UNFUNDED LIST HONOREE:

Cerebral Palsy Alliance Research Foundation

Honoree Proposal Description:

Cerebral Palsy Alliance Research Foundation was established to fund the world's best research to treat, prevent and find a cure for cerebral palsy.

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Organization Website:

https://cparf.org/

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Cerebral Palsy ALLIANCE

RESEARCH FOUNDATION

Our vision: a future without cerebral palsy.

Our purpose: to support the world's best and brightest researchers to prevent and cure cerebral palsy.

Executive Summary

Cerebral Palsy: accelerating breakthroughs in prevention, treatment and cure.

Cerebral Palsy is the most common physical disability in childhood and a condition that affects the movement, posture and speech of 17 million people globally.

Cerebral Palsy Alliance Research Foundation (CPARF) was established by Cerebral Palsy Alliance in 2005 as a world first, dedicated to funding the best and brightest minds in cerebral palsy research around the world, to drive major achievements in the prevention, treatment and cure of cerebral palsy.

The foundation has developed a reputation as a world leader in CP research.

Current CP research is not only re-writing the future for those living with CP. The discoveries made are expected to have a transformational impact for a range of other human conditions and disorders including spinal cord injury, brain traumas, neurological conditions, stroke, Parkinson's, dystonia, epilepsy, autism and many more.

Organizational History and Purpose

CPARF has invested over $36 million into research, funding their own team of researchers as well as over 300 CP projects in the USA, Australia and internationally. The Foundation has established a global CP research collaboration known as IMPACT (International Multidisciplinary Prevention and Cure Team for CP) and hosted 5 global research summits, bringing together the best cerebral palsy scientists in the world. The research leadership team helped to found the 'Australian Cerebral Palsy Register', the largest whole country data register in the world for CP which has been a critical tool in reducing the incidence and severity of cerebral palsy in Australia in the past ten years (from 1 in 400 to 1 in 700 babies.) The Foundation was instrumental in the two most recent research breakthroughs which have identified preventions for CP and these are already being converted into clinical practice (magnesium sulphate and therapeutic hypothermia).

Building on this outstanding history of leadership in 2015 the U.S 'friends of' CPARF, based in New York City was established to further accelerate CP research. The organization comprises of an outstanding scientific team and a senior Board of Directors and Council of Governors.

The Team

Professor Nadia Badawi AM is the Macquarie Group Foundation Professor and Chair of Cerebral Palsy at the CPARF, based at the University of Sydney's Brain & Mind Centre. Prof Badawi was selected as one of the "100 most influential women in Australia" for her leadership of international CP research, and developing research capacity in low income countries. Prof Badawi has dedicated her life to providing high-quality clinical care for critically ill children and to establishing a rights-based inclusive society for children with disability. Her expertise includes over $26M in grants, 92 keynotes and 167 publications.

Professor Badawi AM works with a skilled and dedicated team of researchers committed to prevention and cure of CP through a program of neuro-protective and neuro-regenerative clinical trials.

Achievements and Outcomes:

- Reduction in incidence of CP from 1 in 400 to 1 in 700 Australian live births.
- Reduction in severity of CP – Australia is one of the first countries in the world to achieve this breakthrough.
- Establishment of Australian CP Register, the largest single country register of people living with CP in the world.
- Research breakthroughs translated into practice, including magnesium sulphate to prevent CP in very pre-term babies and hypothermia (cooling) to reduce CP in sick newborns.
- Significant reduction in average age of CP diagnosis (previously 19 months on average), now possible at 12 weeks, opening a vital window for early intervention and neuroplasticity for babies at risk.
- New International Clinical Guidelines for Early Diagnosis.
- Establishment of Australia's first Early Diagnosis Clinic for CP in partnership with NSW Health (to address the currently fragmented diagnostic services for babies at risk of CP).
- Launch of Australia's first cord blood stem cell trial for CP.
- Identification of genetic factors as a significant contributor to CP causation.
- Identification of Cytomegalovirus (CMV) as an important cause of term CP.
- Establishment of Xcellerate, the world's first global CP stem cell research consortium.
- Establishment of IMPACT for CP (International Multidisciplinary Prevention and Cure team for CP), a global network of CP researchers working to accelerate CP research by reducing research duplication and working towards a global research agenda.
- Establishment of the Chair of Technology and Innovation at the University of Sydney.
- Hosting 7 global CP research summits bringing together 170 expert researchers from 15 countries.
- Establishment of CP registers in several lower middle income countries.

Annual Budget

CPARF's annual budget of $2,507,281 supports a team of 16, including:

Professor Nadia Badawi, MACQUARIE GROUP FOUNDATION CHAIR OF CEREBRAL PALSY, THE UNIVERSITY OF SYDNEY

Professor Iona Novak, HEAD OF RESEARCH, CEREBRAL PALSY ALLIANCE RESEARCH INSTITUTE, THE UNIVERSITY OF SYDNEY

Dr Sarah McIntyre, SENIOR RESEARCH FELLOW & NHMRC EARLY CAREER FELLOW, THE UNIVERSITY OF SYDNEY

Associate Professor Karen Walker, SENIOR RESEARCH FELLOW, IMPACT FOR CP

Dr Petra Karlsson, RESEARCH FELLOW

Dr Cathy Morgan, RESEARCH FELLOW

Dr Hayley Smithers-Sheedy, RESEARCH FELLOW

Dr Maria Mc Namara, RESEARCH MANAGER

Zoe Burrell, EXECUTIVE ASSISTANT TO CHAIR OF CEREBRAL PALSY AND HEAD OF RESEARCH

Shona Goldsmith, RESEARCH ASSOCIATE & NHMRC POSTGRADUATE SCHOLAR, PHD CANDIDATE, THE UNIVERSITY OF SYDNEY

Ingrid Honan, RESEARCH OFFICER & PHD CANDIDATE (MACQUARIEU), PROVISIONAL PSYCHOLOGIST

Isabelle Baldé, RESEARCH ASSISTANT

Abigail Townsend, RESEARCH ASSISTANT

Claire Galea, RESEARCH ASSOCIATE, STATISTICIAN

Yana Wilson, RESEARCH OFFICER, CP GENOMICS

Megan Finch-Edmondson, RESEARCH FELLOW, STEM CELL

The Future

Research into CP has reached a critical point. New technologies are providing opportunities to investigate CP in ways never previously possible. New treatment options, such as stem cells provide real hope for the prevention and repair of neurological injury, a known cause of cerebral palsy. With additional funding, the CPARF team will move forward with determination and excellence, accelerating efforts to change the future for people living with CP through funding world class research into prevention, treatment and cure.

Building upon successes to date, the team's future CP research priorities of focus are:

- Implementation of early detection
- Implementation of early intervention strategies
- Active surveillance to decrease complications (hip dislocation and scoliosis)
- International genetics consortium and database
- Stem cells as a treatment
- Harnessing technology to improve the lives of people with CP
- Unravelling the complex causes of CP

In every aspect of our research to date, from diagnosis; to genetics and detection, through to brain scans and mapping; the field has made incredible breakthroughs. Our dedication to accelerating progress continues with our innovative research program targeting the achievement of critical outcomes across key priority areas set by Australians living with cerebral palsy and their families:

Translating Research Into Practice
The translation of research-based information for people with CP and their families, clinicians, service providers and funding agencies ensures this information is available to facilitate discussions and decision making between these stakeholders regarding effective interventions and assessments.

Translational Research Studies
1. Stem cell therapy for premature babies at risk of cerebral palsy;
2. Antenatal melatonin to provide neuroprotection to the growth restricted fetus;
3. Maternal creatine supplementation to protect babies from birth asphyxia.

STUDY 1 | Stem cell therapy for premature babies at risk of cerebral palsy

Funding required: $150,000

For parents of a child with cerebral palsy there is huge interest in stem cell treatments - many overseas private clinics are selling unproven stem cell therapy for profit to families of children with cerebral palsy. The result of this is that Australian families are taking their children overseas for stem cell therapy. Our systematic review data supports preliminary efficacy of stem cells, however larger, earlier, and more rigorous trials are urgently needed in an Australian context.

About 65 babies are born prematurely in Australia each day. Significant advances in neonatal care now mean that most premature babies survive, but many survive with a disability and there is a strong causal link between prematurity and cerebral palsy, with almost 50% of children with cerebral palsy born prematurely. Promisingly, our recent animal data demonstrates that placental stem cells (amnion epithelial cells) and umbilical cord blood stem cells (UCB cells) both provide strong anti-inflammatory benefit when administered early after premature birth, or shortly after brain injury. These cells also induce neuro-regeneration of the developing white matter of the immature brain, which is key for

connectivity. We have established these stem cells are extremely safe in a world first human phase I clinical trial, for the treatment of established lung disease and brain injury (cerebral palsy) in infants.

We are now ready to move to the world's first human clinical trial in premature babies at risk of cerebral palsy. We believe that this therapy will provide the best chance of targeted neuroprotection for this vulnerable group of infants, and if our hypothesis is found to be true, the findings of this study will profoundly influence the care of premature infants world-wide, by offering a cost-effective, easily accessible form of regenerative medicine.

Investigators: A/Prof Rod Hunt, A/Prof Suzie Miller, Dr Rebecca Lim, Prof Iona Novak, Prof Peter Anderson, A/Prof Michael Fahey, Prof Nadia Badawi, A/Prof Michael Fahey, Dr Courtney McDonald , A/Prof Deanne Thompson, Claire Galea, Prof Euan Wallace.

ACTION STEP:
Stem cells offer great promise as a novel treatment for cerebral palsy. Stem cells are capable of reducing inflammation, and improving the environment at the site of the brain injury (trophic effects), thus reducing the size and impact of a brain injury.
Aim: The **aim** is to test the efficacy of placental stem cells (amnion epithelial cells) in reducing the severity of cerebral palsy in a clinical trial. Our **hypothesis** is that extremely preterm infants transfused with amnion epithelial cells, will have superior neurodevelopmental skills (Cognition, Language, Motor, Social-Emotional, and Vision) compared to infants in the placebo-controlled group.
Methodology: Double-blind, placebo-controlled randomised clinical trial (Phase 2). N=490 infants born extremely preterm (<30 weeks) will be randomized to receive either standard Neonatal Intensive Care plus amnion epithelial stem cells in the first week of life, or standard Neonatal Intensive Care (with placebo) as control.

STUDY 2 | Antenatal melatonin to provide neuroprotection to the growth restricted fetus

Funding required: $640,000

Fetal growth restriction is a serious obstetric complication affecting up to 24,000 Australian pregnancies each year. Fetal growth restriction is most often caused by placental dysfunction, resulting in oxygen and nutrient deficiencies, and a fetus that fails to thrive. Low levels of oxygen in the fetus' blood produces a state of 'oxidative stress'. The developing brain is especially vulnerable to oxidative stress, with fetal growth restriction contributing to high rates of morbidity and mortality in these infants, including cerebral palsy.

Melatonin is a naturally occurring hormone that has powerful antioxidant, anti-inflammatory and immune properties. Over the past decade our research in a sheep model of fetal growth restriction has definitively shown that we can prevent brain injury and normalize neurological function by antenatal supplementation with melatonin. Furthermore, from two completed Phase I clinical trials we have shown that Melatonin is safe for both mother and baby, and identified the optimal dose of melatonin in human pregnancy. With this information we are now ready to start a world's first randomised clinical trial of maternal melatonin as a therapy to provide neuroprotection to the growth restricted fetus and ultimately prevent cerebral palsy.

Investigators: Prof Euan Wallace, A/Prof Suzie Miller, Dr Kirsten Palmer, Prof Peter Anderson, A/Prof Michael Fahey.

ACTION STEP:
Preventing the deleterious side effects of fetal growth restriction will reduce the incidence and severity of life-long disability including cerebral palsy.
Aim: The **aim** is to assess the impact of maternal antenatal melatonin supplementation on early childhood neurodevelopmental outcomes caused by fetal growth restriction. Our **hypothesis** is that fetally growth restricted babies born to mothers who receive antenatal melatonin will have better neurodevelopmental outcomes than those born to mothers who received placebo.
Methodology: Double-blind, placebo-controlled randomised clinical trial (Phase 2). N=146 women with a singleton pregnancy complicated by fetal growth restriction, identified at 23-32 weeks gestation. Women will be randomised to receive either melatonin (20 mg/day) or placebo for the remainder of the pregnancy.

STUDY 3 | Maternal creatine supplementation to protect babies from birth asphyxia

Funding required: $560,000

Birth asphyxia (lack of oxygen) is a condition that can strike during the final moments of even the most uneventful pregnancy. The unpredictable nature of birth asphyxia and the widespread organ damage that follows means that birth asphyxia remains one of the leading causes of neonatal brain injury including cerebral palsy. Injury caused by brain reperfusion (when blood supply returns to the tissue) following resuscitation after birth asphyxia is an unavoidable and significant cause of infant morbidity and mortality.

Creatine and its phosphorylated derivative phosphocreatine have long been established as having a critical role in neural development and brain metabolism. Creatine works in the brain to maintain ATP turnover, acid-base balance, and mitochondrial function, and it also has antioxidant, vasodilator, and anti-excitotoxic properties, making it a promising candidate for the treatment of reperfusion-injury that occurs after birth asphyxia. Importantly, preliminary data suggests creatine is effective as a neuroprotectant following deleterious brain injury.

We are currently completing a short-term investigation of the capability of maternal dietary creatine supplementation to prevent the immediate effects of brain injury in a non-human primate model of birth asphyxia. Preliminary data suggests creatine is neuroprotective, preventing a number of motor and behavioral deficits indicative of cerebral palsy. This is also supported by anecdotal evidence of its effectiveness in a number of human pregnancies where it has been used off-label as a desperate measure to prevent fetal demise due to failure of the fetus to grow.

ACTION STEP:
A solid foundation in pre-clinical animal studies is essential for novel findings to be swiftly translated to large scale randomized controlled trials and clinical interventions.
Aim: The aim is to complete a longer-term follow up study of the efficacy of maternal dietary creatine to prevent neurodevelopmental impairments including cerebral palsy following birth asphyxia in a non-human primate model. Our **hypothesis** is that neonates born to mothers who received creatine supplementation will have better neurodevelopmental outcomes following birth asphyxia compared to babies born to mothers who received placebo.
Methodology: Randomised pre-clinical study of pregnant rhesus macaques receiving creatine supplementation (or control) for 30 days before c-section birth with controlled asphyxia. Neonates will then be assessed with comprehensive neuro-behavioural assessments to determine the effectiveness of creatine to reduce disability (in childhood) such as cerebral palsy.

Investigators: Dr Stacey Ellery, Prof David Walker, Prof Rod Snow, Dr Meredith Kelleher, A/Prof Michael Fahey, Prof Larry Sherman.

The time is right to accelerate the search for better treatments and a cure, providing hope, empowerment and lasting change through world-leading translational cerebral palsy research.

Prof Nadia Badawi AM
Cerebral Palsy Alliance
Macquarie Group Foundation Professor and Chair of Cerebral Palsy

Professor Euan Wallace AM
The Ritchie Centre & Monash University
Carl Wood Clinical Professor in Obstetrics and Gynaecology

Partner Research Institutions - in collaboration with

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