Can Molecular and Cellular Neuroprotection Be Translated Into Therapies for Patients?
Yes, but Not the Way We Tried It Before

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**Background and Purpose**—The concept of neuroprotection is based on sound scientific data derived in preclinical studies. However, candidate neuroprotectants have never been successfully translated to patients.

**Methods**—A review of past approaches to cellular and molecular neuroprotection, preclinical neuroprotection studies, and clinical approaches was undertaken.

**Results**—Although there is no evidence for fundamental barriers in biological principles that limit the translation of promising therapies to humans, ample evidence exists as to a lack of rigor in preclinical studies, obstacles posed by the complexities of acute ischemic stroke syndromes, and regulatory barriers. Alternative methods to translating stroke drugs may require trials in restricted stroke indications in well-defined patient populations.

**Conclusions**—The translational gap between cellular and molecular neuroscience and patient therapy may be bridged by first developing therapies for narrow stroke indications. A single success may stimulate further research, funding, and a capacity to generalize initial results to broader stroke populations. (Stroke. 2010;41[suppl 1]:S87-S90.)

Key Words: brain aneurysms | endovascular procedures | neuroprotection | outcome scales | stroke models | surrogate measures
Significant barriers also exist at the clinical phase of translating candidate drugs from preclinical studies. Acute ischemic stroke is a heterogeneous disorder in which relationships between structural brain damage and clinical outcomes are complex and tools to assess these relationships are rudimentary. For example, whereas there may be a relationship between the size of a myocardial infarct and myocardial function, this relationship is less straightforward in the brain due to the varying eloquence of different brain regions and to anatomic variations in collateral vascular supply. A small thalamic infarct may produce a larger neurological deficit than a large frontal lobe stroke. Consequently, clinical trials in which the primary outcome is a measure of gross neurological function such as the modified Rankin Score or the National Institutes of Health Stroke Scale must enroll large numbers of subjects. Due to the paucity of high-quality preclinical data, such trials may also have overestimated the effect size of the intervention and might have optimistically underestimated the sample size needed to show an effect based on conventional outcome scales. Unfortunately, surrogate markers such as CT or MRI measurements of infarct volumes have demonstrated no or modest correlations between infarct volume and clinical outcomes using conventional outcome scales. Thus, imaging surrogates remain unacceptable to regulatory agencies as validated end points sufficient to grant approval of a neuroprotectant. Although the Food and Drug Administration has recognized that stroke is a serious and life-threatening condition, making it eligible for accelerated approval, no surrogate marker has been validated to “reasonably likely to predict clinical benefit” as required under the accelerated approval process.

A Potential Solution

Of the multiple obstacles that stand in the way of translating cellular and molecular therapies to patients with stroke, one barrier that must be scaled is that of the scientific quality of preclinical research. Even before its evaluation in animal stroke models, a candidate drug should have a clearly defined molecular mechanism of action, a valid molecular target, an acceptable toxicity profile, and appropriate pharmacokinetics and pharmacodynamics, including evidence of central nervous system penetration. These features should ideally be vetted by peer review. Although drugs for nonstroke indications have been developed without a molecular understanding of mechanisms, this has clearly not sufficed for neuroprotectants. Thereafter, we must heed the repeated calls for more rigorous testing of candidate neuroprotectants in animal models, a roadmap for which has been established by the STAIR committee. It is acknowledged that, to date, the STAIR recommendations have not been proven to lead to a therapeutic success. However, no candidate neuroprotectant has satisfactorily met all STAIR criteria before its attempted translation to clinical use. The STAIR framework provides a standard of good scientific inquiry that includes randomization, concealment of treatment allocation, and blinded outcome assessment that, although intuitive, is often lacking in previous studies.

Nonetheless, not all barriers must or can be scaled. The heterogeneity of acute ischemic stroke, the complex relationships between structural brain damage and clinical outcomes, the bluntness of conventional outcome measures, the requirements for large sample size, the poor relationship between MRI surrogates and outcome in past studies, and the current lack of enthusiasm for neuroprotectants by commercial partners are realities that cannot be changed in the near future by further preclinical research. Fresh approaches may be necessary to translate a candidate drug to the clinic even when such a drug is deemed extremely effective in rigorous preclinical studies.

One strategy is to circumvent these difficulties altogether. These obstacles are largely associated with neuroprotectants geared toward acute ischemic stroke, which, for the reasons stated, is a difficult indication in which to demonstrate a drug effect in humans. An alternative approach is to first develop neuroprotectants for indications in which cerebral ischemia is more uniform and predictable and also faithfully reproducible in preclinical animal models. Although a focused indication for a candidate drug may not be broadly generalizable, it may provide sufficient proof of concept to trigger interest, additional studies, and funding to broaden such a drug’s scope. For example, by focusing on a specific patient population at high risk of ischemic events, a trial may achieve higher sensitivity and reduced variability in its outcome measures to detect a clinical “signal.” A case in point is the Phase 2 Evaluating Neuroprotection in Aneurysm Coiling Therapy (ENACT; ClinicalTrials.gov Identifier NCT00728182) trial. This is a randomized, double-blind, placebo-controlled, single-dose design investigating the efficacy of the neuroprotectant NA-1 in patients undergoing endovascular repair of brain aneurysms. NA-1 is a neuroprotectant developed from cellular and molecular research of excitotoxic mechanisms. It binds postsynaptic density 95 protein, an abundant protein in synapses that links N-methyl-D-aspartate glutamate receptors to downstream neurotoxic signaling pathways. NA-1 inhibits the interactions of postsynaptic density 95 with proteins that mediate neurotoxic signaling in ischemic neurons without inhibiting glutamate receptor activity, thereby treating a key stroke mechanism without incurring the negative consequences of glutamate receptor blockade. The focus of ENACT on patients undergoing endovascular aneurysm repair arose from findings that a large proportion (up to approximately 90%) of these patients exhibit silent embolic strokes as evidenced by careful MR diffusion and perfusion imaging. A significant proportion (approximately 5%) also exhibit clinically significant strokes. NA-1 or placebo is administered to anesthetized patients immediately after completion of the endovascular aneurysm repair. ENACT replicates faithfully previous preclinical animal stroke studies in which the animals, like ENACT subjects, were anesthetized, subjected to complete control of physiological variables, and administered NA-1 after stroke onset. ENACT obviates difficulties with patient recruitment, because informed consent can be obtained up to 2 weeks preprocedure. The approach also obviates uncertainties about the therapeutic window for stroke in humans, because the timing of drug administration can be reasonably controlled. The trial is evaluating the efficacy of NA-1 to (1) reduce the volume of ischemic embolic strokes; (2) reduce the number of ischemic...
embolic strokes; (3) reduce vascular cognitive impairment; and (4) reduce the frequency of large strokes induced by the endovascular procedure.

A further strategy is to focus outcome assessment on parameters other than the traditional clinical outcomes of past stroke trials. Although outcome measures such as the National Institutes of Health Stroke Scale or modified Rankin Score predict the neurological impairments they were designed to test, they are weighted toward measuring physical clinical impairments and may comprise relatively crude measures of the overall clinical impact of stroke. More sensitive measures such as those of cognition and depression may be required, because these are common and important clinical outcomes of stroke. Moreover, outcome assessments at a single point in time, typically at 3 months posttreatment, do not take into account the cumulative or long-term impact of stroke, and such assessments may need to be repeated at later intervals. Lastly, although surrogate markers such as MRI or CT imaging of infarcts do not correlate well with conventional outcome scales, MRI evidence of cerebral white matter lesions and of previous infarcts has been demonstrated in numerous studies to reasonably predict an increased risk of future stroke, dementia, depression, and other cognitive dysfunction. The ENACT trial described here will investigate the relationship between stroke burden on MRI and vascular cognitive impairment as measured by a neuropsychological test protocol recommended by the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network. Such a trial could potentially provide a signal correlating MRI as a surrogate measure that could reasonably predict neuropsychological outcomes. This, in turn, could qualify a drug for accelerated approval by regulatory agencies. Another reason for developing a putative candidate neuroprotectant in a focused indication is that irreversible ischemic damage likely begins at the infarct core early after ischemia onset and reaches a plateau within hours. Regardless of the potential effectiveness of a drug, the longer the ischemic interval, the less salvageable brain will remain to benefit from treatment. An initial clinical “success” may thus be more readily achieved in a restricted patient population that can be treated as rapidly as possible after stroke onset such as those patients who arrive at active stroke centers with a sophisticated stroke strategy. Ideally, the candidate drug would have a high safety and tolerability profile, so that it may even be administered on the presumptive diagnosis of stroke, for example, in patients destined for thrombolytic treatment after confirmatory studies. An outcome measure in such a trial may be the capacity of such a drug to enhance the benefit, or the therapeutic window, of reperfusion. Although such a trial would not be broadly generalizable to patients who are not candidates for reperfusion, it would provide a therapy for a larger proportion of patients with stroke than those who are presently candidates for reperfusion alone. Importantly, such a trial might be achievable in a smaller number of patients than might otherwise have been required.

We believe that applying a neuroprotective drug to a focused stroke indication may yield success more readily than a large trial in acute ischemic stroke. Trials should also validate imaging surrogates against outcome measures such as neuropsychological functioning. Such data would be invaluable in a dialogue with regulatory agencies about the validity of such surrogates in clinical trials of stroke drugs and provide important strategies for the future. Although a drug such as NA-1 may well have efficacy in various stroke subtypes, its initial testing in procedurally induced strokes in the ENACT trial may constitute a “beachhead” from which additional studies, funding, and interest could be derived. There is no such thing as an “irrelevant” stroke even if it is considered silent by crude measures of neurological functioning. For this reason, a single success in a focused indication may suffice to prove the hypothesis that neuroprotection in humans is feasible.

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Disclosures

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