Bone marrow–derived mononuclear cells (MNCs) are being tested as an autologous cell-based therapy in patients with stroke in early-phase clinical trials. We and others have reported that intravenous (IV) or intra-arterial (IA) delivery of MNCs enhances recovery after acute ischemic stroke in rodent models, and both routes of administration have been brought forward to clinical studies. However, it is unclear which delivery route is better to enhance recovery after stroke.

IA administration carries the theoretical advantage of selective delivery to the injured brain but may not deliver cells to the brain to the same extent. Few studies have directly compared delivery routes, and the results are conflicting. However, it is unclear which delivery route is better to enhance recovery after stroke.

Methods

Animals

In this study, 168 male Long Evans rats (weight, 300–325 g) were used. All animals were housed in pairs with free access to food and water and maintained on a standard 12:12-hour light/dark cycle. All animal experiments and surgical procedures were approved by the University of Texas Health Science Center Animal Welfare Committee and followed National Institutes of Health guidelines and regulations. Experimental group information and flow chart is shown in Figure 1.

Stroke Model

Transient focal brain ischemia was induced by a modified intraluminal middle cerebral artery occlusion (MCAo) suture method as previously described. Briefly, rats were anesthetized with 1% to 2% isoflurane in a mixture of 30% oxygen and 70% nitrous oxide by face mask. Through a midline neck incision, left common, internal, and external carotid arteries were exposed, and a 3-0 nylon filament with blunt tip was inserted through the stump of the external carotid artery. The common carotid artery was then clipped off, and the filament was advanced into the internal carotid artery 19 to 21 mm beyond the carotid bifurcation. Mild resistance indicates proper placement.
of filament in the middle cerebral artery confirmed by laser Doppler flow reduction of the MCA perfusion territory >75% from baseline. Focal ischemic time was 90 minutes, and reperfusion was accomplished by withdrawing the suture and removing the common carotid artery clip. The reperfusion was confirmed using laser Doppler. The body temperature was maintained at 36.5±0.5°C during surgery, and animals were allowed to recover at room temperature.

**Bone Marrow Harvest**
Bone marrow was harvested, as previously described, from tibia at 22 hours after ischemia. Briefly, the rats were anesthetized with 1% to 2% isoflurane. An incision was made through the skin to the medial aspect of the tibia. The periosteum was removed, and a 1.25×1.25 mm burr hole was made extending into the medullary cavity. A 27×1/2 gauge hypodermic needle connected to a heparinized syringe was inserted into the medullary cavity, and the bone marrow (1–1.5 mL) was aspirated while rotating and moving the needle back and forth. In the saline control group, a sham procedure was performed involving a burr hole and needle insertion of the tibia without bone marrow aspiration. The burr hole was sealed with bone wax and the skin closed with a nylon suture. This limited aspiration of the bone marrow did not cause impairment of the limbs, and animals are able to fully participate in neurological testing.

**MNC Isolation**
MNCs were isolated from bone marrow using Ficoll density gradient centrifugation, as we published previously. The cells from the bone marrow aspirate were triturated, centrifuged, and washed in PBS+0.5% BSA. Cells were then suspended in Media 199 and added on top of 20 mL Ficoll-Paque PLUS (GE Healthcare) in a 50-mL conical tube and centrifuged. The MNC layer was collected, washed with PBS+0.5% (BSA), and then counted. Cell viability was >98% by trypan blue detection. Cells were then washed and resuspended in 1 mL of sterile cold saline at the desired concentration for infusion.

**MNC Administration**
At 24 hours after MCAo, animals were randomized to receive saline IV or autologous bone marrow–derived MNCs by an IV route through the left jugular vein or an IA route through the left internal carotid artery. MNC-treated groups received either 1 million cells/kg or 30 million cells/kg. We chose these doses because we previously demonstrated a protective effect of MNCs at 30 million cells/kg (IV) but not at 1 million cells/kg (IV). We hypothesized that an IA delivery of the lower dose might lead to a therapeutic effect. In our experience (data not shown), we have found that IV or IA administration of saline results in indistinguishable behavioral outcomes in our rodent stroke model. We, therefore, chose IV saline as a common control group. Similar to our previous studies, cells were infused with an autoinjection pump at a rate of 0.2 mL/min for 5 minutes.

**Behavior Test**
Animals underwent long-term behavioral testing that was performed by an examiner blinded to treatment allocation. Animals were pretested before MCAo and then tested on days 1, 3, 7, 14, 21, and 28 after ischemia. We used the cylinder, circling, and adhesive removal tests, as we have previously reported, to evaluate dysfunction in our model. We determined that the other tests conducted for these behavioral analyses, beam balance, placing, and flexion, were not sensitive to detect long-term deficits in our model. All animals were pretrained for behavior tests for 2 weeks.

**Lesion Size**
Twenty-eight days after stroke, animals were anesthetized and intracardially perfused with ice-cold PBS, followed by ice-cold 4% paraformaldehyde (PFA) in PBS and decapitated. Brains were harvested, postfixed in 4% PFA in PBS for 24 hours, immersed in 20% sucrose for 2 days, and divided into 6 sections (2 mm). Coronal 20-µm frozen sections from each section were stained with cresyl...
violet. As we reported previously, tissue loss of the ipsilateral chronic infarct was measured using the indirect method and expressed as a percentage of the contralateral hemisphere by a researcher blinded to treatment groups.

**Biodistribution**
Bone marrow MNCs (1 million cells/kg and 30 million cells/kg) were labeled with Q-tracker 655 (red) and then administered IV or IA to rats subjected to MCAo 24 hours earlier. We used 5 rats per group. At 1, 6, 24, and 72 hours after MNC injection, animals were anesthetized and intracardially perfused with ice-cold PBS followed by ice-cold 4% PFA. As we described previously, the brain, lungs, and spleen were removed and postfixed for 24 hours in 4% PFA and then immersed in 20% sucrose and stored at 4°C for 24–48 hours. Twenty-micrometer cryosections were then generated and counterstained with 4',6-diamidino-2-phenylindole (DAPI; blue) for microscopic analysis. Q-tracker–positive MNCs were quantified with the assistance of Image J (National Institutes of Health). Three randomly chosen sections per each organ of predefined regions of interest, involving 9 fields per section under ×400 magnification, were analyzed. The regions of interest were in the peri-ischemic tissue of the brain at the level of sections from +1 to −7 mm relative to the bregma, in the lower lobe of the lungs, and in the spleen. To assess the biodistribution of MNCs in the peripheral circulation, 1 mL of venous blood was sampled from the jugular and femoral vein at 5 and 60 minutes after Q-tracker–labeled MNC infusion IV and IA at 30 million cells/kg. Then, the blood was treated with Immunoprep Reagent System (Beckman Coulter, USA) as per the manufacturer’s instruction and run using Gallios Flow Cytometer (Beckman Coulter, USA). Data were analyzed with Kaluza software (Beckman Coulter, USA).

**Western Blot Analysis**
At 3 or 28 days after stroke, rats were perfused intracardially with ice-cold PBS. Brains were harvested. The injured ipsilateral hemisphere was homogenized on ice in radioimmunoprecipitation assay buffer (Invitrogen, USA). The protein concentration of each sample was determined using the Bicinchoninic Acid Assay (Sigma-Aldrich, USA). Fifty micrograms of protein was separated on a 4% to 12% gradient SDS-PAGE gel using a Novex Mini Cell system (Invitrogen, USA). The proteins were transferred onto a polyvinylidene fluoride membrane (Invitrogen, USA) using the Novex Mini Cell system. Membranes were blocked (5% nonfat milk, 0.1% Tween-20 in Tris-buffered saline, pH 7.6) at room temperature for 2 hours and incubated with primary antibodies overnight at 4°C. For CD31-positive vessel analysis, 6 frozen sections were randomly selected from each of the 2-mm sections for lesion size measurement. Nine views from each 10-μm section were collected in the ipsilateral hemisphere, and the CD31-positive vessels were analyzed. For DCX-positive cell analysis, only sections at the level between −1 and −4 mm relative to the bregma were selected. All sections for analysis were mounted by Vectashield with DAPI (Vector Laboratory, USA). The immunofluorescence signal was captured using fluorescence microscope equipped with charge-coupled device camera, and immunopositive vessels were counted using ImageJ software (National Institutes of Health).

**Fluoro-J Staining**
To test whether IA MNCs cause microinfarcts resulting in cell death, rats were perfused intracardially with ice-cold PBS at 24 hours after MNC or saline infusion. Fresh frozen sections of 40 μm were generated and fixed with cold 2% PFA (for 20 minutes), followed by immersion in 1% sodium hydroxide, 80% ethanol (for 5 minutes), rinsing in 70% ethanol (for 2 minutes), rinsing in water (for 2 minutes), and incubation in 0.06% potassium permanganate solution (for 20 minutes). Slides were then transferred into a 0.0001% solution of Fluoro-Jade B (Histo-Chem Inc, USA) dissolved in 0.1% acetic acid. This was followed by three 1-minute rinses in distilled water. Dried slides were cleared in xylene for 1 minute and coverslipped with a xylene-based mounting media (Richard Allan Scientific, USA). Sections of the hemisphere ipsilateral to the carotid injection were visualized and analyzed for the abundance of fluorescent cells under a fluorescence microscope.

**Serum Cytokine Measurements**
Venous blood serum samples were collected at various time points. Interleukin (IL)-1β, tumor necrosis factor-α, IL-10 (Thermo Scientific, USA), and IL-6 (Invitrogen, USA) levels were detected by ELISA according to the manufacturers’ protocols.

**Statistical Analysis**
Data are presented as means±SD. Repeated-measures ANOVA and Bonferroni post-test were used for comparison among groups at different days after stroke in the behavioral tests. For the lesion size, neurotrophins, and regenerative responses, a 1-way ANOVA was performed with post hoc Tukey–Kramer test. For the cytokine and MNC biodistribution measurement, a 2-way repeated ANOVA and Bonferroni post-test were used. Behavior, cavity volume, histology, and serum markers were analyzed across all groups. Statistical significance was set at P<0.05 level.

**Results**

**Mortality/Model Failure**
Animals that did not have a reduction in cerebral blood flow >75% (4 animals) on MCAo and animals that died within 22 hours after MCAo (6 animals) were excluded from the experiment. The remaining animals were randomly allocated to saline or IV or IA MNCs (high dose at 30 million cells/kg; n=12 and low dose at 1 million cells/kg; n=10 per group). Three animals died in the saline group that served as a control. There was no mortality after MNC administration in the IV and IA groups.

**Behavior Tests**
We found a significant reduction in neurological deficits at 28 days after stroke (Figure 2A) in animals treated with 30 million MNCs/kg, irrespective of the delivery route, compared with saline controls. Both IV- and IA-treated groups achieved similar degree of recovery compared with saline controls, and...
no significant differences were found between the 2 groups by delivery route. In the animals treated with 1 million MNCs/kg, there was no difference in functional scores among IV-, IA-, or saline-treated group (Figure 2A–2C).

Lesion Size
We found a significant reduction in brain lesion size in animals treated with 30 million MNCs/kg in both IV and IA groups compared with the saline-treated controls. The robustness of lesion size reduction was similar for the IV- and IA-treated groups. In the animals treated with 1 million MNCs/kg, there was no difference among the 3 groups (Figure 2D).

Biodistribution
Given that IV and IA delivery of MNCs led to equal functional benefit, we assessed for similarity in the biodistribution of MNCs between these delivery routes. In a separate experiment, rats were subjected to MCAo and randomly divided into 4 groups, where the same high dose (30 million cells/kg) and low dose (1 million MNCs/kg) of MNCs, as described previously, were given IV or IA (n=5 per time point per group). At a dose of 30 million cells/kg, there were significantly more Q-tracker-labeled cells observed in the peri-infarct area at 1 and 6 hours after cell infusion in animals that received IA MNCs compared with animals that received IV MNCs (Figure 3A). However, there were no significant differences in the number of labeled cells between IV and IA groups at 24 hours and 3 days (Figure 3A) after injection. There were also no significant differences in the number of labeled MNCs in the spleen and lungs at all 4 time points examined between IV and IA groups (Figure 3A). At a dose of 1 million MNCs/kg, we found no significant differences in the number of labeled...
cells at any time points after IV or IA injection in the brain, spleen, or lungs (Figure 3A). Representative photomicrographs of labeled cells in the brain are shown for high- and low-dose MNCs (Figure 3B). We then quantified the presence of labeled cells in the venous circulation in the jugular and femoral vein after IV or IA injection of 30 million MNCs/kg. We found a significant reduction in the number of labeled MNCs in both jugular and femoral vein at 5 minutes and 1 hour after cell infusion, respectively. Compared with 5 minutes after cell infusion, there were significantly less labeled MNCs in the venous circulation at 1 hour after cell infusion (n=4 animals; P<0.05). Data are means±SD.

Microstroke Formation
Given that IV and IA lead to equivalent benefit at the higher dose of 30 million MNCs/kg, yet IA leads to higher deposition of labeled cells in the brain, we explored the question whether IA delivery could cause diffuse damage in the form of microembolic strokes (vascular plugging), explaining the limited benefits despite the larger number of MNCs in the affected brain. We, therefore, injected 30 million MNCs/kg IA to healthy rats at 2 rates: 0.2 mL/min and 1.5 mL/min (n=3 per group). The former rate has been used in previous studies, and the latter rate was reported to cause microstrokes by others using neural stem cells. As a positive control for Fluro-J staining, we used a brain from a rat at 24 hours after MCAo. At 24 hours after IA injection, we did not detect Fluro-J–positive cells in the middle cerebral artery territory of healthy rats at the injection rate of 0.2 mL/min nor at the rate of 1.5 mL/min (Figure 3D).

Inflammation
Given similar cell biodistributions between IV and IA delivery routes, we turned to other mechanisms involving the systemic inflammatory response. Recent studies indicate that immune modulation may be an important mechanism underlying how MNCs enhance recovery after stroke. Here, we measured serum cytokine levels before stroke (prestroke), before treatment (pretreatment), and 3 and 28 days after stroke. Compared with saline, MNCs at 30 million/kg IV reduced serum IL-1β,
IL-6, and tumor necrosis factor-α levels while increasing IL-10 at 3 days after stroke. IA MNCs showed a generally similar profile regarding tumor necrosis factor-α and IL-6, although IA MNC did not decrease IL-1β or increase IL-10 to the same extent compared with IV MNCs. At 28 days, all cytokines returned to prestroke levels (Figure 4A). At 1 million MNCs/kg, there were no differences in cytokine levels among saline-, IV-, and IA-treated MNC groups (data not shown). In a parallel experiment to explore the effects more directly of the treatment on inflammation in the brain, we found that high-dose MNCs significantly reduced iNOS expression as assessed at 3 days after MCAo in the ipsilateral hemisphere compared with saline controls (Figure 4B). However, we found no differences between IV and IA MNC-treated groups on this effect. At low dose, MNCs were not effective in reducing iNOS expression.

Neurotrophins

We also explored differences in neurotrophin levels between the MNC delivery routes. At the higher MNC dose, we detected a robust increase in BDNF protein levels but not in nerve growth factor or NT-3 between MNC and saline-treated groups in the injured hemisphere at 3 days after stroke. However, there was no difference between IA or IV MNC groups in BDNF levels (Figure 4C). Lower dose of MNCs at 1 million MNCs/kg did not affect BDNF levels.

Neuroregenerative Response

To address one further mechanism reported to be important in the positive effects of MNCs, we examined changes in various aspects of regeneration and repair. To assess neurogenesis associated with the delivery routes of MNCs, we measured

Figure 4. High-dose mononuclear cells (MNCs) altered the profile of inflammatory cytokines and neurotrophin expression after stroke. A, Line diagrams indicating the alterations of serum proinflammatory and anti-inflammatory cytokines in animals treated with 3×10⁷ cells/kg MNCs via intra-arterial (IA) or intravenous (IV) delivery. Data are means±SD. Animals treated with low-dose MNCs (1×10⁶ cells/kg) are not shown to preserve clarity of the graph because the cytokine profile was not significantly different from saline-treated animals. Statistical tests were performed across all groups, including animals treated with high and low dose. *P<0.05, compared with saline group. #P<0.05, compared with IA delivery route. Saline n=18, MNCs IV n=10, and MNCs IA n=11. B, The Western blots indicate that inducible nitric oxide synthase (iNOS) was reduced in the brain of animals treated with high-dose MNCs IA or IV at day 3 after stroke but not with low-dose MNCs IA or IV compared with saline control. Data are means±SD. n=3 animals. *P<0.05, compared with saline group. C, Representative immunoblots of neurotrophins and a quantitative bar graph. High-dose MNCs by IA or IV routes increased BDNF expression compared with saline controls. However, there was no significant difference between IV and IA delivery. Low-dose MNCs did not change the levels of any of the neurotrophins. Data were analyzed across all groups and represented as means±SD. n=3 animals. *P<0.05, compared with saline group. BNDF indicates brain-derived neurotrophic factor; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-10, interleukin 10; MCAo, middle cerebral artery occlusion; and TNF-α, tumor necrosis factor α.
changes of DCX, a marker of neuroblasts, in the subventricular zone and the striatum near the subventricle zone at day 28 after stroke. In animals treated with IV or IA high-dose MNCs, there were more DCX-positive cells in the striatum compared with low-dose MNC treatment or saline controls (Figure 5A–5C). There was no difference between the IV and IA MNC group. There were no changes in DCX-positive cells between saline and low-dose MNC groups. Interestingly, we also found that GAP-43, an important regulator of synaptic plasticity, was expressed at much higher levels in the ipsilateral cortex of animals treated with high-dose MNCs, compared with saline controls, at 28 days after stroke (Figure 6A). Again, we did not find any differences between IV and IA MNC-treated groups. We then measured changes in the density of CD31-positive vessels in the peri-infarct area at 28 days after stroke. High-dose MNC treatment led to an increase in vessel density compared with saline controls (Figure 6B). There was no difference between IV and IA MNC groups at the higher dose. Low dose of MNCs had no effect on GAP-43 or vessel density.

Discussion
Autologous bone marrow–derived MNCs are a promising potential therapy to promote stroke recovery, but the optimal delivery route of these cells remains unknown and is an important translational issue. IV and IA routes of delivery are being pursued in clinical trials. We, therefore, investigated differences between them to provide important information that could help in designing future clinical trials. We first used a high dose of MNCs that were previously shown by IV administration to exert a therapeutic effect. Considering that more cells in the peri-infarct area might lead to better recovery, we expected that the IA route would allow more MNCs to reach the affected brain and be associated with a better outcome. We also used a low dose of MNCs, which in our hands did not enhance stroke recovery using an IV delivery route, with the expectation that an IA administration of the same dose might, unlike IV, lead to a better outcome. Irrespective of the delivery route, MNCs at the higher dose improved functional recovery, but we found no added benefit of IA compared with IV. The high dose of MNCs improved functional recovery to the same extent by the IV or IA delivery route, and the lower dose had no effect on stroke outcome whether by IV or IA.

There are several possible factors to account for the similar outcomes between the delivery routes at the low and high doses of MNCs. We first explored the biodistribution of MNCs. As expected, IA infusion compared with IV infusion of 30 million MNCs/kg delivered more cells into the peri-infarct area acutely at 1 and 6 hours after injection. Unexpectedly, the presence of a large number of cells in the brain did not correlate...
with the improvement in functional outcome or tissue repair as previously suggested by others. However, infusion of 1 million MNCs/kg deposited a significantly lower number of cells in the brain and was not associated with a therapeutic effect. These results suggest the possibility that the number of cells delivered to the brain may not be critical to influence functional outcomes. However, another possibility is that a minimum threshold of cells delivered to the brain is needed and that a higher cell presence at least acutely does not lead to a greater effect on recovery in our rodent stroke model. The data also suggest that a lower dose of MNCs, that is not efficacious IV, does not lead to better outcomes when more directly administered to the brain with an IA route.

Because MNCs are overall smaller in size than purified stem cells and have a 30-fold increased pulmonary passage than mesenchymal stem cells, IV delivery of MNCs may thus lead to the same effects within the brain as IA because a sufficient number of cells may penetrate the central nervous system. Higher numbers of MNCs thus does not lead to a greater effect (ceiling effect), but lower doses such as 1 million cells/kg do not lead to enough cells entering the brain. This notion is supported by our previous experiment in which pretreatment with a nitric oxide antagonist inhibited vasodilation, significantly reduced the entrance of MNCs into the peri-infarct area, and prevented MNCs from reducing neurological deficits.

In further support of the concept that IV and IA MNCs lead to the same effects within the central nervous system, we investigated various mechanisms that may be therapeutic targets of MNCs. We and others have reported that some types of cell therapies may decrease infarct cavity by possibly reducing infarct maturation and delayed cell loss in the peri-infarct areas in the days to weeks after stroke onset. A high dose of MNCs by IV or IA delivery also led to upregulation of various aspects of the regenerative response, such as DCX-positive cells in the striatum (reflective of neurogenesis), vessel density within the peri-infarct area, GAP-43 (reflective of synaptic plasticity), and the neurotrophin, BDNF. These results suggest that the
intracerebral responses were similar after IV and IA delivery of MNCs. Unfortunately, because 1 million cells/kg had no effect on any of these end points (compared with saline), we could not dissect specific targets in the central nervous system that were differentially affected by the mode of delivery.

Given the lack of differences in brain responses to MNC therapy, we turned to other mechanisms that may account for their positive effects in the stroke model. Some cell therapies may exert their beneficial effects by targeting systemic immune responses emanating from peripheral organs such as the spleen rather than within the brain or in addition to their effects in the brain. In this study, we found similar numbers of MNCs in the lungs and spleen from 1 hour to 3 days after stroke at either dose. It is, therefore, possible that IV and IA led to similar effects on functional outcome because both delivery routes deposited similar numbers of MNCs to these organs. In support of this notion, IV and IA MNCs led to similar reductions of serum proinflammatory cytokines such as IL-6 and tumor necrosis factor-α. However, IV MNCs reduced IL-1p and increased IL-10 more effectively than IA MNCs, suggesting the high level of complexity involving immune regulation.

The similar biodistribution profiles of MNCs by either IV or IA may be because of the possibility that IA delivery flushes MNCs through the microcirculation rather than causing retention in the brain, leading to the deposition of cells into the venous system and then to the heart. We tested this hypothesis by assessing the presence of labeled cells in the circulation and found no differences in the number of cells in the jugular or femoral vein at 5 minutes or 1 hour after IV or IA injection. Therefore, after the initial injection, MNCs seem to circulate to the body to the same extent by IA and IV routes. IA delivery, therefore, does not bypass the filters of the lungs or other organs such as the spleen and may not confer selective advantages over IV in preferentially directing cells to the brain, at least for MNCs. In contrast, mesenchymal stem cells are cultured and adhesive and may, therefore, differ in their retention within the cerebral vasculature.

A final interpretation to account for the lack of differences between the 2 groups could be that the IA route does lead to a greater effect on central nervous system targets such as vessel density or infarct size but also causes brain injury that may offset the benefits. In reports testing mesenchymal stem cells, IA injection causes microembolization, a reduction in cerebral perfusion, and death. Thus, in the present study, we first tested the safety of IA injection with a higher dose from our previous study. We found that there was no mortality after IA or IV injection, which suggests that a high dose of MNCs was safe even when given IA. We then infused the same dose IA and found no evidence for microinfarcts using 2 injection rates: a low rate of 5 minutes and a high rate of 40 seconds; the latter infusion rate IA had been reported to cause neuronal death in animal models using neural stem cells.

Other research groups have investigated the differences between IV and IA delivery of MNCs in the rodent stroke brain. Kamiya et al also used autologous MNCs harvested before stroke and administered the cells immediately after stroke. The authors also found that IA delivery compared with IV led to more homing of cells in the brain at 2 hours but not at 24 hours after injection, but they did find that IA led to better tissue protection. In a previous report, we found no differences in the biodistribution of MNCs that were derived from bone marrow before versus after stroke when the MNCs were examined at 24 hours after injection, but we did not examine earlier time points. In another relevant study, Vasconcelos-Dos-Santos et al labeled donor-derived bone marrow MNCs with 99mTc and found no difference in labeling in the brain or other organs from early time points to 24 hours after delivery and similarly found that both IV and IA led to similar effects on stroke recovery.

Conclusions

We found no evidence that IA delivery is superior to IV as a mode of administration for bone marrow–derived MNCs in our rodent stroke model. Despite a higher number of cells in the brain initially after IA delivery, there was no difference in functional or structural outcomes between the 2 routes. The IA route of delivery does not prevent cell trapping in peripheral organs. Our findings suggest that IA does not confer additional benefits beyond IV administration for MNCs in our animal stroke model.

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Disclosures

None.

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Intra-Arterial Delivery Is Not Superior to Intravenous Delivery of Autologous Bone Marrow Mononuclear Cells in Acute Ischemic Stroke

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