Testimony

of

Kevin Kit Parker

Thomas D. Cabot Associate Professor of Applied Sciences

Associate Professor of Biomedical Engineering

Harvard University

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Mr. Chairman, Ranking Member Kucinich, and distinguished Members of the Committee, thank you for inviting me to testify here today. I am the Thomas D. Cabot Associate Professor of Applied Sciences, Associate Professor of Biomedical Engineering at the School of Engineering and Applied Sciences at Harvard University, with core appointments in the Wyss Institute for Biologically Inspired Engineering, the Harvard Stem Cell Institute in Cambridge, Massachusetts. In addition to these responsibilities, I am a Major in the Rhode Island Army National Guard and have completed two combat tours in Afghanistan with the 82nd Airborne and 10th Mountain Divisions.

I have degrees in engineering and physics and additional postdoctoral training in biomedical engineering and pathology. My research at Harvard has been focused on understanding how cells in the heart build themselves and tissues and how the violation of their structure-function relationships results in heart disease. However, since my first tour in Afghanistan in 2002-03, the threat of improvised explosive devices (IEDs) on the battlefield has consumed an increasing amount of my efforts in my laboratory and in my external work as an consultant to various agencies associated with the DoD concerning themselves with the IED problem . At Harvard now, one third of my ~20 member research team is focused on some aspect of blast-induced traumatic brain injury, known most commonly as TBI.

By virtue of my experience on the battlefield and in the laboratory, I want to tell you the TBI story as I see it, a battlefield to bench perspective. We can start on March 22 2009 in the Tangi Valley of Afghanistan where I was patrolling with a Route Clearance Platoon 13, a group of combat engineers, explosive ordinance experts, IED experts, and myself representing the Center for Army Lessons Learned at Ft Leavenworth, KS. Our first firefight that day had occurred at about 8 AM in the eastern end of the valley in Logar Province and as we approached the western end in Wardak Province, we were subjected to a complex ambush where our lead vehicle was flipped by an IED of approximately 500 lbs of homemade explosives (Fig. 1). When myself and a squad leader, that I will refer to as *Joe* for reasons to be discussed later, dismounted our vehicle to move forward to check for casualties, we received fire in the form of rocket-propelled grenades and small arms from multiple directions. With the road blocked by our overturned vehicle, casualties in the first vehicle, we were pinned against a cliff wall taking fire from

our 9 o'clock position in the valley floor. Eventually the enemy would attempt to flank us at the front and rear of the convoys. Joe ran back and forth along the one lane valley road, under fire, to coordinate the movement of casualties from our forward, disabled vehicle to vehicles he guided forward during the firefight. The four casualties included one soldier with broken vertebrae, another with facial and extremity injuries, and all four suffering TBI to varying degrees. After artillery fire missions and rotary wing close air support, we gained control of the situation and evacuated our casualties and after staying the night in the position, the next day recovered our vehicle and moved out of the Tangi.

Fig. 1. March 22, 2009, ~1700 hrs local time, Tangi Valley Afghanistan. Lead vehicle in RCP 13 route clearance convoy is hit with a 500 lb IED of homemade explosive. Dismounted soldiers in the photograph are recovering casualties from the vehicle. Approximately 2 minutes after this photograph was taken, an RPG hit the cliff wall above the cab of the overturned vehicle, initiating a firefight.

So four soldiers with TBI that have to be treated and should be monitored for life. But I am also worried about Joe and the others like him. In this case, Joe is an old school noncommissioned officer, a seasoned veteran of multiple tours in Iraq before he came to Afghanistan. All on route clearance teams, including the tour in Afghanistan he has been blown up nearly a dozen times at this point, sometimes in a vehicle, sometimes on dismounted patrols. He complains of headaches, trouble sleeping, and other symptoms commonly associated TBI. However, he considers himself still mission capable. Awarded a Bronze Star with V-device that day in Afghanistan, he is somewhere, right now, working some part of this war.

What is TBI?

Traumatic brain injury is brain trauma and can range from a concussion to a penetrating head wound. The scales of the injury can be intimidating. Figure 2 illustrates the spatial scales of the brain, from the nanometer-size proteins, integrins, that traverse the lipid membrane of neurons, brain cells, connecting the extracellular matrix proteins to the intracellular architecture of the neuron, up to the micron scale of the synapse, the chemical information junction between two communicating neurons, to the millimeter and centimeter length scales of the neural networks that allow us to calculate our change at the cash register, recognize a friend, speak, see, and smell. Considering the whole Central Nervous System to include the

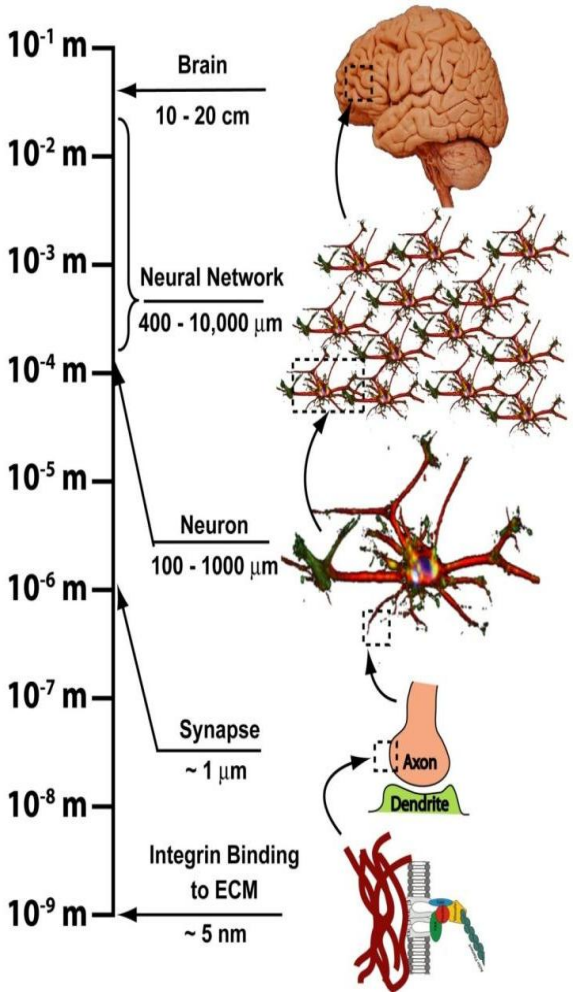

Fig. 2. Spatial scales of interest in the TBI problem, from the integrin proteins that mechanically stabilize neurons to the brain.

brain and spinal cord, we are talking about a spatial scaling problem of nine orders of magnitude.

But it is the temporal scaling problem that most clearly illustrates the TBI problem. In Fig. 3, I want to draw your attention to the right side of the timeline, what we call “right of boom”. What I have tried to do in this figure is capture the range of physiological changes that are occurring as the blast wave propagates into the skull and then over the lifespan of the patient.

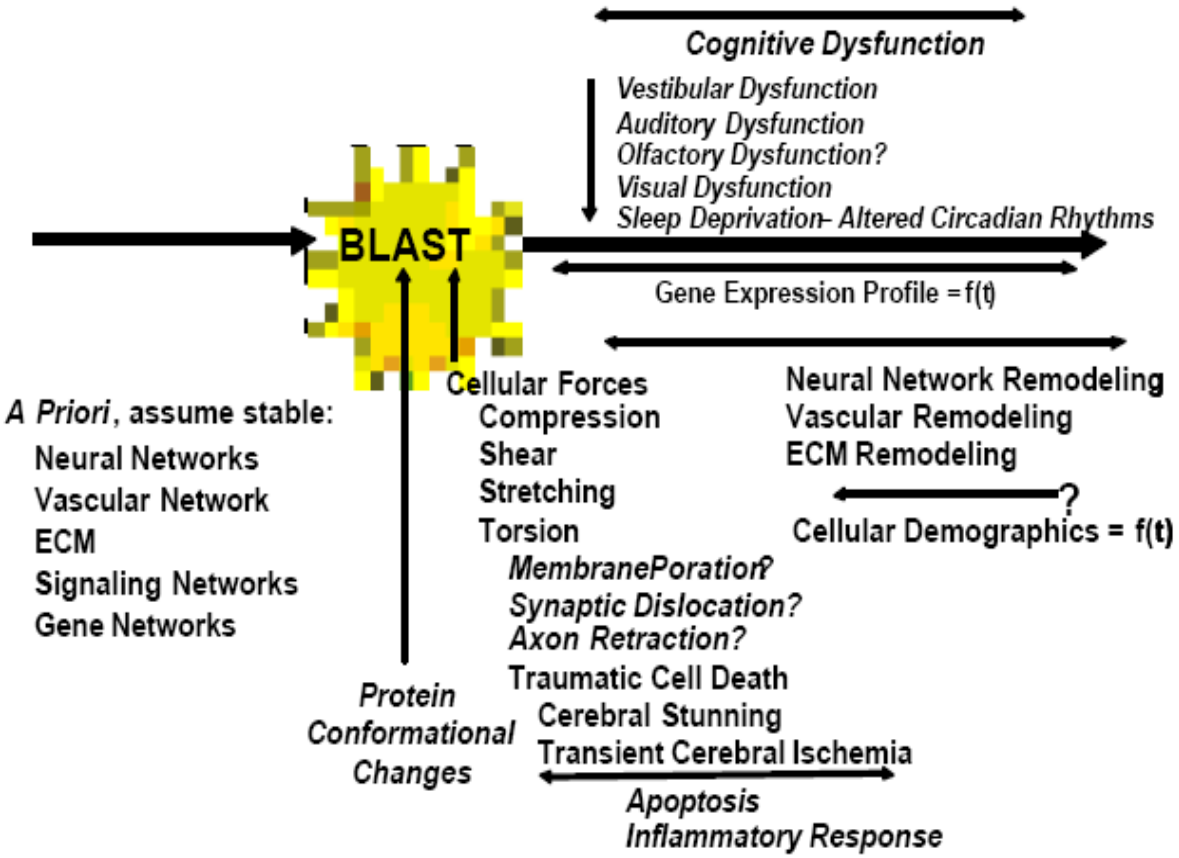

Fig. 3. Timeline of blast-induced traumatic brain injury covering nanometer to meter length scales of the blast wave coupling into neurons, to the behavioral issues these patients suffer, this schematic is the sequelae of a laundry list of neurodegenerative diseases that may develop from TBI, including Alzheimer, Parkinson’s, and Lou Gherig’s disease.

The events depicted are not exclusive to blast-induced TBI (bTBI), they represent all brain trauma. It is important to note that diseases such as Alzheimer’s, Parkinson’s, dementia pugilistica, and the most recent report out of the Veteran’s

Administration that suggested that amyotrophic lateral sclerosis, commonly known as Lou Gehrig's disease, may be linked to brain trauma are all consequences of what you see on the timeline to the right of boom. So it is important to consider TBI as an ignition event for the pathological cascades that lead to the diseases that we might not recognize until we are far to the right of boom. And to date, most of our research, is probably to the far right of boom for TBI and the neurodegenerative diseases that result from it.

So what are we going to do about Joe? What are we doing for Joe?

I am not a TBI or brain expert, but a few years ago, after assessing the problem and the scientific literature, I thought I identified an angle on the problem that was within my research team's expertise. Initially, the effort was funded by Harvard's endowment and myself. Without preliminary data, with no publication track record in the field, and little concerted effort to fund TBI research, traditional funding avenues bore little likelihood of success, where my knowledge of IEDs from Afghanistan and my civilian advisory work may not compute in a typical biomedical grant review process. I was, however, able to get funding from the Defense Advanced Research Projects Agency, DARPA, thru a program called PREVENT, PREventing Violent Explosive Neurologic Trauma headed by an Army neurointensivist, COL Geoffrey Ling, PhD, MD. I would imagine that at DARPA, my downrange experience could be computed along with my scientific expertise in what might be the most complex, interdisciplinary problem to face medical science in its history.

The problem is complex because across the temporal scale of events, it can require a knowledge of explosives, shock physics, cell and tissue mechanics, molecular biology, neurobiology, psychology, and neurodegenerative diseases. I am not an expert in any of these fields, but I know a few words from each and that might be about as good as it gets.

Barriers to Traumatic Brain Injury Research

As an outsider to neuroscience and the TBI problem, I see several barriers to launching a full spectrum attack on the problem of TBI:

A. A lack of awareness within the scientific community. *Recommendation: Funded efforts to evangelize the neuroscience and cell engineering fields about TBI, such as funding one week courses on TBI science at the Marine Biological Laboratory at Woods Hole MA, or at Cold Spring Harbor Laboratory in New York*

B. As I mentioned, a lack of scientific talent trained broadly across a range of fields that have probably never been well represented in the same room unless DARPA is hosting. *Recommendation: DoD predoctoral and postdoctoral fellowship program specifically for students and trainees working in the TBI field, or entering the field*

C. Lack of funding mechanisms for long, sustained, interdisciplinary efforts. We speak of counter-insurgencies like what we have faced in Iraq and Afghanistan as the *Long War*. For those soldiers suffering TBI, their war is going to be a lot longer than the Long War, the *Longer War* if you will. *Recommendation: See later discussion of a full spectrum, interagency effort*

D. Lack of *in vitro* experimental models for basic research and drug discovery. *Recommendation: Specific funding programs to develop technology for bench top research and high thru put screening assays of potential TBI therapeutic opportunities*

E. A hesitancy to do the kinds of unpleasant animal experiments that are going to have to be conducted to understand the disease, identify therapeutic opportunities, and then test them prior to treating patients. *Recommendation: Get the government laboratories to host core facilities to support animal experiments conducted by university or industrial researchers. Actively seek and prosecute animal rights groups that intimidate researchers in this field.*

F. A lack of interagency cooperation and leadership. *Recommendation: An interagency task force composed of representatives from DoD, VA, HHS,*

and Energy, reporting directly to the Vice President, or bipartisan leadership team, on synchronized efforts across the spatiotemporal scales of the problem.

The Longer War: Caring for the Chronically Wounded Warfighter with TBI

In the Golden Hour, the first hour after a soldier has become wounded, we know that immediate medical care can increase his or her odds of survival significantly. What we don't know if what kind of Golden Hour intervention may prevent a neurodegenerative disease. *A goal of our research should be to identify a therapeutic opportunity where we can initiate a prophylactic course of treatment at the time of injury to prevent a neurodegenerative disease 10, 20, or 30 years down the road*. This challenge will focus the scientific effort on identifying the precise mechanisms of injury, the signaling cascades that might be vulnerable to therapeutic exploitation, and candidate molecules.

The Golden Hour is the first chapter in the *Longer War* of caring for these casualties. With each diagnosis of a neurodegenerative disease amongst a TBI soldier in the decades to come, our nation's enemies win again. We need to exploit the ability of the DoD and the VA to maintain detailed personnel and medical records to start a study similar to the Framingham Heart Study to monitor soldiers, both brain injured and not, over the course of their lifespans. Like the Framingham Heart Study run by Boston University in the town of Framingham, MA, we can register data gathered prior to injury with post-injury data to do detailed, longitudinal studies of how TBI evolves into neurodegenerative diseases like Alzheimer's and Parkinson's, understand who is most vulnerable, and determine what courses of treatment work. *A goal of our research should be to identify the relationships between TBI and long term outcomes after diagnosis of Alzheimers, Parkinson's, and other neurodegenerative diseases.* There is no substitute for these kind of studies as far as the scientific community is concerned. Scientists need this data to effectively, and efficiently, evolve therapeutic options.

Who Should Lead the Longer War?

TBI is not a soldier problem and for many in the field, the perception is that NIH considers it DoD's turf. This perception is best corrected by mandated collaboration between DoD, the VA, and HHS on this problem. This will have to be an interagency effort building on NIH's success with vetting competing hypotheses against each other. A good example of the NIH's success is the 'Big Tent' strategy taken by the NCI on the war on cancer. This success must be replicated.

It is important that the epidemiological data available from the DoD and VA be made broadly available to the civilian scientific community in a form that is amenable to statistical analysis, protects national security interests, and used to guide scientific inquiry. It is important to mass as much scientific talent on this problem as possible, and to do it as soon as possible. Interagency tribalism will inhibit progress, as will competition amongst patient advocacy groups that perceive NIH budgets as a zero sum game. Agencies with special talents for running complex, multidisciplinary efforts should be encouraged to take an active role in coordinating this effort. Finally, the leadership of such an effort should be unfettered by political or departmental affiliation.

CONCLUSION

In closing, thank you again for the opportunity to testify here today about my perspectives on the TBI problem. I, speaking for the community of scientists working on TBI, will continue to pursue an understanding of this disease and its role in the genesis of other neurodegenerative diseases more commonly known to this committee. As a soldier and as an officer responsible for the well being of my troops, the weight of responsibility I personally feel in regards to this problem cannot be overstated. What I, and others, need to accomplish this mission, to win this part of the war, is a concerted effort on the part of the USG to choreograph assets and efforts across the various stakeholder agencies for an effort that will lead to the successes seen in the War on Cancer, declared in the 1970s. A Big Tent

strategy, where all who have a piece of this fight are welcome, is the best means of accomplishing this end.

Bibliography

Ling G, Bandak F, Armonda R, Grant G, Ecklund J. Explosive blast neurotrauma. J Neurotrauma. 2009 Jun;26(6):815-25.

National Institute of Neurological Disorders and Stroke. NINDS Traumatic Brain Injury Information Page. http://www.ninds.nih.gov/disorders/tbi/tbi.htm, accessed 27 Sept 2010.

Dekosky, S.T., Ikonomovic M.D., Gandy, S. Traumatic Brain Injury – Football, Warfare, and Long-Term Effects. New England Journal of Medicine 2010 E-pub 22 September.

Johnson V.E., Stewart W., and Smith D.H. Traumatic brain injury and amyloid-B pathology: a link to Alzheimer's disease? Nature Reviews Neuroscience 2010 11:361-370.