



VICKIE AND JACK FARBER INSTITUTE FOR NEUROSCIENCE
OUTCOMES & RESEARCH: VOLUME 3

NEUROVASCULAR TREATMENTS FOR ANEURYSMS AND STROKE



A MESSAGE FROM THE PRESIDENT/CEO, VICKIE AND JACK FARBER INSTITUTE FOR NEUROSCIENCE

Dear Colleagues,

It is an especially exciting time at Thomas Jefferson University Hospital's Department of Neurosurgery and the Vickie and Jack Farber Institute for Neuroscience – Jefferson Health. I am pleased to be sending you the third volume of our series that describes innovative research and superior patient care that our departments and physicians are engaged in at Jefferson. The first in our series described ongoing research in spinal cord injury with a focus on cell-based therapies and our second brochure detailed research into cognitive functioning in temporal lobe epilepsy.

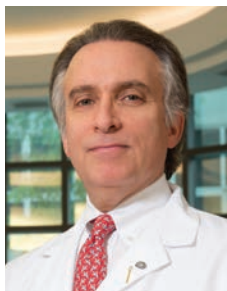
In this current volume, we highlight the work Jefferson Health is engaged in on aneurysm and stroke. This includes Dr. Pascal M. Jabbour's use of a trans-radial approach for neuro-interventions for aneurysms, AVMs, and stroke, which has been published and is notable. Dr. Jabbour, Chief, Division of Neurovascular Surgery and Endovascular Neurosurgery, is one of the first to use this type of endovascular technique for the treatment of neurovascular diseases.

Also, at Jefferson Health and highlighted in this brochure is research on stem cells and stroke where my team is about to embark on a clinical trial, led by myself and Dr. Lorraine Iacovitti, Professor of Neuroscience and Director, Jefferson Health Stem Cell and Regenerative Neuroscience Center. The clinical trial will examine the promise of autologous bone marrow stem cell treatment in patients with ischemic stroke. This emerging work is based on earlier rat models, which are described in the following pages.

At Jefferson Health, we value our clinicians and researchers who contribute to the well-being of patients with neurological impairment and disability. We continue to utilize treatments, such as trans-radial approaches and stem cell interventions, for patients with aneurysms and stroke as well as striving to provide exceptional care for patients with spinal cord injury, epilepsy, and other neurological conditions using treatments based on substantive research.

I invite you to explore these innovative treatment options for our patients in the following pages. I hope you will find it informative to read about some of the ways we are working to enhance the quality of life for our neurological patients.

Sincerely,



A handwritten signature in black ink that reads "Robert H. Rosenwasser". The signature is fluid and cursive, with a long horizontal flourish at the end.

Robert H. Rosenwasser, MD, MBA, FCS, FAHA
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TRANSRADIAL APPROACH FOR THE TREATMENT OF BRAIN ANEURYSMS

Pascal Jabbour, MD, Professor of Neurosurgery, Chief, Division of Neurovascular Surgery and Endovascular Neurosurgery, is engaged in research on aneurysms, stroke, arteriovenous malformation and other neurovascular disorders. It is his work with patients with aneurysms, however, that is gaining national attention.

Currently, there has been an increase in the use of the transradial approach (TRA) among neurointerventionalists, even though few studies in the neurosurgical literature actually demonstrate its benefit and use. In a recent study, Jefferson Health neurosurgeons successfully treated patients with aneurysms using TRA.

TRA Approach for Flow Diversion

Neurointerventionalists most commonly use the transfemoral approach (TFA) – threading instruments through arteries in the groin – for the treatment of aneurysms. This approach has shown to carry challenges, and occasionally limitations, for patients (e.g., femoral atherosclerotic disease or aberrant anatomy of the aortic arch). Jefferson researchers under Dr. Jabbour’s direction are demonstrating that TR surgery, done via the wrist, is safe and effective for a broad range of neuroendovascular procedures. TRA can provide faster recovery with less procedural risk for patients.

In one study, 598 aneurysms (Table 1) were studied retrospectively using either TFA or TRA with Pipeline Embolization Device (PED). The average age of patients was 55.5 years, and 84.28% (n=504) were female. There was no significant difference between both TFA and the TRA in procedural duration, complication rate, morbidity or aneurysm obliteration. The characteristics of the aneurysms in this study are shown in Table 2.

Table 1. Treatment Details

VARIABLE	FEMORAL	RADIAL	P-VALUE
Total Number of Aneurysms	97 % (N=580)	3 % (N=18)	
Length of Hospital Stay	1 ± 5.95 % CI: 2 – 2.9	4.3 ± 6 95 % CI: 1.2 – 7.4	0.12
Procedure Duration (mins)	50 ± 32. 95 % CI 47- 53	49 ± 16.5 95 % CI 41-57	0.916

REFERENCES

1. Sweid A, Starke RM, Herial N, Chalouhi N, Xu V, Shivashankar K, Velagapudi L, Tjournakaris S, Gooch MR, Hasan D, Zarzour H, Rosenwasser RH, Jabbour P. Transradial approach for the treatment of brain aneurysms using flow diversion: feasibility, safety, and outcomes. *J Neurosurg Sci.* 2019 Jul 11. doi: 10.23736/S0390-5616.19.04761-1. [Epub ahead of print]
2. Khanna O, Sweid A, Mouchtouris N, Shivashankar K, Xu V, Velagapudi L, Stricsek G, Amllay A, Texakalidis P, Gooch MR, Tjournakaris S, Rosenwasser RH, Jabbour PM. Radial Artery Catheterization for Neuroendovascular Procedures. *Stroke.* 2019 Sep;50(9):2587-2590. doi: 10.1161/STROKEAHA.119.025811. Epub 2019 Jul 17.

Patients were started on dual antiplatelet therapy (aspirin [81 mg] and clopidogrel [75 mg daily]) for ten days. Once ready for the procedure, patients had the right wrist prepped and draped. Radial artery catheterization was achieved using ultrasound guidance via the double wall puncture technique (Figures 2A and 2B). There were no access site complications in the TRA group compared with 2% in the TFA approach.

Patients were followed and seen for 60 months after the procedure, with treatment response determined by aneurysm occlusion. In selected patients, TRA was seen as a valid approach for the endovascular treatment of acute ischemic stroke and offers better safety with high rates of procedural success. The main advantage of using TRA as shown in this study was lower access site complications, high patient satisfaction, lower hospital costs and early mobilization.

Table 2. Aneurysms Characteristics

	% (N)
Aneurysm size	8.5 + 6.1 95 % CI: 8 – 9
Aneurysm forms	
Saccular	87.3 % (n=522)
Fusiform	6.7 % (n=40)
Dissecting	5.5 % (n=32)
Blister	0.7 % (n=4)

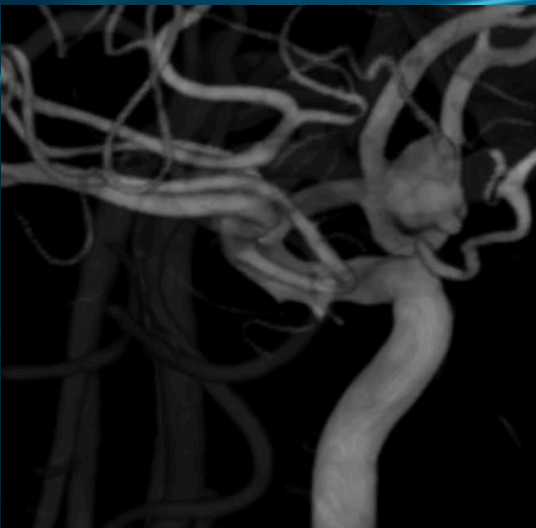


Figure 1. A 3D reconstruction angiogram (right internal carotid artery injection) showing the anterior communicating artery (AComm) aneurysm with excrescences.
Source: Pascal Jabbour, MD

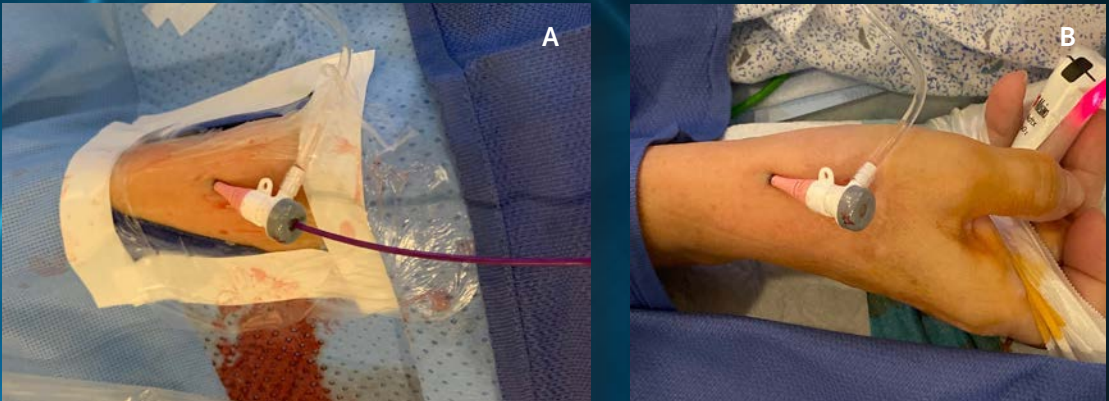


Figure 2. A) The Simmons 2 catheter being introduced in the sheath. B) The sheath in the distal right radial artery at the anatomical snuffbox. Source: Pascal Jabbour, MD

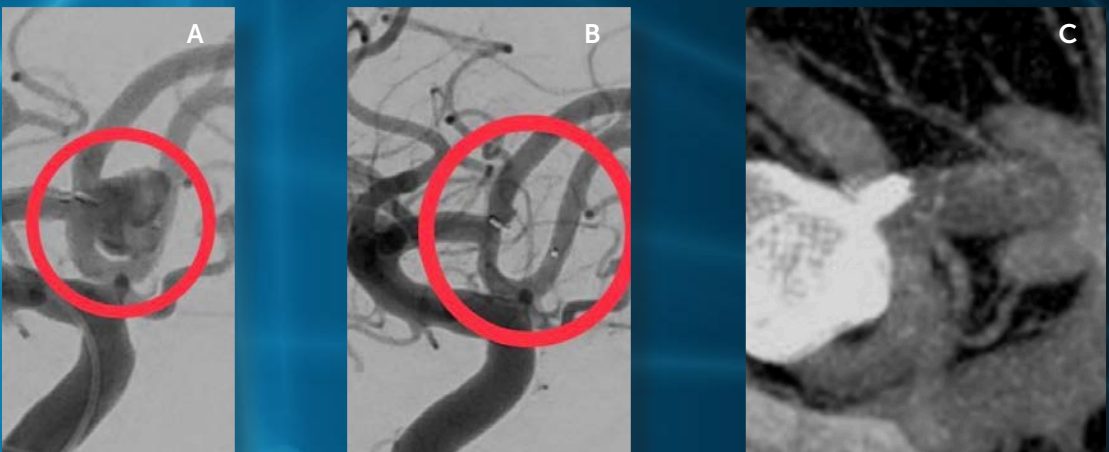


Figure 3. A) A right-sided internal carotid artery injection showing the aneurysm at the time of the treatment with the WEB device. B) A 6 months follow up angiogram showing a complete occlusion of the aneurysm. C) An expert CT (biplane) showing the WEB device fully deployed in the aneurysm at the time of treatment. Source: Pascal Jabbour, MD



Figure 4. A) The preludesync distal closure device over the arteriotomy site in the anatomical snuffbox. B) Picture of the anatomical snuffbox in the radial part of the wrist. It is a triangular depressed groove that is bordered by the tendons of the abductor pollicis longus and extensor pollicis brevis laterally, and the extensor pollicis longus medially. Source: Pascal Jabbour, MD

TRA for Newly FDA-Approved Devices

Dr. Jabbour and his researchers studied three new FDA-approved devices (Table 3), which offer the latest advances in endovascular aneurysm treatment – significantly expanding options available for endovascular treatment of cerebral aneurysms.

A review of 10 patients with an unruptured cerebral aneurysm treated via a TR cerebral angiogram was performed. Aneurysms treated in this series included internal carotid artery bifurcation, middle cerebral artery, anterior communicating artery, basilar tip and posterior communication artery.

All patients underwent radial artery catheterization and none of them had to be converted to femoral artery access. None of the patients had any postoperative complications and were discharged the following day. The patients’ neurological examinations had been assessed preoperatively and then postoperatively using the modified Rankin scale.

Radial artery catheterization has been recently popularized for cerebral angiography with preferential use in diagnostic procedures, yet the paucity of literature on this topic accounts for hesitation in the use of new devices. Dr. Jabbour’s preliminary experience with these 10 patients revealed no limitations during catheterization and deployment of these devices. While this series involves a small number of patients, the goal was to share the experience of using TR access for these new devices in an effort to optimize the procedural workflow and establish radial artery catheterization as the mainstay vascular access, given its lower risk of complications and greater patient satisfaction.

Table 3. Devices Used in the Study

DEVICE	NUMBER OF PATIENTS	MANUFACTURER
Woven EndoBridge (WEB) Aneurysm Embolization	7	Sequent Medical Inc., Aliso Viejo, CA
Surpass Streamline Flow Diverter	2	Stryker Neurovascular, Fremont, CA
PulseRider Aneurysm Neck Reconstruction Device	1	Pulsar Vascular, Inc., Los Gatos, CA

REFERENCE

1. Mouchtouris N, Al Saiegh F, Sweid A, Amllay A, Tjoumakaris S, Gooch R, Rosenwasser R, Jabbour PM. Transradial Access for Newly Food and Drug Administration-Approved Devices for Endovascular Treatment of Cerebral Aneurysms: A Technical Note. *World Neurosurg.* 2019 Jul 26;131:6-9. doi: 10.1016/j.wneu.2019.07.149. [Epub ahead of print]

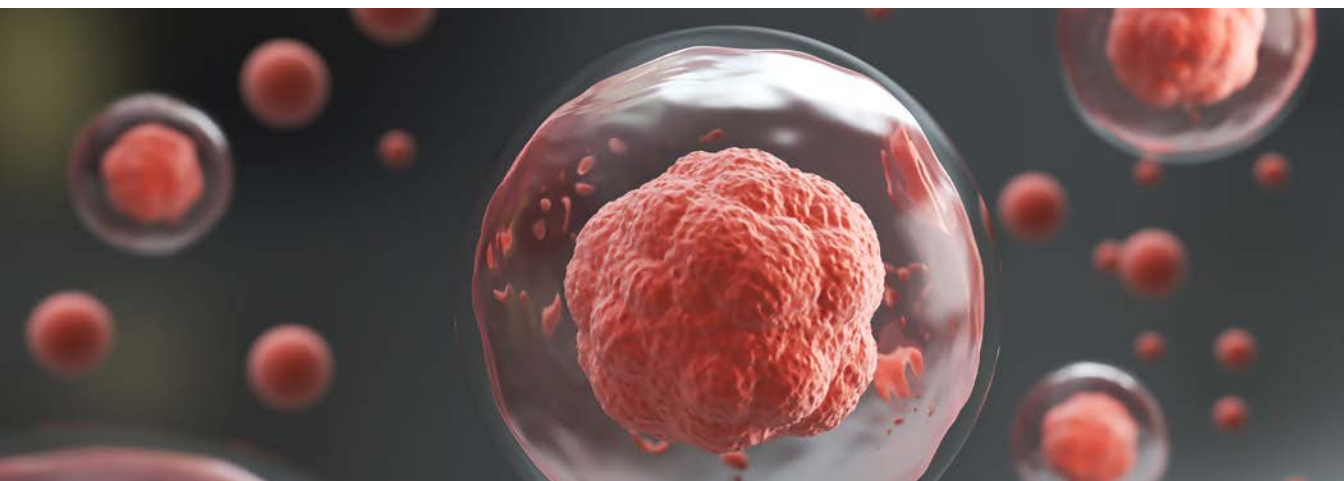
EMERGING TREATMENT FOR STROKE USING STEM CELLS

Robert H. Rosenwasser, MD, Professor and Chair, Department of Neurological Surgery, and President/CEO, Vickie and Jack Farber Institute for Neuroscience and Lorraine Iacovitti, PhD, Professor of Neuroscience, and Director, Jefferson Health Stem Cell and Regenerative Neuroscience Center, are revolutionizing the way neurological diseases and disorders are studied, and possibly treated.

Innovative research always begins with basic science. Twelve years ago, in the Joseph and Marie Field Cerebrovascular Research Laboratory – Jefferson Health, scientists undertook a series of studies using stem cells in animals with induced stroke. Today, Drs. Iacovitti and Rosenwasser and their teams are using collective data based on many years of research experience to begin a clinical study on patients based on these earlier animal studies, which we describe below.

Phase I/II Clinical Trial

A patient study on stem cell treatment for stroke has recently been submitted to the Food and Drug Administration, and we expect to begin recruiting patients in the very near future. Currently, there are no patient efficacy studies or results based on the use of autologous bone marrow stem cells in patients. In this study, stem cells are harvested from the patient's own bone marrow and expanded in number in Jefferson's Bone Marrow Transplant Facility. These autologous cells will then be stereotactically transplanted into the region surrounding the brain infarct in stroke patients. This clinical trial derives from earlier animal studies by Drs. Iacovitti and Rosenwasser, detailed below, and a recent clinical trial using commercially-derived genetically modified allogenic bone marrow stem cells.



REFERENCE

1. Steinberg GK, Kondziolka D, Wechsler LR, Lunsford LD, Kim AS, Johnson JN, Bates D, Poggio G, Case C, McGrogan M, Yankee EW, Schwartz NE. Two-year safety and clinical outcomes in chronic ischemic stroke patients after implantation of modified bone marrow–derived mesenchymal stem cells (SB623): a phase 1/2a study. *J Neurosurg*. 2018. Published online November 23, 2018; DOI: 10.3171/2018.5.JNS173147.

Bone Marrow Stem Cells (BMSCs) in Ischemic Stroke Rats

In 2010, one of the first studies on the effects of bone marrow stromal stem cells (BMSC) in stroke was undertaken. Dr. Ming Yang and colleagues, under the direction of Dr. Iacovitti, argued that the administration of BMSCs after stroke produced a marked reduction in the size of the infarct, long-term sensorimotor recovery and changes in brain inflammatory vascular elements. This study examined the effects of rat and human BMSCs at early and later times following middle cerebral artery occlusion (MCAO) in rats on blood cytokines growth factors, brain glia, and motor behavior.

This study demonstrated that the peripheral administration of BMSCs following MCAO produced profound changes in the host animal, resulting in preserved brain structure and long-lasting improvement in motor function. The timing of stem cell treatment was critical to the magnitude of the observed effects with BMSCs administered soon (1 day) after the ischemic event – producing greater recovery in function than in treatment 1 week later (Figure 1). The study suggested that stem cells induce an important neuroprotective and/or regenerative response in the host organism.

REFERENCE

1. Yang M, Wei X, L Iacovitti. Administration of bone marrow stem cells acutely after stroke produces long-term sensorimotor recovery and changes in brain inflammatory and vascular elements. *Cell Transplantation*. 2010 Apr 21, 19(9):1073-1084. PMID:20412636

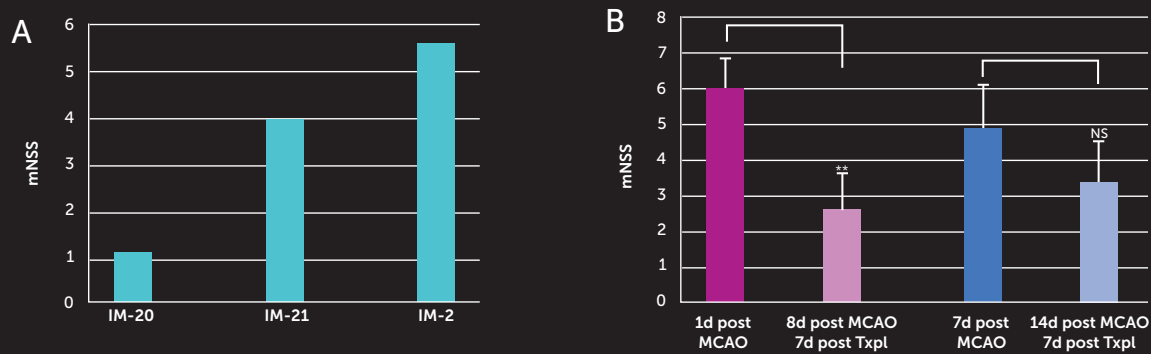
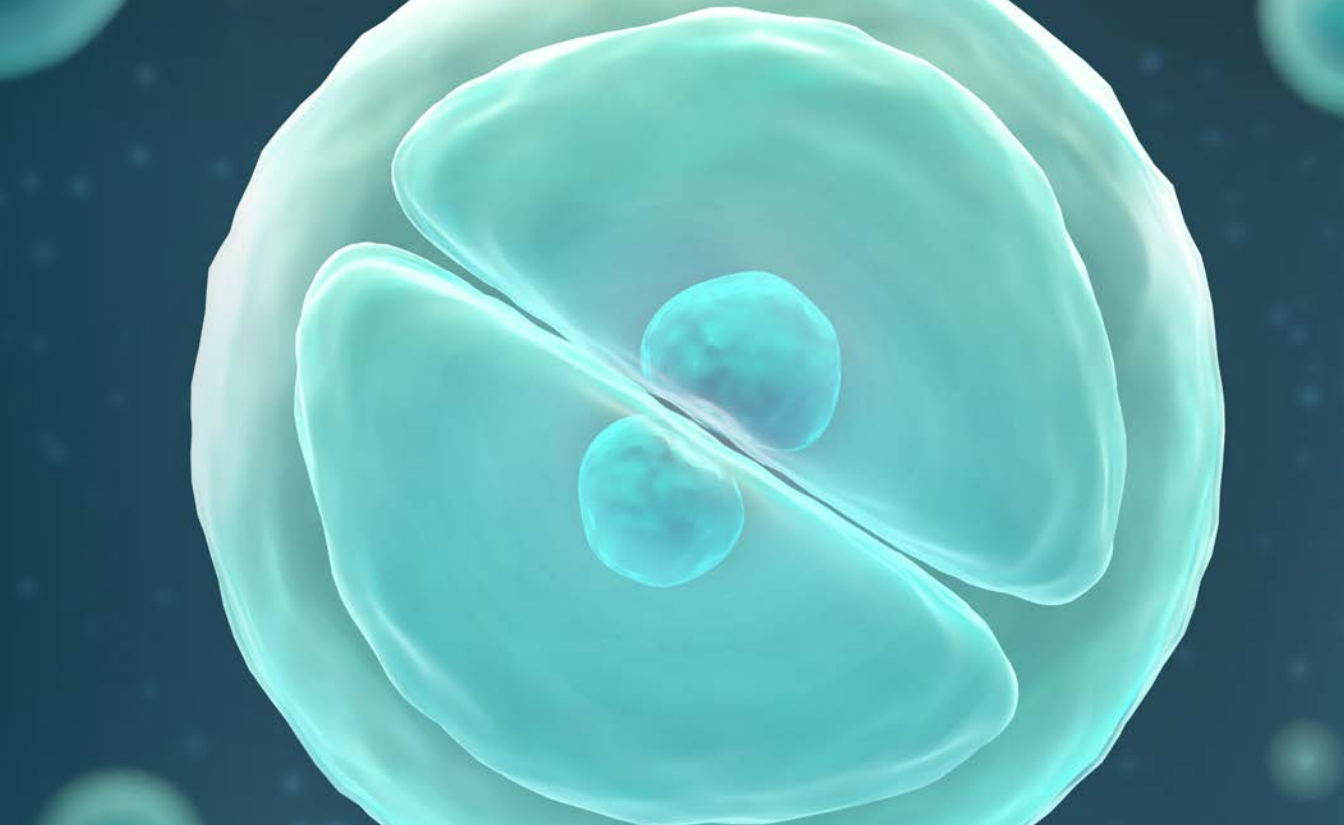


Figure 1. Functional deficits after middle cerebral artery occlusion (MCAO) are proportional to the size of the infarct and change with systemic administration of bone marrow stromal cells (MSCs). Shown in (A) are the individual modified neurological severity score (mNSS) scores for three MCAO rats (IM-2, IM-20, IM-21). Shown in (B) are motor behavior assessments before and after systemic administration of MSCs in the MCAO rat. Tail vein injections of hMSCs (N = 14) (shown) or rMSCs (N = 14) (data not shown) were administered to half of each experimental group either 1 day after MCAO or 7 days after MCAO; 7 days posttransplant (Txpl) motor behavior was assessed again using the mNSS scale. **p < 0.001, a comparison of scores at 1 day post-MCAO with scores 1 week later after hMSC transplantation.

Source: Lorraine Iacovitti, PhD



Tracking Transplanted Bone Marrow Stem Cells

In 2013, Goldmacher et al, employed imaging techniques to track the journey followed by radio-labeled or fluorescently labeled rat bone marrow stromal stem cells (BMSC) after systemic injection into rats with experimental stroke caused by MCAO. As in the Yang study above, the effects of BMSC treatment on blood cell composition, brain glia, and sensorimotor behavior was studied and compared to that which occurred spontaneously during the normal recovery process after stroke.

The effects of BMSC treatment on blood cell composition, brain glia and sensorimotor behavior was chronicled during an extended period following infarction and compared to those that occur during normal spontaneous recovery from stroke. While brain structure and function can partially recover from experimental stroke, peripheral administration of BMSCs greatly increases the extent of that recovery. The latter occurs despite the fact that the vast majority of BMSCs remain in the periphery after systemic injection into the MCAO rat where they produce changes in blood cell composition (Figure 2-3). Likewise, in the brain where few injected BMSCs endure long term, there are dramatic changes in the number and activation of astroglia and microglia in the region of the infarct that is correlated with an improvement in behavioral measures.

This study concludes that the sustained recovery in sensorimotor function observed in BMSC-treated MCAO rats is likely due to the changes in blood and/or brain cells and/or their cytokine/growth factor products.

It is only through these earlier studies that a clinical trial on stem cell therapies in stroke patients would be possible.

REFERENCE

1. Goldmacher GV, Nasser R, Lee DY, Yigit S, Rosenwasser R, Iacovitti, L. Tracking transplanted bone marrow stem cells and their effects in the rat MCAO stroke model. *PLoS One* 2013;8(3). PMID:23555879.

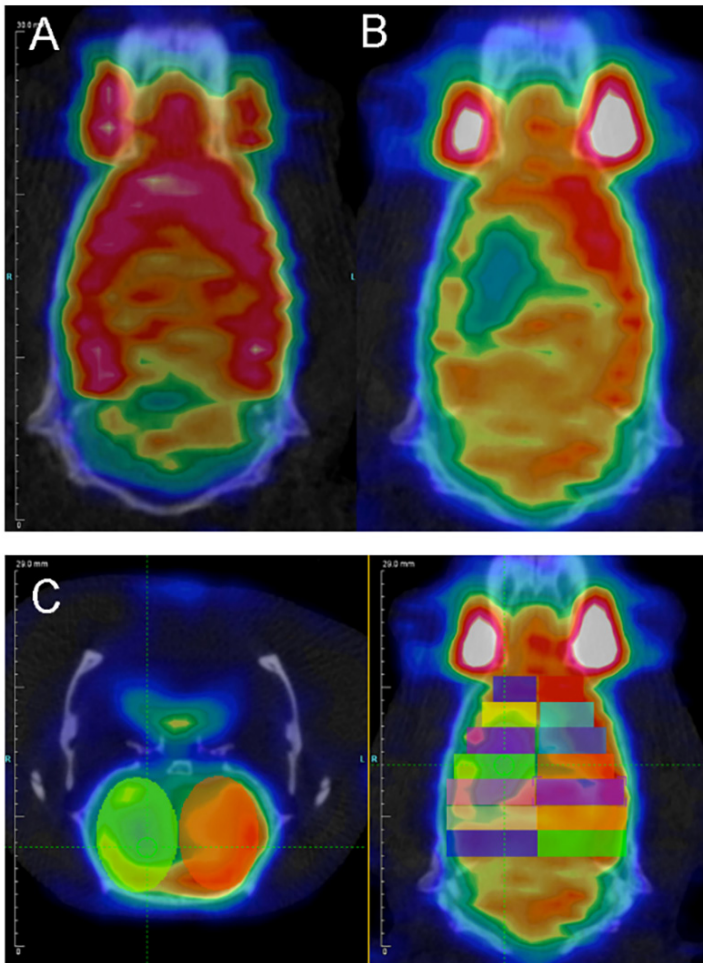


Figure 2. Analysis of infarct severity and extent on PET/CT imaging in representative sham and MCAO brains. A. Coronal view of a sham-operated animal showing normal symmetrical glucose uptake. B. One day post-MCAO, there is decreased uptake on the side of the infarct. C. Axial and coronal images showing placement of 2 mm thick ovoid regions of interest (ROIs) [symmetrical across the midline, arbitrary colors] across the cerebral hemispheres. D. Mean standardized uptake value (SUV) ratios (infarcted to contralateral side ROI) are plotted against slice position comparing infarcted and sham-operated control rat shown in A–C. The severity of the infarct is reflected both by the number of slices affected, and the degree to which activity is suppressed (relative to normal) in each slice. Over 4 weeks, there was a modest spontaneous improvement in FDG uptake, which correlated with the improvement seen in mNSS scores from 6 to 4 (not shown). Imaging was repeated for 3 sham-lesioned and 3 MCAO lesioned rats. doi:10.1371/journal.pone.0060049.g001.

Source: Goldmacher et al., *PLOS One*, 8:60049, 2013

D SUV ratio across cerebral hemispheres



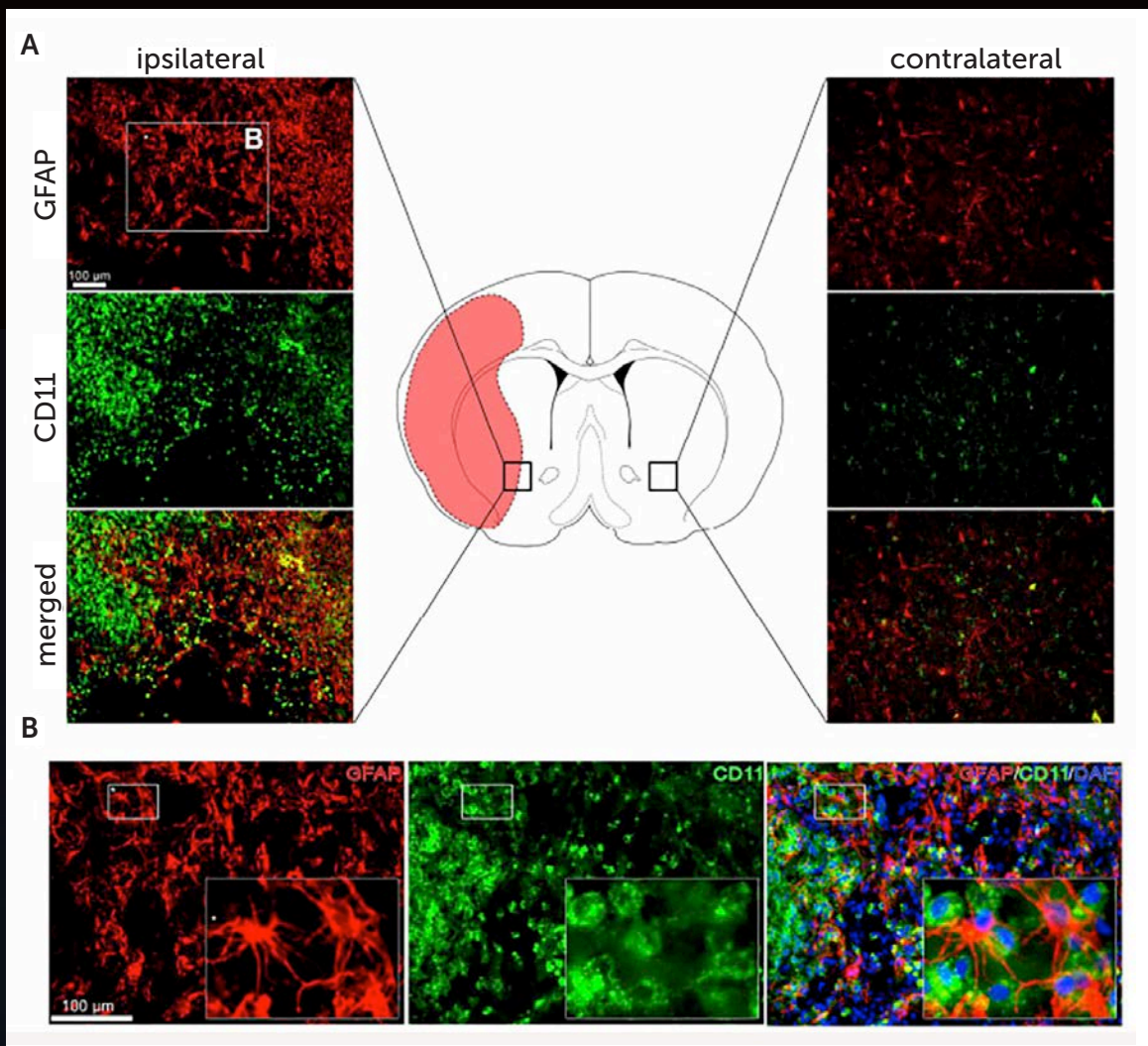


Figure 3. Immunocytochemical analysis of reactive glia and activated microglia in the region of the infarct 4 weeks after BMSC treatment in MCAO rats. Panel A. Representative section through the brain of MCAO rat (center) showing area of infarction (red). Area in rectangle on ipsilateral (left) or contralateral (right) sides of MCAO shown enlarged after staining with GFAP (reactive astrocytes) and CD11 (activated microglia) or merged images in side panels. Panel B. Area labeled "B" in rectangle of Panel A is shown at higher power after staining for GFAP or CD11; Insets: magnified small rectangles of B. Bars in A and B = 100 μm. (N = 4). doi:10.1371/journal.pone.0060049.g006.

Source: Goldmacher et al., *PLOS One*, 8:60049, 2013



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