RICORS-ICTUS

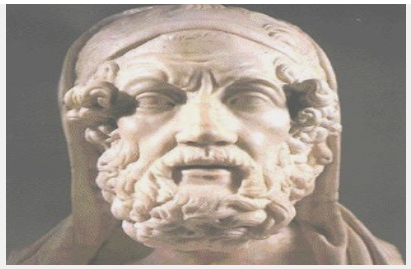
Una historia de investigación traslacional en Reparación Cerebral en Ictus Isquémico: de los estudios preclínicos a los ensayos clínicos

Exuperio Díez Tejedor
María Gutiérrez Fernández
Blanca Fuentes Gimeno

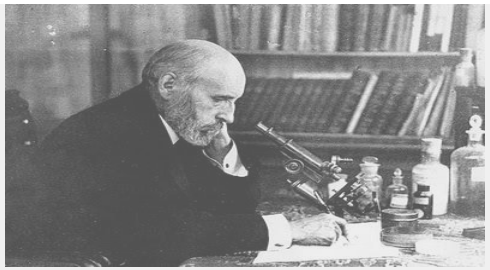
>1026 : 1

Grupo de Neurología y Enfermedad Cerebrovascular
Laboratorio de Ciencias Neurológicas
Instituto de Investigación Sanitaria IdiPAZ
Hospital Universitario La Paz, UAM

Apolo

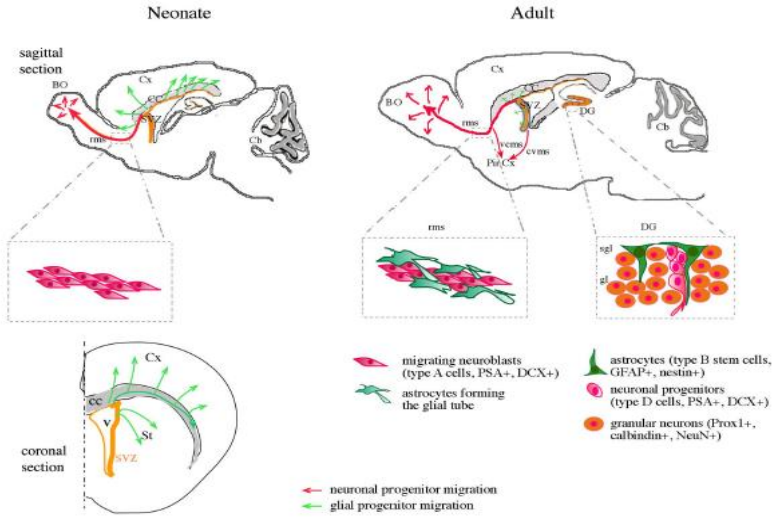


Hipócrates de Cos
(*Ἱπποκράτης*)
S. V AC - S. IV AC.



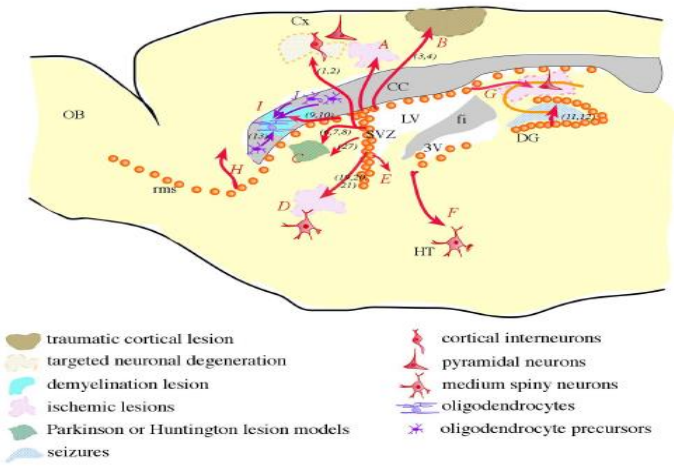
Santiago Ramón y Cajal
1852- 1934

Neuronal and glial migration in the healthy brain

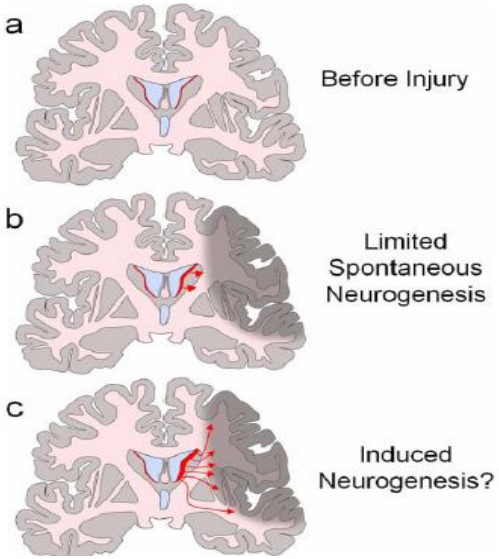


Cayre M, Canoll P, Goldman JE. Progr. Neuribiol. 2009:

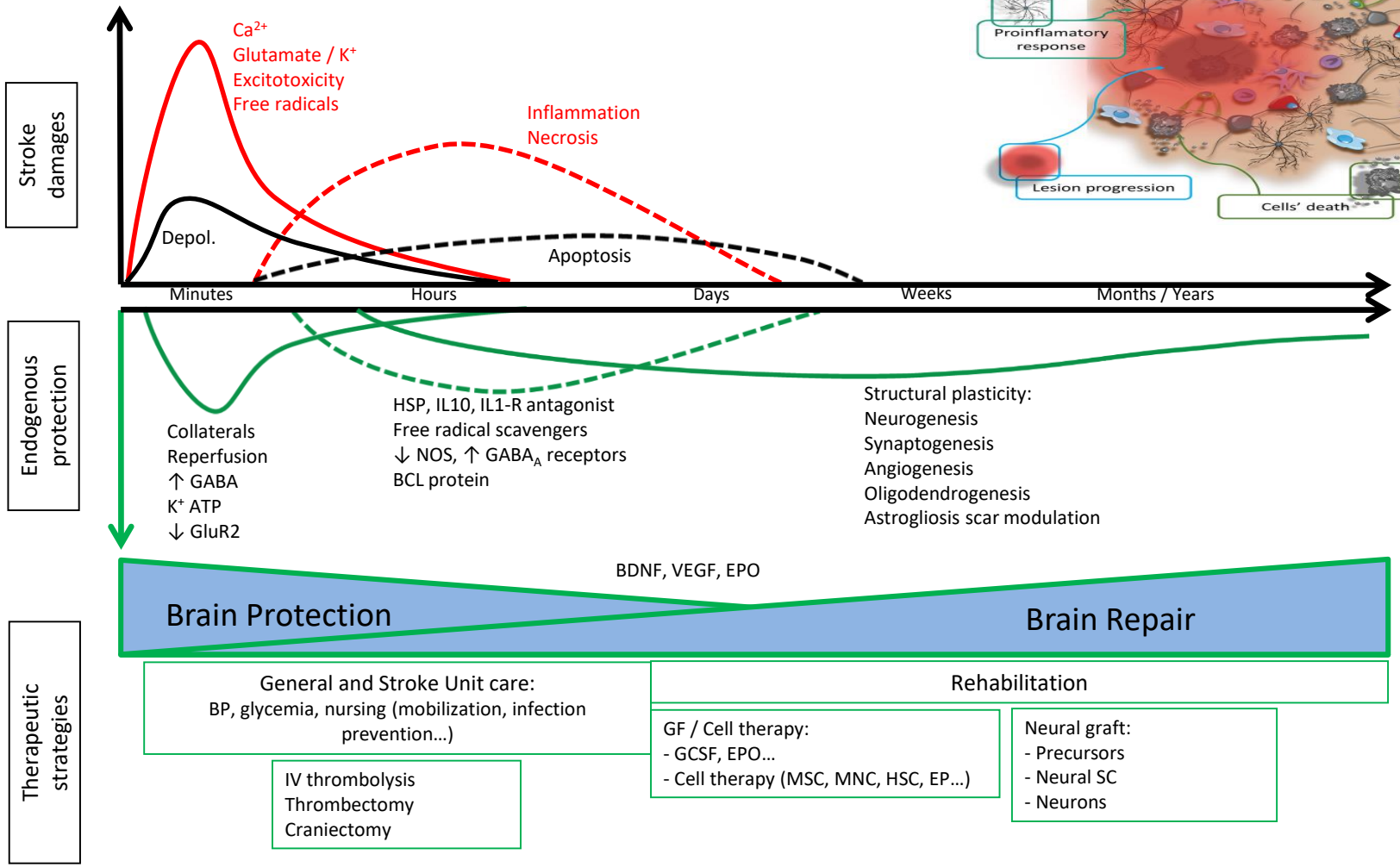
Neuronal and glial migration in the diseased brain

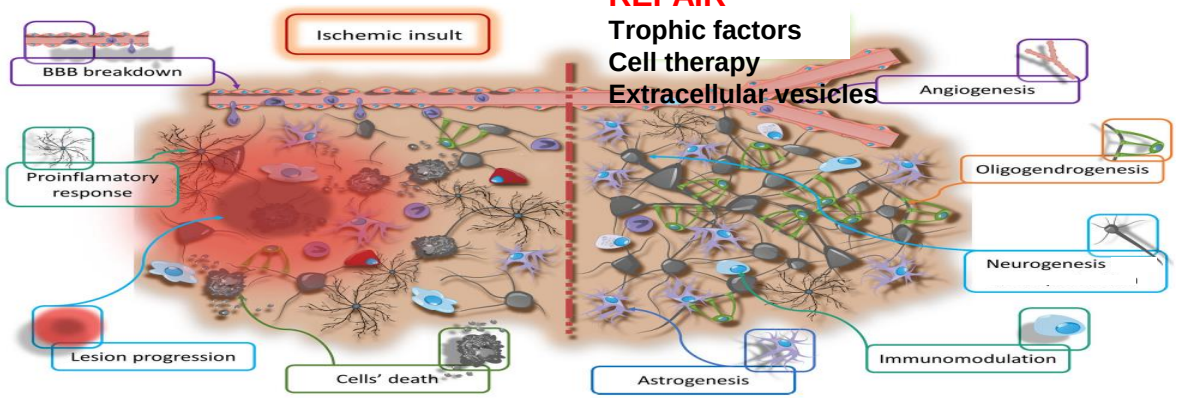


Cayre, M., Canoll, P., Goldman, J.E. Progr. Neuribiol. 2009;



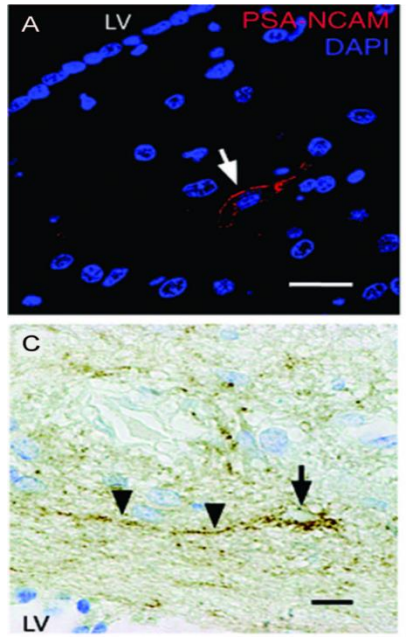
Burns T, Verfaille C, Low W. J. Comp. Neurol. 2009;





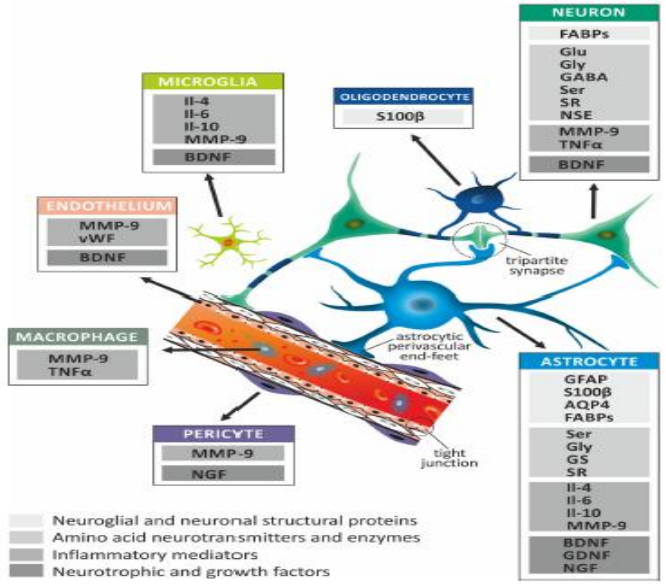
REPAIR
Trophic factors
Cell therapy
Extracellular vesicles

Dabrowska et al; J of Neuroinflam 2019

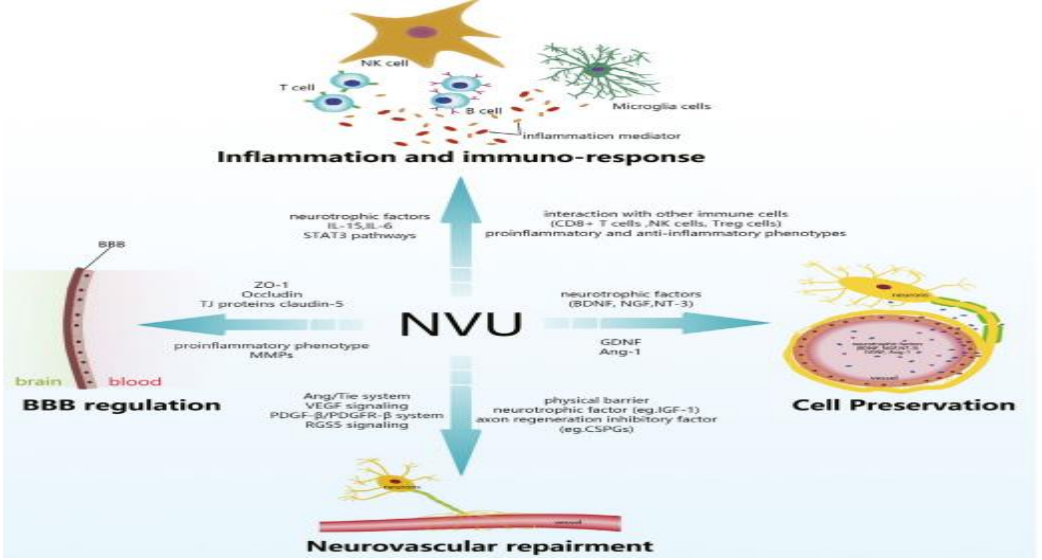


Martí-Fábregas J et al, Neurology. 2010

Gutiérrez M, et al. Cerebrovasc Dis 2009
Detante O, Rev Neurol 2014



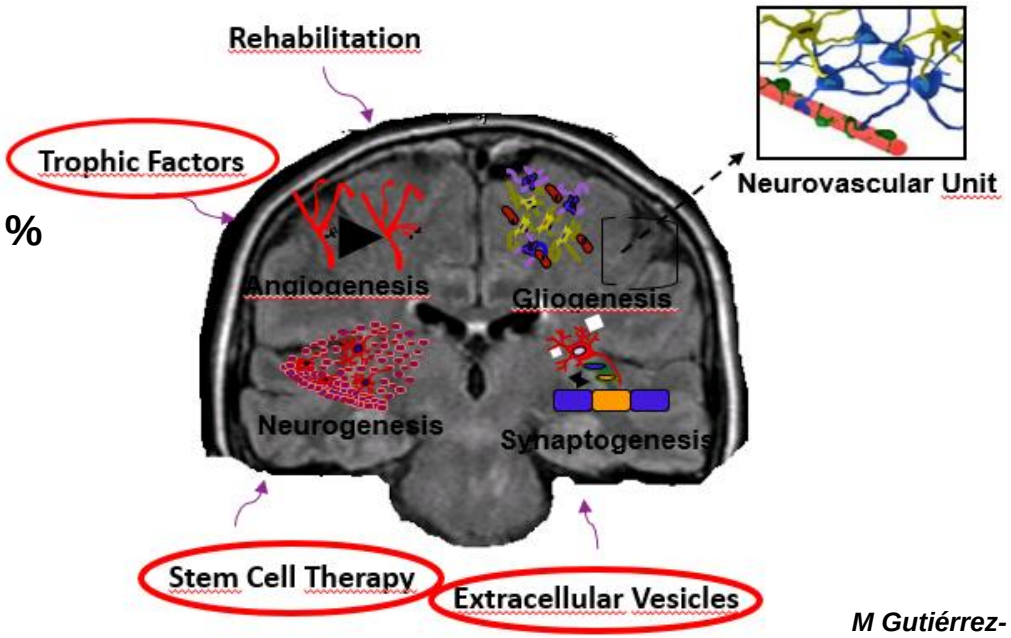
Steliga A et al; Trans Stroke Res 2020



Dabrowska et al; J of Neuroinflam 2019

BRAIN PLASTICITY ------→ BRAIN REPAIR

REPERFUSION THERAPIES : 35 – 40 %
Good Outcome (mRS <2): 55 - 60 %
Need REPAIR THERAPIES : ¿? 50 %

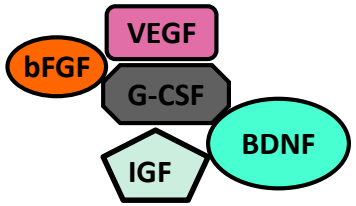


M Gutiérrez- Fernández , B Fuentes...E. Díez –Tejedor.
J Cell and Molec Med. 2012

TROHIC FACTORS

1947

Nerve growth factor (NGF)
Vascular endothelial growth factor (VEGF)
Brain derived neurotrophic factor (BDNF)



Tissue Repair
Reduces Cell death
Increases Cell proliferation
Neurogenesis and oligodendrogenesis *in vitro*
Inmunomodulation

Main results of therapeutic studies with trophic factors or drugs with trophic effects in cerebral infarct animal models and human clinical trials.

	Animal models	**Clinical trials**
Trophic Factors		
basic Fibroblast Growth Factor (bFGF)	Promotes neurogenesis Enhances functional recovery and stimulates progenitor cell proliferation	Phase III (286 patients). Prematurely stopped
Brain-Derived Neurotrophic Factor (BDNF)	Cellular and functional recovery Protects and promotes nerve fiber regeneration Promotes prostacyclin biosynthesis	No studies.
Vascular Endothelial Growth Factor (VEGF)	Reduces neuronal cell death, increases angiogenesis and vascular permeability, reduces infarct volume, improves behavioral recovery	No studies.
Erythropoietin (EPO)	Reduces infarct size and improves neurobehavioral deficits	Safety: open label (13 patients); Efficacy: double blind randomized proof of concept trial (40 patients): Improvement in neurological outcome, and smaller lesion size Phase II/III (522 patients): negative results and safety concerns
Granulocyte colony- stimulating factor (G-CSF)	Promotes new blood vessel formation, has anti-inflammatory, anti-excytotoxic, neuroprotective properties and survival-enhancing capacity and effects on functional outcome	Safety: Phase IIb (60 patients) AXIS-2: safety, tolerability and effect of G-CSF in acute ischemic stroke patients showed no improvement in patient outcome
EPO + G-CSF	Enhances angiogenesis and tissue plasticity, leading to greater functional recovery	No studies.

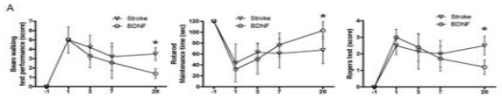
M Gutiérrez- Fernández , B Fuentes...E. Díez –Tejedor. J Cell and Molec Med. 2012; 16(10):2280-90.

TROHIC FACTORS

SUBCORTICAL ISCHEMIC STROKE: BDNF

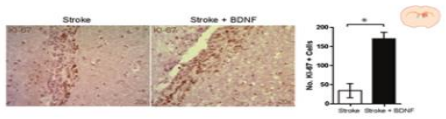
BDNF administration mediated oligodendrocyte differentiation and myelin formation in subcortical ischemic stroke

FUNCTIONAL EVALUATION

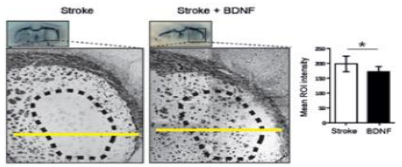


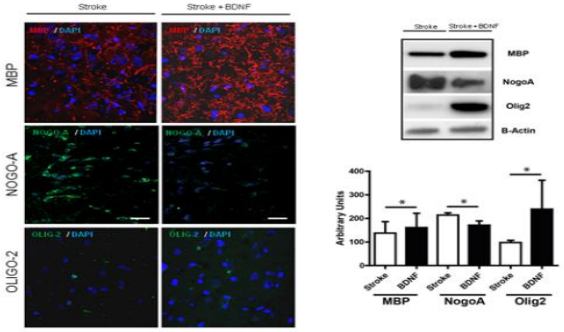
BRAIN REPAIR MARKERS

CELLULAR PROLIFERATION (Ki67)



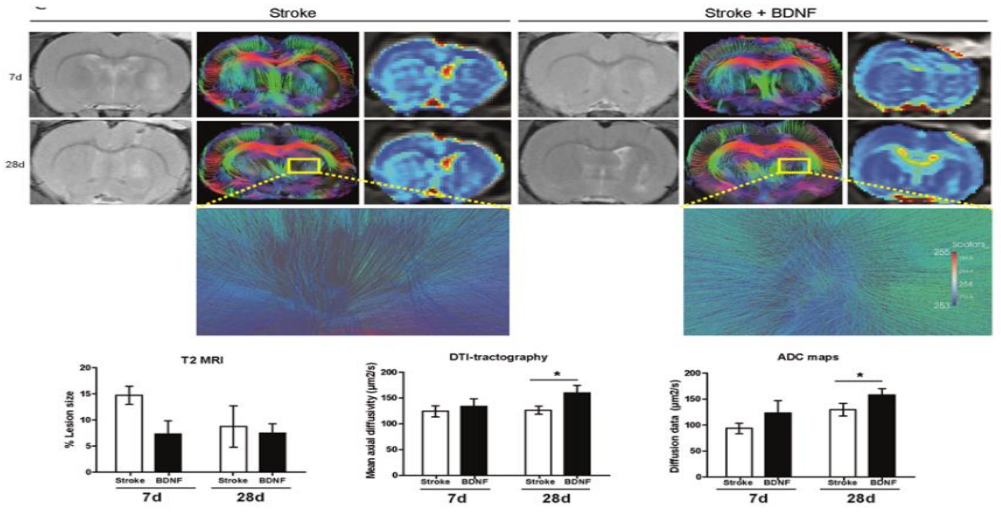
CRYOMYELIN





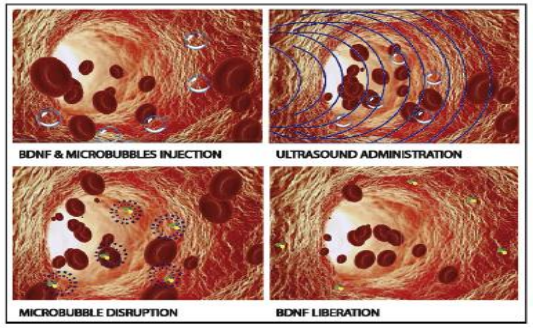
Ramos Cejudo J, Gutiérrez Fernández M.....Díez Tejedor E. Stroke 2015; 46(1):221

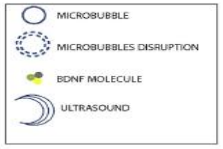
BDNF administration mediated oligodendrocyte differentiation and myelin formation in subcortical ischemic stroke



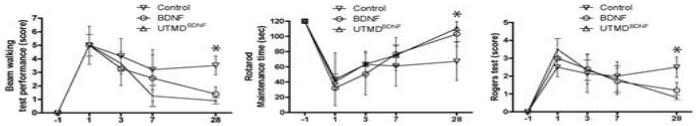
Ramos Cejudo J, Gutiérrez Fernández M.....Díez Tejedor E. Stroke 2015; 46(1):221-8.

BDNF-mediated enhancement to the ischemic rat brain by ultrasound-targeted microbubbles destruction in subcortical ischemic stroke

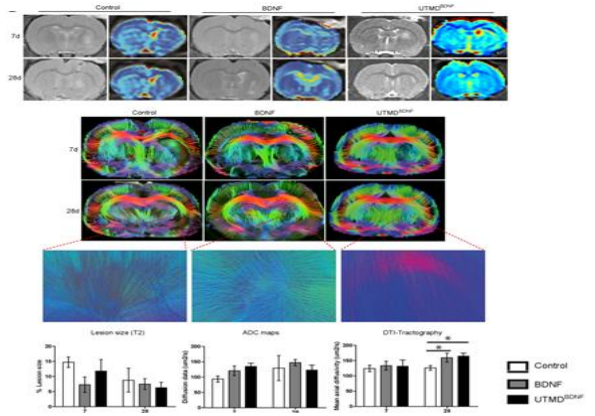




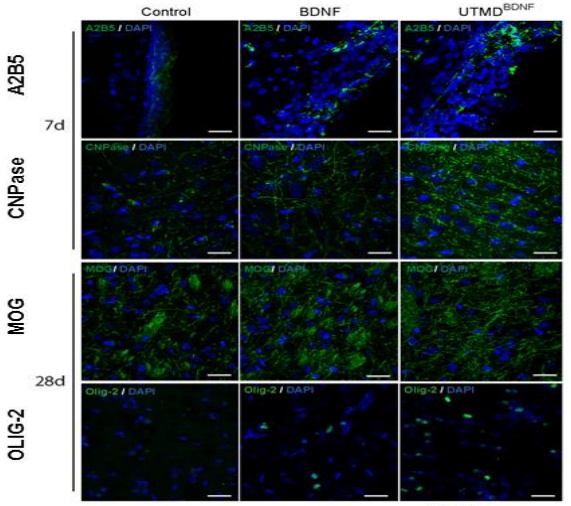
FUNCTIONAL EVALUATION SCALE

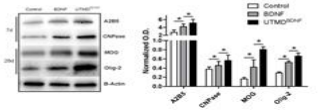


IN VIVO IMAGING ANALYSIS



WHITE MATTER-ASSOCIATED MARKERS

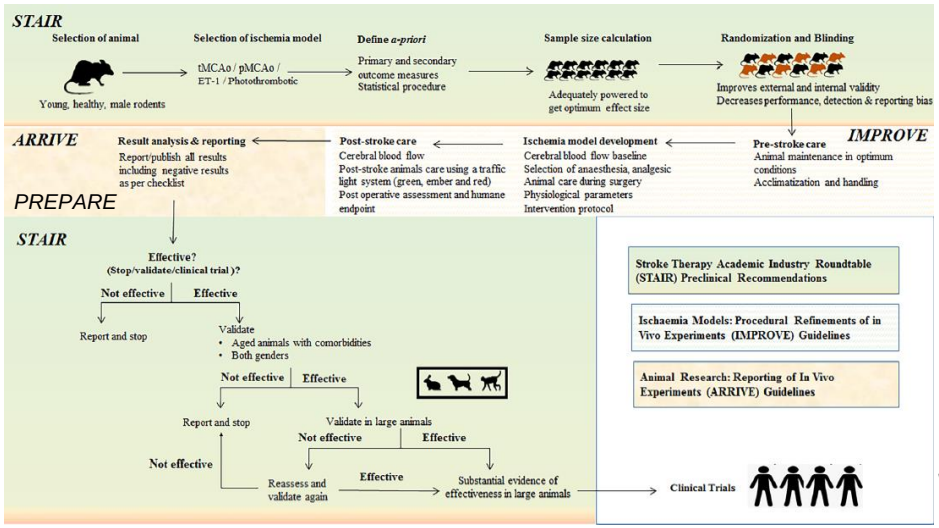




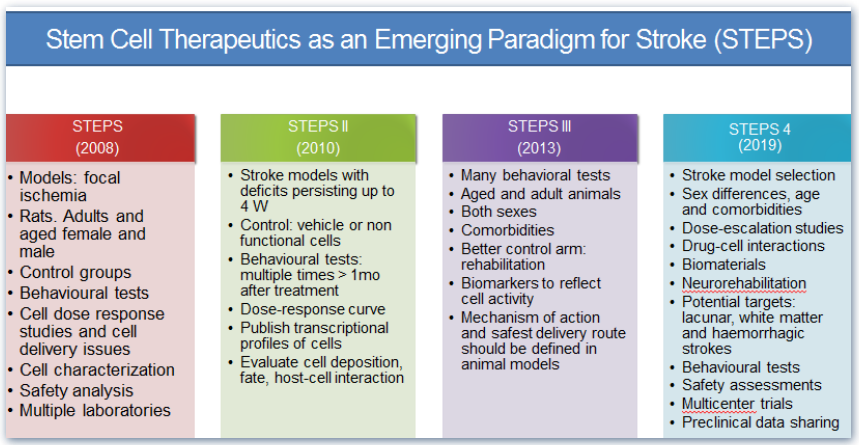
B. Rodriguez-Frutos....Díez Tejedor E, Gutiérrez Fernández M. Biomaterials 2016; 100:41-52

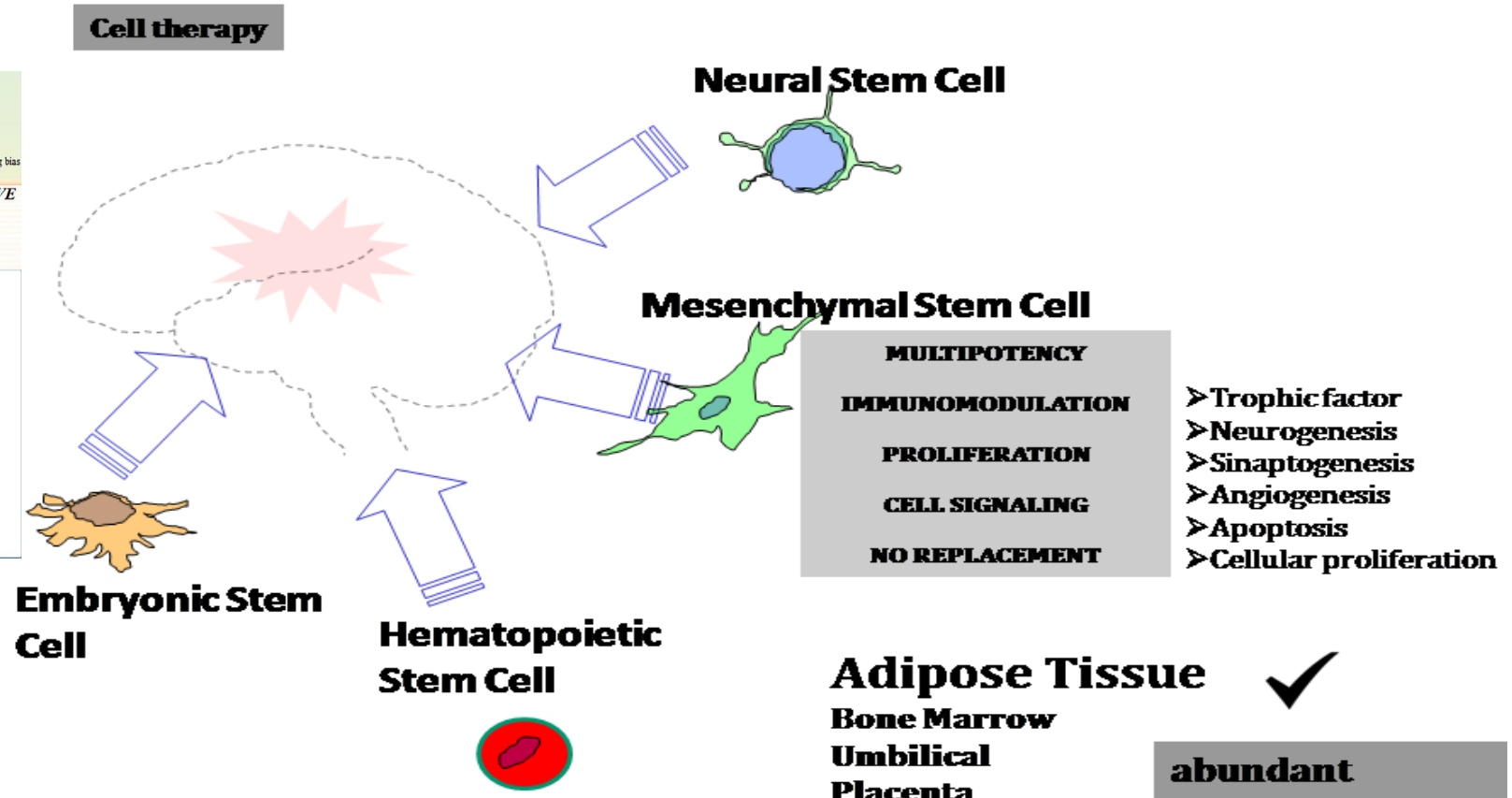
CELL THERAPY

PRECLINICAL STUDIES RECOMENDATIONS/GUIDE



Cellular and Molecular Neurobiology 2021



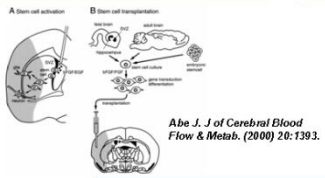


Leu S et al., J Transl Med; 2010
Yu-Ching Lin et al. Stroke 2011
Khalili MA et al. J stroke Cerebrovasc Dis 2012
Gutiérrez-Fernández M ….Díez Tejedor E. Stem Cell Research & Ther 2013

STEM CELLS . PRECLINICAL STUDIES IN STROKE

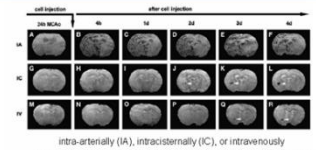
ADMINISTRATION ROUTES

Intracerebral



Abe J. J of Cerebral Blood Flow & Metab. (2000) 20:1393.

Intra-arterial vs Intracisternally vs Intravenously

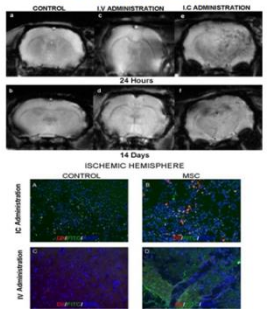


intra-arterially (IA), intracisternally (IC), or intravenously

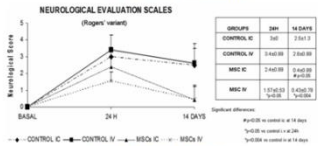
Li J et al; J of Cerebral Blood Flow & Metab. 2010; 30:653- 62

Intra-arterial vs Intravenous

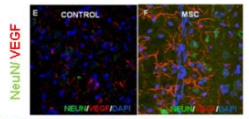
Migration/implantation



Functional evaluation



Brain Repair Markers

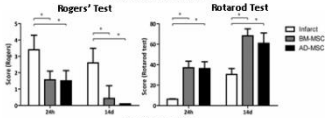


Gutiérrez-Fernández M.,Díez Tejedor E; Neuroscience 2011

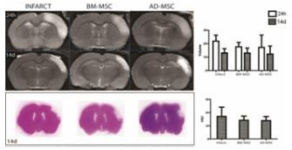
CELL TYPE

Bone Marrow vs Adipose Tissue

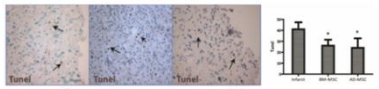
Functional evaluation



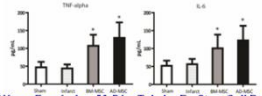
Lesion size



Cell death

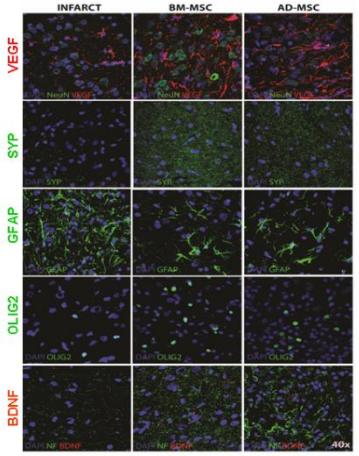


Inflammatory response modulation



Gutiérrez-Fernández M, Díez-Tejedor E.; Stem Cell Research&Ther 2013

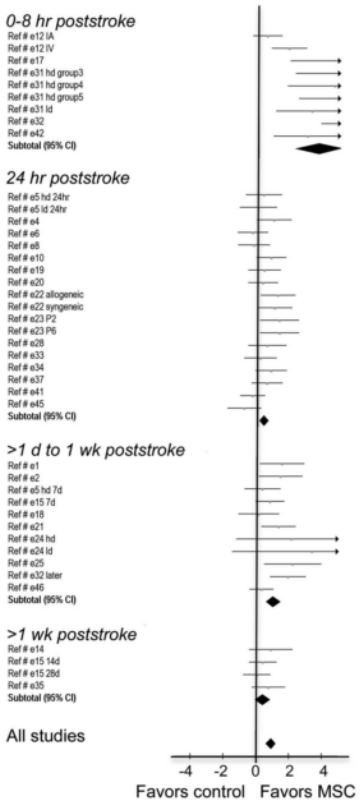
Brain Repair Markers



Meta-analysis of preclinical studies of mesenchymal stromal cells for ischemic stroke

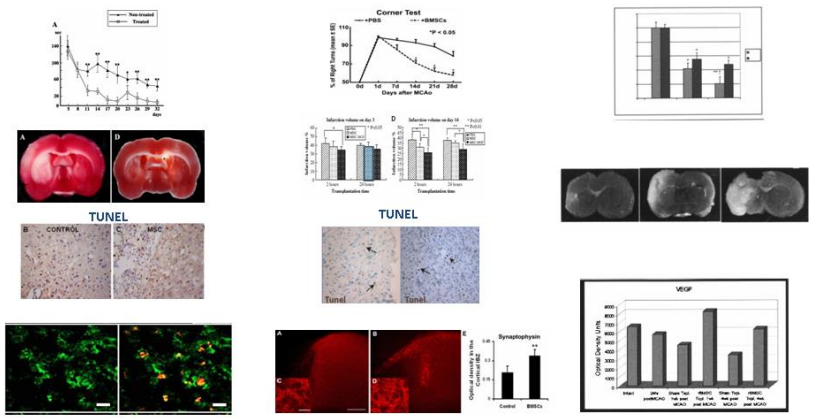
Neurology® 2014;82:1277-1286

B. Infarct volume reduction effect size



ORIGIN

AUTOLOGOUS | ALLOGENIC | XENOGENIC



Iihoshi et al; Brain Research 2004; Leu et al; ; J. Transl. Med 2010,

Chen et al; Stroke 2001; Zhao et al; JCBFM 2006 Shen et al; Neuroscience 2006; Li et al.. Exp Neurol 2006; Gutiérrez-Fernández M, Díez-Tejedor E.; Neuroscience 2011;

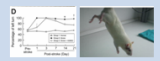
Yang M et al; Cell Transplant 2010; Gutiérrez –Fernández M..Díez Tejedor E; J. Transl. Med 2015;

THERAPEUTIC WINDOW

Time of administration

0 | 12h | 24h | 7 days | 1 month

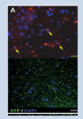
Lesion volume



Improve functional recovery

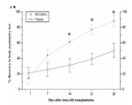
- IL-18 ↓
- TLR4 ↓
- PAI-1 ↓
- GFAP(+) cells ↓

Anti-inflammatory

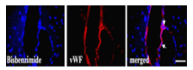


Brain repair markers

Leu et al; J. Transl. Med. 2010
Gutiérrez-Fernández M,..Díez Tejedor E; Neuroscience 2011
Gutiérrez-Fernández M...Díez Tejedor E. Stem Cell Res & Ther 2013

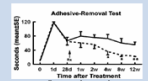


Improve neurological function

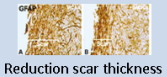


Enhanced angiogenesis

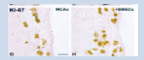
Ding et al; Neurobiol.Dis.2007,



Improve functional recovery



Reduction scar thickness

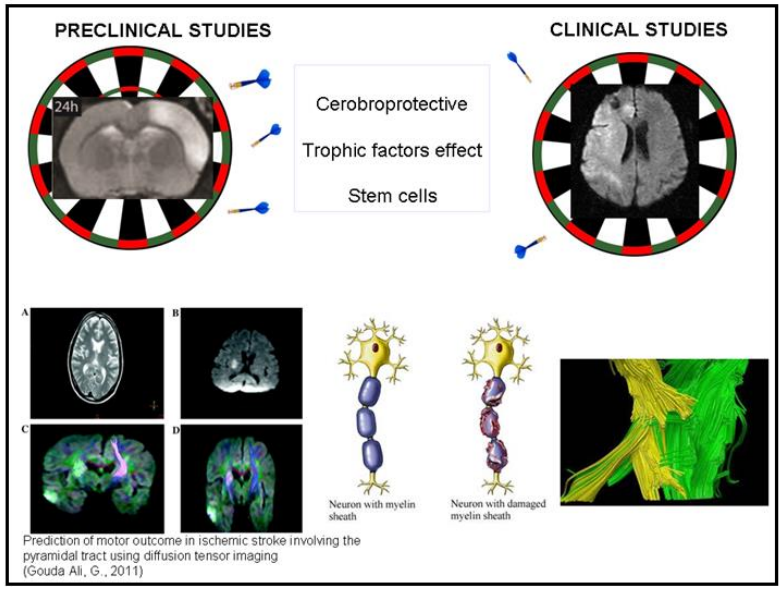


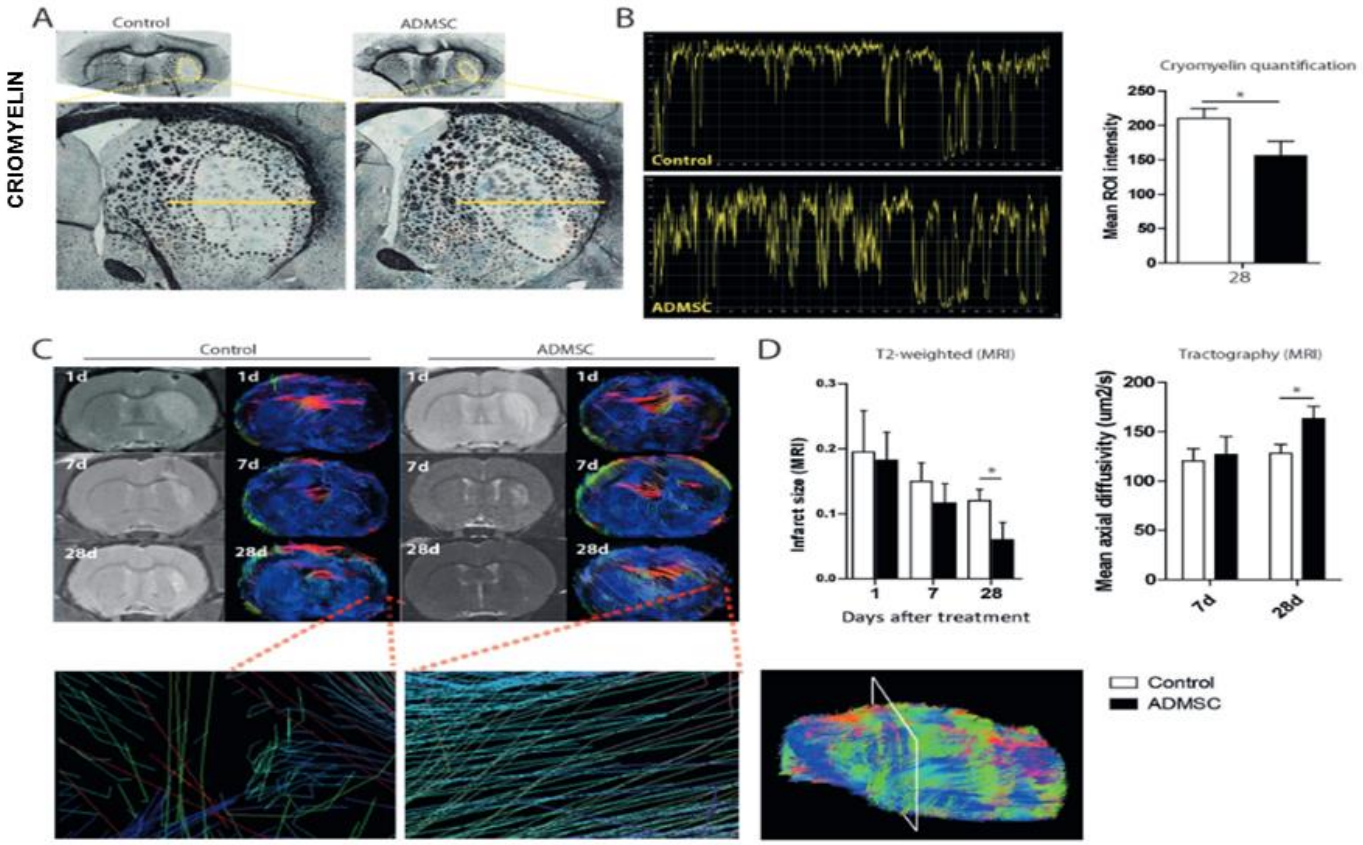
Induction cell proliferation SVZ

Shen et al; J of Cer Blood Flow & Metabolism2007

STEM CELLS
EFECT IN WHITE MATTER AFECTATION

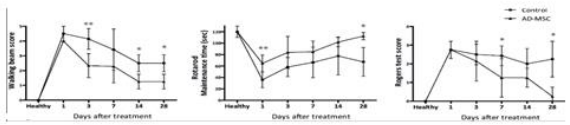
SUBCORTICAL CEREBRAL INFARCT



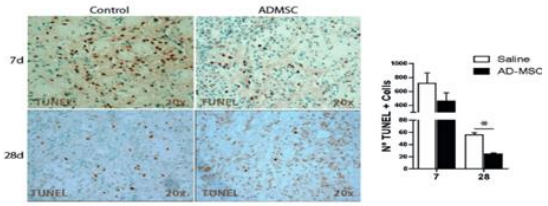


Otero-Ortega O, Gutiérrez Fernández M... Díez-Tejedor E. Stem Cell Res Ther. 2015 Jun 19;6:121

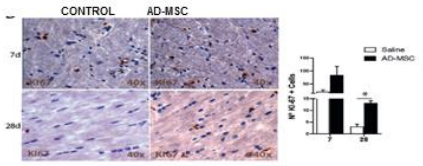
FUNCTIONAL EVALUATION SCALE



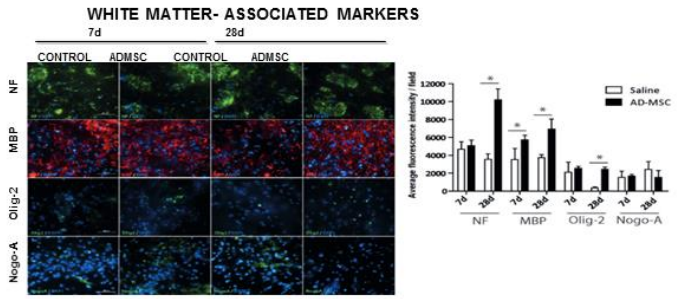
CELL DEATH (TUNEL)



CELULAR PROLIFERATION (Ki67)



WHITE MATTER- ASSOCIATED MARKERS



Otero-Ortega O, Gutiérrez Fernández M... Díez-Tejedor E. Stem Cell Res Ther. 2015 Jun 19;6:121

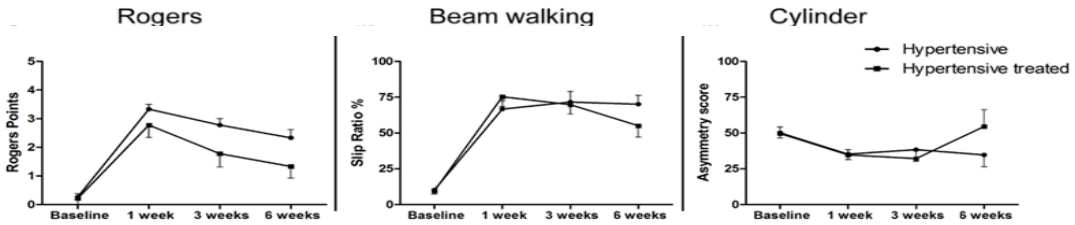
CELL THERAPY

COMORBIDITIES: HYPERTENSION, HYPERGLYCEMIA

Mesenchymal Stem Cells From Adipose Tissue Do not Improve Functional Recovery After Ischemic Stroke in Hypertensive Rats

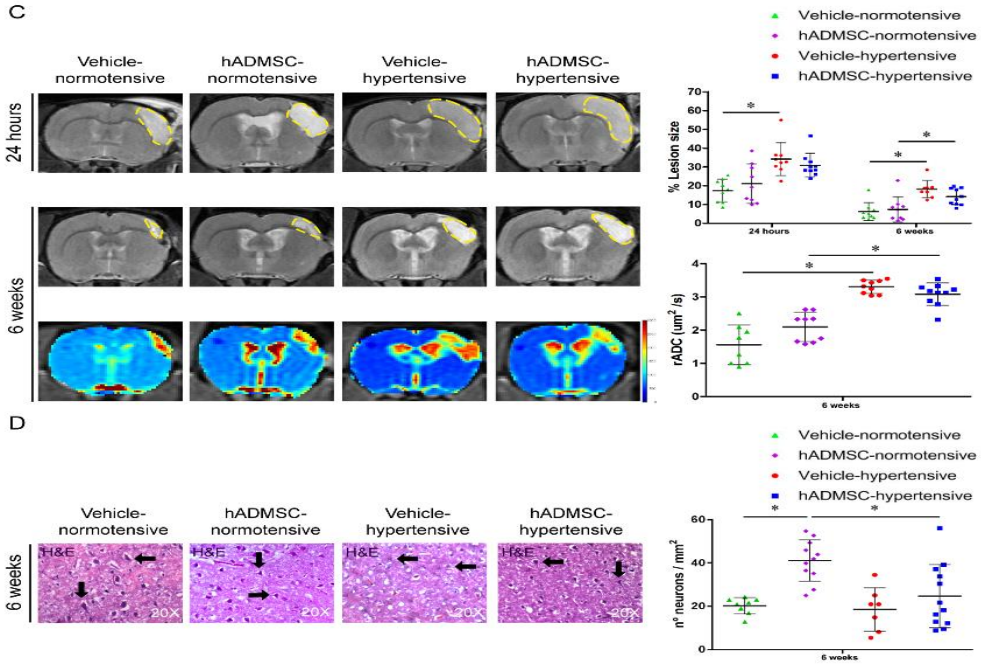
Luke Diekhorst, BiolD*; Mari Carmen Gómez-de Frutos, BiolD*; Fernando Laso-García, BiolD*; Laura Otero-Ortega, PhD; Blanca Fuentes, MD, PhD; Jukka Jolkkonen, PhD; Olivier Detante, MD, PhD; Anaick Moisan, PhD; Laura Leyva, MD, PhD; Arturo Martínez-Arroyo, Tech; Exuperio Díez-Tejedor, MD, PhD; María Gutiérrez-Fernández, PhD; on behalf of RESSTORE Consortium

FUNCTIONAL EVALUATION



ADMSC did not reverse the hypertension-induced increase in functional impairment

LESION SIZE



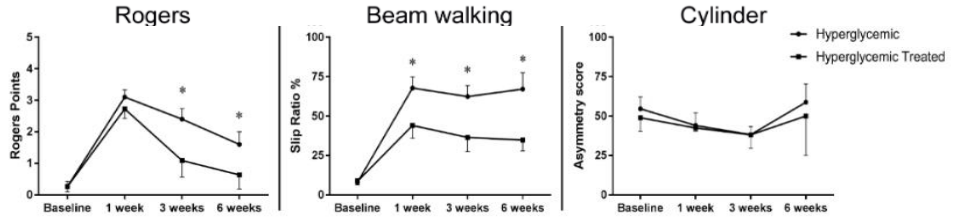
Stroke. 2020;51(1):342-346.

RESEARCH Open Access

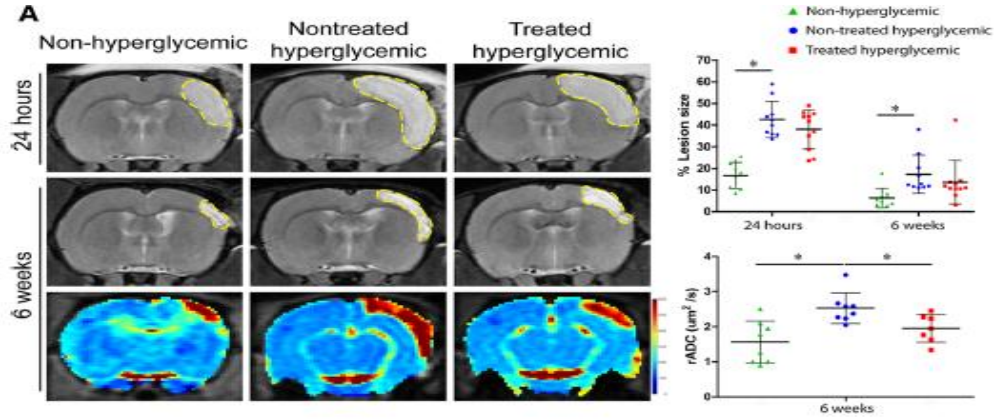
Intravenous delivery of adipose tissue-derived mesenchymal stem cells improves brain repair in hyperglycemic stroke rats

Mari Carmen Gómez-de Frutos[1†], Fernando Laso-García[1†], Luke Diekhorst[1†], Laura Otero-Ortega[1], Blanca Fuentes[1], Jukka Jolkkonen[2,3], Olivier Detante[4,5], Anaick Moisan[5,6], Arturo Martínez-Arroyo[1], Exuperio Díez-Tejedor[1], María Gutiérrez-Fernández[1*] and on behalf of RESSTORE consortium

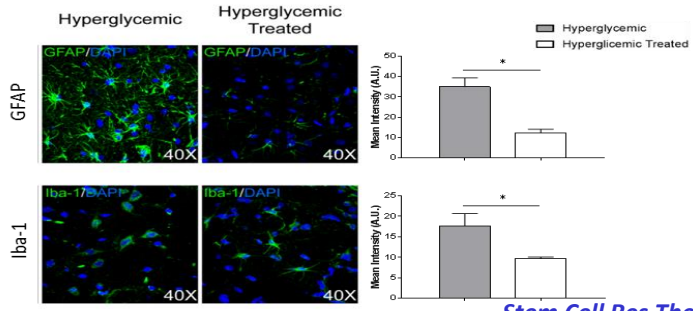
FUNCTIONAL EVALUATION



LESION SIZE



GLIA MARKERS

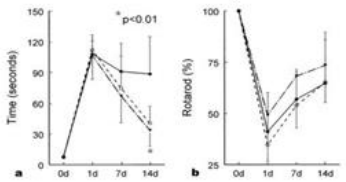


Stem Cell Res Ther. 2019;10(1):212.

STEM CELLS : PRECLINICAL STUDIES IN ISCHAEMIC STROKE

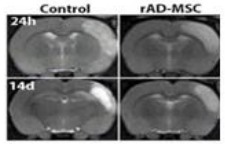
Effects of Stem Cell in Ischemic Stroke

Functional Recovery



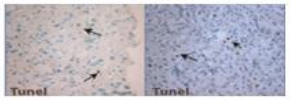
Crigler et al., Exp Neurol, 2006
Gutiérrez-Fernández M..Díez Tejedor E Neuroscience, 2011
Khabbal et al., Cell Transplantation, 2015

Lesion Size



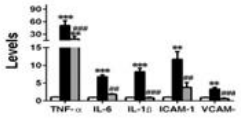
Leu et al., J Trans Med, 2010
Ikegame Y, Cytotherapy, 2011
Gutiérrez-Fernández M..Díez Tejedor E Neuroscience, 2011

Cell death



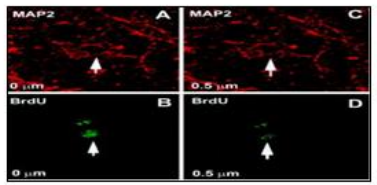
Gutiérrez-Fernández M..Díez Tejedor E .Stem Cell Res Ther, 2013

Inflammatory response modulation



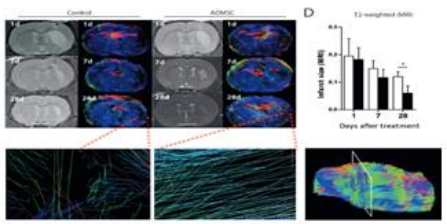
Huang L et al., Stem Cell Res Ther. 2014

Neurogenesis



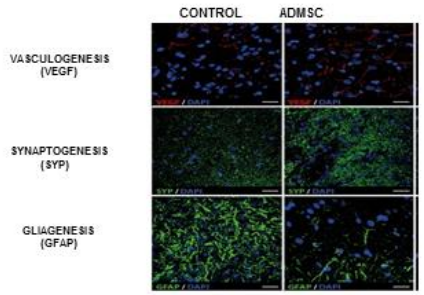
Chen et al; Stroke 2001
Shen et al; Neuroscience, 2006
Gutiérrez-Fernández M..Díez Tejedor E Neuroscience, 2011

Nervous fibers connectivity



Otero Ortega L..Díez Tejedor E; Stem Cell Res Ther. 2015

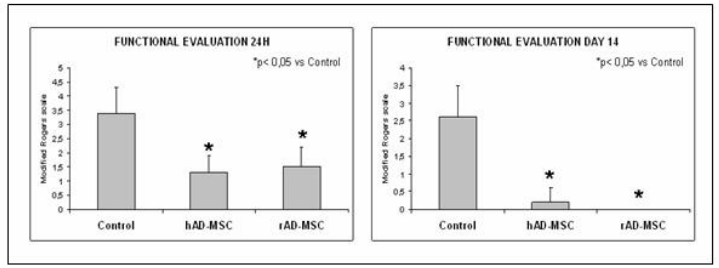
Brain Repair Markers

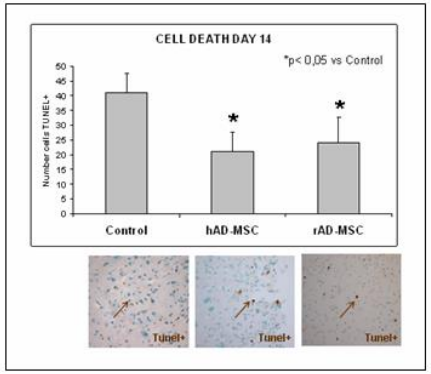


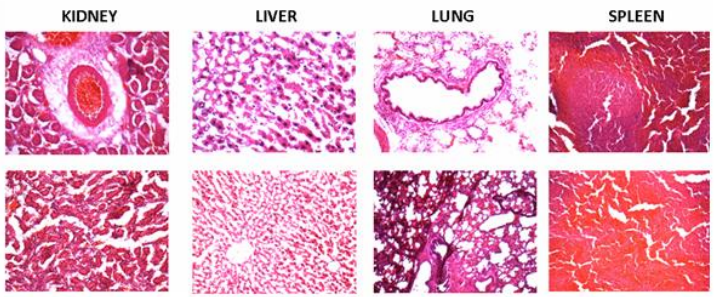
Gutiérrez-Fernández..Díez Tejedor , J Trans Med, 2015

Proof concept

Aims:To study the safety and the of acute intravenous (i.v.) xenogenic administration of hAD-MSC or allogenic rat Adipose Tissue-derived-MSC (rAD-MSC) on functional evaluation in rat model of permanent Middle Cerebral Artery Occlusion (pMCAO).



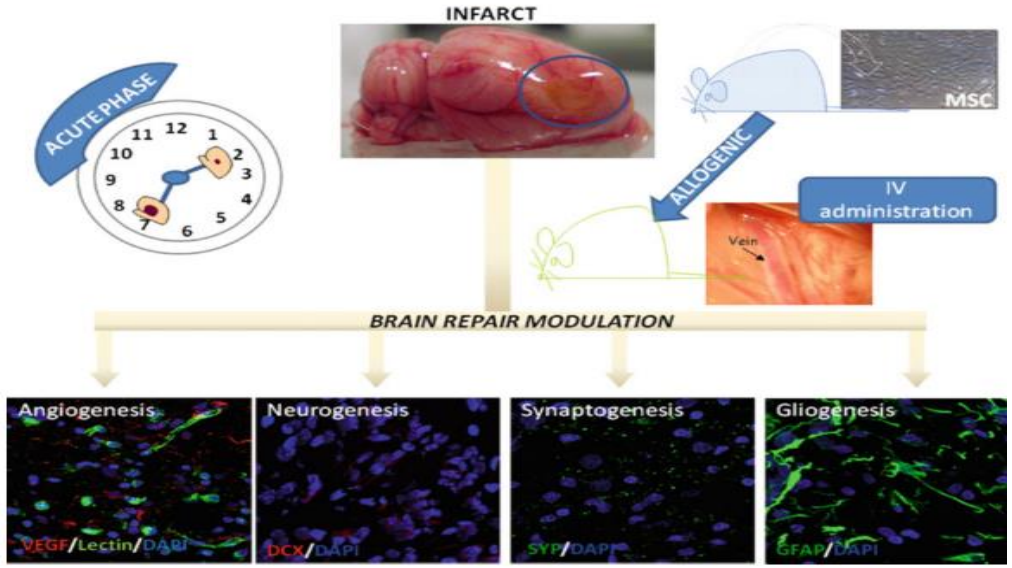




Gutiérrez Fernández M ... Díez Tejedor E. J Transl Med. 2015;13:46.

Clinical Trials

From preclinical results……to Clinical Trial design



Type of administration: Allogenic/ Autologous

Type of stem cells: Mesenchymal Stem Cells

Source: Adipose Tissue/ Bone Marrow

Administration route: Intravenous/ Intraarterial?

Time window: Inclusion Acute stroke (<24h)
(to be treated as soon as possible within 2 weeks)

Endpoints: Safety
Efficacy: Neurological and functional outcome
Biochemical markers

CELL THERAPY

AMASCIS

Hospital Universitario La Paz · IdiPAZ

Ministerio de Sanidad, Servicios Sociales e Igualdad

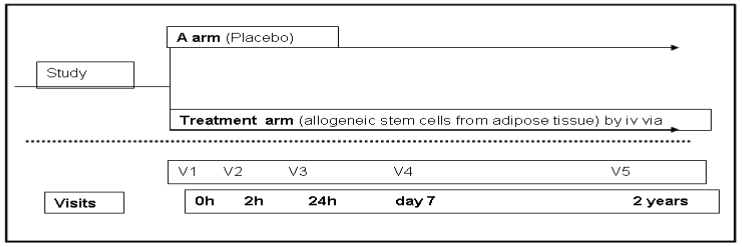
Intravenous allogenic AD-MSC and acute stroke

Reparative Therapy in Acute Ischemic Stroke With Allogenic Mesenchymal Stem Cells From Adipose Tissue, Safety Assessment, a Randomised, Double Blind Placebo Controlled Single Center Pilot Clinical Trial

ClinicalTrials.gov Identifier:
NCT01678534

Aims: to assess the safety of treatment i.v. with allogeneic stem cells from adipose tissue in acute stroke patients.
Design: Phase IIa clinical trial, pilot, single center, prospective, randomized, double-blind, placebo-controlled.

This pilot study will include 20 patients with acute ischemic stroke, which will be randomized to treatment with stem cells or placebo (1:1).



Díez-Tejedor E, et al. J Stroke Cerebrovasc Dis. 2014;23(10):2694-700.

AMASCIS-02

AMASCIS-02. ALOGENIC ADIPOSE TISSUE-DERIVED MESENCHYMAL STEM CELLS IN ISCHEMIC STROKE. A PHASE IIB MULTICENTER DOUBLE BLIND PLACEBO CONTROLLED CLINICAL TRIAL.

DESIGN:
- Phase IIb clinical trial.
- Multicenter: Madrid & Sevilla
- Randomized, double-blind
- Placebo-controlled
- Alogenic treatment
- Adipose-tissue MSC (1M/kg)

MAIN OBJECTIVE:
- **Safety**
- **very early phase** (within 4 days from stroke onset).

SECONDARY OBJECTIVE:
- **Potential efficacy**
  - Neurological and functional scales: NIHSSS, ERm
  - Biochemical markers

MAIN INCLUSION CRITERIA
- Acute ischemic stroke
- Older than 18 years
- NIHSS 8-20 (2 points motor deficit)
- Prestroke mRS ≤1

FUNDING: ISCIII (529.100 euros)

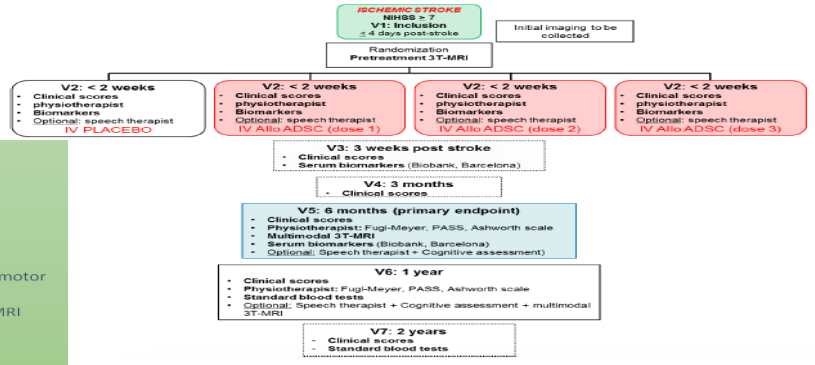
RESSTORE

RESSTORE: a Multicentric and European clinical trials | RESSTORE
www.resstore.eu/ ▾ Traducir esta página
RESSTORE, REgenerative Stem cell therapy for STroke in Europe, is a multicentric project in Personalising health and care (PHC) area financed by the European Commission H2020 programme. The RESSTORE project is focused on the assessment of the efficacy of intravenous cell therapy to improve recovery and/or ...

IP: E. Díez Tejedor.

Hospital Universitario La Paz

Dose-Effect
- 124 patients
- 4 groups:
  - 3 different doses according to results of the toxicity study
  - placebo
- Randomised, double blind
- **Interim endpoint** for dose-effect curve: motor NIHSS at 6 months
- 2 years follow-up with biomarkers and MRI
- All RESSTORE centers



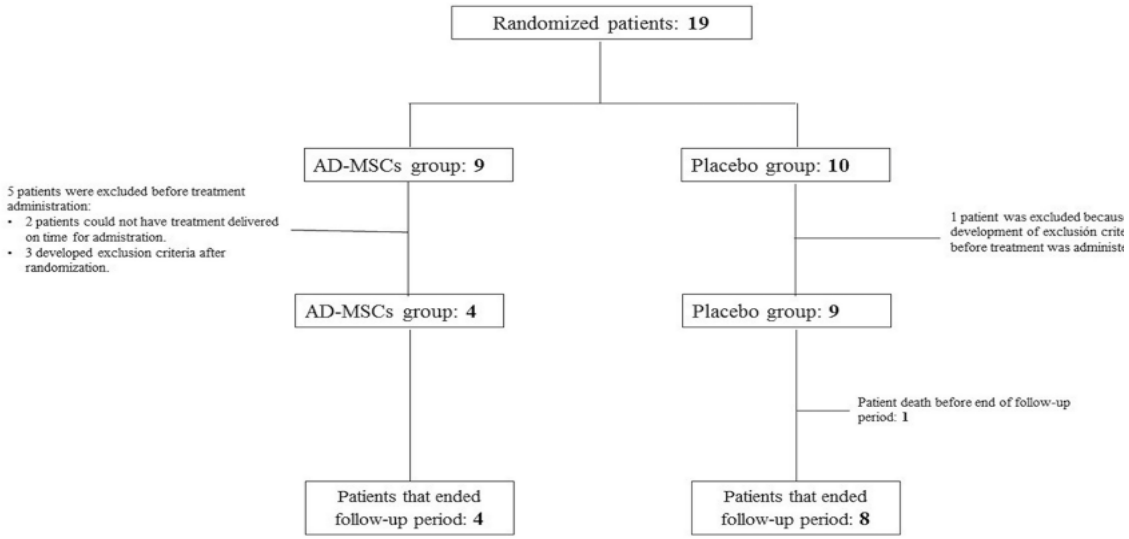
AMASCIS

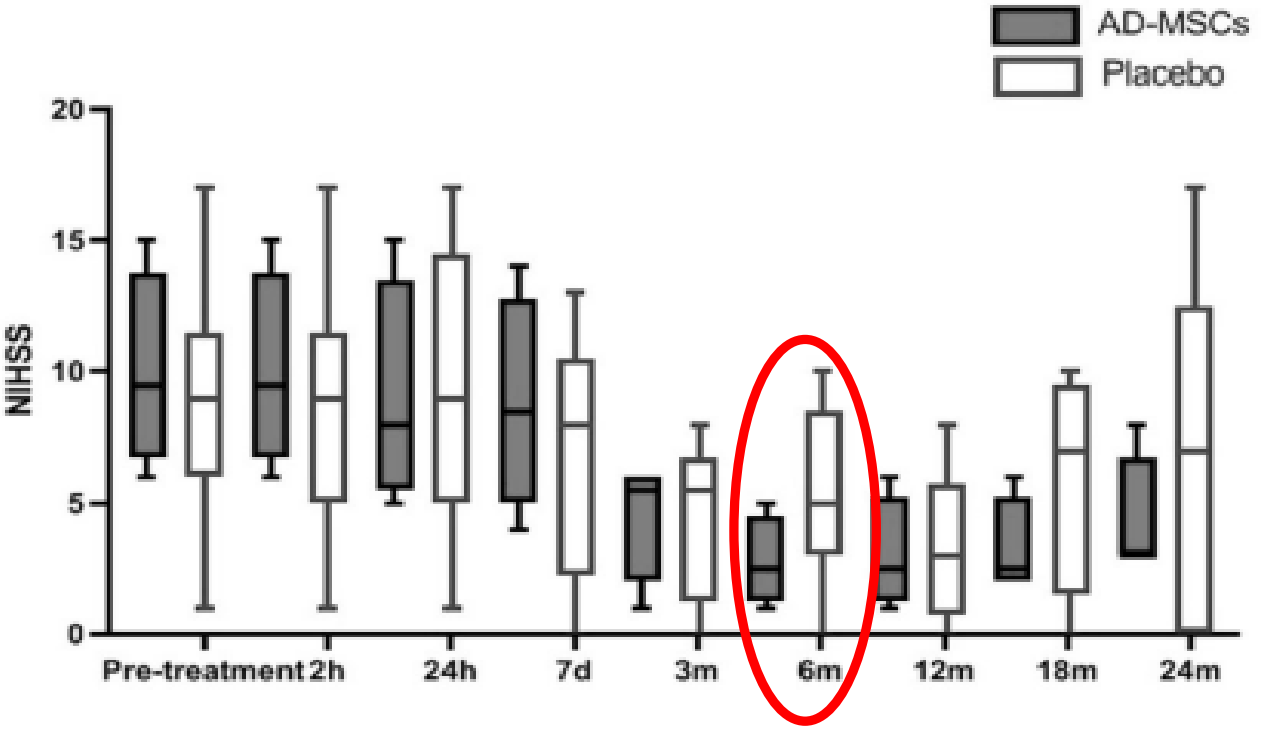
IV ALLOGENIC AD-MSC

Final Results of Allogeneic Adipose Tissue–Derived Mesenchymal Stem Cells in Acute Ischemic Stroke (AMASCIS): A Phase II, Randomized, Double-Blind, Placebo-Controlled, Single-Center, Pilot Clinical Trial

Elena de Celis-Ruiz[1*], Blanca Fuentes[1*], María Alonso de Leciñana[1], María Gutiérrez-Fernández[1], Alberto M. Borobia[2], Raquel Gutiérrez-Zúñiga[1], Gerardo Ruiz-Ares[1], Laura Otero-Ortega[1], Fernando Laso-García[1], Mari Carmen Gómez-de Frutos[1], and Exuperio Díez-Tejedor[1]

Main conclusion: intravenous treatment with AD-MSCs,1M/kg, within the first 2 weeks from ischemic stroke was safe at 24 months of follow-up





Cell Transplantation
Volume 31: 1–11

IV ALLOGENIC AD-MSC EARLY WINDOW

AMASCIS-02

Ongoing

BMJ Open

Allogeneic adipose tissue-derived mesenchymal stem cells in ischaemic stroke (AMASCIS-02): a phase IIb, multicentre, double-blind, placebo-controlled clinical trial protocol

Elena de Celis-Ruiz,[1] Blanca Fuentes ,[1] Francisco Moniche,[2] Joan Montaner,[3] Alberto M Borobia,[4] Maria Gutiérrez-Fernández,[1] Exuperio Díez-Tejedor[1]

BMJ Open 2021;**11**:e051790.

IV AdministrationAD-MSC : 1M/Kg

Start < 4 dias

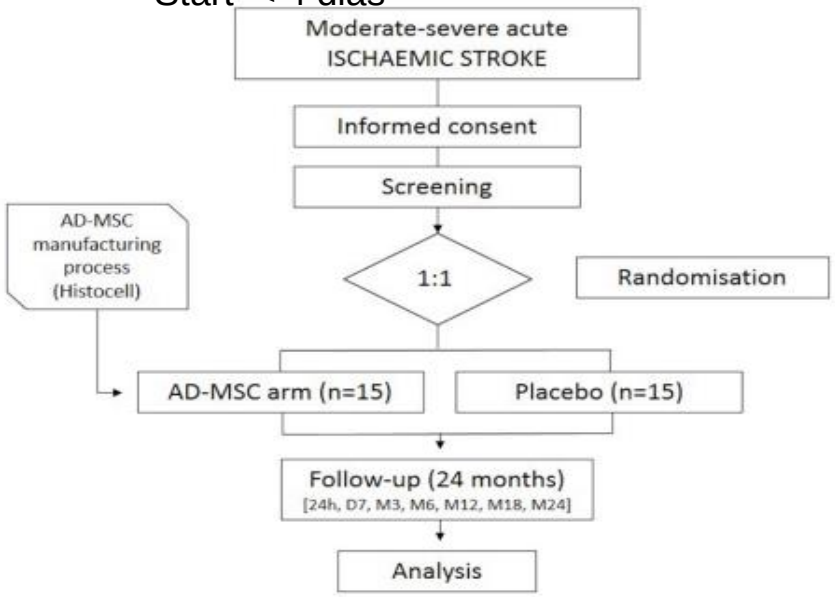


Figure 1 Schematic flowchart of the clinical trial. AD-MSCs, allogeneic adipose tissue-derived mesenchymal stem cells

Table 1 Flowchart of study visits and procedures

Flowchart	Visit 1 Screening	Visit 2 Baseline 0 hour	Visit 3 2 hours	Visit 4 24 hours	Visit 5 Day 7 or discharge*	Visit 6 M3 (±14 days)	Visit 7 M6 (±14 days)	Visit 8 M12 (±14 days)	Visit 9 M18 (±14 days)	Visit 10 M24 (±14 days)
Informed consent signature	X									
Inclusion and exclusion criteria	X	X†‡								
Past medical/surgical history	X									
Physical examination	X			X	X	X	X	X	X	X
Pregnancy test	X									
NIHSS	X	X‡	X	X	X	X	X	X	X	X
Modified Rankin Scale	X				X	X	X	X	X	X
Blood pressure	X	X‡	X	X	X					
Heart rate	X	X‡	X	X	X					
Body temperature	X	X‡	X	X	X					
Oxygen saturation	X	X‡	X	X	X					
Capillary blood glucose	X	X‡	X	X	X					
12-lead ECG	X	X‡		X						X
Neuroimaging (brain CT)	X§									
Neuroimaging (brain MRI)	X§									
Randomisation	X									
Study drug administration		X								
Laboratory assessments: Haematology, coagulation test and biochemistry	X			X	X					X
Blood brain repair markers		X‡			X	X				
Adverse events register		X‡	X	X	X	X	X	X	X	X
Concomitant drugs	X	X‡	X	X	X	X	X	X	X	X

IV ALLOGENIC AD-MSC DOSE-EFFECT TRIAL

RESSTORE
Regenerative Stem Cell Therapy for Stroke
Grant agreement GA/681044

European Commission

ISCHEMIC STROKE
NIHSS ≥ 7
V1: Inclusion
≤ 4 days post-stroke

Initial imaging to be collected

Randomization
Pretreatment 3T-MRI

V2: < 2 weeks
- **Clinical scores**
- **physiotherapist**
- **Biomarkers**
- Optional: speech therapist

IV PLACEBO

V2: < 2 weeks
- **Clinical scores**
- **physiotherapist**
- **Biomarkers**
- Optional: speech therapist

IV Allo ADSC (dose 1)

V2: < 2 weeks
- **Clinical scores**
- **physiotherapist**
- **Biomarkers**
- Optional: speech therapist

IV Allo ADSC (dose 2)

V2: < 2 weeks
- **Clinical scores**
- **physiotherapist**
- **Biomarkers**
- Optional: speech therapist

IV Allo ADSC (dose 3)

V3: 3 weeks post stroke
- **Clinical scores**
- **Serum biomarkers** (Biobank, Barcelona)

V4: 3 months
- **Clinical scores**

V5: 6 months (primary endpoint)
- **Clinical scores**
- **Physiotherapist:** Fugl-Meyer, PASS, Ashworth scale
- **Multimodal 3T-MRI**
- **Serum biomarkers** (Biobank, Barcelona)
- Optional: Speech therapist + Cognitive assessment)

V6: 1 year
- **Clinical scores**
- **Physiotherapist:** Fugl-Meyer, PASS, Ashworth scale
- **Standard blood tests**
- Optional: Speech therapist + Cognitive assessment + multimodal 3T-MRI

V7: 2 years
- **Clinical scores**
- **Standard blood tests**

Dose-Effect

- 124 patients
- 4 groups:
  - 3 different doses according to results of the toxicity study
  - placebo
- Randomised, double blind
- **Interim endpoint** for dose-effect curve: motor NIHSS at 6 months
- 2 years follow-up with biomarkers and MRI
- All RESSTORE centers

IV AdministrationADSC DOSES:

1- 1,1 M/kg
2- 2,1M/Kg
3- 2;5M/Kg

IV ALLOGENIC MULTIPOTENT ADULT PROGENITOR CELLS EARLY WINDOW
MASTERS

IV Administration DOSES within 24-48 h.
-Group 1 : 400 M
-Group 2 : 1200M

Early treatment < 36 h

Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial

David C Hess, Lawrence R Wechsler, Wayne M Clark, Sean I Savitz, Gary A Ford, David Chiu, Dileep R Yavagal, Ken Uchino, David S Liebeskind, Alexander P Auchus, Souvik Sen, Cathy A Sila, Jeffrey D Vest, Robert W Mays

Lancet Neurol 2017; 16: 360–68

	Multipotent adult progenitor cells (n=65)	Placebo (n=61)
Treatment-emergent adverse event	64 (99%)	59 (97%)
Study drug-related treatment-emergent adverse event*	15 (23%)	5 (8%)
Infusion-related allergic reaction	0 (0%)	0 (0%)
Neurological worsening	0 (0%)	0 (0%)
Secondary infection	25 (39%)	29 (48%)
Serious adverse events	22 (34%)	24 (39%)
Maximum severity of treatment-emergent adverse events		
Mild	12 (18%)	14 (23%)
Moderate	33 (51%)	24 (39%)
Severe	11 (17%)	6 (10%)
Life-threatening	3 (5%)	6 (10%)
Death	5 (8%)	9 (15%)

Data are number of events (%). An adverse event was considered treatment-emergent if the start time of the event was on or after the start of treatment infusion. *An adverse event that was definitely, probably, or possibly related to treatment.

Table 3: Treatment-emergent adverse events for groups 2 and 3 combined

	Day 90			1 year*		
	Multipotent adult progenitor cells (n=65)	Placebo (n=61)	p value	Multipotent adult progenitor cells (n=65)	Placebo (n=61)	p value
Efficacy						
mRS ≤2 (scale 0–6)	24 (37%)	22 (36%)	0·93	33 (51%)	27 (44%)	0·46
NIHSS improvement of ≥75%	26 (40%)	23 (38%)	0·79	32 (49%)	28 (46%)	0·71
Barthel index ≥95 (scale 0–100)	30 (46%)	27 (44%)	0·83	40 (62%)	27 (44%)	0·05
NIHSS ≤1 or ≥11 point improvement	25 (39%)	18 (30%)	0·29	..	..	..
mRS shift	..	..	0·29	..	..	0·09
mRS ≤1	10 (15%)	7 (12%)	0·51	18 (28%)	8 (13%)	0·0410
NIHSS ≤1	17 (26%)	10 (16%)	0·17	19 (29%)	12 (20%)	0·20
Excellent outcome†	10 (15%)	4 (7%)	0·10	15 (23%)	5 (8%)	0·0206
Safety						
Life-threatening adverse events or death	..	..	..	8 (12%)	15 (25%)	0·08
Secondary infections	..	..	..	25 (39%)	29 (48%)	0·30
Initial days in hospital	7·6 (4·0)	9·6 (8·1)	0·09	..	..	..

Data are n (%) or mean (SD). Each endpoint was tested independently; no adjustments were made for multiplicity. mRS=modified Rankin Score. NIHSS=National Institutes of Health Stroke Scale. *Assessment of primary and secondary outcomes at 1 year was exploratory. †Excellent outcome is a composite of mRS ≤1, NIHSS ≤1, and Barthel index ≥95.

Table 2: Secondary outcomes for groups 2 and 3 combined

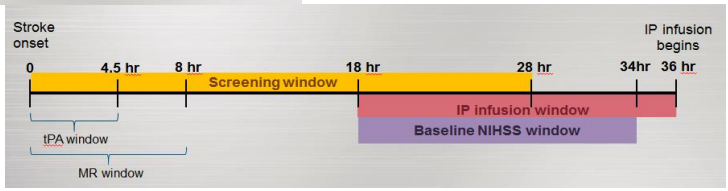
	Day 90			1 year		
	Multipotent adult progenitor cell (n=31)	Placebo (n=61)	p value	Multipotent adult progenitor cell (n=31)	Placebo (n=61)	p value
Efficacy						
mRS ≤2 (scale, 0–6)	14 (45%)	22 (36%)	0·38	16 (52%)	27 (44%)	0·50
Improvement in NIHSS of ≥75%	15 (48%)	23 (38%)	0·33	16 (52%)	28 (46%)	0·61
Barthel index ≥95 (scale 1–100)	18 (58%)	27 (44%)	0·18	22 (71%)	29 (48%)	0·0252
NIHSS ≤1 or ≥11 point improvement	14 (45%)	18 (30%)	0·14	..	..	..
mRS shift	..	..	0·13	..	..	0·07
mRS ≤1 (scale 0–6)	5 (16%)	7 (12%)	0·53	10 (32%)	8 (13%)	0·0281
NIHSS ≤1	10 (32%)	10 (16%)	0·08	11 (36%)	12 (20%)	0·09
Excellent outcome*	5 (16%)	4 (7%)	0·14	9 (29%)	5 (8%)	0·0081
Safety						
Life-threatening adverse events or death	..	..	..	3 (10%)	15 (25%)	0·09
Secondary infections	..	..	..	5 (16%)	29 (48%)	0·0033
Initial days in hospital	6·8 (2·8)	9·6 (8·1)	0·0164	..	..	..

Data are n (%) or mean (SD). Each endpoint was tested independently; no adjustments were made for multiplicity. mRS=modified Rankin Score. NIHSS=National Institutes of Health Stroke Scale. * Excellent outcome is a composite of mRS ≤1, NIHSS ≤1, and Barthel index ≥95.

Table 4: Post-hoc outcomes for early treatment (<36 h) for groups 2 and 3 combined

MASTERS-2
opening the window for stroke treatment

MASTERS II-Phase III

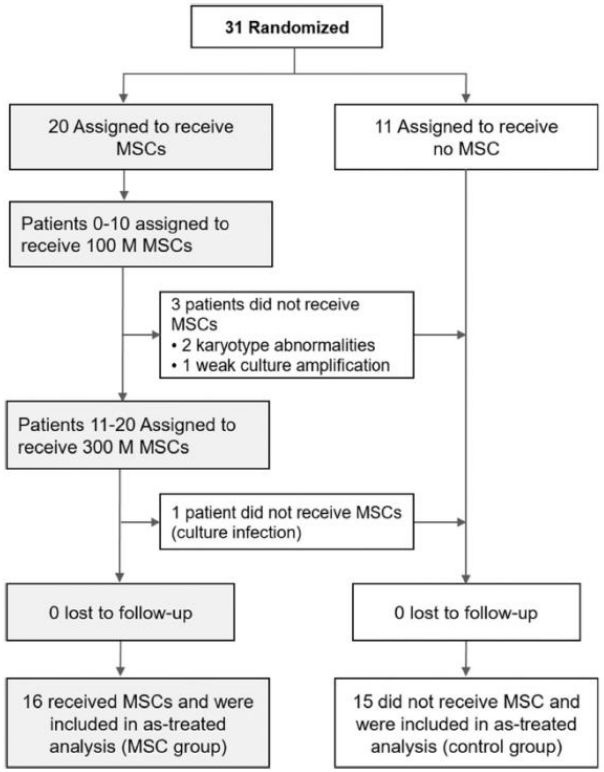


IV AUTOLOGOUS BM-MSC LATE WINDOW

Translational Stroke Research **2020**
https://doi.org/10.1007/s12975-020-00787-z

Autologous Mesenchymal Stem Cells Improve Motor Recovery in Subacute Ischemic Stroke: a Randomized Clinical Trial

Assia Jaillard[1,2,3] · Marc Hommel[2,3] · Anaick Moisan[4] · Thomas A. Zeffiro[5] · Isabelle M. Favre-Wiki[6] · Marianne Barbieux-Guillot[6] · Wilfried Vadot[7] · Sebastien Marcel[8] · Laurent Lamalle[1] · Sylvie Grand[1,9,10,11] · Olivier Detante[6,10,11] · (for the ISIS-HERMES Study Group)



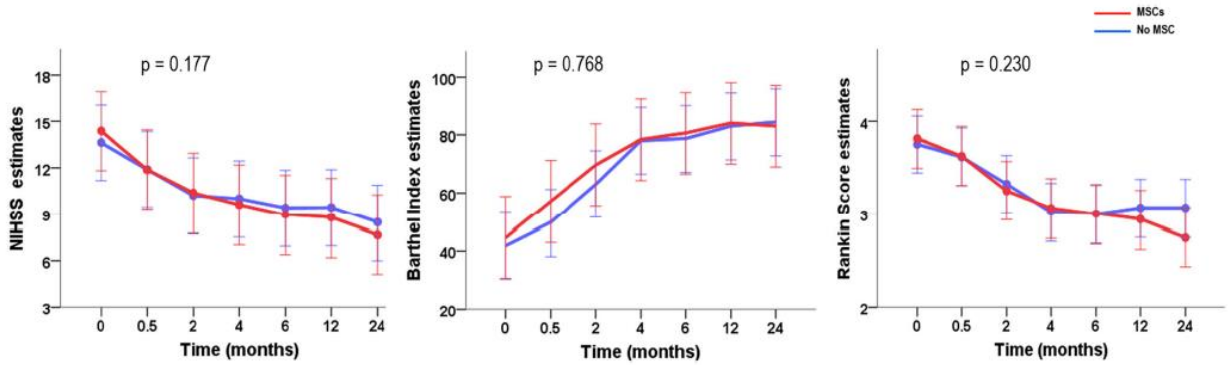
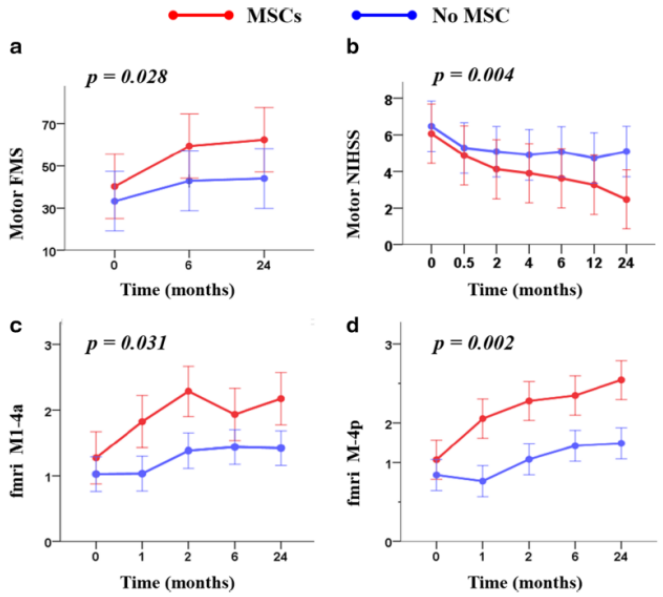
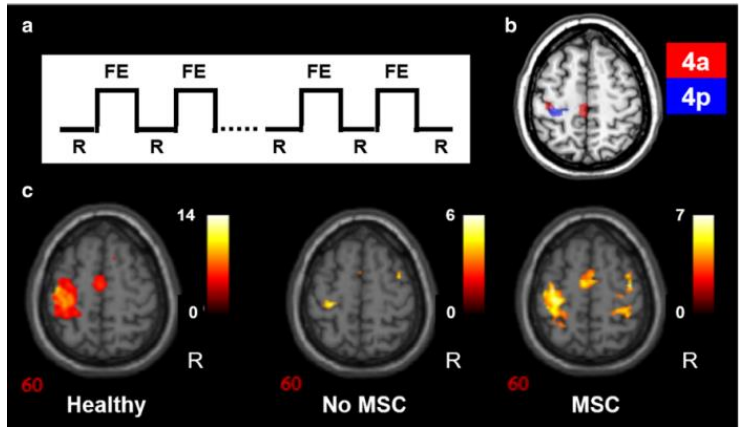


Fig. 4 LMM showing no significant effect of MSC over the 24-month follow-up on behavioral scores: a NIHSS, b Barthel, and c modified Rankin score





IV AUTOLOGOUS BM-MSC EXPANDED WITH AUTOLOGOUS SERUM . LATE WINDOW
STARTING-2

ARTICLE CLASS OF EVIDENCE

Efficacy and Safety of Intravenous Mesenchymal Stem Cells for Ischemic Stroke

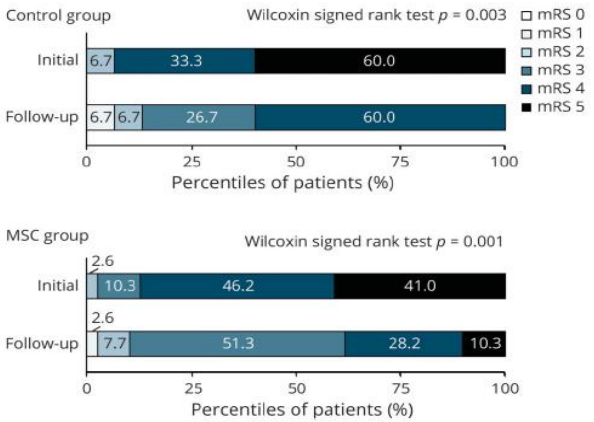
Jong-Won Chung, MD, PhD, Won Hyuk Chang, MD, PhD, Oh Young Bang, MD, PhD, Gyeong Joon Moon, PhD, Suk Jae Kim, MD, MSc, Soo-Kyoung Kim, MD, PhD, Jin Soo Lee, MD, PhD, Sung-Il Sohn, MD, PhD, and Yun-Hee Kim, MD, PhD, for the STARTING-2 Collaborators

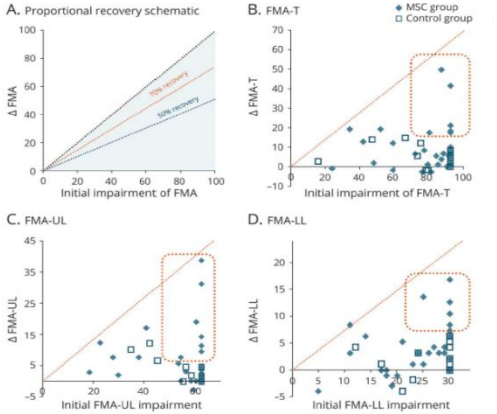
Correspondence
Dr. Bang
ohyoung.bang@samsung.com

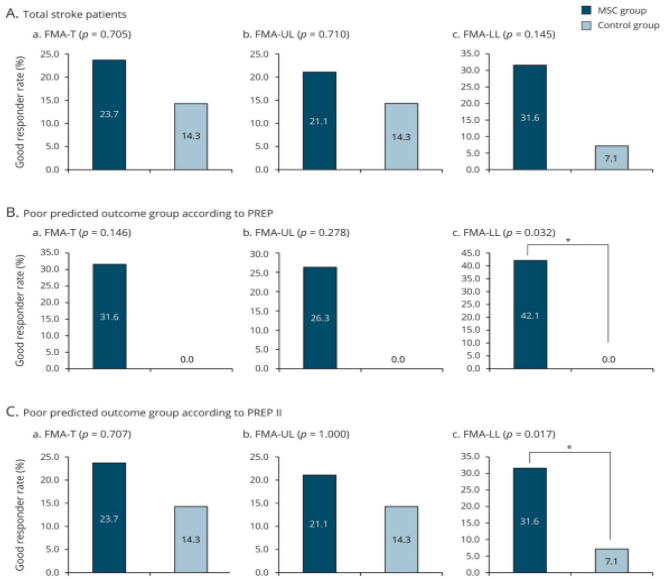
Neurology® 2021;96:e1012-e1023. doi:10.1212/WNL.0000000000011440

Open-label, blinded assessment
Mean time from stroke onset: 20 days

Figure 2 Distribution of mRS Scores







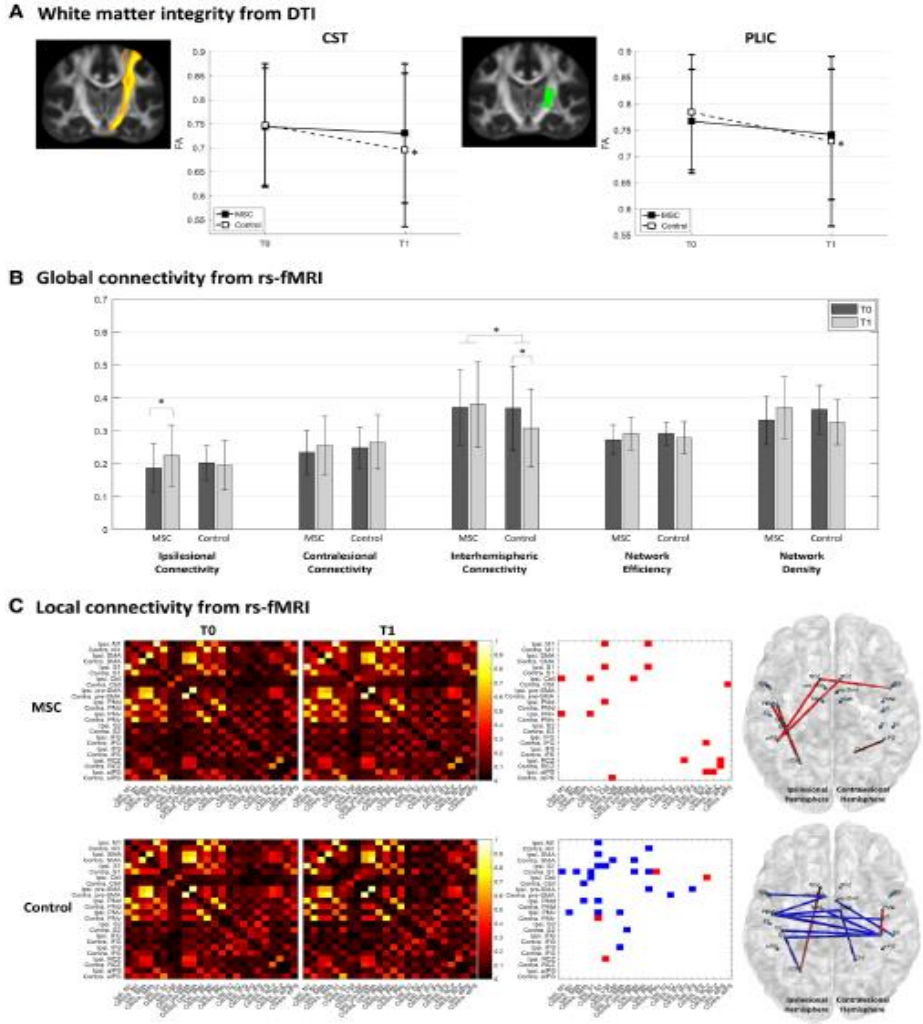
(A) Proportional recovery model. Degree of improvement and baseline impairment in the mesenchymal stem cell (MSC) and control groups in (B) Fugl-Meyer Assessment (FMA) total (FMA-T), (C) FMA upper limb (FMA-UL), and (D) FMS lower limb (FMA-LL) scores. Participants with initial severe impairment but significant improvement are shown as red dashed box.

CLINICAL TRIAL

Efficacy of Intravenous Mesenchymal Stem Cells for Motor Recovery After Ischemic Stroke: A Neuroimaging Study

Jungsoo Lee, PhD*; Won Hyuk Chang, MD, PhD*; Jong-Won Chung, MD, PhD; Suk Jae Kim, MD, MSc; Soo-Kyoung Kim, MD, PhD; Jin Soo Lee, MD, PhD; Sung-Il Sohn. MD. PhD: Yun-Hee Kim. MD. PhD†: Oh Young Bang, MD, PhD†; STARTING-2 Collaborators‡

Stroke. 2022;53:20–28.



IC AUTOLOGOUS BM-MSC ALD-401 ENRICHED. LATE WINDOW. **RECOVER-Stroke**

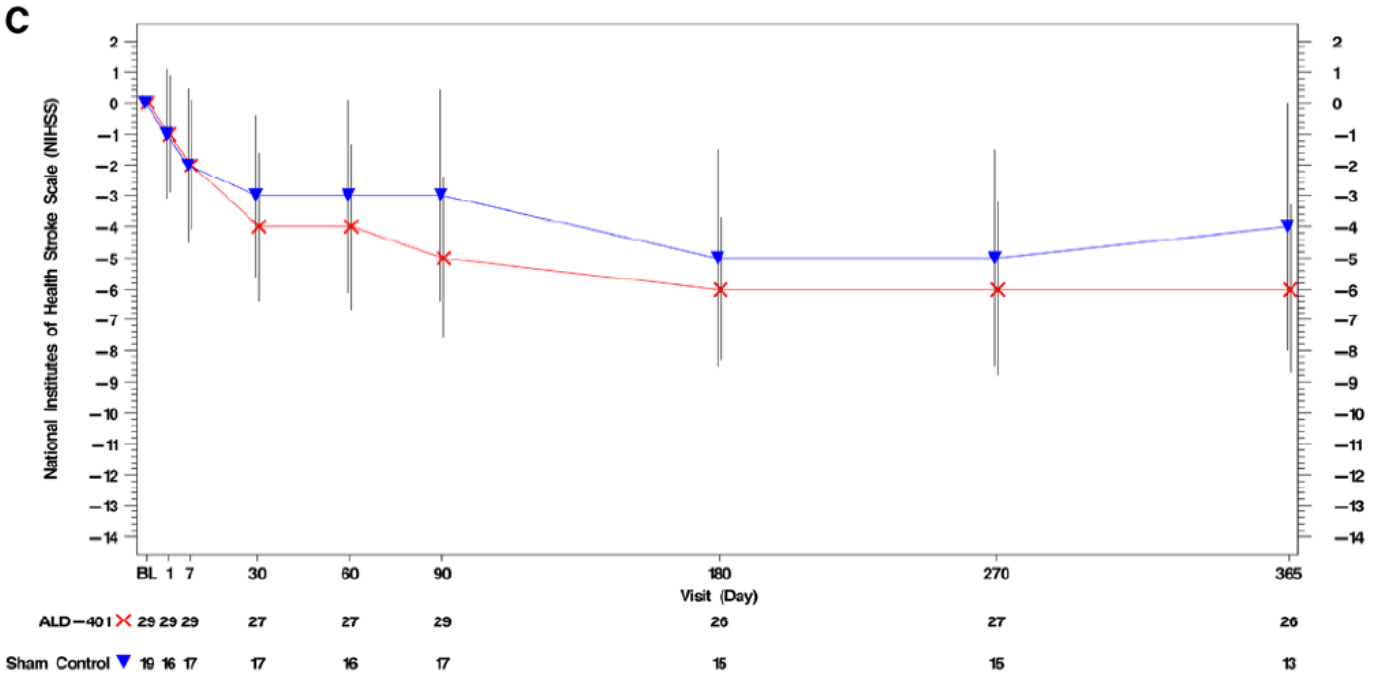
Phase 2, sham controlled
Mean time from stroke onset: 18 days

ORIGINAL RESEARCH ARTICLE

A Phase 2 Randomized, Sham-Controlled Trial of Internal Carotid Artery Infusion of Autologous Bone Marrow–Derived ALD-401 Cells in Patients With Recent Stable Ischemic Stroke (RECOVER-Stroke)

Circulation. 2019;139:192–205.

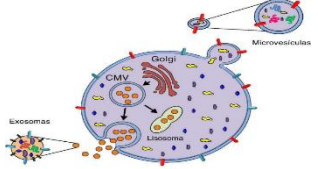
Sean I. Savitz, MD
Dileep Yavagal, MD
George Rappard, MD
William Likosky, MD
Neal Rutledge, MD
Carmelo Graffagnino, MD
Yazan Alderazi, MD
Jennifer A. Elder, PhD
Peng R. Chen, MD
Ronald F. Budzik Jr, MD
Ronald Tarrel, DO
David Y. Huang, MD, PhD
James M. Hinson Jr, MD
On behalf of the ALD-401 Trial Group



Adverse events:

- DWI abnormalities (14% vs. 0%)
- Seizures (14% vs. 9%)

FURTHER DEVELOPMENTS : EXOSOMES (EC Vesicles)



nature REVIEWS IMMUNOLOGY

Small membrane vesicles
Endosomal production
Released to extracelular space

Contain

mRNA, microRNA and proteins

Advantages

Low production cost
They can be frosten and stored in the hospitals

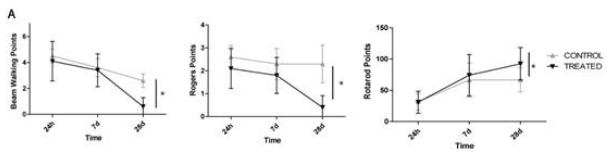
EXOSOMES
Animal model treatment

SCIENTIFIC REPORTS

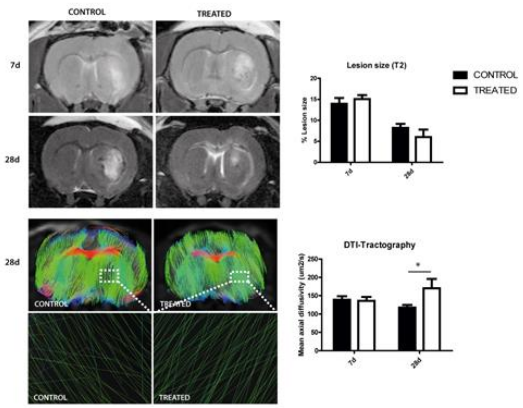
White Matter Repair After Extracellular Vesicles Administration in an Experimental Animal Model of Subcortical Stroke

Laura Otero-Ortega, Fernando Laso-García*, María del Carmen Gómez-de Frutos*, Berta Rodríguez-Frutos, Jorge Pascual-Guerra, Blanca Fuentes#, Exuperio Díez-Tejedor# & María Gutiérrez-Fernández#

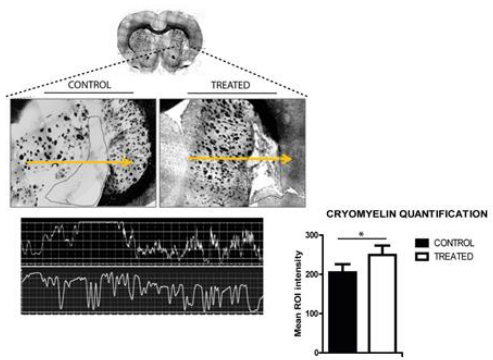
FUNCTIONAL EVALUATION



LESION SIZE AND FIBBER TRACT



MYELIN MARKER



Otero-Ortega L et al; Scientific Report. 2017: 16;7:44433

SCIENTIFIC REPORTS

White Matter Repair After Extracellular Vesicles Administration in an Experimental Animal Model of Subcortical Stroke

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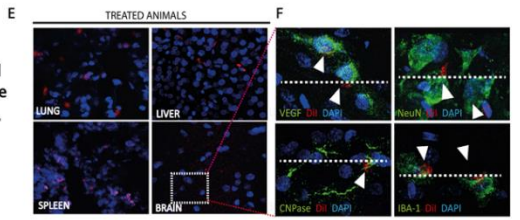
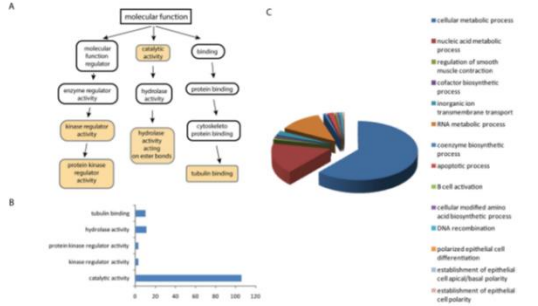
BIODISTRIBUTION



PROTEOMICS ANALYSIS

Protein names	Full name	FASTA
TGFBI	Transforming growth factor beta-induced	D4A605
TGFB1	Transforming growth factor beta-1	P17246
TGFB2	Transforming growth factor beta-2	Q07257
VEGFC	Vascular endothelial growth factor C	O35757
VGFR2	Vascular endothelial growth factor receptor 2	O08775
CTGF	Conective tissue growth factor	Q9R1E9
BDNF	Brain-derived neurotrophic factor	P23363
IGF2	Insulinlike growth factor II	P01346
IBP2	Insulinlike growth factor binding protein 2	P12343
IGF1R	Insulinlike growth factor 1 receptor	P24062
ALS	Insulinlike growth factor-binding protein complex acidlabile subunit	P35858
HDGR2	Hepatoma-derived growth factor-related protein 2	Q92566
QSEBA7	Hepatocyte growth factor activator	QSEBA7
LTBP1	Latent-transforming growth factor beta-binding protein 1	Q08910
LTBP2	Latent-transforming growth factor beta-binding protein 2	O95866



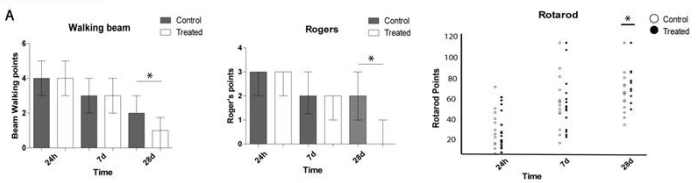
Otero-Ortega L et al; Scientific Report. 2017: 16;7:44433

JCBFM

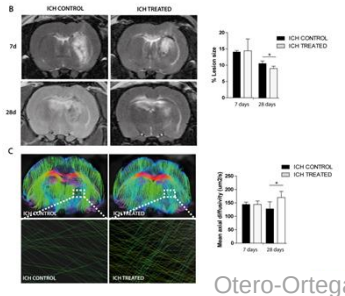
Exosomes promote restoration after an experimental animal model of intracerebral hemorrhage

Laura Otero-Ortega[1], Mari Carmen Gómez de Frutos[1-*], Fernando Laso-García[1-*], Berta Rodriguez-Frutos[1], Esperanza Medina-Gutiérrez[1], Juan Antonio López[2], Jesús Vázquez[2], Exuperio Díez-Tejedor[1] and María Gutiérrez-Fernández[1]

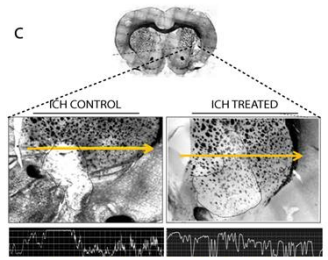
FUNCTIONAL EVALUATION



LESION SIZE AND FIBBER TRACT



MYELIN MARKER



Otero-Ortega L, et al. J Cereb Blood Flow Metab. 2018 May;38(5):767-779

SUMMARY

Brain repair is a **continuum** and it is

linked to **cerebral plasticity**

In brain damage the **REPAIR** **therapeutic targets** are:

neurovascular unit (cells and vessels**)**
neural fibbers

This can be enhanced through to stimulate trophic effect

Stem Cells
Extracellular Vesicles

To improve brain repair and functional recovery .

It is necessary **to continue the translational research** and to demonstrate safety and efficacy in **clinical trials**

Grupo Enfermedades Cerebrovasculares

IdiPAZ Instituto de Investigación Sanitaria

Laboratorio de Ciencias Neurológicas y ECV


M Gutiérrez (PhD)


L Otero (PhD)


MC Gómez (PhD)


L Piniella (PhD)


F Laso (Biol D)


R Gallego (Biol D)


MP López (Biol D)


J Pozo (Biol D)


I García (MD)

Laboratorio de Imagen Experimental


P López (BBCH, PhD)


T Navarro (Técnico)

Servicio de Neurología , Centro de Ictus


B Fuentes (MD, PhD)


M Alonso (MD, PhD)


G Ruiz (MD, PhD)


J Rodríguez (MD, PhD)


R Rigual (MD)


L Casado (MD)


E de Celis (MD)


E Alonso (MD, PhD)


P Franco (Jefa de Enf.)


S Calcedo (Enf.)


Prof. Exuperio Díez Tejedor (MD, PhD) Director

Neurorradiología


R Frutos (MD)


A Fernández (MD)


B Martín (MD)


P Navia (MD)

Neurocirugía


A Gómez (MD)


B Hernández (MD)

Neurorehabilitación


S Moraleda (MD)


D Hernández (MD)

UAM Universidad Autónoma de Madrid

SaludMadrid Hospital Universitario La Paz

Hospital Carlos III

Hospital Cantoblanco

IdiPAZ Instituto de Investigación Hospital Universitario La Paz