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 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.

Updated Preclinical Guidelines

The prior STEPS document 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 regarding 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 neuroana-

### 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 injuries |
| 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

| 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 |

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. 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.

**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
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 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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Contributors

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References

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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(STEMPS)II

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

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

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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(STEMPS)II

新規：細胞療法は、新しい脳卒中治療アプローチである。2007年に大学、主な企業、米国国立衛生研究所の実証機関から研究者が集まり、脳卒中の新たな治療パラダイムとしての幹細胞療法について、動物実験から臨床試験へと前進し、その治療効果を確認するための研究開発を遂げる。その結果、この治療法はStem Cell Therapy as an Emerging Paradigm for Stroke (STEMPS)IIと呼ばれ、Stroke Therapy Academic Industry Roundtable (STAIR)会議モデルとしている。この初のSTEMPS会議の発表以来、脳卒中研究に開かれる細胞の数や種類は飛躍的に増え、神経細胞、網走細胞、神経細胞、運動細胞、骨髄、血球、脳細胞など、さまざまな組織から細胞が採取され、多能性幹細胞に再プログラムする新技術に基づいて作られた多能性幹細胞。神経を構成する神経細胞や他の細胞を含む。このプロセスを含む細胞の一部は、脳卒中治療に寄与する可能性がある。従って、この分野は幹細胞療法における今後の研究拡張を示唆しており、脳卒中に対する治療パラダイムとしての幹細胞療法がますます重要になると考えられる。
表1

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最新の前臨床ガイドライン

過去のSTEPSガイドライン1には、前臨床試験に対する推奨が示されている。細胞内送血法（表1）および細胞内送血法（表2）については初版の記述を踏まえ、さらに臨床試験の重要性を強調している。表記した項目により、今後の臨床試験における推奨を示す（表3）を示す。

細胞特徴の解析

開発を目指した細胞内送血法は、他の研究グループが試験成績に向け、安全面のリスクを評価できるよう、細胞の特徴を特性に試験に綴る必要がある。やさしくても、任意のピアレビュー誌の免疫分類型の推奨に関する論文を発表することが重要である。体外培養培養条件および培養培養条件については、オープンコードによる細胞特性解析アプローチとして、試験プロファイリングを実施し、発明することを提案する。既存の方法を用いて同じ特性をもつ細胞培養法を独自に得た研究を、考慮しうることが望ましい。細胞特性の解析に関するFDAのガイダンス文書では、特数、細胞数、...

脳卒中モデル

脳の異常または皮質下領域が損傷された、さまざまな種類の実体細血卒中モデルや脳内出血モデルがある。細胞療法の評価は、複数の脳卒中/脳卒中または脳内出血モデルにおいて、適切な組織学的検査および行動学的検査を用いることが重要である。脳卒中後3週間程度障害が得られるモルが望ましい。
前臨床試験における安全性の指標

安全性の問題には、血腫形成性、免疫反応、生体内分布、持続性、細胞寿命などがあり、FDAのガイドラインでもこれらの問題が掲げられている（www.fda.gov/sher/guidelines.htm）。STEPS 1のガイドラインで述べられているように、細胞療法の試験ではFDAのガイドラインに従い、腫瘍または異常組織成長、明らかに行動異常、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。安全性試験の期間は細胞の種類によって異なるが、生体内に注入した後に数週間から数年間観察する外来細胞、他の臨床試験を有する患者で安全が証明されている外来組織の場合は、長期の動物試験は不要であると思われる。肝細胞や神経細胞は、高密度性・高分化性のプロフィールをもつ細胞の場合は、異常増殖や腫瘍形成を評価するための臨床的検査をすることにより、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。腫瘍形成や異常増殖の機能性の利用（例：人間可能な場合）や、免疫抑制療法の適応性についても積極的に検討する必要がある。細胞注入後、動物の生存期間中に生存できるかどうか有効な行動の評価を行い、有害な行動が観察される場合は観察を行う。また、細胞組織を用いて、観察された動物の細胞の急激な増殖を実施する。例えば動脈内移植を行う場合には、血管内皮の発生、すなわち血管新生に対する細胞の影響を評価すべきである。また、肺の初期通過フィルタに著しく減少する細胞を経口投与する場合には、肺機能評価を行うべきである。これらの検査では、呼吸数や動脈血ガスの測定が含まれると考えられる。これらの安全性評価項目に関する試験では、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、分離方法、増殖条件を考慮した安全性のリスク評価を主な目標とし、安全性が確認された後、機能評価項目を主要評価項目の中心に据えている。運動制御、感覚、認知機能には、さまざまな行動評価項目がある。治療効果の評価（1）には、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。傷害の程度、傷害部位、障害の程度に対する感度の高い、一つの行動評価項目を選択すべきである。試験は、処置開始から1カ月にわたって観察的に、複数回実施し、肯定的、中立的、否定的な結果をすべて報告すべきである。さらに、安全性および有効性の見極め評価のために、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

用量反応曲線を定義し、急性用量および治療スケジュール、観察される効果の最低限の治療を決定することが重要である。急性用量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は、医師の両者による治療プロトコルと相関している必要がある。単回投与および反復投与の用量は、予想される臨床試験の用量よりも多くなければならない。連続投与の効果や免疫効果に関しては、限られたデータしか得られていないため、今後さらなる研究が望まれる。免疫細胞についてはさまざまな議論があるが、少なくとも、細胞療法の効果を観察しして見ることが望ましい。他の対照としては、細胞の発現は、完全な状態を保っているかが重要である。細胞の発現は望ましいと思われが、死細胞も存在する。

生体内分布および細胞の存続

臨床試験を用いた細胞の汎用性・適性・生存・再発・再発に対する研究は、細胞の活性を定めるうえでの観察があると考えられる。投与した細胞の生存率は、この試験でも低い場合にもとまっているが、生存率が高いければ、その細胞の効果があるとは考えられる。こうした問題を明らかにするための非侵襲的画像診断は、可能な限り必要である。さらに、臨床前用に応用するための代用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

治療の効果を示す作用機序が明らかになり、治療の応用を決定する必要がある。適した臨床評価項目を選定し、治療効果の関連するバイオマーカーを見い出すために、投与前後の変化を示す。エピジェネティクス解析、遺伝子マッピング、その他の技術によって、細胞療法の作用機序に関する洞察が得られることがある。研究で、細胞療法、免疫療法、再生医療の相関作用、細胞療法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関係な細胞が除外され、臨床試験データに対する洞察を得ることもできる。
1. 中性炎の脳血管病変の結果、23所以上の研究報告で2症状以上の
動態を有する確認する。脳血管病変の増悪させる触覚の作用原理
を解明することに意を払う必要がある。
2. 不均一な病態の病学的変動の進行と、診断とそれに伴う病態の
診断と診断を容易にする。脳血管病変の増悪させる触覚の作用原理
を解明することに意を払う必要がある。
3. 温度がある、発熱、出血発熱症の、診断の確立に関する前線における
診断と診断を容易にする。脳血管病変の増悪せる触覚の作用原理
を解明することに意を払う必要がある。
4. 頭痛、血圧の上昇を伴う場合に、皮膚の温度を
観察することができる。
5. 頭痛、血圧の上昇を伴う場合に、皮膚の温度を
観察することができる。
6. 腦血管病変とその病態変動に関する確実な診断と
診断を容易にする。脳血管病変の増悪せる触覚の作用原理
を解明することに意を払う必要がある。
7. 腦血管病変とその病態変動に関する確実な診断と
診断を容易にする。脳血管病変の増悪せる触覚の作用原理
を解明することに意を払う必要がある。

治療経路およびデバイスの生物科学的適性

治療経路およびデバイスの生物科学的適性

治療経路およびデバイスの生物科学の適性を評価する場合と

細胞療法の実施時期

細胞療法の実施時期の種類は、前回のデータ、推測される

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

早期の初期臨床試験の結果、23所以上の研究報告で2症状以上の
動態を有する確認する。脳血管病変の増悪させる触覚の作用原理
を解明することに意を払う必要がある。

患者の選択

治療の適応側について述べる必要がある。脳血管病変の増悪させる触覚の作用原理
を解明することに意を払う必要がある。
表5 この分野が進歩するために、さらに研究が必要とされる課題

| 1. 健康診断で初めての用で、患者が報告した症状の重複性だけに主 CONTEXT に表1の最も重要とされる境界線

| 2. 最初ようした対象マーカーを診断、その後変動を確認する。

| 3. 血管・神経の程度とにおける臨床検査上の評価項目を考慮するため

| 4. 脳神経の回答に関する臨床検査コンソーシアムが必須である。

免疫制御

免疫抑制の検討は、細胞の免疫抑制を自発的に抑制するという観点を含め、安全性と有用性に基づいて判断する。今なお活性化が認められている抗がん剤の変動が重要な役割が必要とされている。免疫抑制は、治療目的に対する細胞の倉庫が必要であるという考え方により重要になる。免疫抑制を行う場合、初期の急激に現れる前回の治療計画と追跡調査が必要である。もう一つの検討事項はHLA適合であり、移植細胞移植の利点はよく知られている。

細胞療法試験における対照

プラセボ群との比較研究は、特に有効性と安全性に関する初回のエビデンスを得ることに用いる性質が高いため、初回の試験で差を検出するたとえ十分な検討が得られない可能性が高い。しかし、初回の試験では安全性が重要であり、対照群が設定すると、情報が得られる患者数が少なくなる。ただし、プラセボ群を設け、実際に細胞を投与した場合と同一条件で同様の患者群に対照を投与することによって、安全性評価項目の合理的な比較を行うことができる。この問題を避けるため、無作為割り付けを行うのではなく、基準群と割り付け患者を対照群より多くすることである。したがって、このように第1ハ期相試験にプラセボ群を組み入れる場合は、その根拠を示すことが望ましい。もう一つの方法は、Virtual Stroke International Trial Stroke Archive (VISTA)などのデータベースに収められたエビデンスを用いることである。対照群の患者ににおいても標準治療を行う、脳卒中後のケアの標準化には、国立脳機能プール(AHA)のリハビリテーションガイドラインを推奨する。結核因子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、おそらく研究者に報告されるが必要である。
ガイドライン作成委員会

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作成に携わった方々


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S.I.S. は、I&J, Celgene, Aldagen 各社より顧問料を受け取ったことがある。S.T.C. は Cortex Pharmaceuticals 社より顧問料を受け取った。

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