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Cell-based neurorestorotherapy in amyotrophic lateral sclerosis – scientific truth should rely on facts, but not conjecture

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A commentary on

No benefits from experimental treatment with olfactory ensheathing cells in patients with ALS
by Piepers, S., and van den Berg, L. H. (2010). Amyotroph. Lateral Scler. 11, 328–330.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal, neurodegenerative disease caused by the degeneration of motor neurons, the nerve cells in the central nervous system that control voluntary muscle movement. Death due to respiratory failure occurs typically 2–5 years after disease onset (Suzuki et al., 2007). Our basic and clinical studies have proven that OECs have neuroprotective effect and can improve quality of life and prolong surviving time (Huang et al., 2007, 2008; Chen et al., 2007, 2012; Li et al., 2011). Dr. Piepers (Piepers and van den Berg, 2010) published a paper to make comment on our work, in which there were some wrong viewpoints and errors. Also there may be someone sharing same viewpoints with his paper. In order to avoid misleading readers, it is our irresistible duty to tell people the truth what happened about treatment study, show more evidences, and facts of development for this disease. Herein, we encourage people to read his original paper with our thoughts in mind. We strongly believe that scientific truth should rely on facts, but not conjecture.

"THESE THERAPIES AIM AT NEURONAL REPLACEMENT OR USE EMBRYONIC OR NEURONAL STEM CELLS TO PREVENT DYSFUNCTIONAL MOTOR NEURONS FROM DYING" IS CORRECT?

In fact, the mechanisms for neurorestoration in ALS are very complex, which lie on neural regeneration, repair, and replacement of damaged components of the nervous system, neuroplasticity, neuroprotection and neuromodulation, vasculogenesis, and recovery mechanisms of immune regulation (Fornai et al., 2008; IANR, 2009; Mitrecić et al., 2009; Huang et al., 2010). Embryonic or neuronal stem cells hardly replace motor neuron in ALS and also are difficult to have useful functions as people expect. Otherwise, transplanted cells can serve as a source of trophic factors providing neuroprotection, slowing down neuronal degeneration, and disease progression. Presently, cell–based neurorestorative treatment has become a new trend (Huang, 2010). Rapidly increasing worldwide data have proven that it has a pivotal therapeutic value in ALS (see **Tables 1 and 2**; Chen et al., 2012). So neruoprotection is one of the most functional neurorestorative strategies for ALS; unfortunately Dr. Piepers fully ignored most of the progress in this research field.

WHAT IDEAL EXPECTATION OF TREATMENT IS AND WHAT CURRENT MEDICINE CAN DO FOR ALS?

To attenuate the rate of deterioration should be considered and encouraged as the main aim at the current time, because the cure has not yet been made available so far. So any improvement is very important for patients with ALS. Based on Dr. Piepers' paper, we at least found three out of a total of seven patients who had reversed their functions after our treatment. Our recent study, multiple transplantations for ALS shows that every single treatment could make functional improvement for patients (**Table 3**; Chen et al., 2012). These essential findings should be translated as highlighted positive results because specialists in the ALS study community around the whole world know there is no way to reverse the clinical course of ALS through routine treatment including Rilutek. People should not require current medicine to get treatment results as their ideal expectation for some untreatable diseases such as ALS.

WHERE SHOULD THE CELLS BE TRANSPLANTED INTO?

We can understand why Dr. Piepers said that "*it is difficult to understand how focal injection of OECs into the corona radiata of ALS patients would result in improved function of motor neurons that are not in close proximity to the injection site.*" We compared two ways by transplanting cells into spinal cord or brain; and there was no difference of functional improvement between two methods (Chen et al., 2007). We are also doing experimental study which will be published soon. People will know more about the progress in this field from our current experimental study, that is, OEC transplantation in corona radiate prolongs the survival of SOD1–G93A rats with protection to not only the upper motor neurons but lower motor neurons in cornu anterius medullae spinalis as well.

"IT HAS BEEN SHOWN THAT INJECTING STEM CELLS INTO THE SPINAL CORD OF ALS PATIENTS IS TECHNICALLY FEASIBLE AND SAFE" IS CORRECT?

It is well known that the spinal cord surgery under the general anesthesia has more risks in ALS patients, so we have improved our treatment from the initial intraspinal cord transplantation since over 5 years ago. Our clinical study proved that local anesthesia and stereotactic procedure has much less body damage for ALS patients

Table 1 | Selected preclinical literatures of cell-based therapy for ALS (data from Pubmed; modified from 5).

Authors	Country	Year	Publications
Demierre et al. (1990)	Switzerland	Demierre et al. (1990)	Grafting of embryonic motoneurons into adult spinal cord and brain
Clowry et al. (1991)	UK	Clowry et al. (1991)	Transplants of embryonic motoneurones to adult spinal cord: survival and innervation abilities
Sagot et al. (1995)	Switzerland	Sagot et al. (1995)	Polymer encapsulated cell lines genetically engineered to release ciliary neurotrophic factor (CNTF) can slow down progressive motor neuronopathy in the mouse
Cooper et al. (1996)	France	Cooper et al. (1996)	Intraspinal injection of embryonic neurons maintains muscle phenotype in adult chronic spinal rats
Mohajeri et al. (1999)	USA	Mohajeri et al. (1999)	Intramuscular grafts of myoblasts genetically modified to secrete glial cell line-derived neurotrophic factor prevent motoneuron loss and disease progression in familial ALS mice
Ende et al. (2000)	USA	Ende et al. (2000)	Human umbilical cord blood effect on SOD mice (plus 800 cGy of irradiation)
Garbuzova-Davis et al. (2002)	USA	Garbuzova-Davis et al. (2002)	Positive effect of transplantation of hNT neurons (NTera 2/D1 cell line) in a model of familial ALS
Kerr et al. (2003)	USA	Kerr et al. (2003)	Human embryonic germ cell derivatives facilitate motor recovery of rats with diffuse motor neuron injury
Garbuzova-Davis et al. (2003)	USA	Garbuzova-Davis et al. (2003)	Intravenous administration of human umbilical cord blood cells in a mouse model of amyotrophic lateral sclerosis: distribution, migration, and differentiation
Corti et al. (2004)	Italy	Corti et al. (2004)	Wild-type bone marrow cells ameliorate the phenotype of SOD1–G93A mice and contribute to CNS, heart, and skeletal muscle tissues
Gao et al. (2005)	USA	Gao et al. (2005)	Human neural stem cell-derived cholinergic neurons innervate muscle in motoneuron deficient adult rats
Li et al. (2005)	USA	Li et al. (2005)	Fate of immortalized human neuronal progenitor cells transplanted in rat spinal cord
Klein et al. (2005)	USA	Klein et al. (2005)	GDNF delivery using human neural progenitor cells in a rat model of ALS
Hemendinger et al. (2005)	USA	Hemendinger et al. (2005)	Sertoli cells improve survival of motor neurons in SOD1 transgenic mice
Corti et al. (2006)	Italy	Corti et al. (2006)	Transplanted ALDHhiSSClo neural stem cells generate motor neurons and delay disease progression of nmd mice, an animal model of SMARD1
Solomon et al. (2006)	Canada	Solomon et al. (2006)	Origin and distribution of bone marrow-derived cells in the central nervous system in ALS mice
Yan et al. (2006)	USA	Yan et al. (2006)	Combined immunosuppressive agents or CD4 antibodies prolong survival of human neural stem cell grafts and improve disease outcomes in ALS transgenic mice
Salah-Mohellibi et al. (2006)	France	Salah-Mohellibi et al. (2006)	Bone marrow transplantation attenuates the myopathic phenotype of a muscular mouse model of spinal muscular atrophy
Huang et al. (2006)	China	Huang et al. (2006)	Effect of transplantation of wild-type bone marrow stem cells in familial ALS mice
Xu et al. (2006)	USA	Xu et al. (2006)	Human neural stem cell grafts ameliorate motor neuron disease in SOD1 transgenic rats
Lim et al. (2006)	Australia	Lim et al. (2006)	Derivation of motor neurons from three clonal human embryonic stem cell lines
Suzuki et al. (2007)	USA	Suzuki et al. (2007)	GDNF secreting human neural progenitor cells protect dying motor neurons, but not their projection to muscle, in a rat model of familial ALS
Zhao et al. (2007)	China	Zhao et al. (2007)	Human mesenchymal stromal cells ameliorate the phenotype of SOD1–G93A ALS mice
Christou et al. (2007)	UK	Christou et al. (2007)	Embryonic stem cells and prospects for their use in regenerative medicine approaches to motor neuron disease
Martin and Liu (2007)	USA	Martin and Liu (2007)	Adult olfactory bulb neural precursor cell grafts provide temporary protection from motor neuron degeneration, improve motor function, and extend survival in ALS mice

(Continued)

Table 1 | Continued

Authors	Country	Year	Publications
Kang and Rivest (2007)	Canada	Kang and Rivest (2007)	MyD88-deficient bone marrow cells accelerate onset and reduce survival in ALS mice
Garbuzova-Davis et al. (2008)	USA	Garbuzova-Davis et al. (2008)	Human umbilical cord blood treatment in ALS mice: optimization of cell dose
Vercelli et al. (2008)	Italy	Vercelli et al. (2008)	Human mesenchymal stem cell transplantation extends survival, improves motor performance and decreases neuroinflammation in ALS mice
Suzuki et al. (2008)	USA	Suzuki et al. (2008)	Direct muscle delivery of GDNF with human mesenchymal stem cells improves motor neuron survival and function in familial ALS rats
Beers et al. (2008)	USA	Beers et al. (2008)	CD4+T cells support glial neuroprotection, slow disease progression, and modify glial morphology in an animal model of inherited ALS
Lepore et al. (2008)	USA	Lepore et al. (2008)	Focal transplantation-based astrocyte replacement is neuroprotective in ALS. [lineage-restricted astrocyte precursors, glial-restricted precursors (GRPs)]
Xu et al. (2009)	USA	Xu et al. (2009)	Human neural stem cell grafts in the spinal cord of SOD1 transgenic rats: differentiation and structural integration into the segmental motor circuitry
Zhang et al. (2009)	China	Zhang et al. (2009)	Multiple administrations of human marrow stromal cells through cerebrospinal fluid prolong survival in ALS transgenic mice
Hwang et al. (2009)	Korea	Hwang et al. (2009)	Intrathecal transplantation of human neural stem cells overexpressing VEGF provide behavioral improvement, disease onset delay, and survival extension in transgenic ALS mice
López-González et al. (2009)	México	López-González et al. (2009)	Transient recovery in familial ALS rats after transplantation of motor neurons derived from mouse embryonic stem cells
Kim et al. (2010)	Korea	Kim et al. (2010)	Dose-dependent efficacy of ALS-human mesenchymal stem cells transplantation into cisterna magna in SOD1–G93A ALS mice
Guo et al. (2010)	USA	Guo et al. (2010)	Characterization of a human fetal spinal cord stem cell line, NSI-566RSC, and its induction to functional motoneurons
Gu et al. (2010)	China	Gu et al. (2010)	Human adipose-derived stem cells enhance the glutamate uptake function of GLT1 in SOD1(G93A)-bearing astrocytes
Mitrecić et al. (2010)	Belgium	Mitrecić et al. (2010)	Distribution, differentiation, and survival of intravenously administered neural stem cells in a rat model of amyotrophic lateral sclerosis
Rizvanov et al. (2011)	Russia	Rizvanov et al. (2011)	Genetically modified human umbilical cord blood cells expressing vascular endothelial growth factor and fibroblast growth factor 2 differentiate into glial cells after transplantation into amyotrophic lateral sclerosis transgenic mice
Xu et al. (2011)	USA	Xu et al. (2011)	Dual transplantation of human neural stem cells into cervical and lumbar cord ameliorates motor neuron disease in SOD1 transgenic rats
Forostyak et al. (2011)	Czech	Forostyak et al. (2011)	Mesenchymal stromal cells prolong the lifespan in a rat model of ALS
Pastor et al. (2011)	Spain	Pastor et al. (2011)	Comparative effects between bone marrow and mesenchymal stem cell transplantation in GDNF expression and motor function recovery in ALS mouse
Lunn et al. (2011)	USA	Lunn et al. (2011)	Stem cell technology for motor neuron diseases
Sanberg et al. (2011)	USA	Sanberg et al. (2011)	Treatment of neurodegenerative disorders using umbilical cord blood and menstrual blood-derived stem cells

than general anesthesia and open spinal surgery (Chen et al., 2007). We suggest that Dr. Piepers should do more clinical investigations or get clinical experience before he comments or discusses on which method is better, feasible, and safe for clinical issue.

IMMUNOSUPPRESSANT IS NECESSARY?

The application of immunosuppressant remains controversial after cell transplantation into the brain and/or spinal cord. In additional, some of the ALS patients are too weak to tolerate the drugs. Most recently, OECs were able to stay alive for at least 12–24 months which has been proven through two autopsies by Italian physicians (Giordana et al., 2010).

In summary, to talk by conjecture is a simple process; however, to really help patients with ALS to improve their neurological functions and quality of life must face

Table 2 | Literatures of cell-based therapy in ALS humans (data from Pubmed; modified from 5).

Authors	Country	Year	Publications
Aebischer et al. (1996)	Switzerland	Aebischer et al. (1996)	Intrathecal delivery of CNTF using encapsulated genetically modified xenogeneic cells in ALS patients
Mazzini et al. (2003)	Italy	Mazzini et al. (2003)	Stem cell therapy in ALS: a methodological approach in humans (BMSCs)
Huang et al. (2007)	China	Huang et al. (2007)	MR spectroscopy evaluation and short-term outcome of OEC transplantation in ALS patients
Chen et al. (2007)	China	Chen et al. (2007)	Short-term outcome of OEC transplantation for ALS
Huang et al. (2008)	China	Huang et al. (2008)	Fetal OEC transplantation in ALS patients: a controlled study
Badayan and Cudkowicz (2008)	USA	Badayan and Cudkowicz (2008)	Mesenchymal stem cell trials in people with ALS
Cashman et al. (2008)	Canada	Cashman et al. (2008)	Pilot study of granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells in ALS
Deda et al. (2009)	Turkey	Deda et al. (2009)	Treatment of ALS patients by autologous bone marrow-derived hematopoietic stem cell transplantation: a 1-year follow-up
Martinez et al. (2009)	Mexico	Martinez et al. (2009)	Stem cell transplantation into the frontal motor cortex in ALS patients. Cytotherapy. [CD133(+) cells]
Choi et al. (2010)	Korea	Choi et al. (2010)	Selection of optimal passage of bone marrow-derived mesenchymal stem cells for stem cell therapy in patients with amyotrophic lateral sclerosis
Karussis et al. (2010)	Israel	Karussis et al. (2010)	Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis

Table 3 | Amyotrophic lateral sclerosis–FRS and Norris scale score and increased score after four treatments.

Cell transplant	ALS–FRS			Norris scale		
	Pre-treatment	Post-treatment	Increased score	Pre-treatment	Post-treatment	Increased score
1st	24.5 ± 7.1	27.1 ± 7.1	2.6 ± 2.4	55.9 ± 20.9	60.8 ± 22.1	4.9 ± 5.2
2nd	20.1 ± 7.3	21.1 ± 7.4	1.1 ± 1.3	43.0 ± 21.6	45.6 ± 21.8	2.3 ± 0.2.9
3rd	18.3 ± 7.7	19.4 ± 8.4	1.1 ± 1.5	36.1 ± 20.9	39.6 ± 23.1	3.4 ± 0.6.9
4th	20.5 ± 4.9	20.5 ± 4.9	0.0 ± 0.0	37.5 ± 24.7	40.05 ± 28.3	2.5 ± 0.3.5

There was statistic difference between pre-treatment ALS–FRS and Norris scale score and post-treatment score after 1st and 2nd cell therapy ($p < 0.01$). Increased scores of ALS–FRS in 1st group was significantly more than the other 3 groups ($p < 0.05$) and no statistic differences were shown between 2nd and 3rd, 3rd and 4th group ($p > 0.05$), but it is difference between 2nd and 4th ($p < 0.05$). There was statistic difference on increased score of Norris scale between 1st and 2nd cell transplant ($p = 0.019$).

hardships and challenges. The community should encourage any efforts to discover effective therapeutic strategies globally. Fortunately, now clinical studies already showed that cell therapy could restore patients' neurological functions by neuroprotection or some other mechanisms.

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