Special Report

Stroke Program Review Group
An Interim Report

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Abstract—The Stroke Program Review Group (SPRG) met for the first time in 2001 to identify and prioritize scientific needs and opportunities in stroke, and to consider strategies to address them. Out of this meeting came a set of scientific and resource recommendations (http://www.ninds.nih.gov/find_people/groups/stroke_prg/index.htm) including the recommendation to review progress after 5 years. In September 2006, the NINDS convened a second SPRG of prominent scientists, clinicians, industry leaders, and patient advocates to discuss progress since the first SPRG and to examine new opportunities in light of more recent advances. The report of the second SPRG meeting is found at http://www.ninds.nih.gov/find_people/groups/stroke_prg/09_2006_stroke_prg_report.htm. In this brief interim report, we list and summarize progress in each of the investigational domains outlined in the SPRG with an emphasis on those advances directly resulting from NINDS-funded research. Also listed are the top 2 or 3 research priorities for the next 5-year cycle for each investigational theme. What emerges from the first 2 reports is a clear set of priorities that have since been complemented by exciting advances that are likely to be the focus of a follow-up report from the next SPRG in 2010. (Stroke. 2008;39:1364-1370.)

Key Words: stroke ■ research ■ ischemia ■ hemorrhage

The Stroke Program Review Group (SPRG) met for the first time in 2001 to identify and prioritize scientific needs and opportunities in stroke, and to consider strategies to address them. Out of this meeting came a set of scientific and resource recommendations (http://www.ninds.nih.gov/find_people/groups/stroke_prg/index.htm) including the recommendation to review progress after 5 years. To facilitate the evaluation of progress and update the research goals in 2006, the NINDS issued an invitation to the scientific community to provide their opinion on the seminal scientific advances made since 2001 that are linked to the SPRG, future research directions, new resources needed, barriers to stroke research, and ways to overcome them. In September 2006, the NINDS convened a second SPRG of prominent scientists, clinicians, industry leaders, and patient advocates to discuss progress since the first SPRG and to examine new opportunities in light of more recent advances. The membership of this second SPRG was changed approximately 50% from the first group to include additional community representation and a perspective from leading young stroke investigators and researchers in related fields. The report of the second SPRG meeting continues to provide a perspective on future needs to advance stroke research. The complete report is found at http://www.ninds.nih.gov/find_people/groups/stroke_prg/09_2006_stroke_prg_report.htm. In this brief interim report, we list and summarize progress in each of the investigational domains outlined in the SPRG with an emphasis on those advances directly resulting from NINDS-funded research. Some summaries highlight advances in basic research or translational research whereas others emphasize administrative progress in early stage clinical research. Also listed are the top 2 or 3 research priorities for the next 5-year cycle for each investigational theme. What emerges from the first 2 reports is a clear set of priorities that have since been complemented by exciting advances that are likely to be the focus of a follow-up report from the next SPRG in 2010.

Summary of Progress

Cerebrovascular Biology and the Neurovascular Unit

Since its conception at the first SPRG, the neurovascular unit has become the focus of much discussion in normal brain and after stroke. Research on the neurovascular unit has led to the seminal discovery that astrocytes and their foot processes are key components in the coupling between neuronal activity and local cerebral blood flow. By applying new technologies (eg, dual photon confocal microscopy), it was determined that release of an arachidonic acid product (eg, prostaglandin) from astrocytes into the perivasular space couples local blood flow to neuronal activity. Astrocytes and their metabo-
tropic receptors respond to synaptic glutamate by generating astrocytic calcium waves that release the prostaglandin precursor, arachidonic acid from membrane lipids on foot processes surrounding blood vessels. This mechanism suggests potential therapeutic strategies targeting the neurovascular unit and its component compartments to modulate blood flow to satisfy the needs of metabolism during health and disease.

Alterations in any of the compartments of the neurovascular unit may affect the normally tight metabolic blood flow coupling within brain. New data from animal models of Alzheimer disease indicate marked changes in cerebral vascular function. Similar to AD, many cardiovascular risk factors affect function of cerebral vessels and potentially neurons and astroglia. Therefore, vascular control mechanisms are potentially disrupted at the neuronal, endothelial, and vascular smooth muscle level by disease. Vascular oxidative stress induced by βamyloid appears as a major culprit in mouse AD models. Thus reactive oxygen species and oxidative stress may serve as a final common pathway for vascular and neurovascular dysfunction, and ROS has been implicated in vascular dysfunction in hypertension, diabetes, and aging. Evidence implicating ROS as both cell signaling messengers as well as perpetrators of tissue injury continues to build.

Endothelium and Hemostasis

Recent discoveries in the protease field emphasize key interactions in the neurovascular unit that impact signaling between brain matrix proteins, blood vessels, and cells. For example, matrix metalloproteinases (MMPs) are expressed by both blood vessels and neurons and along with circulating white blood cells become activated during ischemia, perhaps by oxygen radicals or nitrergic stress. MMPs cleave multiple substrates including endothelial proteins that form the blood brain barrier and basal lamina components, and MMPs disrupt blood brain barrier and promote edema and hemorrhage. MMP downregulation is neuroprotective when given early after stroke onset but disruptive of neurovascular remodeling when given 1 week after onset. Recent clinical studies support the possibility that plasma MMP levels may be a useful biomarker to predict the risk for hemorrhagic conversion following tissue plasminogen activator (TPA) administration. MMPs have also been found to destabilize atherosclerotic plaques and to increase the risk of plaque rupture in coronary vessels. Other proteases are now becoming implicated in cell signaling and inflammation during stroke, including members of the protease activated receptor family (PARS).

Recent experimental and clinical data emphasize the need to target the microcirculation as well as the inflammatory cascade to reduce the burden of stroke. Data from the SPARCL trial studying 4731 patients provided compelling evidence that elevated plasma LDL-cholesterol levels increased the risk of stroke and that lowering these levels reduces stroke risk. Unlike 5 years ago, this association plus the importance of cholesterol lowering in primary and secondary stroke prevention is now quite strong. A secondary end point from that study showed that statin administration also reduced lesion severity in patients who experience a stroke while on treatment. These as well as other evidence are consistent with encouraging results from early stage clinical trials in stroke patients and in patients given statins after subarachnoid hemorrhage. For example, vasospasm as well as ischemia were reduced in subarachnoid hemorrhage patients treated acutely. Because cholesterol lowering takes weeks to months, these findings implicate cholesterol-independent statin effects and drug actions that target the vascular endothelium and smooth muscle as well as suppress the inflammatory response. In this instance, the preclinical results encouraged the use of statins in patients with stroke from bench to bedside.

Neurocerebrovascular Degeneration

Although most at the SPRG agreed that calcium overload is a major mechanism of cell death, new findings implicate several additional high capacitance systems promoting calcium influx beyond the traditional calcium fluxing NMDA/AMPA glutamate receptor models. One such pathway uses divalent cation permeable channels of the transient receptor potential family (TRPM7). Unlike prior models, the opening of TRPM7 explains the rather marked and delayed rise in intracellular calcium after oxygen glucose deprivation that is normally resistant to glutamate/AMPA receptor blockers and that contributes significantly to delayed cell death. Additionally, exposure to oxygen radicals promotes TRPM7 channel opening thereby providing cross talk between oxidative stress and excitotoxicity pathways. Other newly implicated pathways involve cleavage of sodium-calcium exchangers and other membrane calcium pumps that normally promote calcium efflux and maintain low intracellular calcium levels. Cleavage of these proteins by caspases and calpains activated during ischemia provides crosstalk between apoptotic and necrotic mechanisms of cell death. Other mechanisms may serve as potential contributors to calcium overload in stressed neurons and they include acid-sensing ion channels, gap junctions, and hemichannels, and all provide potential targets for therapy.

Vascular Cognitive Impairment

There was much discussion about vascular cognitive impairment and its possible synergistic interaction with biological changes in Alzheimer disease. Most agreed that atherogenesis and ischemic brain lesions may potentiate the course of AD. Population based radiographic-clinical studies concluded that small vessel disease, white matter signaling abnormalities, and silent brain infarction are highly prevalent and significant risks for cognitive impairment of the elderly. White matter T2 abnormalities are an important marker for the presence and progression of small vessel brain disease, although volumetric measurements may prove to be the measure of choice. What seems clear is that white matter lesions pose significant risk for cognitive decline and symptomatic stroke.

Genetics and Platform Technologies

Recent successful identification of robust associations between common genetic variants and dozens of complex traits and diseases highlight the utility of assembling large numbers
of well-characterized individuals for whole genome association studies. Over the past 5 years, thousands of samples have been collected from carefully characterized individuals with stroke across the country expressly for genetic studies. The availability of this resource insures that whole genome association studies can be completed in stroke.

In addition to the creation of these resources, there has been notable progress in elucidating the contribution of genetic variation to stroke susceptibility. The discovery of a link between mutations in the gene for type IV collagen (COLA1) and familial syndromes involving hemorrhagic stroke, leukoencephalopathy, cognitive decline, and, apparently, increased susceptibility to cerebral vessel injury, has added another gene to the list of those with a fundamental role in cerebrovascular disease.

There is now strong evidence for a genetic contribution to leukoaraiosis in 4 different populations with heritability estimates ranging from 0.55 to 0.71. Given its association with risk of symptomatic stroke and cognitive decline, this suggests that this common cerebrovascular phenotype may be a particularly good target for future genetic studies.

Two critical determinants of warfarin dose have been discovered, and variations in these 2 genes account for about 50% of the interindividual differences in warfarin dosing. Such discoveries make prospects for individualized dose initiation of warfarin a tangible reality for patients within the next 5 years and by so doing, offer the prospect of substantially widening the therapeutic index for one of the most effective stroke prevention therapies presently available.

Biology of Repair
The science of brain repair advanced significantly with publication of a cornerstone study showing that improved neurological recovery corresponds to functional MR evidence of recovery of motor, sensory, language, and attention in cortex ipsilateral to a stroke. Activation of cortex contralateral to a stroke did not. Although the neuroscientific implications of such a study are still being digested, these findings emphasize the need to expand imaging capabilities to examine neural correlates of recovery and maximize prognostic correlates for clinical trials. Although still at an early stage, the substrate for such recovery at the cellular and molecular level are likely to involve axonal and dendritic sprouting, neuronal migration to areas of injury, the formation of novel projections, and angiogenesis within partially damaged and intact tissue. The extent to which certain behavioral experiences, exercise, diet, and drugs modulate recovery of function and reflect the impact of gene expression at the cellular and molecular level remains among the key unanswered questions for the emerging science of brain repair, and for the application of multimodal imaging tools.

Epidemiology
NINDS studies have defined the public health burden of stroke across subpopulations of the US including African Americans, Mexican Americans, women, lower socioeconomic groups, and children. Epidemiological studies and clinical trials have validated the importance of modifiable risk factors such as blood pressure, lipids, obesity, inactivity, estrogen therapy, extracranial and intracranial atherosclerotic occlusive disease, unruptured cerebral aneurysms, transient ischemic attacks (TIAs), and cardiac conditions such as atrial fibrillation. Epidemiological and genetic studies are beginning to identify candidate genes associated with stroke.

Prevention of First or Recurrent Stroke
Major studies on stroke prevention have been successfully completed and have provided new preventive treatments in some cases, and eliminated unnecessary or harmful treatments in others. These studies include: Antiplatelets in African Americans (AASPS), Stroke Prevention in Sickle Cell patients (STOP 2), Antithrombotic therapy for intracranial stenosis (WASID), Vitamins (VISP), Aspirin for primary prevention (Women’s Health Study), Choice of antiplatelet therapy (SSPS), Blood pressure control (ALLHAT), aneurysm treatment (ISAT, ISUIA), and Antithrombotic therapy for atrial fibrillation. Each one of these studies has changed the way that millions of Americans are treated to reduce their chances of stroke.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), currently in progress, is expected to provide important guidance about the safety and efficacy of carotid artery stenting as compared to endarterectomy in the United States.

Acute Ischemic Stroke Treatment
Two NINDS sponsored studies are evaluating methods to improve on the only FDA approved treatment of acute ischemic stroke, intravenous rt-PA, for producing cerebral reperfusion after ischemic stroke within the first 3 hours. Intra venous Tenecteplase (TNK), and lower doses of IV rt-PA coupled with intraa rterially administered rt-PA with and without endovascular mechanical lysis, have both gone through the pilot studies phase and are now entering the pivotal efficacy stage of evaluation. Pivotal trials of powerful antiplatelet drugs (GP2b3a antagonist) or antithrombotics (direct thrombin inhibitors) have been completed and have shown that these agents by themselves do not improve outcome. However, within the NINDS sponsored SPOTRIAS (Specialized Programs Of Translational Research in Acute Stroke) program, they are now being tested in combination with IV rt-PA to see if they can amplify its effect. This has been demonstrated successfully in another SPOTRIAS pilot study of transcranial Doppler ultrasound. When this noninvasive source of energy was directed at an obstructing clot in the cerebral circulation, it substantially and safely increased the speed and completeness of arterial recanalization, with a trend to improved clinical outcome.

IMS-3 is an NINDS study aimed at determining whether patients with intracranial emboli recanalitran to intravenous rtPA can benefit from intraarterial therapy.

Much interest is focused on determining whether patients can benefit from reperfusion beyond the 3-hour treatment window. Another NINDS funded study showed that multimodality MRI imaging can select patients who may benefit from reperfusion in the 3- to 6-hour time window, and a pilot study of an endovascular method of mechanical clot extraction is underway to see whether such selected patients may.
benefit up to 8 hours after stroke onset. However, our ability to improve outcomes with extended (ie, >3 hours) time window for thrombolysis still requires further study given the failed industry-sponsored DIAS trial.

The other general approach to acute stroke therapy is by pharmacologically rectifying the imbalances in cellular homeostasis that occur after ischemia. Broadly termed “neuroprotection,” this approach is based on an understanding of disordered brain biology growing from years of NINDS funded research in animal stroke models. Two such drugs are presently under evaluation in phase 3 efficacy studies. Alumil is the first neuroprotective drug to successfully go through the pilot studies program, and a study of magnesium is using prehospital diagnosis of stroke by trained paramedics to allow ultraearly treatment in the field. Other neuroprotective therapies under evaluation within the SPOTRIAS framework include oxygen, statins, hypothermia, and a low dose combination of caffeine and ethanol.

Hemorrhage

Bleeding into the brain causes 20% of strokes, yet no specific treatment has been shown to reduce damage from this type of stroke. The NINDS held a symposium of leading researchers in this field to identify therapeutic targets. A number of therapeutic studies funded by NINDS are consistent with the recommendations of this group. Minimally invasive surgical removal of the hematoma is being tested within the SPOTRIAS network, and in combination with rtPA in another trial. A study of blood pressure lowering to prevent hemorrhage enlargement is about to begin. A large international study of aneurysms, which are the cause of devastating subarachnoid hemorrhage, has clarified the management of aneurysms that have not yet bled, and the role of endovascular coiling compared to surgical clipping to obliterate the aneurysms.

The international STICH trial demonstrated some of the difficulties in improving outcome by surgical removal of clot. Disappointingly, an industry trial of activated Factor VII prevented hemorrhage growth but did not improve outcome in the overall study group.

Recovery and Rehabilitation

In the last 5 years, the field of stroke rehabilitation has been subjected to scientific scrutiny. The first randomized trials of rehabilitation techniques have evaluated constraint movement therapy, amphetamines, and treadmill training. Rodent models of functional recovery after stroke and functional imaging in humans have suggested the advantage of early intervention and improved our understanding of the anatomic and functional relationships among brain structures. Finally, a better understanding of the impact of cognitive, emotional, and psychosocial factors on recovery have allowed targeted interventions for these problems. Among these is the first NINDS sponsored trial of “stem cell” therapy to enhance recovery—a phase 1 pilot safety study of intravenously administered marrow stromal cells.

Imaging

Advances in imaging have been pivotal in much of this progress in stroke prevention, acute treatment, and recovery enhancement. Imaging is now used to select, monitor, and test therapies. Examples are use of Transcranial Doppler ultrasound for sickle cell stroke prevention and for sonothrombolysis, CT for detecting hematoma enlargement, multimodal MRI and CT for penumbral identification and patient selection for reperfusion, multimodal MRI for identifying hemorrhagic risk of reperfusion, and functional MRI, Magnetoencephalography, and Transcranial Magnetic Stimulation for studying stroke recovery. Of course, improved imaging has also resulted in improved diagnosis. Examples include gradient echo better than CT for identifying bleeding (including microbleeds), MRI identification of silent infarcts in TIA patients, MRI for differentiating the characteristics of carotid plaques, and advanced MRA and CTA for detailed imaging of aortic arch, neck, and intracranial vessel pathology.

Health Services Implementation

NINDS has been active in expanding the number of centers and personnel capable of carrying out translational clinical research in acute stroke. In addition to the previously mentioned SPOTRIAS network, and organization and training of paramedics in the SPOTRIAS magnesium trial, NINDS has recently funded the organization of emergency departments throughout the US via the Neurological Emergencies Treatment Trials (NETT) Network. Acute stroke registries (Coverdell, others) have advanced understanding of barriers to implementing secondary prevention strategies and shown that use of standardized orders, etc, have improved adherence to these strategies.

Summary of Priorities

Many common elements emerged among the groups, in particular a call for collaboration among investigators and the desire for NINDS to facilitate shared databases, investigator networks, investigator/government/pharmaco-industry/FDA interactions, and human tissue and genetic repositories. The groups also emphasized the need for more clinically relevant animal models, exploration of surrogate outcome measures, the development of biomarkers for stroke diagnosis, and streamlining the submission, review, and start-up components of clinical research protocols. These points will not be repeated in the following summary of the top research priorities. However, the prevailing message for such assistance from each group speaks loudly for the need to facilitate the stroke research enterprise and make it more user-friendly.

Overlapping recommendations among groups (for instance, both the imaging and recovery groups urged using imaging to predict recovery), are not reiterated in the different group summaries. Below are a list of priorities:

Cerebral Vascular Biology and Neurovascular Unit

Interrogate normal and pathological cerebrovascular function by generating animal models that express human mutations affecting specific cells of the NVU.

Examine the function of those targeted cells using cell culture, coculture, and brain slices and validate new findings using in vivo preparations.
Endothelium and Hemostasis
Investigate whether there are hemostatic mechanisms that are specific to the CNS and the extent to which they provide novel targets for therapy.

Place a high priority on research that clarifies the role of proteases, receptors, and ligands as they impact focal cerebral ischemia, posts ischemic inflammation, and hemorrhagic transformation.

Neurocerebrovascular Degeneration
Refine imaging tools in humans to obtain quantitative surrogates for vascular events (eg, plaque stability [rupture] as well as the molecular and cellular pathophysiology dissected in experimental systems that include inflammation, cell viability, and cell migration; develop imaging tools to better characterize the transition zone between acute injury and delayed remodeling. (This was also a priority of the imaging group).

Generate a series of linked platforms spanning the range from cells in vitro to tissue in vivo to examine pathophysiology and to identify molecular targets and test combination therapies.

Neurovascular Protection
Promote the development of animal models that include key factors such as age, sex, functional outcomes, underlying disease processes, and risk factors that predispose to stroke in humans.

Elucidate signaling pathways involved in maintaining or restoring the integrity of the blood brain barrier and develop therapeutic strategies to reversibly open the blood brain barrier for the transport of therapeutic agents.

Focus greater research efforts on cell signaling within white matter and define with greater precision the correlates of the neurovascular unit within that tissue.

Vascular Cognitive Impairment
Place a high priority on developing experimental systems modeling human small vessel disease and VCI. Develop tools to identify key molecular pathways in small vessel brain injury and explore existing model systems to examine the interaction between various risk factors such as blood pressure, CAA, and CADASIL.

Encourage human studies that define high-risk populations, validate imaging end points, define biomarkers, and identify candidate treatments for VCI.

Evaluate the merits of long-term prevention trials for VCI and other forms of cognitive impairment associated with atherosclerotic risk factors based on preliminary data showing the benefits of aggressive treatment of elevated arterial blood pressure on reversing WMH volume changes.

Genetics
Develop a consensus on definition, selection, and prioritization of clinical and neuroimaging cerebrovascular phenotypes, risk factors, and key environmental exposures for genetic studies.

Accelerate progress by learning from the experience with other complex diseases such as diabetes, rheumatoid arthritis, and myocardial infarction, eg, by assembling large numbers of DNA samples to perform unbiased whole genome association scans to detect gene variants with relatively modest effects on risk while simultaneously limiting false-positive findings via replication. This effort can be facilitated by creating a Stroke Genetics Study Group, modeled on similar, large-scale study groups for complex diseases that leverage the combined resources of distributed sample collections already in biobanks.

Genomics, Proteomics, Metabolomics, and Bioinformatics
Harmonize the data collection criteria for phenotyping and characterizing patient samples with attention to quantitative traits that will yield maximum information for exploratory analyses. Encourage consensus on data entry as well as uniformity of presentation and storage for platforms studies.

Provide training opportunities that bring together interdisciplinary groups of biologists, bioinformaticians, clinical investigators, and trainees to address application of powerful platform technologies to cerebrovascular disease.

Biology of Repair
Synchronize experimental preclinical and clinical methodologies for neurorestorative research and accelerate their development.

Support the development of quantitative imaging markers to define neurogenesis, angiogenesis, and remodeling in the recovering animal and human brain.

Develop a bank of human tissues to evaluate mechanisms relating to neurogenesis, angiogenesis, and neuronal reorganization after stroke.

Epidemiology
Promote further understanding of stroke burden in the United States and disparities in stroke risk and outcome among subgroups. Look for new high-risk groups and redefine race-ethnic categories to reflect changing US demographics, and establish and describe novel risk factors, especially genetic and gene-environment interactions.

Focus research on women and pediatric populations. In women, differences in inflammatory markers, hormonal influences, stroke in pregnancy and preeclampsia all need further study.

Identify factors influencing stroke outcome, including refinement of stroke subtype phenotypes, using epidemiology to characterize the biological process of recovery, and addressing outcome areas such as economic impact, caregiver burden, health care utilization, impact on family, school performance, etc.

Prevention of First or Recurrent Stroke
Address secondary stroke prevention such as timing of blood pressure control and antithrombotic therapy after stroke, stenting of intracranial stenosis, and antiplatelet therapy in children.

Develop high risk population-based primary stroke prevention with aggressive, evidence-based, multi-modal therapy; for instance (1) patients with obesity/insulin resistance/met-
abiotic syndrome, (2) patients with evidence of inflammation (or proinflammatory state), and (3) perinatal stroke prevention based on better understanding of hematologic, autoimmune, and maternal-fetal environmental factors.

Personalize stroke prevention based on the identification of genes predisposing to stroke and pharmaco-genomic information.

**Acute Ischemic Stroke Treatment**
Improve reperfusion therapy; safer and more effective lytic agents, combination of lytics with additional antithrombotic drugs or ultrasound, combination of lytic drugs with endothelial protectants, and further development of mechanical recanalization. Extension of time window in patients using multimodal MRI or CT imaging. Safety evaluation of reperfusion therapy in children.

Develop effective neuroprotection through combination therapy trials not supported by industry and develop statistical methods and surrogate end points for such trials, and field administration of safe agents.

Improve “the process” of stroke care; determine whether stroke center designation improves delivery of stroke care, pursue formal certification for comprehensive stroke centers, determine efficacy of telemedicine, and use this technology for conducting research and assisting in clinical care, develop and validate serological markers of stroke diagnosis.

**Hemorrhage**
Focus on basic mechanisms of cell death after ICH, vascular and hemostatic factors leading to bleeding and clotting, and neurovascular injury after SAH.

Conduct trials of blood pressure reduction and minimally invasive surgery for ICH and evaluate critical care management strategies.

**Clinical Trials**
Address recruitment problems in stroke trials through NINDS workshops, expansion of trial sites, training of investigators, research coordinator support, reexamination of remuneration, emergency medicine collaboration, streamlined trial design and management, minority recruitment, and central site registry.

Improve trial efficiency through careful validation and thoughtful implementation of imaging and blood tests as early markers of success/failure, novel trial design (more futility trials, combining phases 1 and 2, risk stratification, etc.).

**Recovery and Rehabilitation**
Explore neurobiology of recovery including cellular and molecular mechanisms of plasticity, how to prolong or reconstitute the period of plasticity genetic modifiers of recovery, relationship of pretreatment physiology (fMRI, TMS, MEG etc) to treatment response, achieving a better understanding of neural networks.

Conduct randomized clinical trials of present rehabilitation strategies addressing dosage and timing of drug administration and training paradigms, effects of modifying variables such as lesion location, prior lesions, cognitive impairments, and medical comorbidities. Link neurological deficits with disability; what deficits disable, and at what severity?

Evaluate treatments for persons with chronic or severe impairments by testing compensation strategies targeting assistive technology, restorative strategies of training paradigms attempting to reconstitute brain neuroplasticity, and cognitive rehabilitation targeting aphasia, subtle cognitive impairment, and depression.

**Imaging**
Image molecular and cellular events that define pathophysiological mechanisms, for instance imaging inflammatory cells, neurogenesis, cell migration, plaque instability, etc.

Identify and validate imaging markers of vascular cognitive impairment as well as of brain injury and its prognosis; for instance “mismatch” for penumbra, natural history of hematoma growth/resolution/edema formation, blood brain barrier injury, global ischemic injury, etc. Support functional imaging to clarify mechanisms of recovery, predict outcomes, and enhance recovery; for instance, imaging axonal growth and synaptogenesis, multimodal imaging.

**Support the Application of New and Emerging Imaging Technologies to Experimental Preclinical and Clinical Stroke**

**Health Services Implementation**
Identify educational and other motivational methods to galvanize long-term community engagement in the prevention, early recognition, treatment, and optimal social reintegration of stroke survivors.

Measure the effect of evidence-based stroke care systems on reducing the stroke burden in the US, and then improve the quantity and quality of these services by development of valid performance databases, public performance reporting of outcomes, and payment for performance.

Develop and test the impact of innovative methods of stroke care delivery on access to medical services, cost and resource utilization, and ultimately patient physiological and psychosocial outcomes.

**Stroke Progress Review Group Members**
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