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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- NeuroSave (consultant)
SanBio SB623
Phase 1/2a Clinical Study

Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke:
A Phase 1/2a Study
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Cryopreserved SB623 Cells

Expression Vector

Transcription Start - 743
XhoI - 1091
NICD ATG - 1104
SacII - 1475
Stop Codon - 3513
XbaI - 3521
AATAAA - 3573
Transcription Stop - 3723

CMV Pro
In
NICD
pAf1 Ori
SV40 Pr
Neo
Synthetic pA
Amp

Bone Marrow Aspirate

Adult bone marrow derived stromal cells

Transfection and Selection

Expansion
Transient Notch Transfection Causes Changes in the Differentiated State

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<td>SDF4</td>
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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

Exogenous Bone Marrow Derived Stem Cells

- Trophic/Growth Factors
- Bone Marrow Derived Stem Cells
- 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

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<th>Secreted Protein Factors</th>
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<tr>
<td>BDNF</td>
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SB623 Cells are Present 1 Month Post-implant, but not at 2 Months

Human Nuclear Matrix Ab

qPCR

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<tr>
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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
9/14/11
2.5 M modified adult bone marrow stem cells
2 years after Rt bg stroke
SanBio/Stanford

18 pts treated
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)

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)
7) Paresthesias/dysphagia

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

None related to cells; only subdural definitely related to surgery
No correlation between SAEs and cell dosage
Number of TEAEs/SAEs at 0 to 1 Year and >1 to 2 Years

- **Number of TEAEs**: 65
  - 0 to 1 Year: 65
  - >1 to 2 Years: 11

- **Cell Treatment**: 28
  - 0 to 1 Year: 28
  - >1 to 2 Years: 0

- **Surgical Procedure**: 46
  - 0 to 1 Year: 46
  - >1 to 2 Years: 4

- **Number of SAEs**: 7
  - 0 to 1 Year: 7
  - >1 to 2 Years: 2
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

A. ESS Total Score

B. NIHSS Total Score

C. F-M Total Score

D. F-M Motor Function Total Score
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
2.6 months Post Transplant
Benefit sustained at 4.7 yrs post transplant
Benefit sustained at 4.7 yrs post transplant
Benefit sustained at 4.7 yrs post transplant
39 yo ♀, 2y s/p Lt MCA stroke
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)
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
Stanford Cerebrovascular Team 2018

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