation. In support of this, free PrP\textsubscript{C} has been shown to cross the blood brain barrier in a bidirectional manner in mice and after stroke in humans, there is an increase in the plasma concentration of free PrP\textsubscript{C}.

**Pre-clinical Results:** A Defence Research and Development Canada, custom-built Advanced Blast Simulator (ABS) was used for producing exquisitely precise and focused simulated blast waves that result in TBI in a rodent model. Quantitative differences between blast and control group PrP\textsubscript{C} concentration are demonstrated with Western blotting (Fig. 2) ROC analysis was performed for determining accuracy of our ELISA test based on the predictability of control and blast group classifiers (see Fig. 3). ROC analysis allows comparison of PrP\textsubscript{C} sensitivity against the inverse specificity over a range of thresholds for evaluating overall test accuracy. The AUC was determined at 0.944 – 0.032 SE (95% CI, 0.881–1.000, p < 0.0001) indicating ELISA test results to be highly accurate for distinguishing between control and blast groups.

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**Patents:**

US Provisional,  
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**Publications:**

PLOS One, Feb 2, 2015  
J. Neurotrauma, Jan 1, 2015  
Biochem Biophys Res, May 30, 2014

**Future work:**

Validation study with CDRD  
Pediatric study with Boston Children’s Hospital

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Clinical Results: To investigate the possibility that plasma levels of PrPc rise following sport-related concussions (i.e. mTBI; 27) in UofS athletes, soluble PrPc levels were first measured in the general population (18+ years of age) without significant confounds due to illness, health conditions, or concussion within the past six months. No significant difference in mean plasma PrPc levels were observed across gender or age. Blood was also collected from six athletes who sustained concussion as assessed using the SCAT3 criteria by team doctors and physical therapists. Comparison of mean plasma PrPc in post-concussion samples (2.96 ng/mL ± 0.37, n=6) was found to be significantly higher than levels in baseline samples collected in the off season (1.59 ng/mL ± 0.07, n=76) and against combined baselines with the normal population (1.70 ng/mL ± 0.07, n=103) (Fig. 4A).

Of the 76 baseline samples collected from athlete participants during the off season, only three individuals sustained a concussion during the pre- and post-TBI comparison. Average post-TBI PrPc values were higher than those seen in controls; however statistical analysis was hampered by the small sample size (Fig. 4B). In addition to these data, Dr. Taghibiglou’s laboratory has collaborated with Banyan Biomarkers, who have provided access to blood samples collected within hours of injury from adults who have suffered TBI. Results from these experiments revealed similar increases in plasma PrPc levels in adults who had suffered TBI compared to controls, providing further support for PrPc as a biomarker for TBI.

Fig. 1

Figure 1. An external force to the head could dislodge loosely attached, almost entirely extracellularly oriented, PrPc to the extracellular compartment which eventually goes into circulation.

Fig 2.

Figure 2. Western blot of soluble cellular prion protein (PrPC) (A) Results are semiquantitative, and are for the purpose of simple visualization of increased PrPC in blast group plasma compared with control. (B) Numerical (fold) change bar graph represents a mean fold increase of 1.60 – 0.41 compared with control values, given an arbitrary value of 1.0 (n = 4, two tailed test p < 0.05).

Fig. 3

Figure 3. Receiver operating characteristic (ROC) analysis of plasma soluble cellular prion protein (PrPC) for test of blast exposure. Control (n = 19) versus blast (n = 33) area under the curve (AUC) is 0.944 – 0.032 S.E. (95% CI, 0.881–1.000, p < 0.0001).

Fig. 4

Figure 4. Comparison between Normal and Post-Concussion. A) Two-tailed unpaired student’s t-test shows post-TBI PrPc concentrations (n = 6; 2.96 ng/mL ± 0.37 SEM) are significantly elevated compared with either off season athlete baseline concentration (n = 76; 1.59 ng/mL ± 0.07 SEM)(p<0.0001), or both athletes and non-athletes combined (n = 103; 1.70 ng/mL ± 0.07 SEM)(p<0.0001). B) Two-tailed paired t-test shows there was no significant difference between three sets of pre- and post-TBI PrPc values (p=0.1666).