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**Australasian Faculty of
Rehabilitation Medicine**

The Royal Australasian College of Physicians

Australasian Faculty of Rehabilitation Medicine Position Statement on the Use of Stem Cell Therapy for Children with Cerebral Palsy

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Introduction

In the quest to improve the health and well-being of individuals with cerebral palsy (CP), stem cell research is seen as a high priority by Australian and Aotearoa New Zealand families/ whānau, researchers and health professionals (1). Progress in stem cell science, together with success in blood stem cell transplants for other conditions, has led to investigation of these interventions for CP. Whilst there is currently no proven, nor approved, stem cell or cell-based intervention for CP, a number of clinical trials have been undertaken and more research is being published in the area.

Health professionals may be asked by individuals with CP and their families about possible stem cell interventions but lack summary information about current medical research to enable informed discussion. This position statement provides a brief introduction and a concise summary of the current clinical research landscape on stem cell treatments for CP to support discussion between physicians and their patients.

Summary of RACP Recommendations

The RACP acknowledges that many individuals with CP and parents or caregivers of children with CP are seeking stem cell interventions. At present, various cell types have been tested in Phase 1 and Phase 2 trials, but Phase 3 trial data is yet to be completed. The RACP recommends that stem cell and other cell-based interventions for CP should only be provided as part of well-designed clinical trials. Registered clinical trials with respect to stem cell treatments for CP can be accessed via [NIH ClinicalTrials.gov](https://clinicaltrials.gov).

Cerebral Palsy

CP is an umbrella term describing a group of conditions that together constitute the most common cause of physical disability in childhood. There has been a recent reduction in rates in Australia, from 2.1 in 1995-97 to 1.4 children per thousand live births/neonatal survivors in the 2010-12 period (2).

CP is defined as:

- A permanent disorder of the development of movement and posture causing activity limitation
- Due to a non-progressive disturbance that occurred in the developing foetal or infant brain
- Predominantly a motor disorder often accompanied by disturbances of sensation, perception, cognition, communication and behaviour; epilepsy and secondary musculoskeletal problems (3).

CP is described by motor type (e.g., spastic, dyskinetic), motor distribution (e.g., unilateral, bilateral) and by functional scales such as the Gross Motor Function Classification System (GMFCS) (4).

There are many risk factors for CP including genetic predisposition, disorders of early brain development, and infectious, inflammatory, cardiorespiratory, traumatic or vascular insults that may occur at any time during pregnancy or in infancy (5). There is no cure for CP, but treatments and therapies are available to improve function and quality of life for those living with CP (6).

Stem cells

Stem cells are precursor cells that have the capability of either dividing into identical stem cells (self-renewal) or developing into many different specialised cell types in the body (differentiation), for example blood cells, muscle cells or nerve cells (7). As such, stem cells play an important role in growth and development, as well as replenishment and repair. Stem cells occur at all stages of human development, from embryo to adult, but their versatility and numbers change with age (8).

Types and sources of stem cells

The classification of stem cells can be based on their source of origin or their potential to differentiate into other cell types. Types of stem cells include:

- *Embryonic Stem Cells (ESC)* – pluripotent cells obtained from early human embryos. ESCs have the potential to differentiate into all of the cell types in the body. Creation and use of these stem cells involve the destruction of a human embryo and raises ethical issues. Their developmental capacity also raises concerns about their increased risk of tumour development.
- *Adult stem cells* – also called tissue stem cells; found in the organs and tissues of our bodies, including foetal, neonatal and adult tissues. They typically can only generate the types of cells for the specific tissue or organ in which they reside.
- *Induced pluripotent stem cells* – are another type of pluripotent stem cell. These stem cells are made in the laboratory by converting a body cell back to a type of cell very similar to ESCs. While these stem cells do not have the same ethical issues associated with their creation, their capacity to readily differentiate means that these stem cells can carry the risk of developing into tumours if not appropriately prepared.

Other cells that are being investigated for CP include:

- *Haemopoietic stem cells (HSCs)* – are multipotent cells which can be derived from bone marrow or umbilical cord blood and have been shown to reconstitute blood cells and also support immunomodulation.
- *Mesenchymal stromal cells (MSCs)* – are multipotent cells which can be derived from multiple tissues including from bone marrow, umbilical cord blood and placenta. MSCs differentiate into cells such as bone, fat and cartilage. These cells are very unlikely to differentiate into functioning neural cells and instead are highly-immunomodulatory and release trophic factors.
- *Umbilical cord blood (UCB)* – contains many types of cells including HSCs, MSCs, immunomodulatory and neurotrophic factors.
- *Neural precursor cells* – are multipotent cells found in the human central nervous system and can develop into nerve cells or supporting cells (e.g., olfactory ensheathing cells, neural progenitor cells).
- *Endothelial progenitor cells (EPCs)* – are present in peripheral blood and umbilical cord blood. EPCs have been shown to induce neovascularisation.

Regardless of source and cell type, cells for transplantation can be classified as **autologous** (derived from the patient) or **allogeneic** (derived from a donor). When using an allogeneic source, consideration of whether cell engraftment is needed, the immune system of the recipient and if treatment might pose risk of rejection is important (9).

Current clinical use of stem cells

In the past 50 years, HSCs or blood stem cells have been successfully used to treat people with leukaemia, lymphomas and other rare blood diseases. In 2020, almost 1.5 million hematopoietic cell transplants have been performed in more than 1,500 transplantation centres the world over (10, 11). Previously referred to as bone marrow transplants, now over 50,000 people worldwide undergo a blood stem cell transplant each year (12). This information forms the cornerstone and proof that stem cell therapies using adult stem cells can work.

There is recognition that rare cells in many tissues and organs function as stem cells. Researchers hope that these cells can be used in regenerating damaged tissues throughout the human body. For example, stem cells in bone, skin and the cornea can be safely harnessed to assist in treating diseases affecting these organs (13). Other clinical applications are still being developed and evaluated in clinical trials. Failure to administer the right type of cells may lead to unacceptable risks and adverse effects (13, 14).

The use of stem cell therapy for CP

Stem cells have generated considerable interest as a possible therapy for CP due to their potential to replace, support or repair damaged brain tissue. While originally it was thought that a wide range of adult stem cells and progenitor cells might be able to differentiate into nerve cells or supportive cells when transplanted into the body, this characteristic appears to be limited to the neural stem cells within the brain (15). However, the administration of stem cells and other types of cells may prevent some of the damage to the brain by modifying the inflammatory response (16-18) and protect nerve cells from death (19, 20). Some types of stem cells may also help the brain to improve blood flow by forming new blood vessels and producing trophic factors (21, 22). How to harness these potential therapeutic benefits remains a focus of ongoing research activities.

Current research available for families and health professionals

The following presents a brief overview of current clinical research into stem cell treatments for CP. Consumer information about definitions of the phases of clinical trials can be found on the Australian Government [website](#).

Case studies and Phase 1 trials

There are numerous case reports and published Phase 1 studies which address the feasibility and safety of stem and other cells in children with CP. Studies have assessed peripheral infusion of UCB, both autologous (23) and allogeneic (24, 25), and have concluded that these infusions are safe and generally well tolerated. A pilot study of peripherally administered UCB has been undertaken recently in Australia (26). Studies have also assessed the feasibility of introducing intrathecal and intraparenchymal mesenchymal cells (27, 28) and bone marrow or peripheral blood derived mononuclear cells (29-35). None of these phase 1 trials were designed to prove efficacy.

Phase 2 trials

A number of phase 2 controlled trials have been published assessing the efficacy of stem and other cells in CP. Studies have used autologous UCB (36), allogeneic UCB (37, 38), UCB mesenchymal or mononuclear cells (39), bone marrow (40) or peripheral blood (41) and neural-like cells (42, 43). Within these studies, cells have been delivered into the peripheral bloodstream (36-39, 41),

intrathecally (40) or directly into the ventricles or brain (42, 43). In one study, immunosuppression was used in the patients receiving allogeneic cells (37). Serious, low frequency adverse events were reported in two studies (37, 43). Improvements in gross motor function in treatment groups have been reported at short term follow-up (37-43). Limitations of published phase 2 trials include inadequately defined patient populations in terms of the type and severity of CP, wide age range and varied outcome measures (37-41, 43).

Systematic reviews of phase 2 trials with meta-analyses suggest modest gains in gross motor function, particularly in studies of umbilical cord blood (44-46). However, marked heterogeneity between studies preclude a firm conclusion on the interventional effect of stem cells.

Phase 3 trials

Worldwide only a small number of children have been involved in published studies assessing the efficacy of stem cells and other cell interventions in children with CP (47). At the current time, there are no published large Phase 3 trials of stem cells or other cells in CP (47). Highly powered trials with rigorous methodologies are essential to ascertain whether stem cells will be a viable treatment for children with CP.

Implications for families

Potential use of cellular-based intervention for children with CP have been studied in a number of clinical trials, predominantly in Phase 1 and Phase 2, with published results varying in both quality and effect size. Comparison of study findings is challenging due to the variety of cell types, administration techniques, concomitant treatments, outcome measures used and study methods.

Individuals with CP and their families and carers may seek stem cell infusions in the hope of improved outcomes. These include the use of unproven interventions outside of clinical trials, or through commercial clinics. It is critical to recognise that for individuals with CP and their families and carers, delineating between proven and unproven cell-based interventions, as well as novel stem cell or related interventions currently being assessed in clinical trials, can be challenging. Equally important is the recognition that many of those providing unproven interventions outside the clinical trials framework are operating in jurisdictions where appropriate regulatory oversight and enforcement is limited or absent (48).

Where families and carers have chosen to access stem cell intervention outside of a trial they should be encouraged to share their experience with their treating clinician. Such decisions should not impact on ongoing care.

Families and carers should consider the following factors and discuss them with their treating clinicians.

Knowledge gaps

There remain critical gaps in current knowledge on stem cells and other cell-based interventions for CP. The exact mechanism by which peripherally delivered cellular interventions may improve neurological function is still unknown. It is not yet clear what is the best source and cell type to use, the timing of treatment, the dose, mode of delivery and whether adjuvant therapy is needed. For these

reasons families and carers are encouraged to consider limiting their involvement to well-designed clinical trials.

Potential risks

Families and carers should bear in mind that while there has been progress in stem cell research, there remains uncertainty surrounding benefits in improving motor skills when used as a treatment for CP. Of great concern is the potential for serious risks with such treatments, particularly where there are insufficient safeguards around characterisation of administered cells and mode of delivery (14).

Other considerations

- Stem cell interventions may incur significant financial costs as well as disruption to families and carers. Costs may deter families and carers from pursuing other treatments which may potentially improve quality of life.
- Undergoing cell-based interventions outside a clinical trial may disqualify patients from participating in future registered trials.
- Some families and carers of children with CP may have cord blood or sibling cord blood saved in cord blood banks. Use of stored cord blood should only be considered as part of a clinical trial to assess safety and outcomes.

Conclusion

At the current time the published controlled studies of cell-based interventions in CP vary in the methods used and the quality of trials. There is insufficient evidence to make conclusions about the clinical effects of such interventions.

A large phase 3 clinical trial is required to determine the efficacy of stem cell treatments for children with CP. It is recommended that stem cells and other cell-based interventions for CP should only be used as part of well-designed clinical trials.

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