BEIKE BIOTECHNOLOGY

Beike Stem Cell Treatment for Cerebral Palsy (CP)

What is the disease and how does it affect the body?

Cerebral palsy (CP) is a non-progressive disorder of posture and movement resulting from an insult to the developing brain. It means the brain damage doses not worsen, but secondary orthopedic difficulties are common. It is one of the most common chronic disabling conditions of childhood, with a prevalence of 2-4 per 1,000 children aged 3-10 years[1]. The spectrum and patterns of posture and motor impairment are variable but the characteristic signs are: diplegia, hemiplegia and quadriplegia[2]. Additionally, children with CP often have abnormal muscle tone or movement disorders, such as, spasticity, rigidity, hypotonia, dystonia, athetosis, or a mixture of these disorders[1]. In addition to motor disability, children with CP often have other problems including communication, learning disabilities, development delay and musculoskeletal problems such as joint contractures, kypho-scoliosis and hip dislocation. Children and adolescents with CP are also prone to low trauma fractures, which occur for example during normal activities such as dressing and handling[2]. CP is the second-most expensive developmental disability (second to mental retardation) to manage over the span of a person's lifetime, estimated lifetime costs in 2003 dollars are expected to total $11.5 billion for persons born in 2000 with cerebral palsy[1].

The efficacy of current therapy

Thus far, there is no cure for CP. It is important to remember that the earlier treatment begins the better opportunities children have of overcoming developmental disabilities and/or learning new ways to accomplish the tasks that challenge them. Treatment on cerebral palsy may include one or more of the following: physical therapy; occupational therapy; speech therapy; devices assisted modalities (eg, electrical stimulation); orthotics; casting; hyperbaric oxygen; the use of baclofen and botulinum toxin A; surgery (eg, orthopaedic surgery, leg surgery). Nevertheless, there is only some benefit from these therapy [4-5]. Physical therapy, along with orthopedic surgery, has been the mainstay of the rehabilitation management of CP for decades[6]. Traditional therapy approaches have been shown for the most part to be marginally beneficial[7]and demand serious reconsideration by those who still advocate them.

How can stem cells help relieve the disease's symptoms?

Recent studies from multiple laboratories has led to the conclusion that stem cell transplantation has a good result on functional recovery following CP[8-122].

Improvement:

Most Cerebral Palsy patients Beike have treated, utilizing the combination of stem cell therapy and rehabilitation, showed visible signs of improvement: regaining motor development and coordination, regaining eyesight, improving mental retardation, increasing muscle strength, decreasing muscle tone of spasticity etc.

However, when discussing improvements, it is important to remember that improvements might greatly differ from one patient to another due to many factors, such as patient's medical course, physical condition, severity, age and so on. Therefore, improvement cannot be guaranteed.

Mechanism:

Currently, Stem cell transplantation is a good way to treat CP patients. There are many kinds of stem cells which show a promising potential for clinical application. The potential mechanisms of stem cell transplantation are (1) reducing the inflammation response [14,15], avoiding secondary brain lesion; (2) differentiating into astrocyte, microglia, oligodendrocyte, neuronland glia cells[16-21], which may be good for myeline sheath, axon regeneration, transmission of nerve impulse; (3) producing the cytonkines and growth factors, such as glia derived neurotrohic factor (GDNF), brain derived neurotrophic factor(BDNF), nerve growth factor(NGF), neurotrohin 3 (NT-3), neurotrohin 4/5 (NT 4/5) [22] that support brain neuroprotection; and(4) generating new vessels growth, thereby increasing the delivery of oxygen and nutrients to injured and hypoxic tissue[23]; and (5) reducing the intrinsic cell apoptosis [24,25].

References

1. Koman LA, Smith BP, Shilt JS. Cerebral palsy.Lancet.2004; 363:1619-1631. 2. Ward KA, Caulton JM, Adams JE. Perspective: Cerebral palsy as a model of bone development in the absence of postnatal mechanical factors ,J Musculoskelet Neuronal Interact. 2006, 6(2):154-159 3. Centers for Disease Control and Prevention (CDC).Economic costs associated with mental retardation, cerebral palsy,hearing loss, and vision impairment--United States, 2003. 4. Bower E, Michell D, Burnett M, Campbell MJ, McLellan DL.Randomized controlled trial of physiotherapy in 56 children with cerebral palsy followed for 18 months.Dev

5. Butler C, Darrah J. Effects of neurodevelopmental treatment(NDT) for cerebral palsy: an AACPDM evident report. Dev Med Child Neurol.2001,43:778-90 6. Damiano DL.Activity, Activity, Activity: Rethinking Our Physical Therapy Approach

7. DeJong G, Horn SD, Conroy B, Nichols D, Healton EB.Opening the black box of post stroke rehabilitation: stroke rehabilitation patients, processes, and outcomes.

BEIKE BIOTECHNOLOGY CO., LTD.

Head Office

9th Floor, Zhongke Building, 1 South Street South Area, Shenzhen Hi-Tech Industrial Park Shenzhen, China 518057

8. Bartley J,Carroll JE.Stem cell therapy for cerebral palsy.ExpertOpin Biol Ther.2003, 3(4): 541-549 9. Felling RJ, Snyder MJ, Romanko MJ, Rothstein RP, Ziegler AN, Yang Z, Givogri MI, Bongarzone ER, Levison SW. Neural stem/progenitor cells participate in the regenerative response to perinatal hypoxia/ischemia.J Neurosci.2006,19; 26 (16): 4359-69.

10. Hayashi T, Iwai M, Ikeda T, Jin G, Deguchi K, Nagotani S, Zhang H, Sehara Y, Nagano I, Shoji M, Ikenoue T, Abe K.Neural precursor cells division and migration in

11. Back SA, Rivkees SA.Emerging concepts in periventricular white matter injury. Semin Perinatol. 2004,28(6):405-14

Med Child Neurol .2001,43:4-15

to Cerebral Palsy.Phys Ther.2006 Nov;86(11):1534-40.

Arch Phys Med Rehabil. 2005,86(12 suppl 2):S1–S7.

neonatal rat brain after ischemic/hypoxic injury. Brain Res.2005, 15;1038(1):41-9

12. Harris DT.Cord blood stem cells: a review of potential neurological applications. Stem Cell Rev. 2008,4(4):269-74. 13. Murray Goldstein DO. The Treatmentof cerebral palsy: what we know,what we don't know.The Journal of Pediatrics. 2004, 145(2),suppl 1:S42-S46

14. Pimentel-Coelho PM, Magalhães ES, Lopes LM, deAzevedo LC, Santiago MF, Mendez-Otero R.Human Cord Blood Transplantation in a Neonatal Rat Model of Hypoxic–Ischemic Brain Damage: Functional Outcome Related to Neuroprotection in

15. Schwarting S, S Litwak, W Hao, M Bahr, J Weise and H Neumann. Hematopoietic stem cells reduce postischemic inflammation and ameliorate ischemic brain injury. Stroke.2008,39(10): 2867–2875. 16. Kopen GC, Prockop DG, Phinney DG. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection

17. Sanchez-Ramos JR, Song S, Kamath SG, Zigova T, Willing A, Cardozo-Pelaez F, Stedeford T, Chopp M, Sanberg PR.Expression of neural markers in human umbilical

18. Bicknese AR, Goodwin HS, Quinn CO, Henderson VC, Chien SN, Wall DA. Human umbilical cord blood cells can be induced to express markers for neurons and glia. Cell Transplant.2002, 11: 261-264. 19. Sanberg PR, Willing AE, Cahill DW.Novel cellular approaches to repair of neurodegenerative disease: From Sertoli cells to umbilical cord blood stem cells.

20. McGuckin CP, Forraz N, Allouard Q, Pettengell R.Umbilical cord blood stem cells can expand hematopoietic and neuroglial progenitors in vi-tro. Exp Cell Res.2004,295:

21. Buzanska L, Jurga M, Stachowiak EK, Stachowiak MK, Domanska-Janik K. Neural stem-like cell line derived from a nonhematopoietic population of human umbilical cord blood. Stem Cells Develop, 2006,15, 391–406. 22. Peterson DA. Umbilical cord blood cells and brain stroke injury: bringing in fresh

the Striatum. Stem Cells Dev.2010,19(3):351-8.

into neonatal mouse brains. Proc Natl Acad Sci U S A. 1999,14;96(19):10711-6.

cord blood. Exp Neurolog.2001, 171: 109-115.

Neurotox Res.2002, 4: 95-101.

350-359.

BEIKE BIOTECHNOLOGY CO., LTD.

Head Office

9th Floor, Zhongke Building, 1 South Street South Area, Shenzhen Hi-Tech Industrial Park Shenzhen, China 518057

blood to address an old problem. J Clin Invest.2004,114(3):312–314. 23. Buschmann IR, Hoefer IE, van Royen N, Katzer E, Braun-Dulleaus R, Heil M, Kostin S, Bode C, Schaper W. GM-CSF: A strong arteriogenic fac-tor acting by amplification

24. YasuharaT, Hara K, Maki M, Mays RW, Deans RJ, Hess DC, Carroll JE, Borlongan CV.Intravenous grafts recapitulate the neurorestoration afforded by intracerebrally delivered multipotent adult progenitor cells in neonatal hypoxic-ischemic rats. J Cereb Blood Flow Metab. 2008,28:1804-10

25. Xiao J, Nan Z, Motooka Y, Low WC. Transplantation of a novel cell line population of umbilical cord blood stem cells ameliorates neurological deficits associated with ischemic brain injury. Stem Cells Dev.2005, 14, 722–733.

of monocyte function. Atherosclerosis.2001, 159: 343-356.

BEIKE BIOTECHNOLOGY CO., LTD.

Head Office

9th Floor, Zhongke Building, 1 South Street South Area, Shenzhen Hi-Tech Industrial Park Shenzhen, China 518057