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;42:825-829.)

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 and types of cells under investigation for stroke. Cells have been prepared and isolated from a range of different tissues, including blastocysts, embryonic and fetal tissue, neural tissue, bone marrow, peripheral blood, umbilical cord, placenta, amniotic fluid, menstrual blood, dental pulp, and adipose. Induced pluripotent cells have emerged based on new technology to reprogram adult skin fibroblasts into pluripotent stem cells with the potential to differentiate into cells from all 3 germinal layers, including neurons and other cells that comprise the nervous system. Many types of cell-based preparations are composed 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 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 pub-
lish 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 dos-
age (www.fda.gov/cber/guidelines.htm).

Table 1. Guidance on Cell Delivery Approaches

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

Table 2. Guidance on Dosing

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

Animal Species
We refer to the prior STEPS document and add the follow-

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

Stroke Models
There are many types of focal ischemic stroke and intracere-
bral hemorrhage models causing injury in cortical or subcorti-
cal 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 behav-
ioral 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 STEPS1 document, cell therapy
studies should include measures for detecting tumor or |
ectopic tissue formation, overt behavioral abnormalities, and |

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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. Positive controls for tumor formation or overgrowth, when available, and relevance of immunosuppression regimens 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. Pulmonary function should be evaluated for an intravenous delivery route for cells that accumulate within the first-pass filter of the lungs. 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. 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. 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. 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. 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. 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.

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.
biomarkers of recovery are actively being explored. Further surrogates of activity of the cellular therapy. Several 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. 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

**Table 4. Recommendations for Early-Stage Clinical Trials
Testing a Cellular Therapy in Patients With Stroke**

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

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 document 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. 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. 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. 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.

**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
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

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.

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

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脳卒中に対する新たな治療パラダイムとしての幹細胞療法(STEPS)II

Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS) II [Special Report]

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

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Keywords：幹細胞療法、ガイドライン、幹細胞、脳卒中

幹細胞療法は、脳卒中の新たな治療アプローチである。2007年に米国国立衛生研究所の所属機関が発表し、脳卒中の新たな治療法を開発し、脳卒中の新たな治療法を有する大企業の研究者らが集まって発表した。この企画はStem Cell Therapy as an Emerging Paradigm for Stroke (STEPS)と呼ばれ、Stroke Therapy Academic Industry Roundtable (STAIR)会議と呼ばれる。最新のSTAIRガイドラインは発表されており、細胞因子の新Ⓒの数、脳卒中の細胞療法の安全性と潜在的な効果に対する研究が発表されている。

脳卒中に対する新たな治療パラダイムとしての幹細胞療法(STEPS)II

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が治療に関する推奨が述べられ、これらワークショップの推奨は過去のSTAIR会議の形式をとった記述であり、本稿の最後にリストが掲載されているワークショップ参加者により合意されている。

### 最新の前臨床ガイドライン

過去のSTEPSガイドライン2には、前臨床試験に関する推奨が示されている。細胞培養法（表1）および細胞投与量（表2）については初版の記述を基に、さらに虚血性脳卒中と脳内出血の両方および脳卒中発症を含めた細胞内処理に関する推奨について、今回の改訂内容を新たに追加された推奨（表3）を示す。

### 細胞特性の解析

開発を目指す細胞製剤については、他の研究グループが基盤実験を行ったり、安全性のリスクを評価できるよう、細胞の特徴や特性などを詳細に記述する必要がある。そこで、この視点を踏まえた研究内容を一覧表として示すことを提案する。既存の手法を用いて新しい特性をもたらす細胞動態制御を独自に得た研究を、参考としてあげることが望ましい。細胞特性の解析に関するFDAのガイドライン文書では、特徴、細胞、

### 表1 投与量に関するガイダンス

1. 文献を基にMTOを決定する。
2. 用量依存の有無を検討する。
3. 初回の細胞投与量は、治療適応に関する動物試験に基づいて行う。
4. 用量検討は慎重に行い、過去のMTOを考慮し、傾向を出力するうえで決定することになるであろう。

MTO：推奨適用量

### 表3 動物中の多段階的制御を検討する実験プログラムに関する推奨

1. 細胞動態製剤の誘導特性を記載する。
2. ペースラインの測定（体重、体長、頭部、尾部）を含む動物の作成のため、複数の動物の使用量を考慮した細胞動態を測定する必要がある。
3. 細胞動態製剤の作成が、動物動態の誘導、薬剤の生物学的特性を考慮した細胞動態を測定する。
4. 細胞動態を測定した動物を用いることが必要である（表2）。測定後に観察される細胞動態を測定することができる。
5. 新たの動態・動態・動態・動態に関する研究は、動物のモデルを用いることにおいて、その基に測定される細胞動態を測定するうえで重要である。
6. 生理学的解剖学的制御のものが不明な場合、適正な細胞動態を考慮した細胞動態を測定する。
前臨床試験における安全性の指標

安全性の問題には、暗顕形成性、免疫原性、生体内分布、持続性、細胞毒性などがあり、FDAのガイドラインをより進んだ段階で扱われている（www.fda.gov/ohrms/od/div11/guidelines.htm）。STEP 1のガイドラインで述べられているように、細菌療法の試験ではFDAのガイドラインに従い、免疫法または異常免疫組織形成、明らかに行動異常、有害な生物学的変化を検出す方法を含むことが必要である。安全性試験の間は細胞の増殖によって異なるが、生体内に注射した後、数日～数週間で死滅する外来細胞、他の臨床疾患を有する患者で特に安全性が証明されている外来細胞の場合、長期の動物試験は不要であるとも思われる。細胞療法や細胞内乾細胞など、高増殖性・高分化性のプロフィールをもつ細胞の場合は、異常増殖や転移を評価するための臨床試験の検査をより、より広範かつ長期のモニタリングを行う必要があると考えられる。転移形成、異常増殖の陽性陽性の動向（圧縮可能な場合）、免許制限条件の適当性についての検討を必要とす

治療プロトコル

用量反応性を確認し、適切な用量および治療スケジュール、観察される効果の最低施用量を決定することが重要である。治療薬剤の用量サイズを計り、選択した前臨床における投与法は、適切している臨床プラトコールと相違している必要があり、単回投与および返復投与の用量は、予想される臨床試験の用量よりも多くなれない。連続投与の効果や免疫応答に関しては、限られたデータしか得られていないため、今後のさらなる研究が望まれる。陽性対照については特に重要な議論があるが、少なくとも、細胞内所産のシケ育を陰性対照として用いることが望ましい。その他の対照としては細胞残液体の範囲を保存するための内生、完全な状態を保っているが機能は失っている細胞の方が望ましいと考えられるが、死細胞体も含まれるなど、陽性対照の必要性は剿殺細胞と陽性対照の使用について、陽性対照と単独投与群を明確に設定して測定を行うことを推奨する。さらに機能検査ではすべての投与群に対して、臨床的関連のあるリガニシティの評価が検討されてよい。特に、各ホルモンの使用レベルの評価は、この新規領域に大いに寄与するであろうと推奨される。

生体内分布および細胞の存続

脳卒中モデルを用いた細胞の沈着・浸潤・生存・運命に関する研究は、術後にリスクを終了する症例を観察することができる。投与された細胞の生存率は、この試験で最も重要であると考えられる。免疫細胞の増殖や適切な機能を維持するのに寄与するか否かを考慮するため、脳卒中モデルにおける治療の効果は、生存率を推定する方法が必要である。こうした問題を扱うための非侵襲的画像診断は臨床を得るものに有益であり、さらに臨床領域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

治療の基礎となる作用機序が明らかになれば、治療の適応・経時・期間を定め、適切な臨床試験を実施し、治療効果の適切なバイオマーカーを見いだすのに役立つと考えられる。エピネフリン依存性、組織マトリックス、その他の新技術によって、細胞療法の作用機序に関する洞察がもたらされる。研究では、損傷部位、免疫反応、実質細胞との相互作用、神経環境への再構築を含む細胞-宿主相互作用を考慮する必要がある。また、こうしたアプローチをとることで無駄の継続が除外され、臨床試験デザインに対する洞察を得ることもできる。
脑袋中脑を対象とした脳卒中治療法を評価する臨床試験設計に関する推奨

1. 中央的な研究基盤の確保を、2.7所以上の研究施設で2種類以上の
   治療法を用いて調査する。臨床試験は開始する前に必要とされる作業を
   完成することとし、実施に際しては、それに伴う部署が
   同時に確保されていることを確認する。

2. 不同一的脳の脳卒中を対象とした試験の主体は、脳の脳卒中を
   発症した患者で、全ての施設で同一の基準を満たすべきである。なお、
   効果を検出するためには、可能な限りの数の患者を
   含むべきである。

3. 治療法は、脳卒中治療法の推奨、基盤の確立に関する研究基準と
   それに基づいて推奨されるべきである。

4. 健康診断の結果、発症数と結果を推奨される作用機構に基づいて決
   定されるべきである。

5. 診断検査を実施する必要がある、その大きさと位置が確認されるべきである。

6. 以外の調査の精査および健康成績の基準に従って、これを推奨する
   基準が、扱っている、他の領域における、その管理規
   則に基づいて推奨されるべきである。

7. 外来診断の基準における診断は、その結果の定義、検査を含
   むとするべきである。

治療経路およびデバイスの生物学的適性

1. 本項目におけるSTEPス1ガイドライン2を照らし、さらに
   議論経路は、機能、生物学的適性、細胞の種類に
   関する臨床試験データに基づいて決定することとする。

細胞療法の実施期間

細胞の治療的効力の研究の期間は、前臨床データ、推奨され
る作用機序に基づいて決定すべきである。有効な細胞療法の
実施実施時期を検討することに加え、組み入れる時
間を通じて、臨床前治療およびリハビリーションの期間が
実用的な期間である。この期間において、開発される新薬
開発の遅延を防ぐことが重要である。最終的には、生物的活性
に基づき、その結果を得た後、治療の有効性、安全性、効果
的なカナピリフィノンの発見するべきである。現時点では、この
期間のカナピリフィノンを詳細に規定するだけの十分な知見
が得られていない。

初期臨床試験のデザインに関する

初期臨床試験開始時期

中間的な初期臨床試験の結果は、2.7所以上の研究施設で2
種類以上の治療を用いて確証することを推奨する（表2）。
臨床試験を開始または推奨される前には、有効な治療を
検証するためには、安全的な治療を検証するためには
必要とされている。その結果をもとに、治療法を
推奨するにあたって、こちらの推奨がある方が望ま
しい。

患者の選択

初期の試験は健康成人ではなく脳卒中患者を対象として、
安全性アドバイザーとニーズに応じている細胞療法の治
療学的効果に基づいて有益な推奨が得られていることを
踏まえ、推奨される。初期の試験の脳卒中患者（あくまで
種類の多発性脳卒中など）を選択するか、それとも大脳の脳卒中患者（脳卒中脳卒中など）を選択するか、それをもとに推奨される細胞の標識やモニ

臨床試験における画像診断の役割

画像診断の意義は推奨することである。有効な治療を
検証するためには、推奨される有効な治療を検証する
ためには、その結果をもとに、治療法を
推奨するにあたって、こちらの推奨がある方が望ま
しい。
タリングに基づいて、一般に広く認められている方法はなしで、今のこと、現在のジオジオングル、タリング、カトリッジを用いた薬剤など、複数のアプローチが利用可能である。安全性と信頼性が確認された臨床試験結果の発表技術を開発するためには、より一層の研究が必要である。

いずれの標識法を選択する場合でも、標識によって細胞機能の変容が検出されていないかどうかを評価することが重要である。さらに、標識が細胞機能の各種in vitro機能試験に及ぼす影響を調べることが望ましい。

免疫抑制
免疫抑制の選択は、細胞機能性薬剤が生体細胞に同定細胞かという点を含め、多くの要因に基づいて判断される。今回は、脳卒中の臨床試験において、免疫抑制薬の選択が重要であるということである。免疫抑制は、治療効果の観点から細胞機能性薬剤の長期使用が必要であると考えられる場合により重要になると思われる。免疫抑制を行う場合は、初期試験のうるる試験において、確実なモニタリング方法と追跡調査が必要である。もう一つの検討事例はHLA適合であり、移植倉生物の利用はよりよく知られている。

細胞療法試験における対照
プラセボ群との選択の比較、特に有効性に対する初期のエビデンスを得る場合には有用であると考えられるが、初期試験の試験では差を実証するだけの十分な検出力が得られない可能性が高い。しかし、早期の試験では安全性の問題が重要であり、経験を積む者の数が少なくなる。ただし、プラセボ群を設けず、実際に細胞を投与した群と同一条件下で同様の対照群に治療を投与することによって、安全性評価の評価の有効性を高めることが必要と考えられる。しかしこの問題を解決する1つの方法は、Virtual Stroke International Stroke Trial Archive (VISTA)などのデータベースに収められた疫学データを用いることである。対照群の患者が何らかの標準治療を行う、脳卒中後のケアの標準化には、神経回復開発機関（AHA）のリハビリテーションガイドラインを推奨する。経口薬の把握と管理も強く奨励される。

評価項目
安全性評価項目については、おそらく規則当方と編集
参考文献