Two-Year Safety and Clinical Outcomes in Chronic Ischemic Stroke Patients after Implantation of Human Modified Bone Marrow Derived Mesenchymal Stem Cells (SB623): A Phase 1/2A Study

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- Qool Therapeutics (consultant)
- NeuroSave (consultant)

SanBio SB623 Phase 1/2a Clinical Study

1st intracerebral stem cell stroke trial in North America

Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

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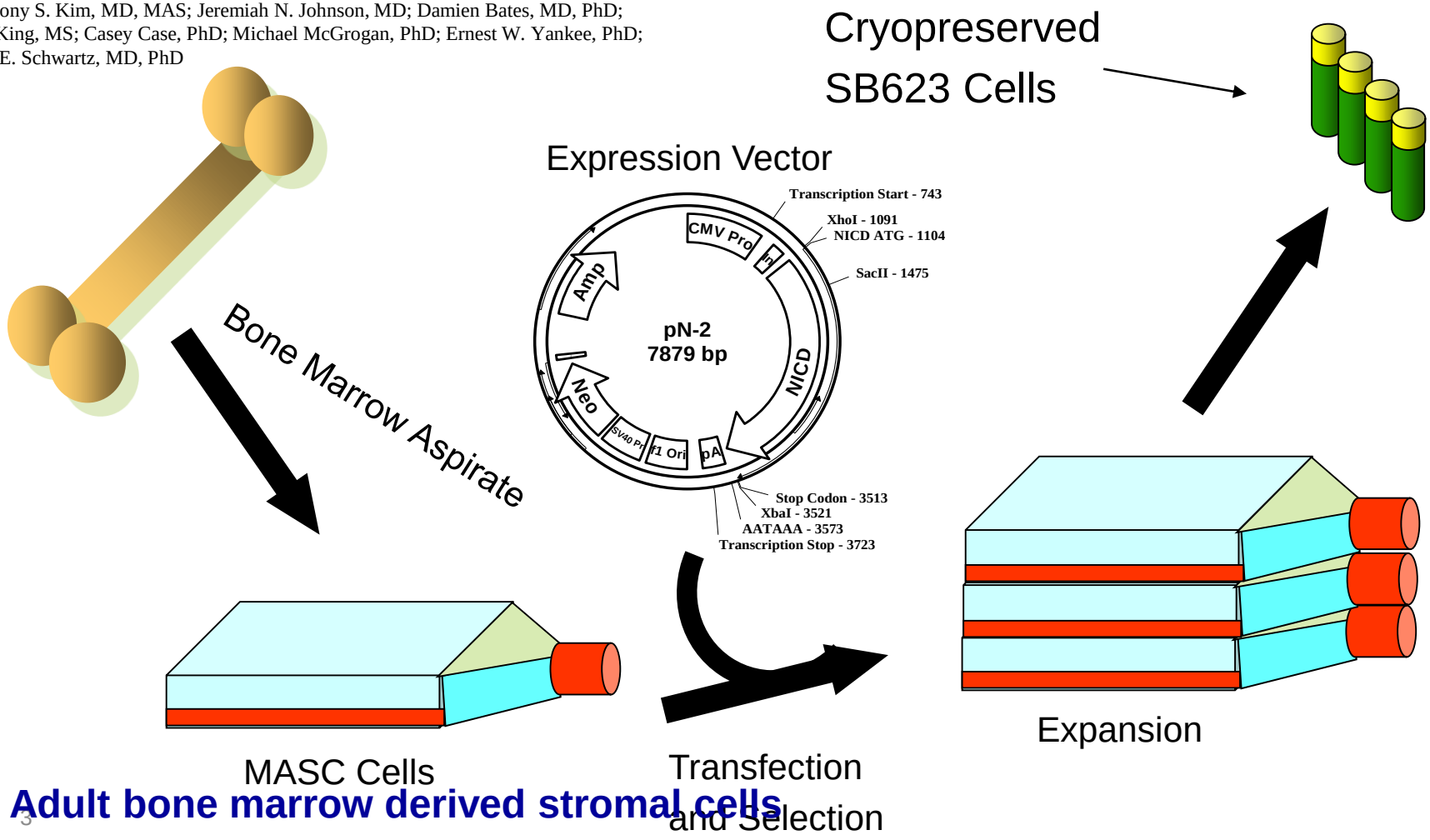
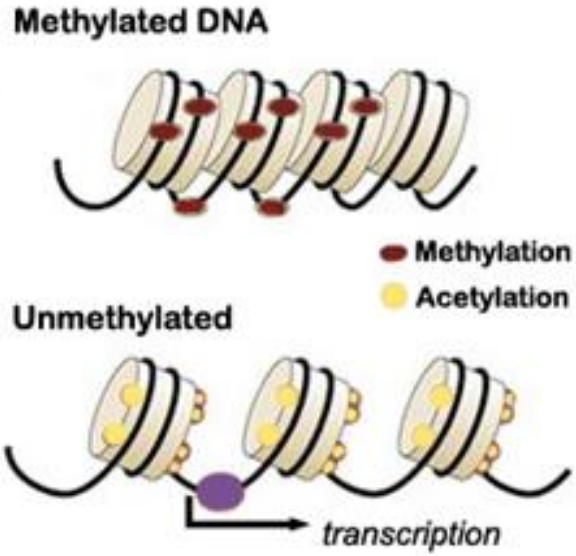
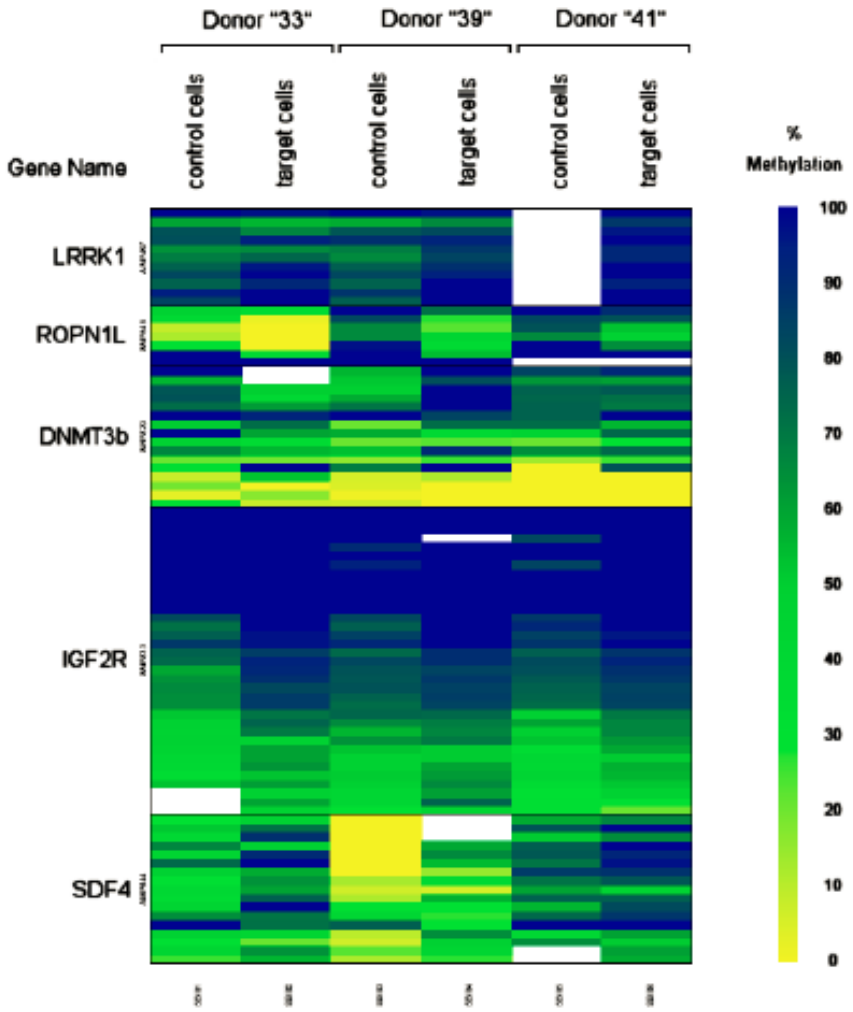


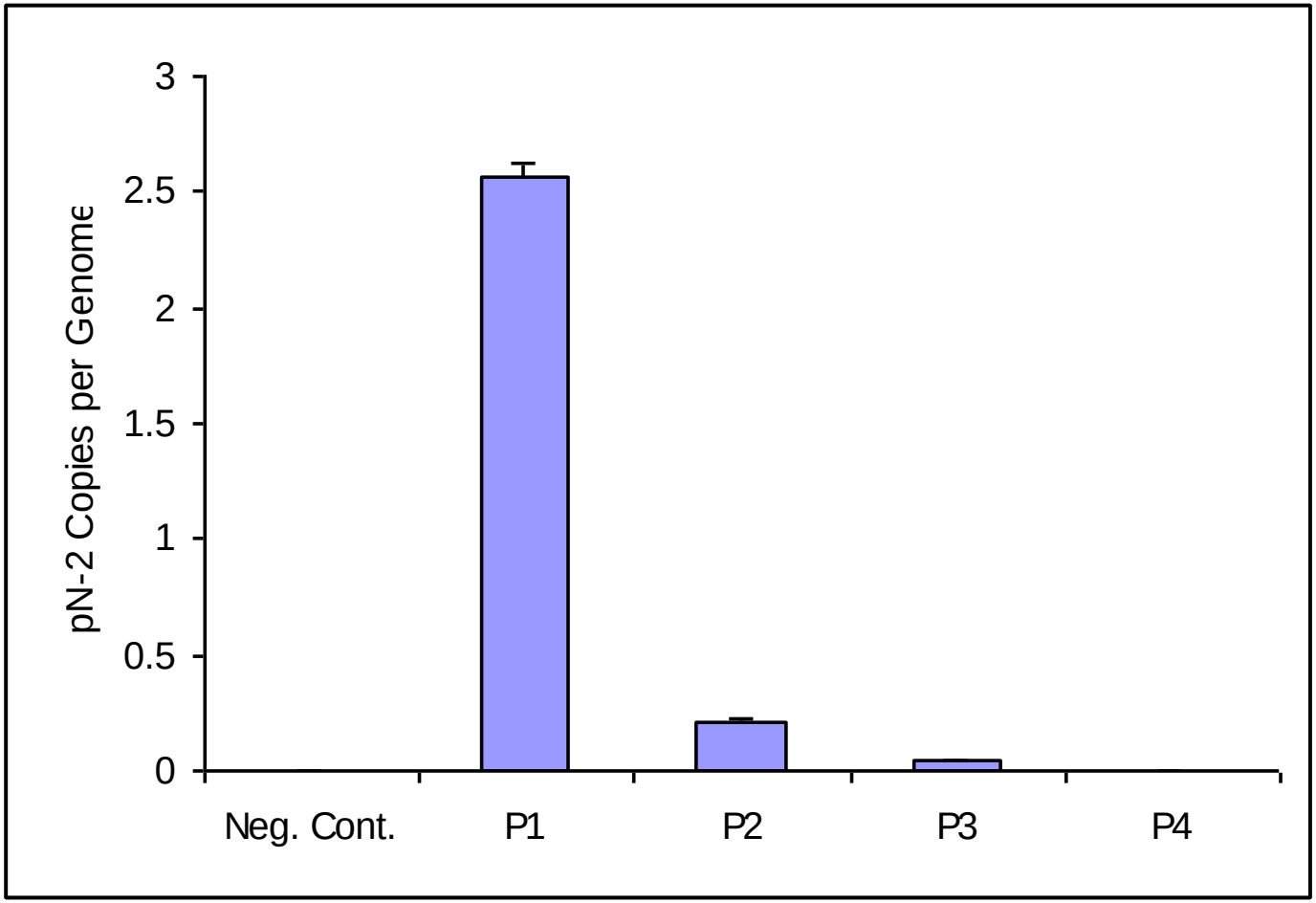
Adult bone marrow derived stromal cells

Transient Notch Transfection Causes Changes in the Differentiated State



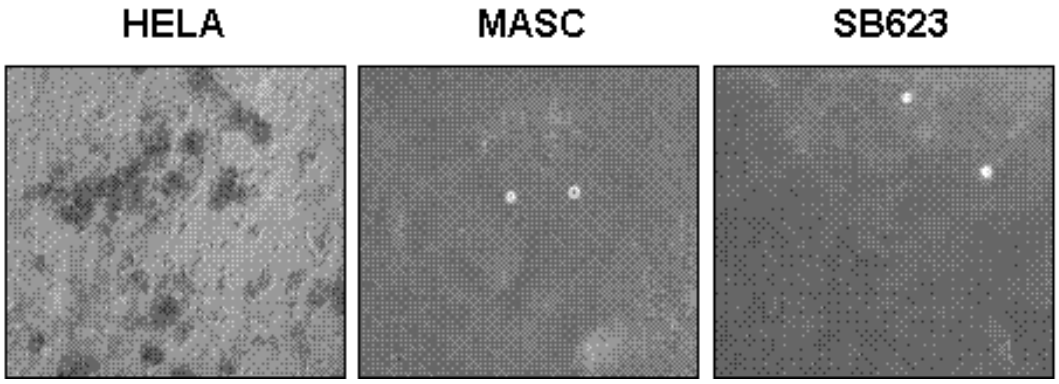


The pN-2 Plasmid is Lost During Propagation of SB623 Cells



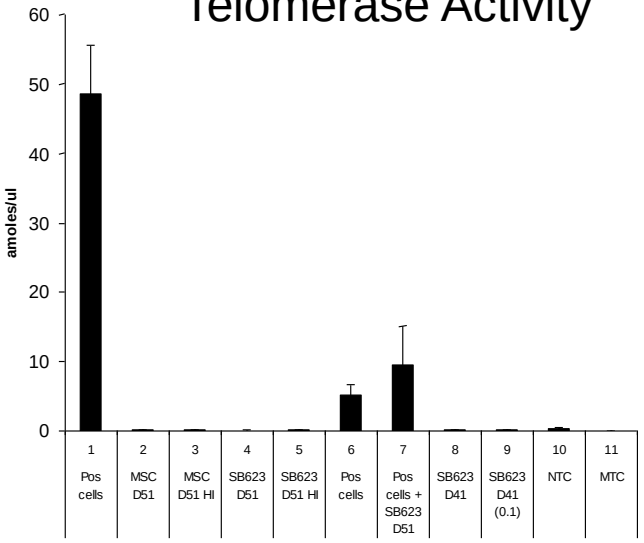
SB623 Cells do not have a Transformed Phenotype

Growth on Soft Agar

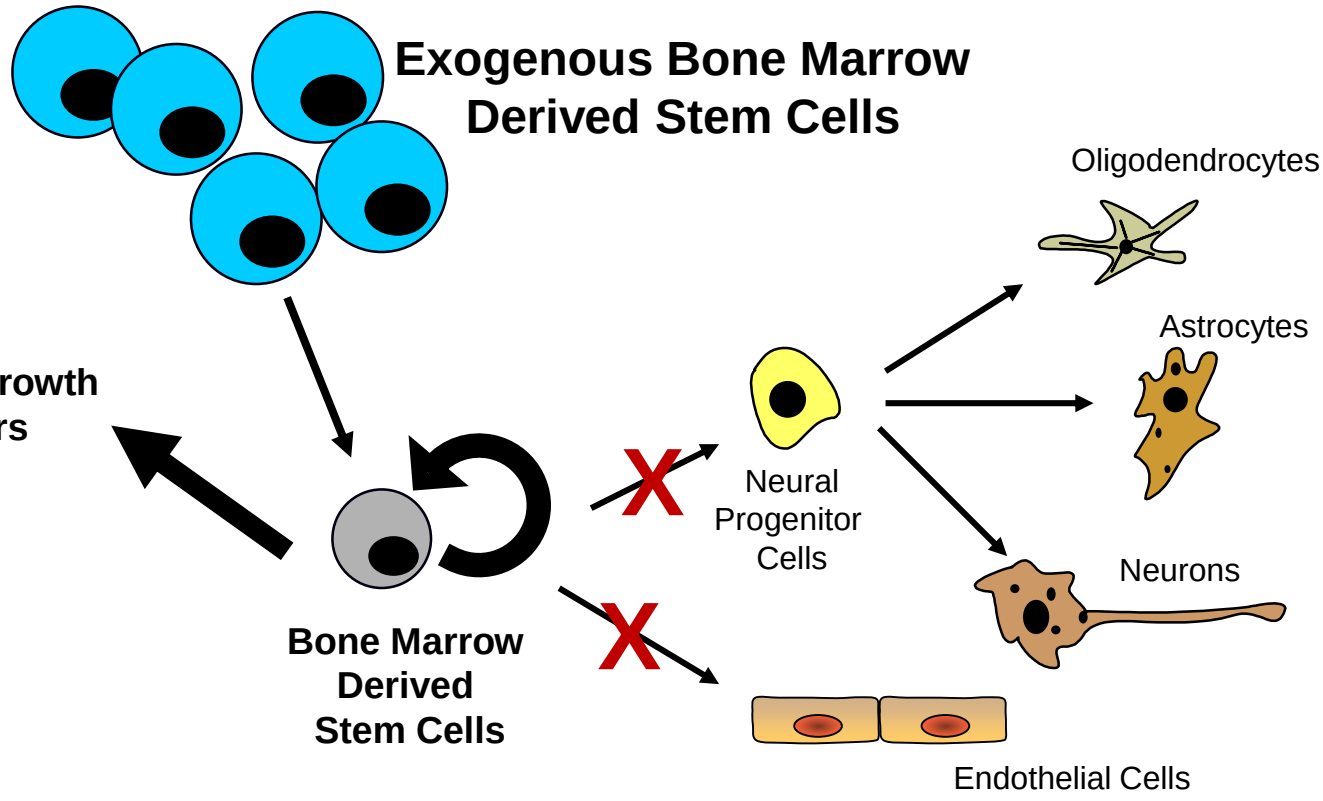


Karyotype

Telomerase Activity



Mechanisms of recovery from stroke after transplanted MSCs

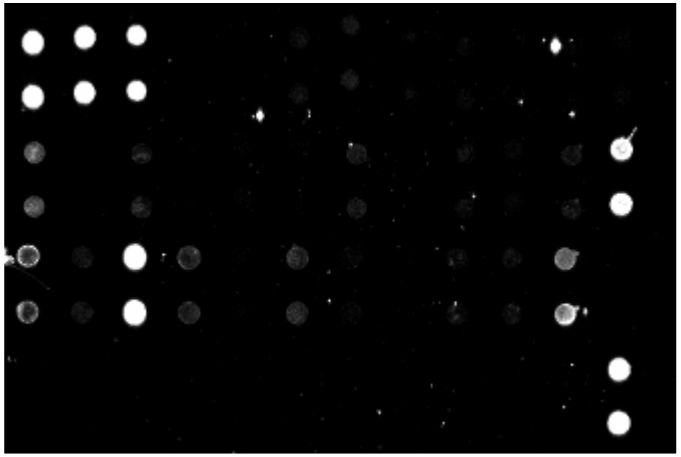


Axonal/Dendritic Sprouting
Angiogenesis/Vasculogenesis
Neurogenesis
Gliogenesis
Synaptogenesis
↓ Inflammation/ Immunomodulation

Enhanced endogenous brain repair mechanisms and plasticity

Secretion of Protein Factors in Conditioned Medium

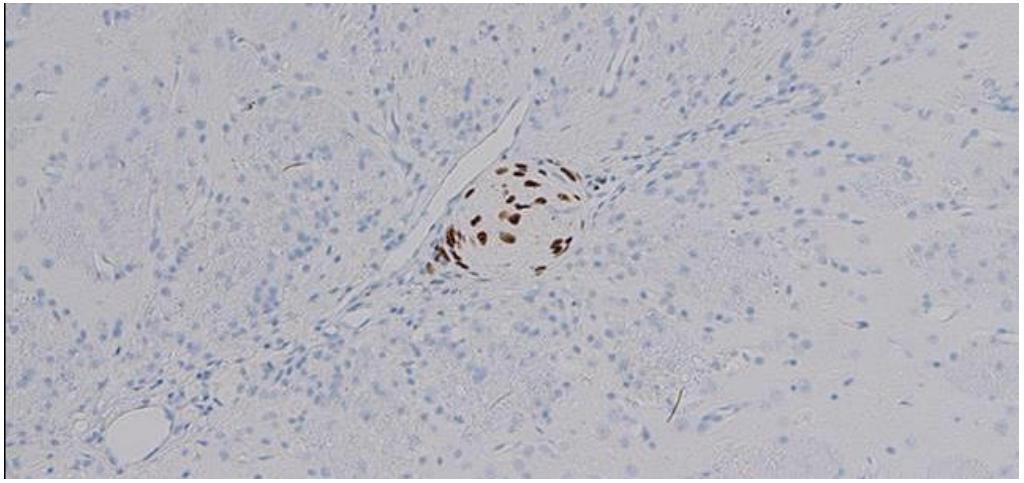
- Custom antibody array (RayBiotech)
- 30 cytokines



BDNF	HGF
BMP-4	IGF-I
BMP-6	IL-1α
BMP-7	IL-6
b-NGF	IL-8
CNTF	LIF
DKK-1	MCP-1
DKK-4	MMP-1
EGF	NT-3
Erythropoietin R	PDGF-AA
FGF-2	SDF-1
FGF-7	TGFα
GCSF	TGFβ
GDNF	TNFα
HB-EGF	VEGF

SB623 Cells are Present 1 Month Post-implant, but not at 2 Months

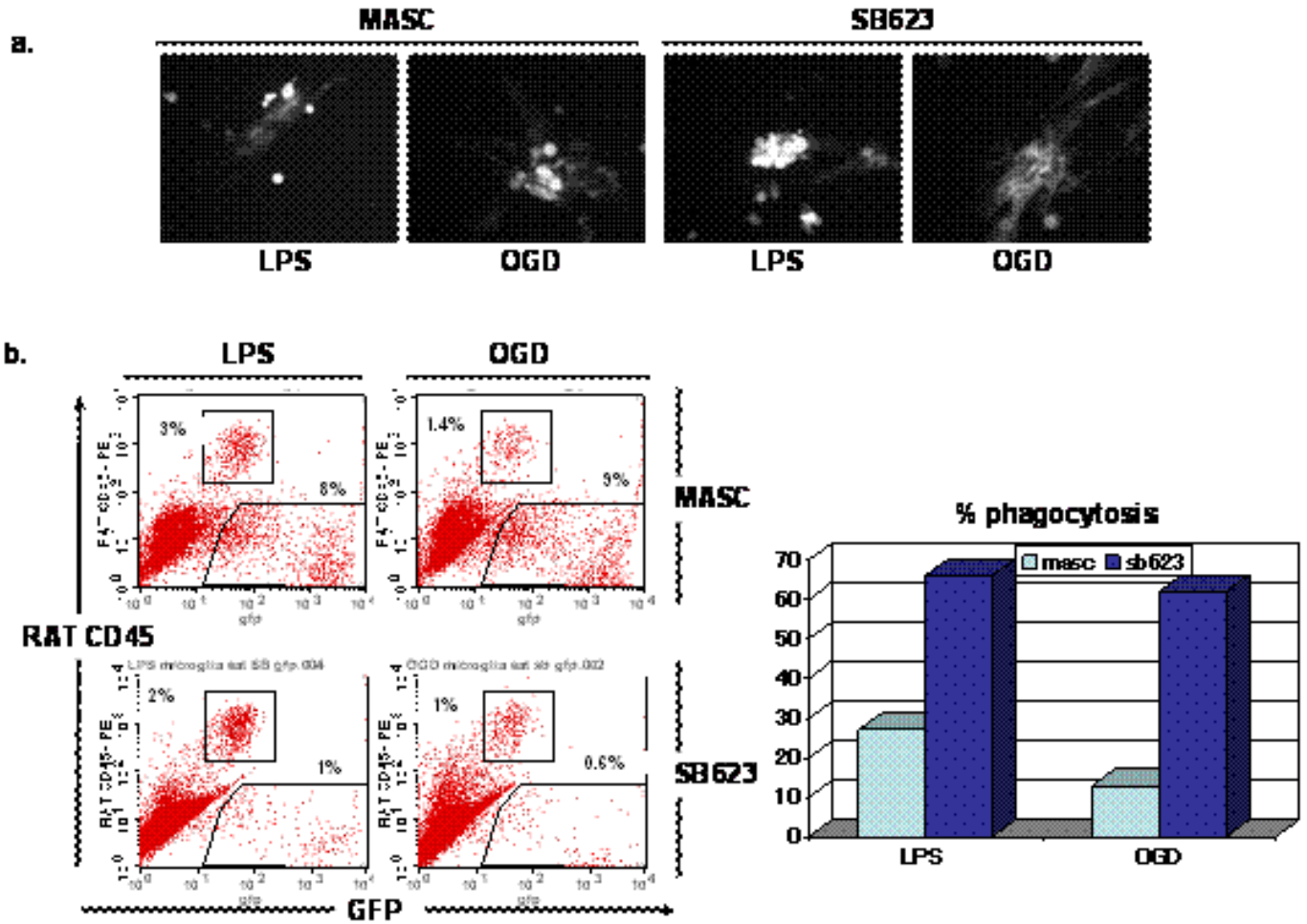
Human Nuclear Matrix Ab



qPCR

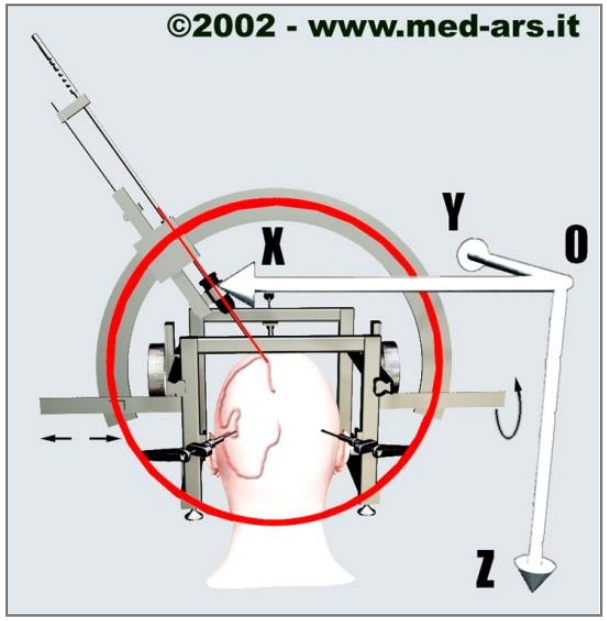
Group	Sex	Animal ID	Block #	Human cell equivalent / µg DNA
1	Male	8001	1	LLD
			2	26
		8002	1	LLD
			2	LLD
		8003	1	LLD
			2	LLD
2	Female	8016	1	LLD
			2	LLD
		8017	1	LLD
			2	NQ
		8018	1	LLD
			2	LLD

SB623 Cells are Phagocytosed by Activated Microglia (Host Innate Immunity)

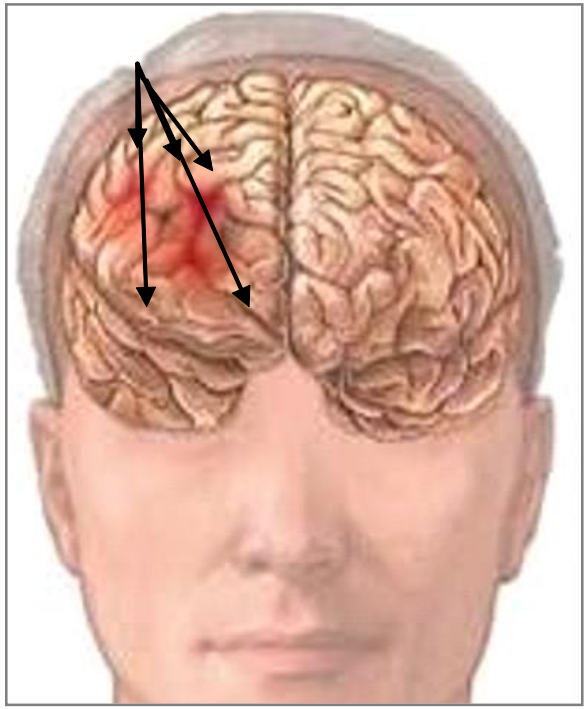


SanBio SB623
Phase 1/2a Clinical Study

- Overall Design
  - Open-label safety study
  - 18 pts (3 dose levels, 6 pts each)—Stanford and Univ Pittsburgh
    - Standard, staggered escalation paradigm (2.5M, 5M, 10M)
  - 6-month efficacy, 2-year follow-up



Stereotactic Frame Positioning



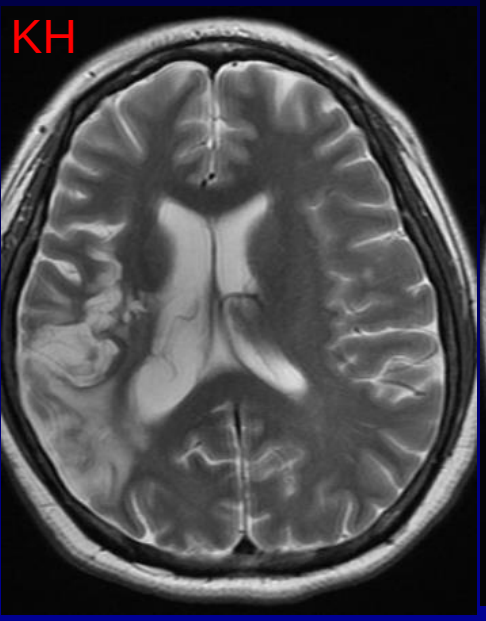
Needle tracks for cell implantation and implant sites

Key inclusion/exclusion criteria

- Inclusion
  - 18-75 years old (33-75 yo tx)
  - Ischemic stroke in subcortical region of MCA or lenticulostriates with or without cortical involvement
  - 6- 60 mos post-stroke (7-36 mos); stable for > 3 weeks prior
  - Modified Rankin Score 3 or 4
  - NIHSS Score >7
- Exclusion
  - Cerebral infarct size >100 cm3 (on MRI)
  - History of > 1 stroke
  - Presence of serum antibodies to donor SB623 cells (HLA Class I or II)

Primary endpoints

- Safety
  - WHO toxicity scale
  - Periodic MRIs
  - **2 years post-implantation follow-up**
- Efficacy
  - Primary
    - European Stroke Scale (ESS) and FDG-PET at 6 months post-implant
  - Secondary
    - ESS, NIHSS, Fugl-Meyer, mRS, and cognitive questionnaire scores at multiple timepoints
    - FDG-PET imaging at multiple timepoints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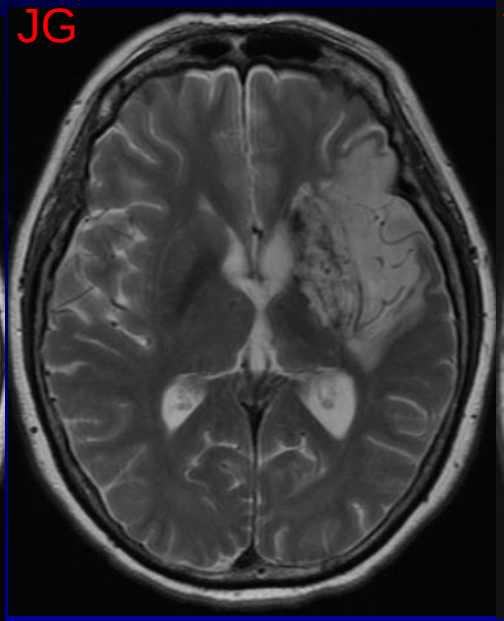
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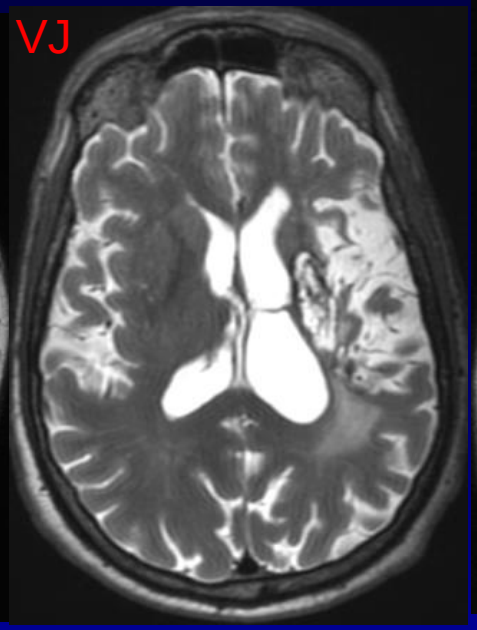
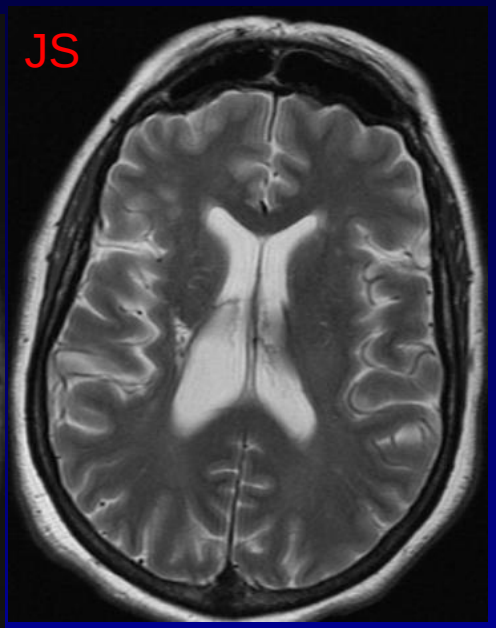

VJ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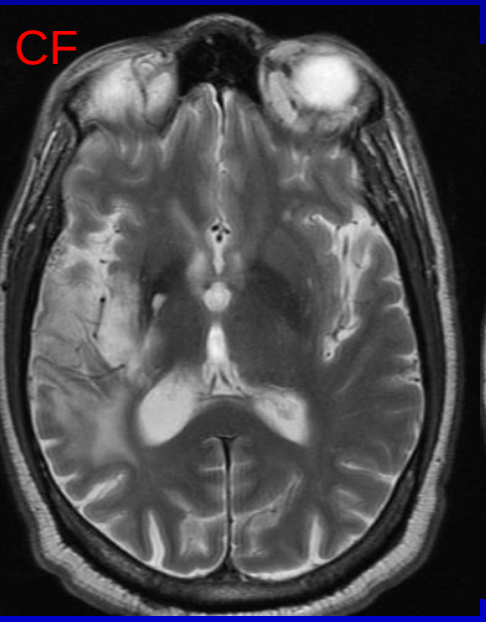
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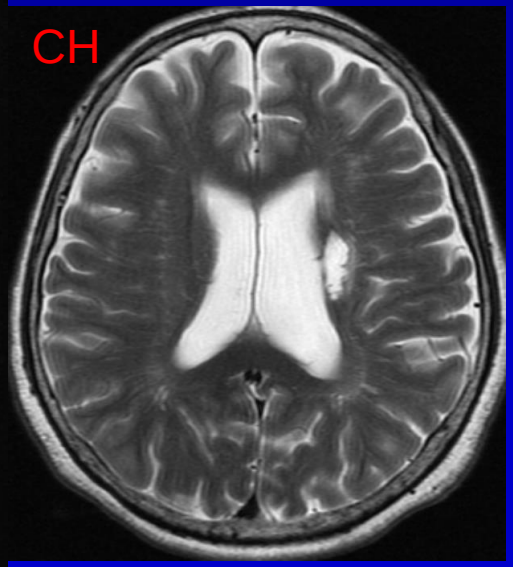
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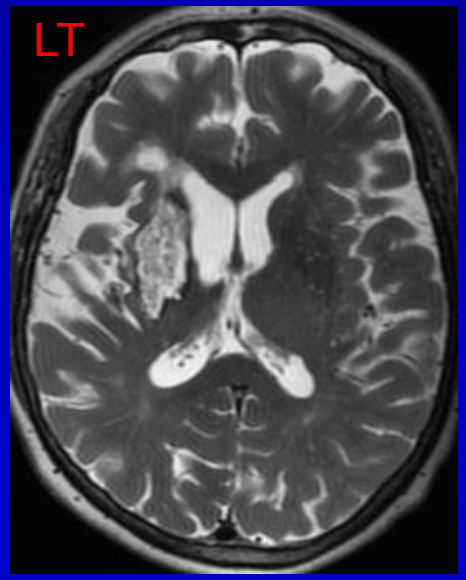
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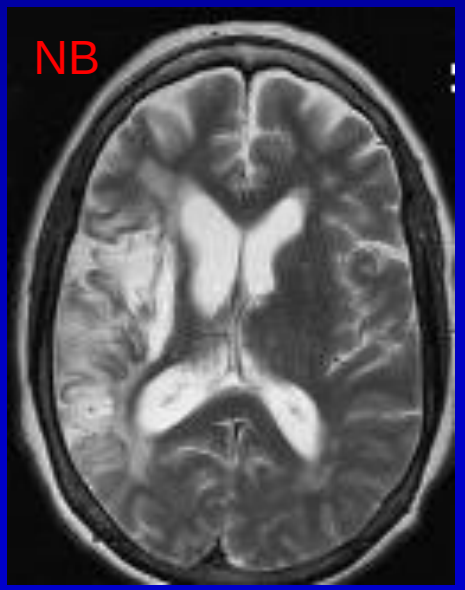
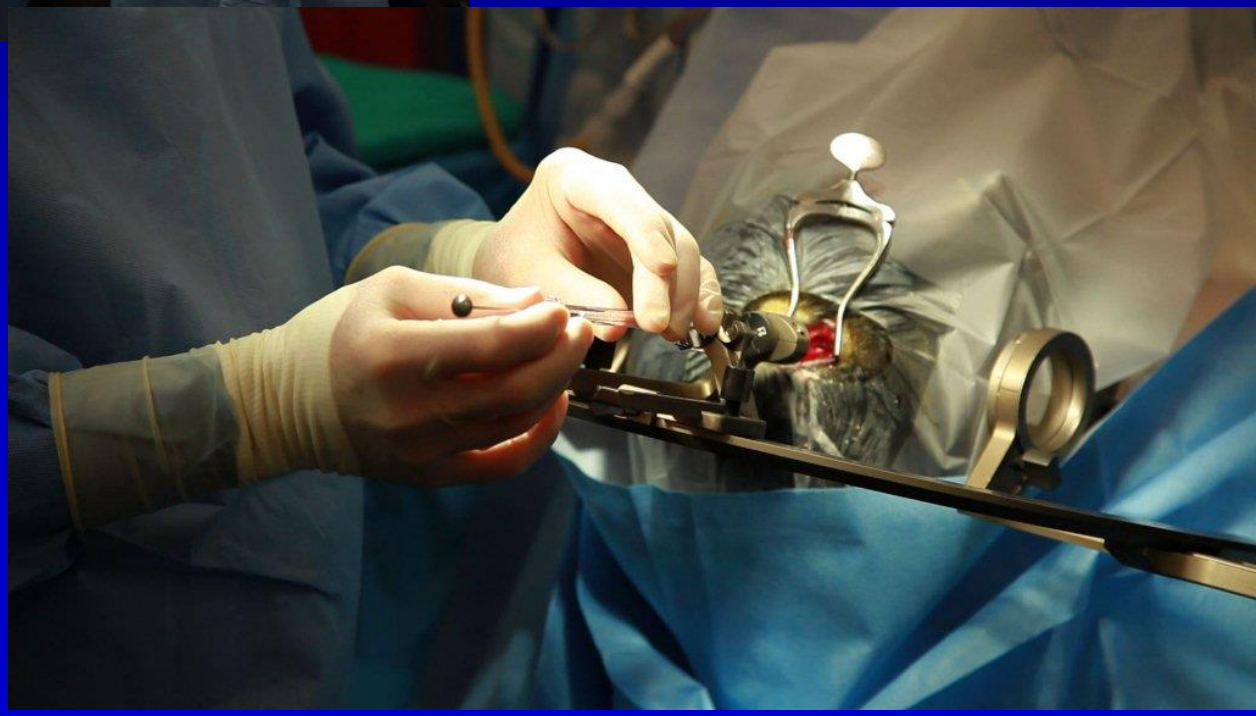

NB

9/14/11
2.5 M modified adult bone marrow stem cells

2 years after Rt bg stroke

SanBio/Stanford



<u>18 pts treated</u>
6 with 2.5M, 6 with 5M
6 with 10M

12 Stanford
6 Univ Pittsburgh

Treatment Emergent Adverse Events (TEAEs)

Procedural Headache (89%)

Nausea/Vomiting (33%/22%)

Depression (22%)

Muscle Spasticity (22%) Fatigue (17%) UTI (17%)

Constipation (17%) Pain in Extremity (17%)

C-reactive protein ↑ (17%) Blood glucose ↑ (17%)

No dose limiting toxicities or deaths
None probably or definitely related to the cells; many related to the procedure
Most TEAEs of mild (11%) or moderate (50%) intensity

Serious Adverse Events (SAEs) (requiring hospitalization)

Yr 1

1) Seizure (70d after transplant)
2) Asymptomatic subdural hygroma/hematoma (drained)
3) Pneumonia
4) Stenting of cervical carotid artery for asymptomatic stenosis
5) UTI/sepsis
6) TIA (worsened facial droop & dysarthria; 11 mos post transplant)

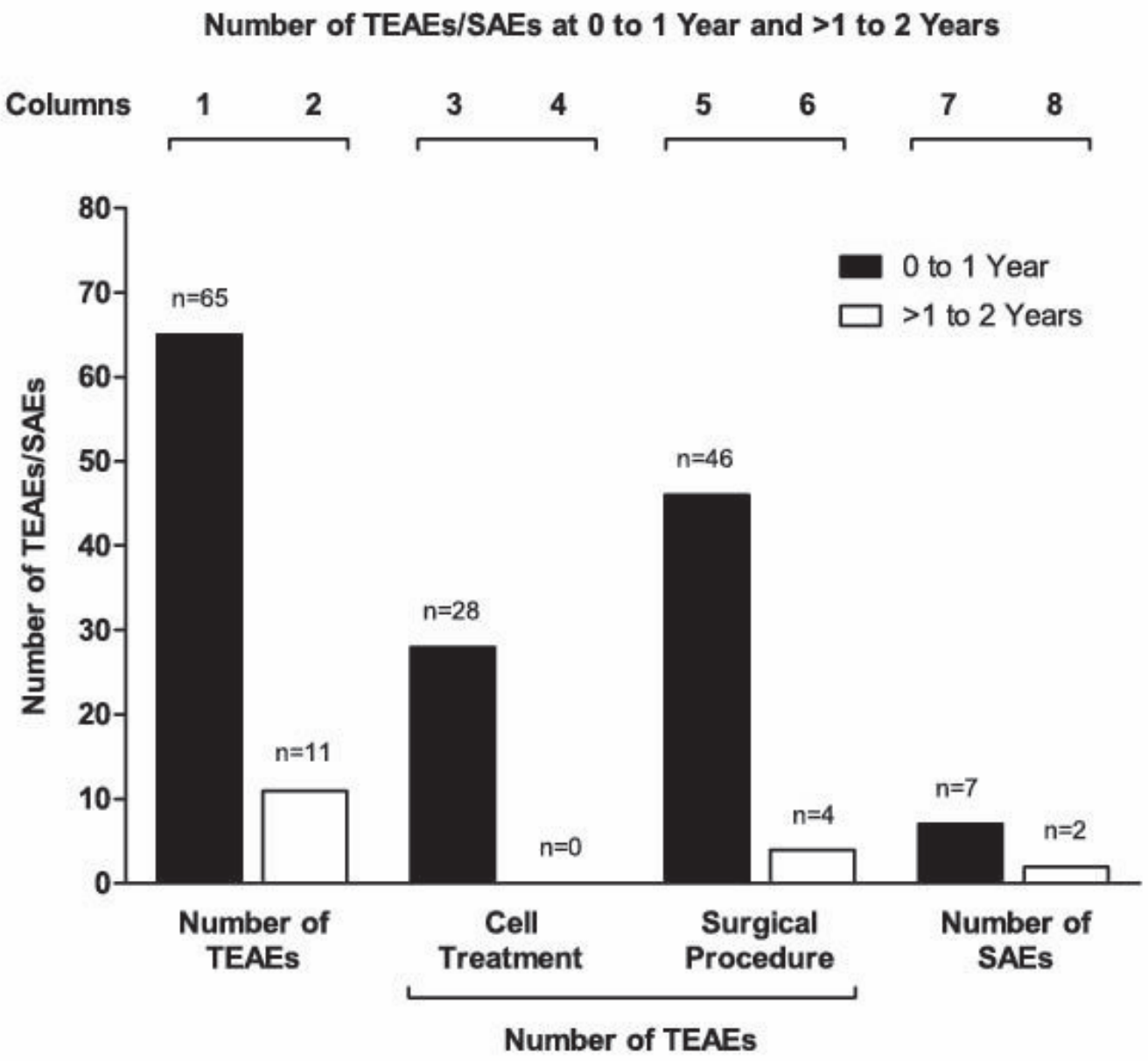
Yr 2

7) Paresthesias/dysphagia

No patient withdrew 2º to adverse events; all resolved without sequelae

None related to cells; only subdural definitely related to surgery
No correlation between SAEs and cell dosage

C


Number of TEAEs/SAEs at 0 to 1 Year and >1 to 2 Years
Columns 1 2 3 4 5 6 7 8
0 to 1 Year
>1 to 2 Years
Number of TEAEs/SAEs
0
10
20
30
40
50
60
70
80
n=65
n=11
n=28
n=0
n=46
n=4
n=7
n=2
Number of TEAEs
Cell Treatment
Surgical Procedure
Number of SAEs
Number of TEAEs

No clinically meaningful change from baseline in plasma:

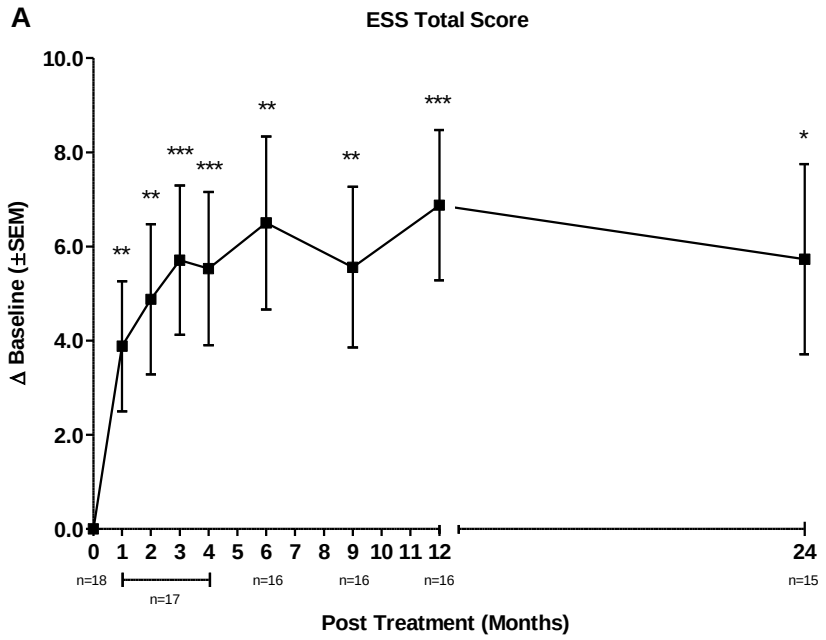
Cytokines (TNF-α, IL-6, and IFN-γ)

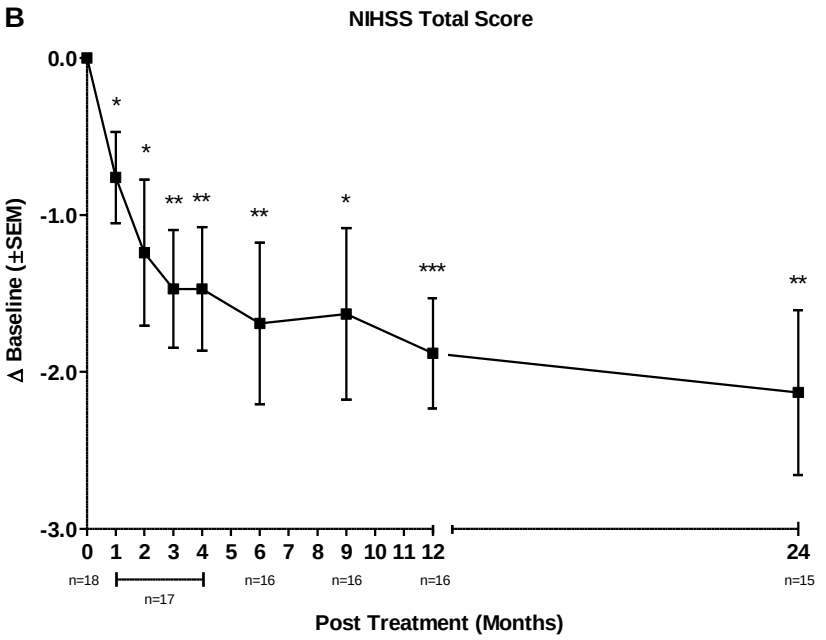
Antibody levels to donor SB623 cell HLA antigens

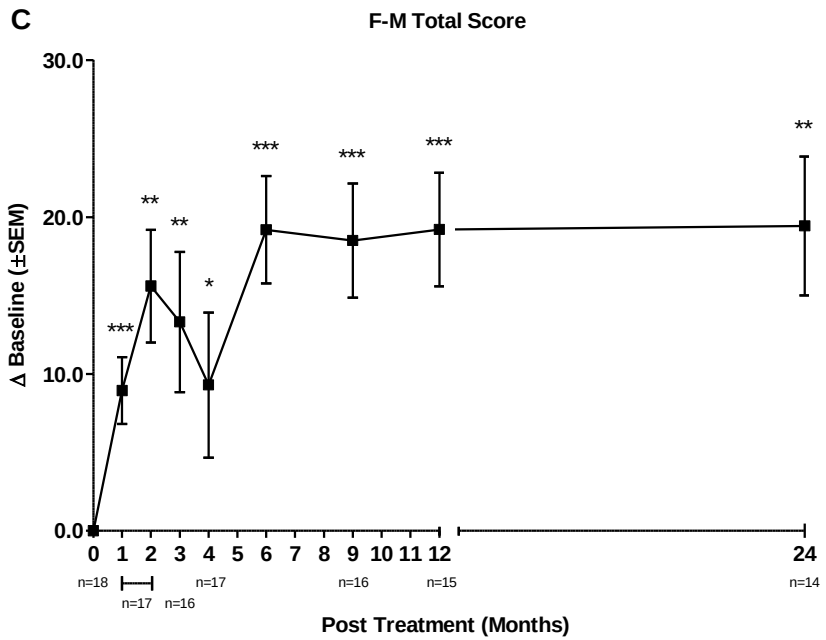
Peripheral blood mononuclear count (PBMC) function

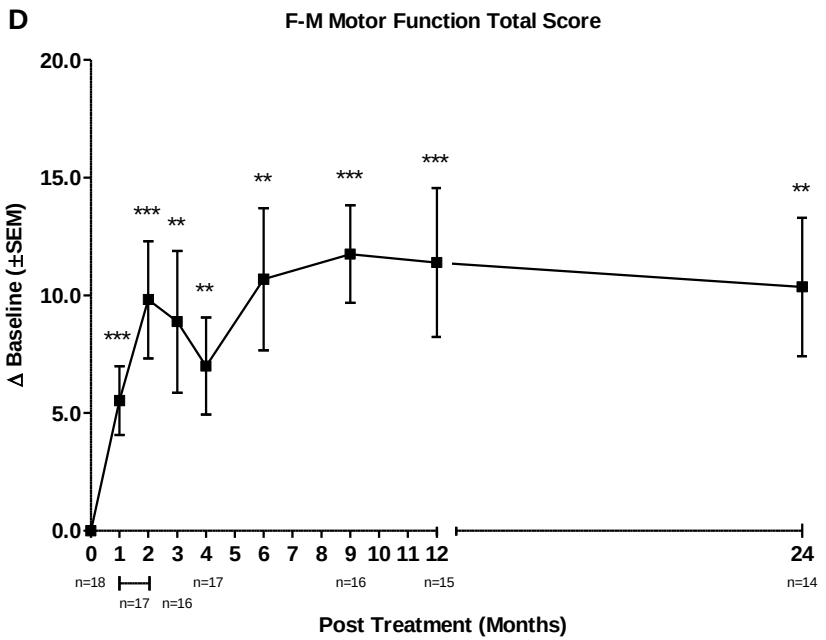
Other biochemical parameters

2 year clinical outcome



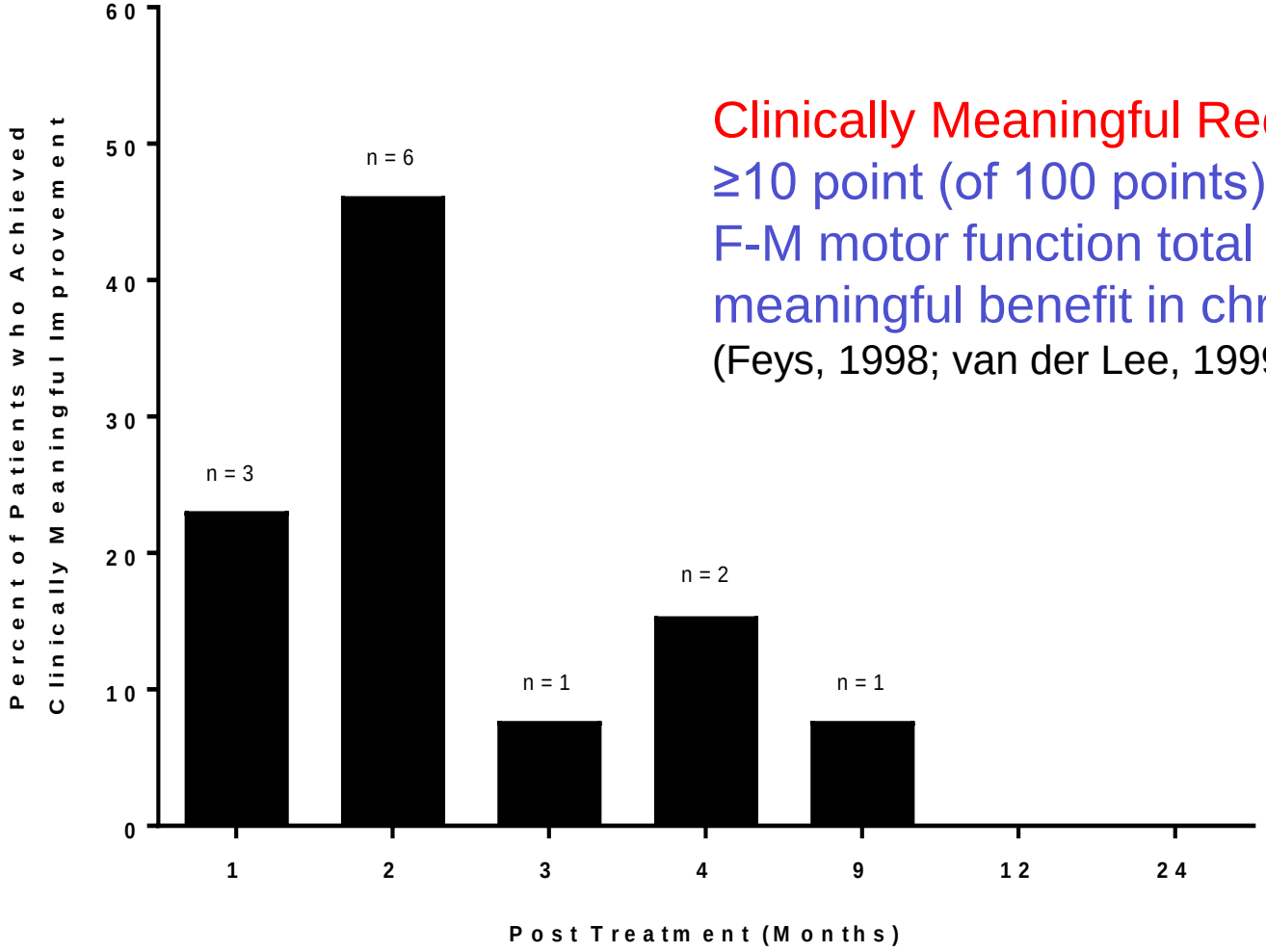






Post Hoc Analysis
(F-M Motor Function Score)

- 13/18 (72%) pts achieved clinically meaningful recovery



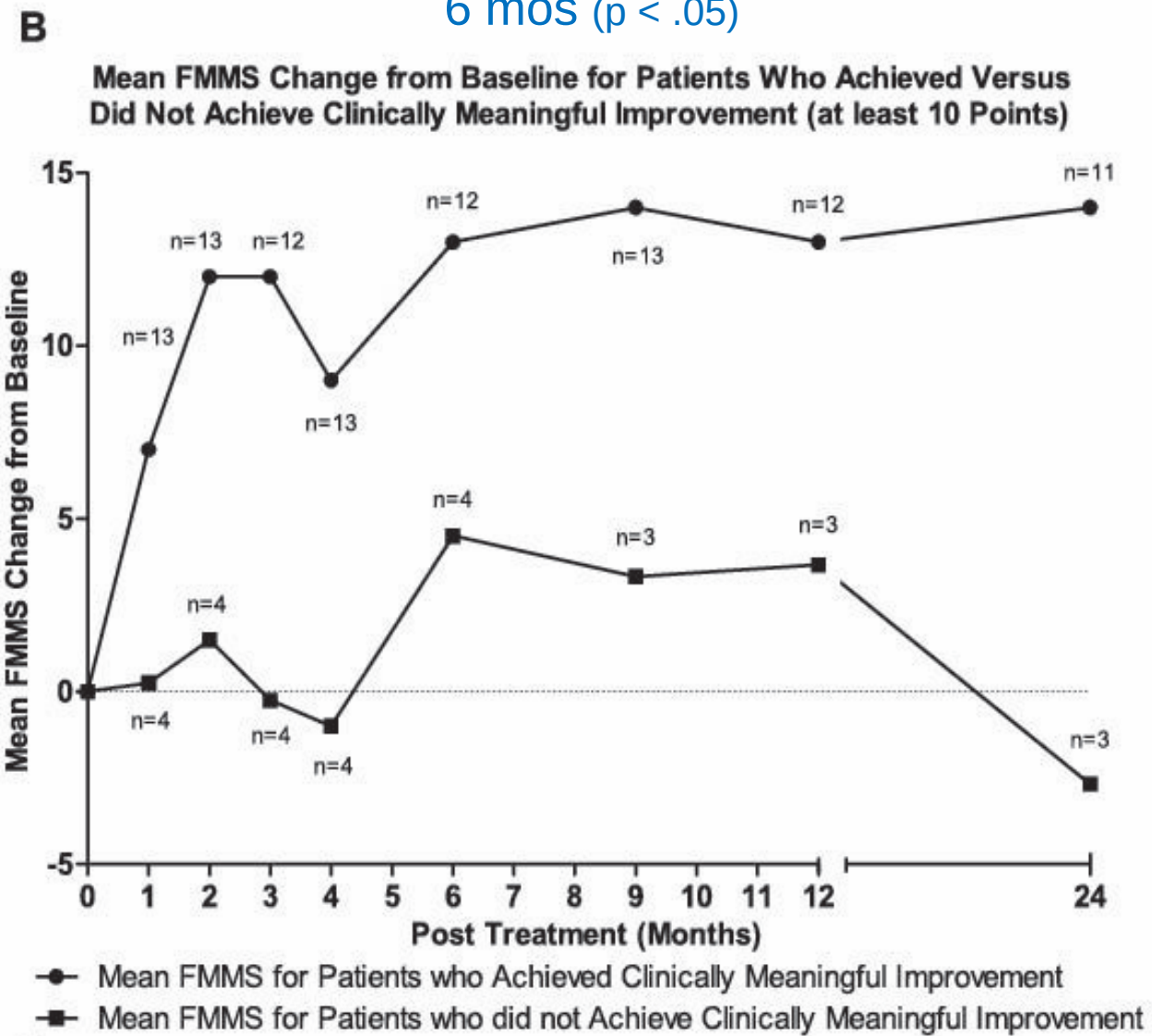
Clinically Meaningful Recovery

≥10 point (of 100 points) improvement in the F-M motor function total score is a clinically meaningful benefit in chronic stroke

(Feys, 1998; van der Lee, 1999 & 2001; Page, 2009)

Those with “clinically meaningful” improvement achieve 75% of maximal improvement by 3 mos

Pts without this degree of clinically meaningful improvement, improve later: 6 mos ($p < .05$)



Cell dose levels did not show any clear dose-response relationships with clinical outcome

No association between improvement in clinical outcome measures and either baseline stroke severity or baseline patient age

39 yo ♀, 2y s/p Lt MCA stroke

39 yo ♀, 2y s/p Lt MCA stroke

2.6 months Post Transplant
Benefit sustained at 4.7 yrs post transplant

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Benefit sustained at 4.7 yrs post transplant

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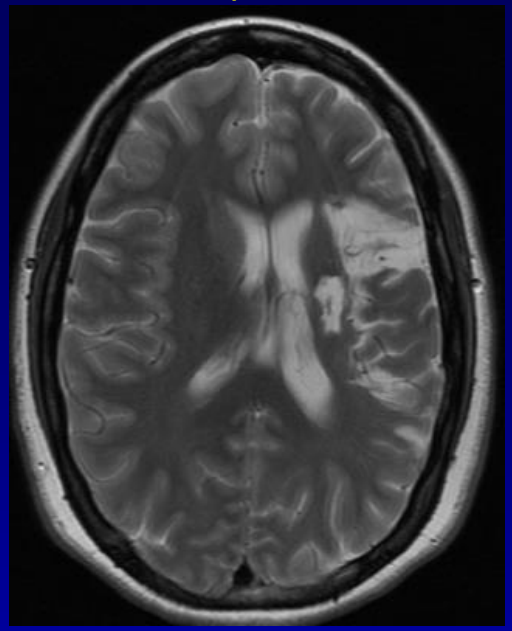
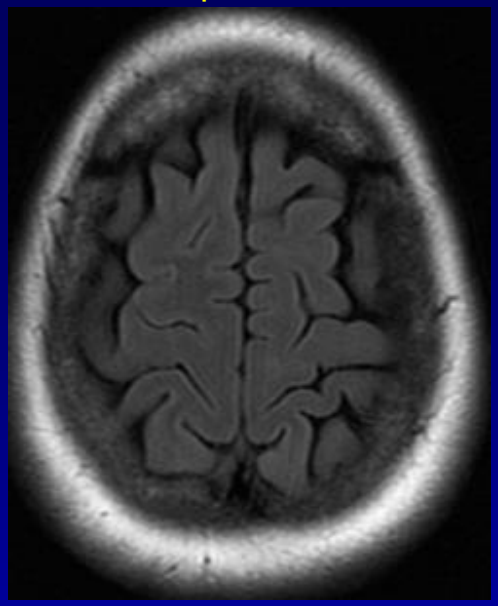
Benefit sustained at 4.7 yrs post transplant

Pre-transplant T2 FSE

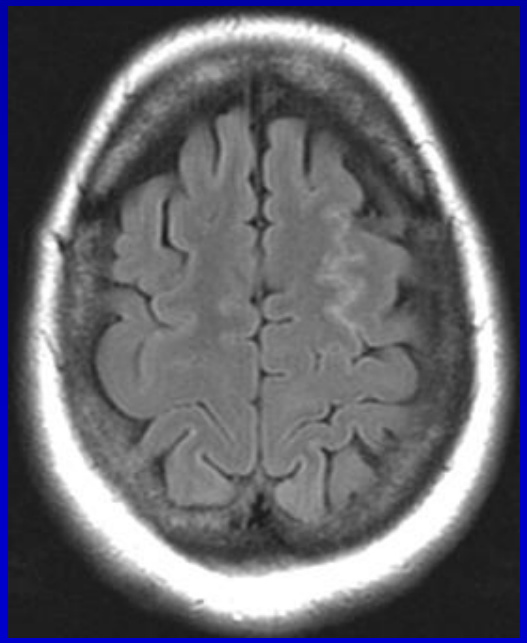


Pre-transplant T2 FLAIR

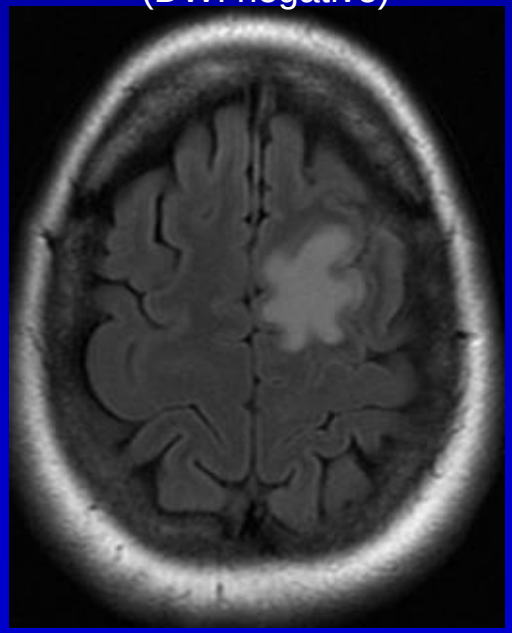


39 yo ♀, 2y s/p Lt MCA stroke

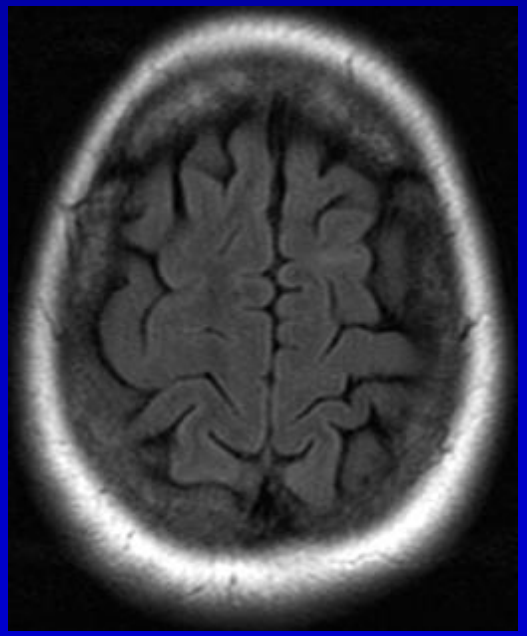
Day 1 post-transplant T2 FLAIR



Week 1 post-transplant T2 FLAIR
(DWI negative)



Month 2 post-transplant T2 FLAIR



Newly appearing T2 FLAIR transient lesions
14/18 pts

Primarily in or adjacent to premotor cortex

Appears at 1-2 weeks; resolves by 1-2 months

Significant correlations between size of the initial post-transplant FLAIR signal changes and neurological recovery at 12 mos
($p<0.001$, ESS; $p< 0.01$ NIHSS, FM & FM Motor Fn)

& 24 mos ($p< 0.05$, ESS; $p< 0.01$, NIHSS)

Conclusions

Intraparenchymal transplantation of human modified bone marrow derived stromal cells in chronic stroke patients is **Safe and Feasible**

This study showed significant neurologic improvement at 6, 12 and 24 months following transplant

Circuits not irreversibly damaged!

Precise mechanisms still being elucidated

Conclusions

- Cell transplantation therapy for stroke holds great promise
- Investigation of neurotransplantation still in early stages
- Many fundamental issues need to be resolved in pre-clinical studies

Multicenter Phase 2B study (156 US pts); initiated Jan, 2016

Double blind, randomized controlled study
2.5M, 5.0M, sham (1:1:1 randomization)
Enrollment/treatment complete 12/21/17; 1 yr f/u

Also Phase 2 Chronic TBI study

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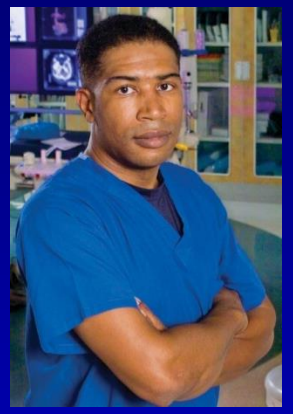

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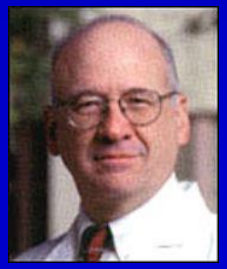

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