



WHY A REVOLUTION?

Variability of causes and cases limits treatments for Traumatic Brain Injuries

During the past decade, traumatic brain injury (TBI) has become a problem of epidemic proportions world-wide. Based on the most recent data from the Centers for Disease Control and Prevention, in 2010, TBI led to more than two million emergency room visits and more than 250,000 hospitalizations. In addition, ER visits during the last decade for TBI have increased by more than 50 percent in children. TBI has been linked to the ultimate development of a broad spectrum of neurodegenerative diseases. The debilitation and poor outcomes of many patients with severe TBI results in a scarcity of individuals with favorable recoveries, hence not leaving many individuals to serve as strong advocates for the disease. This results in a general lack of philanthropic support.

At the same time, TBI is a very complex disease that is difficult for scientists to study due to the variability from case to case and resultant challenges to develop good experimental models. TBI has a list of causes that range from motor vehicle accidents, falls, and sports concussions to blast injuries in terrorist attacks, penetrating head injuries, and child abuse. The variety of causes and severities are a huge challenge for the development of new therapies.

It has also led to difficulties in understanding how TBI serves to initiate or amplify the development of diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) and chronic traumatic encephalopathy (CTE), among others. That knowledge is only beginning to emerge. In 2014, Science Watch published its review of TBI research from the previous 15 years, and the University of Pittsburgh was ranked first. Pitt topped the list of both most prolific and most cited institutions, with 970 papers accounting for more than 16,000 citations. Opportunities for TBI research at the University of Pittsburgh are unparalleled and span across many different centers and programs. Advancements currently in process include:

- Pre-clinical studies in operation brain trauma therapy at the Safar Center for Resuscitation Research
- Research on care of critically ill children with severe TBI at Children's Hospital of Pittsburgh of UPMC
- Development of the IMPACT test to diagnose and monitor sports concussions at UPMC Sports Medicine Concussion Program
- Development of high definition fiber tract brain imaging technology at the Learning Research and Development Center in the Department of Psychiatry and Clinic of UPMC
- Use of phenotype-based therapies for our soldiers and veterans with sequelae of TBI in the Department of Neurological Surgery
- Development of novel imaging methods to identify and treat early cases of post-traumatic Alzheimer's disease and chronic traumatic encephalopathy at Western Psychiatric Institute and Clinic of UPMC
- Testing new approaches to diagnose otherwise missed victims of abusive head trauma at Children's Hospital of Pittsburgh of UPMC

- Testing of novel rehabilitation approaches from bench to bedside in the Department of Physical Medicine and Rehabilitation

Recently, investigators have united to develop novel, targeted therapies for TBI by linking the programs at Pitt to other state-of-the-art research efforts to create a pipeline for therapy development. This is centered on collaboration between the aforementioned TBI investigative teams at the Safar Center, Learning Research and Development Center, and the Department of Neurological Surgery, with investigators at the University of Pittsburgh Drug Discovery Institute and investigators at Carnegie Mellon University. We are applying quantitative systems pharmacology (QSP), which determines the mechanisms of disease progression and drug reactions through integrated experimental and computational methods.

We hope to further develop in-vitro models, including a human brain chip of TBI that can reproduce the cellular and molecular imbalances impacting its progression. Once these imbalances are identified, investigators can work to repurpose existing drugs that can mitigate and construct computational models of disease progression to guide the development of experimental tests. With these tests, scientists can screen targeted libraries of compounds to identify novel compounds that can revert the disease phenotype back toward normal functions. This will allow us to take the most promising therapies identified in the in vitro model studies and advance them to multi-center testing across an array of living TBI models. Finally, we will be able to advance therapies with the highest possible probability of success to clinical trials in patients with TBI. This approach has never been taken and affords the best chance to develop a breakthrough therapy for TBI.

Questions?

For more information on these and other QSP programs currently in development at the University of Pittsburgh, please contact:

D. Lansing Taylor, PhD
412-648-9200
dltaylor@pitt.edu

To find out how to support The Revolution Fund and its efforts to enhance patient-driven therapies through QSP programs, please contact:

Jennifer Griffin
412-623-2617
griffinj4@upmc.edu



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