Traumatic brain injury – a constantly rising health problem

Traumatic brain injury (TBI) is an enormous public health problem across all ages, and in all populations; even in North America and Europe, where TBI incidence is lower than in poorer regions. Since incidence is increasing rapidly in low-income and middle-income countries (mostly owing to road traffic accidents), TBI is predicted to become the third leading cause of global mortality and disability by 2020, according to WHO.

The number of TBI persons is constantly rising, and the personal impact is always difficult to estimate because every single trauma leads to an individual situation. TBI may result in everything from a light neuropsychological disability to a serious neurological disability. In addition, epilepsy, depression, headache and a need for chronic therapy may be present. TBI strongly affects also the caring relatives, the National Health System and social security companies.

In connection with the 35th Annual NeuroTrauma Symposium held at Snowbird, Utah, July 7-12, we spoke to Ramon Diaz-Arrastia, MD, Presidential Professor of Neurology at Penn’s Perelman School of Medicine, University of Pennsylvania. His path-breaking research focuses on understanding the molecular, cellular and tissue level mechanisms of secondary neuronal injury and neuroregeneration, especially through biomarker development. His most recent work explores using MRI, functional MRI and PET scanning to characterize the multiple complex mechanisms involved in traumatic injury to the brain, as well as combining imaging, genomic and tissue biomarkers to better predict patient outcomes after traumatic brain injuries and to develop novel therapies. Ramon Diaz-Arrastia is the author of more than 135 peer-reviewed primary research papers and more than 30 invited reviews and book chapters, Diaz-Arrastia has led major research projects funded by the NIH and Department of Defense, among others, and served on expert panels convened by the Institute of Medicine, National Institute of Neurological Disorders and Stroke, National Institute of Aging and DOD.

What are the treatment options today for a TBI affected person?

Treatment of TBI presently is purely supportive. There are no FDA-approved treatments that change the natural history of TBI recovery.

How would a TBI treatment such as NeuroSTAT change the current treatment landscape?

A treatment which would provide neuroprotection and/or promote neuroregeneration would be transformative. This has been the holy grail in the field for the past 25+ years, since it was first demonstrated in animal models that pharmacologic interventions could limit neurodegeneration after TBI (as well as after
other acute neurologic insults). While these preclinical studies constitute convincing proof of principle, it has been impossible to translate these findings into clinical trials. This is likely because the preclinical models do not fully replicate the heterogeneity and complexity of human TBI, and extrapolation of critical parameters such as dose, timing, and duration of therapy from preclinical models is fraught with error. Our current approach (as well as that of others) is to utilize imaging and molecular biomarkers to identify patients with a particular injury endophenotype, as well as to demonstrate target engagement and physiologic efficacy.

Have you seen any effects on the incidence of TBI given that the security measures in traffic and sports are constantly improving?

In developed countries there has been a dramatic decline in deaths from TBI over the past 25 years, primarily due to improvements in automobile safety, use of seatbelts, airbags, etc. The number of hospitalizations for TBI remains unchanged, however (at approximately 300,000/year in the US). Over the past 10 years there has been a dramatic increase in Emergency (from approximately 2 million/year to 3 million/year in the US), reflecting the increased social awareness of the significance of mild TBI. Most of the additional ED visits are for mTBI. In developing countries, the reduction in deaths and disability from severe TBI has not occurred, and is in general approximately twice of what it is in developed countries.

What would you say is NeuroSTAT’s competitive edge?

Cyclosporine has very extensive pre-clinical data of efficacy. There is also extensive mechanistic information regarding its mode of action, which should facilitate the development and validation of predictive and pharmacodynamic biomarkers. Cyclosporine is also a well-known compound, with an established and favorable safety profile.

How do you think clinical trial designs in TBI will change over the coming years?

Improvements and refinement in clinical trial design has been the focus of clinical research in the TBI field for the past 10+ years, in response to the realization that large and well-conducted clinical trials were failing to demonstrate efficacy for compounds that were effective in preclinical models. The consensus of multiple workshops and expert committees convened by NIH and DoD over the past several years is that biomarkers of drug efficacy should be utilized in early-phase clinical trials. Such early phase clinical studies would use the biomarker to prove that therapy is engaging its proposed molecular target and to demonstrate biologic efficacy. Since the biomarker is mechanistically closer to the biological effect of the therapy than clinically relevant outcome measures, such studies can achieve adequate power with modest sample sizes, and can be useful for fine-tuning important issues such as dose, timing, and duration of therapy before launching large and expensive phase III trials.

Generally speaking, what further actions and initiatives could be taken to improve the patients’ outcomes and decrease the global burden of TBI?

Given the heterogeneity of TBI, and the multiple pathologies which contribute to neurodegeneration after injury, it is likely that combination therapy will ultimately be required to optimize recovery. Such therapies will have to be tailored to the mechanisms of injury present in individual patients. Drug development will have to proceed in tandem with development of predictive and pharmacodynamic biomarkers.
NeuroVive presents at the 35th Annual NeuroTrauma Symposium

At the NeuroTrauma symposium, Michael Karlsson, MD and research scientist at NeuroVive presents results from the preclinical studies performed in collaboration with the University of Pennsylvania, Penn, related to the clinical NeuroSTAT TBI project.

NeuroVive has evaluated the effect of the candidate drug NeuroSTAT in a non-clinical experimental TBI model. Positive results established the pharmacokinetic profile of NeuroSTAT in blood, CSF and brain in the disease model, and showed that NeuroSTAT dose-dependently crosses the blood-brain barrier.

The studies also evaluated several different efficacy parameters related to mitochondrial function and metabolism, as well as advanced translational brain imaging MR techniques. A significantly reduced volume of brain injury (35% decrease) after NeuroSTAT treatment was observed in MRI scans in the experimental TBI studies.

Furthermore, the studies displayed positive changes in brain energy metabolite levels and mitochondrial respiratory function, as well as decreased generation of reactive oxygen species.

About TBI

Traumatic brain injury (TBI) is caused by external violence to the head resulting in immediate damage to nerve cells. The damage continues to worsen for several days after the trauma, which in many cases has a significantly negative effect on the overall injury. At present, there are no approved treatments for the prevention of these secondary injuries. In the US, some 2.2 million people are affected annually, causing more than 50,000 deaths and 280,000 hospitalizations. The direct and indirect costs associated with TBI are an estimated USD 60 billion, and a large number of patients suffer moderate to severe functional disabilities requiring intensive care and various forms of support (www.nih.gov). The aim is that better preventive therapies for secondary brain damage, such as NeuroSTAT, will lead to higher survival rates, and significantly improve quality of life and neurological function of patients post-TBI.
NeuroVive – Newsletter July 2017

NeuroVive welcomes new board members

At the Annual General Meeting on April 27, two new board members were elected, Jan Törnell and David Bejker. In this newsletter we speak with Jan Törnell, Associate Professor and Medical doctor with 20 years' experience from different senior positions within the pharmaceutical industry, to get his views on his new role as Board Member and how he sees the future of NeuroVive.

What made you accept the Board assignment in NeuroVive?
– It is thrilling to be part of leading the company into a new therapy area – oncology – where there are high unmet medical needs and many new exciting opportunities. Particularly when we can work from both a mitochondrial and a metabolic perspective.

What is most exciting with the company?
– I have seen from the outside, and even more now when I am on my "way in", that the scientific competence in the company, internally as well as in the form of external partners, is very high. The exciting thing about NeuroVive is that this is combined with a strong management showing a strong commercial drive.

What questions and areas will you, with your background, focus on in the board?
– Primarily questions of strategy where there is a need to combine medical knowledge and scientific data with a commercial insight. With my background and experience as a doctor, scientist and strategy head within the industry, it comes natural to focus on the interface between the medical need, scientific knowledge and commercial prerequisites.

What do you bring on to the board from your previous roles within the pharmaceutical industry?
– At AstraZeneca, I was part of a management group for the business areas oncology and infection. In this role, I handled both the assessment of the internal projects' potentials as well as the evaluation and valuation of projects for in-licensing or acquisition. With this I have developed a comprehensive and relevant international contact network that can be of use to NeuroVive.

In your view, what are the greatest challenges?
– To constantly balance the development and commercial opportunities with both short and long term perspectives.

Where in the development do you think NeuroVive is in five years’ time?
– By then we have one or a few products out on the market within niche indications. It will be areas where both marketing, distribution and logistics around the products can be handled without transforming NeuroVive into a large company organization wise. I am also convinced that we then have generated a project flow where some have been out-licensed and some has been added to the portfolio.

Jan Törnell, born 1960, is Associate Professor and Medical doctor with 20 years' experience from different senior positions within the pharmaceutical industry, both in Sweden and internationally. Jan has held the position as Vice President in AstraZeneca Oncology & Infection 2009-2011 and Vice President Translational Science 2006-2008. He was Director at AstraZeneca Discovery 1999-2005 and Astra 1996-1999. Jan is Editor-in-Chief for Drug Discovery Today – Disease Models published by Elsevier. Principal supervisor of several students resulting in PhD theses. Author of 80 scientific publications and innovator on 6 patents. Currently, Jan is adjunct Professor at the Institute of Neuroscience and Physiology, Sahlgrenska Academy, Gothenburg University, Chairman of the Board at LIDDS AB, Glactone Pharma AB and Glactone Pharma Development AB, Director of the Board at Stayble AB and Diaprost AB, CEO at Oncorena AB and Innoext AB, Partner of P.U.L.S. AB.
NeuroVive Pharmaceutical AB is a leader in mitochondrial medicine, with one project in clinical phase II development for the prevention of moderate to severe traumatic brain injury (NeuroSTAT®) and one project in clinical phase I (KL1333). The R&D portfolio consists of several late stage research programs in areas ranging from genetic mitochondrial disorders to cancer and metabolic diseases such as NASH. The company’s strategy is to advance drugs for rare diseases through clinical development and into the market. The strategy for projects within larger indications outside the core focus area is out-licensing in the preclinical phase. NeuroVive is listed on Nasdaq Stockholm, Sweden (ticker: NVP). The share is also traded on the OTCQX Best Market in the US (OTC: NEVPF).

ABOUT NEUROVIVE

We wish you a pleasant summer!