Stroke Progress Review Group:

History and Process

The Stroke Progress Review Group (PRG) was formed in 2001 to produce research recommendations to the National Institute of Neurological Disorders and Stroke (NINDS) for the next 10 years. The PRG produced a progress report in 2006, and a final report in 2012. The PRG process used expert study groups covering 16 areas of research. Each group was tasked to summarize progress in their field and then come up with research priorities. The proceedings were published in the journal Stroke and online.1,2

http://www.ninds.nih.gov/find_people/groups/stroke_prg/index.htm
http://www.ninds.nih.gov/find_people/groups/stroke_prg/2012-stroke-prg-full-report.htm

For planning the next decade, NINDS has reconfigured the PRG process with the intention of identifying a narrowed focus on the most critically important priorities, and obtaining more input from the wider community of healthcare workers involved with stroke and from the public using a dedicated web page: http://www.ninds.nih.gov/strokefr

Eventually, work-groups will be configured on stroke treatment, stroke prevention, and stroke repair/recovery/rehabilitation with the intention to narrow down priorities to 2 to 3 per area.

Progress to Date

I will describe progress on the basis of current decision to of NINDS to divide the field into 3 broad topics: acute stroke treatment, stroke prevention, and stroke repair/recovery/rehabilitation. Other aspects of stroke research that were considered priorities by the PRG between 2001 and 2012 will be covered in a fourth category (Other).

Acute Stroke Treatment

1. Improve reperfusion therapy: the first priority in the area of acute stroke treatment that was identified in the reports of 2001, 2006, and 2012 was to improve reperfusion therapy. The following is a list of research progress in this area:
   1. Enhanced thrombolysis—randomized trials: Study of Tenecteplase in Acute Ischemic Stroke (TNK), Ancrod, Desmoteplase in Acute Ischemic Stroke (DIAS) Study of the Combination Therapy of Rt-PA and Eptifibatide to Treat Acute Ischemic Stroke (CLEAR-ER) argatroban, ultrasound
   2. Device development and Food and Drug Administration approval: MERCI, Penumbra, Stent retrievers
   3. Intervention—randomized trials: MR rescue, Interventional Management of Strokes (IMS)
   4. Collateral augmentation: partial aortic occlusion

2. Effective neuroprotection: this priority was also identified in the reports of 2001, 2006, and 2012. The following is a list of research progress in this area:
   1. Completed randomized trials: NXY-059, citicoline, minocycline
   2. Ongoing randomized trials: magnesium, hypothermia, albumin, near-infrared laser, caffeinol, glyceryl trinitrate, lovastatin
   3. Increased clinical focus on blood vessel/clot pathology: this research priority was mentioned in the report of 2001. Little progress has been achieved in this area, at least with regard to acute stroke treatment.

4. Improve stroke care delivery: this priority was mentioned in the report of 2006. The following is a list of research progress in this area:
   1. Development of Stroke centers, Get With The Guidelines QA measures and database, improved reimbursement for thrombolytic and endovascular treatment
   2. Registry for pediatric stroke and organization of thrombolytic trials, additional study of sex and diversity issues
   3. Telemedicine

5. Stroke networks: this priority was mentioned in the most recent report in 2012. The following is a list of progress in this area.
   1. The following network of centers to carry out acute stroke trials was developed: International Pediatric Stroke Study (IPSS), National Emergencies Treatment Trials (NETT), Specialized Program of Translational Research in Acute Stroke (SPOTRIAS).
6. Hemorrhage at the cellular level: a better understanding of the effect of brain bleeding was identified in the reports from 2001, 2006, and 2012. The following areas of research have emerged from National Institutes of Health–funded laboratory studies:
   1. Cortical spreading depression after intracerebral hemorrhage and subarachnoid hemorrhage
   2. Iron toxicity, inflammation
   3. Early brain injury after subarachnoid hemorrhage

7. Trials on blood pressure reduction, minimally invasive surgery, hematoma evacuation, and critical care management: the need for clinical trials in these areas was identified in the reports from 2006 to 2012. The following trials have been completed or are underway.
   1. Hematoma growth: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT), Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH), Factor Seven for Acute Hemorrhagic Stroke Treatment (FAST), The Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT), "Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT).
   2. Vasospasm: clazosentin, magnesium, statins, albumin
   3. Surgery: Surgical Trial in Intracerebral Hemorrhage (STICH), Surgical Trial in Lobar Intracerebral Hemorrhage (STICH-2), Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation (MISTIE), Intraoperative CT guided Endoscopic Surgery for ICH (ICES), Clot lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR 1,2,3)
   4. Inflammation: deferoxamine, pioglitizone
   5. Arteriovenous malformations: A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)

Prevention
1. Aggressive implementation of prevention measures: this priority was mentioned in the reports of 2001 and 2012. One study addressed this issue.
   1. Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)

2. New prevention strategies: this priority was also mentioned in 2001 and 2012. A number of important studies of stroke prevention have been carried out in the past decade, most of which have resulted in substantial changes in our clinical management.
   1. Risk factors: Vitamin Intervention for Stroke Prevention (VISP), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) statins, aggressive blood glucose control, niacin plus statins
   3. Atrial fibrillation: aspirin+ clopidogrel, dabigatran, apixaban and rivaroxaban, prolonged monitoring
   4. Carotid stenosis: Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)
   5. Carotid occlusion: Carotid Occlusion Surgery Study (COSS)
   6. Patent foramen ovale: Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale (CLOSURE-1), Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT), Patent Foramen Ovale Closure with GORE Septal Occluder Plus Antiplatelet Medical Therapy (GORE)
   7. Sickle cell: blood transfusion, hydroxyurea
   8. Aneurysms: International Subarachnoid Aneurysm Trial (ISAT), International Study of Unruptured Intracranial Aneurysms (ISUIA), Familial Intracranial Aneurysm (FIA)

3. Better risk assessment tools: this priority was mentioned in 2001 and 2012, but little progress has been made in this area.
4. Personalized prevention—genetics: this priority was mentioned in 2006, but little progress has been made in this area.
5. Specific secondary prevention issues: this priority was mentioned in 2006.
   1. Stenting of intracranial stenosis
   2. Timing of blood pressure control and antithrombotic therapy
   3. Antiplatelet therapy in children

6. High-risk population-based primary prevention: these populations have been identified as being particularly high risk.
   1. Metabolic syndrome
   2. Perinatal stroke
   3. Proinflammatory states

Repair, Recovery, and Rehabilitation
1. Plasticity: molecular, cellular and network changes in the brain that lead to good recovery: this priority was identified in the reports of 2001, 2006, and 2012. It included a call to develop better preclinical animal models. Much progress has been made in the past decade.
   1. Role of astrocytes and microglia
   2. Responses to restorative therapy—neurite outgrowth, splenic cytokines, gene expression, etc
   3. Sprouting transcriptome—molecular neural repair pathways
   4. Inhibition/excitation balance and stunned circuits in peri-infarct cortex
   5. Behavioral effects on recovery; learned nonuse
   6. Broad time window for intervention

2. Neuroimaging to detect recovery and predict outcome: this priority was identified in 2001 and 2006. The following represents progress in this area.
1. MRI: fMRI, microvessel density, blood brain barrier transfer, diffusion tensor imaging, stem cell migration
2. In vivo imaging of dendritic spines and synaptogenesis; micro‑positron emission tomography of gene expression
3. New clinical interventions: this priority was identified in 2001 and 2012. The following progress has occurred as a result.
   1. Activity-based therapy, robotic therapy, cortical stimulation
   2. Cell-based therapies
   3. Depression treatment

Other Successes/Priorities
1. Appreciation of neurovascular unit
2. Defining stroke at the molecular level using genomic, proteomic, and metabolomic markers
3. Genetic consortia; identification of ischemic risk loci on gp21 and 16g22 and others, and Apolipoprotein E e2 with intracerebral hemorrhage
4. Imaging the penumbra
5. Vascular cognitive impairment—neuroimaging correlates

Conclusion
Although some areas identified have received little attention, there has been huge research progress in the stroke field with many examples reflected in the research presented at this Princeton Conference. There is much to be done to build on these successes, and it will be a challenge to narrow down future priorities to just a few in 3 broad topics.

Disclosures
Dr. Grotta receives National Institute of Neurological Disorders and Stroke funding for Argatroban, Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator (CLOTBUST), Hypothermia, Caffeinol and Pioglitizone studies. He is a consultant for Lundbeck, and holds a patent on Caffeinol.

References
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