Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS) II

Sean I. Savitz, MD; Michael Chopp, PhD; Robert Deans, PhD; S. T. Carmichael, MD; Donald Phinney, PhD; Larry Wechsler, MD

Abstract—Cell-based therapies represent a new therapeutic approach for stroke. In 2007, investigators from academia, industry leaders, and members of the National Institutes of Health crafted recommendations to facilitate the translational development of cellular therapies as a novel, emerging modality for stroke from animal studies to clinical trials. This meeting was called Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS) and was modeled on the format of the Stroke Therapy Academic Industry Roundtable (STAIR) meetings. Since publication of the original STEPS guidelines, there has been an explosive growth in the number of cellular products and in the number of new laboratory discoveries that impact the safety and potential efficacy of cell therapies for stroke. Any successful development of a cell product will need to take into consideration several factors, including the preclinical safety and efficacy profile, cell characterization, delivery route, in vivo biodistribution, and mechanism of action. In 2010, a second meeting called STEPS 2 was held to bring together clinical and basic science researchers with industry, regulatory, and National Institutes of Health representatives. At this meeting, participants identified critical gaps in knowledge and research areas that require further studies, updated prior guidelines, and drafted new recommendations to create a framework to guide future investigations in cell-based therapies for stroke. (Stroke. 2011;42:00-00.)

Key Words: cell therapy ■ guidelines ■ stem cells ■ stroke

Cell-based therapy is a potential new treatment approach for stroke. Over the past 20 years, there have been extensive efforts to develop and translate new stroke therapies, but there remains no proven treatment aside from tissue plasminogen activator for acute ischemic stroke. When neurological deficits persist, despite acute treatment, there is no Food and Drug Administration-approved therapy to enhance recovery. Given the difficulties of identifying new treatments for stroke and the promising results of cell therapy in animal stroke models, investigators from academia, industry leaders, the National Institutes of Health, and the Food and Drug Administration convened in 2007 to discuss research guidelines in the field following the format of the prior Stroke Therapy Academic Industry Roundtable (STAIR) meetings. This meeting was called Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS).

Since publication of the first STEPS meeting, there has been an explosive growth in the number of cellular products in patients with stroke have emerged since the STEPS 1 publication and are mainly focused on the use of heterogeneous cell populations such as umbilical cord blood or the mononuclear fraction of bone marrow. Even some types of more purified populations of bone marrow such as marrow stromal cells may be heterogeneous depending on culture passage and isolation procedures. Not all types of cell-based preparations necessarily include stem cells and the field may be more appropriately termed cell-based therapy rather than stem cell therapy. Clinical trials testing cellular products in patients with stroke have emerged since the STEPS 1 publication and are mainly focused on the use of autologous mixed cell populations. The application of allogeneic, “off-the-shelf” cells to patients with stroke is poised for early-stage clinical testing. It is therefore timely and necessary to update preclinical and clinical trial guidelines for translating cell-based therapies for stroke. A workshop was held on crafting suggestions for preclinical studies that should be performed on any cellular product that is being developed as a potential therapeutic for stroke. A second workshop

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focused on suggestions for early-stage clinical testing of cellular products in patients with stroke. The recommendations from these workshops are described subsequently and agreed on by the participants listed at the end of this article following the format of the prior STAIR meetings.1

Updated Preclinical Guidelines

The prior STEPS document2 described recommendations on preclinical testing. We refer back to the original document regarding cell delivery (Table 1) and cell dosing (Table 2). We now provide modifications and add new recommendations regarding the following factors that apply to both ischemic stroke and intracerebral hemorrhage (Table 3).

Cell Characterization

The intended cellular product needs to be sufficiently described for several purposes, including cell identity and characteristics, conducting experiments by other groups for reproducibility, and evaluating safety risks. At a minimum, it is important to provide immunophenotyping in any peer-reviewed publication. For ex vivo expanded products and nonexpanded products, it is suggested to perform and publish transcriptional profiling as an open code approach to cell characterization. It is recommended that references be provided citing laboratories that have independently derived the same characterized cell therapy product using published methodologies. Guidance documents from the Food and Drug Administration on cell characterization ask for information about the identity, purity, viability, potency, stability, and dosage (www.fda.gov/cber/guidelines.htm).

Animal Species

We refer to the prior STEPS document and add the following recommendations. A stepwise approach would be useful to test a cellular product in models that address the heterogeneity of different types of stroke. Rodent models are well established and multiple strains and genetic backgrounds can be exploited. Large animal models may be helpful for specific situations in which they permit testing of specific neuroanatomical structures (white matter), specific types of imaging, or delivery options. Primates and other large animals also allow for testing in gyrencephalic brains. Animal models should be exploited to examine the effects of age (young versus old), gender, and comorbidities (hypertensive, diabetic, etc) on the therapy being investigated. These baseline conditions are important given that patients with stroke tend to be older and have vascular risk factors. Testing of cellular products in multiple, independent laboratories is crucial for reproducibility, robustness of effect, and to broaden the compendium of preclinical studies.

Stroke Models

There are many types of focal ischemic stroke and intracerebral hemorrhage models causing injury in cortical or subcortical areas of the brain. Evaluation of a cell-based approach is important in multiple focal ischemic stroke or intracerebral hemorrhage models using appropriate histological and behavioral tests. We recommend models that produce deficits that persist up to 4 weeks after stroke.

Preclinical Safety Indices

Safety includes tumorigenicity, immune sensitization, biodistribution, persistence, and cell fate and these issues are referenced in the following guidelines from the Food and Drug Administration (www.fda.gov/cber/guidelines.htm). As stated in the STEPS 1 document, cell therapy studies should include measures for detecting tumor or ectopic tissue formation, overt behavioral abnormalities, and adverse physiological alterations according to Food and Drug Administration guidelines. The duration of safety testing will vary depending on the cell type, but exogenous cells that die within days to weeks after injection in vivo or that already have been proven safe in patients with other clinical disorders may not require long-term testing in animals. Other types of cells with high proliferative and differentiation profiles such as embryonic or neural progenitor cells will likely require more extensive and long-term monitoring such as histopathology to assess for overgrowth and tumor formation.3 Positive controls for tumor formation or overgrowth, when available, and relevance of immunosuppression regimens

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Table 1. Guidance on Cell Delivery Approaches

| 1. Establish compatibility of cells with delivery device and determine optimal cell density and delivery volume necessary for efficacy |
| 2. Intracerebroventricular: requires further safety and feasibility study |
| 3. Direct intracranial injection: may be most suitable for neural stem cells |
| 4. Intra-arterial: requires demonstration that cells do not lead to microembolism and brain infarcts |
| 5. Intravenous: cells may need homing signal to brain; demonstration that cells do not cause organ toxicity or interfere with organ physiology |

Table 2. Guidance on Dosing

| 1. Determine MTD from the literature |
| 2. Determine dose–response curve |
| 3. Initial clinical trials should be based on animal studies of the optimal dose |
| 4. Dose ranges will likely be negotiated with regulatory agencies and historical MTD |

MTD indicates maximum tolerated dose.

Table 3. Recommendations for an Experimental Program

| Testing a Specific Cellular Therapy for Stroke |
| 1. Any cellular product needs to be well characterized |
| 2. Testing should be performed in multiple focal ischemic stroke or intracerebral hemorrhage models including animals with baseline conditions (aged, hypertensive, diabetic, etc) |
| 3. Safety measures include detecting tumor or ectopic tissue formation, overt behavioral abnormalities, and adverse physiological alterations according to Food and Drug Administration guidelines; assessing pulmonary function is suggested for intravenous delivery routes |
| 4. Control groups need to be well designed; examples include the vehicle solution or functionally irrelevant cells |
| 5. Studying cell deposition, migration, persistence and fate is important to investigate in the stroke model in any plan to design a potential clinical trial |
| 6. Defining the underlying mechanisms of therapeutic action may contribute to accurate clinical end point selection and appropriate biomarkers for treatment response |

MTD indicates maximum tolerated dose.
should strongly be considered. All adverse behaviors during the life of the animal after cell injection should be evaluated and tracked if observed. Acute toxicity of relevant organ systems should also be tested based on the delivery route. For example, the effects of cells on cerebrovascular blood flow or cerebral perfusion should be evaluated for an intra-arterial route of delivery.4 Pulmonary function should be evaluated for an intravenous delivery route for cells that accumulate within the first-pass filter of the lungs.5 Such tests might include respiratory rate and arterial blood gases. The rate of infusion is an important variable with respect to assessing these safety outcomes.

**Outcome Measures**

The primary goal of initial testing should be to address safety risks evaluated around cell identity, method of isolation, and expansion procedures. Once safety is established, functional end points should be the mainstay of primary outcomes. There are various behavioral outcomes within the domains of motor control, sensation, and cognition.6 Testing a cellular therapy using multiple different behavioral studies is favored to support robust efficacy. A battery of behavioral end points should be selected that are sensitive to the degree of injury, sites of damage, and severity of impairment.7,8 Testing should be performed multiple times in a longitudinal fashion for at least 1 month after treatment. Positive, neutral, and negative outcomes should be reported. It is also recommended to test cellular therapies in >1 laboratory to assess reproducibility of safety and efficacy.

**Treatment Protocols**

It is important to establish a dose–response curve and determine an optimized dose and treatment schedule as well as the minimum threshold for observed benefit. The chosen preclinical regimen should correlate with the intended clinical protocol, including delivery route and treatment schedule regimen, with single and cumulative dose greater than anticipated in clinical testing. There are limited data available regarding serial dosing for benefit or with respect to immune sensitization; further research is therefore encouraged. Negative controls are the subject of much debate. At a minimum, we recommend the vehicle solution of the cellular product. Other controls include dead cells, although cellular debris might be less desirable compared with cells that remain intact but are nonfunctional. It has been shown that freeze–thawing of grafted cells can worsen outcome after stroke.9 If immunosuppression will be needed in a clinical trial, it is recommended to study the cellular product with immunosuppressive agents along with a separate group receiving the immunosuppressive agents alone. Consideration may also be given to applying clinically relevant rehabilitation to all treatment groups in functional testing.10 Finally, comparing different therapeutic cell products would contribute greatly in this emerging field.

**Biodistribution and Cell Persistence**

Studying cell deposition, migration, persistence, and fate in stroke models may have value relative to defining mechanistic pathways. Because engraftment of delivered cells remains low whenever it has been examined, methods to improve engraftment should be evaluated for those cellular products in which engraftment is necessary to achieve benefit. Noninvasive imaging to address these issues is insightful and could be developed as a surrogate biomarker for translation to the clinical arena.

**Mechanisms of Action**

Defining the underlying mechanisms of therapeutic action may contribute to timing and duration of therapy, accurate clinical end point selection, and appropriate biomarkers for treatment response. Epigenetics, tissue microarray, and other emerging technologies are providing insight into mechanism of action of cellular therapeutics. Studies should consider cell–host interactions, including the site of injury, immune system effects, interaction with parenchymal cells, and remodeling of the microenvironment. Such approaches may also rule out irrelevant pathways and give insight to clinical trial design. Although some studies suggest that certain cell types when injected into the brain after stroke may lead to differentiation of donor cells into host brain cells, the majority of exogenous cells under investigation at the present time exert so-called “nursing functions” to the injured brain such as cytoprotection or stimulation of endogenous repair mechanisms.11 Clarifying the mechanisms of action is generally useful but is not a prerequisite for proceeding to human clinical trials provided sufficient, encouraging, and reproducible preclinical evidence of efficacy exists.

**Guidelines on Designing Early-Stage Clinical Trials**

**When to Start Clinical Trials**

We encourage confirmation of pivotal preclinical results in at least 2 laboratories and 2 species (Table 4). Understanding the mechanism of action is not essential before initiating clinical trials but such information is desirable to plan strategies, including treatment regimen, route of administration, and outcome measures.

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**Table 4. Recommendations for Early-Stage Clinical Trials**

| 1. Confirmation of pivotal preclinical results in at least 2 laboratories and 2 species; identifying the key mechanisms of action is not essential before initiating a clinical trial |
| 2. Including heterogeneous stroke types improves recruitment and provides robust safety information, whereas a more homogeneous stroke population may be more desirable for detecting early efficacy signals or determining a biological target |
| 3. Route of delivery should be based on preclinical data regarding mechanism, biological target, and cell type |
| 4. Preclinical data and the proposed mechanisms of action should drive decisions regarding timing of therapeutic delivery |
| 5. Imaging should be used to establish the size and location of the infarct |
| 6. Safety end points and the duration of patient monitoring will be negotiated with regulatory agencies and should be driven around cell type, delivery routes, biodistribution of cells, and other preclinical data |
| 7. Intravenous delivery of exogenous cells should be monitored for acute infusional toxicities and pulmonary complications |

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Patient Selection
We highly encourage initial testing in patients with stroke, not healthy control subjects, and enroll patients who will be informative based on safety profile and the anticipated biological effect of the cellular product. The selection of heterogeneous (eg, all types of ischemic stroke) versus patients with homogeneous stroke (eg, middle cerebral artery stroke) depends on a number of factors. Including patients with heterogeneous stroke improves recruitment and provides more robust safety information, whereas a more homogeneous stroke population may be more desirable for detecting early efficacy signals or determining a biological target. The size and location of the infarct may be important to use as selection criteria, particularly when efficacy is a consideration. Inclusion and exclusion criteria may vary with the cell type, delivery, and treatment time window.

Route of Therapy and Biocompatibility of Devices
We refer to the STEPS 1 document2 and add that the route of delivery should be based on preclinical data regarding mechanism, biological target, and cell type. Assessing the biocompatibility of devices with the cell product is useful and important.12 More information can be found in the STEPS 1 guidelines.

Timing of Cell Therapy
Preclinical data and the proposed mechanisms of action should drive decisions regarding timing of therapeutic delivery. In addition to exploring the optimal timing for effective cell therapy, the window for enrollment should also consider any information regarding when after stroke the cell product is not effective. A well-defined therapeutic window in animals is therefore highly encouraged. Classifying the timing of injury into categories such as acute, subacute, and chronic based on biological activity will eventually be necessary, but, at the present time, there is insufficient knowledge to fully define these temporal categories.

Role of Imaging in Clinical Trials
It is important to clarify the intended purpose of imaging methods, which can be applied for various purposes, including patient selection, surrogate end points, safety, and exploration of mechanism (eg, repair measures). We advise incorporating imaging to establish the size and location of the infarct. When feasible, advanced imaging techniques may be considered for exploring the mechanisms of action or surrogates of activity of the cellular therapy. Several imaging biomarkers of recovery are actively being explored.13 Further studies are needed, however, to validate imaging end points as surrogate outcomes measures. To this end, a stroke recovery neuroimaging consortium is highly recommended. Imaging is also very useful in the preclinical setting to monitor biodistribution of delivered cellular products. Although there are no accepted techniques to label and monitor cells for clinical testing, several approaches are currently available, including iron, indium, thallium, gadolinium-based agents, etc.14,15 More investigation is urgently needed to develop safe and reliable labeling techniques for deployment in clinical trials. Whatever labeling approach is chosen, it is important to assess that the label does not impair viability of the cellular product. It is also recommended to test the effects of the label on various in vitro functional assays of the cellular product.

Immunosuppression
The decision to consider immunosuppression is based on a number of factors, including whether the cellular product is autologous or allogeneic. At present, it is unknown whether immunosuppression in a stroke clinical trial is necessary for some allogeneic cells that have been shown to exert immunomodulatory effects. Immunosuppression may be more relevant if long-term engraftment of the cellular product is thought to be required for effectiveness. If immunosuppression is used, there should be a robust monitoring plan and follow-up in all early-phase trials. Another consideration is HLA matching, the benefits of which are well known in transplantation biology.16,17

Controls in Cell Therapy Trials
Comparison of outcomes to a placebo arm may be useful, particularly for detecting initial evidence for efficacy, but no early-phase study would likely be sufficiently powered to detect a difference. However, in early-phase studies, safety issues are most important and control subjects reduce the sample size of informative patients. Placebo control subjects, nevertheless, may allow a reasonable comparison of safety outcomes with a similar population treated under the same conditions with the vehicle as patients treated with active cells. One way of addressing this issue is to use an uneven randomization scheme, which assigns a higher number of active to placebo subjects. We therefore recommend justification for incorporating a placebo arm in Phase I/IIa testing. An alternative approach is to use historical data from a database such as Virtual Stroke International Stroke Trial Archive (VISTA). Standard of care should be provided to all control patients. We recommend using American Heart Association guidelines for rehabilitation to ensure standardization of poststroke care. Capturing and controlling for confounding factors is highly encouraged.

Outcomes
Safety end points will likely be negotiated with regulatory agencies and should be driven around cell type, delivery routes, biodistribution of cells, and other preclinical data. Similarly, the duration of monitoring for safety end points needs to be negotiated with regulatory authorities. For cell types that die within days after administration, long-term monitoring beyond 6 months is likely unnecessary. Intravenous delivery of exogenous cells should be monitored for acute infusional toxicities and pulmonary complications. The selection of functional end points in stroke is the subject of much debate. The traditional outcome measures of the National Institute of Health Stroke Scale, modified Rankin Scale, or Barthel Index still have merit but other, more novel end points should be developed and considered. Domain-specific modalities such as language or hand function may also be suitable or even more desirable outcome measures in efficacy studies. Any novel outcome measures should be validated and peer-reviewed.
Table 5. Areas That Require Further Research That Would Advance the Field

1. Develop cell labeling techniques that are safe for clinical testing and are reliable to monitor and track cells administered to patients
2. Develop and validate surrogate markers of stroke recovery
3. Stroke recovery imaging consortium is needed to develop imaging endpoints that could guide Phase IIB testing

Conclusions

Cell-based therapies may represent a new therapeutic modality for stroke. Not all types of cell-based preparations necessarily include stem cells. Therefore, this emerging field may more appropriately be termed “cell-based therapy” rather than solely “stem cell therapy.” Nevertheless, all of these approaches fall under the rubric of “regenerative medicine,” which represents a cutting-edge approach to ischemic injury of the nervous system. To accelerate the field of cell therapy for stroke, we have updated the recommendations from the prior STEPS meeting and identified key translational barriers that need further study, including cell labeling, imaging, biodistribution of exogenous cells in patients, and identifying imaging biomarkers of stroke recovery (Table 5). Given the monumental failures of neuroprotective agents for acute stroke over the past 20 years, these guidelines are based, in part, on the lessons learned from those prior failures in the hopes of facilitating the successful development of cellular therapies for stroke from preclinical studies to early-stage clinical trials.

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Writing Committee

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STEPS II is a promising new treatment approach for stroke. This study builds on the findings of the original STEPS I trial, which demonstrated the safety and feasibility of using mesenchymal stem cells to repair damage caused by stroke. The STEPS II trial aims to further evaluate the efficacy of this therapy by comparing it to standard of care treatments. The study involves multiple centers across the United States and is expected to enroll over 200 patients.

keywords: stem cell therapy, stroke, neuroprotection, outcomes
表3
脳卒中の特異的内服薬療法の検証に際する実施プログラムに関する指針

1. 脳卒中観察時期の特性診断が必要である。
2. ベースラインの観察（重聴、脈拍、脈拍数、脈拍数）を有する動物を対象とする研究を含むものも含む必要がある。
3. 安全性の観点として、FDAのガイドラインに従い、実験動物を含む実験動物を含む必要がある。
4. 実験動物を有する動物を含む必要がある。
5. 実験動物を有する動物を含む必要がある。

表2
投薬量に関するガイダンス

1. 文書を基にMTDを決定する。
2. 有効性の観点を考慮する。
3. 初回の臨床試験は、有効性量に関する動物試験に基づいて行う。
4. 用量増減は慎重に、過去のMTDを考慮し、増減を考慮した投薬量を決定することになるであろう。

MTD：最大投与量。
前臨床試験における安全性の指標

安全性の問題には、腫瘍形態異常、免疫反応、血生検、統制、特異体硬化などがあり、FDAのガイドラインではこれらを考慮している（www.fda.gov/sbir/guidelines.htm）。STEPS 1のガイドラインに従えば、組織学的異常、発生しないな行動異常、有害な生理学的変化を検出する方法を含むことが必要である。安全性評価の開始は細胞の種類によって異なるが、生体内に注入された後、数日〜数週間にわたり観察される外来細胞、または臨床試験を受ける患者の安全を証明されている外来細胞の場合は、臨床的一般的経過は不要であると思われる。腫瘍形態や腫瘍変性細胞など、高増殖性・高分化性の細胞をもつ細胞の場合は、異常増殖や腫瘍形成を評価するための組織学的検査等をより広範かつ長期の動物試験を行う必要があると考えられる。観察細胞や異常細胞の増殖性抑制の利用（実際施設の場合）や、免疫抑制療法の本当性についても積極的に検討すべきである。細胞注入後、動物の生体内に生きるか否か、有害な細胞の行動評価を行い、有害な行動が観察された場合は脱器を行う。また、観察細胞に、毒性測定系の急性毒性試験を実施する。例えば動脈内投与を用いる場合は、脳血管内、血流、すなわち脳灌流に対する細胞の影響を評価すべきである。また、脳の初期通過フィルターに著しい細胞細胞内専用投与される場合には、脳機能評価を行うべきである。これに倣うべきは、呼吸器や動脈内血流の測定が含まれる考えられる。これらの急性評価項目に対する試験では、注入速度が重要な変数となる。

評価項目

初期の試験では、細胞の特徴、分裂方法、増殖形態を含む安全性をリスク評価を主な目標とし、安全性が確立された後、機能評価項目を主要評価項目の中心に据えるべきである。運動制御、感染、顕微鏡観察には、さまざまな行動評価項目がある。治癒効果の評価方法を挙げれば、さまざまな行動試験によって細胞療法の検証を行うことが望ましい。創傷の程度、損傷部位、障害の発症に対する感染の高さ、一例の行動評価項目を選択すべきである。試験は、治癒成績に大いに影響を与える。複数回実施し、同定、中止、否定的な結果をすべて報告すべきである。さらに、安全性および有用性の判定評価のためには、複数の研究施設で細胞療法の試験を実施することが望ましい。

治療プロトコル

用量反応曲線を確定し、適切用量および治療スケジュールを決定することが重要である。送達路線や治療スケジュールの計画を含め、選択した前臨床における投与法は、選択している細胞治療の試験における用量を増減する中に、或いは用量増減のスケジュールの変更が必要とされる。治療効果の変化を示すために、適切な評価尺度の変更を考慮する必要がある。用量増減の変化を示すために、適切な評価尺度の変更を考慮する必要がある。

生体内分布および細胞の存続

脳浮腫モデルを用いた細胞の桜香・遊走・生存・移植に関する研究は、統計に基づく測定を定めると用量の変化が必要である。投与された細胞の生存率は、この試験でも低いほどとされているが、生存率を規定する基準が確定されている細胞療法に関するのは、生存率を高める方法の評価が必要である。こうした問題は、見え隠れの増進像検査法の得られるのに有益であり、さらに臨床分野に応用するための代謝バイオマーカーとして開発することも可能であると思われる。

作用機序

治療の発症と副作用の関係が明らかにされれば、治療の発症と副作用の関係が明らかにされれば、治療の発症と副作用の関係が明らかにされれば、治療の発症と副作用の関係が明らかにされれば、治療の発症と副作用の関係が明らかにされれば、治療の発症と副作用の関係が明らかにされれば、治療の発症と副作用の関係が明らかにされれば、治療の発症と副作用の関係が明らかな関係がある。
初期臨床試験のデザインに関するガイドライン

初期臨床試験開始時期

中核的な知見を獲得するためには、2つ以上の研究施設で2種類以上の動物種を用いて確認することを推奨する（表4）。

| 初期臨床試験開始時期 | 2つ以上の施設で2種類以上の動物種を用いて確認することを推奨する。 |
タリングに関しても、一般に広く認められている方法は少ない。今後、より精度高く、迅速に検査を実施し、診断の迅速化を図ることが重要である。特に慢性の治療において、細胞数の増加が見られる場合、再発の危険性が高いと判断されるため、早期発見が重要である。

### 結論

細胞療法は、脳卒中患者の新たな治療ツールとなる可能性がある。まず、すべての種類の細胞が転換性癌に合っているわけではない。この新しい分野のメリットは、「幹細胞療法」に限定されず、「細胞療法」とする方が適切である。いずれにせよ、これらのアプローチはすべて「再生医療」という名で呼ばれ、神経系の機能障害に対する先駆的な治療アプローチである。脳卒中に対する細胞療法の可能性をさらに高めるためには、今後の研究が急務である。
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開示

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