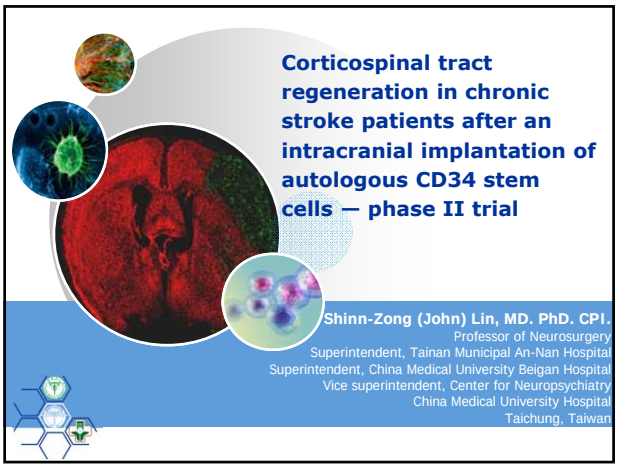
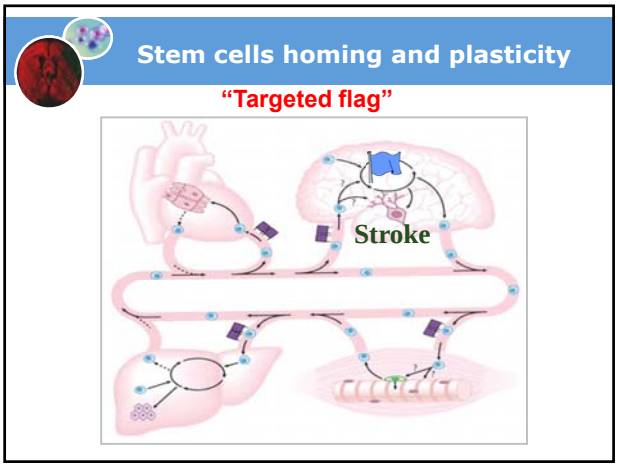
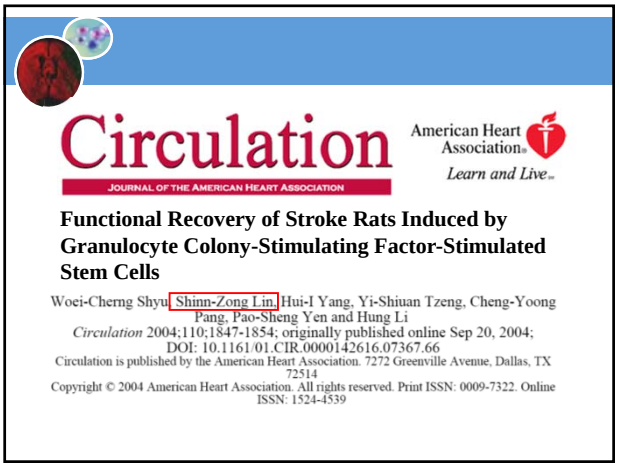
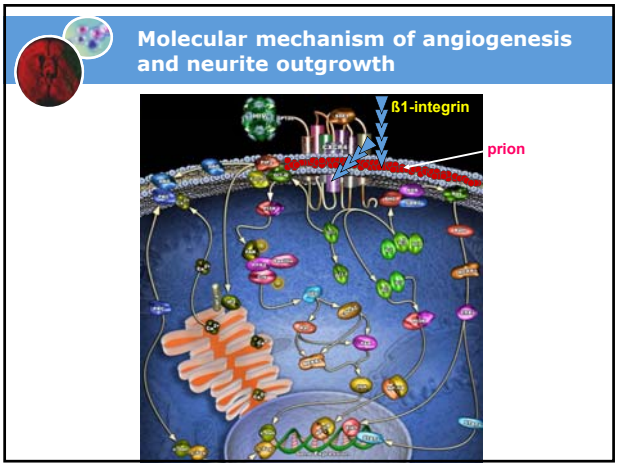
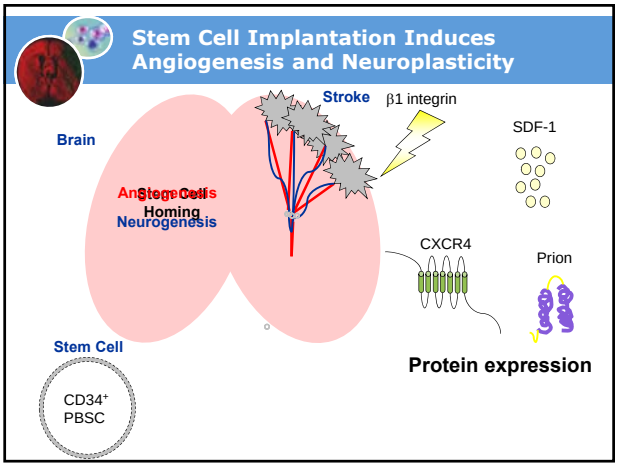

Corticospinal tract regeneration in chronic stroke patients after an intracranial implantation of autologous CD34 stem cells — phase II trial
Shinn-Zong (John) Lin, MD. PhD. CPI.
Professor of Neurosurgery
Superintendent, Tainan Municipal An-Nan Hospital
Superintendent, China Medical University Beigan Hospital
Vice superintendent, Center for Neuropsychiatry
China Medical University Hospital
Taichung, Taiwan

China Medical University And Healthcare System
中國醫藥大學醫療體系


Stem cells homing and plasticity
"Targeted flag"
Stroke


Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live
Functional Recovery of Stroke Rats Induced by Granulocyte Colony-Stimulating Factor-Stimulated Stem Cells
Woei-Cherng Shyu, Shinn-Zong Lin, Hui-I Yang, Yi-Shiuan Tzeng, Cheng-Yoong Pang, Pao-Sheng Yen and Hung Li
Circulation 2004;110;1847-1854; originally published online Sep 20, 2004;
DOI: 10.1161/01.CIR.0000142616.07367.66
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539


Molecular mechanism of angiogenesis and neurite outgrowth
ß1-integrin
prion


Stem Cell Implantation Induces Angiogenesis and Neuroplasticity
Stroke
β1 integrin
SDF-1
Brain
Stem Cell Homing
Neurogenesis
CXCR4
Prion
Stem Cell
CD34+ PBSC
Protein expression

RESEARCH

Granulocyte colony-stimulating factor for acute ischemic stroke: a randomized controlled trial

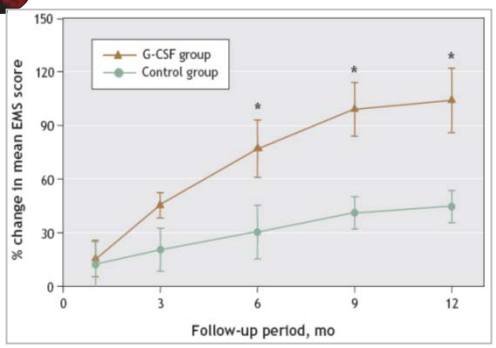
Woei-Cherng Shyu, Shinn-Zong Lin, Chau-Chin Lee, Demeral David Liu, Hung Li

Early release. Published at www.cmaj.ca on Mar. 3, 2006. Subject to revision.

Canadian Medical Association Journal , Mar, 2006, 174 (7):927-33

7

Significant increase in motor score in GCSF- treated patients



8

HIGHLIGHTS OF THIS ISSUE · DANS CE NUMÉRO

Early release, published at www.cmaj.ca on March 3, 2006. Subject to revision.

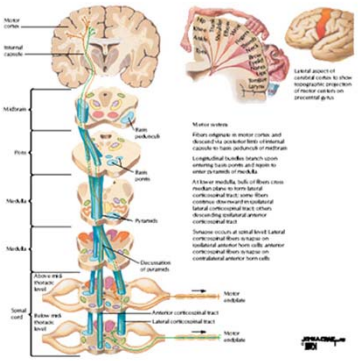
New hope for stroke patients: mobilization of endogenous stem cells

Cesar V. Borlongan, David C. Hess

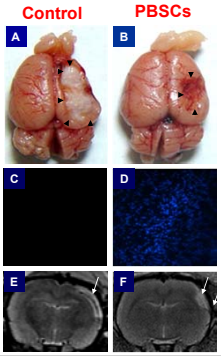
Early release. Published at www.cmaj.ca on Mar. 3, 2006. Subject to revision.

9

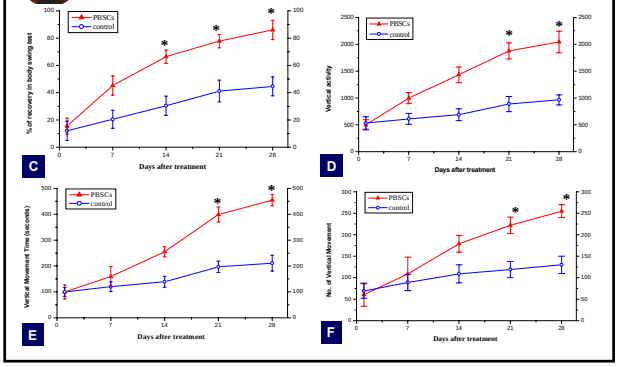
Corticospinal tract



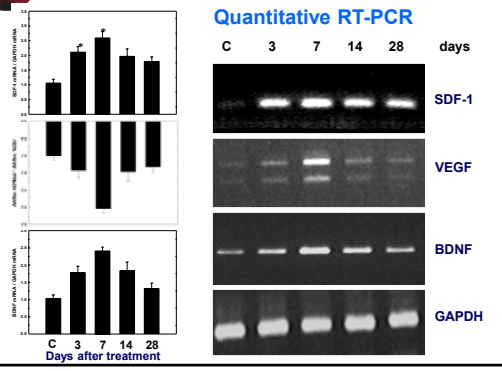
Engraftment of implanted CD34+ stem cells



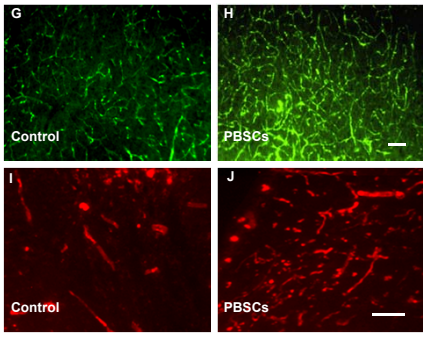
CD34+ Stem cell implantation into the stroke brain improved hemiplegic limb in chronic stroke rats



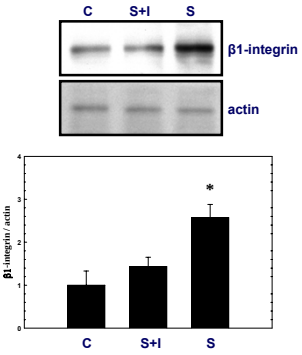
Homing and neurotrophic factors syntheses by the transplanted stem cells in the chronic stroke brain



Angiogenesis after PBSC transplantation



Expression of β1-integrin by the implanted stem cells



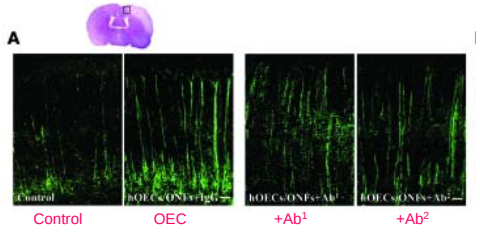
3444 • The Journal of Neuroscience. March 29, 2006 • 26(13):3444-3453

Neurobiology of Disease

Intracerebral Peripheral Blood Stem Cell (CD34$^+$) Implantation Induces Neuroplasticity by Enhancing β1 Integrin-Mediated Angiogenesis in Chronic Stroke Rats

Woei-Cherng Shyu,[1,4] Shinn-Zong Lin,[1,4] Ming-Fu Chiang,[2] Ching-Yuan Su,[3] and Hung Li[3,4]
[1]Neuro-Medical Scientific Center, Tzu-Chi Buddhist General Hospital, Tzu-Chi University, Hualien, Taiwan 970, [2]Department of Neurosurgery, Mackay Memorial Hospital, Mackay Junior College of Nursing, Taipei, Taiwan 112, [3]Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan 115, and [4]Institute of Biochemistry, National Yang-Ming University, Taipei, Taiwan 112

Neurite outgrowth depends on the upregulation of CXCR4 and prion proteins in stroke rats after transplantation



*Shyu WC, Liu DD, **Lin SZ** , etal. Journal of Clinical Investigation, July 2008, 118(7)*

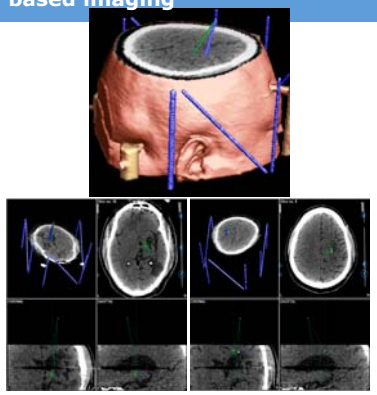
Clinical trial
(Peripheral blood stem cell transplantation)

Subcutaneous G-CSF injection combined with intracerebral mobilized peripheral blood hematopoietic stem cells (CD34+) transplantation--human clinical trial in chronic stroke:

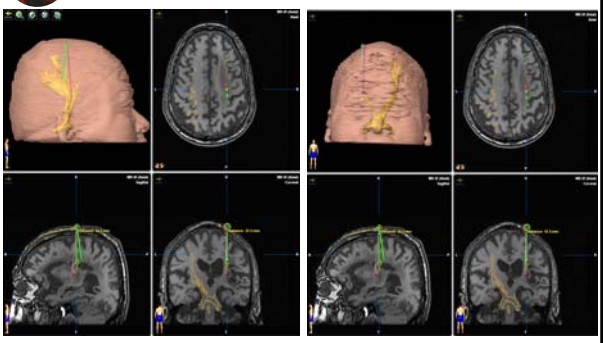
Inclusion criteria:

1) Subjects with cerebral ischemia at middle cerebral artery territory producing a serious measurable deficit by NIHSS scale and who could receive study medication within 6 to 60 months after the onset of the symptom. A serious measurable deficit by NIHSS is defined as the NIHSS≧ 9 and≦ 20
2) Subjects must be≧ 35 and≦ 75 years old , of either sex
3) Subjects or his / her legal guardians must demonstrate their willingness to participate in the study and comply with its procedures by signing a written informed consent.
4) Subjects with Modified Rankin Scale≧ 1

Three targets are identified by fram-based imaging

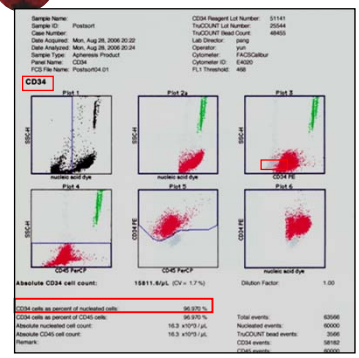


Injured pyramidal tract was identified



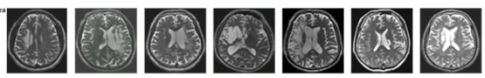
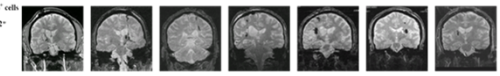
CD34⁺ stem cell were implanted into the brain targets

Assessment of stem cell purity and viability



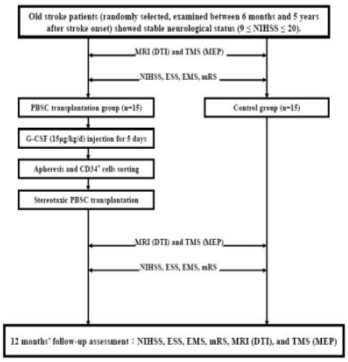
7 old stroke patients were transplanted in phase I trials

Table 4: Characteristics of patients in G-CSF+PBSC-treated group

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
a.S/S	Lt hemiparesis	Rt hemiparesis &aphasia	Rt hemiparesis &aphasia	Lt hemiparesis	Lt hemiparesis	Lt hemiparesis	Lt hemiparesis
b.Infarct area on T2WI							
c.CD34⁺ cells on T2*							
d.Stroke history	3 y	5 y	1.5 y	2 y	3 y	1.5y	0.6y
e.No. of injected CD34⁺ cells	5 x 10^6	7 x 10^6	6.7 x 10^6	8 x 10^6	3 x 10^6	7.5 x 10^6	6.5 x 10^6
f.Purity of CD34⁺ cells	97%	77%	49%	84.5%	33%	90%	96%
g.No. of IC trajectory	4	4	4	3	3	3	3

S/S=symptoms and signs, T2WI= T2 weighted image in MRI, No.=numbers, Lt=left limbs, Rt=right limbs, WBC=white blood cells, y=years, IC=intracerebral

Open-labbeld, randomized, controlled, two-armod trial

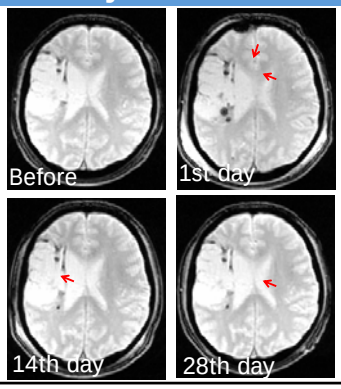


Clinical trial data

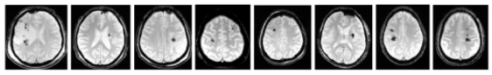
characteristics	PBSCs Group (n=15)	Control Group (n=15)	*p*
Age (years)	50.1 ± 8.7 (35-64)	56.7 ± 6.5 (41-66)	0.02
Men/Female	12/3	8/7	0.25
Duration of stroke (years)	2.7 ± 1.4 (0.6-5)	2.5 ± 1.4 (0.6-5)	0.67
Concomitant diseases:			
Hypertension	11 (73%)	8 (53%)	0.25
Diabetes	6 (40%)	2(13%)	0.22
Hyperlipidemia	3 (20%)	5 (33%)	0.68
Smoking	6 (40%)	1 (7%)	0.08
Prior aspirin or antiplatelet use	15 (100%)	15 (100%)	0.99
Rehabilitation duration (hours/week)	10.1 ± 2.1	11.5 ± 1.6	0.58
Baseline scores:			
Modified Rankin scale	2.9 ± 0.3	2.7 ± 0.4	0.91
NIH stroke scale	9.3 ± 0.5	9.6 ± 1.3	0.93

Table 1: Clinical characteristics of recruited patients (mean ± SEM)

Transplanted cells retained at the injection sites



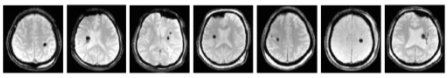
Data of transplantation group (1)

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient5	Patient 6	Patient 7	Patient 8
A. S/S	Lt hemiparesis	Rt hemiparesis	Rt hemiparesis &aphasia	Lt hemiparesis	Lt hemiparesis	Rt hemiparesis	Lt hemiparesis	Rt hemiparesis
B. MRI-T2*								
C. Stroke history	5 y	3.5 y	3 y	1.5 y	4 y	2.5y	1y	4.5 y
D. No. of injected CD34⁺ cells	8 x 10^6	3 x 10^6	8 x 10^6	5 x 10^6	8 x 10^6	7.5 x 10^6	6.5 x 10^6	6 x 10^6
E. Purity of CD34⁺ cells	94%	90%	91%	95%	93%	94%	87%	93%
F. No. of IC trajectory	3	3	3	3	3	3	3	3

S/S=symptoms and signs, MRI-T2*= T2* image in MRI, No.=numbers, Lt=left limbs, Rt=right limbs, y=years, IC=intracerrbral

Table 2: Characteristics of patients in PBSC-treated group

Data of transplantation group (2)

Characteristics	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
A. S/S	Rt hemiparesis	Lt hemiparesis	Rt hemiparesis	Lt hemiparesis	Lt hemiparesis	Rt hemiparesis	Rt hemiparesis
B. MRI-T2*							
C. Stroke history	4 y	2.5 y	2 y	0.6 y	0.7 y	2.5 y	3.5 y
D. No. of injected CD34⁺ cells	3 x 10^6	8 x 10^6	8 x 10^6	5 x 10^6	8 x 10^6	7.5 x 10^6	8 x 10^6
E. Purity of CD34⁺ cells	89%	92%	97%	96%	94%	91%	87%
F. No. of IC trajectory	3	3	3	3	3	3	3

S/S=symptoms and signs, MRI-T2*= T2* image in MRI, No.=numbers, Lt=left limbs, Rt=right limbs, y=years, IC=intracerrbral

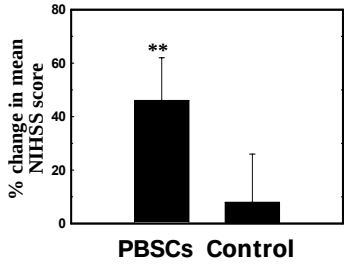
Table 2: Characteristics of patients in PBSC-treated group (continued)

Functional outcomes

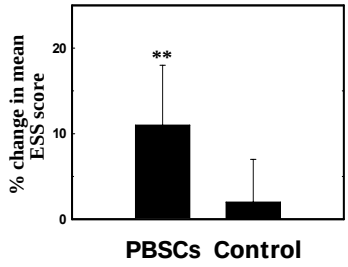
	PBSCs	Control	*p*
NIHSS			
Baseline	9.3±0.5	9.6±1.3	0.41
6-month	6.7±1.7	9.4±1.2	<0.0001
12-month	5.5±1.8	8.7±1.9	0.0002
p for trend	<0.0001	0.08	
ESS			
Baseline	69.3±7.8	66.2±8.1	0.26
6-month	74.1±7.8	66.3±7.4	0.009
12-month	76.1±8.1	67.1±7.6	0.005
p for trend	<0.0001	0.21	
EMS			
Baseline	23.9±8.2	21.0±8.0	0.34
6-month	28.7±8.2	20.9±7.4	0.01
12-month	30.5±8.8	21.7±7.7	0.009
p for trend	<0.0001	0.33	
mRS			
Baseline	2.9±0.3	2.7±0.4	0.65
6-month	2.5±0.5	2.7±0.5	0.15
12-month	2.1±0.3	2.6±0.5	0.004
p for trend	<0.0001	0.13	

Table 3: Results of clinical stroke scale scores at baseline,6-month and 12-month follow-up of PBSCs and control group

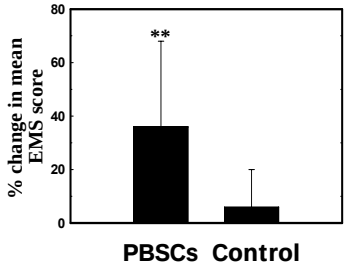
Better in NIHSS



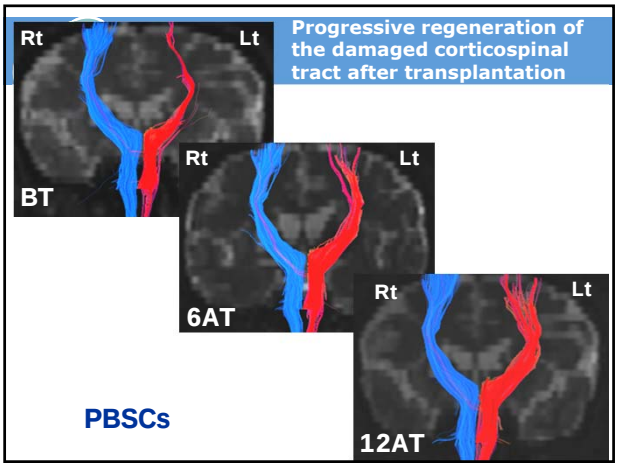
Better in ESS



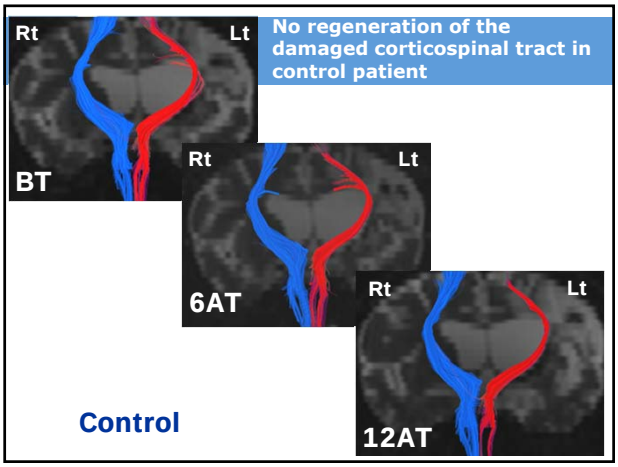
Better in EMS



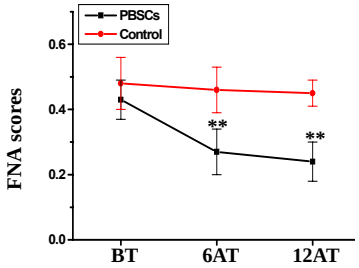
Progressive regeneration of the damaged corticospinal tract after transplantation



No regeneration of the damaged corticospinal tract in control patient



The damaged corticospinal tract regenerated progressively in the transplantation group



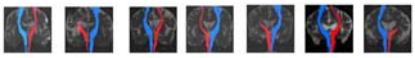
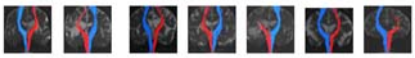
Transplantation group

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
MRI-DTI								
a. BT:								
b. 6AT:								
c. 12AT:								

MRI-DTI= diffusion tensor image of MRI, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT

Table 4: MRI-DTI in PBSC-treated group

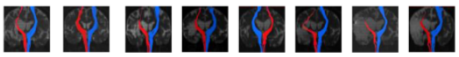
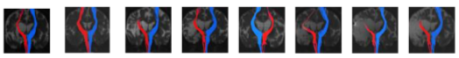
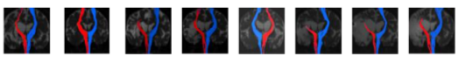
Transplantation group

Characteristics	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
MRI-DTI							
a. BT:							
b. 6AT:							
c. 12AT:							

MRI-DTI =diffusion tensor image of MRI, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT.

Table 4: MRI-DTI in PBSC-treated group (continued)

Control group

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
MRI-DTI								
a. BT:								
b. 6AT:								
c. 12AT:								

MRI-DTI= diffusion tensor image of MRI, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT

Table 4-1: MRI-DTI in control group

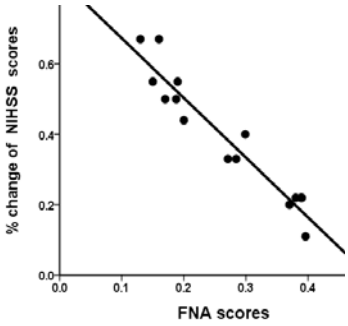
Control group

Characteristics	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
MRI-DTI							
a. BT:							
b. 6AT:							
c. 12AT:							

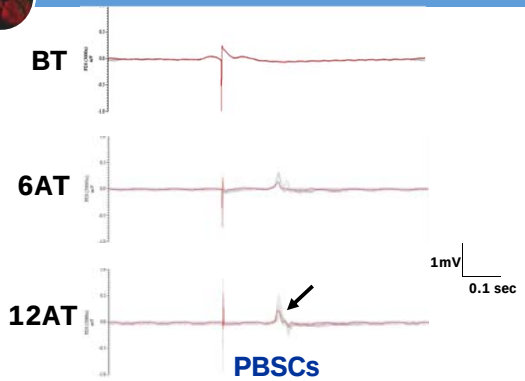
MRI-DTI =diffusion tensor image of MRI, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT.

Table 4-1: MRI-DTI in control group (continued)

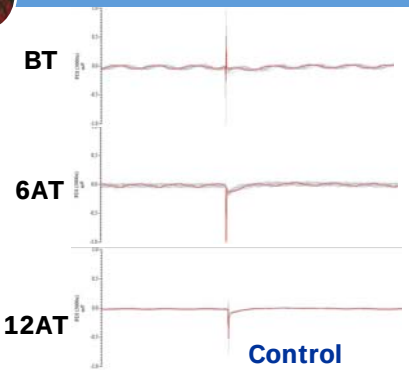
Functional recovery correlated well to nerve fiber tract regeneration



Recovery of motor evoked potential (MEPs) after transplantation



No important in MSPs in control



Data of MEPs in transplantation group

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
TMS-MEP:			MEP (+)	MEP (+)	MEP (+)	MEP (+)	MEP (+)	MEP (+)

a. BT:

b. 6AT:

c. 12AT:

TMS-MEP=motor evoked potential by transcranial magnetic stimulation, MEP (+)=a positive MEP response, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT.

Table 5: TMS-MEP in PBSC-treated group

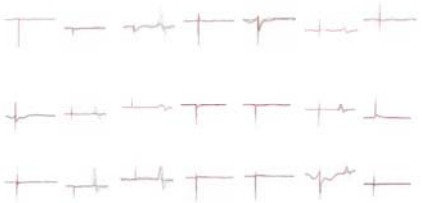
Data of MEPs in transplantation group

Characteristics	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
TMS-MEP:		MEP (+)	MEP (+)			MEP (+)	

a. BT:

b. 6AT:

c. 12AT:



TMS-MEP=motor evoked potential by transcranial magnetic stimulation, MEP (+)=a positive MEP response, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT.

Table 5: TMS-MEP in PBSC-treated group (continued)

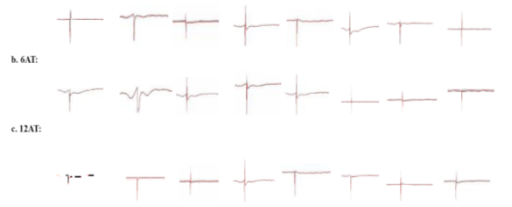
Data of MEPs in control group

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
TMS-MEP:								

a. BT:

b. 6AT:

c. 12AT:



TMS-MEP=motor evoked potential by transcranial magnetic stimulation, MEP (+)=a positive MEP response, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT.

Table 5-1: TMS-MEP in control group

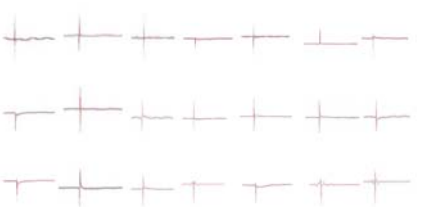
Data of MEPs in control group

Characteristics	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
TMS-MEP:							

a. BT:

b. 6AT:

c. 12AT:

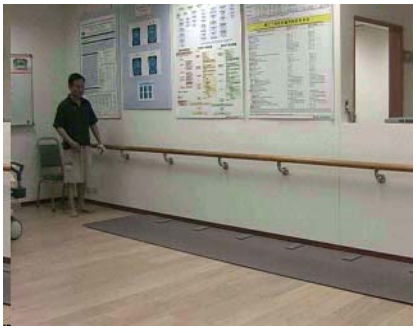


TMS-MEP=motor evoked potential by transcranial magnetic stimulation, MEP (+)=a positive MEP response, before transplantation=BT, 6 months after transplantation=6AT, 12 months after transplantation=12AT.

Table 5-1: TMS-MEP in control group (continued)

Before O.P. (Mr. Huang stroke for 1.5 years)

6 months after O.P.



Improvement in hand fine movement 6 months after O.P.

Improvement in hand fine movement Teeth Brushing

Patient lives independently one year after transplantation

Stem cell team working in the cGMP lab