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National Institute of Neurological Disorders and Stroke Neuroscience Networking: Linking Discovery to Drugs

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Discoveries in the pre-clinical neurosciences have set the stage for bringing new therapies to patients affected by neurological disorders. The National Institute of Neurological Disorders and Stroke (NINDS) is dedicated to promoting the development of new therapies through its funding programs that range from basic neuroscience to translational research and finally clinical research to test the most promising new therapies in patients. In an effort to accelerate the translation of new discoveries to clinical practice, NINDS is piloting novel organizational strategies. In translational research, NINDS is taking the lead on the establishment of a 'virtual pharma' structure, through which researchers will partner with the NIH to accelerate the progress of drug development from early hit discovery through phase 1 clinical trials. In clinical research, the new Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) aims to promote the efficient implementation of scientifically sound, biomarker-informed phase 2 clinical trials that can be initiated by academic or industry investigators.
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Disorders affecting the nervous system create an enormous burden in lost life, disability, and suffering. In recent decades, neuroscientists—many funded by the NIH—have made huge strides in understanding their causes and developing new ideas for treatment. The molecular and cellular mechanisms underlying many nervous system diseases are emerging, along with potential therapeutic targets. High-throughput screening facilities, such as those created through NIH Molecular Libraries Roadmap initiatives, are allowing scientists to identify small-molecule compounds that could eventually become new drugs (Austin *et al*, 2004). The development of new disease models offers increasing opportunities to assess the promise of novel candidate therapeutics.

Despite the opportunities, there is often no clear path for translating these research discoveries into new treatments for patients (Collins, 2011). Industry is increasingly averse to supporting early stages of therapeutics development, particularly for nervous system disorders, where both cost and failure rates are high relative to other therapeutic areas. Although industry efforts in early development continue to shrink, NIH-funded researchers have been slow to move into the gap. Very few academic labs have the resources to conduct industry-scale optimization of therapeutic leads or the studies required by the FDA to test a new intervention in patients. And for the hundreds of nervous system disorders that have no treatment, developing the capacity to conduct meaningful clinical trials can be nearly as challenging as developing interventions to test. With the inherent difficulties of developing an effective treatment for any disorder, these factors conspire to produce an especially bleak picture for translation of neurotherapeutics.

To close the gap between discovery and drugs, the National Institute of Neurological Disorders and Stroke (NINDS) has launched two new programs designed to 'de-risk' promising therapeutic candidates to the point where they can attract industry investment for subsequent development and commercialization. Through the NIH Blueprint Neurotherapeutics Network and NeuroNEXT, NINDS offers the research community access to the infrastructure and the expertise necessary to develop and test new drugs. Importantly, these programs are designed to allow neuroscientists to pursue their most exciting ideas for new drugs without having to invest substantial time and resources in retooling and retraining. In addition, these preclinical and clinical networks enable NINDS to take advantage of economies of scale, making the most efficient use of limited research dollars.

A 'VIRTUAL PHARMA' FOR ACADEMICS AND SMALL BUSINESSES

In 2002, NINDS launched a comprehensive preclinical translational research program (http://www.ninds.nih.gov/research/translational/index.htm) to support investigator-initiated projects in therapy development (Finkelstein *et al*, 2002). This program has been successful in attracting and funding projects that have produced novel interventions for clinical trials in neurology (http://www.ninds.nih.gov/

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funding/areas/technology_development/translational_coop_agreement_program.htm). However, this experience has taught us that not all promising discoveries can move into the translational pipeline with the impetus of funding alone. Many of the resources necessary for efficient therapeutics development, particularly for small-molecule drugs, are not routinely available to academic researchers. For example, academic chemists rarely have the capacity to produce the hundreds of chemical analogs that may be needed to transform a promising starting compound into one that is sufficiently potent and drug-like to warrant clinical trials. Furthermore, the basic researchers who have identified potential therapeutic targets may not wish to shift the focus of their laboratories to translation.

As part of the consortium of 16 NIH Institutes and Centers that participate in the NIH Blueprint for Neuroscience Research, NINDS is taking the lead in developing a 'virtual pharma' network that will pair industry drug development expertise with the innovative disease biology that is the strength of NIH-funded research (http://neuroscienceblueprint.nih.gov/bpdrugs/index.htm). The Blueprint Neurotherapeutics Network (BPN) will provide the neuroscience community access to a complete and seamless pipeline for preclinical drug development, beginning with chemical optimization and concluding after phase I clinical trials. Participants in the BPN will receive funding to conduct bioactivity and efficacy testing in their own laboratories as well as access to millions of dollars in NIH-contracted drug development services, including medicinal chemistry, pharmacology, toxicology, and phase 1 clinical trials. NIH will also provide drug development consultants who have had years of experience working at a senior level in industry. Because the Blueprint is establishing a network of drug development service providers that typically cater to biopharmaceutical companies, neuroscientists who join the BPN can readily plug in to all of the drug development expertise that typically resides in industry. The projects supported through the network will be highly collaborative, and the researchers who initiate the projects will serve as the principal investigators (PIs), directing their projects through the development pipeline with the help of industry consultants. The PIs and their institutions will have the opportunity to attain assignment of intellectual property rights from all other network participants who may have intellectual input into their projects. This will allow the PIs to retain control of the intellectual property for drug candidates developed through the network and eventually pursue licensing and commercialization partnerships.

The NIH Blueprint will invest $50 million over 5 years in the BPN, using milestones to focus funds over time on the projects that are the most successful. The NIH Blueprint anticipates launching up to 20 projects, and seven projects have been initiated to date (http://www.nih.gov/news/health/aug2011/ninds-18.htm). The BPN mission spans the gamut of disorders of the nervous system, and initial disease targets include Alzheimer disease, stroke, major depression, deafness, and vision loss. The BPN is open to investigators at non-profit research institutions or small companies studying any disease or disorder of the nervous system and the final application deadline for new projects is December 15, 2011.

A PHASE 2 CLINICAL TRIALS NETWORK FOR NEUROLOGY

In addition to the continuing opportunities for investigator-initiated trials, NINDS is now making efforts to strengthen early phase clinical trials with a new initiative, NeuroNEXT (http://www.ninds.nih.gov/news_and_events/proceedings/20101217-NEXT.htm). Historically, the NINDS clinical research program has largely operated by building up the infrastructure for an individual trial, optimizing that infrastructure over the course of the trial, closing down the infrastructure at the end of the trial, and then starting the process anew for the next trial. Recent NINDS experiences in developing relatively focused clinical research networks (Neuroprotection Exploratory Trials in PD and the Neurological Emergency Treatment Trials network (http://www.nett.umich.edu/nett/welcome) have illuminated ways in which a network infrastructure can increase the efficiency of implementing clinical trials. Our new clinical trials network, NeuroNEXT, will further broaden this approach through a flexible, shared infrastructure for biomarker-informed phase 2 clinical trials. NeuroNEXT will establish a consortium of clinical sites capable of forming disease-specific cadres of investigators in order to develop and implement trials rapidly in a wide range of neurological disorders that affect adults and/or children. With a stable and experienced research staff, a central IRB model, and master trial agreements, NeuroNEXT will streamline the administrative processes for clinical trials and reduce start-up times. NeuroNEXT will also be able to design and implement evidence-based measures to improve patient recruitment into clinical trials.

An important goal of NeuroNEXT is to attract more novel therapeutics for testing. The NINDS clinical research program has generally been limited to academic studies of existing therapies for new indications, nutraceuticals, or comparisons of the efficacy of two existing interventions. To attract industry partners with more novel therapeutic candidates, the network offers private-public partnerships under a Cooperative Research and Development Agreement (CRADA) mechanism. For companies that would not otherwise conduct trials for neurological indications themselves, the CRADA allows them to partner with NIH without risk to their intellectual property (http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx#MTACTA).

CONCLUSION

History has shown that a single therapy development success, even in a rare disease, can change risk-benefit perceptions and catalyze greater investment in a disease area. In addition to developing new drugs that save and improve lives, successes from these new networks have the potential to revitalize industry interest in neurotherapeutics. For now, we challenge the neuroscience research community to submit their most exciting ideas for drug development

and clinical trials projects and join together in these new experiments in accelerating neurotherapeutics development.

DISCLOSURE

The authors are employees of the US Federal Government and declare no conflict of interest.

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