

Today and Tomorrow's Children Fund Semi-annual Update

Activating the Injured Brain: Restoring Plasticity after Developmental Brain Injury

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Summary:

The last six months have been very productive and we have made substantial progress in many areas. Perhaps the most important are two publications* currently in preparation directly related to basic science research investigating altered brain activation after developmental traumatic Brain Injury (TBI). These data show problems in brain activation and neurotransmission following TBI in our experimental model using molecular biology, behavioral testing, electrical activity and pharmacological MRI (phMRI). Furthermore, we demonstrate that a combination of medication and behavioral training can reverse this TBI-induced impairment and promote good recovery. Our third publication soon to be submitted relates to our prospective cohort of kids with TBI that are seen as part of the UCLA Pediatric TBI program (in the hospital and in clinic). We have also had several excellent opportunities to present our research at national and international venues during the same time window.

Grant-wise, our collaborations have resulted in the funding of 2 clinical pediatric TBI studies through NIH. One is a study of adherence to pediatric severe TBI management guidelines in the ICU, and the other is a neuroimaging and neuropsychological testing study of how kids recover during the first year after a moderate-severe TBI. Our application for NIH funding for the translational work using phMRI and brain activation is currently being revised and resubmitted – this experience just reinforces the challenges of working in this area – straightforward clinical studies are funded, but the more complex, neurobiology-based translational study continues to face funding challenges. **This is where TTCF support has been instrumental in keeping our scientific work on track.** We are optimistic that the publication of our results will strengthen our upcoming grant application (see below for future plans).

1) Scientific presentations in the past six months:

- a) “Hitting a Moving Target: Challenges and Opportunities in Recovery from Developmental Brain Injury” at the Bo Ericsson Pediatric Neurorehabilitation Symposium, Karolinska Institute, Stockholm, Sweden. June 12, 2010. CC Giza.
- b) “Neurotrauma basic research and neurorehabilitation: Results from the Neurotrauma 2009 interactive survey” at the National Neurotrauma Society annual meeting, Las Vegas, NV. June 17, 2010. CC Giza.
- c) “Clinical Outcomes and Interventions for Children with TBI” at the National Neurotrauma Society annual meeting, Las Vegas, NV. June 17, 2010. Hannah B. Valino, BS.
- d) “Hard Knocks for Jocks: Evaluation and Management of Sports Concussions” at the Texas Neurological Society Annual Summer meeting, San Antonio, TX. July 24, 2010. CC Giza.

- e) “Perturbations of Downstream NMDAR Pathways after Developmental TBI” at the 11th annual University of California Neurotrauma meeting, Los Gatos, CA, August 22, 2010. Floyd Buen, AB.
- f) “Pediatric TBI Clinic: Post-Injury Sequelae and Outpatient Management” 11th annual University of California Neurotrauma meeting, Los Gatos, CA, August 22, 2010. Hannah B. Valino, BS.
- g) “Found in Translation: Navigating Between Animal and Clinical Intervention Trials” at the 11th annual University of California Neurotrauma meeting, Los Gatos, CA, August 23, 2010. CC Giza.
- h) “Continuous EEG monitoring after Pediatric TBI” 11th annual University of California Neurotrauma meeting, Los Gatos, CA, August 23, 2010. Joyce Matsumoto, MD.
- i) “Not Just Little Adults: Translational Investigations of Traumatic Brain Injury in Children and Adolescents” at the University of Colorado, The Children’s Hospital, Denver, CO. September 27, 2010. CC Giza.
- j) “Plug It In and Turn It On: Connectivity and Activation in the Traumatically Injured Brain” at the Physical Medicine and Rehabilitation Grand Rounds, University of Alabama, Birmingham, AL. October 1, 2010. CC Giza.
- k) “You are What You Experience: Effects of Environment on Neuroplasticity and Recovery from Brain Injury” at the 8th International Snoezelen Symposium, Birmingham, AL. October 2, 2010. CC Giza.
- l) “The Role of Pediatric Nurse Practitioner in a Pediatric TBI Clinic” at the 2010 Association of Child Neurology Nurses conference, Providence, RI. October 13, 2010. Sue Yudovin, RN, MN, CPNP.
- m) “Found in Translation: A Clinician’s Guide to the Pathophysiology of Pediatric Sports Concussions” at the 39th Annual Child Neurology Society meeting, Providence, RI. October 16, 2010. CC Giza.

Our group presented 8 abstracts at the National Neurotrauma Society meeting this past June. One student, Hannah Valino, was selected for oral presentation [c) above]. Two other graduate students were also selected for the Student Research Competition (top 16 student abstracts) at this meeting. We are very proud of the success of our trainees.

Maxine Reger, Ph.D. program in Psychology. Passed oral proposal in 2009.

- Selected for the *Student Research Competition* (top 16 student abstracts) at the National Neurotrauma Society meeting, 2010.

Naomi Santa Maria, Ph.D. program in Biomedical Engineering, NeuroEngineering Training Program. Passed oral proposal /22/2010.

- Selected for the *Student Research Competition* (top 16 student abstracts) at the National Neurotrauma Society meeting, 2010.

2) **Publications in the past six months:**

- a) Prins ML, Hales A, Reger ML, **Giza** CC, Hovda DA. Repeat traumatic brain injury in the juvenile rat is associated with increased axonal injury and cognitive impairments. *Dev Neurosci*, in press, 7/2010.
- b) Barkhoudarian G, Hovda DA, **Giza** CC. The molecular pathophysiology of sports concussion. *Clinics in Sport Med*, in press, 7/2010.

- c) Babikian T, Prins ML, Barkhoudarian G, Hartonian I, Cai Y, Hovda DA and **Giza** CC. Molecular and Physiological Responses to Juvenile TBI: Focus on Metabolism and Growth. *Dev Neurosci, in press*, 8/2010.
- d) Schober ME, Block B, Beachy JC, Statler KD, **Giza** CC and Lane RH. Early and sustained increase in expression of hippocampal IGF-1, but not EPO, in a developmental rodent model of traumatic brain injury. *J. Neurotrauma, accepted*, 9/7/10.
- e) **Giza** CC and DiFiori JP. Pathophysiology of sports-related concussion. *Sports Health, accepted*, 10/2010.
- f) Deng-Bryant Y, **Giza** CC, Hovda DA and Prins ML. Changes in vascular MCT1 and GLUT1 transporters following traumatic brain injury. *In revision*, 2010.
- g) Cazalis F, Babikian T, **Giza** CC, Copeland S, Hovda DA, Mink RB, Marion S and Asarnow R. Pivotal role of the anterior cingulate cortex in working memory after traumatic brain injury. *Submitted*, 2010.

Plus 3 TTTCF project-related manuscripts currently in preparation for submission.

- h) ***Giza** CC, Santa Maria NS, Buen F, Li QX, Reger ML, Gurkoff GG, Spigelman I, Harris NG, and Hovda DA. Glutamatergic down regulation underlies a deficit in hippocampal activation and neural plasticity following developmental traumatic brain injury. In preparation, 2010.
- i) *Santa Maria NS, Reger ML, Cai Y, Baquing MA, Garfinkel D, Buen F, Ponnaluri A, Hovda DA, **Giza** CC. D-cycloserine restores experience-dependent neuroplasticity after TBI in the developing rat brain. In preparation, 2010.
- j) Valino HB, Breault JE, McArthur DL, Yudovin S and **Giza** CC. Pediatric traumatic brain injury (TBI) clinic: Meeting the medical needs of forgotten patients. In preparation, 2010.

3) Grants submitted and/or funded in the past six months:

Funded:

- a) Reconnection of Neural Networks and Cognitive Recovery after Pediatric TBI. NINDS/NIH R01 HD061504-01A1. 5/1/10-4/30/15. Principal Investigator: RF Asarnow. Co-PIs: CC **Giza**, P Thompson. Annual direct costs requested: \$390,000. Total direct costs requested: \$1,950,000.
- b) Connecting the Dots: Mapping White Matter Connectivity after Developmental Brain Injury. UCLA FRG (Faculty Research Grants Program), 7/1/10-6/30/11. Principal investigator: CC **Giza**. Annual direct costs: \$10,000.
- c) Blueprint for Implementing the Pediatric Traumatic Brain Injury Guidelines. NINDS/NIH R01 RFA-CE-09-005. *Submitted 1/29/10; score 20, percentile 2nd*. Principal Investigator: M Vavilala. Co-PIs: M Bell, CC **Giza**, M Wainwright.

Submitted:

- d) Long-term Outcome from Repeat Traumatic Brain Injury. NFL Charities. *Submitted 6/11/10*. Principal Investigator: ML Prins. Co-PI: CC **Giza**. Total direct costs requested: \$100,000.
- e) Repeat Traumatic Brain Injury. NINDS/NIH R01. Submitted 6/8/10. Principal Investigator: MP Prins. Investigator: CC **Giza**. Annual direct costs requested: \$250,000. Total direct costs requested: \$1,250,000.

4) **Our plan for the next six months:**

The main immediate goal is publication of the 3 studies listed above. Two experimental studies with the preliminary data that was presented to TTCF have now been concluded and are being submitted for peer-reviewed publication. These studies will show the problems with brain activation after TBI, and how we are able to restore brain activation with a combination of medication and environmental stimulation (enriched environment). Our third, clinical study, is an observational description of over 300 children cared for by the UCLA Pediatric TBI program, demonstrating the types of problems faced by these children, as well as their need for access to a specialized pediatric neurology clinic to properly address their ongoing needs.

As part of our improved clinical care, we have updated our pediatric TBI informational brochures with three different levels – one for children, one for teens and one for parents. We are in the process of developing two more detailed educational booklets – one targeted to those suffering more severe TBI who first meet us in the hospital/ICU setting, and one targeted to those recovering from milder TBI/concussions who we encounter in clinic. These should be printed soon and will be provided to families beginning in 2011.

We have two grants related to concussive brain injury that are currently under review, and are revising our proposal for the translational grant to study mechanisms of brain activation after experimental TBI. This revised proposal will be submitted to NIH in the next few months. We are also beginning the design of a clinical trial of combination therapy – medication and neuropsychological training, which will be submitted as a NIH grant proposal early in 2011.

Lastly, we had the opportunity to present a special symposium on Youth Concussions to our national society, the Child Neurology Society, this past month. This symposium was titled “It’s Not All Fun and Games: Understanding Sports Concussions from Pathophysiology to Clinical Care” and featured myself and three other international experts in Youth Sports Concussions. The session was well-attended and was the first such symposium on this important topic ever presented at our national meeting. Our group’s work related to concussions includes both research and public policy (see 11/2/10 article link <http://www.latimes.com/health/la-he-concussions-20101102,0,4379280.story>), as I co-chair the American Academy of Neurology’s committee to develop evidence-based guidelines for the management of Sports Concussions. These guidelines are on schedule to be reviewed and released by 2012.