Translational Research and Development
NINDS

Analysis and Recommendations

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Translational Research and Development Report

Organization of this report: We have seven broad divisions in this report: a) The executive summary, b) A listing of all proposals, c) An introduction to translational research and development, d) Critical topics that are general, e) Criteria for new translational focus diseases, and f) Program/project analysis with recommendations.

Table of Contents

Chapter	Topics	Authors	Page
1	Executive Summary	John McCall, Howard Federoff	3
2	Recommendation List by Topic	Committee	7
3	Preamble	Bob Brown, John McCall, Howard Federoff	15
4	Critical Issues: Target Validation, Animal Models, Biomarkers, Blood Brain Barrier	Dinah Sah and Bill Matthews	18
5	Criteria for New Translational Programs	John McCall, Robi Blumenstein, Howard Federoff, Cristina Csimma, Franz Hefti	20
6	Biomarkers	Cristina Csimma and Franz Hefti	23
7	Outreach	Franz Hefti, Doug Morton, John McCall	26
8	Small Business Program	Doug Morton	29
9	Countermeasures Against Chemical Threats	John McCall	41
10	SMA Project	John McCall, Chris Austin	43
11	Neural Prosthesis Program	Warren Grill	48
12	Translational Research in Muscular Dystrophy	Bob Brown, Cristina Csimma, John McCall	51
13	Medicinal Chemistry Initiative	John McCall	53
14	Cooperative Agreement Translational Research Program	Anne Young, John McCall	54
15	Anticonvulsant Screening Program	Bill Matthew	61
16	CINAPS Drug Evaluation / Parkinson's Disease	Franz Hefti, Dinah Sah	64
17	Stroke Preclinical Trials Consortia	Franz Hefti	67

Executive Summary

Modern neuroscience must translate the remarkable findings of basic science into useful therapies for those who suffer the devastating effects of neurological disorders. The range of activities so encompassed is broad and includes any activity designed to identify or optimize an interventional strategy, including the process of evaluating those strategies in relevant biochemical, cellular or animal models as well as the development of tools necessary to conduct these activities. Within the overall process of drug discovery and development, a translational research program begins when there is a sufficient understanding of disease mechanism(s) and ends with the receipt of an Investigational New Drug (IND) or Investigational New Device Exemption (IDE), at which point the proposed intervention becomes the subject of evaluation in human subjects, or clinical research. This report is restricted to translational research that is carried out before receiving an IND or IDE. This encompasses the various milestone-gated steps in the drug and device discovery process. This broad definition includes small molecules and biologics, gene and cell therapy, biomarker/diagnostics, devices, surgery, and behavioral interventions. Translational research, in the more general sense, extends from target identification and validation to clinical proof of concept and dose setting. We have identified and now emphasize obvious overlaps between the strategic planning advisory panels on translational research, diseases, and clinical research.

Winds of Change. Significant and productive investments in basic research are now ready for harvest. The neurological disorders are ripe for a significant effort in translational research and development that will more effectively harness basic discoveries and spawn new therapies and medical devices. The pharmaceutical industry is also experiencing major changes. The drug development paradigm has been tuned to reduce its risk profile and cost before large investments are made in the clinical phase. This is a logical response to the explosion of new targets, the burden of the current process, and the movement of academic researchers and small companies into translational research. The industry is finally recognizing the importance of and investing in less prevalent diseases, and it is recognizing the need to develop meaningful collaborations in preclinical discovery and development. All these changes work in concert to stimulate changes for neurologic translational research. We see exciting new opportunities, new processes, and new partnerships. NINDS must change and take advantage of this emerging paradigm so that the agency can fully achieve its goals.

Our Committee and Its Output. The NINDS Advisory Panel for Translational Research includes members with deep experience in academic and pharmaceutical research, in venture capital, and in foundation-based research. The views of this heterogeneous group have been blended effectively. We initially selected a cluster of related and significant chapter topics that were addressed by subgroups of the larger committee. These chapters and the recommendations that they contain were both edited and discussed by the total committee. These discussions often expanded these recommendations and explored new and improved approaches to recognized challenges. We have a plethora of recommendations that follow this summary. We've considered each of these with reference to impact, cost, feasibility, and time to delivery. This is a complex analysis with broad scope.

A New Mindset. Translational research is product-driven rather than hypothesis-driven, and so benefits from milestones and more active and proactive NINDS management. Bringing the NINDS translational research program to its full potential will require a different mindset from the Institute's traditional approach to basic and clinical research. The translational research landscape is unique and complex, including players from academia, biotechnology companies, pharmaceutical companies, disease-focused foundations, and the financial sector. The NINDS

should be constantly considering how to leverage its own strengths and the strengths of these other major players toward its goal of reducing the burden of neurological disease through modest, yet strategic investments. For example, by supporting early-stage studies of promising therapeutics and developing key resources, such as animal models and biomarkers, the NINDS may attract private sector investment by de-risking approaches to relatively rare diseases. The NINDS should also consider new models for program management.

Challenges and Recommendations. A number of core needs have been identified. These include technical challenges such as transport across the blood brain barrier, biomarkers, and predictive animal models. Outreach and education are also fundamental needs. We also recognize the importance of engaging translational research and development leaders from multiple disciplines in accomplishing the NINDS mission. Our recommendations are made in the context of these and other challenges. These recommendations are more fully listed in the following section of this report and are fully explored in the report chapters. We offer here a summary of the cross-cutting and other major recommendations.

- **Establish an NINDS Associate Director/Office for Translational Research with broad responsibility for program leadership, coordination, and outreach.** Implicitly, this establishes a formal translational function/department within NINDS. We see this position and supporting staff as a key hires for the NINDS and important to the execution of many of our recommendations and to their integration with recommendations from the other strategic planning advisory panels. The Associate Director should be responsible for oversight, evaluation, and coordination of NINDS translational programs; developing outreach and education activities aimed at academic researchers; and stimulating partnerships with the private sector, academia, clinical research groups, the patient community, and the FDA. The Associate Director is a key hire. The Associate Director will need broad experience, have an established network outside of the agency, and demonstrate excellent team building skills. This person will also need sufficient resources to accomplish objectives.

- **Seek guidance from external advisors on general and program-specific strategic and technical issues.** The NINDS should establish a panel of advisors to the new Associate Director for Translational Research from senior positions in academia, biotechnology and pharmaceutical companies, and the venture capital community for input on broad strategic issues and as an open channel for communication with these communities. The NINDS should consider steering committees with representatives from these same communities and with program-relevant expertise for the Translational Research Cooperative Agreement Program and the Anticonvulsant Screening Program.

- **Proactively stimulate the development of new, more predictive animal models of Parkinson's disease, stroke, and epilepsy. De-emphasize support of research with models that are not predictive of clinical outcome.** The NINDS should identify and communicate to the research community the characteristics that these models should have. The NINDS should consider presenting the goals in terms of "grand challenges" and/or using a prize competition model to galvanize the research community.

- **Define a focused goal for addressing monumental problems around which to galvanize the research community.** The NINDS should develop a "grand challenge"

and/or prize competition for such problems. For example, for manipulation of the blood brain barrier, first propose prototype compounds and criteria for their successful delivery and then invite researchers to develop their most creative strategies. A second example involves the development of animal models of stroke, epilepsy, and Parkinson's that are more predictive of unmet clinical needs.

- **Manage the NINDS translation portfolio proactively.** Direct resources, as much as possible, to prospectively identified and strategically relevant and impactful areas.

- **Pursue outreach activities to facilitate translational research of interest to NINDS and advance therapies to commercialization.** The NINDS should develop a drug discovery short course for investigators. The agency should increase working liaisons with key partner groups, such as foundations, industry, academia, the FDA, and financial institutions. Each group impacts the mission. The committee emphasized the need to understand and impact the FDA with respect to clinical trials of compounds for neurologic disorders.

- **Integrate the discovery, development, and clinical aspects of biomarker development.** The NINDS should prioritize the development of biomarkers that can be used to select drugs for clinical testing or assess target manipulation over biomarkers that can serve as diagnostics. The NINDS should explore ways to combine biomarkers into panels that are more predictive than individual ones. The NINDS should participate in discussions with the FDA on expectations for biomarkers relevant to neurological diseases.

- **Implement a systematic and transparent process, with standard criteria, to identify the most appropriate diseases and strategies for targeted translational research efforts.** Criteria should include the potential to reduce disease burden, appropriateness of biological target, feasibility of modulating that target, availability of research tools and resources, and trajectory to clinical trials and commercial development. The NINDS should engage the research and patient communities in assessing disease readiness and implementing translational strategies.

- **Utilize the SBIR program more effectively and target focused areas.** This Congressionally mandated program could be applied in creative ways to address many of the needs identified by the Advisory Panel. The NINDS should direct some funding toward critical areas such as the development of new animal models, investigate ways to accelerate the transition from phase II funding to commercialization, and involve scientists with a strong business background in the SBIR restructuring and review processes.

- **Fund a medicinal chemistry resource to optimize promising compound into new drugs.** Include sufficient chemistry staff to meet objectives that have not yet been defined clearly. The NINDS should manage this resource with one or more experienced medicinal chemists who, under contract to NINDS, advise and facilitate the contract site. The NINDS should focus resources on projects that have a chemical lead, reliable primary and secondary assays, and compounds that show preliminary evidence of being amenable to chemical optimization.

- **Make risk minimization tools available to investigators.** This includes competitive intelligence, computational predictors of ADME/safety/solubility/rule of 5, and basic informatics. The NINDS should consider providing *in vitro* ADME services as a resource that is shared with other parts of the agency.

This is an overview of our thinking. The remaining document explores these and other recommendations. We believe that we should now discuss our conclusions and documentation with NINDS leadership, integrate NINDS thinking with our own, and then work directly with the Disease and Clinical Strategic Planning Advisory Committees toward a restructuring effort that is both integrated and comprehensive. As a committee, we feel that our recommendations are sound, that they address the new environment, and that they should be implemented.

Chapter 2. Complete Recommendation List

Our recommendations aim at the sweet spot that is defined by the overlap figure (below). This figure recognizes that a recommendation will be best implemented if the science is sound, if resources and organization are appropriate, and if a successful outcome has an economic and/or social impact. We prioritized our recommendations according to whether we felt that they were tractable, whether they are affordable, and whether they would have significant impact. We also gave an overall "enthusiasm" score. The table below is organized alphabetically by the general areas of Process, Funding Mechanism, Cross-disease technologies, and Diseases. Lower rated recommendations are excluded from the table but are discussed in the text.

Topic	Proposal	Tractable	Affordable	Impact	Enthusiasm
Processes: Organization, Outreach, External Links, Information, Medicinal Chemistry, Resourcing, Regulatory					
Organization	We enthusiastically endorse the creation of a new position, with supporting staff, that coordinates translational research and development within NINDS, sets strategy, and interfaces with academia, industry, foundations, financial institutions, and the FDA. Create an extramural advisory team that helps this position achieve the desired results.	H	M	H	H
Organization	Involve advisory groups from academia, industry, foundations, and the finance community more broadly. Make broad use of steering committees that are populated with representatives of pharma, biotech, academia, and NINDS. Define roles and responsibilities. Rotate positions. Involve ad hoc members aggressively. Use groups to set strategy, make choices, and evaluate performance. Develop recognition and reward system for members.	H	H	H	H
Outreach	Sponsor a short course in drug discovery that is taught by industry and academic experts (covering medicinal chemistry, ADMET, pharmaceutics, intellectual property, regulatory affairs, etc.) Include a case study format along with exposure to the language and logic of modern drug discovery and development. We expect enhanced awareness that will facilitate translational work, more patents and startups, and more strategic grants (see chapter).	H	H	H	H

Outreach	Engage a global community of problem solvers. Define a focused goal for addressing monumental problems and either invite grant applications or reward successful solutions (Innocentive model). For example, for manipulation of the blood brain barrier, first propose prototype compounds and criteria for their successful delivery and then invite researchers to develop their most creative strategies. A second example involves the development of animal models of stroke, epilepsy, and Parkinson's disease that are more predictive of unmet clinical needs.	H	M	H	H
Outreach	Create a primer that is mounted on a public server. Primer describes milestone gated research and risk minimization strategies and provides information on suppliers of resources.	M	H	L	M
External Links	Coordinate external spending in neurological diseases with pharmaceutical companies, biotechnology organizations, and other funding groups. Make strategy and focus clear and available to academia, industry, and foundations. Where possible, leverage internal spending with external funding. For example, access risk minimization tools from industry in exchange for participation on steering committees.	L	M	M	M
Inform	Identify and publish unmet needs in the NINDS fields of interest in order to stimulate grants that are targeted toward the most acute needs	M	H	H	H
Inform	Provide timely information on the drug and medical device competitive environments. This will help ensure that proposals will bring something new to the table. This may involve expert searching of the chemical, biological, and patent literature (see medicinal chemistry proposals)	M	M	M	M
Inform	Provide general access to information that is created with NINDS funded studies. Make both positive and negative results available. Some information may be confidential but, in general, the community should have access to research results that are funded by NINDS	H	H	M	M
Medicinal Chemistry	Fund a translational medicinal chemistry resource that is allocated by a multi-disciplinary steering committee to high priority projects where impact is most likely. Employ a full or part-time independent medicinal chemist to oversee the contract resource and who can do literature searches for academic investigators. Attempt to involve industry in a bridging resource once a project is showing promise.	M	L	H	H
Medicinal Chemistry	Utilize medicinal chemistry services for hit-to-lead studies on projects that have good primary and secondary assays and which have already pursued a Structure-Activity Relationship (SAR) by purchase strategy. Involve the independent medicinal chemistry coordinator in the SAR-by-purchase strategy, if necessary.	M	L	H	H
Regulatory	Establish active and recognized communication channels with the FDA neurological disease division	M	H	M	M

Resourcing	Identify which tools NINDS can afford to provide. Example: computational tools that identify metabolic hot spots or safety issues, basic informatics tools, perhaps simple ADME in vitro assays at a reasonable cost. Consider working across the NIH landscape to provide basic tools. Access to tools will probably be limited because of cost. Access should be gated by a multi-disciplinary steering committee.	M	L	H	H
<u>Funding Mechanisms</u>: Cooperative Agreements, Grants, SBIRs					
Cooperative Agreements	Improve access to risk minimization tools. Examples include medicinal chemistry, microsomal oxidation, Cytochrome P450 inhibition, physical chemistry measures, among others.	L	L	H	H
Cooperative Agreements	Review milestones annually for relevance. Does the project still complement on-going activity in industry, as the program intends? Is the project still relevant? Could it be modified to give more impact? Enlist industry-trained discovery experts for the milestone review process. Investigators will need to accept project termination as an acceptable outcome.	H	H	H	H
Cooperative Agreements	Educate PIs. This is described under Outreach. Expect that investigator insights into drug discovery and development will be reflected in their grants	M	M	M	H
Grants	Grants should reflect an understanding of the scientific/competitive program landscape and unmet medical need in order to assess novelty and impact. Projects should reflect strategic integration, with clear milestones and a risk minimization strategy.	M	H	H	H
Grants	All translational research proposals should take into account the path to clinical proof-of-concept. Why is the project important? Where does it fit in the road to clinical trial? How long will it take to reach goals under realistic conditions?	M	H	H	H
SBIR	Manage programs differently. Create SBIR Development Centers. Optimal management requires experience in technology commercialization and translational research. Currently SBIR/STTR grants are dispersed. Focus and manage with NINDS experts and external experts. Model after IC SBIR Development Centers. Centers should assemble expertise, assess commercial potential of priorities, evaluate proposals, solicit topics, expand outreach, and manage grants. Accelerate promising opportunities and stop apparent failures	M	M	H	H
SBIR	Focus on commercially viable technologies. Establish specific technology priorities with high commercial potential. Set aside funds to support these priority areas. Emphasize cooperative funding mechanisms that have more oversight and that are milestone driven. Currently,	H	H	H	H

	only 5% of SBIRs are cooperative agreements.				
SBIR	Initiate an SBIR Bridge Fund Demonstration Project based on a similar (and successful) program from NSF. This program would offer NIH funds to SBIR Phase II companies able to raise matching funds (1:1) from the private sector. Such a program would increase successful commercialization by leveraging external organizations' dollars. Require matching funds from the investment community, pursue lifting SBA restrictions on venture capital (VC) ownership and SBIR eligibility. Establish a shorter time frame for review of the proposals and payment. Behave more like a VC	L	L	H	M
SBIR	Co-invest with the private sector to bridge SBIR products toward commercialization. Address funding gap between end of a SBIR Phase II award and the point where the technology attracts private investment. This gap is worst for new drugs. Using "Phase II Competing Renewal" awards addresses this problem, but these are not milestone driven and don't engage the investment community.	L	L	M	M
SBIR	Set aside a total of approximately $150 million over 3-5 years to support a total of 50 awards ($3 million per award) as a demonstration project. Key components of this demonstration include: a) Require matching funds from the investment community, b) Pursue lifting SBA Restrictions on VC Ownership and SBIR Eligibility, c) Establish a shorter time frame for review and payment of the proposals, equivalent of the VC community.	L	L	M	M
SBIR	Assemble an External NIH SBIR Advisory Committee (NINDS, entrepreneurs, management consultants, venture capital investors, etc) that will advise NINDS staff on future directions and strategic approaches of the SBIR program. NINDS would retain full control over how their resources are allocated. The Advisory Committee will analyze markets and advise NINDS on commercial potential and potential investors	H	H	M	H
***Disease-Crossing Technology*: Blood Brain Barrier (BBB), Biomarkers, Targets.**					
BBB	Focus on methods for delivery drugs across the blood-brain barrier. This area has the potential for high impact on the development of many CNS drugs, e.g. receptor-mediated transcytosis, BBB disruption, investigation of cellular/molecular pathways that maintain the BBB. Focus on approaches that have the greatest clinical potential. Coordinate work with NIMH and oncology.	L	M	M	H

Biomarkers	NINDS should proactively manage the biomarker program as a portfolio with appropriate balance that reflects greatest unmet medical need coupled with unmet need of other resources (e.g. industry). NINDS should consider whether a biomarker is exploratory or registration-supportive. The NINDS funding structure is be more suitable for studies in the exploratory rather than the registration phase of clinical studies. NINDS strategy should involve a) proactive communication of expectations rather than reactive evaluation of applications, b) focus of funding in wasteland areas (e.g. stroke) that are not being heavily worked by the Biomarkers Consortium of FNIH and industry, c) and Focus on high impact studies. Focus funding on practical and realistic goals from with respect to technology, cost, and deliverables. Utility and validity of biomarkers in current and future clinical practice need to be considered and addressed upfront. Biomarkers will be most helpful when they can be used for drug candidate selection at early stages of a development program.	M	M	H	H
Biomarkers	NINDS should actively guide the steering committee of the Biomarker Consortium activities of the FNIH. Such guidance should include the identification of the most significant needs in neurological diseases handled by NINDS, as well as input into the overall structure and way of operation of FNIH.	H	H	H	H
Biomarkers	NINDS should identify synergies across biomarker projects. Functional outcomes relevant to multiple diseases will be particularly useful. E.g., cognition is a component and useful efficacy endpoint for several neurological diseases.	M	H	M	H
Biomarkers	Address biomarker funding gap for neurological diseases where drug development is extremely high risk, high cost and severely limited by the lack of more precise tools upstream of long term clinical benefit (stroke, PD, etc). There is a clear funding gap here and no obvious industry effort to address it.	L	M	M	M
Targets	Encourage human population genetics, which may accelerate the identification of targets important not only to familial disease, but also sporadic disease.	M	L	H	M
Targets	Investigate pathological cellular mechanisms and the role of candidate molecular targets, in the absence of human genetic or clinical validation	H	M	M	M
Diseases: Epilepsy, Muscular Dystrophy, Neural Prosthesis, Parkinson's, SMA, Stroke, Chemical Threats					

Epilepsy	The Anticonvulsant Screening Program (ASP) should focus on epilepsy (rather than diluting efforts by employing ancillary models, e.g. pain models), diminish the focus on generating more prototype anticonvulsants and instead favor the discovery of candidate anti-epileptic drugs that fight drug-resistance and/or the disease itself.	M	M	H	H
Epilepsy	A small and highly knowledgeable Epilepsy Advisory Board needs to be established to direct the future goals of the ASP. This Board needs to include representation from pharmaceutical companies seriously committed to epilepsy drug discovery and development. This Board needs to set priorities for the ASP seeking to maintain the screening service and, importantly, to implement processes that address the future needs for therapeutics in epilepsy	H	H	H	H
Epilepsy	Alignment of the ASP with internal and external NINDS funding mechanisms will be important in developing new animal seizure models for epileptogenesis. One important goal is to develop a reliable genetic model that produces the symptoms of epilepsy on a reliable time path. Other models of epileptogenesis will be critical, e.g., two hit models.	M	M	H	H
Muscular Dystrophy	Encourage industrial participation in the review process.	H	H	H	H
Muscular Dystrophy	Rigorously adhere to definition of translational research. Program results should be actionable: either terminate further research or provide guidance on how to continue in meaningful way. Study design and conduct should foster an understanding of positive or negative results.	H	H	H	H
Muscular Dystrophy	Make both positive and negative results available to the scientific community. If the study results are not published, they should be available. This implies some form of web based project summary that is searchable and accessible to the community. Note that this suggestion applies to other chapters.	M	H	H	H
Muscular Dystrophy	Specifically call for and prioritize grants that address known gaps in the field.	M	H	M	H
Muscular Dystrophy	Don't disregard epidemiology and methodology development studies that have somewhat succumbed to novel targets research.	L	H	M	M
Muscular Dystrophy	Prioritize proposals that address multiple diseases (even outside of muscular dystrophy)	M	H	L	M
Muscular Dystrophy	Include all mechanisms for translational program under the program (i.e., include U24 and U54 mechanisms)	H	H	L	M
Neural Prosthesis	Remove the restriction on Cooperative Development Agreements (CDAs) "to activities that directly focus on preclinical therapeutics and device development that is required before clinical testing". The exclusion of research that requires an IDE from that which is defined as "translational" should be removed to enable translational research in neural prostheses, which often requires an IDE for early human feasibility testing.	H	H	H	H

Neural Prosthesis	Expand the Cooperative Development Agreements program (U01, U54) to include expressly translational studies of neural prostheses. Such efforts require resources to seek, receive and support regulatory approval (e.g., IRB, IDE), to conduct device fabrication under highly controlled conditions (e.g., Quality Systems, Good Manufacturing Practices), to conduct preclinical evaluations of safety and efficacy, and early clinical feasibility testing in humans. Clinical trials not included.	M	M	H	H
Neural Prosthesis	Increase the representation of clinicians on the Neurotechnology (NT) study section to move from technology development and early evaluation toward application of devices and treatment. Increase the clinical relevance of the research portfolio and provide more appropriate review of translational research involving human subjects.	H	H	H	H
Neural Prosthesis	Explore the feasibility of supporting, perhaps in partnership with industry, a national resource for fabrication of hardware (electrodes, implantable pulse generators) for use in neural prostheses. Potential models for such a resource include the National Nanotechnology Resource at Cornell supported by the NSF, the Center for Neural Communication Technology at the University of Michigan supported by an NIBIB P41, and the NCI's Rapid Access to Intervention Development program.	L	M	M	H
Neural Prosthesis	Remove administrative barriers to early human feasibility testing, and allow peer review to determine the appropriateness of human studies supported by the R21 and K01 mechanisms. The objective of these changes is to "accelerate the development of new therapies by allowing more rapid testing in actual use"	M	H	H	M
Neural Prosthesis	Institute efforts in clinician training and education that include neural prostheses. Many physicians are not exposed to the potential benefits of neural prosthetics, and even when considering the most successful device – epidural spinal cord stimulation for chronic pain – the penetration is exceedingly small.	L	L	H	M
Parkinson's	NINDS should continue support of the evaluation of peripheral and imaging markers of Parkinson's disease (PD), with the goal to identify and standardize the most useful ones. Optimally, these biomarkers will also be measurable in the animal models and will provide a direct bridge between animal model and human studies.	M	L	H	H
Parkinson's	NINDS should support the development of predictive rodent models of PD. These evaluations of drug candidates in relevant in vivo models are critical for de-risking subsequent clinical development.	M	L	H	H
Parkinson's	NINDS should further strengthen the interactions with PD advocacy groups, private foundations and biopharma industry engaged in PD-related activities.	H	H	M	H
Parkinson's	NINDS should continue to strongly support research on disease mechanisms of PD, with the goal to identify optimal therapeutic intervention points. Further investigations, which satisfy a broad definition of	H	L	H	M

	translational research, on human population genetics, genetic and environmental risk factors, and pathological pathways linking the known disease genes, seem particularly important although this facet rests with the clinical committee.				
Parkinson's	NINDS should not increase funding for translational research, narrowly defined as generation of small molecule drug candidates based on existing targets, in PD before validated drug targets and animal models have emerged.	M	H	M	M
SMA	Simplify the contract system. NINDS could elect to provide key services to selected investigators. These services could be internal to NINDS or available through a contract. Identify a primary contractor who subs out services without going through the normal bid process.	M	H	H	H
SMA	Learn from the project: Develop reliable secondary assays before launch of major expense.	L	M	H	H
SMA	While key personnel are still with the project, it should be evaluated for process. What worked well? What can be extrapolated to the next project? How can these lesson learned be captured? We suggest a kind of bible that addresses the creation of a NINDS virtual company.	H	H	H	M
SMA	Examine requirement for negotiated pricing before contract award and task award. This is a major hurdle and is problematic for many potential vendors, having the opposite effect of its intent—scaring away competition as opposed to stimulating competition.	M	H	M	M
Stroke	Focus on a predictive animal model for human efficacy, together with a suitable and validated surrogate marker for proof-of-concept clinical study. It will be most beneficial to the stroke field if the funded applications aim at identifying and validating animal models rather than providing scaled-up access to non-validated models. Repeating the paradigm of failure following non-predictive models will counterproductive as it further establishes stroke as a 'graveyard for drug development'.	H	M	H	H
Chemical Threats	Grant reviews for CounterACT should rigorously reflect the stated profiles (ease of administration, preferably after insult, and effective within the likely window of opportunity).	H	H	M	H
Chemical Threats	Provide drug discovery strategies as outlined under outreach	M	M	M	H
Chemical Threats	Continue the annual meetings coupled with milestone review. Continue and emphasize collaborations across labs.	H	H	M	M

Chapter 3. Preamble / Introduction

Definition of Translational Research and Development. The goal of translational research and development is effective disease intervention that is normally predicated upon an understanding of disease mechanism(s). This report is restricted to translational research and development that is carried out before receiving an IND or IDE. This encompasses the various milestone-gated steps in the drug and device discovery and development process. This is a broad definition that includes small molecules and biologics, gene and cell therapy, biomarker/diagnostics, devices, surgery, and behavioral interventions. For this module, we also include any research designed to identify or test an interventional strategy in relevant biochemical, cellular or animal models. Translational research and development, in the more general sense, relies on target identification and validation and extends to clinical proof of concept and dose setting as well as registration-oriented studies. These latter topics are being addressed by other committees.

Characteristics of Translational Research Programs / Projects

- Target has already been linked to disease through genetic or epigenetic studies
- Target is druggable or a tractable target for drug/device/diagnostic development
- Milestones are defined and time to achieving milestones is realistic and acceptable. Investigators must be aware of drug discovery and development strategies
- Milestones reflect a series of tests, with clear go/no go decision making points

Strategic Mission of the NINDS Translational Research and Development Effort. NINDS will apply concepts, insights, and discoveries that have been generated through basic scientific inquiry to the diagnosis, treatment and/or prevention of human neurological diseases. NINDS will facilitate and accelerate toward clinical proof of concept and registration medically important drugs, devices and other therapeutic modalities and methodologies that address such disorders. NINDS will encourage and support projects that have the maximum impact on strategically important targets. In this context, NINDS will engage in a proactive dialogue with academia, industry and other stakeholders. This dialogue should facilitate a greater and more uniform understanding and setting of the standards, requirements and cost of registration driven drug development and a more standardized and temporally workable set of goals

Winds of Change. Industry has revised the drug development model to reduce its risk profile and cost. This is a logical response to the explosion of new targets, the burden of the current process, and the movement of academic researchers and small companies into translational research. Naturally, NIH and academia are rethinking their part of this model. This report contributes to this revision.

General Principles Relating to Translational Research and Development

- Translational research and development is an iterative process that involves the integration of technologies and multi-disciplinary approaches.
- The translational research process is necessarily milestone gated. Translational research's requirement for forward motion toward clinical trials is intrinsic to the activity.

- Projects and programs with the most impact on strategically important targets must be prioritized over lower impact projects and programs. Similarly, programs that are either more proximate to the clinic or which have a higher probability of reduction to clinical investigation should be prioritized over earlier stage projects.

- Projects and programs with impact in underserved areas of unmet medical need should be prioritized over those where significant other effort/funding is already available within NIH and/or in the biotechnology and pharmaceutical industry setting.

- Projects and programs of great potential that are in the funding gap stage between academic and industrial research, that require necessary preclinical risk mitigation, should be prioritized.

- A research project with a single milestone is translational if it is a significant contributor to a pre-clinical to clinical trajectory. Simply stated, translational projects should ultimately have the potential to help patients?

- U-type projects are inherently translational.

- NINDS translational programs are different from industrial translational programs in that they are not profit driven and not necessarily dependent on intellectual property. Because of this, NINDS can address smaller and riskier problems in the research phase. NINDS can succeed by advancing projects through risk to a stage where the project is commercially viable. Challenging diseases which are of low incidence and prevalence are thus aligned with the NINDS mission.

- Success for NINDS is defined as impact on the field and ultimately on human neurological diseases. This is different from the private sector.

- NINDS staff and review groups need to become better informed on what is and what isn't commercially viable. This involves a matrix of science/medicine expertise and understanding of what it takes to hit both the academic and commercial sectors. Translational R&D requires good science, good information, and a broad based group of champion leaders.

General Conclusions from Principles and Logical Responses to Those Conclusions

Conclusion	Response
The scientific/competitive program landscape and unmet medical need for the disease must be understood in order to assess impact.	Investigators should include accurate and comprehensive assessment of the relevant global environment in grant proposals. NINDS could support with independent analysis.
All translational research proposals should take into account the path to clinical proof of concept. Why is the project important? Where does it fit in the road to clinical trial? How long will it take to reach goals under realistic conditions?	Investigators must understand and be accountable to the drug development process. NINDS can better educate investigators about the drug discovery and development process through short courses, information, case studies and/or training grants.

Projects that are strategically integrated will generally have higher impact. Such projects are structured logically and efficiently around clear milestones and include risk minimization steps in the project plan	Emphasize U-type grant model in budget process.
Translational research is generally not uniformly viewed as high value in academia	Since we need to harness academic intellectual ability and resources, we need to better align academic motivators with NINDS translational objectives. Since the latter won't change, we need to address the former in some way. The decline in funding creates an opportunity now for a more attentive audience. NIH can actually help shift the paradigm rather than accept it.
We need to engage experts from a variety of backgrounds in steering NINDS programs	Create steering teams that include members from academia, pharma, and NINDS. Use broadly.

NINDS Translational Research Programs. ASP, SMA Project, Neural Prosthesis Program, Cooperative Programs (U01, U54, U24, R21, SBIR/U44, K01), CounterACT, Neurodegenerative Drug Screening Consortium, Testing of Candidate Drugs for Neurodegeneration in Rodent Models, Translational Research in Muscular Dystrophy, CNS Therapy Development for Lysosomal Storage Disorders, Gene Therapy for Neurological Disorders, Preclinical therapeutics Development for NeuroAIDS, NINDS HTS Service Facility, CINAPS and drug optimization contract, General SBIR program, RAID, Molecular Libraries, Medicinal Chemistry Facility, and the Preclinical Stroke Consortium.

Chapter 4. Critical Issues: Target Validation, Animal Models, Biomarkers, and Drug Delivery Past the Blood Brain Barrier

Introduction. Clinical development of disease-modifying drugs for neurological disorders has been challenging, with no definitive success to-date. Although research on mechanisms underlying disease has identified many possible molecular targets, and animal models have been developed and used for evaluation of drug candidates, major critical technical issues remain in developing drugs against candidate targets. These major technical issues, common to virtually all neurological disorders are:

1) target validation;
2) animal model predictivity for clinical efficacy;
3) biomarkers for early reporting of efficacy;
4) drug delivery across the blood-brain barrier (BBB);

Each of these 4 critical technical issues has a substantial impact on the probability of success in subsequent clinical trials. Significant progress in addressing these issues would significantly mitigate risk inherent in the transition from research to development for a given drug candidate and increase prioritization and funding for clinical trials of novel disease-modifying therapies for neurological disorders.

Target Validation. The best target validation comes from human genetics, with mutant huntingtin in Huntington's disease being an example. Clinical validation with a drug that is reasonably specific for the target of interest also provides compelling evidence that the target has a significant role in human disease. However, most putative targets for neurological disorders are only partially validated, i.e. they lack human genetic confirmation or clinical validation. Increased funding for human population genetics may accelerate the identification of targets important not only to familial disease, but also sporadic disease. Specific examples where initial identification of a mutant gene led to implication of the wild-type molecule in disease include β-amyloid in Alzheimer's disease and α-synuclein in Parkinson's disease. A better understanding of pathological cellular mechanisms and the role of candidate molecular targets, in the absence of human genetic or clinical validation, is also critical to identifying the best targets for drug development. For example, what is the role of axonal transport in neurodegenerative disease, and which molecular mediators of axonal transport may represent important drug targets?

Animal Model Predictivity for Clinical Efficacy. Animal models provide a critical step in the transition of a drug candidate from research to development, with efficacy in such models typically representing a key milestone for a drug discovery and development project. The underlying assumption is that such animal models are predictive for the clinic, and that efficacy of a drug candidate in an animal model significantly increases the probability that the drug candidate will demonstrate efficacy against human disease. However, most animal models of neurological disorders are not optimal and do not recapitulate key pathologies underlying disease. For example, in Parkinson's disease, the most widely used animal models, even for testing disease-modifying therapies, are generated with chemical toxicants such as 6-OHDA and MPTP that result in acute neuronal death and are unlikely to reflect the processes underlying chronic neurodegeneration. In ALS, the animal model in which virtually all therapies are tested is the G93A mutant SOD1 transgenic mouse; whether molecular and cellular pathologies in this mouse model recapitulate those in clinical ALS is unknown, and therefore, useful therapies for sporadic ALS may be eliminated with such studies. Clearly, the NIH should strongly support the development of predictive animal models for neurodegenerative diseases such as Parkinson's disease and ALS.

Biomarkers for Early Reporting of Efficacy. A significant hurdle in the clinical development of disease-modifying therapies for neurodegenerative diseases is the relatively lengthy trials needed for evaluating impact on symptoms that may progress relatively slowly over years. The development of surrogate markers to monitor progression in clinical trials of disease-modifying drug candidates, as well as in animal models, that would serve as early read-outs of efficacy, would significantly shorten the time, investment and risk in conducting such trials. This topic will be the focus of a separate chapter.

Drug Delivery Across the Blood-Brain Barrier (BBB). The BBB hinders the delivery of potentially important therapeutic molecules to the brain, including proteins/antibodies, oligonucleotides and many small molecules. For CNS drug development, an understanding of the molecular and cellular biology of the BBB and the identification of strategies to circumvent, disrupt or manipulate the BBB to facilitate drug entry is critical.

Which are the most significant existing problems in the area?

- How cellular/molecular pathways contribute to the maintenance of the BBB
- Receptor-mediated transcytosis strategy for drug delivery
- BBB disruption strategy for drug delivery

How has NINDS addressed these needs?

- In 2007, NINDS invested $27M (>80 projects) focused on the BBB
    - How to circumvent the BBB to deliver targeted therapeutics to treat neurological conditions
    - How BBB compromise contributes to disease pathology; how various pathogens traverse the BBB
    - How neurological conditions lead to increased permeability of the BBB
    - How cellular and molecular interactions contribute to the formation and maintenance of the BBB
- $7.6M (18 projects) invested on translational research aimed at therapeutic delivery across the BBB, most supported under disease-specific programs

Recommendations

- It is recommended that NINDS focus a substantial fraction of resources on one or two approaches for drug delivery past the BBB that are potentially high impact for drug development for CNS disorders, e.g. receptor-mediated transcytosis.

- In is recommended that NINDS support the development and use of imaging methods and probes in animal model and human studies, to evaluate drug delivery strategies past the BBB. The availability of such imaging methodologies will provide critical information on extent of delivery to the CNS and permit separate evaluation of drug efficacy and drug delivery.

Chapter 5. Criteria for New Translational Initiatives

Purpose and Introduction. We are developing criteria and a process for the identification of diseases upon which NINDS can focus major efforts. We call these NINDS Focus Diseases. Current examples of such NINDS Focus Diseases include SMA and muscular dystrophy. This chapter outlines a process through which disease oriented translational opportunities can be identified in the future. In addition, we describe a methodology by which diseases that currently do not meet criteria can be advanced.

The Challenge. NINDS already ensures that individual translational grants/projects have well-designed milestones. The agency also requires that study sections adhere to the translational review criteria. However, there exists no process for identifying the best disease for a large-scale translational research investment. For example, several years ago, NINDS selected SMA as the focus for a contracts-based approach to drug development. Although there were many good reasons for choosing SMA, the disease selection process was not transparent. As another example, the Institute launched a cooperative agreement program in muscular dystrophy several years ago. The decision was made based on the merits of muscular dystrophy alone, not by looking across all diseases and deciding that muscular dystrophy was the best suited. The culture of NINDS endorses "program director-initiated" ideas for new initiatives, but the concern is that some important translational opportunities are being missed because they lack a champion. The challenge is to define what a good translational opportunity would look like so that NINDS can systematically scan its disease portfolio and select appropriate Focus Diseases. The criteria that we outline below are intended as tools with which candidate diseases can be triaged. This should result in a set of tractable strategically selected diseases for investment. When a disease qualifies as a NINDS Focus Disease, that disease clearly must be ready for a translational research initiative.

Definition of Translational Research and Development. Translational research and development aims to develop interventions, predicated upon an understanding of disease mechanism(s), for the screening, diagnosis, prediction of patient response to, and treatment or prevention of human disease. This includes research designed to identify or test an interventional strategy in relevant biochemical, cellular or animal models when this work helps drive the discovery and development of new drugs and devices. Translational research will have an obvious trajectory that extends toward clinical proof of concept.

Characteristics of Disease Related Translational Research and Development

- Target has already been linked to disease through genetic or epigenetic studies
- Target is druggable or a tractable target for drug/device/diagnostic development
- Milestones are clearly defined and time to achieving milestones is realistic and acceptable. Milestones reflect clear go/no go decisions.
- Disease translational strategies should be developed with a good understanding of the drug and device discovery and development process.

Criteria for Diseases That Fit Translational Research Criteria

The Disease

- The disease/disorder should lie within the NINDS mission. NINDS translational programs are different from industrial translational programs in that they are not profit driven and not necessarily dependent on intellectual property. Challenging neurological diseases that are of low incidence and prevalence are thus aligned with the NINDS mission
- Research on the Focus Disease will clearly and directly contribute to the diagnosis, treatment and/or prevention of those neurological diseases.
- The contribution of NINDS to the Focus Disease should be unique. This contribution should not be competitive with a well-established effort in pharma or academia. This mandates that the global competitive environment should be critically evaluated and understood. NINDS Focus Diseases will lie in the funding gap between academic and industrial research (e.g. stroke and muscular dystrophy, vs. Alzheimer's disease and multiple sclerosis, where industry is very active).

Biological Target

- The biological target has been clearly associated with human disease. Manipulating the biological target is expected to have a beneficial effect on the Focus Disease
- Ideally, biological targets that are logically related to the target of interest will have proven tractable.

Tools

- Are there relevant in vitro biochemical or cellular assays that allow one to test for drug effects on the biological target?
- Are there relevant in vivo animal models that predict pharmacologic success against the disease target or a direct effect on the biological target?
- Are there biomarkers that are relevant to the disease?

Chemical Matter

- Are there chemistry starting points for a discovery program?
- Is there any evidence of structure activity relationships?
- Can a high throughput screen be run in order to discovery chemical matter?

Biological Matter

- Evidence for target engagement/interdiction
- Evidence for clinically relevant delivery methodology
- Evidence for manufacturing to scale under cGMP

Long-Term Trajectory

- Timing. Can the disease be addressed in a reasonable amount of time?
- Are clinical trials reasonable, or even possible? Can patients be identified and are they available? Are clinical endpoints established? Is there a trial network, patient registry, etc. that can facilitate the movement to clinical studies? Are there disease related measures of disease progression (wet biomarker, rating scale,)?
- From an economic point of view, will pharma be attracted to a candidate in this disease area no later than clinical proof of concept?

Resources. Are there research resources that the proposed translational research program could leverage against (e.g., RAID or others)?

Milestones. Does the disease lend itself toward milestone gated research? Simply stated, translational projects should clearly be on a path to help patients (e.g. entry into clinic, accelerate development via biomarker/patient selection or endpoint, etc).

The Process. Extramural involvement is important at all stages of NINDS-supported focus disease research and development. We imagine that disease leadership groups will consist of key players from NINDS, from academia, and from industry. These tri-partite teams (TPTs) should engage during the following stages:

Disease selection. Diseases that are proposed for NINDS focus must be evaluated against the criteria that are suggested above. Candidate diseases should be reviewed by a TPT and prioritized against the criteria. Diseases that substantially meet disease criteria can advance to Focus Disease status. During this triage, some diseases may be promising, but still not acceptable for focus disease status. However, the TPT can identify key shortfalls that can be addressed in order to advance the status of such a disease. These shortfalls can be addressed while the proposed disease is in a pre-focus stage and the proposal for focus disease status can be reviewed after identified milestones are met. An evaluation that targets "disease-readiness for translation" should involve the disease associated lay and scientific communities. These groups can help "make the case" that a particular disease is ripe for a translational campaign.

Translational Progress on Focus Diseases should be monitored by a TPT. This could be a portfolio type review of several focus diseases. The TPT should not be a simple outgrowth of the project leader. The TPT will be responsible for recommendations for triage if projects are not moving well against established milestones. The TPT will review strategies and recommend accelerators. The TPT may recommend increases or reductions in resources.

Chapter 6. Biomarkers.

Biomarkers were earlier described as a critical area for NINDS. This chapter further explores the biomarkers area.

Introduction. Biomarkers are urgently needed for most neurological diseases, and they should represent a crucial part of translational research activities. Biomarkers are acutely needed as drug development tools and ultimately expected to be useful for diagnosis and differential diagnosis of neurological diseases, monitoring progression of diseases, selection and stratification of subjects for clinical studies, for making treatment decisions and for monitoring effects of therapeutic agents.

Achievements and Strengths. NINDS has supported biomarker research studies and has interacted effectively with other branches of the NIH and with industry. Key strengths include:

- NINDS has funded an impressive number of biomarker studies, reflecting a strong emphasis for this area.

- NINDS has contributed to substantial progress in the identification and use of biomarkers in multiple sclerosis (MS) and epilepsy.

- NINDS established active and inclusive interactions with industry, and advocacy groups provide a forum for critical discussion and peer-review.
- NINDS is a key participant in the activities of the Biomarkers Consortium, a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health (FNIH), which includes the NIH, industry, and non-profit advocacy and funding organizations. The Biomarkers Consortium has the goal to identify and qualify biomarkers to support basic and translational research, guide clinical practice and, ultimately, support the development of safe and effective medicines and treatments. A neuroscience steering committee has been meeting regularly to identify suitable programs relevant of NINDS and NIMH. In addition, FNIH supervises the Alzheimer's Disease Neuroimaging Initiative (ADNI) which is supported by the NIA.

Challenges. Review of the NINDS biomarker studies generated the following observations

- The funded studies appear skewed toward diagnosis rather than treatment response. Early diagnosis in the absence of a therapy is interesting but not as impactful as early diagnosis that directs the patient toward an effective therapy. Early diagnosis in absence of treatment raises ethical issues. Furthermore, early diagnosis during the phase of development of disease-modifying drugs may have more limited utility since the FDA typically requires starting development in most severe patients with the disease.

- There appears to be no funding for studies on biomarkers that are directed towards patient selection and stratification for clinical studies, an aspect with potential impact on facilitating and accelerating development. Our charge doesn't involve clinical, but biomarkers are a bridge area between the preclinical and clinical areas.
- The funded studies seem to reflect opportunities presented by investigators and do not reflect a response to a general plan proactively outlined by NINDS.

- In the Biomarker Consortium of FNIH, there have been inconsistencies regarding the overall approach. At the beginning, the neuroscience steering committee followed a bottom-up approach, inviting and discussing all submitted proposals. More recently, this was changed to a top-down approach, mandated by the executive steering committee of FNIH, which favors this approach and focus on 'big ideas'. In addition, the source of funding for individual proposals is not clear, and groups submitting proposals sometimes erroneously assume that 'approval' means 'funding'. The structure and participants of FNIH does not include small biotech companies.

Recommendations

General recommendations

- NINDS funding will be most effective when focusing on practical and realistic goals with respect to technology, cost, and deliverables.
    - Utility and validity of biomarkers in current and future clinical practice need to be considered and addressed upfront.
    - Biomarkers will be most helpful when they can be used for drug candidate selection at early stages of a development program.
    - Grant support should be awarded based on specific milestones.

- It is recommended that NINDS identify synergies across biomarker projects. Functional outcomes relevant to multiple diseases will be particularly useful. E.g., cognition is a component and useful efficacy endpoint for several neurological diseases.

- NINDS should confirm that biomarker programs funded under the umbrella of translational medicine are indeed 'translational'. Perhaps a checklist along the following lines will be useful:
    - Is there a clear trajectory to meaningful clinical decision-making?
        - Is it actionable?
        - Does it provide a clear go/no-go decision point for further studies?
        - Does it accelerate path to clinic or clinical development?
    - Does the biomarker do more than confirm a clinically obvious change, or does it indeed contribute to clinical studies and/or therapy by:
        - Predicting the future effect or adverse effect to a drug?
        - Helping in patient selection?
        - Reducing the cost of the treatment?
    - Does the biomarker help to generate a more predictive animal model of the disease? Most useful biomarkers are those applicable in patients and the relevant animal disease models, which thus greatly increase the predictive power of the animal model.
        - Positive examples include: Imaging in MS, which has spearheaded biomarkers in clinical trials; Free fatty acid biomarkers for PPAR compounds.
        - Negative examples include: MPTP mice in PD, which are useful for selecting palliative therapeutics but not disease-modifying therapeutics; SOD1 mutant mouse in ALS, which has not been predictive; animal models in stroke; none of which have been predictive.

- It is recommended that NINDS consider regulatory issues in its overall biomarker strategy. Again, we recognize that clinical research is beyond the purview of this chapter, but we want to draw attention to the bridging aspect of biomarkers.
    - Biomarkers used during Phase III clinical studies locks biopharma companies into registering the biomarker as well as the drug, since the two will be tied together. Consequently, many companies avoid use of the biomarker in Phase III studies, thus harming medical progress. The NINDS may be able to help the FDA address this complex issue.
    - NINDS should consider whether a biomarker is exploratory or registration-supportive. The NINDS funding structure may be more suitable for studies in the exploratory rather than the registration phase of clinical studies.
    - If biomarker studies have the potential to be registration-supportive, NINDS needs to address the issue of 'utility' of a biomarker, as defined by FDA guidance documents.
    - For registration-supportive biomarkers, potential reimbursement is a critical issue. Ample venture capital will be available to support development of biomarkers with high probability of reimbursement.

- Regarding the Biomarker Consortium activities of the FNIH, it is recommended that NINDS take an active role and provide guidance to the steering committee. Such guidance should include the identification of the most significant needs in neurological diseases handled by NINDS, as well as input into the overall structure and way of operation of FNIH.

Specific recommendations regarding the new initiative for Molecular Biomarkers

- It is recommended that NINDS consider its activities in the context of biotechnology and pharma companies. As outlined above, there are many small companies active in this area, despite limited reception by the large pharma companies.

- There is great unmet developmental need in many neurological diseases where drug development is extremely high risk, high cost and severely limited by the lack of more precise tools upstream of long term clinical benefit (stroke, PD, etc). There is a clear funding gap here and no obvious industry effort to address it. Filling this need is in line with NIH mission and could subsequently encourage an influx of pharma interest to help gain more momentum in some of these diseases

Chapter 7. Outreach.

Responses to Standard Questions

What is important about outreach to the NINDS mission? Translational research that is sponsored and encouraged by NINDS supports drug and device discovery and development with the intent of making available new therapies and devices. A basic understanding of the processes and principles of discovery and development is essential in this pursuit. In addition, understanding the role and modus operandi of the regulatory agencies (e.g., FDA and EMEA—European Medicines Agency) and the biopharmaceutical industry are important. Outreach is the process by which NINDS can achieve up to six goals:

- Make information available to researchers;
- Offer access to consultation expertise essential for effective translation;
- Collect data that helps NINDS achieve its goals;
- Encourage productive translational research;
- Educate on and facilitate interactions with FDA and other regulatory agencies;
- Educate on biopharmaceutical industry and the formation of spin-out companies with private investment.

What are the needs in the area? Will this project add significant value or largely duplicate prior or ongoing work within or outside of NINDS? The fives needs in the outreach area which reflect the six goals are:

- A mechanism through which NINDS can provide educational materials to its customer base;
- An awareness of the evolving discovery and development environment and its requirements;
- A process that produces innovative and effective translational research;
- A process that facilitates interactions with regulatory agencies and industry;
- A process that facilitates interactions with biotechnology organizations and other private sources of funding for translational research and development.

Recommendations

Need 1 is largely educational. This need can be addressed by the creation of a drug <u>discovery and development primer</u> that can be mounted on a public server. This primer would specify key milestones in the drug and medical device discovery and development processes and would discuss the activities that are triggered by achieving each of these milestones. Translational research grant proposals would then be structured with these milestones and activities as a framework. Make available <u>a one day short course in drug and device discovery and development</u> that would cover the processes from target

identification to IND-stage drug candidate or from device conception and prototype development to IDE or 510k application. The course would be taught by scientists and entrepreneurs with expertise and experience in medicinal chemistry, ADMET, pharmaceutics, intellectual property, bioengineering and regulatory affairs, among others. Make available a slide set to help ensure consistency in the educational process. NINDS or its agents could visit major research institutes and present drug discovery and development talks. The NINDS drug and medical device discovery course could also become a road show. Covering both drug and medical devices processes will be a significant undertaking, and it may be advisable to focus on one or the other to make sure implementation is successful. The other process could be incorporated at a later time when a clearer understanding of what works and what doesn't is developed. Finally, it is important to provide a tutorial and/or refresher course concerning intellectual property. This is often the foundation required for an innovation and invention to secure the interest of an industrial partner and external sources of funding.

Need 2 assumes that NINDS should itself be well informed about the translational research environment and how it is evolving. This need is related to the others. Staff could be expected to assist investigators in understanding the discovery and development processes and/or in searching licensed databases. Staff could be expected to provide input to investigators in understanding the regulatory environment and expectations and the drug discovery and development efforts in industry. NINDS staff should thus be given opportunities for their own education in the discovery and development areas.

Need 3 addresses the need for innovative and effective research that can logically lead to a 'product' that will address an important medical need. A number of possibilities are envisaged:

- Fundamental to this need is access to quality information. NINDS should consider providing access to information regarding the drug and medical device competitive environments. What are others doing in a given area? What are the unmet needs? This would be a valuable tool for both investigators and grant reviewers. Various commercial databases are available for license.

- Grant proposals need to be strategically sound. Implicitly, the milestone-gated process requires key resources that are often not available to the PI who will probably not be knowledgeable about his/her options. NINDS could help with strategy and identification of key resources. Need 1 (education) will help with strategic thinking. Identification of typical and trusted resource suppliers will help facilitate reasonable resourcing. Translation is often impeded because a particular vendor of a service or resource was not qualified to deliver what was promised. This leads to loss of momentum, wasted capital, and most importantly the potential loss of a potentially valuable 'product.'

- Drug discovery and development processes routinely and almost universally need access to tier 1 ADMET surrogate assays and medicinal chemistry. NINDS could contract with a validated provider that could provide these resources, upon approval, to NINDS investigators. Examples of essential assays include microsomal oxidation and mechanistic cellular toxicity assays.

Need 4 reflects the reality that academic translational research is affected by regulatory agencies (FDA and EMEA). In addition to providing education in this area, the NINDS could

significantly accelerate progress by establishing active communication channels with the relevant divisions at the FDA to proactively discuss the challenges in neurological disorders. Topics for such discussions could include acceptance criteria and tolerance for adverse effects in neurological disorders, and the risk-benefit balance for the most devastating diseases. This suggestion should be relayed to the clinical committee.

Need 5 reflects the reality that academic translational research takes place in an environment of substantial similar efforts in the biopharmaceutical industry and that very significant private investment is available for some of the translational research. The NINDS could significantly accelerate progress and leverage its own efforts by establishing active communication channels to biotechnology organizations and funding groups. These interactions should have the goal to facilitate the formation of spin-out companies and private investment into translational research.

Chapter 8. Small Business Program

Introduction. Essentially by design and federal mandate, the Small Business Programs of the NIH are perhaps the longest standing initiatives within the NINDS/NIH that are intended to address translation of innovation most directly. More recent strategies also address translation of innovation (e.g., the NINDS Cooperative Agreement Translational Research Program), and these are dealt with in separate chapters.

The Small Business Programs are intended to increase the likelihood of commercial application of results from federally supported research, in particular that research which meets federal research or research and development needs. Additionally, the Programs aim to foster and encourage participation by socially and economically disadvantaged and/or women-owned small business concerns. Eligible organizations must be 'for profit', have a place of business in the United States, and operate primarily within the United States.

Available funding mechanisms are several, including Small Business Innovative Research grants (SBIR; Phase I under mechanism R43; Phase II under mechanism R44), Small Business Technology Transfer grants (STTR; Phase I under mechanism R41; Phase II under mechanism R42), Cooperative Small Business Awards in Translational Research grants (under mechanism U44), and special funding mechanisms to handle fast-track and competing renewal applications. The SBIR and STTR programs are among the most heavily funded mechanisms in the NINDS in support of translation of innovation (see Achievements Section). The SBIR grants (R43 and R44) are the focus of Small Business Concerns (as the eligible participant), while the STTR grants (R41 and R42) are the focus of Small Business Concerns in partnership with research institutions. For both programs, the intent is that technological feasibility of the innovation and small business concern track record of performance be established in Phase I before a larger Phase II award is considered and approved. The SBIR program is the oldest funding mechanism, having been started in 1983 and reauthorized in 2000. The STTR program is the next most mature program, having been started in 1993 and reauthorized in 2001. Award amounts for the different mechanisms are based on guidelines that are flexible (to a degree) depending on the opportunity under consideration and the specific needs of the Institute, and progress is measured against milestones that are determined based on the application and award process.

Achievements and Strengths

- The Small Business Program at the NINDS appears to be consistent with the overall NIH program and objectives and the mission and objectives of the NINDS. The NINDS has actively and effectively participated in the Small Business Programs of the NINDS/NIH. The amount available for all mechanisms of funding under this program is based on a set-aside percentage of the total NINDS budget in each fiscal year. The mandated SBIR set-aside is currently 2.5% of the total NINDS budget, and it will remain at this level until revisited this year (2008). The mandated set-aside for the STTR mechanisms is currently 0.3%, and it will remain at this level until revisited in 2009. An important strength of the program is that significant flexibility can be realized in its management. This flexibility is largely a result of flexibility around level of funding and overall duration of supported grants.

- The following table summarizes the funding allocations by the NINDS for the major mechanisms of the Small Business Programs since 2004 (amounts in thousands of US dollars):

	Year	2004	2005	2006	2007
Mechanism	Code				
STTR Ph I	R41	2,084	1,641	1,300	2,265
STTR Ph II	R42	1,822	2,349	2,675	1,779
SBIR Ph I	R43	10,762	8,624	7,298	6,308
SBIR Ph II	R44	19,234	24,543	25,744	26,387
CSBATR	U44	2,000	0	0	936
Total		35,902	37,157	37,017	37,675

A high level summary of the Small Business Program grants as of the end of Fiscal Year 2007 is appended to this chapter. The results are sorted by: (1) year of grant; (2) mechanism of funding; and finally (3) year of grant end. Only two active R44 grants were initiated prior to 2000, and it is assumed these grants are for work that is showing significant progress toward commercialization of innovation that is of high value to the NINDS. Access to level of individual grant funding was not obtained.

- In Fiscal Year 2007, a total of $37,675,000 was awarded for the mechanisms highlighted in the table above, and based on the appended table, the grants appear to be allocated toward projects that generally address disease areas of importance to the NINDS.

- One index of success of the effort to encourage translation of innovation can be seen in the number of Phase I grants that move on to an award under the corresponding Phase II mechanisms. It's too early to meaningfully assess this for 2006 and 2007; however, analysis of the awards granted in 2004 and 2005 are more revealing. In 2004, 62 out of 64 SBIR awards were determined by staff to be translational projects, and of these, 23 went on to a Phase II award (37%) in subsequent years. In 2005, this measure of success resulted in 49 translational awards going on to receive Phase II awards (29%) in subsequent years. While there are undoubtedly other and equally important measures of Program success, progression to Phase II is a good benchmark to include in subsequent analyses.

- For fiscal year 2007, twenty-five (25) of active Small Business Program grants were coded by NINDS staff as Translational Research. These grants are summarized in Table 2 (appended) and highlighted in Table 1. Impact on the various stages of the translational pipeline is indicated. It appears there has been a significant drop in the percentage of total grants coded as translational in fiscal year 2007 compared to 2004 and 2005 as indicated in the previous paragraph. Reasons for this change were not clear.

- The NINDS is aware of and looks for opportunities to encourage participation by grant award recipients in the NIH/OD Technical Assistant Program for funded grants. This includes participation in the: (1) Niche Assessment Program (NICHE); the Commercialization Assistance Program (CAP); the Manufacturing Assistance Program (MAP); and the Pipeline to Partnerships Program.

- The NINDS also participates in the NIH Small Business Town Hall Meetings to encourage and facilitate coordination between Small Business Programs across the larger NIH. More importantly, the NINDS has developed its own Small Business Working

Group, comprised of program staff, that examines issues related to the Small Business Program in the NINDS and to seek alternatives to resolve these issues.

- In fiscal year 2007, the NINDS Small Business Program achieved several objectives as indicated by the list of Small Business Program grants in Table 1. This program also funded approximately 9% of women-owned businesses and approximately 2% of socially and economically disadvantaged businesses in 2007. In the last year, pre-IND meetings were held by two different grantees for treatments for acute ischemic stroke. An IND was submitted by a grantee for a novel pain medication, and an IND for West Nile Virus has been approved. There are also examples of progress being made toward commercialization from specific small business concerns that benefitted from NINDS funding through these mechanisms (e.g., product development from Pinnacle Technology, Inc., Lawrence, KS and from Synapse Biomedical, Inc., Oberlin, OH).

Challenges. The NINDS and its staff face a number of challenges with respect to the Small Business Program. Many of these challenges are consistent with those encountered by other Institutes within the NIH. Within the broader NIH, there appears to be a desire to strengthen the Small Business Program, and some specific recommendations have been put forward (information provided by NINDS leadership). These recommendations will be incorporated as appropriate below.

- Within the NIH as a whole, apparently the number of new SBIR applications has declined. To date, the NINDS has only experienced this in the R43 (SBIR Phase I) applications and is prioritizing applications from new companies in an effort to increase participation. There are probably a variety of reasons for the leveling off or decline of applications, but it's important to make sure that participation and competition for Phase I grants (both SBIR and STTR) remain strong to provide a good foundation and source for follow on Phase II applications.

- There appear to be an increasing number of mechanisms to fund translational research, and it may be less clear to applicants which are the most appropriate for them to pursue and apply for. It will be a challenge to effectively integrate these mechanisms and at the same time make sure the NINDS realizes high quality and successful applications to address the most important projects to meet its expectations as an Institute. In particular, it will be important to make sure that this integration minimizes gaps in the spectrum of grant applications received in view of the Institute's stated priorities.

- At this time, the major set aside from the NINDS budget is for SBIRs (Phases I and II), with a lesser amount for STTRs. This is counter to the Institute's desire to encourage cooperation and collaboration between principal investigators at research institutes and universities with viable and capable small business concerns (i.e., the primary emphasis of STTRs). Even within the SBIR part of the Small Business Program, it is not always clear how 'committed' a single investigator's company is for commercialization of innovation of the grant application(s) submitted.

- The amount of total funding in support of the Small Business Program is relatively small in comparison to the amount of financial resource needed to effectively drive a single innovation to the commercial sector. Spreading this small level of funding over a larger number of projects makes the likelihood of having a significant impact on translation efficiency lower than perhaps expected.

- Without having evaluated the commercial impact statements in the current roster of Small Business Program grants, it is nevertheless important to make sure that commercialization plans (including intellectual property strategies and plans) that are presented in grant applications are realistic and contemporary. The commercial receptivity of new innovations is seemingly changing every day, and it will be important for the NINDS staff and the funded Small Business Concerns and principal investigators to have a contemporary understanding of what is being required and expected from other external funding sources such as venture capital groups. To ignore this is to decrease the chances that an innovation will be successfully translated to the commercial sector. This author's experience is that business plans submitted to venture capital sources are weakest with respect to descriptions of intellectual property, commercial applicability and competition, and risk analysis. Training and education to fill this gap would be an important step in the right direction.

- As will always be the case, it will be important to continue to seek ways to meaningfully foster participation by minorities and disadvantaged persons in technological innovation. This is an important aspect of the goals for the Small Business Program, but it must be implemented with sensitivity and expectation that quality of outcomes and deliverables will not be compromised.

General Recommendations. Based on a top level analysis of the Small Business Program at the NINDS/NIH, the following recommendations are proposed for consideration:

- Consistent with the larger NIH recommendation, the NINDS should continue to focus the Small Business Program on innovations that address important and commercially viable needs. The Institute can continue to 'receive' grant applications from small business concerns that address the Institute's priority areas, but it should also be proactive in seeking application from investigators with a proven track record of innovation with commercial potential and of performance of delivery of results and affiliation with viable small business concerns. Perhaps an increased emphasis on translational cooperative agreements (U44 mechanism) and the STTR mechanisms should be considered.

- The Institute should continue to emphasize the development of materials and training courses and workshops to educate its staff and current and future applicants about the importance of a strong commercial potential and intellectual property foundation for their innovations. Without these important aspects, translation efficacy of innovations will suffer, and the Institute will suffer from lost opportunities over the long term. This recommendation ties in with the recommendations from the 'Outreach' chapter (Chapter 5).

- Continue to strengthen the NINDS Small Business Working Group along the lines outlined by the NINDS staff, and if appropriate, consider elevating this group (or a similar function) to a higher operational level to better coordinate the Small Business Program with the other translational mechanisms sponsored by the Institute. Importantly, populate the Working Group with individuals with relevant and contemporary translational experience or secure this expertise on an external advisory basis. If external, the expectation should be that participants will be expected to 'roll up their sleeves' and contribute to the strengthening of the Institute's Small Business Program on a significant and consistent basis.

- The NINDS should especially take a hard look at all Phase II awards on a continuing basis to make sure that the tough questions around intellectual property foundation and portfolio and true commercialization potential are addressed and re-examined on an annual basis. The NINDS staff has a good sense of what needs to be done here, but it basically comes down to 'active management' of these later stage grant awards to help increase the likelihood of innovation commercialization. Facilitating workshops between Phase II awardees and other external sources of funding (e.g., foundation support, angel and venture capital funding, and other sources of financial leverage) is something that should be emphasized. Direct feedback from these sources of funding is an important aspect of maturation and growth of the small business concern.

- Given the legacy and complexities of the Small Business Program both within the NINDS and its connection to the larger NIH, it will probably be difficult to bring about any 'radical change' in a timely manner. However, aspects of the Program should be examined, and perhaps this is something that should be followed up separately from this advisory initiative and in greater depth and detail. For example, the amount of documentation required to be read and understood for an SBIR or STTR Phase I application seems out of proportion to the amount that could be realized for a successful grant application. Further, it seems as if a separate industry is developing just to support the preparation and submission of SBIR and STTR grants, and this comes at an added cost. Perhaps this is a factor that is resulting in the decrease in Phase I grant submissions. In any event, it would be important to understand why certain Small Business Program applications are leveling off or decreasing. Coupling this with training and education mechanisms outlined in the 'Outreach' section might be a way to connect with the 'customer base' to understand their points of view.

Specific Recommendations

- Focus on commercially viable technologies. Establish specific technology priorities with high commercial potential. Set aside funds to support these priority areas. Move toward a balance between NINDS-directed and investigator-initiated grants (i.e., bottom up and top down).

- Increase use of cooperative agreement mechanisms from current level of 5%. Contract-type arrangements allow more management and oversight of progress.

- Manage programs differently. Create Small Business Development Centers. Optimal management requires experience in technology commercialization and translational research. Currently SBIR/STTR grants are dispersed. Focus and manage with the aid of NINDS and external experts. Model after IC SBIR Development Centers. Centers should assemble expertise, assess commercial potential of priorities, evaluate proposals, solicit topics, expand outreach, and manage grants.

- Assemble an External NIH SB Advisory Committee (NINDS, entrepreneurs, management consultants, venture capital experts, etc.) to advise NIH staff on future directions and strategic approaches of the SB program. NINDS would retain full control over how Institute resources are allocated. Analyze markets and advise NINDS on commercial potential and potential investors.

- Co-invest with the private sector to bridge SB products toward commercialization. Address funding gap between the end of a SBIR/STTR Phase II awards and the point where the technology attracts private investment. This gap is more challenging for new drugs. Using "Phase II Competing Renewal" awards addresses this problem, but these are not milestone driven and don't engage the investment community.

- Initiate an SB Bridge Fund Demonstration Project based on a similar (and successful) program from NSF. This program would offer NIH funds to SBIRSTTR Phase II companies able to raise matching funds (1:1) from the private sector. Such a program would increase successful commercialization by leveraging external organizations' dollars.

- Set aside a total of approximately $150 million over 3-5 years to support a total of 50 awards ($3 million per award) as a demonstration project. Key components of this 'experiment' would include: a) require matching funds from the investment community; b) pursue lifting SBA restrictions on VC ownership and SBIR/STTR eligibility; c) establish a shorter time frame for review and funding (i.e., payment) of the proposals, equivalent of the VC community.

- Consider taking further evaluation of the NINDS SBP offline with a panel of experts who would complete a broader and more in-depth review of funded projects. Consider evaluating the outcome of funded projects since FY2000. Identify projects to 'accelerate' and projects that should be 'stopped'. Confirm/reject recommendations provided herein. Identify other SBP alternatives. One such alternative would be to consider utilizing SBP funds for important technology platforms needed to advance other translational research and development objectives (e.g., target validation, animal model of diseases development, and other services).

Table 1
FY 2007 Small Business Program Grants (complete)

Grant Number	Mechanism	PI Name	Project Title	Year Start	Year End	Duration
5R44NS036119-06	R44	HSIA, CARLETON	PNA for Stroke	1997	2008	11
2R44NS037290-04	R44	SHRAIRMAN, RUTH	Biometric Instrument to Monitor Neurological Disorders	1998	2010	12
5R44NS039716-06	R44	WILDER, STEVEN	Improved EEG Patient Interface	2000	2008	8
5R44NS041113-05	R44	ECKHARDT, HELMUT	Insulating Coatings for Implant Devices and Ribbon Cables	2000	2009	9
2R44NS040597-04	R44	MICHALOS, ANTONIOS	ABSOLUTE NEAR-INFRARED BRAIN OXIMETER	2000	2010	10
5R44NS042977-06	R44	KAYYALI, HANI	Emergency Brain Monitor with Telemetry	2001	2009	8
5R44NS044658-04	R44	LIANG, YIQING	Digital Video Monitor and Analysis of Seizures with EEG	2002	2008	6
5R44NS044654-06	R44	BOADO, RUBEN	Neuroprotection in Stroke Drug Development	2002	2009	7
5R44NS042451-05	R44	KAYYALI, HANI	Pre-Operative PSG Assessment of Cardiac Surgery Inpatients	2002	2009	7
2R44NS050642-06	R44	DECHARMS, CHRISTOPHER	Treatment of Chroinc Pain Using Real Time Functional MRI	2002	2010	8
5R42NS046824-03	R42	HARLOW, BRADLEY	Refinement of non-invasive approach to the determination of intracranial pressure	2003	2008	5
5R44NS045371-03	R44	NARDUCY, KENNETH	Novel drug combinations for the management of pain	2003	2007	4
3R44NS045407-03S1	R44	ZHANG, HONGXUAN	Surgical Monitor for Detection of Spinal Cord Injury	2003	2007	4
5R44NS046121-04	R44	BRYAN, JAMES	Intracranial Brain Function Mapping System	2003	2009	6
5R44NS046976-03	R44	GIUFFRIDA, JOSEPH	Untethered Home Therapy System	2003	2009	6
5R44NS047955-03	R44	JOHNSON, DAVID	Glutamate Biosensors for Ischemia In Vivo and Tissue Studies	2003	2009	6
2R44NS046951-02	R44	NEMENOV, MIKHAIL	Laser Diode for Ion Channel Stimulation	2003	2009	6
5R44NS046825-03	R44	SCOUTEN, CHARLES	Stereotaxic Accessory for Reproducible Neurotrauma	2003	2009	6
2R44NS047746-02A2	R44	SMITH, JACK	Extensible System for Disseminating Polysomnography Data	2003	2009	6
2R44NS045488-04A1	R44	CHEN, BO	Adult Optical NonInvasive Brain Oxygenation Monitor	2003	2010	7
2U44NS046891-02	U44	NARDUCY, KENNETH	Preclinical Development of SCP-123 for Neuropathic Pain	2003	2010	7
5R42NS048777-03	R42	CARLTON, SUSAN	Non-Peptide Somatostatin Agonist Analgesics	2004	2008	4
2R42NS050007-02	R42	BARBOUR, RANDALL	Closed-Loop Functional Diffuse Optical Tomography (fDOT) Imaging System for Traum	2004	2009	5
3R43NS048731-01S1	R43	OLSON, GARY	MHC Class II inhibitors for Multiple Sclerosis	2004	2008	4
3R44NS048706-03S1	R44	KENNEDY, PHILIP	Implant Design and Development for Human Cortical Recording	2004	2008	4
5R44NS049666-03	R44	MYERS, SCOTT	pH-Sensitive Glutamate Receptor Inhibitors: Clinical Candidate Selection	2004	2008	4
2R44NS049945-02A1	R44	PARKER, B	A Handheld Device for Pain Assessment	2004	2008	4

5R44NS048734-03	R44	SAWYER, EVELYN	Salmon fibrin gels for surgical applications	2004	2008	4
2R44NS049734-02	R44	BARBOUR, RANDALL	Functional Brain Imaging by Optical Tomography	2004	2009	5
5R44NS051076-03	R44	BOADO, RUBEN	Stroke neuroprotection with a recombinant fusion protein	2004	2009	5
5R44NS049687-03	R44	COGAN, STUART	Functionalized Coatings for Enhanced Neural Interfaces	2004	2009	5
2R44NS049680-02	R44	DROST, CORNELIS	A Flow Monitor for Pediatric Hydrocephalic Shunts	2004	2009	5
5R44NS048706-03	R44	KENNEDY, PHILIP	Implant Design and Development for Human Cortical Recording	2004	2009	5
5R44NS048689-04	R44	MCKENNA, SUZANNE	ENHANCING PEPTIDE DELIVERY TO THE BRAIN	2004	2009	5
2R44NS048685-02	R44	OLI, MONIKA	Development of Novel Biomarkers for Traumatic Brain injury	2004	2009	5
2R44NS047952-02	R44	PRYCE LEWIS, HILTON	Coatings for Biostable Chronic Neural Prostheses	2004	2009	5
2R44NS049703-02	R44	RISO, RONALD	LCP Nerve Cuff with Telemetry for Prosthetic Sensation	2004	2009	5
2R44NS049918-02A1	R44	SMITH, THOMAS	Sustained Release Apomrophine for Parkinson's Disease	2004	2009	5
5R44NS047763-03	R44	TURNER-BOWKER, DIANE	Computerized Adaptive Assessment of Headache Impact	2004	2009	5
5R44NS047815-03	R44	ZIKOV, TATJANA	Intraoperative Brain Dysfunction Monitor/Detector	2004	2009	5
2R44NS048607-02	R44	HALDI, MARYANN	In Vivo Screen for Neuroprotective Agents	2004	2010	6
2R44NS048743-02A1	R44	RUEHLMAN, LINDA	Development of the Pain Self-Management Program	2004	2010	6
2R42NS054348-02	R42	RAPP, EDWARD	Side-by-side comparison of blood-brain barrier models	2005	2009	4
5R44NS051918-03	R44	RUSSELL, GERALD	VLSI for Ambulatory EEG Epilepsy Monitoring	2005	2008	3
2R44NS053129-02	R44	GIBSON, PAUL	Ambulatory Real Time High Channel Count Electroencephalograph	2005	2009	4
2R44NS054351-02	R44	HEDIN, DANIEL	Novel System for EMG Instrumentation	2005	2009	4
5R44NS052066-03	R44	KRAMER, KEVIN	Wireless System-on-a-Chip EEG IC For Animal Studies	2005	2009	4
2R44NS052920-02	R44	LI, FENG-QIAO	Novel Therapy for Multiple Sclerosis (SBIR-Phase II)	2005	2009	4
2R44NS053152-02	R44	NARAYAN, PRAKASH	Novel Small Molecule Therapeutic for Spinal Cord Injury	2005	2009	4
5R44NS051926-03	R44	WELLS, JONATHON	Development of an optical brain/nerve stimulator	2005	2009	4
2R44NS053110-02	R44	LIM, MARK	Advanced Molecular Diagnostic Test for Neurofibromatosis	2005	2010	5
2R42NS055606-02A1	R42	BORLONGAN, CESARIO	Stem Cells for Neonatal Hypoxic-Ischemic Brain Injury	2006	2010	4
1R43NS057917-01	R43	MYERS, SCOTT	Neuroprotection of pH Sensitive NMDAR Antagonists in Cardiopulmonary Bypass Surge	2006	2008	2
5R43NS054332-02	R43	TUCKER, TIMOTHY	A High Throughput System for Multichannel Neurophysiology	2006	2008	2
2R44NS054346-02	R44	HETKE, JAMILLE	Deep Brain Microelectrode Array for Functional Neurosurgery	2006	2009	3
5R44NS053325-05	R44	LEES, DAMON	Commercialization of a Monitor to Assess Neurological Health in Neonates	2006	2009	3
2R44NS055377-02	R44	SHAH, KANAI	High Resolution PET Detectors for Combined PET-MR Small Animal Imaging	2006	2009	3
5U44NS057961-02	U44	GOSWAMI, KISHOLOY	FIBER GRATING-BASED CHEMOSELECTIVE AND	2006	2009	3

			REVERSIBLE SENSOR ARRAY			
5U44NS057951-02	U44	WILSON, SCOTT	A first-responder EEG device for seizure management in a nerve gas attack	2006	2009	3
7U44NS058229-02	U44	NAGY, JON	Development of a selective biosensor for detecting organophosphate exposure	2006	2010	4
5U44NS057843-02	U44	ZHANG, YUFENG	Targeted Paraoxonase Fusion Protein as a Neurotherapeutic for Nerve Gas Agents	2006	2010	4
5U44NS057969-02	U44	MODARRES-ZADEH, MOHAMMAD	Field Deployable, Automatic, EEG Seizure Detector and Brain Dysfunction Monitor	2006	2011	5
5U44NS057966-02	U44	SHERMAN, DAVID	Automated Seizure Detection Following Nerve Agent Exposure	2006	2011	5
1R41NS056844-01A1	R41	BARBOUR, RANDALL	Functional Imaging of Freely Moving Animals	2007	2008	1
1R41NS055444-01A1	R41	CHANG, STEPHEN	STTR: Herpes Based RNAi Vectors	2007	2008	1
1R41NS061502-01	R41	HONE, ROBERT	PD Wii: Computer-based Gait and Balance Training for Parkinson's Patients	2007	2008	1
1R41NS059133-01	R41	MURPHY, THOMAS	An Internet-Based Evaluation System for Postacute Acquired Brain Injury	2007	2008	1
1R41NS053128-01A2	R41	NOVAK, VERA	Dynamical Assessment of Cerebral Autoregulation	2007	2008	1
1R41NS060348-01	R41	SELLERS, ERIC	Hybrid EEG Sensor Array for Brain/Computer Interfaces	2007	2008	1
1R41NS062408-01A1	R41	SIGWORTH, FREDERICK	Patch Clamp Amplifiers on a Chip	2007	2008	1
1R41NS059086-01A1	R41	MOORE, STEVEN	Long-term Ambulatory Gait Monitor for Parkinson's Disease	2007	2009	2
1R41NS060231-01	R41	REITMAIR, ARMIN	Highly Multiplexed Sensitive Specific & Automated Test for Neurogenetic Disorders	2007	2009	2
1R41NS059095-01	R41	STYNER, MARTIN	High Throughput web-base Image Analysis of Mouse Brain MR Imaging Studies	2007	2009	2
1R41NS058244-01	R41	WEILAND, JAMES	Hermetic Nanowire Interconnects for Neural Prostheses	2007	2009	2
1R41NS057860-01A1	R41	ZUTSHI, REENA	Targeted Blood Brain Barrier Permeability Changes with Ultrasound & Microbubbles	2007	2009	2
1R42NS055475-01A2	R42	ZUBAL, I	Automated Parkinson's Disease Dopamine Transporter Scan Analysis Fast Track	2007	2010	3
1R43NS057859-01	R43	SORENSEN, MICHAEL	A low-cost, high-speed platform for neural modeling.	2007	2007	0
1R43NS060471-01	R43	CHAUDHARY, NILABH	Small Molecule Drug Therapy for Stroke	2007	2008	1
1R43NS060175-01	R43	CHEN, RIDONG	Preclinical Validation of Human Apyrase in Stroke Models	2007	2008	1
1R43NS059250-01	R43	CHEN, WEILIAM	In Situ Gelable Filler for Obliteration of Cerebral Aneurysm	2007	2008	1
1R43NS059140-01A1	R43	CHIANG, LILLIAN	Accelerated Discovery and Development of New Pain Therapeutics	2007	2008	1
1R43NS056645-01A2	R43	CHRISTENSEN, DALE	Novel Treatment for Parkinson's Disease	2007	2008	1
1R43NS060192-01	R43	CORDO, PAUL	EMG Biofeedback with AMES	2007	2008	1
1R43NS060197-01	R43	ENTINE, GERALD	Solid-State Photosensor for PET	2007	2008	1
1R43NS058201-01A1	R43	GABBITA, SOMASUNDAR	Thiothalidomides as neuroprotectant drugs for PD.	2007	2008	1

1R43NS057890-01	R43	HARTMAN, ERIC	Stimulation Augmented Recumbent Stepper for Stroke Rehabilitation	2007	2008	1
1R43NS058065-01	R43	JENG, PATRICIA	Non-Invasive Instrument for Monitoring Changes in Intracranial Pressure	2007	2008	1
1R43NS057849-01A1	R43	KIRSCH, DONALD	Novel Therapeutic Agents for ALS	2007	2008	1
1R43NS055421-01A1	R43	LANNING, BRUCE	Wireless Multi-Modal Brain Monitoring	2007	2008	1
1R43NS059089-01	R43	LEMDIASOV, ROSTISLAV	Sodium/Proton Imaging for Assessment of Stroke Pathology	2007	2008	1
1R43NS061392-01	R43	LI, FENG-QIAO	Development of Remyelinating Agents	2007	2008	1
1R43NS056848-01A1	R43	LIU, YONGCHENG	A Nanocrystal Biosensor for Detection of Multiple TBI Neurochemical Biomarkers	2007	2008	1
1R43NS059082-01	R43	LOWERY, ROBERT	HTS Assays for Modulators of GPCR Signaling	2007	2008	1
1R43NS059215-01	R43	MAPES, JAMES	Biomarker Profiles for Predicting Stroke Using Stroke-Prone Rats as a Model	2007	2008	1
1R43NS051880-01A2	R43	NARDUCY, KENNETH	Development of Non-Narcotic Intravenous Analgesics	2007	2008	1
1R43NS060377-01	R43	PRYCE LEWIS, HILTON	Silicone Coatings for Biostable Chronic Neural Prostheses	2007	2008	1
1R43NS059247-01	R43	ROSENBERG, YVONNE	A Plant-Derived Recombinant Bioscavenger to Prevent Insecticide Neurotoxicity	2007	2008	1
1R43NS059098-01	R43	VANDENBURGH, HERMAN	High Content Screening for Muscular Dystrophy	2007	2008	1
1R43NS060269-01	R43	VETTER, RIO	Deep Brain Stimulation Array for Neuromodulation	2007	2008	1
1R43NS055601-01A2	R43	WESTLUND, BETHANY	COMPOUNDS ACTIVATING DJ-1 AS THERAPEUTICS FOR PARKINSON'S DISEASE	2007	2008	1
1R43NS057839-01	R43	DONNETT, JAMES	Digital Wireless Recording of Wideband Neuronal Activity in Freely-Moving Humans	2007	2009	2
1R43NS052020-01A2	R43	HELDMAN, DUSTIN	Multivariate Parkinson's Disease Prediction System	2007	2009	2
1R43NS057845-01A1	R43	IGNAGNI, ANTHONY	Development of Natural Orifice Translumenal Endoscopic Neurostimulation	2007	2009	2
1R43NS057921-01	R43	MAN, ALBERT	c-FN as a predictor of hemorrhagic transformation in t-PA treated stroke patients	2007	2009	2
1R43NS060226-01	R43	PARKER, B	Assessing the Functional Impact of Chronic Pain	2007	2009	2
1R43NS059219-01	R43	THACHER, SCOTT	Feasibility Study of Novel Drug Target for Multiple Sclerosis	2007	2009	2
1R43NS053116-01A2	R43	WEIMER, SARAH	Novel Fast Install EEG electrode (FIG)	2007	2009	2
6R43NS062437-02	R43	ZHOU, JIA	Development of GSK-3 Beta Inhibitors for the Treatment of Parkinson's Disease	2007	2009	2
1R44NS059223-01	R44	FEINBERG, DAVID	Cerebral Perfusion Imaging with 3D Arterial Spin Labeling GRASE MRI	2007	2010	3
1U44NS059084-01	U44	KARLSSON, JENNY	Intrathecal Cyclosporin for the Treatment of Amyotrophic Lateral Sclerosis (ALS)	2007	2010	3

Table 2. FY 2007 SBIR/STTR Grants Coded Translational Research

Translational Pipeline

Grant	Intervention	Disease	Assay Development	Animal Model Development	Library Screening	Validation in a Cell Model	Animal Efficacy Study	Med Chem/ Lead	Pharmacokinetics and toxicity
R43NS059098-01	Small Molecule	MD	X						
R44NS048607-02	Small Molecule	Neurodegenerative Diseases	X		X		X		
R43NS057849-01A1	Small Molecule	ALS			X		X		
R43NS056645-01A2	Large Molecule	PD				X	X		
R43NS060471-01	Small Molecule	Stroke				X	X		
R43NS061392-01	Large Molecule	MS				X	X		
R43NS057917-01	Small Molecule	Stroke					X		
R43NS055421-01A1	Devices	Epilepsy					X		
R44NS054346-02	Devices	PD					X		
R43NS059219-01	Small Molecule	MS					X	X	
R43NS051880-01A2	Small Molecule	Pain					X	X	X
R44NS051076-03	Large Molecule	Stroke					X		X
R44NS052920-02	Small Molecule	MS					X		X
R44NS053152-02	Small Molecule	Trauma					X		X
R43NS059247-01	Large Molecule	Chemical tox						X	
R44NS036119-06	Small Molecule	Stroke							X
R44NS045371-03	Small Molecule	Pain							X
R44NS048689-04	Large Molecule	Trauma							X
R44NS049918-02A1	Small Molecule	PD							X
U44NS059084	Small Molecule	ALS							X
U44NS046891	Small Molecule	Pain							X
R44NS048734-03	Large Molecule	SCI							
R44NS049680-02	Devices	Hydrocephalus							
R44NS049703-02	Devices	Amputation							

R43NS059089-01	Devices	Stroke							
Totals			**2**	**0**	**2**	**3**	**13**	**3**	**10**

Chapter 9. Countermeasures Against Chemical Threats

Introduction. The CounterACT program is administered by NINDS but spans the NIH (NEI, NIAID, NIAMS, NICHD, NIEHS, NIGMS, and NINDS). The program targets diagnostics and therapies for civilian victims, particularly those therapies and diagnostics that can be applied after a chemical attack or accident. Research funds are translational and highly targeted. Funds for the CounterACT program total $50M per year and are appropriated by the NIH Office of the Director. Partnerships across agencies and between investigators are actively encouraged. The portfolio consists of 30 U01 and U44 grants, four U54 grants, four inter-Agency Agreements, and two contracts. Grants are made for a period of 3 years and are milestone gated. The expected outcome of each grant is a lead compound or a validated model for screening relevant therapeutics.

Every April (this is the 2nd year of the program), all principle investigators (PIs) under the program meet and share the results of their research. PIs submit a list of the year's milestones and their progress against these milestones. After the meeting, all of the program directors who manage the CounterACT grants meet and review the milestones and then decide whether specific projects should be continued. In 2008, a satellite meeting for SBIR grantees who are developing portable EEGs and EMS technicians was held.

Accomplishments

- 40 peer reviewed articles cite support from CounterACT.
- Several lead compounds have been identified (midazolam IM and galantamine for nerve agents and cobinamide for cyanide exposure). These are advancing through clinical trials.
- Other lead compounds are being actively investigated.
- Diagnostic prototypes to detect non-convulsive seizures and chemicals in biological matrices are advancing toward testing. The goal is a rugged, field EEG instrument. This is progressing well.
- Ideas are shared at the Annual CounterACT Research Symposium Meeting. This has forged alliances. Some U01/U44 investigators have joined recently to propose U54 collaborations.
- Held seizure detection technology review on 4/17/2008. Beginning in Sept 2006, three U44 applications related to portable seizure detection were funded through this program to the following small business concerns: Clevemed, Persyst, and Infinite Biomedical Technology. As part of their year 2 milestones, each of the groups were required to participate in a technology demonstration to coincide with the 2008 April CounterACT Symposium. An additional group, Ripple LLC, which is supported through an Army Phase 2 SBIR to develop a portable seizure detection monitor (MRMC A05-162, Field Deployable Electroencephalogram for Assessing Nonconvulsive Seizures) was also invited to participate. Progress was evaluated and ideas shared.

Strengths

- Network of excellent investigators built who are engaged in monitored and targeted translational research

- Plays to NINDS strength in epilepsy, stroke, pulmonary disease, neurodegeneration, and toxicology

- Collaborations are encouraged. Annual meeting appears to be a productive forum for interchange of ideas amongst key stakeholders. Rigorous attention to milestone triggered downstream funding is part of the program.

Challenges

- The program commitment is 5 years and this is less time than it takes to develop a drug or diagnostic. Bridge funding will be required.

- The nerve gas toxins, in particular, cannot be handled in most academic labs. National and regional centers need to be established where pharmacology studies can be conducted with these very toxic agents.

- This is inherently a very difficult area, particularly for nerve gas toxins in that, once they irreversibly interact with acetyl cholinesterase, the injury is not easily reversed. Most approaches involve scavengers (oximes) and anticonvulsants. If we assume that a civilian attack is unanticipated, the window of opportunity for effective therapy may be smaller than the likely response time.

Recommendations

- Support and coordination of testing facilities, particularly in the area of neurotoxins, is a must.

- Grant reviews should rigorously reflect the stated profiles (ease of administration, preferably after insult, and effective within the likely window of opportunity).

- Continue the annual meetings coupled with milestone review. Continue and emphasize collaborations across labs.

- Translational research requires access to a toolkit that is essential for downstream success. Academic investigators generally do not have either a full awareness of the strategic use of or access to these tools. If drugs and not just interesting compounds are to be developed, then an integrated approach to reduction of manageable risk at an early stage is required. (Examples: medicinal chemistry, microsomal or hepatocyte oxidation, informatics, animal models, whole animal PK, cellular safety, formulation support).

Responses to Standard Questions

Is the project truly translational and does it meet its stated objectives? This program is inherently translational. The program is nascent, but it appears to be meeting the stated objectives.

Is the program consistent with the NINDS mission? This is an inter-agency program that is coordinated by NINDS. The program takes advantage of NINDS strengths and experience. To the degree that seizure, stroke, and mitochondrial collapse are woven into the NINDS fabric, this project certainly does have links into NINDS.

What aspects of the program are particularly strong? Weak? What strengths can be adapted by other areas? See strengths, challenges, and recommendations. The idea of an annual meeting where collaborations are encouraged and information is exchanged is a real strength.

Objectives: are they appropriate and well defined? Are the milestones measurable? The program objectives are strict and narrow, which is appropriate for this effort.
Is the program impactful? Is it practical? The program has generated lead compounds and new collaborations so it is impactful. From a practical point of view, the window of opportunity for organophosphate irreversible inhibition of AChE is narrow and we worry that post-challenge therapy will not generally be given in time for successful intervention.

Is the program cost and time effective? We don't know yet. It appears so, at this point.

Is the program integrated across appropriate fields and are the individuals from the other relevant fields engaged and able to support? Does it engage the right people and technologies? See comments re in vivo testing

Chapter 10. SMA Project

Introduction. Spinal Muscular Atrophy (SMA) was identified as a NINDS Focus Disease. The SMA Project intends to turn chemical leads into a drug for the treatment of spinal muscular atrophy (SMA) through the creation of a virtual drug discovery and development company that uses industry standard strategy and methodology. This is a new approach to translational research at NINDS and, as such, is an experiment. SMA was selected for this experiment because the mechanism of the disease is understood, because there are tractable strategies for protein compensation, and because assays exist that can be used in the discovery and development process. The project began in 2003 and is still very active.

The SMA project is a novel experiment within NINDS. It is unlike any translational grant program. The project is multi-year and is guided by a development team and a steering committee. Project monitoring and other support is provided through SAIC, which is the primary contractor for the program. Jill Heemskerk of NINDS provides consistent and detailed management of the project. The project is guided by experts from industry, academia, from the FDA, and from NINDS. Subcontractors provide medicinal chemistry, in vitro assays, pharmacology, toxicology, informatics and in vivo pharmacology. PTC Therapeutics and two SMA family groups have collaborated. The SMA project is managed by NINDS with active day-to-day participation of a Lead Development team that is chaired by John McCall. A Steering Committee that is chaired by Robert Pacifici provides broad, high level guidance and goal-setting. Jill Heemskerk is the NINDS executive sponsor for this program.

SMA is a progressive degenerative motor neuron disease with a well-understood cause. The SMN1 gene is deficient. Prompting the related SMN2 gene to produce a functional protein is a logical approach to new therapies. Indoprofen increased smn2 expression. The project's goal was, starting with indoprofen, create a safe and effective drug that has good brain penetration. The multi-year project has progressed through the activities of a virtual company that has medicinal chemistry, ADMET, pharmacology, and legal resources. This network is both academic and commercial. A candidate that increases protein production through a translational read through mechanism is entering the pre-IND stage. New screening and early medicinal chemistry have discovered hits that increase protein production through a splice and a promoter mechanism.

Responses to Standard Questions

Is the project truly translational and does it meet its stated objectives? The stated objective is the discovery and development of effective therapies for spinal muscular atrophy. The project appears to be on track. The measures of this are:

- Mechanism of action of indoprofen and its analogs identified (read through);
- Two patent filings;
- Candidate for development and backups identified (read through mechanism);
- Promoter mechanism hits identified;

- Project that is focusing on compounds that work through a splice mechanism started.

Is the program consistent with the NINDS mission? The mission of translational research is the discovery and development of new and effective therapies and devices. Inherently, the SMA project is consistent with these goals.

Objectives: are they appropriate and well defined? Are the milestones measurable? The target candidate profile for this project is a drug that increases protein expression by smn2 in the brain, which is well tolerated, and which can be given per oral. Patients which have the smn1 defect but who have higher levels of smn2 have milder disease. Therefore, compounds that meet the TCP should be effective in humans. This project began with a hit (indoprofen) which did not enter brain and which had a significant safety issue. Through milestone driven research, a family of compounds that works via translational read-through is at the candidate stage. The classic drug discovery and development milestones were addressed and met during this process. High throughput screening has identified new scaffolds that work, respectively, through splice correction and promoter activation. These provide a backup for the lead candidates.

Is the program impactful? Is it practical? Impact can be direct or indirect (downstream). In terms of direct effect, the program is achieving its stated objective of discovering new therapies for SMA. In terms of indirect effects, the program has highlighted those services that are required for an integrated and successful drug discovery and development program. These lessons learned contributed to the Institute's decision to establish a neurotherapeutics medicinal chemistry resource that can be accessed by NINDS investigators. In addition to the translational read-through activity for which these compounds were optimized, the SMA team identified a second activity of a subset of these compounds in a reporter assay designed to detect activity of the promoter of the EAAT2 gene. EAAT2 is a glutamate transporter that allows uptake of extracellular glutamate and is thus thought to be potentially neuroprotective against glutamate excitotoxic insults linked to stroke, ALS, and other neurodegenerative diseases. The translational read-through activity of these compounds has potential usefulness for hundreds of genetic diseases caused by stop codon mutations. The team obtained preliminary data suggesting that one of these compounds promotes translational read through of a stop codon mutation in the MECP2 gene, which causes Rett syndrome.

Is the program cost and time effective? The expenditures to candidate stage have been significantly less than pharma reports for carrying a compound to candidate stage. By creating a virtual company, most of the personnel have been under contract so NINDS has paid only for the time applied to this project. In terms of speed, pharma reports that hit to lead takes about 12 months, and lead optimization takes 18-24 months. This project identified a candidate at the end of lead optimization in a little over 3 years so the speed is within the area typically taken by pharma for these steps. Extrapolation from a solitary example is problematic, however, and there's no reason to believe that the next project would follow the same time and cost patterns shown by the SMA project.

Is the program integrated across appropriate fields and are the individuals from the other relevant fields engaged and able to support? Does it engage the right people and technologies? The project has engaged experienced pharmaceutical drug hunters on this project in order to create a "company" that employs an integrated, risk minimizing approach to discovery and development

Strengths

- An integrated research project that follows drug discovery and development / risk reduction strategies. Program has assembled medicinal chemistry, informatics, project management, biochemistry, pharmacology, and pharmacokinetic resources;

- Cost is low relative to industry standard and speed is similar to the industry for hit-to-lead and lead optimization;

- Alternate mechanism for funding and monitoring subcontracts;

- Access to industry seasoned advisors and focus on drug discovery and development.

Challenges

- Some key assays have been run in academic labs which often view this work as a side project. Primary and secondary assays were not bulletproof when the project started;

- Contract negotiation can be cumbersome and slow;

- Many of the resources were identified and incorporated on the fly. Subsequent projects which follow this model will be able to build on the lessons learned from this first endeavor;

- Team does not have free access to all assays due to restrictions placed on use for drug discovery and development by companies, universities and foundations. This illustrates a paradox in a field where the goal should be development of a therapeutic;

- The clinical situation for potential therapeutics remains unclear as no drug has undergone successful clinical trial. The team is left with a target candidate profile that requires access to brain, the ability to increase expression of smn2, decent PK, and safety. On the other hand, the knowledge that disease severity is inversely proportional to smn2 levels does support the candidate profile as reasonable.

Recommendations

- This project has illustrated that access to basic drug discovery and development tools is essential. The normal contract process is slow and tedious and, for reasons of simplicity, favors large multi-service providers rather than smaller, single service providers which may both lower cost and yield higher competence. We imagine two ways to simplify the contract system. NINDS could elect to provide key services to selected investigators. These services could be internal to NINDS or available through a contract. Examples of such services include microsomal and/or hepatocyte in vitro metabolism, permeability, rodent PK, molecular modeling, medicinal chemistry, and informatics. The second possibility involves identification of a primary contractor who subs out services without going through the normal bid process.

- Examine requirement for negotiated pricing before contract award and task award. This is a major hurdle and is problematic for many potential vendors, having the opposite effect of its intent: scaring away competition rather than stimulating competition.

- Develop reliable secondary assays before launch of major expense.

- While key personnel are still with the project, it should be evaluated for process. What worked well? What can be extrapolated to the next project? How can these lesson learned be captured? We suggest a kind of bible that addresses the creation of a NINDS virtual company.

Chapter 11. Translational Research in the Neural Prosthesis Program

Introduction. Neural prostheses are devices that use electrical stimulation and / or electrical recording of the nervous system to alleviate the burden of neurological injury or disease. They are most often fully implanted devices, akin to cardiac pacemakers, that restore function following disease or injury, by alleviation of symptoms rather than by treatment of the underlying pathology. Examples include cochlear implants to restore hearing to the deaf, spinal cord stimulators to treat chronic pain, and deep brain stimulators to treat movement disorders. “With the financial success of device companies, a quicker and cheaper path to approval, and strong [physician] incentives for implementation, the pace of development [of neurological devices] is likely to accelerate” [3].

Strengths. The NIH Neural Prosthesis Program (NPP) has been a model of successful translational research. The NPP supported the preclinical development and translation of several devices now in clinical practice. In addition to supporting early implementation of devices in humans, the Neural Prosthesis Program has generated innovative technologies that enable neuroscience research (e.g., high-density multi-channel electrode arrays), as well as fundamental knowledge that enables new clinical applications (e.g., electrochemistry of stimulating electrodes and thresholds for tissue damage).

Due to high costs and regulatory complexity, eventual clinical impact likely requires the transfer of knowledge and technology from the academic research lab to a commercial entity for product development and deployment [3]. Indeed, ALL of the implanted neural prosthetic devices using electrical stimulation to restore function that are presently on the U.S. market emerged from academic research labs. The strong participation of industry in the NPP is reflected in the continued strong support of SBIR grants in the NPP portfolio and the participation of industrial scientists in peer review.

The NPP has clearly demonstrated that “the intellectual riches flooding from biomedical discovery and development can be converted into practical riches from which humanity can benefit” [2], and changes to the Program in the past decade have created opportunities to enhance the translational success of the research and development supported by the program.

Challenges. Historically, the NPP used contract mechanisms (N01) to support long-term research and development projects, as well as early feasibility demonstrations in human subjects. These contracts have now been largely supplanted by traditional investigator-initiated research grants (R21 and R01). This transition was enabled to some degree by the advent of the Bioengineering Research Grant (BRG), which has review criteria consistent with developmental milestones, not traditional hypotheses-driven exploration, and the Bioengineering Research Partnership (BRP), which provides larger-scale support for multi-institutional collaborative development programs.

The current portfolio of NPP grants appears to have less emphasis on translational work, while this was a clear hallmark of the contract program. Further, traditional grant mechanisms have measures of success (e.g., publications) that may be inconsistent with true progress in translational of neural prostheses, e.g., number of patients impacted. Further, the timeframes of traditional grant mechanisms may be inconsistent with the pace of translation and implementation of neural prostheses, which often

requires navigating several layers of regulation for device fabrication (e.g., establishing quality systems, Good Manufacturing Practice, Good Laboratory Practice), and testing (e.g., IRB, FDA). Innovative mechanisms of support are required to continue to advance the field and recapitulate the success of the contract program in translational research.

There are somewhat different concerns when considering translation of a device as compared to translation of a drug. While the early translation of a drug is often focused on toxicity, this is rarely the case for a device. There are indeed safety concerns for devices, but the passive biocompatibility of the materials used in modern devices is well established and non-damaging parameters of stimulation have, in many instances been established. Thus, the emphasis of early device evaluation and translation is often to determine clinical feasibility – that is, does what was learned in preclinical animal evaluations translate to persons with the target disease or disorder. The objective of these efforts is often to bridge the "valley of death" between preclinical proof of concept and subsequent demonstration of clinical feasibility [1].

Recommendations

- Remove administrative barriers to early human feasibility testing, and allow peer review to determine the appropriateness of human studies supported by the R21 and K01 mechanisms. The objective of these changes is to "accelerate the development of new therapies by allowing more rapid testing in actual use" [3].
    - The restriction from conducting human subjects research in NINDS-sponsored R21 grants, which might include early feasibility studies in human subjects, is a barrier to translational research.
    - Similarly, the restriction from conducting "patient-oriented" research within the K01 award is a barrier to translational research.

- Remove the restriction on Cooperative Development Agreements (CDAs) "to activities that directly focus on preclinical therapeutics and device development that is required before clinical testing." The exclusion of research that requires an IDE from that which is defined as "translational" should be removed to enable translational research in neural prostheses, which often requires an IDE for early human feasibility testing.

- Expand the Cooperative Development Agreements program (U01, U54) to include expressly translational studies of neural prostheses. Such efforts require resources to seek, receive and support regulatory approval (e.g., IRB, IDE); to conduct device fabrication under highly controlled conditions (e.g., Quality Systems, Good Manufacturing Practices); to conduct preclinical evaluations of safety and efficacy; and to conduct early clinical feasibility testing in humans. It is anticipated that this support at the early phase of such efforts will result in an acceleration of translation and will increase the likelihood of success.

- Explore the feasibility of supporting, perhaps in partnership with industry, a national resource for fabrication of hardware (electrodes, implantable pulse generators) for use in neural prostheses. Design, development, and appropriate testing of hardware intended to function reliably inside the human body for decades is an expensive and time-consuming process. Presently, new applications of neural prostheses often require re-development of new hardware

even when the objective is to test clinical feasibility, and this is an inefficient duplication of effort and resources. Potentials models for such a resource include the National Nanotechnology Resource at Cornell supported by the NSF, the Center for Neural Communication Technology at the University of Michigan supported by an NIBIB P41, and the NCI's Rapid Access to Intervention Development program.

- Increase the representation of clinicians on the Neurotechnology (NT) study section. This new study section emerged from two long-running special emphasis panels that reviewed, among others, large numbers of proposals on neural prostheses. The panel, however, consists primarily of technologists, and the resulting portfolio of grants is heavily weighted toward technology development and early *in vitro* or *in vivo* evaluations. Stronger representation of clinicians, especially physicians who are treating patients and applying devices, will increases the clinical relevance of the research portfolio and provide more appropriate review of translational research involving human subjects.

- Increase the commitment to the second broad challenge of translational research, which is "ensuring that new treatments and research knowledge actually reach the patients or populations for whom they are intended" [4]. Although not an element of the biomedical research portfolio, addressing this challenge is a critical component of the continued success of "production of a promising new treatment that can be used clinically or commercially" [4]. Indeed many physicians are not exposed to the potential benefits of neural prosthetics, and even when considering the most successful device – epidural spinal cord stimulation for chronic pain – the penetration is exceedingly small. Therefore, efforts in clinician training and education that include neural prostheses are required to ensure the continued success of these promising therapies.

References

[1] Butler D. Crossing the valley of death. *Nature* 453:840-842, 2008.

[2] Campbell P. To thwart disease, apply now. *Nature* 453:823, 2008.

[3] Johnston SC, Hauser SL. Neurology and medical devices. *Annals of Neurology* 60:11A-12A, 2006.

[4] Woolf SH. The meaning of translational research and why it matters. *JAMA* 299:211-213, 2008.

Chapter 12. Muscular Dystrophy (Translational Research in Muscular Dystrophy (U01) and Exploratory/Developmental Program for Translational Research in Muscular Dystrophy (R21)

Introduction. This program is designed to implement a pre-clinical translational research program that encompasses a variety of mechanistic targets for the muscular dystrophies. The program should identify and develop new and more effective treatments. Implicitly, the program must be able to evaluate the value of proposed therapies. The program is based on the NINDS Cooperative and Exploratory/Developmental Programs in Translational Research and uses the same programmatic requirements and review process. The focus is preclinical. Basic research is not supported. Projects usually include an assay that is relevant to the disease or candidate therapeutic approaches. Technologies such as high throughput screening, functional genomics, and medicinal chemistry are supported through this program. The projects are supported through U01 and R21 grants. U54 (multi-component translational research projects) and U24 (translational research and resource center) grants are encouraged. Projects which are submitted under this program must include an overall plan for therapy development.

This program was initiated in November, 2005 and is scheduled to continue through January, 2009. Total investment through 2007 (including funding by partners) totaled $862K for 5 projects.

This cooperative agreement program is a partnership between NINDS and the National Institute of Arthritis and Musculoskeletal and Sin Diseases.

Strengths. Although the program supports only U01 cooperative grants, its existence has attracted investigators to the U24 and U54 mechanisms. Two U54s in the muscular dystrophy area (year 1 costs $4.853M) were awarded through the broader program in 2007 and one U24 is likely to be paid in 2008.

Concerns

- Communication of the program to potential applicants has been a challenge. This is a relatively young program that is just being recognized by researchers who are not necessarily muscle specialists but who may be able to make contributions to the dystrophies

- Changing the mindset of academic investigators to milestone driven translational research orientation has been a challenge.

- Have investigators been responsive to time lines and milestones? Is this rigorously reviewed at NINDS for gated funding decisions?

Recommendations

- Include under the program all mechanisms for translational research (i.e., include U24 and U54 mechanisms)

- Rigorously adhere to definition of translational research. Program results should be actionable: either terminate further research or provide guidance on how to continue in meaningful way. Study design and conduct should foster an understanding of positive or negative results.

- Specifically call for and prioritize grants that address known gaps in the field. E.g., does a proposal address the critical early development/funding gap between academic research and more de-risked late stage research?

- If a proposal addresses multiple diseases (even outside of MD), it eventually will have more traction for later funding by industry. This should net a higher priority.

- Encourage industrial participation in the review process.

- Provide drug discovery and development education (See Outreach section). Investigators must understand the drug discovery and development process, milestone gated research, and risk mitigation strategies.

- Drug discovery and development is a highly integrated process that requires reduction of manageable risk at an early stage. Investigators should be aware of and have access to the various tools that are standard in strategically grounded drug discovery and development (e.g., medicinal chemistry, tier 1 and tier 2 ADME tools, informatics, cellular and in vivo safety tools, formulation resources, etc).

- Don't disregard epidemiology and methodology development studies that have somewhat succumbed to novel targets research.

- Positive and negative results should be available to the scientific community. If the study results are not published, they should be available. This implies some form of web based project summary that is searchable and accessible to the community. Note that this suggestion applies to other chapters.

Chapter 13. Medicinal Chemistry Initiative

We understand that NINDS intends to contract a small group of medicinal chemists (4 to 8) who will be employed on NINDS grant projects. We have recommendations on how this resource can be managed.

- NINDS should employ one or more experienced medicinal chemists to provide guidance and oversight to the contract resource. This individual could be a medicinal chemist recently retired from a pharmaceutical or biotechnology company, who would be familiar with both the demands of a lead optimization program and coordinating with outside chemists who may be doing the actual lab work. This individual would help triage requests for medicinal chemistry feasibility, monitor progress, and summarize activities to the agency.

- NINDS could contract with a U.S.-based chemistry provider, or with chemistry providers in other countries where expertise exists and costs are lower – the latter are in Eastern Europe, India, and China.

- The chemistry resource can be used to synthesize standard compounds for evaluation, compounds of interest from the literature, or compounds that support structure-activity relationship (SAR) studies. In the case of SAR, 1-2 chemists per project could support hit-to-lead activities. At least two chemists should be used to support lead optimization. We define hit-to-lead as activities that confirm the existence of SAR, and that generates scaffolds that are potent, selective, and free enough from potential reactivities or liabilities to move to lead optimization. During lead optimization, the multiple rounds of analogue production in small libraries of 20-50 compounds are made around selected scaffolds to produce compounds that meet the target candidate profile.

- Projects that are candidates for medicinal chemistry support should be rigorously evaluated by an external panel of industry and academic medicinal chemists before being accepted, and equally rigorously followed for progress and halted if no progress against milestones is achieved over six months or more. Before being adopted for lead optimization, the investigator should have good primary and secondary assays in which the lead is active at a reasonable level, typically at least low micromolar. The investigator should have evidence of SAR. Often, this will result from a purchase strategy. The oversight medicinal chemist can help identify compounds that can be purchased that are similar to the hit that the investigator has identified already. We should wait some reasonable amount of time so that a number of projects can be considered for resourcing. Resourcing could begin with a subset of the total that could be expanded when one or more projects graduates to lead optimization.

- Progress can be monitored by projects that move through accepted milestones and by patent activity.

Chapter 14. Cooperative Agreement Program in Translational Research

Introduction. The scope of this program is restricted to activities that directly focus on pre-clinical therapeutics and device development that is required before clinical testing. Mechanistic or basic studies are not supported nor are clinical trials. The cooperative agreement program began in 2002. The NINDS total investment in this area has increased substantially during the life of the program. Translational research funded under these agreements can include the following:

- Characterization of new assays, models, tools and technologies that facilitate translational research. These efforts are usually funded by R21 grants. The definition of translational hinges on whether the project will lead directly to a therapy development project if it is successful

- Drug discovery and development through pre-IND work

- Device development through the pre-IDE phase.

The distribution of effort in 2007 for U01, U54, and U44 grants (total spend = $17.596M) is summarized in the following table. Clearly, these grants are heavily weighted to drug discovery and development.

Assay Development	**Animal Model Development**	**Animal Model Evaluation**	**Rational Drug Design**	**Library Screening**
0	**1**	**1**	**2**	**3**
Validation in a Cell Model	**Animal Efficacy Study**	**Vector Development for Gene Therapy**	**Med Chem/ Lead Optimization**	**Pharmacokinetics and toxicity**
2	**19**	**6**	**4**	**14**

Translational research is intrinsically interdisciplinary and milestone gated. It proceeds along a path with measurable go/no go hurdles that must be crossed in order to proceed to the next milestone. The program is seeking collaborative arrangements between academics, drug, and device companies with a spirit of sharing in the tasks, risks, and rewards. The cooperative program in translational research is funded through U01, U54, and U24 grants that are intended to catalyze the development of partnerships between investigators and centers. Since intellectual property is governed by the Bayh Dole Act, investigators and their institutions can secure intellectual property under this and other NINDS programs

Cooperative agreements are funded through R21, U01, U24, and U54 grants. The table below describes these grants and the 2007 agency expenditures which total $25.730M.

Mechanism	Description	2007 Dollars
R21	Exploratory / developmental grants that are translational in nature. The total project period	$6.248M

	cannot exceed 2 years. The median cost per year for the 67 projects supported to date is $173K	
U01	Single component translational research project. Project period cannot exceed 5 years. U01s support the majority of programs in this area. The median cost per year per project is $585K	$11.229M
U24	Translational research center grant. This provides infrastructure support for multi-component grants	$2.168M
U54	Multi-component translational research project	$6.085M

Milestones are reviewed by NINDS staff on an annual basis to determine future funding. This is done through the Translational Research Oversight Committee (TROC). The process by which NINDS manages milestones has evolved since the start of the program. In August of 2007, the institute set up the TROC to review and approve milestones for all of the awards. Before that, milestone review was entirely managed by the individual program directors who managed cooperative agreements. (Cooperative agreements are assigned to program directors according to disease area.) The institute has also become far more proactive in helping grant applicants develop appropriate milestones and a product development plan. For these reasons, the first few awards made under the program are probably not representative of the current generation of projects.

A Steering Committee meets annually to make strategic decisions on goals and research implementation for U54 and U24 mechanisms. This includes establishment of shared resources and development of collaborations.

Achievements

- INDs have been filed as a result of these grants (see table at end of this chapter)
    - Two INDS for the use of viral vectors to treat PD
    - One IND for treating muscular dystrophy

- Multiple projects are proceeding successfully through the target milestones, all of which are translational in nature.

Strengths

- Milestone gated research where success is both monitored and rewarded

- Focus on practical endpoints

- Fills gap between basic science and clinical trials.

- Projects are more favorably reviewed than when they competed directly with blue sky or hypothesis oriented grants

- Pre-application consultation with NINDS personnel

- Review criteria stated. Reviewers instructed on purpose of program

- Investigators required to discuss overall plan, milestones, timings, significance.

- Procedures have evolved to meet program needs

Challenges

- Review culture favors hypothesis driven, basic research rather than translational research. By pooling translational grants for review purposes, this problem is blunted.
- Many PIs do not understand the drug and device discovery and development process and its requirement for milestone gated research and risk minimization strategies.

- The existing culture is not inherently collaborative.

- Based on industry average success figures, the program has a low success rate (see below).

- Procedures were changed to ensure final report from investigators who sometimes failed to provide this information.

Recommendations

- PIs should have easy access to information that facilitates an in depth understanding of the drug discovery and development process. This can include written material and short courses that the NINDS can provide.

- Drug discovery and development requires a variety of resources that many investigators lack. The agency should either make available through internal resource or contract or, at a minimum, point out the kinds of studies that are important and where they can be contracted (and at what cost). Examples include medicinal chemistry, microsomal oxidation, Cytochrome P450 inhibition, physical chemistry measures, among others.

- Require collaborations where they appear to increase the probability of success with particular programs.

- Milestone review must be rigorous. Consider enlisting industry trained discovery and development experts for the milestone review process. Investigators will need to accept project termination as an acceptable outcome.

- Drug discovery and development is a dynamic process and the state of the art can change after a proposal is submitted and funded. Milestones may need updating periodically. In addition to achieving milestones, the relevance of existing milestones should be reviewed annually. Does the project still complement on-going activity in pharma, as the program intends. External input may be valuable for project refinement.

- NINDS cost less but requires more attempts to achieve success. IND numbers that are directly derivative of NINDS funding may not be a crisp measure of success. Impact on IND filing that is enabling is important.

Responses to Standard Questions

Is the project truly translational and does it meet its stated objectives? Reasonably. Perhaps we should be somewhat surprised that the program has not brought more projects to an IND stage given the number of shots on goal. Pharma runs, on average about 6.5 projects to produce one IND. By this standard, the program has a low yield. On the other hand, the expenditures per project in the NINDS program are FAR less than that invested by industry on a per project basis. This inefficiency may also be a function of the nascent status of drug/device discovery and development in academia, the newness of definitive gating milestones rather loose specific aims. Also, NINDS takes on projects that industry is not funding and these are probably inherently risky.

Is the program consistent with the NINDS mission? Yes

What aspects of the program are particularly strong? Weak? What strengths can be adapted by other areas? See above

Objectives: are they appropriate and well defined? Are the milestones measurable? Yes. This is a fundamental strength of this program.
Is the program impactful? Is it practical? Very practical and has demonstrated impact that will hopefully increase with increasing sophistication by the academic community.

Is the program cost and time effective? The total expenditures on this program are about $26M. Longman has recently published "The 100M Dollar IND" that estimates the cost of a single IND, based on cost of capital and risk, at $100M. Excluding cost of capital reduces the total to about $65M. By this measure, the program is cost effective. In terms of time, it takes about 4 years in industry to move a project from screen development to IND. The NINDS program has been in place for about 6 years. Again, the program appears to be time efficient. However, we would hope to see a number of INDS that reflect the increased spend coming to fruition in the next few years.

Is the program integrated across appropriate fields and are the individuals from the other relevant fields engaged and able to support? Does it engage the right people and technologies? This is very difficult to assess since success (IND/IDE) may only retrospectively reinforce the choice of people and technologies. The range of expertise required includes medicinal chemistry (small molecule), molecular biological (biologics and gene transfer), pharmacology, toxicological, animal modeling, statistical, regulatory and intellectual property.

Chapter 15. Anticonvulsant Screening Program (ASP)

Background. The ASP was established in 1975 as a component of a larger program known as the Antiepileptic Drug Development (ADD) Program, which began in the mid 1960s. At its peak, the ADD Program had approximately 50 staff and incorporated both intramural and extramural activities. The intramural side had an inpatient epilepsy monitoring unit and basic science activities. The extramural component consisted of a clinical trials section and preclinical screening activities of the ASP.

Today the ASP is under the leadership of Jim Stables, MS Admin., R.Ph. with an internal staff of four. The ASP has screened, evaluated and cataloged structural and corresponding biological information for over 26,000 small molecules in a searchable computer format linking both biological and structural information.

Researchers from academia, industry and government agencies send promising compounds to the ASP for preclinical efficacy and optimization testing in animal seizure models. The studies are performed on a blinded basis via contract at the University of Utah with Dr. Steve White acting as the principle investigator. Initial hits are characterized by generating basic toxicological and biological activity profiles. Approximately 650 compounds will be screened this year: approximately 66% from academia, 34% from industry. Currently there are over 470 participants worldwide who periodically submit compounds to the ASP for pharmacological evaluation – half are outside the U.S. The entire budget for ASP in 2008 is $2.4 million.

The ASP has an excellent track record for success in a disease area that remains a high unmet medical need for an estimated worldwide prevalence of 50 million people. Approximately 25-30 percent of epilepsy patients remain resistant to therapeutic interventions. Currently, there are no treatments to prevent epilepsy or to intervene in the disease process following brain trauma or other triggering events.

Central to the success of the program is the strategic management of Intellectual Property, which is held by the researchers who come to the ASP with a promising compound. The data generated by ASP and other proprietary information are protected under confidentiality agreements in order to preserve strategic requirements necessary for successful long-term drug development required for FDA approval and marketing. Chemical structures are considered proprietary unless otherwise specified by the supplier or through open publication. Contracted personnel are blinded to both the structure and the source of submitted compounds.

There are eight ASP-delineated compounds currently in various stages of clinical development in the U.S.:

- Lacosamide (Vimpat) – UCB; Preregistration
- Carisbamate – RWJ; Phase III
- Retigabine – Valeant, Phase III
- YKP3089 (Epilepsy & Anxiety) - SK Bio-Pharm; Phase II
- DP-VPA - D-Pharm; Phase II (Israel)
- Valrocemide - Shire/Univ of Jerusalem; Phase I
- Fluorofelbamate – Medpointe; Phase I
- Add 348059 - J&J;

Critical Review. As the longest continually supported translational activity at the NINDS the ASP has demonstrated remarkable success in translating basic research into improved anticonvulsant therapies. ASP activities have led to hundreds of peer reviewed scientific papers, investigator initiated grant applications, validation of new assays, screening methods and models, successful creation of international public-private partnerships, numerous clinical trials, novel trial designs, and several marketed products.

Historically, two important animal models have driven drug discovery and development in Epilepsy: Maximal Electroshock Seizure (MES) and subcutaneous Pentylenetetrazol (Metrazol) Seizure Test (scPTZ). MES is a model for generalized tonic -clonic seizures (generalized seizure effecting entire brain and body). It is highly reproducible with consistent endpoints. The behavioral and electrographic seizures generated in this model are consistent with the human disorder. The scPTZ model as employed by ASP is a model that assesses clonic convulsions (muscle contractions and relaxations) as an end point. The interpretation is that drug candidates suppressing clonic convulsions may possess activity against both myoclonus (generalized seizures with muscle jerks) and absence epilepsy (lapse of awareness/staring into space) in humans. With some exceptions, the pharmacological profile of the scPTZ seizure model is consistent with the human condition. These two models remain as the primary screening tool for the ASP, and this needs to be questioned on the premise that “old models discover old drugs.”

The goals for epilepsy research and development have changed dramatically in the past few years. Looking forward, the critical goals for epilepsy are threefold: 1. to control drug resistant seizures; 2. to abort epileptogenesis; 3. to cure epilepsy. Building on a successful 33 year track record, the ASP has begun to approach these goals, e.g. through the use of lamotrogine-resistant amygdala kindled rats. However, this model is better described as a lamotrogine tolerance model, not a drug resistance model. Furthermore, such models are employed only as secondary or, more often, tertiary in the screening cascade.

The ASP is now faced with a critical decision in allocating its resources. The existing program that relies on MES and scPTZ models is an important resource for academic laboratories and for many foreign institutions. From this viewpoint the program needs to maintain this service. However, to meet the critical future needs of epilepsy therapy a different strategy is needed.

Recommendations

- The ASP should focus on Epilepsy (rather than diluting efforts by employing ancillary models, e.g. pain models), diminish the focus on generating more prototype anticonvulsants and instead favor the discovery of candidate anti-epileptic drugs that fight drug-resistance and/or the disease itself.

- A small and highly knowledgeable Epilepsy Advisory Board needs to be established to direct the future goals of the ASP. This Board needs to include representation from pharmaceutical companies committed to epilepsy drug discovery and development. This Board needs to set priorities for the ASP seeking to maintain the screening service and, importantly, to implement processes that address the future needs for therapeutics in epilepsy.

- Alignment with internal and external NINDS funding mechanisms will be important in developing new animal seizure models for epileptogenesis. One important goal is to develop a reliable genetic model that produces the symptoms of epilepsy on a reliable time path. Other models of epileptogenesis will be critical, e.g., two hit models.

Chapter 16. CINAPS (Committee to Identify Neuroprotective Agents for Parkinson's) Drug Evaluation Contract

Responses to Standard Questions

What are the needs in the area? Parkinson's Disease (PD) is a devastating, progressive neurodegenerative disorder and represents a significant unmet medical need. While there are several types of palliative drugs available to alleviate the symptoms of the disease, there are no drugs that stop or attenuate the progression of the disease and are able to prevent patients from becoming severely disabled. Goals for the NINDS in this area include:

- Accelerate research on PD disease mechanisms to
    - Identify intervention points for future therapeutics (drug targets)
    - Identify predictive animal models for PD
    - Identify biomarkers to monitor disease progression and drug efficacy

- Promote translational research to generate drug candidates for effective disease-modifying drugs

- Promote decisive clinical studies with promising drug candidates, in particular for disease-modifying/curative drugs

What are the most significant achievements by NINDS in the area in recent years? The PD field has seen exciting progress and break-through discoveries in the understanding of disease-mechanisms and the establishment of investigator networks, who can execute decisive clinical trials. Despite this progress no effective disease-modifying therapy has emerged as yet. Key NINDS achievements include:

- Established effective mechanisms for clinical testing of drug candidates (CINAPS, NET-PD).

- Provided support for research on PD mechanisms, which, together with the support of foundations and other granting agencies, have led to substantial break-through progress in this area.

- Initiated support for animal model testing of drug candidates at RTI International.

- Supported research on biomarkers, including imaging biomarkers which provide reasonably effective in vivo monitoring of disease progression.

- Increased awareness and direct funding for PD through effective public relations work and interactions with foundations.

Which are the most significant existing problems in the area?

- None of the clinical trials with candidates for disease-modifying drugs has been successful.

- Existing animal models have not been predictive for clinical success.

- Research on disease mechanisms has identified a large number of putative drug targets for future disease-modifying drugs. The number of these putative targets vastly exceeds the capacity clinical trials to select among them by clinical testing of drug candidates.

What are the prevailing opinions in the expert community on how to address the issues? There appears to be no easy consensus among experts. Two diverse opinions prevail:

- Focus funding and efforts on clinical trials, move as many drug candidates into decisive clinical studies as possible, de-emphasize animal model data and target validation studies in animals.

- Focus funding and efforts on PD disease mechanisms, in order to identify therapeutic intervention points for future drug candidates with a high probability of success in clinical studies and, additionally, to generate animal models that are predictive of clinical success.

The two prevailing opinions appear to be mutually exclusive. They are exclusive in a situation of limited and fixed funding, since they propose preferential allocation of a fixed amount of funds to either research on disease-mechanisms or clinical drug trials. They are not mutually exclusive in a situation of abundant funding, since they can succeed independently. For NINDS, this could be an opportunity to ensure an appropriate balance between the two for the programs funded.

Both prevailing opinions emphasize that translational research, narrowly defined as preclinical drug development between target identification and selection of an IND-stage drug candidate is not the key issue for PD at this time. In absence of drug targets and therapeutic intervention points with a reasonable degree of validation it does not make sense to generate drug candidates for clinical studies.

Both prevailing opinions imply animal models as a most significant issue. The preclinical testing facility established at RTI International provides broad access to animal models, which, however, were not predictive in the past.

Recommendations. We have several specific proposals that address the key needs and issues.

- The two prevailing views summarized above merit further competitive discussion. It may make sense to address them in a broad and inclusive way and consider this “tension” in the criteria for a balanced allocation of resources

- It is recommended that the NINDS strongly supports the development of predictive rodent models of PD. Optimal animal models will permit the evaluation of candidates for drugs that postpone the initiation of PD pathology as well as slow down the progression of PD in the context of in vivo systems that recapitulate key pathologies underlying PD. These evaluations of drug candidates in relevant in vivo models are critical for de-risking subsequent clinical development, where a substantial step-up in cost occurs, and for elevating the prioritization of development of disease-modifying therapies for PD by pharmaceutical and biotech companies, as well as NINDS and PD foundations.

- It is recommended that the NINDS continue to support the evaluation of peripheral and imaging markers of PD, with the goal to identify and standardize the most useful ones. Optimally, these biomarkers will also be measurable in the animal models and will provide a direct bridge between animal model and human studies. The availability of such biomarkers, particularly for development of disease-modifying therapies for PD, will provide early clinical readouts of drug activity, in the context of the relatively lengthy trials required for evaluating efficacy of disease-modifying therapies.

- It is recommended that the NINDS continue to strongly support research on disease mechanisms of PD, with the goal to identify optimal therapeutic intervention points. Further investigations, which satisfy a broad definition of translational research, on human population genetics, genetic and environmental risk factors, and pathological pathways linking the known disease genes, seem particularly important.

- In the current situation, it is recommended that NINDS not increase funding for translational research, narrowly defined as generation of small molecule drug candidates based on existing targets, in PD.

- It is recommended that the NINDS further strengthens the interactions with PD advocacy groups, private foundations and biopharma industry engaged in PD-related activities.

Chapter 17. Stroke Preclinical Trials Consortia

Introduction. Acute ischemic stroke of the brain represents a most significant unmet medical need. Clot-dissolving tPA therapy is effective in reducing infarct duration and extent for some patients and when administered during the first hours of the infarct. However, there is no effective therapy preventing neural damage in the infarcted areas and/or to increase compensatory regeneration, despite the fact that increased awareness about stroke has led to many drug development programs and clinical trials. The failure of most development programs coupled with the enormous cost of stroke clinical trials has reduced the industry efforts in this area and redirected potential compounds to other indications. In this situation, general goals for the NINDS in this area include:

- Accelerate research on stroke disease mechanisms to identify intervention points for future therapeutics, generate predictive animal models for human ischemic stroke, and find biomarkers to monitor infarct progression, recovery, and regeneration.

- Promote translational research to generate drug candidates for effective disease-modifying drugs and define endpoints and protocols for decisive, small clinical proof-of-concept studies.

Specific translational goals are:

- Identify and generate predictive animal models for human stroke.

- Identify biomarkers that bridge from animal to human studies and that are useful as surrogate endpoints in clinical proof-of-concept studies. This is a critical need that would encourage and enable novel compounds to be entered in development in a manner that allows staging of risk.

- Promote activities to generate IND-stage drug candidates in all available therapeutic modalities (i.e., small molecules, proteins, and sRNAs.)

Achievements. The stroke programs of the NINDS appear overall very well guided, and they have made significant contributions to the advancement of the field. Key NINDS achievements include:

- Provided support for research on stroke mechanisms and related biomarkers, which have led to further insights and the realization of the complexity of the biological events during and following a stroke.

- Established Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS).

- Issued the ‘Stroke Preclinical Trials Consortia’ RFA, which reflects the realization that the no animal model has been predictive as yet and invites applications directly focusing on this key issue.

- Established an international collaboration with the Canadian Stroke Network (CSN).

Strengths

- Strong expertise within NINDS and outstanding interactions with key academic researchers

- SPOTRIAS provides effective network for multi-center clinical studies and data sharing.
- Proactive identification of and focus on the key bottlenecks in stroke translational research: validation of animal models, surrogate markers, trial design of proof-of-concept studies.

Challenges

- None of the clinical trials with candidates for drugs other than clot-dissolving agents has been successful. In particular, general 'neuroprotective' approaches have failed so far.

- Existing animal models have not been predictive for clinical success.

- Research on disease mechanisms has identified a large number of putative drug targets for future disease-modifying drugs. The number of these putative targets vastly exceeds the capacity of clinical trials to select among them by clinical testing of drug candidates. This is further amplified in the context of less development activity in industry.

- Decisive clinical trials need to be very large in their current design. There is no trial design to establish clinical proof-of-concept within reasonable cost and time intervals. Because of the high costs of decisive trials in stroke, many proof-of-concept studies have been poorly designed and led to inconclusive results. E.g., despite robust efficacy in animal models, none of the trials has provided conclusive positive or negative data on the efficacy of NMDA receptor antagonists in human stroke.

- Despite MRI imaging methods, which are operationally used to define the penumbra, there is no validated biomarker to monitor efficacy of putative stroke drugs in the brain of patients.

- Because of several significant failures of phase III clinical trials, despite positive predictions in animal model studies, the overall enthusiasm for stroke drug discovery programs and stroke trials has been diminished in biotechnology and pharmaceutical companies.

Recommendations

- Providing a predictive animal model for human efficacy together with a suitable and validated surrogate marker for proof-of-concept clinical study should remain the dominant goal of stroke translational research at NINDS.

- The Stroke Preclinical Trials Consortia RFA has prompted submission of several applications, which will be reviewed in the near future. It will be most beneficial to the stroke field if the funded applications aim at identifying and validating animal models rather than providing scaled-up access to non-validated models. Repeating the paradigm of failure following non-predictive models will counterproductive as it further establishes stroke as a 'graveyard for drug development.'

- Outreach functions will be helpful in educating industry in animal model validation and clinical trial design and in rekindling the interest in drug discovery and development programs in stroke.