

Report from the Stroke Research Priorities Meeting: Top scientific research opportunities from Workgroups on Stroke Prevention, Treatment, and Recovery Research

In 2011, the NINDS began a two-phase planning process in order to identify the highest priority research areas in stroke to address over the next five to ten years. In Phase 1, the NINDS asked the Stroke Progress Review Group (SPRG) to conduct a final review of the stroke research landscape, ten years after the first SPRG established research priorities for the field. The resulting report, published in January of 2012, recognized 48 priority areas (see the [Final Report of the SPRG](#)).

Phase 2 of the stroke planning process was designed to build on the comprehensive analysis of the SPRG, identifying a smaller number of areas that represent the most promising opportunities in stroke research. This process was guided by a working group of the NINDS Council chaired by Drs. Tom Brott and Barbara Vickrey. It capitalized on the expertise of three working groups of external scientists representing prevention, treatment, and recovery. To solicit potential research priorities for Phase 2, NINDS released a Request for Information (RFI) in May of 2012. The RFI called for broad input from the public and research community to identify opportunities for which significant, community-based effort and focus could lead to major advances in stroke research over the next five to ten years. In advance of a planning meeting, members of the three working groups—prevention, treatment, and recovery—rated over 180 RFI responses on impact, feasibility, need for targeted NINDS investment, and overall merit.

Top priorities were identified and strengthened at the Stroke Research Priorities Meeting held on August 29 and 30, 2012. Pre-meeting scores were used to identify which proposals were discussed and further optimized, and after discussions, individuals in each working group re-rated the proposals. The top proposals for each group were identified through further discussion and voting within the working groups. To encourage input from all working group participants, discussions were led by an impartial moderator, and ratings were done anonymously. The top proposals from each group were then further refined and presented to the Steering Committee, NINDS staff and other attendees.

Through this process, each of the working groups developed two or three proposals, as well as one joint proposal (cross-cutting), that represent combined, modified and optimized versions of the best ideas presented in the RFI proposals. Each research opportunity identified by the working groups is presented below with a description of the goals, impact, feasibility, barriers, rationale, relevant ongoing efforts and potential approaches.

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Crosscutting

Accelerating the Translation of Stroke Research in Preclinical Animal Models into Clinical Studies of Highly Promising Treatments

1. Description of scientific opportunity to be achieved in 5- to 10-year period

Development of novel and more effective strategies to prevent stroke, protect the brain during ischemia and reperfusion, and facilitate its recovery after stroke hinges on basic and translational preclinical research. However, despite large investments at the bench (preclinical research) and bedside (clinical trials), investments in translation have not yielded the anticipated bounty of new, efficacious therapies. For example, it has been over 15 years since the the only proven pharmacologic therapy for acute stroke was demonstrated to be effective by a landmark clinical trial and approved by the FDA for use in clinical practice. In most cases, however, therapies with promising results in early studies have failed in phase III clinical trials. Improving the quality of early, preclinical studies would have immediate and substantial impact on their predictive power for success in later stages of translation.

Shortcomings of preclinical studies have included: lack of validity (including bias), lack of broad applicability, poor predictive value (including power, sample size), lack of independent replication, and publication bias toward positive findings. In recent decades the quality of human clinical trials and hence the robustness of their results -- not only in stroke but in many other therapeutic areas -- has improved. This was due to development of strategies to minimize bias, advances in biostatistical methods, increased data monitoring and auditing, among others. It is time that the stroke research community facilitates a similar evolution in preclinical practices to improve the quality of bench research.

Systematic, evidence-based criteria are needed to inform decisions to proceed from preclinical to clinical studies. Scientific milestones at each stage should ensure that only therapies with robust and repeatable results move forward. Potentially, this would greatly accelerate the development of novel and effective strategies for prevention, treatment and recovery. With systematic, evidence-based progression along the translational pathway, identification and translation of one or more positive, highly vetted candidates into human studies would be feasible within the next decade.

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

Within five years implement a milestone-driven process in which stroke therapies being developed or tested must meet high quality evidence standards for progression to the next stage of development. Under this system, all studies will contribute to a body of published evidence (both positive and negative) for therapies tested in preclinical animal model trials of stroke and comorbidities, according to defined criteria for quality, such as replication, power, and other benchmarks. The longer term goal of an initiative to address this opportunity would be to identify and vet through this process several highly promising, "robust" candidates for stroke therapies, and advance to phase II trials those that meet defined criteria.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

Improving the predictive value of preclinical studies will allow for the progression of one or more highly promising stroke therapies through successful phase II trials to phase III trials. A new, proven treatment -- even with a modest beneficial effect -- could have a large public health impact given the 700,000+ new strokes that occur each year. Focusing the development of drugs on robust candidates could conserve valuable research resources and increase the impact of research investments, and could also benefit patients by decreasing exposure to potentially harmful or futile drugs in trials. Successfully achieving these goals may have spillover effects in preclinical research for other neurologic diseases beyond stroke, particularly with broad strategies to promote higher quality through journal policies, data sharing mechanisms, and development of new quality methods.

4. What is the readiness/feasibility of accomplishing the goals of this opportunity in 5 to 10 years?

Because of the existing momentum and resources, improving preclinical research in the near future and thereby attaining the goals above is feasible. Robustness in preclinical research is of high priority to the scientific community and at the NIH/NINDS. There is a large body of quantitative evidence identifying key weaknesses in preclinical studies, and these data can contribute to the development of research guidelines. The Stroke Therapy Academic Industry Roundtable (STAIR) criteria have been developed to address quality and generalizability issues in preclinical animal translational research. Several international groups and an NIH workshop have convened in the past year in recognition of the significance of the problem, generating enthusiasm and momentum around this topic among the scientific community.

Existing resources to support this proposal include scientific expertise and momentum, many validated animal models, and companies that are being created to provide as a service the replication of data from experiments.

5. What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?

Improvements in preclinical research require a cultural shift, driven in part by incentives from funding sources and publishers and supported by specific training for investigators. Current funding review criteria and journal policies do not give sufficient attention to issues such as statistical power, broad applicability, and independent replication. Enforcement of existing guidelines, such as the STAIR criteria, as well as adapting new rigor guidelines into review and benchmark evaluation, regardless of funding mechanism, will be necessary. Funding priorities and strategies should incorporate sustainable support for independent replication in order to make adherence to guidelines and benchmarks by investigators feasible. Quality improvement efforts should also include better mechanisms and incentives to: share data or biomaterials, collaborate internationally, conduct multi-site animal trials, and coordinate between industry, regulators, funders and researchers.

6. What is the rationale for a targeted initiative by NINDS?

Industry is not currently investing in initiatives or strategies to address this problem in stroke research. NIH may be in a position to partner with sponsors internationally to promote an initiative, particularly as there appears to be considerable European interest in addressing these issues. NINDS has already expressed general and widespread concern about quality of preclinical research, need for replication studies and the risk/investment tradeoffs of large-scale clinical trials. A vetted, high quality body of evidence in support of human studies would decrease risk and increase confidence in the investment, and increase the likelihood of identification of an efficacious therapy.

7. What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other ICs, other Federal agencies, or non-Federal entities?

STAIR criteria have been developed that, if implemented, would heighten quality of preclinical translational trials. NINDS convened a workshop on this topic in July, 2012, which led to a review article that includes recommendations for the future¹. Guidelines based on these recommendations are also posted on the NINDS website.

http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf

At two recent workshops (Barcelona, Spain, May 2011; Potsdam, Germany, May 2012), stroke researchers from North America, Europe, and the Asia-Pacific region explored the challenges and opportunities of international cooperation in preclinical stroke research, and concrete steps for immediate action have been outlined. Editorials in *Stroke*² and the *Journal of Cerebral Blood Flow and Metabolism*³ have called for such cooperation, and international funding agencies (Europe, China, and US) have expressed interest. International consortia (e.g., European Stroke Network together with Canadian Stroke Network, the Leduc Foundation) already serve as catalysts for collaboration. Leadership from the European Commission and the NINDS will take part in a session discussing this issue at the 2013 American Association for the Advancement of Science (AAAS) meeting.

8. What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5- to 10-year timeframe?

- Promote the implementation of quality standards for preclinical stroke research to increase internal and external validity. This could be achieved by including adherence to these high quality standards as review criteria for NIH-sponsored research.
- Promote mechanisms to monitor and audit quality (e.g. cross-laboratory audits, round robin tests, etc.)
- Ensure that replication studies of pivotal findings are conducted.
- Tie support to implementation of quality improvement measures.
- Support research on quality in preclinical research, and measure how improvements in quality affect translational success.
- Encourage (and support) training of young scientists in 'good scientific practice', experimental design, and specific quality measures in the experimental stroke field.
- Encourage dialogue and promotion of requirements for quality measures in experimental stroke research among investigators, funding agencies, journal editors, professional societies, and industry. NIH could lead this by adopting changes in grant review criteria, which could be further enforced by journals and other funding agencies.

- Establish and implement a platform for international, multi-center preclinical stroke trials using the repertoire of randomized clinical trial design and the complexities of a multi-center, multimodal paradigm. Develop a trial design which exploits the potential for randomized stratification to enhance generalizability.
- Support replication studies prior to initial publication so all contributors to the data share academic credit.
- Develop and promote one or more platforms for stroke research data repositories to collect data about results or planned experimental trials, and a catalogue of models and methods platforms to facilitate data sharing, exchange of protocols, development of robust and clinically relevant outcome measures, and meaningful analyses that accelerate the process of translation.

Prevention

Prevention of Vascular Cognitive Impairment

1. Description of scientific opportunity to be achieved in 5- to 10-year period

Cerebral small vessel disease is a major contributor to age-related cognitive impairment, arguably the greatest threat to quality of life faced by the aging US and worldwide populations. Small, asymptomatic brain infarcts, for example, are present in 20-25% of the population over age 60, rising to 40% at more advanced ages. Diffuse white matter disease or leukoariosis is even more common, affecting 40-70% of individuals by the fifth decade. Both are associated with increased risk of cognitive and motor deficits as well as with incident stroke and dementia.

The prevalence of vascular cognitive impairment (VCI) is greater than all clinical strokes combined. The underlying small vessel and white matter biology is incompletely understood, and there are no targeted therapies that exist for small vessel disease. The contribution of vascular pathology to the biology of Alzheimer's disease is also incompletely understood. Prevention of vascular cognitive impairment thus represents both a huge public health challenge and a major opportunity. This initiative would address both preclinical and clinical scientific opportunities, by (1) identifying key biological pathways that promote small vessel disease underlying VCI and agents that interfere with them, as well as (2) developing pilot clinical trials of targeted therapies using imaging biomarker outcomes.

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

- Investigate the interactions between small vessel and microvascular disease, ischemia, and Alzheimer's disease biology.
- Develop and apply novel animal models that more faithfully replicate small vessel and microvascular changes relevant to VCI and its interactions with Alzheimer's and other dementias.
- Evaluate a set of agents likely to interfere with key pathogenic pathways or enhance endogenous protective mechanisms.
- Obtain pilot human data identifying candidate agents and, based on the results of animal and pilot human studies, conduct definitive trials with clinical endpoints.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

The impact of successfully identifying one or more treatments that slow progression of small vessel and microvascular disease that contributes to dementia would be extraordinarily high. This conclusion is based on both the very high prevalence of cerebral small vessel disease (95% of population-based subjects age 60 and older demonstrated MRI-detectable white matter lesions in the Rotterdam Scan Study⁴) and the sizable risk for subsequent cognitive impairment associated with this process.

Insights in VCI are likely to have broad implications for other forms of hypoxic-ischemic white matter injury. In addition, from the patient perspective, a successful initiative on VCI would have a huge impact due to its high prevalence and interaction with Alzheimer's pathology.

4. *What is the readiness/feasibility of accomplishing the goals of this opportunity in 5 to 10 years?*

There is growing understanding of common pathways that underlie cerebral small vessel damage, such as oxidative stress and inflammation. There has also been marked improvement in noninvasive measurement of ultrastructural brain injury (using MRI-based methods such as diffusion-tensor and high-field structural imaging) and small vessel pathology (using BOLD and ASL-based measures of blood flow and vascular reactivity, and ligand-based imaging of beta-amyloid). These advances form the framework for selecting protective approaches and testing them in elderly individuals for their effects on slowing progression of brain injury and vascular dysfunction.

Feasibility would be supported by existing knowledge, tools and materials already available for studies on preventing VCI. These resources include:

- Scientific knowledge of large and small vessel biology exists but has yet to be fully applied to the study of cerebral microvascular disease.
- A large number of agents affecting vascular mechanisms are already approved for other indications.
- Human autopsy tissue from subjects with age-related cognitive decline and VCI is available through ongoing NIH-funded population-based studies of brain aging and dementia.
- Some animal models [SHRSP, Tg-APP, Tg-Notch3, hypertensive mice (BPH, renin-Tg, DOCA-salt)] of microvascular disease exist but are relatively underutilized for VCI research^{5,6}.
- The 17q25 locus has recently been associated with burden of white matter disease.
- Neuroimaging tools are available for diagnosing small vessel disease in patients and for following the disease longitudinally. Amyloid imaging, microbleed imaging, and sensitive measures of cerebral atrophy can be incorporated in subject selection.
- Tools also exist for measuring small vessel injury (T2, T2*, DTI, MTR, high-resolution T1) as outcome markers in intervention studies.
- The widespread availability of advanced high-field (3T and eventually 7T) MRI and advances in standardization of MRI across multiple sites would make it possible to consider large-scale, MRI-based, multicenter investigations and clinical trials.
- The human connectome project will lead to better maps of white matter connections that are damaged in patients with VCI, and functional connectivity techniques may allow demonstration of the consequences for circuit function.

Multiple perspectives were expressed on which phase of research is most ready for investment through a VCI initiative. Advocates of an immediate investment in clinical research argued that animal modeling could be less informative in the 5- to 10-year timeframe because of the difficulty in modeling patients with multiple risk factors. Others, however, thought that 'readiness' of the preclinical stage was promising for achieving the stated scientific goals in a 10-year period.

5. What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?

There are major gaps in scientific understanding and technical challenges in the study of small vessel disease and its relationship with dementia. The relationship between small vessel and microvascular damage and cognitive changes is not well characterized. The science that underlies VCI and cerebral small vessels is still in early development, so advances in this area of research are required for the development of effective therapies. Arteriolar, capillary, and venular pathology is more difficult to visualize than large vessel pathology, white matter blood flow is more difficult to measure than the higher cortical rates, and there is currently no method of identifying task-activation of white matter tracts.

6. What is the rationale for a targeted initiative by NINDS?

Despite progress and increased support for research on VCI during the past 10 years, there is still a large need to better understand, both preclinically and clinically, how to prevent VCI and to develop therapies. NINDS and other NIH Institutes have built resources for research on VCI and related dementias, so prioritization of VCI research now has potential for great scientific and public health payoff. Given the focus of NIA and past collaborations, NIA would be a natural partner for an initiative on this topic.

7. What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other NIH Institutes and Centers, other Federal agencies, or non-Federal entities?

- An NIH Consensus Development conference on Preventing AD and Cognitive Decline was held in 2010.
- The NINDS, NIA and NHLBI each have a scientific interest and support grants in this research area that include: basic research on the neurovascular unit, neurovascular coupling, blood brain barrier, ischemic white matter injury, chronic hypoxia; some disease-focused basic research on small vessel disease, microbleeds, lacunar stroke; and some clinical research (imaging and epidemiology) on cerebral amyloid angiopathy, vascular dementia, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and VCI.
- The National Alzheimer's Project Act (NAPA) includes non-AD dementias, and NINDS is preparing a 2013 workshop that will include VCI.
- The Stroke Progress Review Group (PRG) identified VCI as an area in need of additional research now and in the near future.
- The NINDS and NHLBI support several large cohort studies on cardiovascular disease that include measures for cognitive impairment. These include, for example, ARIC, MESA, SPRINT-MIND, and REGARDS, which has found that stroke risk factors may lead to cognitive decline⁷. NIA also supports human autopsy studies that include many subjects with VCI. These include, for example, the Adult Changes in Thought (ACT) study, a population-based study of brain aging and the Oregon Brain Aging Study (OBAS), which studies subjects with dementia and advanced age ("the oldest old"; ≥ 85 year old).
- The Alzheimer's Disease Neuroimaging Initiative (ADNI), NIH's largest public-private partnership for brain research, is examining the potential for serial magnetic resonance imaging, positron

emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease. However, ADNI excludes persons with MRI evidence of stroke, though the largest population of individuals with dementia has both stroke and AD.

8. *What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5- to 10-year timeframe?*

Much of the existing research has been on epidemiology, so work on therapy development is needed at all levels from preclinical to clinical. Additional research is needed on understanding the basic biology of vascular cognitive impairment, preclinical research using current and novel animal models of cerebral small vessel and microvascular disease, and clinical studies to pilot new approaches in humans. The following strategies would address these needs:

- Human pathology studies that define molecular and cellular pathways mediating cerebral white matter injury related to small vessel disease.
- Apply vascular biology tools to current and novel animal models of cerebral small vessel disease that replicate key features of human VCI.
- Simulate clinical risk factors (e.g. age, hypertension, hypoxia) in animal models.
- Pilot human studies in selected subjects with imaging outcome markers.
- Support randomized, factorial-designed trials of agents targeted to protect from small vessel-related brain injury:
 - Candidate drugs would be derived from preclinical biological studies on VCI.
 - Individuals would be selected based on vascular risk factors and followed by serial neuroimaging for progression of small vessel brain injury.
- Encourage collaboration and impact beyond initial studies:
 - Hold symposia to bring together multidisciplinary basic and clinical investigators.
 - Develop partnerships with other NIH Institutes, including NIA, NHLBI, NIDDK, and with external organizations including the American Heart Association/American Stroke Association and the Alzheimer's Association.

Imaging Biomarkers in Stroke Prevention: From Bench to Bedside

1. Description of scientific opportunity to be achieved in 5- to 10-year period

Advances in brain imaging have transformed medical care for stroke and many other neurological disorders. Imaging provides an opportunity for early identification of an individual at risk for stroke and a means to determine whether interventions to prevent stroke have their intended effect. Current techniques can sensitively monitor large artery vascular stenosis, brain infarction, leukoencephalopathy, microbleeds, amyloid angiopathy, cerebral perfusion, and cardiac function. New imaging methods promise to non-invasively identify: a) features of atherosclerotic plaque that increase risk of stroke, b) thrombus in the heart or diseased arteries, c) breakdown of blood-brain barrier in hypertensive small vessel disease, and d) inflammatory cell trafficking in brain, neural progenitor cells and a variety of other cell types and extracellular proteins. Imaging biomarkers could allow physicians to diagnose brain disease and stroke before irreversible brain damage has occurred, opening the door to prevent or slow disease onset. Imaging biomarkers should reveal more quickly and with substantially fewer subjects whether experimental protective treatments have the intended effect.

Imaging is one approach to the development of biomarkers, which are measurable indicators of disease risk, onset, progression, and response to therapy. The potential applications of biomarkers are to guide early neuroprotective and reperfusion interventions, to monitor neuroplasticity in stroke recovery, and to expedite therapy development. These applications can be applied to both large vessel occlusive and small vessel disease. Developing biomarkers highly predictive of stroke risk or occurrence could leverage more investment from industry to develop therapies for neurological disorders. Highly valid biomarkers could potentially revolutionize therapy development and preventive stroke care.

Usually, the endpoint of a stroke clinical trial is a clinical event. Using an endpoint that occurs so infrequently requires enormous numbers of patients, long timeframes, and very large budgets, and thus creates a barrier to progress in the field of stroke prevention. Adoption of an imaging surrogate could dramatically improve the efficiency of clinical stroke prevention trials. Imaging biomarkers would also allow for an intervention to prevent the stroke from occurring. The ability to use *in vivo* imaging to perform serial assessments of biology in an undisturbed environment can transform the field scientifically. With imaging, researchers can avoid *ex vivo* / post-mortem artifacts, follow dynamic processes and provide pre- and post-intervention imaging that allows each patient to serve as his or her own control.

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

The two primary goals of an initiative on imaging biomarkers in stroke prevention would be: 1) to develop an imaging toolbox for basic stroke research and provide novel tracers that can enter the translational pipeline, and 2) to validate imaging markers as outcome measures in prevention trials. Validating imaging biomarkers will require studies explicitly designed to demonstrate a specific role for the biomarker in question (e.g., diagnosis, risk assessment, prognosis, and treatment selection) and that target specific stroke populations and treatments of interest. For instance, with a concerted effort, infarction on MRI (which would include silent infarction) could complement clinical stroke events in prevention trials, serving as an FDA-qualified biomarker.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

Validation of an imaging surrogate could dramatically improve the efficiency of clinical stroke prevention trials, leading to more rapid testing and to shorter trials of new prevention therapies. Imaging biomarkers could also accelerate proof-of-concept testing for emerging treatments. Having a validated set of imaging biomarkers would enhance other investigations into stroke, including epidemiology, acute treatment and rehabilitation. Using imaging biomarkers before clinical stroke occurs could help identify those patients who could most benefit from stroke prevention interventions. Implementing new effective prevention therapies as a result of these expedited clinical trials would have a huge public health impact given the large number of strokes that occur annually in the US.

4. What is the readiness/feasibility of accomplishing the goals of this opportunity in 5 to 10 years?

Technology development in the neuroimaging field is dynamic, and scientific/technical advances create new potential for imaging to transform stroke research. The last decades have seen a rapid evolution of a) imaging systems, including the development of completely new modalities, b) chemistry of imaging agents, c) ability to measure cerebral perfusion, and d) identification of key molecules that govern disease processes and could serve as imaging targets. It is now an opportune time to harvest these advances by combining expertise in imaging with stroke research. The solid foundations of engineering and basic science are an excellent spring board and make the goals achievable.

5. What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?

From a basic science perspective, it is important to connect stroke research with imaging science to develop useful new tools. There is a mature knowledge base on newer imaging science, especially in the field of cancer. Imaging scientists and stroke researcher have to forge teams in which they adapt the tools to stroke relevant questions and targets.

Challenges to this effort further include the lack of formal criteria for testing and validating critical aspects of imaging biomarkers. This would require standardization of acquisition and analysis and minimizing inter-observer variability across a network of stroke centers. Imaging biomarkers are only useful if they are shown to predict relevant clinical endpoints/reference standards. Clinical studies of predictive validity would likely need to be large and longitudinal, and therefore expensive.

6. What is the rationale for a targeted initiative by NINDS?

There is little or no support for developing and validating imaging biomarkers for stroke from pharmaceutical companies and the level of funding needed is probably too large for foundations. No other NIH institute is developing imaging biomarkers applicable for stroke.

7. *What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other NIH Institutes and Centers, other Federal agencies, or non-Federal entities?*

- The Alzheimer’s Disease Neuroimaging Initiative (ADNI), NIH’s largest public-private partnership for brain research, has demonstrated the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer’s disease. Fortunately, many criteria for testing and validating critical aspects of imaging biomarkers, including standardization of acquisition and analysis, inter-observer reliability, and linkage to relevant clinical endpoints are being addressed.
- The NINDS along with several other neuroscience institutes (NIMH, NIA, NIAAA, NIDA) solicited grants on the development of novel radioligands for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies. Currently, NIMH is funding 7 R21s under this program, and NIBIB and NIDA are each supporting 1.
- The Stroke PRG reported on a variety of useful imaging and surrogate biomarkers. These biomarkers have been refined and implemented in phase II stroke trials for more rapid identification of the most promising drug dose and now include:
 - For recanalization treatments: transcranial Doppler TIBI scale score, the MR reperfusion ratio, and CTA/MRA noninvasive angiographic assessment of vessel patency (NINDS-supported CLOTBUST, DEFUSE);
 - For all acute ischemia treatments: salvage of penumbra defined on diffusion/perfusion MR or CBV/CTP CT imaging (NINDS-supported DEFUSE, MR RESCUE);
 - For intracerebral hemorrhage treatment: frequency of hemorrhage expansion on serial CT/MR imaging (NINDS-supported HEME-Surgery, MISTIE, STOP-IT, and industry-funded FAST trial).

8. *What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5-year timeframe?*

To make progress toward useful predictive biomarkers, various study designs will be essential, including those common to diagnostic test evaluation. Depending on the imaging test and study population in question, these studies can be performed in a range of preclinical and clinical settings, for example:

- Create preclinical imaging tools to accelerate basic research on identification and progression of cerebrovascular disease.
- Consider all modalities (MRI, nuclear, CT, optical, ultrasound) for potential biomarker development.
- Validate preclinical and clinical imaging biomarkers, establishing a correlation with outcome.
- Adapt imaging approaches from cardiovascular disease and from cancer imaging to enhance sensitivity and specificity for stroke prevention.
- Facilitate FDA and industry involvement and buy-in, which is critical to acceptance of imaging surrogates for clinical stroke prevention trials.

Expediting High Priority Comparative Effectiveness Trials in Stroke Prevention

1. Description of scientific opportunity to be achieved in 5- to 10-year period

Many stroke therapies in clinical practice are not guided by a strong evidence base. Some have associated risks and some are costly. Without a strong and comprehensive body of evidence, effective stroke prevention therapies may be unknowingly under-utilized, and/or less effective treatments may be over-utilized. Inappropriate treatment choices based on this lack of knowledge may increase the risk of medical and surgical complications and excess healthcare costs. As a result, CMS (the Centers for Medicaid and Medicare Services) and other insurers may not have the necessary data to make informed payment decisions. In addition to generating evidence on the most effective interventions overall, a closely related and important goal is to understand which treatments work for which patients and under which circumstances (i.e. personalized medicine). The current evidence base for stroke prevention therapies is based on aggregate effects in a population that likely includes those who benefit, those who do not benefit, and those who are harmed. Identifying which sub-populations benefit from specific interventions would allow for more targeted, effective, and efficient use of available therapies.

Some examples of treatments that are in use despite having a limited evidence base relative to alternative management approaches include:

- Endarterectomy and stenting for asymptomatic carotid stenosis
- Coiling and clipping of small unruptured cerebral aneurysms
- Device closure of patent foramen ovale (PFOs)
- Surgical or endovascular intervention on arterio-venous malformations that have never bled

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

Once there is evidence that a treatment is efficacious, the most critical question is how it compares with existing alternatives. Within 5 to 10 years, a targeted CER initiative should:

- Establish structures and mechanisms to encourage pragmatic clinical trials, which have inclusive eligibility criteria and reflect a diverse population with a range of co-morbidities.
- Complete at least one high priority/public health impact prospective randomized trial.
- Train leaders and a broader range of practitioners in the design and conduct of pragmatic clinical trials.
- Engage patients in the process of selection and design of pragmatic trials.
- Plan for effective dissemination and implementation of key results.
- Design trials to identify prospectively subsets of patients who will benefit from a stroke prevention intervention and who will not.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

At least one stroke CER trial would enable the use of most effective preventative therapies in the care of individuals at risk for stroke and abandonment of ineffective therapies. This evidence to support change in clinical care and potentially in reimbursement could yield reduced risk, better outcomes for patients

and substantially reduced costs to the healthcare system. As an example, it remains unclear whether modern medical therapy or carotid endarterectomy for asymptomatic carotid stenosis is more effective in the long term. A report suggested that the US spends as much as \$21 billion on unnecessary endarterectomies in the US⁸, illustrating the potential cost savings and public health impact CER trials can achieve.

4. What is the readiness/feasibility of accomplishing the goals of this opportunity in 5 to 10 years?

- NIH, CMS, FDA (Food and Drug Administration), and PCORI (Patient Centered Outcomes Research Institute) are already discussing opportunities for collaborative work in CER.
- There is a recognized need for a stronger link between evidence and reimbursement. Misaligned incentives have compromised the evidence-reimbursement link.

5. What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?

- Though there are communication channels among the various Federal agencies, currently there is not a mechanism by which CMS, PCORI, FDA and NINDS join forces to plan and prioritize comparative effectiveness research. Each agency is under its own regulatory mandate.
- Pragmatic stroke prevention trials require participation by a large number of practicing physicians with limited time to engage in research.
- Issues around reimbursement make it difficult to study interventions that are highly remunerated as part of existing standard of practice.

6. What is the rationale for a targeted initiative by NINDS?

Comparative effectiveness studies of treatments that are already approved and reimbursed are usually not of interest to industry. However, such trials have the greatest yield in changing practice for patients, and there is considerable interest in CER more generally from a number of agencies in HHS and by PCORI. By partnering with these agencies, NINDS can help drive essential CER for stroke.

7. What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other NIH Institutes and Centers, other Federal agencies, or non-Federal entities?

- The Patient Centered Outcomes Research Institute, PCORI, was established by the Health Care Reform Act to fund CER, and NINDS has suggested stroke prevention trials to PCORI. PCORI is also sponsoring research on CER methodology.
- Several CER grants have been funded by the NINDS through the ARRA Programs. These include RC1 grant opportunities, administrative supplements and Mentored Career Development Awards.
- The Health Care System Collaboratory is an NIH Common Fund program that solicits and funds pragmatic CER trials. No stroke trials have been submitted to date.
- The NIH Comparative Effectiveness Research Coordinating Committee coordinates CER activities at NIH.

- A number of NINDS trials are in fact comparing approved therapies in stroke prevention: SPS3 and POINT include > 3,000 patients in studies comparing dual antiplatelet agent treatment to single agent in prevention of stroke after TIA and small vessel stroke, respectively. WARCEF compared anticoagulants versus antiplatelet therapy for preventing stroke in heart disease patients. NINDS supports an R01 on “A Multiethnic Comparative Effectiveness Study for Diagnosis of Cardiogenic Stroke” (Jeff Gulcher, PI). NINDS also supports long-term follow-up of the CREST patients to assess clinical and anatomic durability of carotid stenting compared to carotid surgery.

8. *What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5-10 year timeframe?*

In order to achieve the 5- to 10-year goals, a CER-focused program would need to do the following:

- Create a new support mechanism for comparative effectiveness trials in stroke.
- Develop the infrastructure needed to improve feasibility of large CER studies.
- Encourage broader participation in pragmatic clinical trials that are executed in a “real world” setting and include the entire population likely to be treated.
- Prioritize of a subset of trials to conduct based on public health impact.
- Promote importance and unique design features of CER trials.

To promote CER goals, NINDS should leverage existing CER efforts and collaborate with other Federal agencies and commercial partners. Convene CMS, FDA, PCORI, and insurers with NINDS leadership to accomplish the following:

- Establish a more formalized mechanism for enhanced collaboration.
- Secure input from partners on review of proposed trials.
- Select projects based on public health needs and potential impact.
- Fund at least one prospective randomized trial through this mechanism.
- Include consideration of reimbursement ONLY for patients in trials.
- Engage large healthcare systems to execute pragmatic trials, the results of which would be implemented in their system.

In addition, NINDS should leverage existing opportunities for CER research on stroke through the NIH and PCORI structures described in the previous sections.

Treatment

Expand and Integrate Existing Stroke Trial Networks to Accelerate Translation

1. Description of scientific opportunity to be achieved in 5- to 10-year period

For nearly four decades, the NINDS has invested in clinical trials to advance new therapies for treating stroke. However, clinical trials in stroke are time consuming and expensive, often requiring as many as 10 years or more to complete. Like all clinical trials, they require support for protocol design, regulatory review, and data management, and recruiting enough participants is often also a challenge for clinical trials. These constraints may serve to discourage innovative or start-up strategies as well as drain the good will and resources of funding agencies, investigators, clinical establishments, and patients.

The NINDS established several complementary network/consortia aimed at improving treatment and care for individuals who experience a stroke. The Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) helps move experimental therapies for acute stroke from the lab into early-phase clinical studies. The Neurological Emergencies Treatment Trials (NETT) network creates a similar collaborative framework among neurologists, neurosurgeons, and emergency medicine physicians to facilitate phase III clinical trials that can be initiated in the emergency room. More recently, the NINDS established the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) which has been created to more broadly conduct early or phase II studies of promising treatments across all neurological diseases through partnerships with academia, private foundations, and industry.

These existing networks have improved support for stroke interventions as they move through the clinical research stages, from early phase I through phase III. The scientific opportunity that could be realized in the next 5 to 10 years is to expand and improve upon these existing network/consortia to more efficiently and effectively streamline the transition of basic discoveries through early phase and on to large pivotal human trials. However, there are gaps and suboptimal aspects to the current networks. At the phase II level, the NeuroNEXT provides opportunities and infrastructure more appropriate to testing prevention and non-acute therapies, outside the window of emergency stroke care; the SPOTRIAS network is appropriately focused on acute stroke, but is structurally designed as a loose confederation of somewhat independent program projects rather than a unified research network. At the phase III level, the NETT is focused on therapies initiated in the pre-hospital and emergency department setting, and has not addressed interventions that are started early post-admission in the neurocatheterization lab, neurosurgical operating room, or neurointensive care unit. There is the opportunity to create more seamless transitions between phase I/II clinical trials and phase III clinical trials through more closely collaborated efforts. Such coordination would allow for innovative adaptively designed trials or studies that begin with a phase II question and milestone-driven criteria to allow it to seamlessly continue into a phase III trial, thus reducing the time needed to confirm the potential effectiveness of promising therapies. Further, enhancing and coordinating the efficiencies of existing networks would permit more rapid exploration of the universe of promising therapies and permit the best ideas in the field to surface and be tested.

The second opportunity for network integration and enhancement is that core Data Management Centers and Statistical Management Centers within the SPOTRIAS network/consortia could be

coordinated for efficiency. This would bring efficiency to the management of translational trials and also ensure synchronized and uniform collection of clinical and biological data across all consortia. Coordinated data management would facilitate comparison of results across studies and allow for metadata analysis. This would increase the value of collected data.

Lastly, enhancing these networks ensures that NINDS can support trials that span the pre-hospital setting, emergency department, catheterization lab, operating room and intensive care unit. Conducting research in these settings poses many logistic challenges, especially when multiple studies are being conducted simultaneously. Efficient coordination allows priorities to be established and managed to facilitate the completion of NINDS trials in a timely and efficient manner.

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

- Expand and improve design and network infrastructure for acute stroke phase III trials (NETT).
- Redesign and reboot network infrastructure for acute stroke phase II trials (SPOTRIAS “2.0”).
- Arrive more rapidly at “go/no-go” decisions in phase II and confirm or refute efficacy in phase III.
- Improve coordination and collaboration between preclinical studies, pilot human trials, and pivotal human trials.
- Accelerate the accumulation of knowledge about safety and preliminary efficacy, as well as “pivotal” efficacy, for a number promising acute stroke therapies. Multiple ‘shelf-ready’ promising candidates are available now, awaiting testing.
- Meaningfully reduce the pipeline duration for one or more acute stroke therapies.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

Expanding and integrating the existing network structures would accelerate accumulation of knowledge about efficacy in NINDS acute treatment stroke trials. Improved coordination would lead to faster development of new treatments for improved patient care. Better coordination would also reduce the risk and burden on research participants (by increasing trial efficiency), and increase the value of research data by facilitating data sharing. The long term impact from this effort would be the rapid transition of successful therapies from pivotal trials to clinical practice.

4. What is the readiness/feasibility of accomplishing the goals of this opportunity in 5 to 10 years?

This project is highly feasible, building upon successful NETT, NeuroNEXT and SPOTRIAS infrastructures. Each of these programs has been previously established and buy-in in the scientific community has already been accomplished. Expansion and coordination could occur very rapidly.

It will be important to analyze the current ‘queue’ of acute stroke therapies to develop a list of vetted, highly promising potential targets / therapies that are ready for testing.

5. *What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?*

For rebooting the SPOTRIAS network, variability in practices (such as data management) among different existing networks and among clinical researchers could pose barriers to integrating networks. For enabling more complicated, post-admission trials in NETT, expansion of center expertise would be needed. For more rapid, seamless transitions from phase II to phase III, flexible funding approaches aligning support with meeting research milestones would be required.

6. *What is the rationale for a targeted initiative by NINDS?*

National networks devoted to research for the public good in acute stroke depend on NINDS support, and the existing NINDS-funded networks have demonstrated benefit for stroke research and care. Improved and more fully integrated networks would provide even more benefit and would be a more efficient use of NINDS resources. Currently, proven acute treatments for the 790,000 stroke patients annually are delivered to less than 5% of patients who are served by a subset of hospitals. Through the existing stroke trial networks conducting trials at a range of clinical institutions, treatment delivery has become available at a wider range of hospitals. Through trials, “best practices” have been shared with a wider range of health professionals on the front-lines delivering stroke care. Expanded, evidence-based networks can simultaneously advance the science and serve the public health. Such networks are only sustainable with targeted NINDS investment.

7. *What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other NIH Institutes and Centers, other Federal agencies, or non-Federal entities?*

The NINDS supports Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS), a national network of centers perform early phase clinical projects, share data and promote new approaches to therapy for acute stroke. The first centers were funded in 2002, and the last of the 8 current centers were initially funded in 2008. Overall, the program is entering its 10th year and center funding begins to expire in 2013 with all centers completing their funding by 2014.

Neurological Emergencies Treatment Trials (NETT) is a cooperative and highly integrated clinical trials network supported by the NINDS and includes a Clinical Coordinating Center, a Statistical Data Management Center, and 17 enrollment hubs at academic medical centers around the country. Each center and hub is supported by its own cooperative infrastructure award and individual trials are supported by their own awards. The original awards to the coordinating centers and hubs were issued in 2006 and current funding of the NETT goes through 2017. The NETT is currently supporting three stroke studies: SHINE, POINT and ALIAS.

The Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) clinical research network is designed to conduct exploratory clinical trials evaluating the most promising therapies, whether from academia, industry, foundations, the NINDS intramural laboratories or the NINDS translational program. Examples include phase II clinical trials and clinical research studies aimed at validating biomarkers and clinical outcomes in preparation for clinical trials. The network includes 25 clinical recruitment sites, one Clinical Coordinating Center, and one Data Coordinating Center. The network is designed to increase the efficiency of clinical trials, to facilitate patient recruitment and retention, to increase the quality of

neuroscience clinical trials, and to enable public-private partnerships. Funding for this network was initiated in 2011 and currently goes through 2018.

8. What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5- to 10-year timeframe?

Refining the existing stroke clinical trials networks and increasing their collaboration will facilitate the goals of more efficient and effective clinical trials from phase I through phase III. Some specific approaches that could be implemented in optimized networks include:

- Establish centralized coordination for SPOTRIAS.
- Support enough sites to streamline recruitment.
- Increase efficiencies by use of central IRBs, master contracts, and uniform monitoring processes.
- Enhance industry collaboration by establishing mechanisms to accelerate the initiation of new studies.
- Use factorial and adaptive designs in trials, when appropriate.

Preclinical and Clinical Studies to Improve Early Reperfusion Therapy and Establish the Limitations of Late Reperfusion Therapy (REPERFUSE)

1. Description of scientific opportunity to be achieved in 5- to 10-year period

In 1995, the results of two linked NINDS-sponsored stroke trials led to the first ever approved therapy for acute stroke. Tissue Plasminogen Activator (t-PA), which works by dissolving blood clots that block arteries in the brain, remains the only FDA approved and proven therapy for the acute treatment of an ischemic stroke. Among patients receiving tPA, 30 of every 100 have a less disabled final outcome, including 12 of every 100 who have recovered from their stroke with little or no disability after three months. Despite this benefit, there remain several scientific challenges that limit the use of this drug. Brain tissue damage increases rapidly with time after the stroke, so t-PA is most effective if administered within 90 minutes from symptom onset, and only approved for use for up to three hours when the potential benefits and chance for recovery outweigh risk of hemorrhagic complication. t-PA is imperfect; even with optimal use, reperfusion rates are limited, with 40-50% success in opening different blocked arteries in the brain.

Improvements in lytic drugs, in imaging selection of patients for treatment, and in catheter-based approaches to reopening blocked arteries all represent promising scientific opportunities to improve reperfusion therapy. Over the last decade, there have been significant technology developments for intravascular approaches, including devices that can aid in the retrieval or removal of large occlusions causing an ischemic stroke. A number of devices have now been cleared by the FDA for use in reopening blocked arteries. However, despite some evidence that they can effectively open blocked arteries, these emerging endovascular therapies are limited by incomplete evidence of whether they improve final clinical outcome, which patients are most likely to benefit, how to limit hemorrhagic complications, and when recanalization attempts are futile and likely harmful. Thus, with the limitations of currently available reperfusion therapies, there remains an urgent need to improve early reperfusion and establish the therapeutic window of late reperfusion therapy.

To achieve the 5- to 10-year scientific and clinical goals of advancing new reperfusion therapies, evaluating the efficacy and therapeutic window of existing therapies, and implementing the best practices in the clinic, research in this area must be prioritized.

2. What would be the goals (5- to 10- year) of an initiative to address this scientific research opportunity for stroke?

- Expand and improve biological understanding of reperfusion's beneficial and untoward effects.
- Establish whether reperfusion therapy improves outcome for pediatric stroke.
- Increase the reperfusion rates achieved with IV therapies.
- Shorten the lower end of the time from ED arrival to treatment range in clinical practice to approach \leq 30-minutes for a substantial number of patients (as has been achieved by select centers in Europe and Asia).
- Expand the time window for treatment by developing new agents with improved safety profiles and testing them preclinically and clinically.

- Expand the time window for therapy by defining imaging and other selection methods that identify patients who still harbor substantial salvageable tissue 3-12 hours after the time they were last seen well.
- Reduce the rate of hemorrhagic transformation and other complications of intravenous and endovascular reperfusion therapy.
- Understand the role of collateral blood flow for different treatment options.
- Test the efficacy of combined/multiple treatments (e.g., neuroprotection plus reperfusion, combined thromboactive agents, combined intravenous and endovascular).
- Identify the best preclinical models for development of novel intravenous and intra-arterial therapies.
- Study fundamental biological properties of clot formation and dissolution.
- Improve neurothrombectomy devices by expanding understanding of thrombus physiochemical properties and the effect of mechanical techniques on thrombus traction and vessel wall injury.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

Because of uncertainties about treatment efficacy and treatment windows, many people who could potentially benefit from reperfusion therapy do not receive treatment. Research in this area would define treatment times and establish safer and more effective therapies. Currently, only 5% of patients receive reperfusion therapies and only 40% of them achieve reperfusion in a useful time frame. It is conceivable that an expanded portfolio of reperfusion interventions could be delivered to 20% of all ischemic stroke patients and be effective in achieving recanalization in 75% or more of them. The resulting increase, by an order of magnitude, in the proportion of patients achieving therapeutic reperfusion would have dramatic clinical and public health benefits.

4. What is the readiness/feasibility of accomplishing the goals of this opportunity in 5-10 years?

This proposal is highly feasible, building upon past NINDS research, primary and comprehensive stroke centers, and wide dissemination and implementation of intravenous and endovascular therapy in practice.

5. What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?

A lack of infrastructure capable of performing phase III endovascular trials and multimodal imaging trials in an efficient manner creates logistical barriers that would slow the efficient and effective execution of studies that would be needed to address this research opportunity. These barriers could be overcome more readily with coordination and re-engineering of existing networks, such as SPOTRIAS, NETT and NeuroNEXT. Reluctance of centers to engage in randomization when device therapies are available outside of trials slows recruitment in endovascular treatment trials. The neutral results of recent trials will further help establish scientific equipoise, facilitating enrollment. Improvements in aligning CMS and third party reimbursement with the need to obtain clinical trial evidence of benefit would further accelerate study completion.

6. *What is the rationale for a targeted initiative by NINDS?*

Targeted NINDS investment is needed because efforts to improve intravenous and endovascular therapy are not a major target for industry investments. Randomized, controlled trial evidence on the clinical benefit of endovascular therapy is not a primary focus of the industry. An NINDS initiative would permit studies of multiple interventions and devices in a single framework, and such coordination is needed to be able to develop and evaluate the best interventions for this complex disease.

7. *What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other NIH Institutes and Centers (ICs), other Federal agencies, or non-Federal entities?*

Other than the SPOTRIAS network which supports a number of phase II reperfusion projects, there are no active initiatives by the NIH or other government agencies that address this proposed opportunity. However, research in this area is supported by investigator-initiated proposals funded by the NINDS, NHLBI and NIA, which address the basic, translational and clinical issues on brain reperfusion. Vascular networks, collateral flow and intrinsic mechanisms of blood flow regulation are promising therapeutic avenues, but are understudied areas and the focus of only few current grants. NINDS supports a few Small Business Innovation Research (SBIR) grants on endovascular therapies; however, none address the basic biological issues of thrombus physiochemical properties and device effects on the brain and its blood vessels. NHLBI's scientific portfolio includes research on systemic clot and plaque formation and vascular biology, and a small amount of work is funded by NHLBI and NINDS on cerebrovascular clot and plaque formation, including inflammation of blood vessels. In addition, several translational grants are focused on improving the efficiency of t-PA or extending the time window.

8. *What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5- to 10-year timeframe?*

Clinical studies of new or improved reperfusion therapies should be carefully designed and reviewed to ensure that research will be generalizable and applicable to treatment situations. Evidence-based milestones or endpoints should also be incorporated into study design. Any clinical trial funded to test reperfusion therapies must defend inclusion or exclusion of endovascular therapy into the design. Specific mechanisms should be in place to minimize time-to-treatment, in both the pre-hospital and hospital settings. Patient selection criteria should establish which patient populations respond to different treatments and use the broadest possible entrance requirements to include all eligible patients in the trials. Associated medical and interventional care should be standardized to establish better guidelines for treating stroke. Factorial designs should be implemented to allow comparison across multiple approaches. Preclinical and translational studies should be coordinated and progress toward informing the design of human clinical trials.

Coordination within NIH and with regulatory agencies is essential to success in this field. Efforts and partnerships should involve other NIH institutes (particularly NHLBI) and cardiology as a discipline, to leverage parallel investments and common interests and to learn from established experts in vascular biology. Regulatory hurdles could be overcome by working with regulatory agencies and Institutional Review Boards (IRBs) for the consideration of Exception From Informed Consent (EFIC waiver) or developing quicker and easier ways to get consent for patients enrolled in these rapid treatment trials. In addition, support is needed to develop new mechanisms to minimize time-to treatment.

Preclinical and Clinical Studies to Achieve Robust Brain Protection

1. Description of scientific opportunity to be achieved in 5- to 10-year period:

Despite the potential for achieving significant public health benefits through improving clinical outcomes with available reperfusion therapies, access to acute neurological emergency care is a major logistical challenge which limits the rapid delivery of these therapies within a time window sufficient enough to maximize the rescue of affected brain tissue. Neuroprotective therapies can augment the benefits of available reperfusion therapies for patients who have a stroke. Neuroprotection has shown some evidence of benefit in a number of preclinical trials using animal models, although much of this progress is through individual, uncoordinated efforts of independent laboratories and has not been widely validated. Deficiencies in past preclinical and clinical cytoprotective development programs have since been understood, permitting a renewed and reinvigorated research focus in this area, with special emphasis on the need for experimental rigor in preclinical studies and the need for early treatment initiation in clinical trials. Further, direct and remote ischemic pre-conditioning have emerged in recent preclinical studies as a novel cytoprotective strategy, inducing endogenous mechanisms of neuroprotection. Remote ischemic pre-conditioning is likely highly feasible in the acute setting and needs to be evaluated.

The scientific initiative that is proposed is a focused effort to promote studies to evaluate various therapeutic agents for neuroprotection after stroke, their potential combinations, and treatment windows for administration, through rigorous preclinical and clinical trials. Further efforts would focus on enhancing early administration, enhancing cytoprotection (glial as well as neural protection), and investigating synergies with reperfusion therapy.

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

- Identify informative biomarkers for neuroprotection and cytoprotection in clinical trials.
- Identify agents that are able to prevent reperfusion injury.
- Identify immune targets and potential therapeutic agents for neuroprotection.
- Explore induction of endogenous mechanisms of neuroprotection.
- Define and maximize treatment windows for neuroprotection and cytoprotection.
- For promising new agents, define the concentrations within the core and penumbra of ischemic injury necessary for neuroprotection and cytoprotection.
- Advance methods to initiate agents in the prehospital setting, with the first hour after acute stroke onset.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

Achieving these goals in research on neuroprotection and cytoprotection would have enormous, widespread impact on public health of stroke patients by expanding the availability of potential therapies to a larger number of affected stroke victims. In acute ischemic stroke, neuroprotection therapy is likely to be more widely applicable, albeit less potent than reperfusion therapy. In addition, it offers even greater potential benefit in intracerebral hemorrhage, subarachnoid hemorrhage, and surgical/procedural prophylaxis for which there is no approved drug treatment.

4. What is the readiness/feasibility of accomplishing these goals in 5 to 10 years?

Making advances in neuroprotection and cytoprotection is highly feasible. The emerging international consensus among preclinical researchers for increased rigor will help move the science forward more efficiently, reinvigorating scientific interest in this area, and existing human clinical trial networks are poised to perform pre-hospital and emergency department treatment initiation.

Because single agent neuroprotective therapy is not as powerful an intervention as reperfusion therapy, applications of neuroprotection are likely to benefit from combination therapy approaches and neuroprotection trials are currently best suited as additions to existing reperfusion therapy. Neuroprotection requires significant investment in basic science research. Immediate benefit would be achieved by discovery of neuroprotective agents that would extend the therapeutic potential of reperfusion beyond the current three-hour window. It may therefore be worthwhile to establish a combined initiative on neuroprotection and reperfusion. Prioritization of reperfusion advances might be the most appropriate first step, to be followed later by complementary research on neuroprotection therapy.

5. What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?

The lack of translational models to advance promising preclinical data to successful clinical application has been a barrier to the development and discovery of potential neuroprotective therapies. The need for improved application of translational principles for stroke research (i.e. rigor, replication, comorbidities, species differences, etc.) was identified during the last decade by the Stroke PRG and the STAIR criteria for preclinical trial rigor. A number of NINDS efforts have begun to address these preclinical and translational issues, including several recently funded investigator-initiated grants on various topics (gender differences, hypertension and diabetes modeling, aging effects, embolic vs. middle cerebral artery occlusion comparisons, blood-brain barrier penetration, independent replication, etc). The NINDS translational U01 program projects have taken on some of these translational issues through a milestone-driven process. Deferoxamine for intracerebral hemorrhage progressed to an IND stage in the program and is now being evaluated in a phase II trial. Seventeen percent of the active U01 translational projects include stroke treatments. Increased emphasis on preclinical stroke research is needed, however, there are currently no standards or coordinated efforts for conducting preclinical translational stroke research.

6. What is the rationale for a targeted initiative by NINDS?

NINDS investment is needed because neuroprotection therapy is not a major current target of industry, yet NINDS-funded research on neuroprotection continues to identify promising targets. A targeted initiative is needed to establish approaches and infrastructure (such as a consortium) for preclinical study quality, because this is not easily amenable to investigator-initiated or single-lab mechanisms. A targeted NINDS investment would permit coordinated studies of multiple neuroprotective agents and combined neuroprotection and reperfusion in a single framework.

7. What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other NIH Institutes and Centers, other Federal agencies, or non-Federal entities?

With the exception of the SPOTRIAS phase II network, the committee is not aware of any active initiatives by NIH or other government agencies that address the needs described in this proposal. Protecting the brain from ischemic and/or hemorrhagic insult remains an active and robust area of basic, investigator-initiated research in the NIH stroke portfolio. The neuroprotection portfolio has recently expanded to include vasoprotection and glioprotection. Grants in these areas have focused on basic science and fundamental disease-related issues that include hypothesis-testing of mechanisms to protect brain blood vessels, the blood brain barrier, extracellular matrix, astrocytes, and/or microglia which could lead to the protection of neurons and other brain cells. Some projects investigate targeting common mechanisms observed among several cell types in the brain as a way to address the multifactorial pathology evident in stroke. Pre-treatment and pre-conditioning the brain to ischemic insults in at-risk patients is an emerging area of research, as is intra-ischemic pre-conditioning. Combination neuroprotection therapies (mostly done with thrombolytics) are being explored through both basic and preclinical translational funding mechanisms. Neuroprotection research would benefit from developing and maintaining a stroke therapeutics infrastructure that facilitates the development of our most promising basic discoveries to translation through clinical trials.

8. What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5- to 10-year timeframe?

- Include age, gender, and co-morbidity variables and consider the systemic environment (temperature, glucose, etc.) in the design of these studies.
- Greater efforts are needed to develop approaches for delivery in hyper-acute 0-1 and 1-2 hour time windows (pre-hospital, emergency department arrival).
- Improve preclinical rigor for selection of potential neuroprotective agents through emphasis on blinding, replication in multiple laboratories, quality audits, open labs, robust sample size, and robust treatment effects.

Recovery

Translational Research Using Neural Interface Devices for Stroke and Other Neurologic Disorders

1. Description of scientific opportunity to be achieved in 5- 10-year period

For several decades, NIH investment in fundamental systems neuroscience and neural engineering, initiated through the early Neural Prosthesis Program, has led to creation of a few early-stage devices that can either be implanted in the brain or used relatively non-invasively to restore lost function. These neural interfaces have the potential to allow people to control computer cursors or prosthetic limbs, and they also have the potential to serve as rehabilitation training aids. In the last year, ‘proof-of-concept’ studies of both brain-computer interfaces (BCIs) that allow control of a robotic limb and intracortical technologies that detect brain signals to allow people to move a mouse cursor have demonstrated utility of these devices in humans^{9,10}.

The research opportunity described here is to expand these demonstration efforts in a broader spectrum of paralytic disorders in which motor cortex is relatively undamaged, including brainstem stroke, by establishing a cohesive and coordinated Federal support system for pilot trials, device development and their commercialization. That is, there is an opportunity for NIH to put in place a vehicle or set of mechanisms to overcome the barriers to taking such implantable devices out of the laboratory setting, so that device companies have both the translational and clinical data necessary for potential commercialization efforts.

A second opportunity is to advance research that will produce ‘proof of concept’ human data for BCI for people with severe and moderate cortical stroke with hemiplegia. In current studies the neural signal comes from motor cortical areas. These are often damaged in cerebral infarct or hemorrhage and cannot be used as a source of volitional control signals. However, it is likely that other undamaged regions (such as the hemisphere contralateral to the damaged side, or undamaged ipsilateral areas) may serve in this capacity. Preliminary results show that motor cortical activity is modulated by same-side arm movement in normal monkeys. Furthermore, recent work has shown that the patterns of motor cortical activity used to control prosthetic devices are highly adaptable. This suggests that BCI devices could be developed that would be a highly effective therapy for the large population of individuals who are paralyzed by cortical strokes, but human research is needed to ascertain whether a control signal can be extracted for an ipsilateral prosthetic while the intact, contralateral arm and hand are being used.

Reverse-translational opportunities from these efforts will elucidate new fundamental understandings of cortical function at the level of single neurons and neuronal ensembles following stroke. Data generated from these devices may also affect and provide new opportunities to acquire knowledge about plasticity and functional adaptive recovery.

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

Potential goals of an initiative to address this opportunity would be:

- One or more approved/commercial BCI devices for severe paralysis due to brainstem stroke, spinal cord injury, and ALS,
- Human 'proof of concept' studies supporting BCI that were developed for people with severe and moderate cortical stroke with hemiplegia,
- A platform or process for rapid and efficient translation of future implanted (invasive) neurological devices, and,
- Acquisition of sufficient fundamental knowledge about plasticity from human studies of these BCI devices to launch a pilot human device trial to promote neuroplasticity.

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

Device-based therapeutic approaches offer opportunities for restoration of neurological function through mechanical, electronic, and neural interfacing technologies. They complement other cellular and molecular strategies under development, in their roles of reducing the burden of disease borne by patients with neurological conditions. Neural-controlled prosthetic upper-limb remains one of the primary options for patients with upper-limb amputation (especially for injured war veterans) or paralysis-related disorders, such as spinal cord injury, amyotrophic lateral sclerosis, and brainstem stroke. Restoration of purposeful movement and associated functional independence could be profound for these individuals and associated with reduced caregiver burden.

The iterative process of clinical research in this field also provides neurophysiological insights into post-stroke cortical function and plasticity that are not possible to gain by other study methods. Eventually, implanted neural devices could contribute to direct feedback and training for neurons (including stem cells) during recovery and regeneration of brain tissue after stroke.

4. What is the readiness/feasibility of accomplishing the goals of this opportunity in 5 years?

Pilot, proof-of-concept clinical trials have demonstrated real-time control of cursors and robots with motor cortex functions after brainstem stroke.

There is a strong base of fundamental science on neural movement coding and synaptic plasticity with electrical stimulation. Pilot devices for recording and stimulation are already available. Several labs around the US are currently doing this work, with several more potentially able/interested in engaging in clinical studies.

The scientific opportunity to expand proof-of-concept support to cortical stroke could be carried out by research groups working on closed-loop neural prosthetic control and by those investigating basic cortical mechanisms of arm and hand control. The necessary infrastructure and research capacity is currently sufficient for evaluation of the technology in non-human primates. There are a few facilities that could test this in human subjects at the current time. Right now, this should be at the initial investigation stage. Some feel that it should first be investigated in non-human primates, in which the subjects use one of their own limbs in conjunction with the prosthetic effector. These studies could

then be performed as BCI is being evaluated for upper-extremity-paralyzed subjects. Initially the etiology of paralysis would not have to be specific to cerebral stroke as experiments could be designed in which two effectors could be controlled simultaneously from the same hemisphere.

5. What are the barriers that would need to be overcome? What must happen to realize this opportunity in this timeframe?

Research on neurological devices requires a process very different from drug development involving iterative testing and development and complex regulatory hurdles, and warrants a specialized translational pipeline. Currently there is only a patchwork of funding from the Department of Defense for clinical studies in traumatic brain injury that build on pilot clinical trials in order to provide the additional information that would interest commercialization/pick-up of the devices by companies. There is currently no such effort to address this need for the stroke research field.

Unique barriers and knowledge gaps that must be bridged in order to take these brain implantable devices forward to commercialization include:

- Technical issues - proof of longevity, stability, and reliability remain to be demonstrated;
- Adequate performance acceptable to users, including speed and complexity, portability and wireless technology; and,
- Demonstration of a broader user base (for strokes with different severities and not just brainstem stroke).

6. What is the rationale for a targeted initiative by NINDS?

Companies are unwilling to invest in BCIs until sufficient additional studies and technical advances are resolved. This field is of primary scientific interest to NINDS as opposed to other NIH institutes. NINDS has made prior investments in the field through the Neural Prosthesis Program and now Neural Interfaces Program, and held a recent workshop on this topic.

Necessary scientific and technological developments are too high risk for companies to invest in at the present time, especially as there is no evidence as yet for a larger patient base. Yet the cost to do these studies is beyond currently available NIH funding mechanisms. Further, there are regulatory hurdles that make these studies cumbersome to conduct even at research institutions in which earlier stage studies have occurred.

Team science is required for the development of successful neural interfaces for restoration/rehabilitation of function after stroke. Vascular neurologists, neuroscientists, neurosurgeons, engineers, computer scientists, rehabilitation specialists, regulatory experts, and others must work in close collaboration to create sound devices with near-term clinical viability.

7. What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other ICs, other Federal agencies, or non-Federal entities?

Translational devices intended to treat stroke are many and varied, and include imaging and diagnostic tools to measure recanalization, perfusion, and oxygenation of tissue, stents to increase vessel patency, surgical tools to remove clots, non-invasive and invasive neuromodulation strategies to induce plasticity

and increase blood flow around a clot, and rehabilitation/assistive tools such as the brain-machine interface. Moreover, new devices to treat stroke that are completely different from any of the above are constantly being developed. Not surprisingly, these devices differ greatly in terms of complexity, regulatory pathway, and underlying engineering, clinical, and scientific expertise necessary for clinical development and application. Consequently NINDS has typically utilized general program mechanisms broadly intended for both translational device and drug development to address this area, instead of developing a mechanism specific to devices intended to treat stroke.

NINDS has previously funded device translation to clinical use through several mechanisms. The Neural Prosthetics Program was initially funded through contracts, and has since segued into the Advanced Neural Prosthetics Cooperative Agreement Program. Development of neuroprosthetics is only a portion of the NINDS device portfolio, which also includes device translation through the SBIR/STTR Program, the Translational Cooperative Agreement Program, and other investigator-initiated research project grants.

8. What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5- to 10-year timeframe?

- Establish infrastructure for device development, including support for clinical research (including clinical oversight, surgery, safety monitoring). Such an investment would additionally provide the opportunity for multiple, simultaneous, hypothesis-driven studies in neural decoding, neural engineering, and fundamental neuroscience.
- The field of restorative neural interfaces is well suited for focused, milestone-based (rather than hypothesis-based) grant mechanisms.
- Spearhead collaboration among multiple Federal agencies (FDA, NIH, DARPA, VA, NSF), foundations, and industry partners to drive engineering, clinical, and molecular advances.
- Encourage public-private partnership at an early stage in device development.
- Since translation is a mission of the Clinical and Translational Science Award (CTSA) program, consider engaging/incentivizing a subset of CTSA institutions with investigators who have expertise in this area to develop the institutional expertise to facilitate translational research with devices. In fact, the CTSA fact sheet from NCATS <http://www.ncats.nih.gov/files/ctsa-factsheet.pdf> has information on developing devices for paralyzed patients, including the charge to collaborate with industry and other stakeholders.

Program for Translational Research Targeting Early Recovery after Stroke in Humans

1. Description of scientific opportunity to be achieved in 5-10 year period

Most patients who survive a stroke experience some spontaneous return of neurologic function in the following months, but the degree of recovery is variable and often less than desired. Understanding how to manipulate the biology of recovery to improve functional outcome is a relatively unexplored scientific area with great potential public health benefit given there are 7 million stroke survivors in the US annually.

While there have been substantial advances in our understanding of neuroplasticity and brain remodeling after stroke, we still do not understand the biology of recovery and whether we can enhance that recovery with specific interventions. Furthermore, there is now a wealth of preclinical studies that have identified a number of promising neurorestorative approaches ready for translation to clinical trials (pharmacologic, stem cells, devices, etc.). Small clinical trials suggest benefits of devices for enhancing rehabilitation.

There have been almost no studies in humans exploiting the three-month window for maximal motor, sensory and cognitive recovery. The vast majority of studies of new rehabilitative treatments have been conducted in patients with chronic stroke (> 6 months out), even while data from animal experiments suggest a limited time window of heightened plasticity after stroke within which most recovery occurs. We should target the first three months after stroke in a manner not attempted up until now. Ultimately, determining the time period in which stroke patients can derive the most lasting benefits from therapies will allow rational decisions in the delivery of acute inpatient and subacute outpatient rehabilitation.

2. What would be the goals (5- to 10-year) of an initiative to address this scientific research opportunity for stroke?

The 5- to 10-year goals of this proposal are to assess the impacts of various interventions and to determine the time course of recovery and most effective time period for intervention.

- Assess the impact of stimulation, pharmacological agents, devices, stem cells, and combination therapies on clinically meaningful enhancement of recovery in the early period (~three months) after stroke, aiming for a strategy that will enable a large number of these therapies to be tested in an efficient fashion and with the needed interdisciplinary expertise (stroke, rehabilitation, behavioral science, engineering, biology of recovery, others). It is anticipated these would be primarily phase II mechanistic studies.
- Determine the sensitive period during which rehabilitation interventions may be most effective after stroke, and characterize common recovery processes (natural history) via multiple modalities (clinical, physiological, and imaging).

3. What would be the 5- to 10-year scientific and/or public health impact of achieving the goals of this initiative?

Over 700,000 new strokes occur in the United States each year. While acute treatment with tPA can improve outcomes for those who receive tPA during the therapeutic window, final outcomes depend heavily on post-acute rehabilitation. The majority of stroke survivors receive rehabilitation services currently, yet the rehabilitation service industry lacks a large evidence base. There are millions of stroke patients in the US with residual cognitive and motor deficits, and evidence-based therapies are urgently needed beyond the acute stage.

In addition, defining the sensitive period during which rehabilitation interventions (physical, pharmacologic, other) are effective would provide an evidence base for the selection of stroke patients likely to benefit from existing stroke rehabilitation services as well as optimal timing and duration of rehabilitation approaches in clinical practice. As stroke care costs are skewed heavily to treatment of long-term disability, an improvement in functional outcome in stroke survivors could have a major impact on health care costs.

4. What is the readiness/feasibility of accomplishing the goals of this opportunity in 5 to 10 years?

Feasibility of achieving the goals outlined above is supported by a growing body of animal research and by recent scientific and technological advances. A number of approaches have demonstrated the potential biological mechanisms of recovery after stroke. Recently, functional imaging techniques have enabled the study of the dynamic changes in neural systems that occur in stroke patients and their correlation with functional outcome. NINDS supports mechanistic studies of neuroplasticity in general, which are relevant to stroke recovery. Animal models have shown a cascade of molecular and cellular events after stroke, some of which support the recovery of function and response to therapy. Animal studies have also shown greater effects of repetitive task practice early after stroke, at least after an initial few days of increased brain damage with overuse of the affected side. Rodent studies show heightened plasticity after stroke that lasts about 4 weeks. Enriched environments and intense training early increase the amount of behavioral recovery and structural plasticity seen in rodent models. A recent trial of fluoxetine given in the first three months after stroke (the FLAME study) in patients showed significant larger reductions in impairment compared to the control group. Epidemiological and clinical studies of stroke recovery indicate that most motor and sensory recovery from impairment occurs in the first three months after stroke while major cognitive improvement occurs over months to a year or longer.

A significant amount of research in animal models of stroke has shown that there is a window of heightened plasticity after ischemia that lasts for about 4 weeks¹¹. A similar window likely also exists in humans¹². Recovery in this window is predictable in most patients and is likely independent of the compensatory recovery promoted in acute rehabilitation. Functional imaging has also identified patterns of brain activation early after stroke that predict subsequent recovery at the level of impairment¹³. Thus there is identifiable substrate that is a potential target for new therapies.

A variety of factors have come together to make it feasible to conduct intense, impairment-focused treatment studies during the initial three months after stroke. These include better quantification of

behavior, 3D exoskeletal robotics for the arm and hand, and a better understanding of the concepts and components of motor learning.

Through basic and translational research, a variety of non-invasive brain stimulation techniques and pharmacology are available for testing, addressing complex issues such as timing, duration, and potentially combination therapy.

5. What are the barriers that would need to be overcome/what must happen to realize this opportunity in this timeframe?

As this would be the first initiative to assess the science of spontaneous recovery and ability to augment recovery (within first three months) in patients, there is no existing infrastructure or mechanism to encourage multi-disciplinary teams to pursue this agenda at present and under existing, traditional mechanisms. Also, there is not a cadre of interdisciplinary scientists focused on stroke recovery.

The heterogeneity of stroke recovery in individual patients makes this research challenging. Most patients with stroke have some recovery over time, but the extent of recovery varies widely, and there are limited data on predictors of spontaneous recovery. This has been a barrier to studies of efficacy of an experimental rehabilitation treatment layered on top of standard rehabilitation, because with that natural recovery, the numbers needed to be enrolled in such studies would be relatively large, even larger than large chronic phase stroke rehabilitation studies of the recent past (e.g. EXCITE). Another barrier is lack of standardization of rehabilitation approaches across facilities, clinical practice, and academic medical centers.

6. What is the rationale for a targeted initiative by NINDS?

The need for science in rehabilitation is pressing, particularly given the aging-related increases anticipated in the number of patients with stroke. NINDS and - to a lesser extent - NIA, are perceived as the only institutes that would have the interest and the level of support to accomplish these goals.

Although the charge of this proposal is broad, support directed at research on stroke recovery and rehabilitation is necessary. The care is provided in a setting different from that of acute intervention and involves different providers with different research expertise, so that this area of research would not work well with current acute stroke networks.

Coordinated data collection and management will be a challenge for large-scale clinical studies. We are now in a position to obtain multimodal data longitudinally in recovering patients. These methods include structural and functional imaging, non-invasive brain stimulation, and detailed measures of motor, sensory and cognitive performance. These will allow us to begin to track and characterize common recovery processes and also determine where inter-individual differences come into play. For such an effort to be successful, studies are required across institutions with large databases and specialized analytical cores. This kind of research is not possible under the auspices of single R01 in terms of either scope or time frame.

7. What is already being done to achieve the stated goals of the scientific research opportunity by NINDS, other NIH Institutes and Centers, other Federal agencies, or non-Federal entities?

There has been animal research (described briefly above) that supports zeroing in on the early time window for augmenting spontaneous recovery. However, there appears to be very little concerted effort on characterization of the natural history of stroke recovery in the first months. Efforts have also been limited to testing therapies that are being developed for other conditions and that are now being applied to stroke recovery.

8. What are potential approaches that might make possible achieving the goals of this scientific research opportunity in a 5-10 year timeframe?

Establish a national (and international) network of scientists with expertise in stroke, neurorecovery, and other relevant disciplines to advance new therapeutic approaches for stroke recovery. The network could be set up with selected sites designated as hubs or spokes. Projects including therapeutic interventions (e.g. stimulations, pharmacological agents, stem cells) as well as observational studies (e.g. neuroplasticity, neural networks, biomarker development, functional-neuroanatomical relationships) could be proposed and the highest priority ones completed through site collaborations. Such a network could also help to achieve the following:

- Establish repositories to improve data and sample-sharing (e.g., imaging to study substrates of recovery, tissue such as blood for genotyping, and others), which could be made available for use by the broader research community. Integrate system-level neuroscientists (human neuroscience) with clinical research scientists.
- Establish career development and education programs to attract and train the next generation of interdisciplinary clinical neuroscientists focused on recovery.
- Develop better, standardized measurements of motor and cognitive impairment through centralized data capture/analyses and common data elements. Engage the rehabilitation hospitals, including a push for national program for accreditation of stroke rehabilitation services. Such a program could be modeled after the evidence-based (and evidence-adapting) program for accreditation of acute stroke care administered by the Joint Commission for acute care hospitals.

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