



# Brief Report

## *Stem cell Transplantation for Spinal Cord Injury*

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***Important Note: This brief report summarises information on stem cell transplantation for spinal cord injury. A reasonable attempt has been made to find and review papers relevant to the focus of this report. It does not claim to be exhaustive. This document has been prepared by staff of the ACC, Evidence Based Healthcare Advisory Group. The content does not necessarily represent the official view of ACC or represent ACC policy.***

## ***Glossary***

<b><i>Embryo</i></b>	The product of conception from the point of fertilisation up to the eighth week of gestation <sup>1</sup> . The pre-embryonic stage is considered the first two weeks after fertilisation. At two weeks the fertilised egg is then fully implanted in the uterus.
<b><i>Foetus</i></b>	After the eighth week of gestation an embryo is considered a foetus <sup>1</sup> .
<b><i>Gamete</i></b>	A male or female sex cell. Male gametes are usually small and motile (spermatozoa) whereas female gametes (oocytes) are larger and nonmotile <sup>2</sup> .
<b><i>Mesenchymal stem cell</i></b>	A rare cell, mainly found in bone marrow, that can give rise to a large number of tissue types such as bone, cartilage, fat and connective tissue <sup>3</sup> .
<b><i>Progenitor Cell</i></b>	A progenitor cell is an early descendant of a stem cell that can differentiate itself, but no longer renew itself. A stem cell can both differentiate and renew <sup>3</sup> .

## ***Background***

Spinal cord injury (SCI) usually results in significant life-long physical impairment and disability. Reliance on aids, appliances and caregivers for everyday functional tasks occurs to varying degrees. In New Zealand the total estimated life-cost for individuals with current claims for SCI is over 2.2 billion dollars<sup>4</sup>. The estimated annual social rehabilitation for each individual varies from \$15,651 (incomplete SCI)-\$115, 243 (high level tetraplegic SCI). ACC currently has 275 claims for spinal cord injury at varying levels. Information also suggests that approximately 70 new cases occur per year<sup>3</sup>.

Recent Australian statistics<sup>5</sup>, taking into consideration population growth, ageing, and an increasing incidence of SCI injury in the elderly due to falls estimate an increase in SCI annual case numbers over the next 15 years. SCI from ageing is expected to increase seven-fold<sup>5</sup> by 2021. It has, therefore, been recommended that treatment centres should not only be developed to deal with this, but an emphasis also be placed on prevention strategies<sup>5</sup>. Stem cell transplantation for SCI along with new pharmaco-therapies research may offer the potential to restore function and, therefore, ease the social and economic burden in the years ahead.

## ***Objective***

This review provides information on the current state of stem cell transplantation technologies for spinal cord injured patients, and critically appraises the evidence. This information may assist ACC in determining future funding for stem cell transplantation therapies in New Zealand.

## ***Health Technology – Stem Cells***

Stem cells (SC) are body cells which have the ability to replicate indefinitely and have the capability of differentiating into almost any other type of bodily cell<sup>6</sup>. They can be further classified as ‘multipotent’ (the ability to differentiate into multiple cell types e.g. haematopoietic SC into red and white blood cells and platelets<sup>6</sup>) and ‘pluripotent’, which refers to the ability of the stem cell to differentiate into any cell body type<sup>6</sup>. Stem cells are therefore considered potentially invaluable to assist the repair of non-regenerating tissues. Stem cells may be derived from early embryos and foetal tissue and are present in blood and bone marrow in adults. Stem cells have been shown to differentiate into oligodendrocytes and cell-ensheathing axons<sup>7</sup>. Although spinal cord cells can give rise to neurons and related cells, spinal cord cells are incapable of producing all the cell types necessary for recovery after injury<sup>7</sup>. Researchers envisage that stem cells may (i) act as a cellular bridge assisting axons above and below the injury site, (ii) act as a new source of neurons, (iii) secrete neurotropic substances (substances that have an affinity for neural tissue) which promote repair, (iv) modulate the immune response after injury, (v) induce breakdown of inhibitory scars within the spinal cord and eliminate cell debris and (vi) protect neurons<sup>8</sup>.

## ***Ethical Issues***

There are concerns on moral and ethical grounds around stem cell research; particularly with regard to the use of foetal, umbilical cord and embryonic stem cells. A report written for the New Zealand Ministry of Research Science and Technology (MoRST, 2005) discusses the social, cultural and ethical issues associated with stem cell research in New Zealand in detail; other concerns have arisen around the safety of stem cells. As stem cells are cultured and/or maintained using animal serum or animal feeder cells, there are concerns that exotic animal viruses may be introduced<sup>9</sup>. Embryonic stem cells (hESC) form “disorganised tumours”<sup>9</sup> in mice, and it is also suggested that a foreign sugar molecule expressed during culture may tag cells for destruction by the immune system<sup>9</sup>. Finally, scientists express concerns about the possibility of new mutations occurring during the cell culture process.

## ***Stem Cell Types Used for Transplantation***

### ***Bone Marrow Stem cell Autografts***

The patient's own bone-marrow cells are harvested and then are injected into the spinal cord vessels<sup>10</sup>.

### ***Human Embryonic Stem cells (hESC)***

Human Embryonic Stem cells are pluripotent. It is reported they “...are more likely than other types of dividing cells to give rise to genetically normal cells... and they are easy to manipulate genetically”<sup>7</sup>. Progenitors (ancestors) of HESC have been shown to differentiate into neurons and related cells after transplantation<sup>7</sup>. It has been reported that foetal spinal cord transplants have been used in the U.S., Russia and Sweden for spinal cord injured patients, and that foetal schwann-cell transplants have been implanted into humans<sup>10</sup>.

### ***Olfactory Cells/Tissue***

Olfactory Ensheathing Cells (OEC) are special types of neuronal support cell that guide olfactory neurons and support their elongation<sup>11</sup>. Olfactory cells regenerate constantly (every 60 days) and the ‘progenitor stem cells’ that reside at the olfactory tissue's base and their ensheathing cells have been studied as a source of stem cell and tissue graft for transplantation. “OEC's have been shown to penetrate the inhibitory glial scar at the injury site, and then migrate to their correct targets, restoring function”<sup>11</sup>. ***OEC's are themselves not considered stem cells<sup>8</sup>***. Using the individual's autologous nasal cells avoids the controversial issue of extracting stem cells from a human embryo. As they are also the patient's own cells, there is no concern regarding rejection. Some researchers are in fact implanting olfactory mucosal tissue, not just isolated cells<sup>12</sup>.

## ***Umbilical Cord Stem Cells***

Umbilical cord blood cells and mesenchymal stem cells are being clinically trialled for spinal cord injury<sup>13</sup>. Umbilical cord blood is stored in international stem cell “banks”. It is reported that these transplants are well tolerated by the immune system<sup>14</sup>. These cells are injected into the affected area of the spinal cord or intravenously along with specific nerve growth factors<sup>13</sup>.

## ***Literature Search***

The following databases were searched using the Ovid platform: Medline 1996-October 2006 and pre-medline, CINAHL (1982-October 2006), the Cochrane Database for Systematic Reviews (CDSR), Cochrane Controlled Trials Register (CCTR), and the Database of Abstracts of Reviews of Effectiveness (DARE) and Embase. In addition, Turning Research into Practise (TRIP), Health Technology Assessment sites and clinical trials registers were searched. The search terms used for database searching were “stem cell”, “mesenchymal cell”, “spinal cord injury”, “paraplegia”, “tetraplegia” and combinations of these terms. The search was limited to humans, and generally to the English language. Research hospitals or private research institutions’ web-sites were also searched as literature and web-information sourced indicated that many human clinical trials were currently being undertaken<sup>15</sup>. Two researchers were sent electronic mail communications regarding their clinical trials, requesting additional information and any preliminary results.

Four case series and two case reports were identified that report on stem cell therapy for spinal cord injury<sup>12 16-20</sup>. Three clinical trials were found that used either mesenchymal or embryonic stem cells<sup>16-18</sup>. The results of two further trials using olfactory tissue and/or OEC’s in spinal cord injured patients<sup>12 19</sup> were also identified. Although not strictly speaking stem cells, it was relevant and appropriate to include the research on olfactory tissue/cells. Of the two researchers approached for information, one responded with general information only.

## ***Results***

The literature identified essentially represents what is known as Phase I trials<sup>21</sup>, trials with small sample sizes to evaluate safety and dose and to identify side effects. Evidence levels are provided in the study tables and assessed as per the Scottish Intercollegiate Guidelines Network Criteria (SIGN) (see Appendix A).

Rabinovich et al., 2003<sup>16</sup>, undertook a prospective case series (n=15) transplanting fetal haematopoietic neural stem cells and OEC’s into SCI patients. All subjects had sustained incomplete SCI, between 1 month and 6 years prior to the treatment. The subjects’ age ranged from 18-52 years. All subjects had a

Frankel Neurological Scale status of 'A' (see Appendix B) pre-treatment, defined as "complete motor and sensory function disorder"<sup>16</sup>. Follow-up was 1.5-3 years. The authors reported that "noticeable clinical improvements were noted in 11/15 patients". Frankel scores improved from A (A="complete motor and sensory function disorder") to C ("incomplete motor function below injury") in five patients and from Frankel Score A to B/C (B="sensory function below injury level only") in three patients. Scores were unchanged in four. Functionally, five patients "became able to move with support" and one was able to "walk without any help". Three patients who improved from Frankel Score A to B could stand with support. Most change was seen in those patients that received treatment within one year of SCI. The authors compared the five most improved from the treatment group with five other SCI "comparable" patients (followed-up for 1.5 years) to remove the potentially confounding effect of natural recovery. Of these five patients, two only changed from A to B. Furthermore, the authors reported seven additional patients with complete SCI in the cervical region of which three changed from Frankel Score A to B only. The authors do not state whether either of the comparison groups ('controls') were planned and documented concurrently with the stem cell treatments. This study is of low level evidence and numbers are small. The authors have used inappropriate comparison groups (e.g. complete SCI patients/different times since injury).

Lima et al., 2005<sup>12</sup> reported on seven patients (18-32 years) who underwent olfactory mucosal grafts between 6 months and 6.5 years post SCI. American Spinal Injury Association (ASIA) scores of either A or B were eligible for inclusion (see Appendix B). As respiratory epithelium replaces olfactory mucosa with age, an age limit of 35 years was set for inclusion to this prospective case series. Patients underwent pre-treatment tests including Electromyography (EMG), Magnetic Resonance Imaging (MRI), computed tomography (CT), psychological testing, urodynamic and rectal examinations. Patients were followed-up at 6, 12 and 18 months post-treatment. They received "minimal rehabilitation" either pre or post-operatively. Variable sensory and motor recovery occurred with improvement in ASIA scores occurring in all except one patient. This ranged from muscle activity detected in the hip flexor, hand, arm and finger muscles to patchy sensory gains. Small gains in Motor Index Scores were reported in three tetraplegic patients (improvements 4, 8 and 7/100), and lower limb Motor Index Scores (Appendix C) improved by 1-7 points/100 (n=7). The authors reported that sensory, upper and lower limb motor gains were, however, statistically significant (light-touch, p=0.02; upper limb motor, p=0.047; lower limb motor, p=0.003). Much greater sensory gains were reported than motor and subjects reported that their function improved significantly. This recovery did not follow a proximal to distal pattern. Two patients reported improved "self-sufficiency" e.g. independent transfers, and three were able to step with assistance due to the returned hip-flexor capacity. The authors stated there was no correlation with clinical outcomes and time since injury or injury level. Two patients reported improvement in bowel and/or bladder parameters; this was confirmed with urodynamic studies in one.

MRI findings indicated no neoplastic growth in the spinal cord and no adverse responses were reported with respect to spasticity. Olfactory sense which was altered in many patients post-operatively had recovered in all patients by three months. One patient had a reduction in ASIA score post-operatively (sensory only; score decreased from 73 to 60 at 18 months) and two patients reported temporary pain which was relieved by medication. This study has reported more specifically on patient outcomes, however, it also provides relatively low-level evidence because of a small sample and a case series design.

Féron et al., 2005<sup>19</sup> injected cultured autologous OEC's into three paraplegics, between 6 and 32 months post complete SCI. The cells were harvested and cultured for four weeks prior to injecting. One patient underwent concurrent laminectomy, and all three had spinal cord adhesions removed prior to injecting the stem cells. The cells were injected into the proximal normal region of the spinal cord and also into the injured part of the cord. The results are reported for one-year follow-up, and outcomes were to be monitored for three years in total. Three SCI patients that did not undergo the treatment acted as the controls. Over 600 patients enquired about the trial, 21 were considered suitable for assessment, but only 12 underwent initial assessment. Three declined consent, three were excluded, leaving three subjects only in the treatment group. No adverse effects of any kind were reported. The authors were interested only in the feasibility and safety aspects of the procedure and no other outcomes were assessed.

In a Chinese language article, Zhou et al., 2004<sup>20</sup> briefly reported on 70 cases following Bone-marrow stem cell (BMSC) transplantation. 37 of these were SCI patients, others had suffered mainly stroke or traumatic brain injury. The stem cells were either injected or implanted. Patients received various therapies post-treatment including physical therapy, hyperbaric oxygen therapy and acupuncture. The authors briefly reported that positive outcomes for the SCI patients were that sexual function improved in three patients and sensation and function improved in five cases. It is unknown, however, whether these were SCI patients. There were three cases of intra-cranial infection. This article lacked additional detail regarding the procedure and the baseline characteristics of the patients.

Moviglia et al., 2006<sup>18</sup> presented two case reports of patients having received bone-marrow stem cells (BMSC) co-cultured with the patient's autologous (the patient's own cells) auto-immune T-cells. Auto-immune T(AT) -cells were sourced from the peripheral blood. BMSC were sourced from the iliac crest. Cells were cultured for 4-6 weeks; the auto-immune T-cells were infused prior to the BMSC which were then infused into the patients' vertebral arteries. The authors believed the AT cells were essential to assist the reparative process. The AT cells would, due to their controlling inflammatory activity, "generate the micro-environment for the subsequent administration of the in vitro transdifferentiated Neural Stem cells (NSC)"<sup>18</sup>. A 19-year old SCI male (T8 level, injury 8 months prior) showed improvement two months after treatment as indicated by MRI and somatosensory-evoked potential (SEP) results. Uncoordinated spontaneous pelvic girdle to knee muscle contractions reappeared. The patient received a further treatment of stem cells within three months due to a plateau in his progress and subsequently regained his ability to walk with two canes and "short prostheses". A 21-year old female also underwent stem cell treatment (C3 level). She developed the ability to hold her head up, move her upper limbs, brush her teeth, feed herself, paint and write using an assistive device (approximately 8 weeks after treatment). The authors reported her motor and sensory levels correspond to T1 and T2 respectively. No pre- or post-treatment ASIA scores were reported.

Lastly, Kang, 2005<sup>17</sup> presented a single case report of a 37-year old female almost 20 years since ASIA A SCI injury (T10 level). A laminectomy and stem cell transplantation of umbilical cord cells into the distal normal cord region and into the injured cord area was performed. Prior to treatment, somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) were non-responsive. The patient was able to sit upright at day 13 and moved her feet and hips day 15 post

treatment. The authors reported that the SEP and MEP responses had improved to L2 level from T10. Whether the patient improved functionally as a result and/or continued to improve medium to long-term was not reported. The authors did, however, state that the effect of the laminectomy itself may have contributed to the improvements seen.

## ***Stem Cell Research – Internationally and in New Zealand***

There is currently much attention on stem cell research internationally<sup>22</sup>. There is much literature that reports current human clinical trials involving foetal tissue, olfactory ensheathing cells and adult stem cells in spinal cord injured patients are underway<sup>15</sup>, although there are few published studies. It is also apparent that much of this is *privately* funded research as some governments have placed restrictions on the type of stem cell research that can be undertaken due to moral and ethical grounds. The United States passed policy in 2001 allows federal funds to be used for research with a limited number of existing embryonic stem cell lines research as long as the research was from an embryo created for reproductive purposes. Currently researchers in Australia are permitted to carry out research on any embryonic stem cell line derived from surplus in-vitro fertilisation embryos<sup>1</sup> and a bill has recently been passed (December 2006) that allows the legal cloning of human embryos for stem cell research. Other countries have adopted a variety of positions ranging from a complete ban on the use of embryos in research (Republic of Ireland), to allowing research to be undertaken on embryonic stem cells (Germany) and the creation of embryonic stem cells for research purposes (United Kingdom).

Patients can personally fund stem cell transplants in China. Nan-Shan hospital/Beike Biotech Co. Ltd, have an information pack detailing the procedure. Four umbilical cord stem cell treatments are administered (injected) over a period of four weeks. Daily rehabilitation is provided.

A comprehensive report on stem cell and progenitor cell technologies was written in 2005 by Dr Garry Udy of Innovation Waikato for the Ministry of Research Science and Technology (MoRST), New Zealand<sup>3</sup>. The aim of the report was to detail New Zealand's research interests and capability within the contexts of the New Zealand Biotechnology Strategy and the Biotechnology Taskforce Report. New Zealand at present has no clear policy or legislation controlling hHESC research or importation to New Zealand<sup>3</sup> nor is there any current research into hHESC's in New Zealand<sup>3</sup>. There are several programmes currently underway that are researching adult and foetal stem cells and the organisations involved and the specific research being undertaken is detailed in the MoRST report. The focus of the research in New Zealand is currently on human stem cell function in relation to human biology and development. Other institutes are researching animal stem cells, two programmes of which are specifically focused on developing stem cell based therapies for human application. The derivation of neural cells from adult stem cells to assist in the repair of spinal cord injury is of note<sup>3</sup>. This report calculated total expenditure for stem cell therapies in New Zealand of \$NZ 2.77 million per annum.

CordBank Ltd<sup>23</sup> and the New Zealand Blood Service both currently store umbilical cord blood for potential use in stem cell therapies. The Ministry of

Health released a discussion document concerning entitled “Guidelines on Using Cells from Established Human Embryonic Stem Cell Lines for Research” in 2005 and has recently published a summary of the submissions received (September 2006)<sup>24</sup>. New guidelines were subsequently developed<sup>25</sup>. All New Zealand researchers may now undertake research using established hHESC lines, with mandatory ethical review and specific restrictions, some of which concern research design, consent and how excess cells are disposed of.

The Advisory Committee on Assisted Reproductive Technology (ACART) is an independent advisory committee established to develop advice and guidelines for the regulation of assisted human reproduction and developments in human reproductive research and works from the guiding document Human Assisted Reproductive Technology Act (HART, 2004). This act does not explicitly prohibit embryonic research, but currently there are only guidelines to undertake research with donated non-viable embryos. The HART Act also does not cover the use of established hHESC lines for non-reproductive research. A discussion document was released for public comment in December 2006 by ACART. Note this discussion paper does not extend to the use of gametes from foetuses. The paper outlines the four broad areas of research for gamete and embryo research; (a) the contribution to fundamental science to realise the therapeutic goal of gamete and embryo research, (b) understanding fertility and infertility (c) prevention of hereditary diseases and (d) curing human disease in general<sup>1</sup>. Submissions closed March 2, 2007.

The Spinal Cord Society (New Zealand) aims to replicate clinical trials performed by a Portuguese surgeon, Dr Carlos Lima (trial discussed earlier), who transplanted olfactory mucosal grafts into spinal cord injured patients<sup>12</sup>. The Spinal Cord Society (New Zealand) web-site<sup>26</sup> reports the first step towards bringing this therapy to New Zealand, is to undertake an external audit of Dr Lima’s clinical results. The study aims to “demonstrate in a New Zealand environment that the treatment is safe and that cell transplantation is better than intensive rehabilitation alone”<sup>26</sup>. A rehabilitation control group is also planned. Currently ethics approval is being sought<sup>26</sup>. Similar trials are currently underway in Griffith University, Brisbane, Australia by Dr Alan MacKay-Sim.

## ***Other Spinal Cord Injury Research***

### ***“ProCord” – A clinical trial for spinal cord injury***

This international multi-centre randomised controlled “Phase II” (how well does the treatment work?) clinical trial involves injecting cultured autologous macrophages into the spinal cord of spinal cord injured patients. The researchers believe that as the blood-brain barrier does not permit the spinal cord to behave in an ‘inflammatory’ way after injury, by introducing macrophages, an immune response to assist repair can commence. This treatment must commence within 14 days of injury to meet the study criteria. Currently the web-site reports recruitment is temporarily discontinued. The web-site states it is not due to study complications or adverse effects.

## ***Summary***

There is currently a paucity of literature reporting human clinical trials involving stem cell transplantation for spinal cord injury. As this is a new therapy for SCI, the present literature is accordingly "Phase I" clinical trials, the main aim of which is to evaluate the safety and side-effects. The trials, although presenting low-level evidence appear promising in terms of safety. There is much money and effort currently being spent internationally on stem cell therapies. Stem cell transplantation is currently offered in some countries to fee-paying patients. The results of this clinical work need to be published in order to build an appropriate body of evidence regarding safety and efficacy. The ethical and safety concerns around the research of certain types of stem cells for transplantation mean stem cell therapy for spinal cord injury and other neurological disorders is likely to be slow. New Zealand has recently developed guidelines for using established hHESC lines for research and there are many organisations in New Zealand undertaking stem-cell research in the laboratory setting. Some of this concerns spinal cord injuries directly. The New Zealand Spinal Cord Society in conjunction with the University of Otago appears to be the only group thus far that is working towards trialling stem cell therapy for spinal cord-injured patients in New Zealand.

## ***Study Tables - Stem cell Transplantation***

<b><i>Author/ Yr</i></b>	<b><i>Design/Enrolment</i></b>	<b><i>Population and Inclusion, Exclusion Criteria</i></b>	<b><i>Intervention</i></b>	<b><i>Results</i></b>		<b><i>Level of Evidence/Conclusions</i></b>
				<b><i>Outcomes</i></b>	<b><i>Adverse effects</i></b>	
<b><i>Moviglia et al 2006<sup>18</sup></i></b>	<b><i>Case report (N=2) Bone-marrow mesenchymal stem cells (BMSC)</i></b>	<b><i>(1)19 year old male T8 paraplegic T6 dermatomal level  (2) 21 year old female C3-5 tetraplegic C2 dermatomal level</i></b>	<b><i>BMSC co-cultured with patient's own auto-immune T-cells (purified). These cells "are essential for the repair process of damaged tissue". BMSC removed from iliac crest and purified  Intra-venous infusion of T-cells 48 hours prior to injection of trans-differentiated NCS  Six months of neuro- rehabilitation followed treatment. One further session of NSC for male patient</i></b>	<b><i>Subject 1 Improved spine somatosensory evoked potentials (SEP) and Magnetic Resonance Imaging (MRI) at two months after first injection Reappearance of spontaneous muscle contractions around the pelvic girdle Plateuxed at three months which led to the second treatment. Improved to walking with two canes and two short prostheses. S1 dermatomal level Planning third NSC treatment Subject 2 SEP and MRI changes. Subject developed the ability to hold own head, move upper limbs and demonstrate voluntary trunk and lower limb movements. T1 motor and T2 sensory levels. Awaiting further treatment</i></b>	<b><i>Nil</i></b>	<b><i>"Our laboratory has proved that in vitro co-culture of MSC and anti-CNS Auto- immune T-cells can induce the transdifferentiation of Mesenchymal SC into Neural SC" The authors state that by using autologous Mesenchymal SC there is reduced risk of neoplastic formation, no risk of rejection or any need for immunosuppressant drugs.  Evidence level= "3"</i></b>

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<b>Féron et al 2005<sup>9</sup></b>	<b>Case Series</b>  <b>Feasibility and safety of transplantation of autologous olfactory ensheathing cells into (spinal cord injury) SCI patients</b>	<b>Single-blinded (assessors)</b>  <b>Matched group as control</b>  <b>Complete SCI ≥ 18 yrs (American Spinal Association Injury Level (ASIA) "A"</b>  <b>T4-T10 injury level (to "reduce the risk of significant adverse neurological changes should the procedure lead to damage above the injury")</b>  <b>6 months-3 yrs post-injury</b>	<b>Olfactory cells harvested and cultured for four weeks</b> <b>Patient 1 received 12 million cells, patient 2, 24 million and patient 3, 28 million</b>	<b>21 persons suitable for screening. 9 excluded.</b>  <b>12 underwent initial assessment; 3 declined to participate, 3 were excluded, 6 enrolled. 3 controls, 3 transplant recipients</b>  <b>No deterioration of neurological function was noted at 1 year post-op. No changes in neuropathic pain or worsening of spasticity. No worsening of psycho- social status</b>	<b>No pathogens detected during the culturing process</b> <b>No peri-operative complications or at one year post-op</b>  <b>MRI at 1 year post-op indicated no overgrowth of introduced cells or development of post- traumatic syringomyelia</b>	<b>"Stringent inclusion criteria led to slow recruitment" (over 2 years)</b>  <b>"..we cannot state whether any cells remained within the injection sites immediately after transplantation or at 1 year... they did not form a discernable mass on MRI"</b>  <b>Authors continuing to monitor patients for three years post-op</b>  <b>Level of Evidence = "3"</b>

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				<i>Outcomes</i>	<i>Adverse effects</i>	
<i>Lima et al., 2005<sup>12</sup></i>	<i>Case series Olfactory mucosal graft transplants</i>	<i>N=7 Age: 18-32 Male=4; female=3 Unknown if incomplete SCI 6 month-6.5 years since injury; para or tetraplegic ASIA scores A or B could be included</i>	<i>Posterior laminectomy and simultaneous  Olfactory tissue graft  "Minimal pre and post-op rehabilitation"</i>	<i>All patients were ASIA A MRI/CT of the nose/ASIA score/otolaryngological exam./nasal endoscopy/psychological assessment/urodynamics (n=2 post- op only) Follow-up up to 42 months post-op  MRI (6 months post-op) showed complete filling of lesion site in all but one patient No evidence neoplastic tissue ASIA scores (6/12/18 months post- op); unchanged in 5 patients; A to C in 2 patients, although motor and sensory in 4/5 patients who were unchanged with ASIA scores Statistically significant improvement seen at 18 months post-op (light touch, p=0.02; pinprick, p=0.043; motor arms, p=0.047; motor legs, p=0.003) Functional improvements reported in some patients</i>	<i>Slight sensory loss in one patient  New temporary neuropathic pain in two patients. This resolved with medication</i>	<i>No comparison group  Sensory loss thought to be due to damage due to surgical procedure  The laminectomy performed concurrently may be responsible for some of the changes seen ASIA scores may be insufficiently responsive and therefore clinically significant changes in patients may not be reflected  Level of evidence="3"</i>

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<i>Kang et al 2005<sup>17</sup></i>	<i>Case report Human Umbilical cord cells</i>	<i>37-year -old female T11/12 injury level complete injury 19 years and 6 months post- injury  Authors report "... range of motion absent and Grade I spasticity was noticed on lower extremity using the Ashworth's scale" pre-op</i>	<i>1 x10<sup>8</sup> cells of cord blood multipotent stem cells injected into subarachnoid space of most distal part of the normal spinal cord  An additional 1 million cells injected into intradural and extradural space of the injured spinal cord</i>	<i>Patient able to sit upright (day 13 post-op)  Patient able to move hips and feet on day 15 post-op  Somatosensory and motor evoked potentials improved to L2 (day 41)</i>	<i>No reporting of complications or adverse effects</i>	<i>"Cord cells less likely to attack a recipient's body than bone marrow cells" Authors also state" we cannot exclude the act of laminectomy, which can release compressed areas of the spinal cord"  Evidence level="3"</i>

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Zhou 2004	<p>Case series</p> <p>Enrolment period January 2002 to December 2003. Zhujian Hospital, GuangZhou, China,</p> <p>Injury diagnosis: Spinal cord injury caused by traffic accidents (n=37) Traumatic brain injury (n=14) Hemorrhagic stroke(n=16) Firearm injury (n=3) Time between injuries and stem cell transplantations: 1-60 months</p>		<p>Bone marrow stem cells were cultured and differentiated 9 to 14 days in laboratory, to obtain "neural stem cells" for transplantation.</p> <p>Cells injected or surgically implanted</p> <p>Following stem cell transplant patients received: Antibiotics, Pharmaceutical agents, Hyperbaric oxygen therapy, Physiotherapy an Acupuncture</p>	<p>N=70 Males=60; females=10</p> <p>Mean age 35.6 (range=7-60)</p> <p>Improvement was observed in GCS scores (n=2) Symptom improved in one patient with Parkinson's disease</p> <p>Sensory and functional improvement observed in 5 patients</p> <p>Sexual functional improvement was observed in 3 spinal cord injury patients.</p>	<p>Intracranial infection requiring antibiotic treatment (n=3)</p>	<p>Baselines before transplantation were not clearly reported.</p> <p>No information about the time of follow up/outcome measured.</p> <p>Heterogeneous patient group</p> <p>Lack of details of the intervention e.g. how to culture and differentiate "neural stem cells"</p> <p>Evidence level= "3"</p>

Author/ Yr	Design/Enrolment	Population and Inclusion, Exclusion Criteria	Intervention	Results		Level of Evidence/Conclusions
				Outcomes	Adverse effects	
Rabinovich et al 2003 <sup>16</sup>	Case series with two comparison groups Using foetal neural and haemopoietic tissues	N=15; all incomplete SCI 18-52 years  1 month-6 years following SCI  Assessed neurological status using Frankel scores for 1.5-3 years	Cells cryopreserved until injection  1-4 cell transplants grafted subarachnoidally via lumbar puncture  In 11/15 patients cell transplantation combined with operative partial disruption of a spinal connective tissue cyst and implantation into the lesion of a fetal spinal cord fragment in addition to ensheathing cells	N=15  Cervical or thoracic SCI 11/15 patients improved Frankel scores. Many improvements were functionally significant.  Remaining four demonstrated no clinical improvements  Five best-performed patients in intervention group compared with 5 "random" patients for 1.5 years Authors state "...an additional seven patients with cervical SCI used as comparison. ? follow-up time. Data not presented	Nil reported	Authors neither state which patients received additional tissue implant and cells nor were the number of cell treatments were clearly reported for specific patients  Comparison groups dissimilar and ?an afterthought  <b><i>Frankel scores alone may be insufficiently responsive and therefore clinically significant changes in patients may not be reflected</i></b>  Level of Evidence="3"

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## ***Appendix A***

### ***Scottish Intercollegiate Guidelines Network Levels of Evidence<sup>27</sup>***

#### ***Levels of evidence***

- 1++ High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
  - 1+ Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
  - 1 - Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 
- 2++ High quality systematic reviews of case-control or cohort studies  
High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
  - 2+ Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
  - 2 - Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
- 
- 3 Non-analytic studies, e.g. case reports, case series
- 
- 4 Expert opinion

## ***Appendix B***

### ***Neurological Scales***

#### ***Frankel Neurological Scale*<sup>28</sup>**

A= complete paralysis

B=sensory function below the injury level only

C=incomplete motor function below injury

D=fair to good motor function below injury level; E=normal function

#### ***American Spinal Injury Association (ASIA) Impairment Scale*<sup>29</sup>**

A= Complete: No motor or sensory function is preserved in the sacral segments S4-S5

B= Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5

C= Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

D= Incomplete: Motor function is preserved below the neurological, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

E= Normal: motor and sensory function are normal

## ***Appendix C***

### ***Motor Index Scale<sup>30</sup>***

***Motor index scoring*** – 5 key muscles in each limb are scored out of a maximum of 5 points each. This is then totalled to give a total 25 per extremity and a total possible score of 100. The key muscles are listed below:

- C5 - Elbow flexors (biceps, brachialis)
- C6 - Wrist extensors (extensor carpi radialis longus and brevis)
- C7 - Elbow extensors (triceps)
- C8 - Finger flexors (flexor digitorum profundus) to the middle finger
- T1 - Small finger abductors (abductor digiti minimi)
- L2 - Hip flexors (iliopsoas)
- L3 - Knee extensors (quadriceps)
- L4 - Ankle dorsiflexors (tibialis anterior)
- L5 - Long toe extensors (extensors hallucis longus)
- S1 - Ankle plantar flexors (gastrocnemius, soleus)