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Translational Stroke Research Vision and Opportunities

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Stroke risk and poststroke disability have steadily decreased in the United States over the past 2 decades because of improved prevention and access to reperfusion therapies for acute ischemic stroke, such as tPA (tissue-type plasminogen activator; alteplase) and endovascular thrombectomy. Despite the efficacy and safety of thrombolysis and thrombectomy, not all patients who receive the treatment improve to full, independent recovery, and most patients are ineligible for treatment. Additionally, there are no efficacious treatments to improve long-term outcomes for patients after the acute phase of ischemic stroke or to reduce brain injury induced by acute intracerebral hemorrhage. Therefore, development of new therapies for both acute and chronic stroke is sorely needed.

Stroke occurs because of a variety of vascular pathologies and injury mechanisms, some of which are difficult to model in animals. With the exception of reperfusion therapy, preclinical

research end points do not generally reflect clinical outcomes. Pharmacodynamics, pharmacokinetics, and target engagement in the human brain need to be further developed and optimized for stroke interventions so that drug level in brain tissue, time to initiation, and duration of treatment can be accurately measured in clinical trials. Many variables, such as heterogeneity of vascular pathologies, patient demographics, and a host of comorbid conditions, as well as the lack of validated biomarkers to stratify patient populations, limit the ability of typical stroke clinical trials to detect a treatment effect.

To address these gaps, the National Institute of Neurological Disorders and Stroke organized and sponsored the workshop Translational Stroke Research: Vision and Opportunities, which was held in Bethesda, Maryland, on November 1 to 2, 2016. The workshop gathered over 180 registered participants from academia, industry, the Food and Drug Administration,

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Table. Scientific Priorities From the NINDS-Sponsored Workshop Translational Stroke Research: Vision and Opportunities

	Recommendations
	1–3 years
Preclinical outcome measures	Development of preclinical outcome measures that align with phase II human outcome measures, including cognitive and other outcome measures, with a reasonable therapeutic window. Different approaches and outcomes may be needed based on the type of study (discovery vs confirmatory). Identify reliable biomarkers.
Experimental animal models	Improve the understanding of how experimental animal models are similar or different in recapitulating human stroke. More research is needed to validate preclinical targets to make sure they are applicable for the human population. Moreover, many features associated with human stroke are not adequately recapitulated in experimental studies. Adequate animal models for age, comorbid human conditions, atrial fibrillation, hypoperfusion, transient ischemic attacks, white matter damage, or chronic stroke with persistent deficits need additional development and emphasis. End points should depend on the particular question being addressed. It may be valuable to use different models and different outcomes.
Preclinical standards and common data elements	Develop best preclinical practices guidance, small animal imaging guidelines, and preclinical CDEs for stroke, for clinical, radiological, molecular, and other forms of measurement. Preclinical stroke researchers should agree on a set of common data elements for reporting of their results. Minimum quality criteria (standards) should be established for exploratory (discovery) and confirmatory studies (prevention of bias, statistics, etc).
Collaboration between preclinical and clinical scientists	Incentivize Team Science between clinical and preclinical investigators via T32 funding for trainees, or a Clinical and Translational Science Awards–based mechanism, or through hands-on approach specialized training courses.
Multicenter network approach for late preclinical testing of promising therapies	Preclinical multilaboratory trials of a putative treatment may be valuable before investing in a clinical trial. Such multicentered preclinical testing is complex and should include, at a minimum, an agreed upon protocol that all laboratories would follow; rigorous good laboratory practices; a centralized randomization and data center; on-site source verification of data; and early validation of targets in humans. Such approaches should only be considered for a highly promising therapy that is under consideration for late-phase human trials. Incentives and requirements for participation should be discussed.
Independent replication	Preclinical results should be independently replicated before moving into clinical testing. Specifics of such a requirement need to be worked out (definition of successful replication, strength of evidence, degree of interlaboratory standardization, multisite, academia vs Contract Research Organization, etc).
Publish/report negative data	Publication or public use data set of negative findings is critical for moving translational stroke research forward. This could be a requirement for all NIH-funded preclinical stroke research.
	4–5 years
Clinical outcome measures	Develop new and better outcome measures for phase II and phase III clinical trials. Clinical trials traditional end points are widely used and well validated. However, new predictive and standardized end points that also incorporate cognitive outcomes and recovery of function are needed. A workshop specifically targeting end points, such as the workshop held during the NINDS tPA for acute stroke trial that resulted in the global outcomes measure, is desirable.
Stroke repositories and biobanks	Create data repositories and include stroke in biobanks.
Interaction with vascular contributions to dementia and other fields	Facilitate interaction and collaboration with the field of small vessel disease/vascular dementia/cerebral amyloid angiopathy and vascular contributions to cognitive impairment and dementia. Consider systemic effects, not just the brain (eg, cardiology, immunology).
Standardization and monitoring of preclinical studies	Confidence in results from preclinical studies must be underpinned by verification. Specifics of such monitoring/auditing need to be defined (random inspection, peer vs institutional, responsibility of funders and journals, funding, etc).

CDE indicates common data elements; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; and tPA, tissue-type plasminogen activator

and other public and private funding agencies. In the context of this workshop, translation refers to the research necessary to move a promising therapeutic along the drug development pipeline. Preclinical translational studies need to be designed differently depending on whether they are exploratory or confirmatory. Exploratory approaches may focus on disease mechanisms and use simpler rodent models to gain rigorous information on a putative therapeutic target. However, later-stage confirmatory studies of putative therapies would benefit from the same design features adopted in clinical trials, including heterogeneous populations, adequate sample size, end points predictive of clinical outcomes, and routes of administration similar to therapeutic use, as well as reporting of study results, including negative findings. This special report outlines the discussions and recommendations developed by

the workshop participants to help advance translational stroke research, which are summarized in the Table.

Animal Models

The development and selection of the appropriate animal models depend on whether the study aims to address mechanism or target of interest, to document preclinical efficacy, or to establish safety/toxicology evidence to support human trials. A class of agents with a defined biological target and demonstrated safety in humans may require only directed limited preclinical research for support, whereas unproven treatment modalities may require a more rigorous and extensive preclinical evidence before proceeding to expensive human trials.

The entire spatiotemporal evolution of stroke pathology needs to be better understood, both early after the ischemic event,

when reperfusion and neuroprotection are key targets, as well as days–weeks–months poststroke, when repair and regeneration are critical. Many preclinical studies focus on lesion volume as the primary outcome, as well as behavior outcomes at early time points postinfarct. Unlike stroke patients, however, rodents often show full spontaneous recovery of function, particularly when crude behavioral tests are used. There is a need to further develop animal models with persisting deficits that mimic the human condition. In addition, outcome measures that include the poststroke recovery stage are needed to better characterize long term brain adaptation and plasticity. Without examining sensitive outcome measures at later time points (30–90 days or longer) in preclinical models, translational potential may be limited. Since rodents may exhibit masking of functional deficits and a parallel compensation of sensor and motor disability, more sensitive and specialized tests to help discriminate recovery from compensation are needed. There is also a need to recapitulate the impact and heterogeneity of cortical, subcortical, and combined ischemic injury in animal models. To better translate optimal dosing from animals to humans, confirmatory preclinical studies should provide full dose–response curves, pharmacokinetic and pharmacodynamic modeling, and measurements of drug concentrations within the blood and cerebrospinal fluid. The Food and Drug Administration–published guidelines on dose translation are applicable to multiple disease states and are based on body surface area rather than body weight.¹

The panel discussed whether data from large animal models are needed to justify moving into human trials. Although small and large animal models may be similar at the cellular level, they differ at the system level and in their immune responses. Furthermore, the organization of descending pathways differs between rodents and primates, and the repertoire of behavioral tests available for nonhuman primate studies is more extensive than those used in rodents. Nonhuman primates also offer the opportunity to generate informative data about important facets of human stroke pathophysiology, such as collateral flow, gyrencephalic white matter injury, adaptive recovery and return of physical function, cognitive testing, scaling studies of leptomeningeal arteries or astrocyte volume, and complex immune response. Understanding mechanisms in multiple rodent models prior to nonhuman primate research was considered important. Most importantly, a strong rationale, for instance, a target that cannot be modeled in rodents, is needed to ethically justify the use of nonhuman primates or other large animal species (eg, dog, sheep, pig models) with a statistically meaningful sample size.

An additional translational tool for predicting efficacy in humans, albeit less well documented, involves testing agents *in vitro*. With increased availability of human cell lines/tissues, organoids, and inducible pluripotent stem cell technologies and high-throughput assays, *in vitro* strategies, in combination with data from animal models, may hold increasing prominence in future drug development strategies.

Biological Variables: Age, Sex, and Comorbidities

The impact of age should be considered carefully in preclinical studies because the mechanisms of stroke and response to drugs may be different in the developing, juvenile, adult, and

geriatric brain. Similarly, sex can impact both the extent of stroke pathology and drug actions, and so evaluating agents in both sexes was considered critical. While using female rodents may seem to present challenges because of the estrous cycle, effective strategies to minimize these concerns are available. Using aged females after the cessation of the estrous cycle is a preferred approach to limit estrogen's interference and to model perimenopause/menopause in women, typically associated with a higher risk of stroke. However, the demonstration of a beneficial effect in female animals, regardless of estrous stage, would also inform a potential therapy's applications.

Preclinical studies are typically conducted in homogeneous groups for practical reasons, unlike patient populations typically enrolled in clinical trials. It is critical that investigators consider the variability in animal strain, stroke subtype and severity, collateral status, time to and degree of reperfusion, immune status and response, and end points, to name a few, so that the preclinical premise is adequate to inform clinical trials. Animal models can also be designed to incorporate comorbidities, such as hypertension, obesity, diabetes mellitus, and hypercholesterolemia, which are highly prevalent in the targeted patient groups and may play important roles in stroke pathogenesis and outcome. Additionally, the possible interactions of potential stroke therapies being tested and drugs routinely used to treat relevant comorbidities should be further explored. Some, however, felt that using more basic, simple animal models would limit the confounders in the interpretation of the results, particularly in early exploratory studies.

Preclinical and Clinical Outcome Measures

Preclinical outcome measures should recapitulate human clinical features as nearly as possible, including infarct volume, neuroanatomical metrics, and behavioral/functional end points. However, the relationship between infarct volume and functional outcome has not been well validated in rodents or humans and complicates the transition to clinical trials. There are substantial measurement difficulties that remain a chronic problem of under-recognition in both the preclinical and clinical worlds. Infarct volume assessment in preclinical studies using 2,3,5-triphenyltetrazolium chloride may identify cells that are damaged but could eventually recover. Clinically, there is significant measurement uncertainty on exactly what magnetic resonance imaging or multimodal computerized tomography modalities are measuring in humans. Studies should, thus, go beyond looking at only final infarct volume and instead more rigorously characterize ischemic injury in terms of changes in the core and penumbra over time. In preclinical studies, changes in cell numbers should be quantified using unbiased stereological approaches. New neuroimaging modalities are available for use in both rodents and humans and should be further developed as complementary outcome measures in translational studies. Furthermore, the importance of lesion location in addition to infarct volume as a determinant of functional outcome should be underscored. Housing conditions, animal husbandry, and the presence or absence of an enriched environment should also be considered and reported because they might affect stroke outcome.

The selection of measures that lack good cross-species validity can derail translational efforts from the outset. Functionally relevant outcome measures that bridge across species, such

as edema formation, cerebral blood flow, and collateral status, may provide translationally valuable data and need to be deployed more globally. In addition, some higher order behavioral tasks for cognition and quality of life measures, such as depression, social isolation, and others, could interrogate neurobiological substrates common to rodents and humans.

Chronic Stroke and Stroke Recovery

Developing better animal models for chronic stroke and addressing mechanisms of stroke recovery were viewed as priorities. There are several animal behavioral and motor outcome measures that assess distal extremity and fine motor control with relevance to human recovery.²⁻⁴ Sophisticated executive function tests in rodents capturing deficits seen in stroke patients were recently reported.⁵

Long-term consequences and natural history of stroke in humans need to be better characterized. There is also a disassociation between quality of life measures from the patient perspective and neurological measures of recovery that needs further consideration. The modified Rankin Scale, considered as the gold standard for acute stroke reperfusion trials, presents limitations in its ability to capture smaller, but clinically significant treatment effects on recovery after stroke and neurological deficits, such as aphasia, neglect, dexterity, and so on.⁶ A better tool to measure sensorimotor recovery after stroke is the Fugl-Meyer scale.⁷ Validation of more sensitive outcome measures for clinical trials should be a priority.

StrokeNet, Reverse Translation, and Team Science

The National Institute of Neurological Disorders and Stroke established the NIH StrokeNet (<https://www.nihstroke.net>) to maximize efficiencies in the development and conduct of NIH-funded multisite exploratory and confirmatory phase III clinical trials in stroke prevention, acute treatment, and recovery and to bridge the gap between basic clinical scientists and clinicians.

The StrokeNet infrastructure and trial development help to address challenges for multisite trials, such as patient selection, effect size, study power, feasibility at sites, patient recruitment/retention, and selection of most relevant end points. StrokeNet could advance preclinical research by providing rigorously collected patient information to translational researchers, by incorporating biomarkers validated in preclinical studies, and by facilitating the dynamic interaction between clinical researchers, biostatisticians, and translational researchers to critically evaluate all facets of study design.

Generally, the stroke field lacks validated prognostic and diagnostic blood-based or neuroimaging biomarkers to stratify patients or assess treatment outcomes. An available but underutilized resource for investigators at all phases of biomarker discovery research is the NIH NeuroBioBank (<https://neurobiobank.nih.gov>). Well-described tissue or imaging brain banks with preclinical and clinical samples could accelerate early target validation.

Training of early career basic and clinical investigators could be enabled by a specific institutional training grant mechanisms, such as the NIH T32 or via the Clinical

and Translational Science Awards-based training mechanisms supported by the NIH National Center for Advancing Translational Sciences. Relevant examples are StrokeNet and the Canadian Partnership for Stroke Recovery course, Stroke Program in Neurorecovery (<http://www.canadianstroke.ca/en/training/events>).

Lessons Learned From Previous Translational Efforts

Several tPA and endovascular trials for acute ischemic stroke indicate that when an intervention is beneficial, it shows efficacy across several complementary outcome measures, with large effect sizes in patients who have salvageable brain tissue at the time of treatment. Key findings learned from reperfusion trials include the axiom “time is brain,” reperfusion is generally helpful, the patient population is heterogeneous, spontaneous recanalization in the first 6 hours after ischemic stroke is uncommon, and it is difficult to predict prior to intervention which patients are likely to respond. Furthermore, neuroprotective agents have been more effective in models of ischemia-reperfusion than in permanent ischemia. Most of the previous clinical trials for neuroprotection, however, enrolled patients in generally long-time windows (>4 hours); included only a minority of patients who underwent reperfusion; and enrolled a significant proportion of heterogeneous subjects who may or may not have salvageable brain tissue (ie, treatment target was not directly verified).^{8,9} Results from animal models generally agree with these central tenets, but still there is a failure of translation. Is the problem, thus, with human trials or preclinical studies, or both? The answer to this question would seem that there are deficiencies in both domains. Preclinical studies need to be more rigorously performed and embrace mechanisms to reduce both testing and reporting bias. Clinically, several recent human trials, eg, ACTION (natalizumab in acute neuroprotection)¹⁰ and AVERT (early mobilization in stroke),¹¹ could have more carefully considered preclinical data. To challenge the assumption that animal studies need to model sex and comorbidities, the NA-1 (Tat-NR2B9c) ENACT trial (Evaluating Neuroprotection in Aneurysm Coiling Therapy) was conducted in patients with iatrogenic stroke after endovascular aneurysm repair without previous testing in animals with comorbidities.¹²

Publication and Reporting of Negative Data

Publication bias represents a key gap in translational research. Publication of incomplete data sets and negative or null findings at both the exploratory and confirmatory stage is critical to understand the entire research landscape. Yet for numerous reasons, negative findings are less likely to be published. Some avenues to disseminate negative data are becoming available through either traditional scientific journals or through the use of citable database descriptions. Thus, even if not published in article form, such data can be made publically available and could be used to generate more complete meta-analyses of prior research on potential therapies. A change in culture at universities and other institutions of higher learning to appreciate the value of rigorously performed experiments that provide negative results should be promoted.

New Approaches in Preclinical Stroke Research

A systematic review of the recent published literature on preclinical stroke studies indicated that the quality of experimental design, as reflected in the use of randomization, blinding, and power calculation, was generally inadequately rigorous.^{13,14} Because identical genetic backgrounds can develop different phenotypes based on environment, different drug candidates should be tested in multiple laboratories and with different methods to ensure the robustness and reproducibility of the effect prior to investing in expensive clinical trials. In this regard, efforts from the Operation Brain Trauma Therapy consortium and the European Multicenter Preclinical Animal Research Team group demonstrated the feasibility of a multi-laboratory approach embracing rigorous research principles.^{15,16}

A multisite and interdisciplinary network for preclinical confirmatory studies could minimize bias, ensure quality control and adequate sample size, promote standardization across animal models, optimize and accelerate the selection of the most promising treatment candidate for clinical trials. If such a collaborative network can be developed, it could potentially lower the overall cost of preclinical testing by leveraging existing infrastructure. Issues such as incentives for the investigators, ensuring the expertise, training, and retention of highly qualified personnel, protecting intellectual property, a rigorous selection process for candidate interventions, and increased upfront costs need to be carefully considered for this type of approach.

Replicating the phase I to III progression used in clinical trials, with progressively increased complexity and centralized oversight, could be a valuable approach in preclinical studies. Although intuitive, it remains uncertain if preclinical studies would be more predictive if conducted with the same standards as clinical trials. Another possible and parallel approach would be to design future clinical trials to more closely match the conditions of preclinical studies, by stratifying patient selection to include a more homogeneous stroke population in terms of subtype, mechanism, location, size, and severity of insult, matching end point selection, and excluding patients who are not likely to respond to treatment. For example, using neuroimaging to identify patients with salvageable penumbral tissue enabled successful completion of trials such as MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)¹⁷ and other endovascular trials. Selecting narrow patient populations would permit detection of small treatment effects but would also limit recruitment and generalizability of the results, potentially reducing feasibility of a trial. This approach is consistent with the precision medicine initiative and could have advantages in increasing efficiency and ultimately allow for targeting interventions to just those patients most likely to benefit.

Ensuring quality is a high priority for translational research. The value and feasibility of auditing/monitoring preclinical research, particularly in the confirmatory phase, to ensure data are gathered in a rigorous and standardized manner and could parallel the oversight that is used in clinical research. This topic and possible approaches for auditing (ie, journals, funding agencies, or reverse site visits between laboratories with similar expertise) were matters of debate and need to be further explored. Another approach, which can be done in

concert with any auditing, would be to encourage or require reporting of all variables and bias controls such as excluded animals, method of randomization, postop care, and so on.

Harmonization and standardization of preclinical translational end points and the development of common data elements for data collection and reporting may help to reduce outcome variability and improve comparative analyses of the most informative measures. This approach has been embraced by clinical investigators and other preclinical fields,^{18–24} and its value for stroke translational research should not be underestimated.

Conclusions

Preclinical research continues to play an essential role to increase the confidence to further invest in potential new therapeutic candidates. Understanding the mechanisms of action across multiple experimental conditions is critically important. Success in neuroprotection could be enhanced by improving outcome measures, enabling more patients to access endovascular reperfusion and administering therapy by first responders. A robust signal of preclinical efficacy, with the highest quality standards, is necessary before moving an agent to a phase II/III clinical trial.

Ultimately, progress in promoting recovery and implementing the potential new approaches and the cross-cutting priorities in preclinical and clinical research discussed at this workshop should facilitate future stroke therapeutic development.

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