Published in final edited form as:

Ann Neurol. 2017 December ; 82(6): 859–862. doi:10.1002/ana.25108.

Building on NeuroNEXT: “Next Generation” Clinics to Cure Chronic Neurological Disability

Rajiv R. Ratan, MD, PhD

Winifred Masterson Burke Professor of Neurology and Neuroscience, Associate Dean (affiliate), Weill Cornell Medicine, Executive Director, Burke Medical Research Institute, office (914-597-2851), fax (914-597-2225)

Chronic disability from neurological conditions is a looming, if not present, epidemic. The combination of an increasingly aged population, and our improved ability to keep patients alive after acute neurological injury, means that the ranks of the chronically disabled are swelling. Indeed, it is estimated that by 2050, the leading causes of motor and cognitive disability in the United States—stroke and Alzheimer's disease—, will cost the country \$1.4 trillion per year¹⁻³. If these daunting numbers do not provoke action to accelerate progress on their own, the human suffering wrought by these conditions should.

What are the barriers to progress for treating neurological disability? Whereas the list is exhaustive, I will focus on three pivotal areas in considering a prescription. The first is the issue of recruiting sufficient numbers of patients for multiple phase II studies at the same site; a problem termed *scalability*⁴. Second, inadequate patient recruitment has led to a backlog of promising therapeutic interventions that have not been tested in humans. As a consequence of this clinical “law of mass action”, *outstanding preclinical science is not being adapted for clinical evaluation*⁴. Third, the evaluation of therapies to reduce neurological impairment cannot be evaluated with biomarkers of function, as is typical with organs such as liver and kidney, but must be based on the ability to make clinically-meaningful improvements in function⁵. It is clear from nervous system development and repair studies that brain and spinal cord plasticity must be “educated” by experience to optimally restore function⁶. *Thus, how biology and technology come together to optimize training and reduce impairment* in the nervous system is a third and important potential hurdle⁶.

Many solutions have been proposed to these and other extant problems in the pursuit of cures for neurological disability; however, many are not practicable to implement, and few have been evaluated. Here I outline an innovative and feasible approach distilled from strategic planning discussions with faculty, staff and Board members of the Burke Medical Research Institute, the CTSA at Weill Cornell Medicine, outside academicians (especially Jonathan Wolpaw at Wadsworth and Brad Berk at The University of Rochester), biotech and pharmaceutical companies, insurance companies, and population health organizations. The

Address correspondence to RRR at rrr2001@med.cornell.edu.

Potential conflicts of interest: RRR is the Chair of the SAB for Neuronasal, Inc., a company which has licensed intellectual property from Cornell developed by the Ratan laboratory.

plan has been heavily influenced by the ingredients of success that have led to diminished mortality for many types of cancers⁷. A key feature of the oncology approach was that multicenter phase II studies did not involve a single therapeutic agent, but multiple agents tested in parallel using the same clinical trial paradigm. This enabled the opportunity not only to detect statistical significance of an intervention, but also its *relative robustness*. The more robust an intervention, the greater the chance for success in phase III where patient populations become more heterogeneous pathophysiologically, genetically and medically. Thus, the decisions of academics or companies to move therapeutics into expensive phase III trials are based not only on whether your “best” agent shows statistical significance in meeting primary endpoints, but also on how it performs relative to other “best” agents tested in the same phase II study.

Our model to reduce these barriers to progress for treating neurological disability is to establish *quaternary care neurorestoration clinics (QCCs)*. These will be purely research clinics that will focus only on patients with chronic disability who have exhausted everything that the health care system has to offer to reduce their impairment (e.g. motor impairment, vision impairment, cognitive impairment, or sensory/pain) in a host of monophasic, multiphasic and chronic neurological conditions. Our astonishing inability in the field to predict long-term outcomes at the acute and subacute stages of prevalent neurological diseases often makes it difficult for clinical investigators to make a strong case to patients to participate in trials. The NeuroNEXT facilitated study presented in this issue of *Annals* makes important steps forward to fill this natural history gap for Spinal Muscular Atrophy^{8,9}, but for most other diseases, patients in the early stages of disease are often disinclined to participate in trials because there can be significant risk, and we have little confidence in predicting who will do well and who will do poorly. By contrast, those in the chronic phase of their illness who have significant residual and stable, sometimes growing, impairment understand and conceptualize the challenges of living with disability and are more inclined, if not highly motivated, to participate in trials.

Second, as the QCCs will be for trials only, private practitioners, medical groups, health care networks and academic institutions can send their patients with full understanding that after the trial(s) are over, patients will continue to follow up with them for ongoing primary and secondary care. Thus, the QCCs complement, but don't compete with, existing health care interests, and develop a formula for a healthy, long-term partnership between clinicians, researchers and patients for conquering chronic disability.

Third, we will apply a “hub and spoke” organization to the clinics which follows the success of NeuroNEXT, but focuses on several complementary goals. Clinics will be geographically centralized within a population region, and will pay for patients to be transported from a 50-75 mile radius. For metropolitan areas like New York City, this would allow the clinics to draw on more than 200,000 patients chronically disabled from stroke and more than 160,000 chronically disabled from Alzheimer's disease¹⁻³. Marketing and education to inform patients, families and clinicians about trials that are available will be essential in realizing annual patient recruitment goals, and relatively efficient to do in this model.

We expect that the QCCs will enhance our ability to recruit sufficient numbers of patients to conduct multiple phase II trials simultaneously. This improved scalability will provide a mechanism for the best scientifically driven therapies from academia, foundations, or industry, once an established set of criteria are met, to be tested in humans. Whereas we can be enthusiastic about the results of preclinical studies and what they might teach us about human neurological recovery¹⁰, what happens in human trials is the ultimate therapeutic test of a target or a hypothesis. When Alfred Goldberg at Harvard Medical School proposed that inhibitors of the proteasome might be good chemotherapeutic agents for cancer, many experts were pessimistic that a drug whose target was central to the physiology of all cells of the body would ever be a viable therapeutic. Indeed, fourth generation proteasome inhibitors are now transforming clinical cancer care¹¹. This anecdote, which is not unique, shows that our ability to predict what will work and won't work in a human is limited, and thus, as long as an intervention has favorable profiles for safety and target engagement, therapeutic interventions with promising efficacy from preclinical models or humans, should be tested. Indeed, therapeutic tests of a target may be one of the most important strategies by which mechanisms of disease and repair are divined in humans. For therapy, it only matters if it matters in a human.

Many clinician researchers are understandably skeptical of results emerging from preclinical laboratories about novel targets and their related interventions, as the number of clinical trial failures in neurological disease accumulates. We are proposing a plan to break this cycle. By creating a clinical research strategy capable of assessing the relative robustness of an intervention in phase II, we will be better informed to make investments in phase III trials. This has great potential to create efficiency in therapy development, and to free up the resources to increase the number of “shots on goal”.

The last and critical feature of the QCC model is to bring technology together with biology to optimally reduce impairment. The nervous system is a unique organ, in that re-acquisition of function requires integrity, activity and/or plasticity of neural circuits, coupled with the right training^{12,13}. Technology has enabled the development and use of devices to train visual¹⁴, motor¹⁵ and cognitive function¹⁶, and new strategies are on the horizon. Such devices serve an important dual role: They not only provide impairment-specific training where dose and intensity can be modulated over a wide dynamic range, but they also provide quantitative measures of outcome¹⁵. Indeed, the repeated measurement of neurological function with robots has been shown to improve statistical power in studies, and thereby enhance scalability¹⁵. Studies in animals and humans suggest that the nervous system is receptive to training for a short window of time after injury, but that therapeutic modalities such as drugs can reopen this window after it has been closed¹⁷. Accordingly, combinatorial trials could couple robotic training with interventions designed to protect (Ab to β -amyloid) or repair a circuit (stem cells), re-open circuit plasticity (e.g. fluoxetine), enhance axonal conduction (e.g. ampyra), alter immune system trajectories¹⁸, or leverage advances in brain-computer interfacing¹⁹ in separate phase II trials. This would enable the ability to assess the relative contributions that different therapeutic targets make to reducing impairment after stroke or Alzheimer's disease, for example. Although it is unlikely that training, or circuit modulating agents alone, will provide an optimal therapy, there is growing evidence that

therapeutic benefit can be increased when they are combined. Testing this possibility is now feasible, since training devices to reduce motor impairment are available and FDA approved¹⁵.

QCCs represent a feasible plan to redefine the therapeutic pipeline to build *scalability* in trials for chronic neurological disability; to accelerate and increase the translation of *basic research findings to patients*; and to connect strategies designed to *prime the injured nervous system to receive training*. The model makes several assumptions. First, that currently available strategies for training the motor, cognitive, or visual systems are optimized. They may not be. Second, that by using combinatorial approaches with training as part of the combination, we will achieve reductions in impairment in the chronic phase of acute injuries (e.g. stroke) or chronic neurodegeneration (e.g. Alzheimer's disease). We will not know until the idea is fully tested²⁰. Thus, there may be failure on the way to success, but we anticipate that by testing many combinations in phase II, we will be able to identify some that are superior. And whereas there is always concern about whether a reduction in impairment will translate into reduced disability or handicap, we suspect that large changes in impairment will provide the enabling substrate. In other words, if a patient with a right upper extremity hemiparesis due to a stroke cannot cut her/his steak or brush her/his teeth, then restoring significant movement to the right arm and hand will provide the enabling resource to restore these abilities. Most significantly, we propose that QCCs will allow us to evaluate many targets in search of those that will provide the instructions for repairing the acutely and/or chronically damaged nervous system. We expect this logic, once uncovered in humans, can be applied to a panoply of neurological conditions characterized by chronic disability.

A key deficiency in the care of patients with neurological disorders is lack of knowledge of how best to optimize function and quality of life in the chronic phase of disability. Finding the best therapeutics for chronic disability requires a drastic restructuring of the scientific pathway that has been paved by our ability to keep patient's alive longer. There is a fundamental need to widen our perspective, from the construction of animal models of chronic disability to a clearer understanding of key contributors to chronic recovery. QCCs will provide, for the first time, a research-oriented framework for understanding and curing chronic disability. QCCs could ultimately, in collaboration with primary caregivers and population health organizations, track outcomes over a long period for a large population of people with chronic disability, and will provide the infrastructure for well-powered clinical trials done at the same site with different combinations of disease modifiers with training.

Finally and of most importance, QCCs will send a strong message to patients and their families: a message of hope and accompaniment. Although most scientists and clinicians appreciate the long-term potential for improvement after acute neurological injury, patients are often sent home mere days to weeks after their injury, with little infrastructure for chronic recovery. In patients with chronic neurodegenerative diseases such as Alzheimer's disease, this infrastructure is similarly limited. While some patients and families become ferocious seekers of novel therapies and avid readers of the most current medical discoveries, many patients and their families become lost and overwhelmed by a chronic medical and functional need that is often neither advocated by medical professionals nor

reimbursed by insurance. QCCs provide patients a “home” in which they not only gain access to the most innovative and promising therapies, but also are provided the support and guidance for continued devotion not only to wellness but also curing their disability. Our urgency to provide real hope through successful therapies could not be greater.

Acknowledgments

I would like to thank Kathleen Friel (Burke/Cornell), Allan Levey (Emory), Glen Prusky (Burke/Cornell), Lauren Sansing (Yale), Tomoko Kitago (Burke/Cornell), Jason Carmel (Burke/Cornell), Dianna Willis (Burke/Cornell), Botir Sagdullaev (Burke/Cornell), Dylan Edwards (Burke/Cornell) and Dale Corbett (Ottawa) for their thoughtful and insightful comments and suggestions on this manuscript. I am also grateful to Mr. Robert Baldoni, Chairman of the Board of the Burke Medical Research Institute for facilitating discussions that nucleated the ideas presented here. RRR is supported by the NIH, the Dr. Miriam and Sheldon G. Adelson Foundation, the Goldsmith Foundation, the Burke Foundation and The Laster Program in Peptide Therapeutics.

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