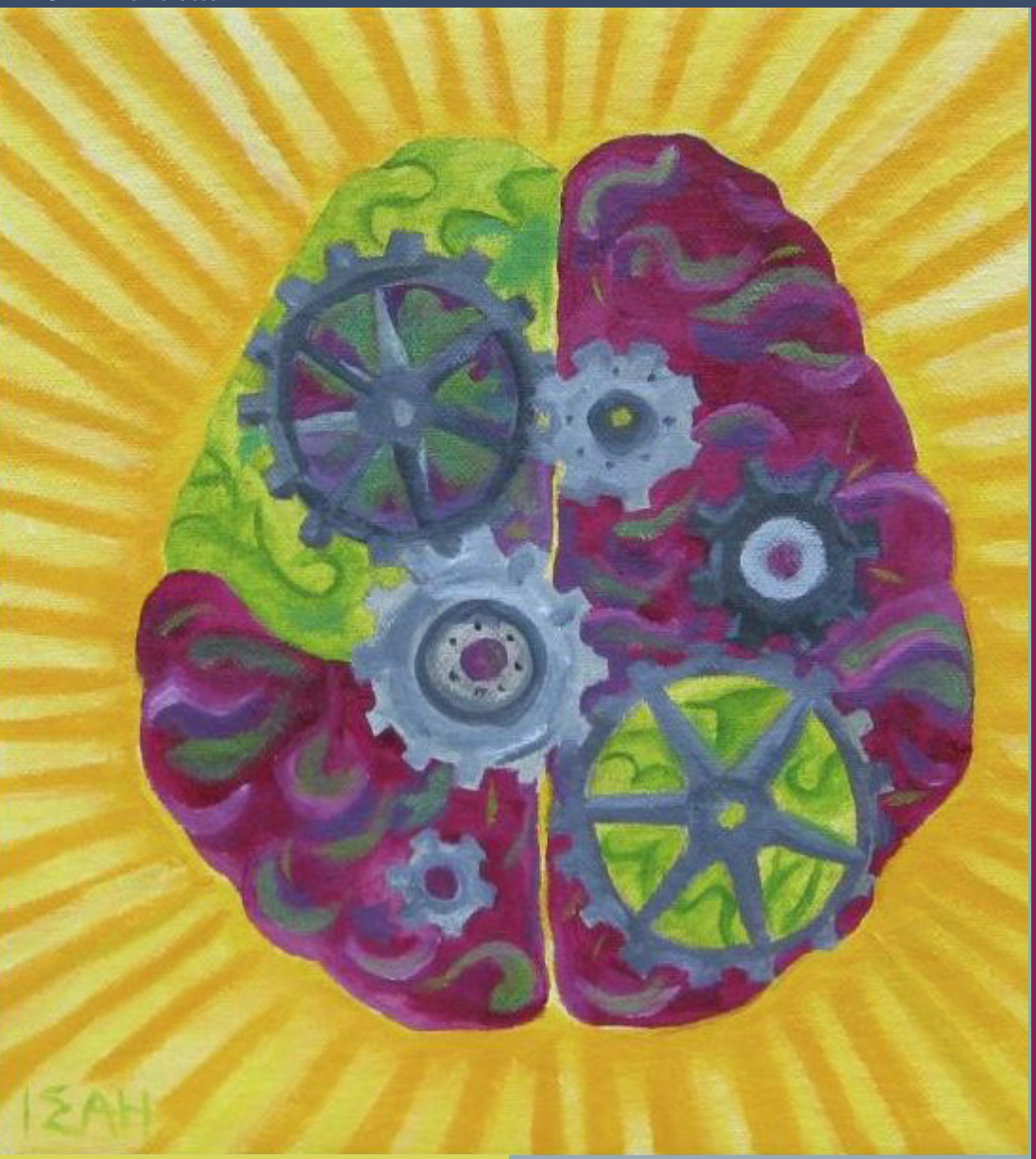
Society of Vascular and Interventional Neurology

THE CORE

SVIN Newsletter September 2015



'Thinking Machine' by Leah Guzman

SVIN FUNDRAISER

30% of proceeds go to SVIN

Leah Guzman will present her beautiful Brain Series paintings at the SVIN 2015 Annual Meeting and **30% of the proceeds** from her sales will go to SVIN. She will also offer this promotion again for any purchases generated from the September Newsletter. To view her artwork and make your purchase, please visit her website: www.leahguzman.com

Leah Guzman, ART-BC
The Artful Experience

In This Issue

Editor's Corner
p. 2

Fellow of SVIN Program (FSVIN)
p. 3

SVIN 3rd Annual Stroke Center Workshop & 8th Annual Meeting
p. 4

Acknowledgement of SVIN Top Supporters
p. 5

Mobile Stroke Treatment Unit
p. 6 - 7

Visualization and Role of Collateral Supply in Acute Ischemic Stroke
p. 7 - 11

An Update on Cell Therapy for Stroke
p. 11 - 14

Stroke Trial Network fellowship
p. 15

Editor's Corner

Mouhammad A. Jumaa, MD

Ashutosh P. Jadhav, MD, PhD

In this edition of The CORE, we are very pleased to include several contributions from SVIN members and reviews of recent trials. Our authors discuss new and exciting frontiers in stroke care spanning different diagnosis and treatment methods. Among several interesting topics, we are very excited to include an overview of the Cleveland Clinic mobile stroke unit project and an excellent review of recent stem cell therapy trials for stroke recovery. We thank our newsletter staff and we hope to continue to receive your contributions. We welcome any ideas or interest in writing articles, editorials, or commentary for future SVIN newsletter editions.

Mouhammad A. Jumaa, MD

Ashutosh P. Jadhav, MD, PhD

Fellow of SVIN Program (FSVIN)

The Society of Vascular and Interventional Neurology offers a program that denotes "letters" to recognize exceptional service, academic excellence, and leadership in the field of vascular and interventional neurology. This program is called Fellow of Society of Vascular and Interventional Neurology. Individuals who meet the requirements of this Fellowship will add the letters, FSVIN, to their respective titles. A FSVIN candidate must meet the following criteria along with submitting the outlined items:

- Completed application form
- Current curriculum vitae
- A personal statement outlining the applicant's reasons for applying
- A copy of the applicant's primary certification which must be completed and up to date.
- Two written letters of recommendation from active SVIN members outlining why the applicant should be accepted as a fellow
- Applicant must be an active member of the Society of Vascular and Interventional Neurology for a minimum of 5 years and must have attended at least 3 annual meetings. Details for these are required on the application.

If you meet the above mentioned criteria, we would like to encourage you to apply for the Fellow of Society of Vascular and Interventional Neurology (FSVIN)!

The applications for fellowship will be reviewed by the Review Committee.

Visit the www.svin.org and find complete application details and requirements for the FSVIN program under the 'Members' tab.

Deadline: September 14, 2015
Please note that the next application deadline window will re-open after the SVIN Annual Meeting.

Questions?
Please contact the SVIN Executive Office at (952) 646-2045 or email info@svin.org.

The SVIN Annual Meeting Committee has put together a very innovative program. Make plans to join us for the upcoming meeting! It is one that you won't want to miss.

Visit www.svin.org/meetings/svin2015/ for registration, hotel reservation and complete program details!

Stroke Center Workshop

The Stroke Center Workshop will kick-start the Annual Meeting. There is an unmet need for expanding stroke centers of excellence across the country and healthcare systems, stakeholders involved in the stroke chain of survival, and industry need to join hands in making this a reality. This workshop is intended to bring together healthcare system leadership and administrators, hospital administrators, service line leaders, physician and nurse stroke champions, emergency department (ED) and emergency medical services (EMS) leaders, and industry leaders (Tele-health, Pharmaceutical, and Medical Device) who are interested in learning the requisite components of building, certifying and sustaining a successful stroke center. The workshop will also highlight the business side of developing Stroke Centers and Stroke Systems of Care.

SVIN Annual Meeting

The SVIN Annual Meeting has become a premier academic venue with scientific presentations covering the full spectrum of cerebrovascular diseases and stroke. Topics to be addressed include embolectomy, aneurysms and AVMs, subarachnoid and intracranial hemorrhage, endovascular saves and innovative approaches, new device review, international perspectives, and other related topics. Our speakers are leaders in the field. Given the high level of the field-specific presentations, we anticipate continued attendance by a large proportion of interventional neurology and related endovascular practitioners as well as neurologists interested and subspecialized in the care of patients with vascular diseases.

Continuing Education Credits

AMA PRA Category 1 and ANCC Credits will be offered for both the Stroke Workshop and SVIN Annual Meeting. ABPN Self-Assessment (SACME) credits will also be provided.

IMPORTANT DEADLINES:

Pre-Registration: September 18th
Hotel Reservation: September 24th

Acknowledgment of SVIN Top Supporters

SVIN would like to thank the following Top Supporters of the SVIN 3rd Annual Stroke Center Workshop and 8th Annual Meeting. Their support remains essential to our efforts as a society and interventional neurology as a field.

Double Platinum

stryker® Neurovascular

Medtronic Further, Together

Platinum

Penumbra

Gold

CODMAN NEURO

DePuy Synthes

MicroVention® TERUMO

MOBILE STROKE TREATMENT UNIT:

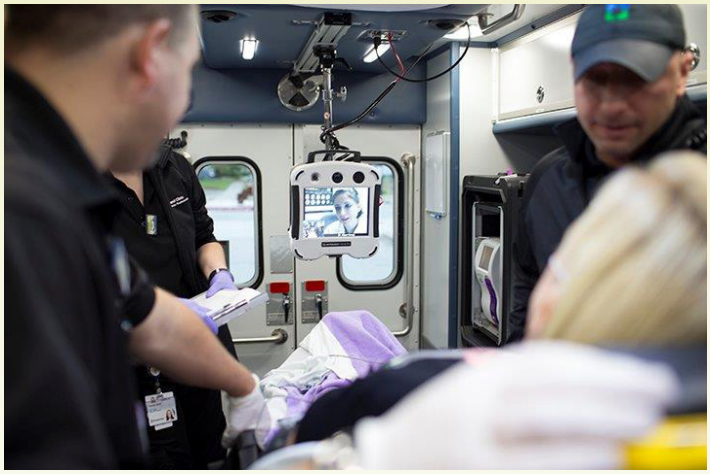
A Revolution in Acute Stroke Management

Muhammad S. Hussain, MD; Seby John, MD

The stroke community is acutely aware of the time dependent nature of acute stroke management. Ischemic stroke patients who present and are treated quickly have the greatest opportunity to benefit from recanalization therapy from intravenous recombinant tissue plasminogen activator. However, less than one-third of patients treated with IV rtPA have door-to-needle times ≤ 60 minutes.

Prehospital delay continues to contribute the largest proportion of delay time. The Mobile Stroke Treatment Unit (MSTU) offers a novel solution to the "time" problem. The MSTU strategy dictates that we no longer wait for the stroke patient at the ER, but bring the CT scanner to the patient. The MSTU, though, is not is just a mobile CT scanner. The unit is a mobile ER with emergency personnel, telemedicine and point of care diagnostics, facilitating truly acute and remote diagnosis. This enables initiation of treatment at the scene, thus cutting down time-to-treatment decisions and importantly time-to-treatment. In addition, it also aids in the treatment of many other acute neurological conditions.

The MSTU concept, which was first proposed in by Dr. Fassbender and colleagues in Germany in 2003, was developed and shown to be feasible in 2010. Initial experience of the MSTU experience from Germany in the region of Saarland and the city of Berlin were



reported in 2012 and 2014 respectively, and showed remarkable improvements in time to intravenous thrombolysis. The Cleveland Clinic launched its MSTU project in July of 2014, and is only one of two centers in the United States with this program. Our MSTU was funded by a generous donation from the Maltz family, and is a joint venture with the City of Cleveland. Our MSTU is equipped with a registered nurse, paramedic, emergency medical technician and CT technologist. A vascular neurologist evaluates the patient via telemedicine (InTouch RP-Lite) and a neuroradiologist remotely assesses images obtained by Ceretom mobile CT. Images are sent via 4G Verizon network with a dedicated bandwidth. The MSTU is also equipped with a portable point of care laboratory that can measure hemoglobin, platelet count, white blood cell count, prothrombin time/INR, blood glucose and serum electrolytes.

Initial analysis on 100 patients successfully transported by our MSTU has revealed impressive gains with mean door-to drug times of 31.5 minutes, and 48.4% of patients with probable stroke receiving IV tPA. In addition, 5 transported patients underwent successful mechanical thrombectomy. First picture-to-puncture time was 82 minutes, which is dramatically lesser, compared to patients who were first transported to a primary stroke center before eventually being transported to our center.

Mobile Stroke Treatment Unit, CONTINUES on page 7

VISUALIZATION AND ROLE OF COLLATERAL SUPPLY IN ACUTE ISCHEMIC STROKE

Tomas Bryndziar
Faculty of Medicine, Masaryk University and International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic

Sunil A. Sheth, MD
Division of Interventional Neuroradiology, University of California, Los Angeles, CA, USA

Collateral blood supply has been long recognized as one of the homeostatic mechanisms able to protect the brain from ischemia and hypoxia.[1-3] However, its significance for clinical decision making in the setting of acute ischemic stroke has been elucidated only recently, for both medical and endovascular stroke treatment. The recently published endovascular stroke trials and their positive results showed that in addition to the clear benefit of endovascular therapy in acute ischemic stroke over medical management alone, the assessment of collaterals can be used to identify the patients who are most likely to benefit from the intra-arterial therapy. In this article, we briefly review commonly used methods to visualize the collateral circulation, and then discuss their implications in patient selection for endovascular therapy.

Collateral status can be assessed with both structural and functional imaging techniques (Table 1 and Figure 1).[1,2] Structural imaging methods include conventional digital subtraction angiography and non-invasive approaches such as CT or MR angiography (CTA and MRA). DSA is still considered the gold standard of anatomic visualization of the cerebral vasculature and collateral connections. Beyond detailed anatomic information, it also provides information about the dynamics of blood flow. While the quality of these data provided by DSA is currently unmatched by non-invasive imaging methods, with advancements in technique such as 4D CTA and NOVA MRI, the gap continues to narrow. Beyond structural assessments, the influence of collaterals can be determined through functional imaging approaches. CT and MR perfusion imaging both allow for the identification of hypo- and hyper-perfused territories of brain that are under the risk of further ischemic damage or hemorrhage, respectively. These determinations can now be performed in automated and semi-automated methods using software packages such as RAPID.[4] As a result, perfusion imaging has played an important role in the selection of patients in most of the recently published endovascular trials.

The evidence that collaterals have a significant impact on the effectiveness and outcomes of endovascular therapy for acute ischemic stroke was successfully demonstrated in subset analyses of the first generation endovascular stroke trials (Table 2). A post hoc analysis of the IMS-III cohort showed that the angiographic collateral grade was a significant predictor of both recanalization and downstream reperfusion rates.[5] More importantly, it was also a significant predictor of good clinical outcome (mRS score at 90 days). Similar

Mobile Stroke Treatment Unit, ***CONTINUED from page 6***

The MSTU concept of taking stroke care to the streets is a paradigm shift in the way we practice stroke. It is a visionary venture that enables delivery of life-enhancing and saving treatment for both ischemic and hemorrhagic disease. The potential of such a system of care is immense, with impact on health outcomes and economics.

Acute Ischemic Stroke, CONTINUES on page 8

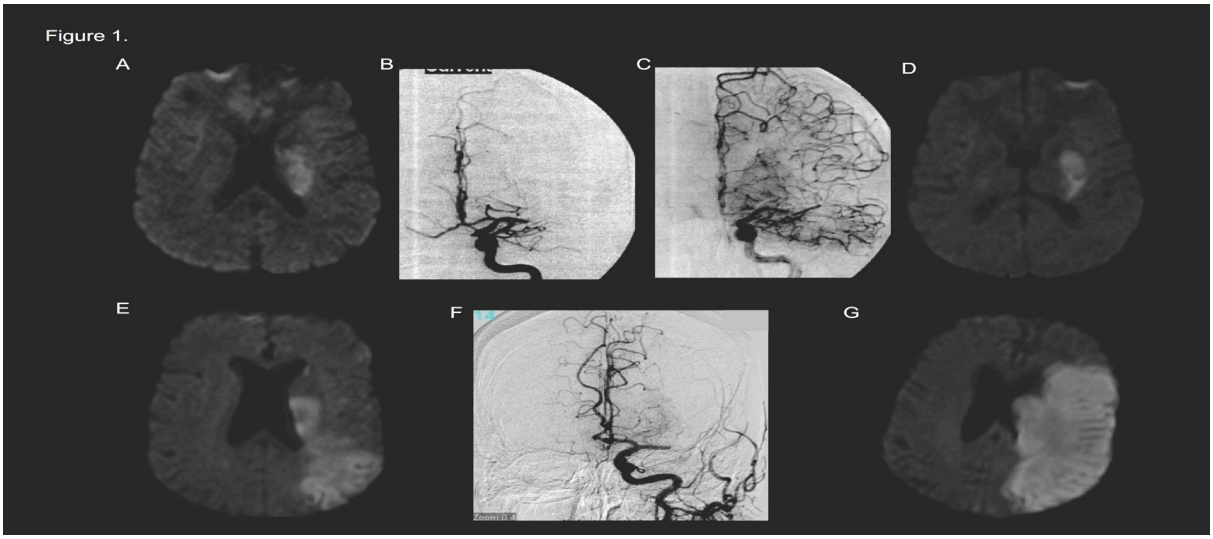
VISUALIZATION AND ROLE OF COLLATERAL SUPPLY IN ACUTE ISCHEMIC STROKE

findings have been found with the retrospective analysis of SWIFT.[6,7] In this analysis, angiographic collateral status prior to endovascular therapy was associated with better reperfusion rates (TICI ≥ 2b/3), and also with good clinical outcome at seven (NIHSS) and 90 days (mRS score). In addition to the findings of these large trials, multiple retrospective studies have shown that collateral status correlates with the functional outcome after acute ischemic stroke.[8-13]

These findings of the first generation of endovascular trials provided a basis for the implementation of collateral imaging-based selection metrics in many of the second generation of endovascular trials. RAPID was used to select patients in EXTEND-IA[14] and partially in SWIFT PRIME[15], while ESCAPE[16] used multiphase CTA. The overwhelmingly positive findings of these trials indicate that assessing collaterals to select the best candidates for intra-arterial stroke therapy is a major advance. By comparison, it is worth noting that while also clearly demonstrating a benefit for endovascular therapy, MR CLEAN17 reported markedly smaller effect sizes than these other three trials, possibly in part due to selection criteria that did not involve collateral imaging.

The 1st and 2nd generation endovascular stroke trials have now shown that collaterals are important factors not only for the prognostication of patients with ischemic stroke (in terms of expected recanalization, reperfusion, and functional outcome), but also for the selection of patients for endovascular therapy. The recent results have firmly placed endovascular therapy within the standard of care for patients presenting in acute time windows with large vessel occlusions. Moving forward, as we begin to study the role of ET for expanded indications such as distal occlusions, longer time intervals and "wake up" strokes, collateral imaging will continue to play a key role in advancing endovascular treatments for stroke.

Figure 1. Examples of cerebral collaterals found during angiography for endovascular treatment of acute stroke. A 70-year-old patient with a history of atrial fibrillation developed right-sided weakness and aphasia. (A) MRI revealed infarct of the left basal ganglia. (B and C) Angiography confirmed left proximal MCA occlusion, with robust ASITN/SIR grade 4 collateral filling from leptomeningeal branches. Complete recanalization was achieved with and (D) follow up imaging showed a stable infarct, and the patient had no residual deficits at 90 days. (E) A 70-year-old patient presented with right hemiplegia and was found to have an infarct of the left frontal and parietal lobes with perfusion mismatch. (F) Angiography revealed a left MCA occlusion with ASITN/SIR grade 1 collateral filling. (G) Complete recanalization was achieved but the patient proceeded to expand his infarct and his clinical condition deteriorated.



Acute Ischemic Stroke, CONTINUES on page 9

Table 1. Selected Collateral Grading Scores

Name	Modality	Summary
ASITN/SIR Angiographic Scale[18]	Catheter Angiography	5 point scale describing degree and pace of collateral flow to ischemic bed
CTA Leptomenigeal Vascularity Scale[8]	CT Angiography	5 point scale comparing the affected to unaffected hemisphere
Regional Leptomenigeal Score[19]	CT Angiography	20 point scale examining contrast opacification in ipsilateral arteries of cortical and deep structures
Collateral Score[12]	CT Angiography	4 point scale based on percent filling of affected MCA territory
Qureshi Scale[20]	Catheter Angiography	7 value scale based on location of occlusion and presence or absence of collateral flow
Capillary Index Score[21]	Catheter Angiography	4 point scale based on area of capillary blush of affected hemisphere

Table 2. Influence of Collaterals on Outcome in Endovascular Trials

Trial Name	Collateral Grade				
	0	1	2	3	4
IMS III (mRS ≤ 2)[22]	21%	25%	34%	52%	50%
SWIFT (mRS ≤ 2)[23]	10%*		27%	56%	67%
ENDOSTROKE (mRS ≤ 2)[24]	13%*		42%	44%^	

* Grade 0-1 combined, ^ Grades 3-4 combined

REFERENCES:

1. Liebeskind DS. Collateral Circulation. *Stroke; a journal of cerebral circulation*. 2003;34(9):2279–2284. doi:10.1161/01.STR.0000086465.41263.06.

2. Sheth SA, Liebeskind DS. Imaging Evaluation of Collaterals in the Brain: Physiology and Clinical Translation. *Curr Radiol Rep*. 2013;2(1):29–9. doi:10.1007/s40134-013-0029-5.

3. Sheth SA, Noorian AR, Liebeskind DS. Cerebral Hemodynamics and Homeostatic Mechanisms. In: Toga AW, ed. *Brain Mapping: an Encyclopedic Reference*. Vol 3. Elsevier; 2015:799–805. doi:10.1016/B978-0-12-397025-1.00092-0.

4. Straka M, Albers GW, Bammer R. Real-time diffusion-perfusion mismatch analysis in acute stroke. *J Magn Reson Imaging*. 2010;32(5):1024–1037. doi:10.1002/jmri.22338.

5. Liebeskind DS, Tomsick TA, Foster LD, et al. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke; a journal of cerebral circulation*. 2014;45(3):759–764. doi:10.1161/STROKEAHA.113.004072.

6. Liebeskind DS, Jahan R, Nogueira RG, Zaidat OO, Saver JL, SWIFT Investigators. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. *Stroke; a journal of cerebral circulation*. 2014;45(7):2036–2040. doi:10.1161/STROKEAHA.114.004781.

Acute Ischemic Stroke, CONTINUES on page 10

7. Liebeskind DS, Jahan R, Nogueira RG, et al. Early arrival at the emergency department is associated with better collaterals, smaller established infarcts and better clinical outcomes with endovascular stroke therapy: SWIFT study. *Journal of NeuroInterventional Surgery*. 2015. doi:10.1136/neurintsurg-2015-011758.

8. Lima FO, Furie KL, Silva GS, et al. The Pattern of Leptomeningeal Collaterals on CT Angiography Is a Strong Predictor of Long-Term Functional Outcome in Stroke Patients With Large Vessel Intracranial Occlusion. *Stroke; a journal of cerebral circulation.* 2010;41(10):2316–2322. doi:10.1161/STROKEAHA.110.592303.

9. Bang OY, Saver JL, Kim SJ, et al. Collateral Flow Averts Hemorrhagic Transformation After Endovascular Therapy for Acute Ischemic *Stroke. Stroke; a journal of cerebral circulation.* 2011;42(8):2235–2239. doi:10.1161/STROKEAHA.110.604603.

10. Souza LCS, Yoo AJ, Chaudhry ZA, et al. Malignant CTA Collateral Profile Is Highly Specific for Large Admission DWI Infarct Core and Poor Outcome in Acute Stroke. *American Journal of Neuroradiology.* 2012;33(7):1331–1336. doi:10.3174/ajnr.A2985.

11. Nambiar V, Sohn SI, Almekhlafi MA, et al. CTA collateral status and response to recanalization in patients with acute ischemic stroke. *American Journal of Neuroradiology.* 2014;35(5):884–890. doi:10.3174/ajnr.A3817.

12. Seeta Ramaiah S, Churilov L, Mitchell P, Dowling R, Yan B. The Impact of Arterial Collateralization on Outcome after Intra-Arterial Therapy for Acute Ischemic Stroke. *American Journal of Neuroradiology.* 2014;35(4):667–672. doi:10.3174/ajnr.A3862.

13. Sheth SA, Sanossian N, Hao Q, et al. Collateral flow as causative of good outcomes in endovascular stroke therapy. *Journal of NeuroInterventional Surgery*. 2014. doi:10.1136/neurintsurg-2014-011438.

14. Campbell BCV, Mitchell PJ, Yan B, et al. A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA). *Int J Stroke*. 2014;9(1):126–132. doi:10.1111/ijs.12206.

15. Saver JL, Goyal M, Bonafe A, Diener HC. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke — NEJM. … *England Journal of .... 2015.*

16. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019–1030. doi:10.1056/NEJMoa1414905.

17. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11–20. doi:10.1056/NEJMoa1411587.

18. Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2003;34(8):e109–37. doi:10.1161/01.STR.0000082721.62796.09.

19. Menon BK, Smith EE, Modi J, et al. Regional Leptomeningeal Score on CT Angiography Predicts Clinical and Imaging Outcomes in Patients with Acute Anterior Circulation Occlusions. *American Journal of Neuroradiology*. 2011;32(9):1640–1645. doi:10.3174/ajnr.A2564.

20. Qureshi AI. New grading system for angiographic evaluation of arterial occlusions and recanalization response to intra-arterial thrombolysis in acute ischemic stroke. *Neurosurgery*. 2002;50(6):1405–14– discussion 1414–5.

21. Ali Al F, Jefferson A, Barrow T, et al. The capillary index score: rethinking the acute ischemic stroke treatment algorithm. Results from the Borgess Medical Center Acute Ischemic Stroke Registry. *Journal of NeuroInterventional Surgery*. 2013;5(2):139–143. doi:10.1136/neurintsurg-2011-010146.

22. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368(10):893–903. doi:10.1056/NEJMoa1214300.

Acute Ischemic Stroke, CONTINUES on page 11

AN UPDATE ON CELL THERAPY FOR STROKE

Cynthia Kenmuir, MD; Vivek Reddy, MD and Lawrence R. Wechsler, MD University of Pittsburgh

Several new trials using cell therapy for stroke treatment have been completed and reported at international meetings. Earlier Phase I/II clinical trials completed in the 2000s demonstrated safety, and in some cases suggested efficacy, in the use of cell therapy to treat chronic stroke. These studies mostly treated chronic stroke months to years after stroke onset and used fetal or primitive neuronal cells injected directly in the area of infarction using stereotactic techniques (Savitz et al, 2004). More recent trials presented at the 2015 European Stroke Organization Conference have used intravenous, intraarterial and intraparenchymal routes to treat both acute and chronic strokes. The basic design and reported results for these trials are listed in Table 1 and briefly reviewed here.

Sanbio (allogeneic, marrow-derived, chronic stroke, intraparenchymal)

Sanbio sponsored a Phase 1/2 clinical trial evaluating allogeneic, bone marrow-derived stem cells that had been transiently transfected with a plasmid encoding Notch-1 (SB623 cells) in the treatment of chronic subcortical strokes. These SB623 cells have been shown to improve motor and cognitive performance versus traditional bone-marrow derived stem cells in a rodent model (Mimura et al, 2005). Patients aged 18-75 who had a subcortical stroke with or without a cortical component that occurred 6-60 months earlier and had been stable for at least 3 weeks with an NIHSS of at least 7 and a modified Rankin score (mRS) 3-4 were included. Cells were delivered under stereotaxic guidance around the site of infarct in a standard, dose-escalation paradigm. Of 18 patients enrolled, there were 5 reported serious adverse events (SAEs) though none were cell-related. Outcome measures including European Stroke Scale (ESS), NIH Stroke Scale (NIHSS) and Fugl-Meyer Score were all significantly improved at 6 and 12 months after cell infusion.

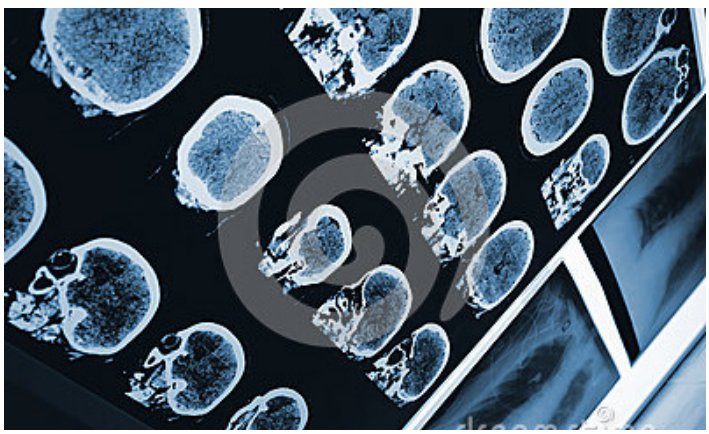
Aldagen (autologous, marrow-derived, late subacute stroke, intraarterial)

Aldagen sponsored Phase 1/2 clinical trials evaluating intracarotid infusion of autologous, bone marrow-

Acute Ischemic Stroke, ***CONTINUED from page 10***

23. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *The Lancet.* 2012;380(9849):1241–1249. doi:10.1016/S0140-6736(12)61384-1.

24. Singer OC, Berkefeld J, Nolte CH, et al. Mechanical recanalization in basilar artery occlusion: the ENDOSTROKE study. *Ann Neurol*. 2015;77(3):415–424. doi:10.1002/ana.24336.



Update on cell therapy, CONTINUES on page 12

AN UPDATE ON CELL THERAPY FOR STROKE

derived stem cells (ALD401 or ALDH^{br}) in the treatment of late subacute strokes. For ALD401 cell Phase 1 safety study, patients aged 30-83 who had a predominantly cortical stroke with persistent symptoms with NIHSS of at least 22 and an mRS of at least 3 were included. Cells were delivered intraarterially (IA) within the carotid artery of the affected hemisphere between 13-19 days after the stroke. Of 100 patients enrolled, there were 0 reported SAEs. For ALDH^{br}, patients aged 30-75 who had anterior circulation strokes with or without a subcortical component with an NIHSS of 7-22 and an mRS of at least 3 were included. Cells were delivered within the internal carotid artery just distal to the ophthalmic artery between 13-19 days after the stroke. Of 29 IA and 19 sham control patients enrolled, there were 12 reported SAEs in the IA group and 11 reported SAEs in the sham group. No difference was reported in mRS, Barthel index or NIHSS at 90 days or at 12 month after cell infusion.

Athersys (allogeneic, adult-derived, early subacute stroke, intravenous)
Athersys sponsored a Phase 1/2 clinical trial evaluating allogeneic, adult-derived stem cells (Multistem®) in the treatment of early cortical strokes. Patients aged 18-83 who had a cortical stroke of 5-100cc, NIHSS of 8-20 and a premorbid mRS of 0-1 were included. Cells were delivered intravenously 24-48 hours after onset of symptoms. Of 140 patients enrolled, there were significantly less SAEs and lower mortality in the treated group. No difference was reported in mRS, Barthel index, NIHSS or Global stroke recovery assessment at 90 days after cell infusion. There was a trend towards improved outcome with earlier delivery of cells.

ReNeuron (allogeneic, human fetal neural stem cells, chronic stroke, intraparenchymal)
ReNeuron sponsored Phase 1/2 clinical trials evaluating allogeneic, human fetal neural stem cells (CTX0E03 DP) in the treatment of chronic strokes. For PISCES, men older than 60 who had a subcortical stroke with persistent hemiparesis 6-60 months prior and had a stable NIHSS over 4 weeks were included. Cells were delivered under stereotaxic guidance into the putamen of the affected hemisphere. Of 12 patients enrolled, there were 16 reported SAEs in 9 patients though none were cell-related. There was a significant improvement in NIHSS at 2 years following cell infusion, but no change in mRS, Barthel, mini-mental status exam, or Ashworth scale. PISCES-II is of similar design except that patients aged 40-89 were enrolled between 28-56 days after cortical or subcortical stroke with the cells delivered under stereotaxic guidance into the striatum of the affected hemisphere.

These recently reported cell therapy trials have used a variety of delivery techniques - each with their own pitfalls. While intravenous administration of cells is the quickest and least invasive, it carries the risk of multiorgan exposure as well as the need for higher cell volumes. Intraarterial therapy is more invasive and can result in cell clumping within the smaller intracranial vessles, but affords the use of lower cell volumes and more direct exposure to the tissue of interest. Stereotaxic infusion is the most invasive and carries the associated surgical risks, but allows for the most direct infusion into the tissue of interest while using the smallest volume of cells.

Some stem cell studies have used cells obtained from embryonic and fetal tissues, but these studies are now somewhat limited due to ethical concerns. Human stem

Update on cell therapy, CONTINUES on page 13

AN UPDATE ON CELL THERAPY FOR STROKE

REFERENCES

cells may also be obtained from adult neural tissue, peripheral blood, adipose tissue, bone marrow, and immortalized cell lines from primitive tumors. Notably many of these cell lines are composed of heterogenous cell populations including stem cells and have a variety of proposed functions once within the nervous system (Savitz et al, 2004). The most recent cell therapy trials for stroke have utilized mesenchymal stem cells derived from allogeneic (SB623) or autologous (ALD401, ALDH^{br}) bone marrow, an adult-derived "off-the-shelf" frozen cell population (Multistem), or allogeneic neural stem cells (CTX0E03 DP). Allogeneic cell preparations allow for more homogenous cell populations that can be highly expanded for a consistent product. Some of these can be stored for years affording an always available "off-the-shelf" product, though they do require preparation prior to administration. Although the most recent clinical trials using allogeneic cells (SB623, Multistem, CTX0E03 DP) did not require immunosuppression, the potential for allergic reaction remains. Autologous cells require bone marrow harvest, resulting in variable stem cell yield and require time for expansion prior to administration, but carry less concern for allergic reaction or rejection.

Cell therapy may provide a promising new treatment for stroke, and hopefully will reduce stroke-related disability. The recently presented results from clinical trials investigating the use of cell therapies for the treatment of acute and chronic stroke demonstrate adequate cell safety, with some trials demonstrating efficacy similar to that seen in rodent models. Although the mechanisms by which cell therapy may help improve recovery after stroke are not well-understood, cell therapy is most likely exerting a multimodal effect to modulate the post-ischemia milleau including immune modulation, enhancement of angiogenesis, neurogenesis and secretion of growth factors, cytokines and other factors capable of augmenting the endogenous repair process in the brain. Further investigation is needed to determine specific effects of cell therapy and to optimize cell delivery methods, cell dosing, type of cells used, timing of delivery, infarct size, and location of infarct that may benefit from cell therapy.

'Big Pictures and Details' by Leah Guzman

REFERENCES:

1. Mimura T, Dezawa M, Kanno H, Yamamoto I. Behavioral and histological evaluation of a focal cerebral infarction rat model transplanted with neurons induced from bone marrow stromal cells. J Neuropathol Exp Neurol. 2005;64:1108–1117.
2. Savitz SI, Dinsmore JH, Wechsler LR, et al. Cell therapy for stroke. NeuroRx 2004:1;406-14.

Table 1: Summary of recent human cell therapy trials for stroke. Preliminary data as presented at European Stroke Organization Conference in April, 2015 in Glasgow, Scotland, United Kingdom.

Update on cell therapy, CONTINUES on page 14

AN UPDATE ON CELL THERAPY FOR STROKE

Clinical Trial	Age	Time after stroke	Additional Selection Criteria	Cell type	Route	Stroke Location	Number of patients	Safety Results	Efficacy Results
Sanbio	18 - 75	6 - 60 mo	NIHSS ≥7, mRS 3-4, stable symptoms >3 weeks	SB623 allogeneic marrow-derived stem cells transiently transfected with plasmid encoding Notch1	Sterotaxic infusion peri-infarct	Subcortical +/- cortical component	18	5 SAE, 0 cell-related SAE	Improved ESS at 6 mo (p=0.02) and 12 mo (p=0.004) Improved NIHSS at 6 mo (p=0.004) and 12 mo (p=0.0006) Improved Fugl-Meyer at 6 mo (p=0.0002) and 12 mo (p=0.000006)
Aldagen	30 - 83	13 - 19 days	Persistent symptoms with NIHSS ≤22, mRS ≥3, patent carotid (and MCA unless good collaterals)	ALD401 autologous marrow-derived stem cells	Intracarotid infusion	Predominantly cortical	100 (10 for Phase I safety study)	0/10 SAE	
Aldagen (RECOVER-Stroke)	30-75	13 - 19 days	NIHSS 7-22, mRS ≥3	ALDH^{br} autologous marrow-derived stem cells	Intracarotid infusion distal to ophthalmic	Anterior circulation +/- subcortical	29 IA, 19 sham	12 SAE versus 11 SAE sham	No difference in mRS, Barthel, NIHSS at 90 days or 1 year
Athersys	18 - 83	24 - 48 hours	NIHSS 8-20, infarct 5-100cc, premorbid mRS 0-1	Multistem® adult-derived stem cell product	Intravenous	Cortical	140	Less SAE, p= 0.04 Lower mortality - 4 deaths (6.2%) versus 9 deaths (14.8%) in placebo	No effect on 90 day Global Stroke Recovery Assessment, mRS, NIHSS, Barthel Trend towards improved outcome with earlier delivery of cells
ReNeuron PISCES	≥60, male only	6 - 60 mo	Persistent hemiparesis,Stable NIHSS over 4 weeks	CTX0E03 DP allogeneic human neural stem cells	Sterotaxic infusion into putamen	Subcortical	12	16 SAE (in 9 patients), 0 cell-related SAE	Improved NIHSS at 2 years (p=0.002) No change Barthel, MMSE, Ashworth, mRS
ReNeuron PISCES-II	40 - 89	28 - 56 days	Paretic arm with NIHSS motor arm score 2-3	CTX0E03 DP allogeneic human fetal neural stem cells	Sterotaxic infusion into striatum	Cortical or Subcortical MCA	41		

ESS: European Stroke Scale; MMSE: mini-mental status exam; mRS: modified Rankin Score; PISCES: Pilot Investigation of Stem Cells in Stroke; SAE: Serious Adverse Events

STROKE TRIAL NETWORK (STROKENET) FELLOWSHIP

Stacie Demel DO, PhD and Srikant Rangaraju, MD

In September 2013, the NIH created the Stroke Trials Network (NIH StrokeNet) to conduct clinical trials and research studies to advance acute stroke treatment, stroke prevention and stroke recovery. Born out of NIH StrokeNet, the StrokeNet fellowship is a national training program which supports and molds trainees interested in a career in stroke research. Each regional coordinating center (RCC) is allowed one trainee per academic year. If the RCC has more than one institution, then each institution may have a trainee. Promising trainees who are committed to a career path in academic stroke research are prioritized and given protected research time, suggested to be at least 50% of their time dedicated to research and research training. A trainee may only receive funding for one year.

With the exception of showing an interest in becoming a stroke researcher, the requirements for a trainee are purposefully broad. While most trainees have a background in neurology, other subspecialists such as neurosurgeons, epidemiologists, physical therapists and biomedical engineers have been trainees during the first full year of this program. Nurses and nurse practitioners are also encouraged to apply. NIH StrokeNet trainees can also be junior faculty members, not just fellows or residents. Last year there were 25 trainees from various backgrounds and seven were faculty members. Research topics for trainees were extremely diverse, and included behavioral interventions, acute stroke trials, stroke epidemiology, stroke prevention trials, stroke imaging, and stroke recovery interventions, among others.

There are many benefits to being an NIH StrokeNet trainee. One has the opportunity and expectation to interact and connect with stroke experts throughout the United States. This opportunity greatly increases exposure and therefore collaborative efforts outside of a trainees' home institution. Another benefit is the opportunity for educational advancement that comes in the forms of webinars from stroke experts. The webinars cover a wide range of relevant clinical and scientific topics. A few examples of prior webinar topics include "inflammatory biomarkers in acute stroke and stroke prevention" and "post-stroke fatigue." In addition, professional development sessions focused on important topics such as grant writing and data presentation are timely and highly informative. More information about specific presentations can be found at nihstrokenet.org/education. Finally, the NIH StrokeNet meeting that precedes the International Stroke Conference provides an opportunity for trainees to get face-face feedback and interact with stroke experts from across the country and funds to attend national stroke meetings are made available to each candidate.

The NIH StrokeNet training core also serves as a resource for trainees and mentors. It is a mechanism for tracking trainee progress, maintaining contact for current and past trainees and posting job and workshop opportunities such as the NINDS Clinical Trials Workshop. Overall, the NIH StrokeNet fellowship training program provides an opportunity to combine excellent clinical training with focused research mentorship for candidates interested in a career in academic vascular neurology. Entrance into the program is decided by each individual regional coordinating center. Contact information for these centers is listed on their website: nihstrokenet.org/education.

SVIN
Society of Vascular and Interventional Neurology

8TH ANNUAL MEETING & 3RD ANNUAL STROKE CENTER WORKSHOP

October 15-18, 2015

Hyatt Regency Coconut Point | Bonita Springs, FL

CONTACT US

SVIN Executive Office
5841 Cedar Lake Road Suite 204
Minneapolis, MN 55416

P: (952) 646-2045 | F: (952) 545-6073 | info@svin.org

Visit us on the web at www.svin.org

Follow SVIN on Facebook