DRAFT ONLY

Victorian NeuroTrauma Initiative Application for Funding

Project: Spinal Cord Injury, Traumatic Brain Injury and Stroke Recovery

A. Hyperbaric Oxygenation
B. Lokomat Robotic Gait Assisted Training
C. Cerebrolysin

Summary

1. Executive Summary

To advance functional outcomes for persons suffering spinal cord injury, traumatic brain injury and stroke recovery through novel and unique applications.

2. Background

Spinal Cord Injury (SCI), Traumatic Brain Injury (TBI) and Stroke are common and growing causes of neurological disability and death throughout the world. Spinal Cord injury occurs in most countries at an annual rate of 20-40 cases per million. The main causes of trauma are motor vehicles accidents, sports, work related accidents and falls at home. Most of these patients are young and otherwise healthy. The economic cost of SCI is estimated as $200,000 per case annually. TBI and Stroke are among the leading causes of acute and chronic disability in Western countries. TBI accounts for 34% of all deaths due to injury and 1750-2000 per million of the population in the developed world is affected by head injuries, and 623 per million of the population aged 15 and over are disabled due to TBI. Stroke is among the leading causes of death in both Australia and many other countries for women and men, with an incidence of just more than 500,000 individuals each year (USA). Stroke accounts for nearly one-half of all those hospitalized for acute neurological conditions annually. Although the majority of individuals who sustain a stroke survive, a significant proportion of survivors require rehabilitation, and nearly one-third have some type of permanent disability. Among those who survive stroke, 50 percent are alive more than five years after the event, which means that rehabilitation needs continue well after the initial event. The rehabilitation needs and goals of individuals with neurovascular injury vary considerably. For some, the goal may be to return to full independence and resumption of all previous life activities. For others, the goal may be to return home with family assistance. Source: The economic cost of spinal cord injury and traumatic brain injury in Australia 2009; American Paralysis Association for Brain Initiatives 2007 and Stroke Foundation 2009.

According to the World Health Organisation estimates, the prevalence of TBI, SCI and Stroke are even higher in the developing world. These conditions cause life long disability with no effective treatment available at present.

3. Impact Of Brain, Spinal Cord Injury and Stroke

Spinal Cord Injury (SCI), Traumatic Brain Injury (TBI) and Stroke have a significant impact on quality of life, life expectancy and economic burden, with considerable costs associated with primary care and loss of income. Patients are typically injured at a young age and are disabled for the remainder of their lives leading to very high costs. The lifetime cost of newly acquired brain (TBI and Stroke) and spinal cord injury occurring in 2008 was $10.5 billion in Australia (Victorian NeuroTrauma Initiative June 2009).

The extent of disability after injury varies greatly, depending on the severity and location of the injury and which nerve fibers are damaged. The resulting neurological deficit can be temporary or permanent, complete or incomplete; one of the primary goals for people with neurologic disability is to improve locomotor function. This capacity to regain functionality including the ability to walk is based on the principles of neuroplasticity notwithstanding the therapeutic window diminishes over time.

Traditional goals are designed to assist the general needs of the brain and spinal patient; these goals are not focussed on facilitating functional outcomes for patients. The vast majority of neurologic patients become stagnant in their rehabilitative outcomes. Many suffer a range of secondary complications associated with injury including cardiovascular problems, type II diabetes, muscle wasting, osteoporosis, immune deficiencies, and other life-threatening problems. Evidence supports both acute and chronic phases of rehabilitation may have continuing prospects for further recovery.

Neuroplasticity is the term describing the body's ability to salvage back what has been damaged by developing new connections through life. This is a relatively new concept in Australian rehabilitation which is typically focussed on living and coping with disability.

Neuroplasticity: The brain's ability to reorganize itself by forming new neural connections throughout life. *Neuroplasticity allows the neurons (nerve cells) in the brain and spinal cord to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment.*

- *Neural stem cells (NSCs) migrate* through the parenchyma along non-stereotypical routes in a precise directed manner across great distances to injury sites in the CNS, where they might engage niches harboring local transiently expressed reparative signals

- *Neuronal reorganization takes place by mechanisms such as "axonal sprouting"* in which undamaged axons grow new nerve endings to reconnect neurons whose links were injured or severed. Undamaged axons can also sprout nerve endings and connect with other undamaged nerve cells, forming new neural pathways to accomplish a needed function
- For example, if one hemisphere of the brain is damaged, the intact hemisphere may take over some of its functions. The brain compensates for damage in effect by reorganizing and forming new connections between intact neurons. *In order to reconnect, the neurons need to be stimulated through activity which must be accurate and repeated many thousands of times*
- Neuroplasticity sometimes may also contribute to impairment. For example, people who are deaf may suffer from a continual ringing in their ears (tinnitus), the result of the rewiring of brain cells starved for sound. For neurons to form beneficial connections, they must be correctly stimulated. 'Spinal cord activation often causes increased spasms and uncontrolled movements'
- Neuroplasticity (brain plasticity and or spinal plasticity) is often referred to as *neural malleability*

4. NeuroVascular Insult

Damage to the brain and spinal cord is categorised as primary (immediate consequences) and secondary (processes that occur after initial impact). The secondary processes involve an activation of complex cascades leading to death of nerve cells and other brain cells. Neurovascular insult causes extensive bruising, and massive swelling resulting in tissue hypoxia. Hypoxia triggers a cascade of destructive cellular responses. Hypoxic damage causes destructive Apoptotic cells from the immune system to migrate to the injury site causing further damage to some neurons and death to others that survived the initial trauma.

Within weeks of the initial neurovascular injury cystic changes and neurodegeneration is often evident. Localized myelomalacia (spinal cord) or encephalomalacia (brain) emerges (morbid softening at the injured site due to hypoxic necrosis). Continuing hypoxic induced apoptosis may result in progressive myelomalacia due to hypoxic induced ischemic degeneration – a watershed spread and enlargement of the original injured site is often evident associated with continuing degeneration. This secondary cascade potentially leads to further loss of neurologic function and neural atrophy severely inhibiting the capacity to regenerate and recover function.

5. Research Program

This research program involves the development of novel and unique strategies to enhance the latent regenerative mechanisms in the spinal cord and brain. Emphasis is directed towards early intervention to minimize this cascade of programmed cellular destruction.

1. **Hyperbaric Oxygenation** (HBOT) impacts tissue hypoxia by displacing oxygen molecules greater than normal circulatory dynamics. HBOT fosters the formation of 'new capillary dynamics' (neovascularization) into damaged regions of the body. HBOT accelerates neuroplasticity - activating damaged and dormant nerve cells. HBOT mobilizes the patients own target specific circulating stem cells (CD34+). HBOT diminishes the cascade of secondary apoptosis. Evidence exists that early HBOT intervention potentially has the greatest impact to the destructive spread of hypoxia but also chronic neurologic disorders have also been reported to benefit with HBO saturation. Functional BOLD (Blood Oxygen Level Dependency) MRI measures progressive hypoxic damage and apoptosis spread.

2. **Lokomat (Robotic Gait Assisted Walking)** Over 31-countries feature Lokomat Gait Training with in excess of 250-Lokomats world wide. One exists in Australia. Clinical studies demonstrate that brain and spinal circuitry have capacity to re-train and relearn function. Studies on spinalized cats demonstrate that spinal reflex generators below the level of injury remains active (even years after injury) and functional neuronal properties can respond to peripheral input from *below* the level of injury. Treadmill cats can be trained to walk. Evidence exists that lack of appropriate and 'accurate' stimulation induces functional incapacity called the 'learning non-use'. Motor cortex centers in the brain also show signs of functional loss due to brain and spinal cord injury. Functional BOLD MRI demonstrate that the motor cortex and cerebellum parts of the brain re-allocate functional capacity lost through injury. These changes are frequently associated with Mental Health issues that further contribute to the burden of disability. Patients with brain and spinal cord injuries who have been wheelchair bound for many years are still potentially able to ambulate. Improving a patient to the point that he/she no longer needs a wheelchair to move would definitely lead to reducing the yearly costs of his/her neurological disease as well as the financial burden of wheelchair-associated complications such as; pressure ulcers, circulatory disorders, osteoporosis and attendant care. Lokomat Gait Training also records improved cardiovascular performance and reductions in spasticity, bone loss and bladder/bowel complication.

Additionally, it has been revealed that Lokomat Gait Training can lead to functional improvements in patients with different neurological diseases such as; Multiple Sclerosis, Chronic Stroke, Parkinson's Diseases, Cerebral Palsy (CP), as well as the other various types of idiopathic and secondary muscular dystrophies and neurological disorders in adult and children. In stroke hemiparetic patients BWSTT has been shown to improve balance, lower limb motor recovery, walking speed, endurance, and other important gait characteristics such as symmetry, stride length and double stance time. Functional BOLD MRI measures the capacity to retrain function in both the brain and spinal cord neural pathways. The injured neurovascular person has capacity to 'wake-up' - salvage back tissue damage, re-activate and re-train dormant neural pathways improving functionality.

3. **Cerebrolysin** The additional administration of compounds such as Cerebrolysin could enhance the survival of these new cells and increase the number of cells differentiating into neurons, potentially contributing to augment neurogenesis and improved functional outcome. Cerebrolysin is a compound with neurotrophic and neuroprotective activity that causes neuronal differentiation (sprouting of axons and dendrites) and maintains the functional integrity and recovery of the nerve cell.

The combination approach is unique and could potentially accelerate the capacity towards functional neuroplasticity and neurogenesis. Enhancing the therapeutic window significantly impacts the economic burden of long term injury.

6. Research Strategy

We propose a clinical trial to measure functional outcomes of individuals suffering various degrees of SCI, TBI and Stroke.

All subjects will be evaluated at periodic intervals during the trial including:

- Functional BOLD MRI
- CD 34+ Stem Cells
- Brain Derived Neurotrophic Factor (BDNF)

7. Expected Outcomes

- Hyperbaric Oxygenation provides the available fuel and acts as a catalyst to the underlying central issue (hypoxia). Lokomat (Robotic Gait Assisted Walking) provides intensive physical therapy required to 'drive' neuroplasticity - the ability of the neurons in the nervous system to develop new connections and 'learn' new functions. Cerebrolysin could enhance the survival of these new cells and increase the number of cells differentiating into neurons, potentially contributing to augment neurogenesis and improved functional outcome. The rate of neuroplasticity is directly impacted by the levels of continuing hypoxia which blocks recovery. This combined Hyperbaric Lokomat Cerebrolysin approach 'awakens' dormant neural pathways and provides accurate neurological repetition enhancing and re-training connections and pathways in the brain and spinal cord. Improved functionality achieving greater independent mobility for previously non-ambulatory and highly dependent patients would lead to positively changing the quality of life of the affected individuals, boost up their physical capacity, their confidence and increase the valuable time they spent in their community.
- Morphological and behavioural demonstration of improved neurological status of patients undertaking this trial.
- Insight into the molecular mechanisms that mediate regeneration and or limits degeneration following SCI, TBI and Stroke.

8. Estimated Program Budget

- Trial number 30 each SCI, TBI and Stroke
- Estimated trial period per subject 8-months
- Estimated period of total trial 3-years

- Hyperbaric Oxygenation pressure and hours TBA. Estimated per individual $17,500
- Lokomat Robotic Gait Training hours TBA. Estimated per individual $16,500
- Cerebrolysin dosage TBA. Estimated per individual $3800
- Functional BOLD MRI. Estimated per individual $4500
- Immunological. Estimated per individual $2500
- Budget per individual $44,800
- Total Research Project $4,032,000

9. List of Research Units and Investigators

Director: Malcolm R Hooper HyperMED NeuroRecovery 13th floor 15 Collins St Melbourne.
Detailed list of Chief and Associate investigators to be advised.

1. Hyperbaric Oxygenation: Chief Investigator Malcolm Hooper, (TBC) Dr Martin Hodgson
   - HyperMED 13th floor 15 Collins St Melbourne 3001
   - Vaucluse Hospital Moreland Rd Brunswick
   - Berwick Hospital

2. Lokomat: Chief Investigator Malcolm Hooper HyperMED 13th floor 15 Collins St Melbourne 3001
3. Functional BOLD MRI: Chief Investigator (TBC) - A/Professor Peter Mitchell Department of Neurology, Royal Melbourne Hospital
4. Laboratory Unit : (TBC) - CSIRO
5. Cerebrolysin: Manufacturer Ebewe Pharma
6. Behavioral NeuroScience Evaluation: (TBC) - Dr Dennis Velakoulis, Director, Neuropsychiatry Unit, The Royal Melbourne Hospital Clinical Director, Melbourne Neuropsychiatry Centre
7. Patient Advocacy Group: Mr. Gary Allsop Honorary Director Spinal Cure Australia