

DRAFT ONLY

Application for Funding October 2009

Project: Cerebral Palsy Functional Outcome using Hyperbaric Oxygenation, Lokomat and Cerebrolysin

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

Summary

1. Executive Summary	2
2. Background	2
3. Cerebral Palsy	2
4. Research Project	2
5. Research Strategy	7
6. Expected Outcomes	7
7. Estimated Project Budget	7
8. List of Research Units and Investigators	7
9. Supporting References	8

1. Executive Summary

To advance functional outcomes for children and adults suffering Cerebral Palsy through novel and unique applications including Hyperbaric Oxygenation, Lokomat (Robotic Gait Assisted Walking) and Cerebrolysin.

2. Background

Access Economics 2007 released a report on the economic impact of cerebral palsy in Australia. Launched by the Hon Bill Shorten, MP, the report found that the financial cost of cerebral palsy (CP) in Australia was \$1.47 billion or 0.14% of GDP. When the value of lost wellbeing (disability and premature death) was added, the cost rose a further \$2.4 billion. Access Economics estimates that 33,797 Australians had CP in 2007. At an annual financial cost of \$43,431 per person, the cost to the individual is estimated at 36.7% of the total – or \$306 per week.

3. Cerebral Palsy

About 8,000 babies and infants are diagnosed with cerebral palsy (CP) each year in the United States; Australia reports similar percentages. CP is a generalized term used to describe a group of chronic conditions affecting body movement and muscle coordination. It is caused by hypoxic induced damage to one or more specific areas of the brain, which usually occurs during fetal development, birth or infancy. CP is associated with arrange of hypoxic related events occurring prenatal and post-natal. The condition is not caused by problems in the muscles or nerves but is instead due to hypoxic associated complications causing faulty development or damage to sensory and motor development areas in the brain.

Cerebral refers to the brain and palsy refers to muscle weakness. CP itself is not ‘classified’ as a progressive condition however most CP cases develop a host of other secondary conditions as they age - muscle spasticity and orthopedic disorders typically emerge and progress over time. The abnormal developing brain may continue to undergo hypoxic neurovascular degeneration. Early signs of CP usually occur before 18 months of age, and parents are often the first to suspect their infant is not developing motor skills normally. Infants with CP are frequently slow to reach developmental milestones, such as learning to roll over, sit, crawl, smile, or walk.

Cerebral Palsy states are characterized by the inability to fully control motor function, particularly muscle control and coordination. Muscle tightness, involuntary movement, difficulty swallowing, difficulty seeing, seizures, and problems with speech are often found in patients with CP. Other problems that may occur are difficulties in feeding, bladder and bowel control, problems with breathing, skin disorders, and learning disabilities. Presently, no curative therapies or successful methods of prevention on a population level are available for children with one of the cerebral palsy syndromes. However, since 2004 the American Academy of Neurology (AAN) has recommended that neuroimaging of the CNS be part of diagnostic process for cerebral palsy. Although the guideline was initially met with controversy and criticism, neuroimaging has allowed a broader appreciation of timing of lesions, extent of white matter involvement, and the complexity of the motor spectrum of disability. Functional imaging can assist to monitor the value of emerging therapeutic interventions.

Traditional therapy goals in Australia have typically been designed to assist the general needs of Cerebral Palsy individual; orthopedic, rehabilitation, neuropharmacological, and other management interventions can help maintain mobility, prevent deformity, and promote quality of life for children with CP. However 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.

4. Research Program

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

1. Hyperbaric Oxygenation

At the onset it must be understood that not all patients are automatic candidates for HBOT. HBOT may only be beneficial in treating primarily cases of CP associated either with traumatic brain injury (TBI) or with toxic,

hypoxic or anoxic encephalopathy. HBOT has also been reported to assist children with mitochondrial cytopathies (usually considered to be fatal).

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 hypoxic induced 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.

Numerous studies have been published on this controversial topic. The use of HBOT in the pediatric patient is relatively common in Russia for respiratory failure, cranial birth injuries, and hemolytic disease of the newborn. HBOT was reported to reduce high serum bilirubin levels and prevent development of neurologic disorders. Italian physicians began treating small fetus in utero in 1988 demonstrating a reduction in cerebral damage. Patients were hospitalized before the 35th week and HBOT were given every 2 weeks for 40-minutes at 1.5 ATA. Fetal biophysical profile showed a remarkable improvement as soon as the second treatment. In 1989 results of 230 CP patients treated in Brazil (Machado 1989). Results showed a 50% reduction in spasticity reported in 94.78% of patients. Twelve patients (5.21%) remained unchanged. However follow-up of 82 patients saw 62 of these (75.6%) had lasting improvements in spasticity and improved motor control. Parents reported positive changes in balance and intelligence with reduced frequency of seizure activity. Additional results of this initial work in Brazil were presented in 2001 and at 2nd International Symposium on Hyperbaric Oxygenation and Brain Injured Child held in Florida. The initial Brazil study expanded to include 2,030 patients suffering from childhood chronic encephalopathy that had been treated since 1976 using HBOT. 232 were evaluated with long-term follow-up; age between 1-34 years. The improvements noted included spasticity reduction, improved global motor coordination, memory, comprehension, reasoning, visual perception, sphincter control. It was concluded from this study that HBOT should be instituted as early as possible in such cases.

Another study also presented at the 2nd International Symposium was by Chavdarov, Director of the Specialized Hospital for Rehabilitation of Children with Cerebral Palsy in Bulgaria. HBOT is used as an integral part of management with children since 1997. The study included 50-children with various forms of CP. Overall an 86% improvement with motor ability, mental ability, functional development and speech following HBOT.

Montgomery et al. (1999) reports the use of HBOT in 23-children (10-female, 15 male; age range 3.1-8.2 years) with spastic diplegia. Absence of previous surgical or medical therapy for spasticity was one of the prerequisites for inclusion as well as a 12-month clinical physiotherapy plateau. The study was conducted at McGill University Hospital using a monoplace chamber at 1.75 ATA (95% oxygen for 60-minutes daily and at Rimouski Regional Hospital in a multiplace chamber (60-minutes at 1.75 ATA twice daily) for 20-treatments in total. Assessments pre and post including gross motor function (GMFM), fine motor function (Jebsen's Hand Test), spasticity assessment (Modified Ashworth Spasticity Scale) as well as patient questionnaire and video analysis. Results were an average of 5.3% GMFM improved and a notable absence of complications or clinical deterioration in any of the children. Cognitive changes were observed, but recorded as non-specific. Video analysis was also positive. The obvious flaw was the lack of placebo control and application of two different HBOT protocols. The Montgomery study achieved improvements in CP children using 20-treatments at 1.66 ATA oxygen (1.75 ATA 95% O₂) but the children experienced rapid regression of neurologic gains after cessation of treatments. The number of treatments was inadequate according to Richard Neubauer and Paul Harch (Ch 21 HBO in Management of Cerebral Palsy) Text in Hyperbaric Medicine Prof K.K. Jain 2004. Neubauer and Harch cite 40 treatments at 1.5 ATA/60-minutes because 'consolidation of gains does not occur until 30-35 treatments.

The controversial Collet et al study included 111 children ages 3-12 randomized into 2-groups; either 1.75 ATA 100% O₂ or 1.3 ATA room air which is equivalent to 28% Oxygen at 1.0 ATA. Both groups received 1-hour HBOT for a total of 40 treatments. Gross motor function, fine motor function, memory, speech, language and memory were assessed. Improvement in global motor function was 3% in the HBOT air -group and 2.9% in the HBOT 100% O₂ group. Although both groups were statistically similar the HBO 100% O₂ had a more rapid

response rate in the more severely disabled children. HBOT was scheduled for 1-hour for a total of 40-treatments over a 2-month period. The interesting findings was the absence of a statistically significant difference in the improvements in global motor function, self control, auditory attention and visual working memory seen between the oxygen exposed group and the 'sham' pressure control. There were no improvements seen in either group for visual, attention, verbal span or processing speed. Interestingly both groups demonstrated improvement in self control, auditory attention and visual working memory – no statistical differences.

Mild HBOT has also been reported to be effective in improving SPECT as well as attention span and reaction times (Heuser and Uszler 2001). The Collet study demonstrates that the 'sham' 1.3 ATA normal air was not a true inert or placebo, but had a real effect on the partial pressure of blood gases and perhaps other physiological effects as well. Compressed air at 1.3 ATA increases the plasma oxygen tension from 12.7 KPa (95mmHg) to 19.7 KPa (148 mmHg) and the increase of a concentration of a reactive substrate by 50% is substantially notable. The effect of the Collet study instead of fostering a range of additional studies using various pressures and oxygen levels simply confused the scientific community not familiar with hyperbaric oxygenation. The unequivocal finding of these studies is that both pressure protocols achieved statistically significant neurocognitive gains, a phenomenon that cannot be attributed to placebo.

The Collet study is not a blinded study. Sham HBOT at 1.3 ATA using air is still a 30% increase in oxygen in a pressurized environment meaning that the mild 1.3 ATA group was not a true sham but in fact a mild therapy group also. The fact that both groups improved does not indicate that the overall study was flawed as positioned by the critics. Both groups demonstrate that at pressure ranging between 1.3-1.75 ATA using either air or 100% O₂ will impact a child's functionality.

Shortly after the Collet study the US Army conducted a small study on functional outcomes in children with anoxic brain injury - United States Army Study on Adjunctive HBOT of Children with Cerebral Anoxic Injury. Children in the study ranged from near drowning and cerebral palsy related disorders. Pre treatment gross motor function, lying, rolling, crawling and kneeling, sitting, standing, walking, running and jumping; in addition Modified Ashworth Scale (MAS) for spasticity and rigidity, flexion/extension, the Functional Independence Measure of Children regarding self care, sphincter control, transfers, locomotion, communication and social cognition, video, 24-hour time measure, parental questionnaire and SPECT (Single Photon Emission Computerized Tomography) scanning. Testing was conducted every 20-treatments and parental questionnaire completes at 40 and 80-sessions. All subjects received 80 HBOT sessions in a multiplace chamber (100% O₂ at 1.75 ATA) daily (Monday to Friday) for 4-months. Improvements in GMFM in categories of lying and rolling, crawling and walking, sitting and walking, running and jumping were statistically significant ($p < 0.05$). Also reported was the reduction in parental care in custodial care and time. Overall improvements were 26.7% at 30 treatments, up to 58.1% at 80-treatments. Their conclusions were that HBO therapy seemed to effect overall improvement with CP children although the optimum number of treatments remains undetermined since the improvements were noted at the end of the study. They advised further research and follow-up studies to determine the true potential of HBO for children with anoxic injury and CP.

The impact of these and other studies is the fact that there is no fixed regime using HBOT when treating chronic pediatric brain injury. Every child is different and simply HBOT protocols may also be required to vary from child to child. Low pressure increased oxygen signaling appears to occur impacting chronic brain injury. This reinforces the merits of neuroimaging as surrogate markers to monitor pre and post outcomes which will be part of this project.

2. Lokomat (Robotic Gait Assisted Walking)

Robotic Assisted Rehabilitation is emerging providing functional training for an increasing range of those living with disability. Evidence supports the feasibility of applying therapeutic robotics to children and adults with severe to moderate impairment due to cerebral palsy (CP). These results suggest that robot-mediated therapy may be an effective tool to ameliorate the debilitating effects of CP and provide new opportunities for reducing impairment and improving coordination.

Over 31-countries feature Lokomat Gait Training with in excess of 250-Lokomats world wide. One exists in Australia.

Cerebral palsy is another complex disorder that also benefits from Lokomat Gait Training. Cerebral Palsy is an occurrence in which the nerves and muscles of the body function improperly; damage to the brain causes it to transmit incorrect electrical impulses to the muscles including both too many and too few signals. Without the correct cohesive electrical impulses to balance the opposing muscles of a joint, normal everyday tasks that most of us take for granted become very difficult to learn and perform. As robotic assisted exoskeletons become more advanced and practical, their applications have a lot of room for growth. Cerebral Palsy is one portion of the medical field that can benefit from the development of exoskeletons and in particular Pediatric Lokomat.

It is common practice in physical therapy to move a patient's limbs and joints through natural motion in order to improve function. Gait ability is a complex motor activation pattern organized hierarchically with the upper most level (initiation of the movement) mediated through the primary cortex and the lowest levels (organization and execution of the movement) mediated through the spinal motor neurons. The deficit induced by a central nervous system lesion depends on which group of cells is damaged: lesions of the upper motor neuron let some muscle contractions even with an altered highest cortical control. Lesions of the lower motor neuron result in flaccid paresis without the ability to recover some movements. Therefore central nervous system lesions produce different symptoms: paresis, somatosensory deficits which induce inactivity and loss of function.

This inability to realize a movement combined with the neuroplasticity of the central nervous system may induce a secondary functional incapacity called the "learning non use" similar to teaching a person to remain seated in a wheelchair. Functional incapacity is challenging for the cerebral palsy patient, supporting family and therapist. Acquired deformity results in a cascade effect of adaptation and secondary complications notwithstanding psychological effects under the banner of 'mental health'. Task specific training such as Lokomat Gait Assisted Walking enables repair and reorganization of innate processes in the central nervous system.

Winstein et al reports task specific training such as Lokomat Gait Assisted Walking enables repair and reorganization of innate processes in the central nervous system. In order to walk or regain functional capacity the injured patient must re-learn to walk. Re-organization of processes refers to the development of the brain to find alternate pathways sending improved electrical signals. It is possible for the brain to transfer function responsibility to another part of the brain. It has also been demonstrated that strength training in CP patients can increase strength as well as result in higher gait velocity. Similar to strength training, treadmill training with partial body weight support, as discussed can improve walking speed and endurance of CP patients who have partial walking ability. Furthermore, it has been found that, in some cases, treadmill training with partial body weight support can achieve completely independent mobility for previously non-ambulatory brain and spinal patients.

Pediatric Lokomat offers opportunity to practice a most physiological gait pattern in a high intensity and frequency for children with gait impairment due to spinal or cerebral motor disorder including cerebral palsy. With this new tool, not only longer distances and therefore "higher dosages" of gait therapy, but also various and higher speeds can be trained, which is not possible to this extent with conventional physiotherapeutic methods. The Pediatric Lokomat raises many new topics of research about the effectiveness, dosage and age related application of this new therapy.

Children with cerebral palsy have an 'acquired dysfunction which their central nervous system function deems normal'. This is evident when CP children undertake an intensive Lokomat Gait Training protocol. Many of these children demonstrate a 'normal gait' whilst on the Lokomat which raise question of acquired neural pathways and motor function wrongly developed and reinforced over time. When these same children come off the Lokomat they immediately return back to the acquired gait. Intensity and repetition enables the CP child to generate a new functionality which resembles a 'normal gait'. It is a frequent finding to observe the bewilderment of both parents and CP child when the child sees themselves 'walking normal' on the Lokomat. Visualization whilst on the Lokomat is an important paradigm shift for not only the CP child and parent but also the therapist.

The central nervous system develops function through interaction. Activities that we take for granted shape our nervous system developing healthy skills and mental function that ensures a healthy functioning nervous system.

When the brain and spinal cord suffer 'hypoxic injury' the normal functioning skills become replaced by abnormal signals leading to disabilities the brain recognizes as 'normal'. Abnormal signals need to be corrected through functional re-organization. Lokomat treadmill training is a task-specific rehabilitation strategy that enhances neurologic re-organization impacting cognitive function and development.

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.

All the above mentioned improvements 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.

What are the advantages of using Robotically Assisted Gait Training (Lokomat) compared to manual bodyweight supported treadmill training (BWSTT)?

Because manual assisted bodyweight supported treadmill training has high therapist labor requirements, research groups around the world have developed a host of robotic devices to assist treadmill stepping. In manual BWSTT, at least three to four specially trained therapists are required to move the patient's legs and body. The purpose of these robotic machines is to replace therapist manual assistance, increasing the amount of stepping practice and accuracy while decreasing therapist effort.

Manually assisted treadmill training (BWSTT) has several major limitations. The training is labor-intensive and biomechanically challenging to the active therapist; therefore, training duration is usually limited by personnel shortages and therapist, not patient fatigue. Furthermore, therapists often experience back pain because the training is performed in an ergonomically unfavorable seating posture. Consequently, training sessions are shorter than may be required for an optimal therapeutic outcome. The most compelling argument for Lokomat is that manually assisted treadmill training lacks accurate repeatability and objective measures of patient performance and progress. In contrast, the duration and number of sessions in Lokomat Gait Training can be accurately repeated and increased while reducing the number of therapists required for each patient. Indeed, one therapist may be able to train two or more patients at a time in the future.

Lokomat has great advantage providing intensive task specific repetitive training that induces neuronal plasticity and subsequently cortical reorganization after brain and spinal cord damage. Patients with high level spasticity causing compensatory gait dysfunction are better suited on the Lokomat than manual BWSTT. Lokomat parameters can be initially set at very low and controlled setting providing a safe environment for the patient to develop confidence and allow functional reorganization through repetition and patterning. These parameters can then be built on and individually tailored to the specific requirements and functional responses of the individual patient. Lokomat provides task specific accuracy and repetition stimulating innate central pattern reflexes and higher cortical function.

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.

5. Research Strategy

We propose a clinical trial to measure functional outcomes of individuals suffering various degrees of adult and child Cerebral Palsy.

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

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

6. 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 functional changes

7. Estimated Program Budget

- Trial number 25-children age range 5-10 years; 25-adult age range 21-35 years
- Estimated trial period per subject 8-months
- Estimated period of total trial 2-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 \$2,240,000

8. 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. Behavioural 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

9. Supporting References

1. Montgomery D, Goldberg J, Amar etc (1999) **Effects of Hyperbaric Oxygen Therapy on children with spastic diplegia cerebral palsy: a pilot project.** Undersea Hyperb Med 26: 235-42.
2. Machado J (1989) **clinically observed reduction of spasticity in patients with neurological diseases and in children with cerebral palsy from hyperbaric oxygen therapy.** Proceedings of New Horizons in Hyperbaric Medicine. American College of Hyperbaric Medicine.
3. Collet JP, Vanasse M, Marios P et al (2001) **Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial.** HBO-CP Research Group. Lancet 357: 582-586.
4. **United States Army Study on Adjunctive HBO Treatment of Children with Cerebral Anoxic Injury** Text Hyperbaric Medicine K.K Jain pp 291.
5. **Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain and spinal cord trauma and neurologic disease.** Adv Ther. 2005 Nov-Dec;22(6):659-78. Life Support Technologies, Inc., and NewTechnologies, Inc., The Mount Vernon Hospital, New York Medical College, New York, USA. Hyperbaric oxygen (HBO) therapy has been used to treat patients with numerous disorders, including stroke. This treatment has been shown to *decrease cerebral edema, normalize water content in the brain, decrease the severity of brain infarction, and maintain blood-brain barrier integrity.* In addition, *HBO therapy attenuates motor deficits, decreases the risks of sequelae, and prevents recurrent cerebral circulatory disorders, thereby leading to improved outcomes and survival.* Hyperbaric oxygen also *accelerates the regression of atherosclerotic lesions, promotes antioxidant defenses, and suppresses the proliferation of macrophages and foam cells in atherosclerotic lesions.* HBO therapy has *improved the function of damaged cells, attenuated the effects of hypoxia on the neonatal brain, enhanced gross motor function and fine motor control, and alleviated spasticity.* In the treatment of patients with migraine, HBO therapy has been shown to reduce intracranial pressure significantly and abort acute attacks of migraine, reduce migraine headache pain, and prevent cluster headache. In studies that investigated the effects of HBO therapy on the damaged brain, the treatment was found to *inhibit neuronal death, arrest the progression of radiation-induced neurologic necrosis, improve blood flow in regions affected by chronic neurologic disease as well as aerobic metabolism in brain injury, and accelerate the resolution of clinical symptoms.* Hyperbaric oxygen has also been reported to *accelerate neurologic recovery after spinal cord injury by ameliorating mitochondrial dysfunction in the motor cortex and spinal cord, arresting the spread of hemorrhage, reversing hypoxia, and reducing edema.* HBO has *enhanced wound healing in patients with chronic osteomyelitis.* The results of HBO therapy in the treatment of patients with stroke, atherosclerosis, cerebral palsy, intracranial pressure, headache, and brain and spinal cord injury are promising and warrant further investigation.
6. **Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats.** Undersea Hyperb Med. 2008 Mar-Apr;35(2):113-29. Division of Neonatology, Department of Pediatrics, Xiang Ya Hospital, Central South University. **BACKGROUND AND PURPOSE:** Studies suggest that after brain injury, *hyperbaric oxygen (HBO2) is neuroprotective by stimulating neural cell proliferation. HBO2 promotes neural stem cells (NSC) to proliferate and differentiate in neonatal hypoxic-ischemic (HI) rats.* **METHODS:** Seven-day-old rat pups were subjected to unilateral carotid artery ligation followed by 2 hours of hypoxia (8% O₂). HBO₂ was administered (2 ATA (atmospheres absolutes), once daily for 7 days) within 3 hours after HI. The proliferating neural stem cells in the subventricular zone (SVZ) and dentate gyrus (DG) were dynamically examined by 5-bromo-2-deoxyuridine (BrdU)/nestin immunofluorescence. Nestin protein was detected by western blot analysis at various time points (from 6 hours to 14 days) after HI. The migrating NSC were examined by BrdU/doublecortin (DCX) immunofluorescence 7 and 14 days after HI. The phenotype of the newborn cells was identified by BrdU/beta-tubulin, BrdU/ glial fibrillary acidic protein (GFAP) and BrdU/O4 (oligodendrocyte marker) immunofluorescence. Myelin basic protein (MBP) was examined by immunohistochemistry and pathological changes of the brain tissue were detected 28 days after HI.

RESULTS: In neonatal HI rats treated with HBO₂, the proliferation of endogenous NSC was observed in the SVZ and DG. Cell numbers peaked 7 days after HI and proliferating NSC migrated to the cerebral cortex at 14 d after HI. Twenty-eight days after HI, an increase in newly generated neurons, oligodendrocytes and MBP was observed in the HBO₂ group compared to the untreated and HI-treated rats. **CONCLUSIONS:** *This study suggests that HBO₂ treatment promotes 'target specific neurogenesis' of the endogenous NSC in neonatal HI rats, contributing to repair of the injured brain.*

7. **Stem cell infusion and Hyperbaric Oxygenation improves Pancreatic function in Diabetes** Source: Cell Transplantation Center of Excellence for Aging and Brain Repair (Vol. 17 No.12) A study to determine if patients with type 2 diabetes can benefit from a combination of autologous (patient self-donated) stem cell infusions (ASC) and hyperbaric (above the normal air pressure of) oxygen treatment (HBO) before and after ASC has found "significant benefits" in terms of "improvements in glycemic control" along with "reduced insulin requirements." The combination therapy could decrease type 2 diabetes morbidity and mortality, said the authors. 'Autologous stem cell therapies are an emerging with promising results and low side effects profiles,' said Esteban Estrada, MD, of Stem Cell Argentina. 'In addition, hyperbaric oxygen therapy, used primarily in the treatment of carbon monoxide poisoning, air embolism suffered by divers, and as an enhancement to wound healing, has been shown to increase stem cell mobilization and the release of endothelial progenitor cells via a nitric oxide-dependent mechanism.' The clinical trial evaluated the ASC-HBO combination treatment in 25 patients with type 2 diabetes. According to the researchers, it is well known that with type 2 diabetes, there is an ongoing inflammation of the pancreas. Their hypothesis suggested that *mobilizing stem cells would cause the growth of blood vessels (angiogenesis) and release factors that would result in the local differentiation of progenitor cells with a resulting anti-inflammatory effect.* Diabetes has been shown to impair progenitor cell mobilization, a problem that local stem cell infusion could remedy. The effect of the *hyperbaric oxygen therapy would be to increase stem cell mobilization* in such a way as 'to target more than one crucial reparative step' to counteract the chronic injury that attack the endothelial progenitor cells and the islet cells. 'Overall, our results show that a close follow-up with intensive diabetic management alone could not be the only cause of the positive, progressive and consistent outcomes we obtained in this trial over one year of follow-up,' said Dr. Estrada. 'A decade ago, research had explored stem cell transplantation and hyperbaric oxygen therapy as stand-alone treatments. This Stem cell infusion and Hyperbaric Oxygenation improves Pancreatic function in Diabetes study highlights the potential benefits of using an unusual combination therapy to treat diabetes' said Dr. Cesar V Borlongan, Professor University of South Florida College of Medicine.
8. **Stem cells and neurological diseases** Cell Prolif. 2008 Feb;41 Suppl 1:94-114 Department of Neurology, Medical College of Georgia, Augusta, GA 30912, USA. Cells of the central nervous system were once thought to be incapable of regeneration. This dogma has been challenged in the last decade with studies showing *new, migrating stem cells in the brain and spinal cord* in many rodent injury models and findings of new neurones in the human hippocampus in adults. Moreover, there are reports of *bone marrow-derived cells developing neuronal and vascular phenotypes and aiding in repair of injured brain*. These findings have fuelled excitement and interest in regenerative medicine for neurological diseases. There are numerous proposed regenerative approaches to neurological diseases. These include cell therapy approaches in which cells are delivered intracerebrally or are infused by an intravenous or intra-arterial route; *stem cell mobilization approaches in which endogenous stem and progenitor cells are mobilized by cytokines such as granulocyte colony stimulatory factor (GCSF) or chemokines such as SDF-1; trophic and growth factor support, such as delivering brain-derived neurotrophic factor (BDNF) or glial-derived neurotrophic factor (GDNF) into the brain to support injured neurones; these approaches may be used together to maximize recovery.* While initially, it was thought that cell therapy might work by a 'cell replacement' mechanism, a large body of evidence is emerging that *cell therapy works by providing trophic or 'chaperone' support* to the injured tissue and brain. Angiogenesis and neurogenesis are coupled in the brain. *Increasing angiogenesis with adult stem cell approaches in rodent models of stroke leads to preservation of neurones and improved functional outcome.* A number of stem and progenitor cell types have been proposed as therapy for neurological disease ranging from neural stem cells to bone marrow derived stem cells to embryonic stem cells. Currently, bone marrow-derived cell populations such as the marrow stromal cell, multipotential progenitor cells, umbilical cord stem cells and neural stem cells meet these criteria the best. Of great clinical significance, initial evidence suggests these cell types may be delivered by an allogeneic approach, so strict tissue matching may not be necessary. The most immediate impact on patients will be achieved by making use of the trophic support capability of cell therapy and not by a cell replacement mechanism.
9. **Stem cell mobilization by hyperbaric oxygen** Am J Physiol Heart Circ Physiol. 2006 Apr;290(4):H1378-86. Institute for Environmental Medicine, University of Pennsylvania, Philadelphia, PA 19104-6068, USA.

We hypothesized that exposure to *hyperbaric oxygen (HBO(2)) would mobilize stem/progenitor cells from the bone marrow by a nitric oxide (*NO) -dependent mechanism.* The population of CD34(+) cells in the peripheral circulation of humans doubled in response to a single exposure to 2.0 atmospheres absolute (ATA) O(2) for 2 h. Over a course of 20 treatments, *circulating CD34(+) cells increased eightfold*, although the overall circulating white cell count was not significantly increased. The number of colony-forming cells (CFCs) increased from 16 +/- 2 to 26 +/- 3 CFCs/100,000 monocytes plated. Elevations in CFCs were entirely due to the CD34(+) subpopulation, but increased cell growth only occurred in samples obtained immediately posttreatment. A high proportion of progeny cells express receptors for vascular endothelial growth factor-2 and for stromal-derived growth factor. In mice, HBO(2) increased circulating stem cell factor by 50%, increased the number of circulating cells expressing stem cell antigen-1 and CD34 by 3.4-fold, and doubled the number of CFCs. Bone marrow *NO concentration increased by 1,008 +/- 255 nM in association with HBO(2). Stem cell mobilization did not occur in knockout mice lacking genes for endothelial *NO synthase. Moreover, pretreatment of wild-type mice with a *NO synthase inhibitor prevented the HBO(2)-induced elevation in stem cell factor and circulating stem cells. *We conclude that HBO(2) mobilizes stem/progenitor cells by stimulating *NO synthesis.*

10. HyperMED/Lokomat - **Australian Experience HyperMED NeuroRecovery.pdf**
11. **Spinal Abstracts Sept 2008 - Specific locomotor (LOKOMAT) versus unspecific weight training and their effects on gait function and corticospinal conductivity after chronic incomplete spinal cord injury**
R. Labruyère, V. Dietz, H.J.A. van Hedel Spinal Cord Injury Center, Balgrist University Hospital, CH-8008 Zurich, Switzerland Bodyweight supported treadmill training improves locomotion in patients with a chronic incomplete spinal cord injury (iSCI). This improvement occurs in parallel to an increase in corticospinal conductivity of lower leg muscles (Thomas and Gorassini 2005). The aim of the present study is to investigate whether a specific locomotor training (Lokomat - automated locomotor training with a driven gait orthosis) is accompanied by larger changes in corticospinal conductivity of the lower limb compared to unspecific training (conventional lower extremity strength training) in such subjects. Methods: 30 ASIA C and D subjects are randomly assigned to one of the training groups. All of them receive 32 training sessions of each 45-minutes within 8 weeks. Directly before and after the intervention and at 6 months after finishing the intervention, corticospinal conductivity will be assessed by the use of transcranial magnetic stimulation. *Corticospinal conductivity improves more after specific compared to unspecific locomotor therapy.*
12. **Neuroimaging and cerebral palsy in children** Msall ME, Limperopoulos C, Park JJ. *Minerva Pediatr.* 2009 Aug;61(4):415-24. Section of Developmental and Behavioral Pediatrics University of Chicago, Pritzker School of Medicine, JP Kennedy Research Center on Intellectual and Neurodevelopmental Disabilities, Chief, Comer and LaRabida Children's Hospitals Chicago, IL, USA. Cerebral palsy (CP) is a description of a spectrum of central nervous system (CNS) impairments that affect mobility, communication, intellectual ability, and neurobehavior as a result of developmental brain dysfunction. CP is the most common contributor to motor disability in children with prevalence of about 2-3/1000 live births globally. Presently, no curative therapies or successful methods of prevention on a population level are available for children with one of the cerebral palsy syndromes. Despite these challenges, orthopedic, rehabilitation, neuropharmacological, and other management interventions can help maintain mobility, prevent deformity, and promote quality of life for children with CP. Typically, the diagnosis of CP is based on clinical observations and parent concerns regarding delays in attaining motor milestones (e.g., rolling, sitting, crawling, walking), not on laboratory testing or neuroimaging. However, since 2004 the American Academy of Neurology (AAN) has recommended that neuroimaging of the CNS be part of diagnostic process for cerebral palsy. Although the guideline was initially met with controversy and criticism, neuroimaging has allowed a broader appreciation of timing of lesions, extent of white matter involvement, and the complexity of the motor spectrum of disability. In this article we shall describe the major types of neuroimaging techniques and review their roles in identification and evaluation of children with one of the cerebral palsy syndromes. The authors will focus on the emerging knowledge of how brain structure can inform us about children's functioning, especially among children with prematurity, recognizing that we are only beginning to understand brain plasticity and developmental resiliency. PMID: 19752850 [PubMed - in process]
13. **Neuroimaging and cerebral palsy in children** Msall ME, Limperopoulos C, Park JJ. *Minerva Pediatr.* 2009 Aug;61(4):415-24. Section of Developmental and Behavioral Pediatrics University of Chicago, Pritzker School of Medicine, JP Kennedy Research Center on Intellectual and Neurodevelopmental Disabilities, Chief, Comer and LaRabida Children's Hospitals Chicago, IL, USA. Cerebral palsy (CP) is a description of a spectrum of central nervous system (CNS) impairments that affect mobility, communication, intellectual ability, and neurobehavior as a result of developmental brain dysfunction. CP is the most common contributor to motor disability in children with prevalence of about 2-3/1000 live births globally. Presently, no curative

therapies or successful methods of prevention on a population level are available for children with one of the cerebral palsy syndromes. Despite these challenges, orthopedic, rehabilitation, neuropharmacological, and other management interventions can help maintain mobility, prevent deformity, and promote quality of life for children with CP. Typically, the diagnosis of CP is based on clinical observations and parent concerns regarding delays in attaining motor milestones (e.g., rolling, sitting, crawling, walking), not on laboratory testing or neuroimaging. However, since 2004 the American Academy of Neurology (AAN) has recommended that neuroimaging of the CNS be part of diagnostic process for cerebral palsy. Although the guideline was initially met with controversy and criticism, neuroimaging has allowed a broader appreciation of timing of lesions, extent of white matter involvement, and the complexity of the motor spectrum of disability. In this article we shall describe the major types of neuroimaging techniques and review their roles in identification and evaluation of children with one of the cerebral palsy syndromes. The authors will focus on the emerging knowledge of how brain structure can inform us about children's functioning, especially among children with prematurity, recognizing that we are only beginning to understand brain plasticity and developmental resiliency. PMID: 19752850 [PubMed - in process]

14. **Investigation of goal change to optimize upper-extremity motor performance in a robotic environment** Brewer BR, Klatzky R, Markham H, Matsuoka Y. *Dev Med Child Neurol.* 2009 Oct;51 Suppl 4:146-53. University of Pittsburgh, PA 15260, USA. Robotic devices for therapy have the potential to enable intensive, fully customized home rehabilitation over extended periods for individuals with stroke and traumatic brain injury, thus empowering them to maximize their functional recovery. For robotic rehabilitation to be most effective, systems must have the capacity to assign performance goals to the user and to increment those goals to encourage performance improvement. Otherwise, individuals may plateau at an artificially low level of function. Frequent goal change is needed to motivate improvements in performance by individuals with brain injury; but because of entrenched habits, these individuals may avoid striving for goals that they perceive as becoming ever more difficult. For this reason, implicit, undetectable goal change (distortion) may be more effective than explicit goal change at optimizing the motor performance of some individuals with brain injury. This paper reviews a body of work that provides a basis for incorporating implicit goal change into a robotic rehabilitation paradigm. This work was conducted with individuals without disability to provide foundational knowledge for using goal change in a robotic environment. In addition, we compare motor performance with goal change to performance with no goal or with a static goal for individuals without brain injury. Our results show that goal change can improve motor performance when participants attend to visual feedback. Building on these preliminary results can lead to more effective robotic paradigms for the rehabilitation of individuals with brain injury, including individuals with cerebral palsy. PMID: 19740223 [PubMed - in process]
15. **Robot-assisted task-specific training in cerebral palsy** Krebs HI, Ladenheim B, Hippolyte C, Monterroso L, Mast J. *Dev Med Child Neurol.* 2009 Oct;51 Suppl 4:140-5. Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA. Our goal was to examine the feasibility of applying therapeutic robotics to children and adults with severe to moderate impairment due to cerebral palsy (CP). Pilot results demonstrated significant gains for both groups. These results suggest that robot-mediated therapy may be an effective tool to ameliorate the debilitating effects of CP and provide new opportunities for reducing impairment and improving coordination. PMID: 19740222 [PubMed - in process]
16. <http://www.thescizone.com/news/9548/new-robotic-therapy-helping-children-with-cerebral-palsy-walk>
17. HyperMED/lokomat reference list.pdf
18. Text: Hyperbaric for Neurologic Disorders Edited J. Zang MD
19. Textbook of Hyperbaric Medicine 4th Edition K.K. Jain
20. www.hypermed.com.au