Comments to the National Institutes of Health (NIH) in response to their request for information on the Roadmap initiative

November 17, 2006

Rare Disease Lead Development

Obstacle: Biotechnology and pharmaceutical companies have narrow interest in rare/genetic conditions because of the perceived limited ROI. In these conditions, there exists a critical need for assay development. In certain instances where assay development is developed for these conditions, it is done in academic centers where knowledge of the drug discovery process is minimal or nonexistent. It is necessary to address the critical issue of assay development and to partner academic research with industry in order to facilitate the drug development process. There are approximately 7000 genetic conditions. Because these disorders affect relatively small numbers of people, they are ignored by the private sector because of their small market size. As NIH seeks to translate basic science discoveries into clinical advances, it is critical that it is attentive to this area where industry fears to tread– an opportunity to speed development of effective therapies for rare diseases. Rare diseases currently offer particularly exciting scientific opportunities because the molecular basis of many of these conditions is now known, and they are simpler model systems of pathogenesis, in many instances.

Proposed Initiative: Genetic diseases need infrastructure to support to the development of assays/screens and to facilitate the drug development process to the lead IND candidate(s). Development of one drug is estimated to be in excess of 300 M to 1 B dollars. Based on current financial constraints, it seems reasonable to develop a public/private partnership mechanism to facilitate drug discovery in rare genetic disease. Establishing incentives for Industry to partner with academics for assay development and technical assistance for selection of targets, target prioritization and validation of selected targets would be useful in the development of new treatments for given disease(s). Academics would analyze and compare each drug target to others based on their association with a specific disease and their ability to regulate biological and chemical compounds in the body. Once a lead compound or substance is selected, industry would assign medicinal chemists to assess individual molecules to determine if they possess acceptable properties needed in a new drug and select the compound or compounds with the greatest potential to be developed into safe and effective medicine(s). Academicians in partnership would conduct animal and human in vivo and in vitro studies to compare various lead compounds, how they are metabolized and how they affect the body, and the disease process.

Data-Sharing Systems

Obstacle: At present, the research enterprise functions in a competitive environment – investigators must vie for resources, data, publications, promotions and tenure. While this competition may have fostered an accelerated pathway for basic science in the age of limited commodities, it will not facilitate the translational research that must occur in the age of abundant information.

Proposed Initiative: Open access data systems for sharing information are a critical element in the translational research enterprise. Large databases, with firewalls like the one that is proposed for Genetic Association Information Network (GAIN) will be necessary for robust use of data. Genetic Alliance member organizations have devised systems and methods to share phenotype and genotype information with the research community. We are impressed with the results of such systems enabling sharing of data on a broad and focused scale 1-4 . Researchers are able to advance their understanding at a more rapid pace, participants are able to see incremental results in a reasonable length of time and are more inclined to participate fully. In addition, researchers report that they are able to leverage the shared information and combine their efforts into shared projects that coordinate research on a larger scale 5 . Translational research will require better integration of systems, more information sharing and novel constructs, including disease research models that may not follow the traditional single lab or organ system model. NIH has indicated its understanding of this trend thorough a number of initiatives including the recognition of co-PIs, integrated Roadmap initiatives and large translational research mechanisms such as National Institute of Arthritis Musculoskeletal and Skin Diseases' Center for Translational Research (CORT), which even requires the participation of advocacy organizations in an advisory capacity. Another current best practice model of industrialized standard if the sample, data and resource sharing platform for the Genetic Alliance BioBank, an advocacy owned and managed bio- and data repository. Organizations that have used the bank have seen an enormous acceleration of research and discovery 6 . Genetic Alliance and its member organizations have a long history of supporting an open access model for scientific literature 7 , and the same principle is applicable here.

CETT Program:

Obstacle: The translation of human genetic research discoveries to clinical genetic tests is essential to ensure public benefit from the Human Genome Project, yet has not kept pace with the progress of knowledge. A growing number of genetic tests (nearly 300) remain in research laboratories, limiting public access and impeding clinical research. Genetic testing is essential to genotype/phenotype correlations, targeted therapies (e.g. pharmacogenetics) and new knowledge of disease biology. A quality genetic test (reliable, understandable with clear clinical utility) is a critical outcome of research for clinicians, patients and their families; necessary for

diagnosis and management. A new integrated model of collaboration (i.e., researcher/clinician, clinical laboratory, and patient advocacy) is needed to translate research into clinical practice, increase research opportunities, improve test interpretation, and provide education on the genetic disease and the clinical impact of testing.

Proposal: "To fully address the problem of genetic test translation from research to public health benefits, the approach taken must incorporate representation of key constituents of the involved community. To achieve this goal, a pilot was launched in March 2006 entitled CETT (Collaboration, Education and Test Translation) for Rare Genetic Diseases Program. The CETT Program represents a new model of genetic test translation that requires a collaboration of research (research lab/clinician scientist), clinical laboratory and patient advocacy (Collaborative Group) in order to request funding to develop genetic testing currently not available from a CLIA certified laboratory. The CETT program goals are: To promote new genetic test development; To facilitate the translation of genetic tests from research laboratories to clinical practice; To establish collaborations and provide education about each genetic disease; To identify new related genetic research opportunities; To assess the clinical impact of testing. The process requires that each Collaborative Group provide: Information on the test's clinical use; test results interpretation for clinical care providers, patients and their families, and the clinical utility regarding payor reimbursement; Methods to collect and store clinical information on each sample in publicly accessible databases while respecting patient confidentiality; Methods to collect and store test result information in publicly accessible databases. To support the collection and storage of clinical and genetic information, NCBI is providing direct assistance to the Collaborative Group to meet these goals. The application development and review process is facilitated by CETT Program staff (scientific advisor, program coordinator, NCBI liaison officer, review board coordinator, NIH program director). The review process consists of a Review Board, constituted by teams of 5 members each: a certified clinical geneticist; a certified laboratory geneticist; a patient advocate experienced in genetic disorders; a research scientist whose focus is genetic diseases; and a healthcare provider whose primary focus is not genetics. The review domains are: scientific evidence, proposed methodology, impact on healthcare, laboratory qualifications, data collection, educational materials, and evidence of collaboration. This limited pilot is a feasibility program of a multi-component process that has been vetted through the trans-NIH Rare Diseases Research Working Group, Federal agencies, professional associations, patient advocacy groups, and others, and is responsive to Congressional and public interest in genetic testing. As new genetic discoveries continue to be made, this program has potential to become a model for test translation of genetic diseases that would be useful to the community in general, regardless of funding source for the actual test translation. To have full impact, this pilot, through OPASI, would be integrated across the NIH. "

Trans-NIH Initiatives for Genetic Diseases

Obstacle: Rare and genetic conditions affect multiple systems – these diseases do not adhere to the one organ model around which NIH is largely built. While it may work well to silo research in one institute when it is in the basic end of the continuum to disease intervention – this works less well in the translational realm. Genetic diseases, chromosome abnormalities and other complex conditions involve multiple organ systems.

Proposed Initiative: Prior Roadmap initiatives and the Office of Portfolio Analysis and Strategic Initiatives (OPASI) itself is an inaugural foray into the kind of focused, coordinated research that must be conducted to alleviate the burden of genetic disease. NIH must develop a mechanism to more easily fund cross-institute proposals for the purpose of excellent science.

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Genetic Alliance increases the capacity of advocacy organizations to achieve their missions and leverages the voices of millions of individuals and families living with genetic conditions. We are committed to capacity building in all communities. The technical assistance we provide to advocacy organizations results in measurable growth: increased funding for research, access to services, and support for emerging technologies. Our membership includes, in addition to health professionals, academia and industry, more than 600 advocacy organizations, representing 1000 conditions serving 14 million Americans.

For more information: www.geneticalliance.org.

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Organizations

Alpha-1 Association
Alpha-1 Foundation
Angioma Alliance
APS Foundation of America, Inc.
Ara Parseghian Medical Research Foundation
ARPKD/CHF Alliance
BCCNS Life Support Network
Claire Altman Heine Foundation, Inc.
Coalition of Heritable Disorders of Connective Tissue
Cutaneous Lymphoma Foundation
FACES: The National Craniofacial Association
FOD Family Support Group
GeneDx
Genetic Alliance BioBank
Hadassah, the Womens' Zionist Organization of America
HS-USA, Inc.
Jewish Genetic Disease Consortium
National Alopecia Areata Foundation
National Association of Social Workers
National Ataxia Foundation
NBIA Disorders Association
Organic Acidemia Association
PCD Foundation
PKD Foundation
PXE International
Saving Lana Foundation

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