Stem Cell Repair in Neuroscience

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New York University

Disclosure:
San-Bio research support
Brainlab research support
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University of Pittsburgh

Departments of Neurosurgery, Neurology and Rehabilitation Medicine, New York University
Traumatic Brain Injury and Chronic stroke are major health care problems.

There is no effective treatment once rehabilitation therapy is completed.

Options:

1. More rehabilitation therapy
2. Cortical stimulation during rehabilitation (research ongoing)
3. Cellular transplantation
2 episodes of left hand weakness with full recovery, each over 2-4 days.  
Active, driving, living alone.  
Installing solar panels onto churches.  
Age 83.
World Health Organization Disablement Model

I  II  III  IV  V

Problem    motor weakness    functional    quality of life    cost of care
balance, other deficits
to society

Limited participation
in life-role activities

Verbrugge and Jetta, 1994
…numerous small animal studies show recovery after cellular repair in stroke and cortical contusion TBI models
The Clinical Trial Issues

1. Is the bioengineered construct appropriate?
2. Inclusion: age, type of injury, size?
3. How many cells, implants?
4. How to implant cells?
5. Measuring outcome?
6. Immunosuppression?
7. Planning trials
Pre-Clinical Research

1. Cells have appropriate characteristics
2. Cells are safe in small & large animal models*
3. Cells graft into normal brain and survive*
4. Cells reverse deficits due to disease*
5. Animal models are relevant to human disease
6. Human surgical delivery tools are reliable
7. Outcomes tools available to assess results

Clinical Trials

* reproducible
Transplantation of cultured human neuronal cells for patients with stroke

D. Kondziolka, MD; L. Wechsler, MD; S. Goldstein, MD; C. Meltzer, MD; K.R. Thulborn, MD, PhD; J. Gebel, MD; P. Jannetta, MD; S. DeCesare, E.M. Elder, ScD; M. McGrogan, PhD; M.A. Reitman, MD; and L. Bynum, MD
First ever:
- Use of a manufactured human cell line
- Use of cryopreserved cells
- Use of cells not developed on-site
- Clinical transplantation study for stroke
Neurotransplantation for patients with subcortical motor stroke: a Phase 2 randomized trial

Douglas Kondziolka, M.D., Gary K. Steinberg, M.D., Ph.D., Lawrence Wechsler, M.D., Carolyn C. Meltzer, M.D., Elaine Elder, Sc.D., James Gebel, M.D., Sharon DeCesare, Tudor Jovin, M.D., Ross Zafonte, D.O., Jonathan Lebowitz, M.D., John C. Flickinger, M.D., David Tong, M.D., Michael P. Marks, M.D., Catriona Jamieson, M.D., Ph.D., Desiree Luu, R.N., Teresa Bell-Stephens, R.N., and Jeffrey Teraoka, M.D.

Departments of Neurological Surgery, Neurology, Radiology, Physical Medicine, Medicine, and Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania; and Departments of Neurosurgery, Neurology, Radiology, Hematology, and Physical Medicine and Rehabilitation, Stanford University, Stanford, California.
Evaluation of Surgical Techniques for Neuronal Cell Transplantation Used in Patients With Stroke

Douglas Kondziolka,* Gary K. Steinberg,† Sean B. Cullen,‡ and Michael McGrogan‡

*Department of Neurological Surgery, University of Pittsburgh and the McGowan Institute for Regenerative Medicine, Pittsburgh, PA
†Department of Neurosurgery, Stanford University, Stanford, CA
‡Layton BioScience, Inc., Sunnyvale, CA
Serial $^{18}$F Fluorodeoxyglucose Positron Emission Tomography after Human Neuronal Implantation for Stroke

Carolyn Cidis Meltzer, M.D., Douglas Kondziolka, M.D., Victor L. Villemagne, M.D., Lawrence Wechsler, M.D., Steven Goldstein, M.D., Keith R. Thulborn, M.D., Ph.D., James Gebel, M.D., Elaine M. Elder, Sc.D., Sharon DeCesare, Alan Jacobs, M.D.

Departments of Radiology (CCM, VLV, KRT), Psychiatry (CCM), Neurological Surgery (DK, SD), Neurology (LW, SG, JG), Pathology (EME), and the Stroke Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, and Layton BioScience, Inc. (AI), Sunnyvale, California
Neuropathology of the Graft

Clonal Human (hNT) Neuron Grafts for Stroke Therapy

Neuropathology in a Patient 27 Months after Implantation

P. T. Nelson,* D. Kondziolka,† L. Wechsler,‡
S. Goldstein,† J. Gebel,† S. DeCesare,†
E. M. Elder,‡ P. J. Zhang,* A. Jacobs,§
M. McGrogan,§ V. M.-Y. Lee,* and
John Q. Trojanowski*

From the Department of Pathology and Laboratory Medicine,*
the Division of Anatomical Pathology, University of
Pennsylvania, Philadelphia, Pennsylvania; the Departments of
Neurological Surgery‡ and Neurology,¶ University of Pittsburgh,
Pittsburgh, Pennsylvania; and Layton Bioscience, Incorporated,§
Sunnyvale, California

Am J Pathology, April 2002
Changes in cognitive function after neuronal cell transplantation for basal ganglia stroke

C.S. Stillely, PhD; C.M. Ryan, PhD; D. Kondziolka, MD, MSc, FRCSC; A. Bender, PhD; S. DeCesare, RN; and L. Wechsler, MD

Neurology, 2005
# Neuropsychological Test Battery: Univ. of Pittsburgh

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Visuospatial processing and Executive Functioning

control

6 months
Pre-surgery 6 months
Commentary

Who’s in Favor of Translational Cell Therapy for Stroke: STEPS Forward Please?

Michael Chopp,* Gary K. Steinberg,† Douglas Kondziolka,‡ Mei Lu,* Tonya M. Bliss,†
Yi Li,* David C. Hess,§ and Cesario V. Borlongan§‖

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§Department of Neurology, Medical College of Georgia, Augusta, GA, USA
‖Department of Neurosurgery, University of South Florida, Tampa, FL, USA

A consortium of translational stem cell and stroke experts from multiple academic institutes and biotechnology companies, under the guidance of the government (FDA/NIH), is missing. Here, we build a case for the establishment of this consortium if cell therapy for stroke is to advance from the laboratory to the clinic.

Key words: Stem cell transplantation; Tissue regeneration; Cellular therapy; Clinical translation
Cellular transplantation for the nervous system: impact of time after preparation on cell viability and survival

Laboratory investigation

GLENN T. GOBBEL, D.V.M., PH.D.,¹,² DOUGLAS KONDZIOLKA, M.D., M.SC., F.R.C.S.C.,¹,² WENDY FELLOWS-MAYLE, PH.D.,¹ AND MARTIN URAM, M.S.³

¹Department of Neurological Surgery, and ²McGowan Institute for Regenerative Medicine, University of Pittsburgh; and ³MEDRAD, Inc., Indianola, Pennsylvania
The Neural Stem Cell Niche

Figure adapted from: Watts C, et al. (2005) Anatomical perspectives on adult neural stem cells. J. Anat. (207) 197-208.
- Creation of a transplantable neurovascular niche for recovery
- Preclinical studies in rodents
- Creation of a preclinical subhuman primate model (monkey) of chronic stroke using endovascular technique
- Testing of the neurovascular construct in the monkey model
- Then: Human phase 1 clinical trial
Scaffold implant covers area of damage
Neuroscaffold fills lesion cavity
Traumatic Brain Injury

- Mechanisms for cellular repair
- Neurotrophin release vs cellular integration
- Specific injury types suitable for research
- Acute vs chronic TBI models
- Human trials
A Novel Phase 1/2A Study of Intraparenchymal Transplantation of Human Modified Bone Marrow Derived Cells in Patients with Stable Ischemic Stroke

Gary K. Steinberg, MD, PhD*, Douglas Kondziolka, MD†, Neil E. Schwartz, MD, PhD*, Lawrence Wechsler, MD†, Dade Lunsford, MD†, Maria L. Coburn, BA*, Julia B. Billigen, RN†, Hadar Keren-Gill, MA*, Michael McGrogan, PhD#, Casey Case, PhD#, Keita Mori, MBA#, Ernest W. Yankee, PhD#

*Departments of Neurosurgery and Neurology and Stanford Stroke Center
Stanford University, Stanford CA

†Departments of Neurological Surgery and Neurology,
University of Pittsburgh, Pittsburgh, PA

#SanBio, Inc, Mountain View, CA
SanBio SB623
Phase 1/2a Clinical Study

1st intracerebral trial in North America

Bone Marrow Aspirate

MASC Cells

Expression Vector

Cryopreserved SB623 Cells

Transfection and Selection

Expansion

Adult bone marrow derived stromal cells
Transient Notch Transfection Causes Changes in the Differentiated State
Notch Transfection Improves MSC Function in Experimental Stroke (MCAo)

Balance Beam

Limb Placing

Morris Water Maze (Memory Component)

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

![Graph showing the loss of pN-2 plasmid copies per genome during propagation.](image)
Mechanisms of recovery from stroke after transplanted MSCs?

Bone Marrow Derived Stem Cells

Exogenous Bone Marrow Derived

Trophic/Growth Factors

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

Enhanced endogenous brain repair mechanisms and plasticity

Neural Progenitor Cells

Neurons

Endothelial Cells

Oligodendrocytes

Astrocytes
SB623 Mechanism(s) of Action?

- **Trophic Factors**
  - BMP-4/7, DKK-1, FGF-7, HG-EGF, IL-6/8, MCP-1, MMP-1, PDGF-AA, VEGF

- **Extracellular Matrix**
  - Enhance neurite outgrowth

- **Anti-inflammatory effects**
  - SB623 prone to phagocytosis to suppress inflammation
  - Reduces inflammation caused by mixed lymphocyte reaction

Robust Potency via Multiple MOAs
SB623 Cells are Phagocytosed by Activated Microglia (Host Innate Immunity)
Sub-human Primate Studies

**Figure 47**  Primate Needle Track

Male SB623 cells are localized in the female primate brain using Y chromosome in-situ hybridization. SB623 cells show up as brown against a blue background. The needle track is shown.

**Figure 48**  Primate Y-ISH Staining

A close-up of Y-ISH staining of SB623 cells implanted in primate brain.

<table>
<thead>
<tr>
<th>Animal Species/Model</th>
<th>Study Type</th>
<th>SB623 Dose, Route</th>
<th>Results</th>
<th>Study Reference</th>
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</table>
| Cynomolgus Monkey    | Pilot primate safety and SB623 survival| One-time administration  
 and SB623 survival 7 days                             | Minimal evidence of cell death or necrosis of the host tissue  
 Total 5.8 million cells per hemisphere in 4 needle tracks in either cortical or subcortical areas  
 No local or systemic toxicities at 7d  
 SB623 cells persist for at least 7d by Y-ISH assay | N-03213 (SanBio PSP021) |
SB623 Cells are Present 1 Month Post-implant, but not at 2 Months

Human Nuclear Matrix Ab

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Six Month EBST

Cells transplanted 1 month after stroke
Cells transplanted 1 month after stroke
CsA is not Needed: Six Month EBST

Rats Administered SB623 One Month Following MCAo. Evaluated Over Six Months for Locomotor Function by Elevated Body Swing Test.

Cells transplanted 1 month after stroke
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
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)
  - 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) 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

18 pts treated
6 with 2.5M, 6 with 5M
6 with 10M

12 Stanford
6 Univ Pittsburgh
Evaluation of Surgical Techniques for Neuronal Cell Transplantation Used in Patients With Stroke

Douglas Kondziolka,§ Gary K. Steinberg,† Sean B. Cullen,‡ and Michael McGrogan‡

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†Department of Neurosurgery, Stanford University, Stanford, CA
‡Layton BioScience, Inc., Sunnyvale, CA

J Neurosurg 113:666–672, 2010

Cellular transplantation for the nervous system: impact of time after preparation on cell viability and survival

Laboratory investigation

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1Department of Neurological Surgery, and 2McGowan Institute for Regenerative Medicine, University of Pittsburgh, and 3MEDRAD, Inc., Indiana, Pennsylvania

Object. Cell transplantation has shown promise for the treatment of various neurological disorders, but the factors that influence cell survival and integration following transplantation are poorly understood. In fact, little is known regarding how simple but potentially critical variables, including the method of cellular preparation and administration, might affect transplant success. The goal of the present study was to determine the impact of time between tissue preparation and implantation on cellular viability. Time can vary with cell preparation, delivery to the operating room, and surgical technique. This study was also designed to evaluate the sensitivity of various methods of assessing implant viability.

Methods: Cell lines of neural progenitor cells and bone marrow stromal cells were generated from healthy adult mice. On the day of experimentation, the cells were collected, suspended in a balanced salt solution, and sequentially assessed for viability for up to 3.5 hours based on their appearance under phase-contrast microscopy, their ability to retain a fluorescent dye, and their attachment to a cultivation surface for 24 hours.

Results: When viability was measured based on the ability of cells to retain a fluorescent dye, there was a decrease in viability of 10–15% each hour. Based on the ability of the cells to attach to a culture surface and grow for 24 hours, viability decreased more rapidly at approximately 20% per hour. In addition, only about one-third of the cells judged viable based on phase-contrast microscopy or acute dye retention were found to be viable based on plating, and only 10% of the cells initially judged as viable were still capable of survival after 3 hours in suspension.

Conclusions. The authors’ results indicate that that there can be significant losses in viability between preparation and implantation and that more sophisticated methods of evaluation, such as the ability of cells to attach to a substrate and grow, may be required to detect decreases in viability. The time between preparation and implantation will be an important factor in clinical trial design. (DOI: 10.3171/2009.10.JNS09252)
Fig. 2. Graphs of cell number and viability as a function of time after preparation as measured by phase contrast (top) and uptake of a red fluorescent dye by viable cells (lower). The experiment was carried out in BMSCs (left) and NPCs (right). Each point represents the mean ± SEM of 3 aliquots of cells collected at between 30 minutes and approximately 3.5 hours after preparation.

**Figure 2.** Concentration of viable bone marrow stromal cells (BMSCs) (A) and neural progenitor cells (NPCs) (B) within the delivered volume as measured immediately after a series of injections. Each series consisted of a single withdrawal of the cell solution followed by 3 subsequent 10-μL injections. When indicated, *p < 0.05; **p < 0.01; †p < 0.01.
Serious Adverse Events
(requiring hospitalization)

Seizure

Asymptomatic subdural hygroma/hematoma (drained)

Pneumonia

Worsened neurologic symptoms (paresthesias/dysphagia)
(16 mos; no new infarct; resolved <48 hrs)

UTI

None related to cells
No 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
Clinical Outcome

ESS

Change from Baseline (+SEM)

Months Post-treatment

P=.003

P=.02

P=.004

n=18

n=17

n=17

n=15

n=12

n=9
Clinical Outcome

NIHSS

Change from Baseline (+SEM)

Months Post-treatment

P=.004

P=.03

P=.0006

n=18

n=17

n=17

n=17

n=15

n=12

n=9
Clinical Outcome

Fugl-Meyer

Change from Baseline (+SEM)

Months Post-treatment

P=.0002
n=17

P=.0006
n=15

P=.000006
n=12

n=9
Figure 53: Mean FMMS Change from Baseline for Patients Who Did Achieve Versus Did Not Achieve Clinically Meaningful Improvement (>10 Points)
MRI (FLAIR)

1 d post-op 1 wk post op 2 mos post op

(DWI negative)

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39 yo ♀, 2y s/p Lt MCA stroke

(benefit sustained at 8 mos)

Pre-op MRI

MRI (FLAIR)

1 d post op

1 wk post op

2 mos post op
DTI (fiber tracts)

Pre-op

Post-op
Pre-implant post day 1 post day 7

Post-implant contrast enhancement at cell delivery site

Post day 30
Post-implantation MRI flair images after cell delivery, 3 tracks
Post implant contrast enhancement along the surgical tracks

1-4 weeks

8 weeks
Pre-implant  post implant day 1  one month
Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

Gary K. Steinberg, MD, PhD; Douglas Kondziolka, MD; Lawrence R. Wechsler, MD; L. Dade Lunsford, MD; Maria L. Coburn, BA; Julia B. Billigen, RN, BS; Anthony S. Kim, MD, MAS; Jeremiah N. Johnson, MD; Damien Bates, MD, PhD; Bill King, MS; Casey Case, PhD; Michael McGrogan, PhD; Ernest W. Yankee, PhD; Neil E. Schwartz, MD, PhD

Background and Purpose—Preclinical data suggest that cell-based therapies have the potential to improve stroke outcomes.

Methods—Eighteen patients with stable, chronic stroke were enrolled in a 2-year, open-label, single-arm study to evaluate the safety and clinical outcomes of surgical transplantation of modified bone marrow–derived mesenchymal stem cells (SB623).

Results—All patients in the safety population (N=18) experienced at least 1 treatment-emergent adverse event. Six patients experienced 6 serious treatment-emergent adverse events; 2 were probably or definitely related to surgical procedure; none were related to cell treatment. All serious treatment-emergent adverse events resolved without sequelae. There were no dose-limiting toxicities or deaths. Sixteen patients completed 12 months of follow-up at the time of this analysis. Significant improvement from baseline (mean) was reported for: (1) European Stroke Scale: mean increase 6.88 (95% confidence interval, 3.5–10.3; P<0.001), (2) National Institutes of Health Stroke Scale: mean decrease 2.00 (95% confidence interval, −2.7 to −1.3; P<0.001), (3) Fugl-Meyer total score: mean increase 19.20 (95% confidence interval, 11.4–27.0; P<0.001), and (4) Fugl-Meyer motor function total score: mean increase 11.40 (95% confidence interval, 4.6–18.2; P<0.001). No changes were observed in modified Rankin Scale. The area of magnetic resonance T2 fluid-attenuated inversion recovery signal change in the ipsilateral cortex 1 week after implantation significantly correlated with clinical...
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<td>Open-label, Phase 1/2a Study of the Safety and Efficacy of Modified Stromal Cells (SB623) in Patients with Stable Ischemic Stroke</td>
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<td>2 years</td>
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<td>48 weeks follow-up</td>
<td>Sham, 2.5M, 5M SB623 cells</td>
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<tr>
<td>TBI-01</td>
<td>Double-Blind, Controlled Phase 2 Study of the Safety and Efficacy of Modified Stem Cells (SB623) in Patients with Chronic Motor Deficit from Traumatic Brain Injury (TBI)</td>
<td>52 (Planned)</td>
<td>48 weeks follow-up</td>
<td>Sham, 2.5M, 5M, 10M SB623 cells</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>