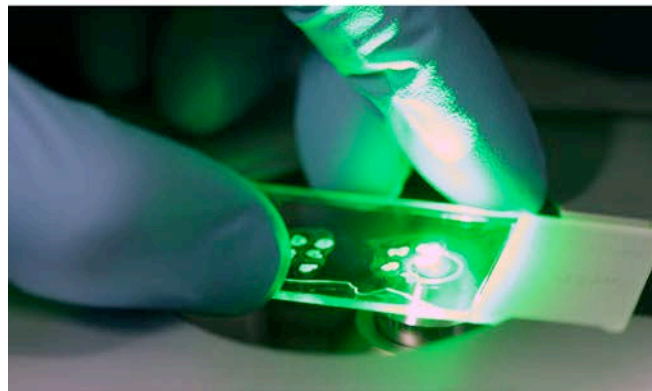




National Institute of
Neurological Disorders
and Stroke

**Stroke Preclinical
Assessment Network
(SPAN): a preclinical
network to support
translational studies for
acute neuroprotection
prior to endovascular
reperfusion therapy in
stroke**

Webinar
September 2018



Housekeeping issues

- **The webinar is being recorded.**
- **Slides will be available on the NINDS website with FAQs.**
- All phone lines will be muted during the call.
- If we disconnect due to technical issues, please remain on the line and wait until we re-connect.
- There are no webinar “chat” or “raise your hand” functions: all communication will be done through the Q/As.
- After the ~40 minute presentation, we will address questions emailed during the webinar.
- Frequently asked questions already received will be addressed in the presentation.
- The identity of persons who email questions will not be revealed to the other participants.

Presentation Outline

- Overview, structure, and goals of the network
- Submission requirements for applications
- FAQs

Targeting neuroprotection

- **2012 NINDS Stroke Research Priorities Meeting** key priorities:
 - Accelerating the translation of stroke research in preclinical animal models into clinical studies of highly promising treatments.
 - Preclinical and clinical studies to achieve robust brain protection.
- **European planning effort Multi-PART** (Multicenter Preclinical Animal Research Team; 2012-2014) proposed a paradigm shift to perform preclinical studies with the same rigor and central coordination used in phase III randomized controlled human trials.
- **NINDS workshop “Translational Stroke Research: Vision and Opportunities”** recommendations (Stroke, 2017) included preclinical multi-laboratory trials of a putative treatment, with an agreed upon protocol, rigorous good laboratory practices, a centralized randomization and data center, and on-site source verification of data as a valuable approach before investing in a clinical trial.
- **Stroke Treatment Academic Industry Roundtable (STAIR)** 2017 meeting placed a high priority on evaluating agents that could further improve outcomes following endovascular therapy. Establishing the most promising agents to take into clinical trials is an important first step.

Stroke Preclinical Assessment Network (SPAN)

Objectives and structure of SPAN:

- Will test if neuroprotection can provide additional benefit to reperfusion alone (by either improving functional outcome or extending the therapeutic window of intervention), in an experimental controlled setting.
- Up to 6 leading academic sites with published expertise with the transient middle cerebral artery occlusion (tMCAO) model of stroke and related comorbidities will test interventions (including their own) in parallel.
- A Coordinating Center will provide overall study coordination, statistical analysis, randomization and blinding, data sharing, and monitoring of the individual sites.

Vision for SPAN:

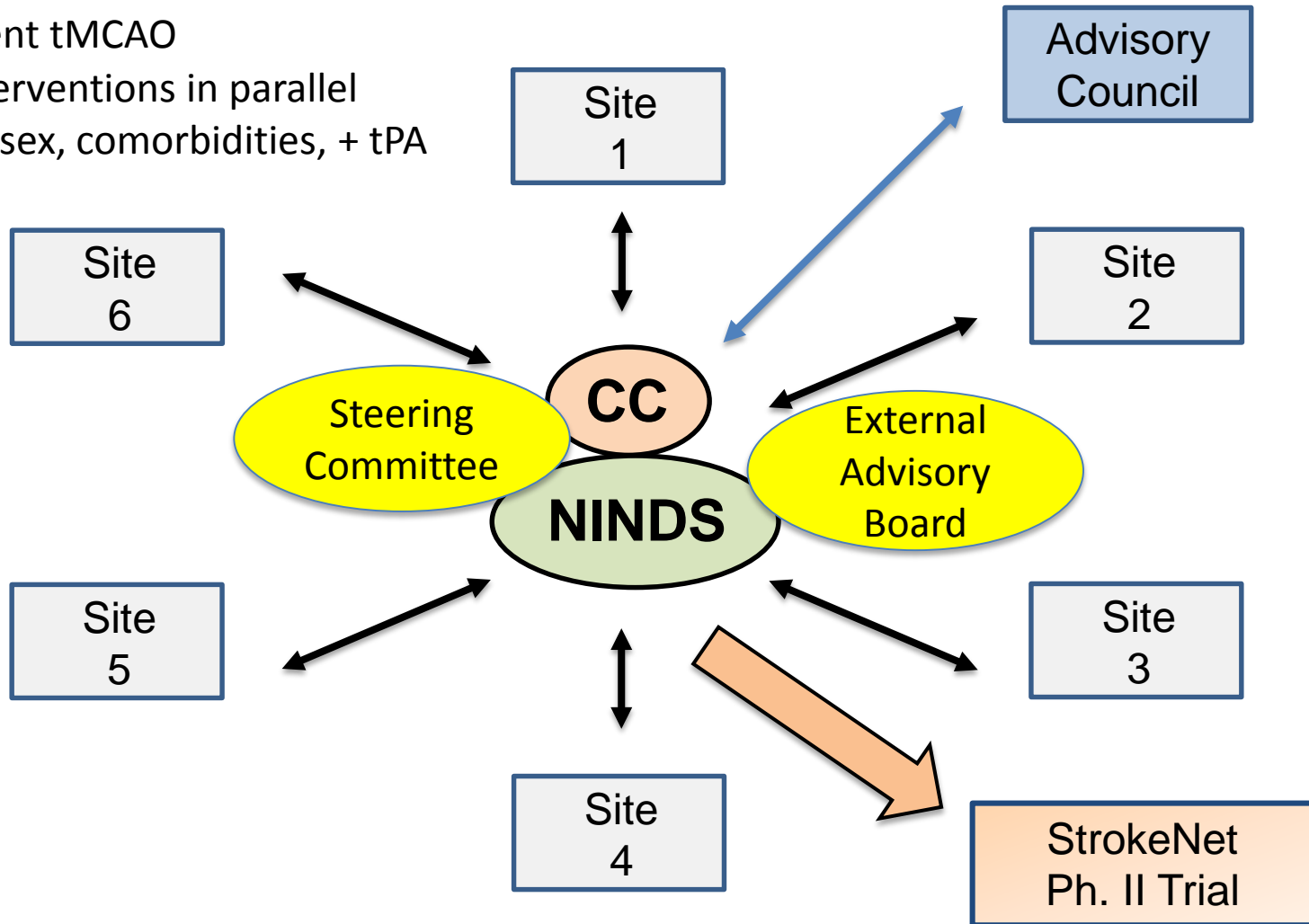
To create a novel translational model that if successful, will accelerate the identification of the most promising neuroprotective therapies for future pivotal clinical trials and span the gap between preclinical and clinical testing, in a cost-and time-effective fashion.

Key Features of SPAN Network

- Built-in replication: at least 2 labs will do the same experiments at all times;
- Built-in robustness: testing in different models of aging and comorbidities;
- Coordinating center (similar to clinical trials) will ensure rigorous and unbiased approach and overall coordination;
- Robust sample size (e.g., if each site is testing 20 animals per group, the total sample size for the network would be 120 animals per group);
- Time- and cost-effective approaches, with adaptive design, to test up to 6 interventions in parallel;
- Clinically-relevant methodologies and outcome measures;
- Steering committee with preclinical, clinical and industry representation to help transition to clinical trials.

SPAN Network Infrastructure

- Rodent tMCAO
- 6 interventions in parallel
- Age, sex, comorbidities, + tPA



SPAN Governance

- Cooperative agreements (U01/U24)- NINDS involvement
 - Adjustment of research protocols/approaches as warranted
 - Input into final milestone development
 - Serve on SPAN committees
 - Assist in promoting availability of data and resources
 - Can withhold or reduce support for failure to comply with conditions of award

- SPAN Steering Committee- PI of CC, PI of each of the network sites, NINDS program staff, three representatives from NIH StrokeNet
 - One in-person meeting per year (including initial Kickoff Meeting)
 - Frequent network calls

- External Advisory Board- basic and clinician scientists with expertise in neuroprotection, pharmaceutical and biotech representatives, and experts in regulatory affairs, statistics, and clinical trial design.

- NINDS Director

Who may apply?

- The network will include:

- Up to 6 preclinical network sites (RFA NS-18-033)
- One coordinating center (RFA NS-18-034)

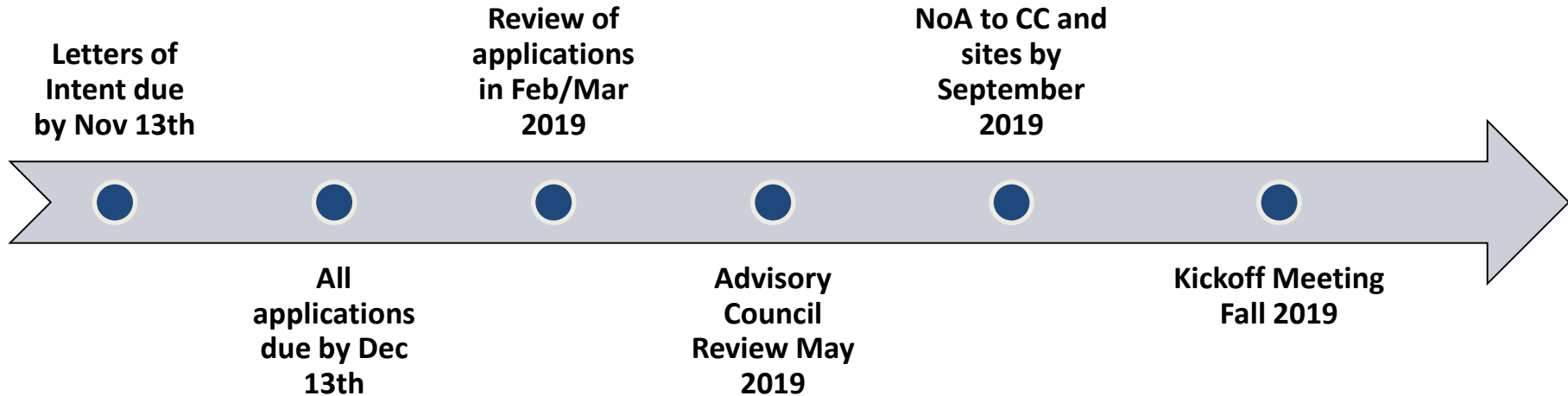
- Eligible to apply:

- U.S. Organizations (Non-U.S. entities **are not** eligible)
- Applicant organizations may submit more than one application, provided that each is scientifically distinct
- Institution being awarded as a network site **cannot** be the SPAN CC (to avoid conflict of interest) and viceversa

- PI qualifications:

- Published expertise in tMCAO model of ischemic stroke, neuroprotection, behavioral motor and cognitive outcomes, and preclinical models of stroke comorbidities (aging, hypertension, diabetes, etc.)
- Neuroimaging capabilities
- Documented expertise in leading multiple complex projects in parallel
- Minimum of 3 person months effort

SPAN Funding Timeline



SPAN Coordinating Center: RFA NS-18-034

Funding Opportunity Title

Stroke Preclinical Assessment Network (SPAN) to Support Translational Studies for Acute Neuroprotection - Coordinating Center (U24 Clinical Trial Not Allowed)

[U24](#) Resource-Related Research Projects – Cooperative Agreements

Key Dates

Posted Date

August 6, 2018

Open Date (Earliest Submission Date)

November 13, 2018

Letter of Intent Due Date(s)

November 13, 2018

Application Due Date(s)

December 13, 2018, by 5:00PM local time of applicant organization.

Expectations of the SPAN Coordinating Center

- Scientific and organizational leadership to oversee the conduct of preclinical studies within SPAN.
- Administrative center of the network with responsibility for maintaining the network's infrastructure relevant to best practices consistent with those routinely used in clinical trials.
- Must have strong expertise in data management; statistical analysis, including adaptive trial design; drug formulation; complex project coordination; randomization; and blinding.
- Expertise in stroke research is **desirable**, but **not required**.
- Leads and manages the SPAN Steering Committee.
- Specific activities could be performed through subcontracts, but the activities and the facilities need to be clearly described in the application.
- Coordinate with the network sites to ensure that testing of the selected drugs/ intervention will start no later than 1 year after the award and will be completed in the remaining 2 years of the award.

Coordinating Center Responsibilities

- Providing scientific leadership and regular communication to SPAN sites regarding protocols and study progression
- Overseeing multiple concurrent protocols
- Managing ongoing operational issues, such as subcontracts, protocol-specific site training, and site monitoring
- Developing and implementing investigator and staff training programs
- Organizing and implementing investigator meetings, including an annual in-person meeting to discuss progress and pitfalls and enhance synergy across the network
- Drug/intervention and placebo control acquisition, formulation and distribution
- Developing operational guidelines and assuring compliance with protocols and reporting
- Developing a plan for conflict resolution
- Coordinating editorial and manuscript preparation
- Managing data and resource sharing activities
- Analyzing data and adjust protocols and interventions to be performed at each site, based on the adaptive design approach
- Monitoring compliance with milestones to be determined at the time of the award.

Budgets for SPAN Coordinating Center

- NINDS intends to commit up to \$500,000 in direct costs per year to fund one award for up to 3 years
- Application budgets may not exceed \$500,000 in direct costs per year but need to reflect the actual needs of the proposed project
- The maximum project period is 3 years

NS-18-034: Key Application Components

Senior/Key Personnel Profiles:

- Description of PD/PI's qualification and experience to manage a multi-site geographically dispersed consortium or network in:
 - Statistical analysis and adaptive trial design
 - Drug formulation
 - Data monitoring, data sharing
 - Randomization, blinding and other rigorous procedures
- Commitment a minimum of 3 person months effort and documented expertise in leading multiple complex projects in parallel
- Must also include a dedicated staff member who will be the point of contact, is highly motivated, has excellent communication skills, and has significant experience with information technology and biological data management

NS-18-034: Key Application Components

Investigator Review Criteria:

- Do the PD(s)/PI(s)/Directors and other personnel have experience and an ongoing record of accomplishments in managing complex multi-site network or consortium projects?
- Expertise in drug acquisition, formulation, and distribution?
- Expertise in implementing procedures routinely used in clinical trials?
- Adequate expertise in statistical analysis, including sample size determination and adaptive trial design?
- Experience overseeing selection and management of subawards, if needed?
- A minimum of 3 month effort and dedicated staff member?

NS-18-034: Key Application Components

Research Strategy Section:

- Organize the research strategy section by-
 - Significance
 - Approach
 - Innovation
 - Milestone Plan

- Significance
 - Description how the proposed CC infrastructure and organization will address primary goal of rapid identification of neuroprotective interventions as adjunctive therapies to recanalization

 - Justification and rationale indicating that the proposed team and plan can fulfill the role of the CC as the network's information, data, and administrative hub

 - Work closely, collaboratively and effectively with the individual projects' PIs and their teams, the NINDS/NIH Program staff and the Steering Committee and External Advisory Board

NS-18-034: Key Application Components

Significance Review Criteria:

- Does the proposed Center address the needs of the research projects/network that it will coordinate/administer/serve?
- Is the scope of activities proposed appropriate to meet those needs?
- Will successful completion of the aims bring unique advantages or capabilities to the research projects/network?
- Clear understanding of the SPAN goals and the commitment to work closely, collaboratively and effectively with the individual projects?

NS-18-034: Key Application Components

Research Strategy Section:

- Innovation

Description of the leading and innovative tools and approaches offered to the network in terms of data management, communication strategies, information technology, approaches to organization of meetings and conference calls, drug development, distribution and other activities.

NS-18-034: Key Application Components

Innovation Review Criteria:

- Does the application propose novel organizational concepts, management strategies, or instrumentation in coordinating the research projects/network/ the Center will serve?
- Are the concepts, strategies, or instrumentation novel to one type of research program or applicable in a broad sense?
- Is it a refinement, improvement, or new application?
- Does the CC offer innovative tools and approaches for data management, communication, information technology, organization of meetings and conference calls, and other activities under its purview?
- Does the application describe how an innovative preclinical adaptive design would be implemented?

NS-18-034: Key Application Components

Research Strategy Section:

- Approach
 - Description of current and/or planned organizational structure under which it proposes to operate
 - Address administrative commitment, resources and ability to carry out the duties
 - Description of relationship of component(s)/affiliate(s) to each other and to the CC
 - Include the distance between these institutions (including administrative offices and shared resources) and location of proposed personnel.

NS-18-034: Key Application Components

Approach Review Criteria:

- If more than one component/affiliate institution, are the relationship and distance of component(s)/affiliate(s) to each other and to the CC reasonable to allow efficient communication and operation?
- Have the required expertise in implementing procedures routinely used in clinical trials?
- Include well described and appropriate communication and conflict resolution plans?
- Include a feasible description of how the CC will organize, coordinate and administratively drive network-specific activities?
- Is the description of how the CC will work with multiple and de-centralized investigators and schedule large interactive conference calls including with visual support feasible and appropriate?

NS-18-034: Key Application Components

Approach Review Criteria:

- Is it described how the CC will establish infrastructure, including for real time electronic data entry, to collect, curate for quality, display, house, and distribute data and how the CC will facilitate efficient and accurate incorporation of new and/or extant data via electronic data entry from remote locations?
- Is it described how the CC will assist in developing and build into its infrastructure the core set of de-identified data elements agreed upon by the network and how the CC will receive in real time, and by remote electronic submission, data from up to 6 sites, and distribute data to approximately the same number of sites?
- Does the application explain how the CC will harmonize compatible but not identically coded extant data across platforms for sharing and meta-analyses?

NS-18-034: Key Application Components

Approach Review Criteria:

- Is the plan to monitor performance and collect data from the individual project sites included and appropriate?
- Include a description of appropriate procedures for data collection and study monitoring, as well as internal quality assurance plan and procedures of the CC?
- A clear scientific, administrative, and institutional commitment to collaborate with other funded network project investigators/sites to maximize time- and cost-efficiency?
- Include an appropriate and feasible Milestone Plan, with a timeline to full functionality?

NS-18-034: Key Application Components

Research Strategy Section:

▪ Milestone Plan

- Must include 1-year well-defined milestone plan with a timeline for establishing the CC to full functionality
- Should be unambiguous, quantifiable, and justified. The final milestone plan is subject to concurrence by the CC and NINDS.
- Some examples of topics to consider include:
 - Initiate calls to organize the Steering Committee by 1 month after Notice of Grant Award.
 - Organize the SPAN Kickoff Meeting to be held within 4 months of receiving a Notice of Grant Award.
 - Organize Annual meetings (1 per year within a month of annual date of original Notice of Grant Award).
 - Develop and test the CC's information technology infrastructure for receiving real-time data entry from multiple remote locations (including imaging data) by the end of year 1.

NS-18-034: Key Application Components

Milestone Plan Review Criteria:

- Does the project include an appropriate and feasible Milestone Plan, with a timeline for establishing the CC to full functionality?

NS-18-034: Key Application Components

Resource Sharing Plan:

- Application are required to comply with the instructions for the Resource Sharing Plan as provided in the Guide
- In addition, this must also include:
 - Data Sharing Plan. The sharing infrastructure and protocols must be able to facilitate sharing within the network and with scientists outside of the network (after projects are completed).
 - Clear administrative and institutional commitment to data sharing, including strategies and ability to share raw data, images, and protocols both within the network and among other investigators.

SPAN Network Sites: RFA NS-18-033

Stroke Preclinical Assessment Network (SPAN) to Support Translational Studies for Acute Neuroprotection (U01 Clinical Trial Not Allowed)

Activity Code

[U01](#) Research Project – Cooperative Agreements

Key Dates

Posted Date

August 6, 2018

Open Date (Earliest Submission Date)

November 13, 2018

Letter of Intent Due Date(s)

November 13, 2018

Application Due Date(s)

December 13, 2018, by 5:00PM local time of applicant organization.

Characteristics of Responsive Applications

Proposed neuroprotective interventions **MUST:**

- Be supported by extensive and rigorously obtained preliminary data in a relevant experimental stroke model (tMCAO)
- Have rigorously obtained evidence of safety in humans
- Be ready to enter a Phase II clinical trial at the end of the award period

PIs and applicant sites **MUST:**

- Demonstrate expertise in assessing clinically-relevant long-term functional outcomes
- Have access to advanced preclinical imaging facilities
- Agree to test up to 6 interventions in parallel, in collaboration with the other network sites, in a randomized and blinded fashion
- Incorporate SPAN network infrastructure into their proposed study, including central coordination and data management/analysis by the CC
- Agree to become active members of the SPAN Steering Committee

Characteristics of Unresponsive Applications

- FOA is limited to neuroprotective interventions for ischemic stroke in preclinical models of cerebral ischemia followed by reperfusion
- **No human subjects** research will be supported
- Preclinical models/studies **out of scope** for this initiative include those focused on:
 - Pathophysiology of stroke
 - Primary intracerebral hemorrhage
 - Target identification/validation
 - Neonatal hypoxia-ischemia
 - Biomarker studies
- Pilot studies of neuroprotection not supported by rigorous preliminary data and/or relevant publications will not be considered
- Neuroprotective interventions that have not shown evidence of safety in humans will not be considered
- All studies not focused on transient cerebral ischemia models are out of scope

Budgets for SPAN Preclinical Sites

- NINDS intends to commit up to \$4,000,000 in direct costs to fund up to 6 awards for 3 years
- Application budgets are limited to a total of \$725,000 in direct costs over the 3 year award period
 - \$75,000 direct cost during year 1 to set up the network
 - \$325,000 direct cost during years 2-3

NS-18-033: Key Application Components

Senior/Key Personnel Profiles:

- Description of PD/PI's and investigative team's experience in:
 - Preclinical modeling of transient cerebral ischemia and neuroprotection
 - Advanced imaging and drug development
 - Clinically relevant short- and long-term outcome measures
 - Preclinical modeling of stroke comorbidities in rodents and other species
- Description of PD/PI's experience in leading and participating in complex multi-site projects
- Must also include a dedicated staff member who will be the point of contact, is highly motivated, has excellent communication skills, and has significant experience with information technology and biological data management

NS-18-033: Key Application Components

Investigator Review Criteria:

- Do the PI and investigative team have published experience in preclinical modeling of ischemic stroke?
- Neuroprotection?
- Drug development?
- Advanced imaging?
- Clinical outcome measures?
- Stroke Comorbidities?

NS-18-033: Key Application Components

Research Strategy Section:

- Organize the research strategy section by-
 - Significance
 - Approach
 - Innovation
 - Milestone Plan

- Significance-
 - Description of rationale and supporting data demonstrating the merit of the proposed neuroprotective intervention
 - Description of existing safety data in humans
 - Preliminary data and/or published literature demonstrating feasibility and efficacy should be included
 - Description of a plausible biological mechanism that is expected to be of benefit in ameliorating a specific aspect of transient cerebral ischemia

NS-18-033: Key Application Components

Significance Review Criteria:

- Are the supporting data rigorous? Do they suggest feasibility and efficacy of proposed neuroprotective intervention?
- Is there evidence of target engagement and is the mechanism of action plausible for brain ischemia/reperfusion?
- Is there evidence of safety in humans?
- Is it likely the proposed intervention will be ready for testing in clinical trials by the end of the award?

NS-18-033: Key Application Components

Research Strategy Section:

- Innovation-

- Description of cutting edge and clinically relevant attributes brought to the field of neuroprotection
- Description of overall technical advances and innovative strengths the application can offer the network

Innovation Review Criteria:

- Are long-term outcome measures and neuroimaging endpoints clinically relevant and/or novel?
- Is the proposed concept timely and does it have the potential to advance the field of neuroprotection in the context of acute ischemic stroke?

NS-18-033: Key Application Components

Research Strategy Section:

▪ Approach-

- Description of overall strategy, methodology and analyses that will be used to accomplish the aims of the project
- Address relevant biological variables, such as sex, age and the use of ischemic stroke-related comorbidities
- Description of how the proposed intervention can be blinded, sample size calculation, study power, and plans for training of site personnel
- Although CC will be responsible for drug formulation, details on the source, acquisition and formulation criteria of proposed compound will accelerate the process
- Description of the site's ability to run multiple studies in parallel
- Provide clear scientific, administrative, and institutional commitments to collaborate with other network sites and the CC

NS-18-033: Key Application Components

Approach Review Criteria:

- Are the techniques and assays proposed appropriate and clinically relevant?
- Are the assays and outcome measures appropriate, quantitative, robust, reproducible and clearly linked to neuroprotection?
- Is the interaction between the site and CC clearly described?
- How appropriate are the methods of blinding, sample size calculation, study power, data management plans, and plans for training site personnel?
- Does the application include clear commitments to collaborate with the other network sites and CC to test up to 6 neuroprotective drugs/interventions? Does this include data sharing?

NS-18-033: Key Application Components

Research Strategy Section:

▪ Milestone Plan-

- Must include 1-year well-defined, stage-appropriate milestones for the proposed intervention, with clear go/no-go criteria and a realistic timeline
- Some examples of topics to consider include:
 - Set-up of infrastructure and animal models to be ready for testing by end of year one
 - Agreement to test interventions from other sites, according to timeline established by NINDS and the CC
 - Participation in all scheduled SPAN teleconferences and annual meetings
 - Develop all resources and expertise required for data sharing with the CC and other sites

NS-18-033: Key Application Components

Milestone Plan Review Criteria:

- Are the one year milestones well defined and quantitative?
- Do they include clear go/no-go criteria?
- How likely is the study to be completed within the project period?
- How will the site collaborate with other sites and the CC in a time- and cost-effective manner?

NS-18-033: Key Application Components

Resource Sharing Plan:

- Application are required to comply with the instructions for the Resource Sharing Plan as provided in the Guide
- In addition, this must also include:
 - Data Sharing Plan
 - Clear administrative and institutional commitment to data sharing, including strategies and ability to share raw data, images, and protocols both within the network and among other investigators

SPAN Contact Information

Contact(s)

Francesca Bosetti, Pharm.D., Ph.D.

National Institute of Neurological Disorders and Stroke (NINDS)

Email future additional questions to **SPAN@mail.nih.gov**

FAQs

- Can I submit a multi-site/multi-PI application?
- Are foreign sites or CC allowed?
- Can I propose more than 1 putative drug/ intervention?
- Do I have to propose an intervention to be part of the network or can just apply to be a testing site?
- Is the purpose the test “neuroprotectants” in the classical sense, i.e., drugs that protect neurons from ischemic injury, or is the notion of neuroprotection more broad, and including anything that improves outcomes whether working on endothelium, BBB, inflammation, neurons, etc.?
- One of the drug target requirements is that there is human safety, so that it could move quickly into human trials. Are you thinking of a pipeline for NINDS/StrokeNet trials or for NINDS/pharma partnerships and does this impact how you will review proposed candidates?
- How much of the review will be based on the team and ability to run a testing core, expertise in translational stroke research, etc. and how much on the specific drug candidate?
- Do you expect the team to have published on the drug they propose or is it equally acceptable to propose a target based on the mechanism and scientific rationale if others have shown efficacy in ischemic stroke models?