Cerebral Palsy: Causes to Prevention

Project Summary:

Cerebral palsy (CP) is the most common cause of physical impairment encountered in pediatrics. It is a ‘symptom complex’ that is heterogeneous in all its manifestations. The core essential feature of CP is a neuromotor impairment that is the result of either a developmental or acquired injury to the not-yet mature brain. Though all individuals with CP share a neuromotor impairment, frequent co-morbidities are experienced such as epilepsy, cognitive limitations, primary sensory impairments, language difficulties, behavioural challenges and orthopedic deformities (i.e. scoliosis), that may constitute the major burdens of care. CP is a lifelong disorder which has considerable additional costs at individual, familial and societal levels.

The proposed CP Demonstration Project (CPDP) brings together an interdisciplinary team with complementary levels of expertise (clinical research, epidemiology, molecular genetics, advanced imaging techniques, animal models, regenerative medicine, outcomes and health services research) to form a new collaborative network that will work synergistically to increase our understanding of the causes of CP, and to explore potential avenues for both prevention and treatment. This collective effort is directed at both preventing future cases of CP and ameliorating those cases of CP already existing in our population.

The project has a number of specific objectives: a) establishing a multi-regional Canadian CP Registry that will serve as a platform for identifying the profile of CP in the Canadian population and its risk factors, b) providing a subject base for advanced imaging and genetic studies, and c) informing and modifying existing animal models and regeneration innovation that address specific issues in causation and novel treatment approaches. It is anticipated that clinical observations will inform animal models, and basic research will modify existing clinical understanding and practice. Features of children with CP often overlap with the phenotypic features of individuals experiencing the other neurodevelopmental disabilities (fetal alcohol spectrum disorder [FASD], autistic spectrum disorder [ASD]) that are also a focus of NeuroDevNet. Thus the CPDP fits well within the overall mission of NeuroDevNet: to increase our understanding of how brains develop and how abnormal development or acquired injury results in activity limitations for some Canadian children. Through this collective effort, it is anticipated that the burdens of cerebral palsy in the Canadian population will be lessened at a variety of different levels.
## Project Team & Roles

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Objectives:

Cerebral Palsy Demonstration Project Research Program

1. To describe the type, severity, suspected etiology, co-morbidities and geographic distribution of CP in multiple regions in Canada.

2. To identify the antepartum, intra-partum, and postpartum fetal, maternal, and environmental factors which enhance risk for a diagnosis of CP.

3. To compare extent of white matter injury on neuroimaging in preterm survivors with and without CP, and relate differences observed to perinatal risk factors.

4. To apply a candidate gene approach to determine if allelic variants are associated with the type, severity, and co-morbidities of CP.

5. To develop animal models of CP and its attendant co-morbidities that reflect the ‘human’ condition and to utilize these models to enhance our knowledge of underlying genetic and environmental mechanisms of injury.

6. To develop and test, initially in animal models, and then bring to human clinical trial, novel, safe, and effective preventative and regenerative therapies that will improve the lives of children with CP.
Key Milestones & Deliverables

Year One
CP Registry and Genetics
- Restart the Quebec CP registry, register children from 2003 to 2007 birth cohorts, and begin registration from 2008 onwards.
- Obtain scientific and ethical approval for northern Alberta for CP registry, greater Toronto area for CP registry.
- Submit LOI to Public Health Agency of Canada for study on health services and family impact of CP. If LOI/application is successful, obtain scientific and ethical approval at all three registry sites.
- Begin registry inscription in northern Alberta and Greater Toronto area (2008- ); inscription at all sites to include blood-taking of child and parent(s) for genetic studies.
- Provide the neuroimaging project with a list of eligible subjects from Quebec CP registry

Animal Models and Regenerative Approaches
- Characterize the long-term phenotypic, molecular, and biochemical expression of CP and developmental dysfunction in a model of placental insufficiency.
- Characterize the utilization and effectiveness of nonviral iPS-derived NSCs in shiverer mice as proof of principle for adaptation to models of CP.
- Train a student from the Fehlings laboratory in preclinical models of CP to enable scientific linkage with the Yager lab.

Neuroimaging
- Obtain scientific and ethical approval; begin enrolment of half the sample (65 cases/controls).

Year Two
CP Registry and Genetics
- Continue annual registry inscription at all three sites.
- Submit grant application for case-control study to CIHR. Obtain scientific and ethical approval for study.
- Begin data collection as part of the registry platform/inscription process at all three sites if PHAC grant application is successful in year one.
- Complete preliminary genetic analysis of at least one hundred cases collected through the (microarray, genotype/phenotype relationships).
- Identify potential partners for registry expansion to southern Alberta and British Columbia (lower mainland). Consider funding reallocation and new funding options.

Animal Models and Regenerative Approaches
- Complete milestones one, two, and three year one.
- Examine the effectiveness of iPS-derived NSCs in animal models of CP (focusing on models of placental insufficiency).

Neuroimaging
- Complete data collection: neuroimaging and clinical evaluations of sixty-five remaining subjects.
- Begin MRI post-processing of studies on half of sample.
Year Three

CP Registry and Genetics
- Continue annual registry inscription at all sites.
- Complete data collection for PHAC.
- Initiate case-control study.
- Continue genetic analysis on at least five hundred cases by year three.
- Implementation of CP registry in southern Alberta and mainland British Columbia, if funding available.
- Inform animal models project of preliminary prenatal/perinatal risk factors identified from the CP registry.

Animal Models and Regenerative Approaches
- Initiate preclinical studies of ZFP-VEGF bioengineered strategies to attenuate neurological dysfunction in animal models of CP.
- Begin studies for preventive therapies using NHP and VEGF.
- Apply for funding for phase one clinical trials for the use of NHP in prevention of CP.
- Develop biomarkers for prediction of infants at risk for CP based on information gained from animal data and CP registry.
- Explore the potential for commercialization of biomarkers and use of NHP as preventive therapy in pregnancies at risk for CP.

Neuroimaging
- Complete MRI post-processing analyses.
- Explore relationships between brain injury differences (preterms with/without CP) as related to prenatal/perinatal risk factors.
Schematic of Project Plan

**CP: Causes to Prevention → Knowledge Synthesis, Translation, and Exchange**

Schematic of Milestones and Linkages Between Research Projects

- **Regenerative Approaches**
  - Dr. M. Fehlings

- **Animal Models**
  - Dr. J. Yager

- **CP Registry**
  - Dr. M. Shavell
  - Dr. D. Fehlings
  - Dr. J. Andersen

- **Genetics**
  - Dr. S. Scherer
  - Dr. M. P. Dubé

- **Imaging**
  - Dr. C. Limperopoulos

**Timeline**

- **6 mos**
  - Obtain subject list from CP Registry

- **12 mos**
  - Begin recruitment, data collection

- **18 mos**
  - Begin MRI post-processing of imaging studies

- **24 mos**
  - Complete data collection

- **30 mos**
  - Compete MRI post-processing

- **36 mos**
  - Analyze relationships between brain structure with risk factors

- **Hiring Staff; Scientific and Ethical Approval of Projects**

- **CP Registry; Begin inscription of CP cases; Collect blood from registrants**

- **Apply neural stem cells to models of CP**
  - Develop animal model of placental insufficiency
  - Apply to PHAC (family impact study)
  - Begin PHAC study if funded
  - Begin microarray analysis (Scherer Lab)

- **Examine effectiveness of NCS in models of CP**
  - Refine animal models
  - Review genetic findings with team
  - Begin CIHR case-control study

- **Initiate preclinical studies of ZFP-VEGF**
  - Identify potential biomarkers and inform registry
  - Begin CIHR study or reapply
  - Complete microarray on initial 500 subjects

- **Apply for funding for Phase I clinical trials**
  - Explore commercialization of biomarkers for CP prediction
  - Inform animal models of potential risk factors
  - Complete microarray on initial 500 subjects
  - Genotype-phenotype statistical analyses (Dubé lab)

- **Begin to explore use of natural health products**

**Note:** 1 page space restriction limits opportunity to add KT and training milestones as part of the schematic.
References


