Big Idea: The Stanford Neuroscience Institute Collaborative Stroke Network

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Vision: Stroke is arguably one of the most important neurological diseases, and Stanford is uniquely suited to ameliorate its impact. We propose a Collaborative Stroke Network whose goal is to bring together disparate disciplines to generate scientific solutions for stroke. This transformative research initiative contains 34 scientists from 14 different departments with expertise in mechanical, electrical, and biological engineering, systems and molecular neuroscience, neuroimmunology, and clinical stroke. Already, ongoing studies span a wide spectrum of stroke research including haptic devices, brain-machine interfaces, novel MRI techniques, brain stimulation to rewire circuits, mechanisms of post-stroke seizures and synaptogenesis, neuroinflammatory consequences of stroke, blood-brain-barrier manipulation, acute stroke therapies, pediatric stroke, and many others. The network will strive to support the individual genius of its investigators and to together create solutions that could not be achieved separately. Similar to other targeted initiatives, the most famous being the space program, we expect that along the way our efforts will not only generate practical solutions for stroke survivors but also uncover basic truths about the brain and generate new engineering solutions with applications to other neuroscience problems. The network will accomplish its goals using a multipronged approach. First, the group will collaboratively select “flagship projects” on which to focus our efforts. These will be re-evaluated by the group yearly, and supported creatively using both traditional and non-traditional methods. Second, the group will interact scientifically via seminar series and training of interdisciplinary postdoctoral fellows. Third, the network will, in addition to the flagship projects, facilitate traditional collaborations between investigators that will generate research advances and grant applications. The group will also work together to raise funds, with a goal of becoming self-sustaining.
1. **Background**

A stroke happens every 45 seconds in the US, adding up to an incidence of 800,000 per year. Stroke is the fourth leading cause of death, and yet 75% percent of patients survive. The annual cost of stroke in the US is 39 billion in 2009 dollars. Furthermore, aside from clot-busting therapies that reverse or ameliorate a stroke within hours, there are no proven treatments. Of the 6,800,000 adult stroke survivors currently living in the US, one third to one half are left with a disability. This makes stroke a leading cause of disability in the US and worldwide. Quality of life also declines significantly after stroke due to functional decline, fatigue and depression.

There are **significant barriers** that have prevented the development of new treatments. Most importantly, there has not been good communication between basic scientists and clinicians. As a consequence, discoveries made in animal models have not successfully translated to therapies. Over 100 phase III clinical stroke trials focused on neuroprotectant therapies have failed. This has dampened the pharmaceutical industry’s enthusiasm to invest in stroke research and resulted in a sense of fatalism about stroke. Despite the fact that significant recovery can occur in some patients after stroke, it is often perceived as the end stage of a disease, rather than as a modifiable, treatable condition. Together, these factors have resulted in a slow-down in basic research and stalled the development pipeline for new treatments for stroke.

2. **Intellectual Goal: A Stanford Neuroscience Institute Collaborative Stroke Network focused on improving the function and quality of life of stroke survivors.**

Stanford is uniquely suited to **bridging the barriers** between basic science, engineering, and clinical research, and to thus advance stroke science. We are a leader in neuroscience, engineering, and innovation, and our network will contain a large group of outstanding investigators who are interested in stroke, highly collaborative, and span a wide range of fields. The individuals who have committed to joining the collaborative network bring expertise in a wide spectrum of science, including mechanical, electrical, and bio-engineering, systems and molecular neuroscience, imaging/radiology, neuroimmunology, neurology, neurosurgery, and genetics. Many of these fields have experienced recent advancements that have yet to be applied to stroke.

Stanford is also already a worldwide leader in clinical and translational stroke research, as well as in stroke patient care. The Stanford Stroke Center, founded in 1992, is widely recognized as a leader in clinical and experimental research with a particular emphasis on treatment trials, novel MRI techniques for early detection, moving laboratory discoveries into the clinic (such as mild hypothermic neuroprotection) and patient selection for therapies. We were designated the first comprehensive stroke center in the United States, and in 2013 we were designated by NINDS as a clinical trials coordinating center for stroke. Stanford is currently building a new outpatient clinic building that will contain stroke clinic and rehabilitation facilities.

A Neuroscience Institute-sponsored network will bring together the basic and clinical scientists that are already here at Stanford, and potentially recruit others to fill gaps in knowledge. The network will be unique—there is no such research initiative at any other university or research institute. Together, the network will define the big picture questions most likely to ultimately help stroke survivors. Acceleration of stroke research at Stanford will occur via support of “flagship” projects, training programs, and seminar series. Networking within the group will also provide collaborative opportunities, break down communication barriers between clinical and basic scientists, and facilitate solutions to fundamental scientific questions relevant to stroke (see examples below).

3. **Specific Proposal:**

1. Faculty would meet yearly for a one-day retreat at which they will present ongoing work and evaluate the network’s priorities. A planning retreat will be the first such meeting and will chose 2-3 “flagship projects” on which the group will initially focus. These could be either one-year or renewable efforts (see examples below). The group will dedicate resources to these goals based what will most help to accomplish each goal. For example, the group could fund more traditional collaborative pilot grants but could also choose to fund shared equipment, joint trainees, visiting scientists who would teach courses, new faculty recruits, etc.

2. To facilitate an inclusive, interactive group of faculty, we will welcome new members. However, to garner support from the network (e.g. for grants for research or postdoctoral fellows) we will require participation in its activities. All faculty agree to actively comment on online discussions, and participate in the seminar series, annual retreats, philanthropy, community outreach, and any grant reviewing or writing processes.
3. We will organize a weekly trans-disciplinary stroke seminar series with both outside speakers and lab meeting style presentations from the group.

4. Philanthropy and community outreach–Members would participate in community outreach to stroke interest groups and stroke survivors, and work with the Development office to facilitate our goals.

5. Seek support for a T32 and/or privately funded postdoctoral collaborative stroke science fellowships. Fund some fellows for either flagship projects or for research spanning disciplines. We hope to improve the overall quality of stroke science by training stroke researchers with exposure to a broad range of outstanding stroke research, including both clinical and basic science aspects of stroke.

**Candidate “Flagship” Projects (suggested by the network faculty):**

1. How does the brain rewire after stroke (assayed using molecular, systems, imaging, and optogenetics approaches), and in what ways is this successful vs. not successful in terms of producing recovery? Does this create therapeutic opportunities? Seek basic mechanisms that differentiate the plasticity-based processes that lead to successful recovery vs. post-stroke seizures or spasticity, and design therapies that target only recovery.

2. How do stem cells or other treatments help vs. harm stroke recovery at a molecular and systems level? Is it going to be possible to design drug-based rather than biologic-based treatments?

3. What is the role of the cerebrovasculature in causing, preventing, or mitigating an initial stroke, and how can we manipulate it to yield either acute treatment or stroke prevention?
   a) Engineering solutions for improved real time endovascular imaging of intimal plaques and endothelium.
   b) “Omics” of normal and pathological gene and protein expression on intracranial endothelial cells.
   c) Develop nanoparticles that through endocytosis can selectively incorporate into endothelial and vascular smooth muscle and serve as a radiosensitizer for radiosurgery, or directly target vascular pathologies.
   d) Definition of molecular signals that regulate the blood-brain barrier and brain angiogenesis and their manipulation to explore potential therapeutic opportunities for stroke therapy.

4. Are there better measures of recovery than the ones we have now, e.g. ones that are tailored to which parts of the brain are injured, or more quantitative? Can we get better at predicting outcomes?
   a) Novel imaging measures to predict and quantify recovery, including resting state MRI and fMRI.
   b) Remote monitoring and personal accelerometer technology to improve quantification of stroke recovery.

5. Spasticity is a huge debilitator, and there are few useful treatments and little understanding of how this maladaptive rewiring occurs. Can we develop animal models to understand the underlying circuitry and develop treatments? This project includes basic electrophysiology, molecular and systems remodeling of basal ganglia and spinal cord after injury, and haptic devices engineered to model and overcome spasticity.

6. How does inflammation after stroke help vs. harm? Do late adaptive immune responses after stroke contribute to post-stroke dementia and can they be prevented?

7. Can we improve quality of life measures after stroke? How does post-stroke dementia differ from fatigue and depression, and how do each contribute to worsened quality of life?

8. Can we improve assistive and rehabilitative devices that will improve quality of life or motor recovery after stroke? This spans brain machine interfaces, haptic devices, and basic neuroinflammation research to understand how the brain’s injury response impairs the lifespan of implanted devices.

**4. Expected Outcomes:**

1. An interactive Collaborative Stroke Network with an exceptional level of communication and collaboration and meaningful contributions from engineering and quantitative sciences, basic science, and clinical sciences.

2. Clear advancements in stroke research within the first 5 years.

3. A funded T32 or other funding to support postdoctoral fellows within 4 years.

4. Philanthropy: Support for 2-3 “flagship” projects aimed a tackling the big questions chosen by the group as most important and most do-able, and aim to become sustainable going forward.

**5. Planning Budget:**

$7500 for a one-day retreat with a clinical presentation, talks outlining Stanford resources for stroke research in engineering, basic neuroscience, and clinical resources for stroke research, and a brainstorming session over dinner where faculty will chose the flagship projects and begin planning the full application.