

## **FY 2012 Budget Request**

The FY 2012 Budget Request reflects NIH's strong commitment to advance biomedical research. NIH will support many of its ongoing research efforts, will curtail other lower priority activities, and will make strategic investments in the key scientific opportunities. The budget request reflects the high priority placed on biomedical research within the current budget climate as an engine promising both better health and economic growth in the future.

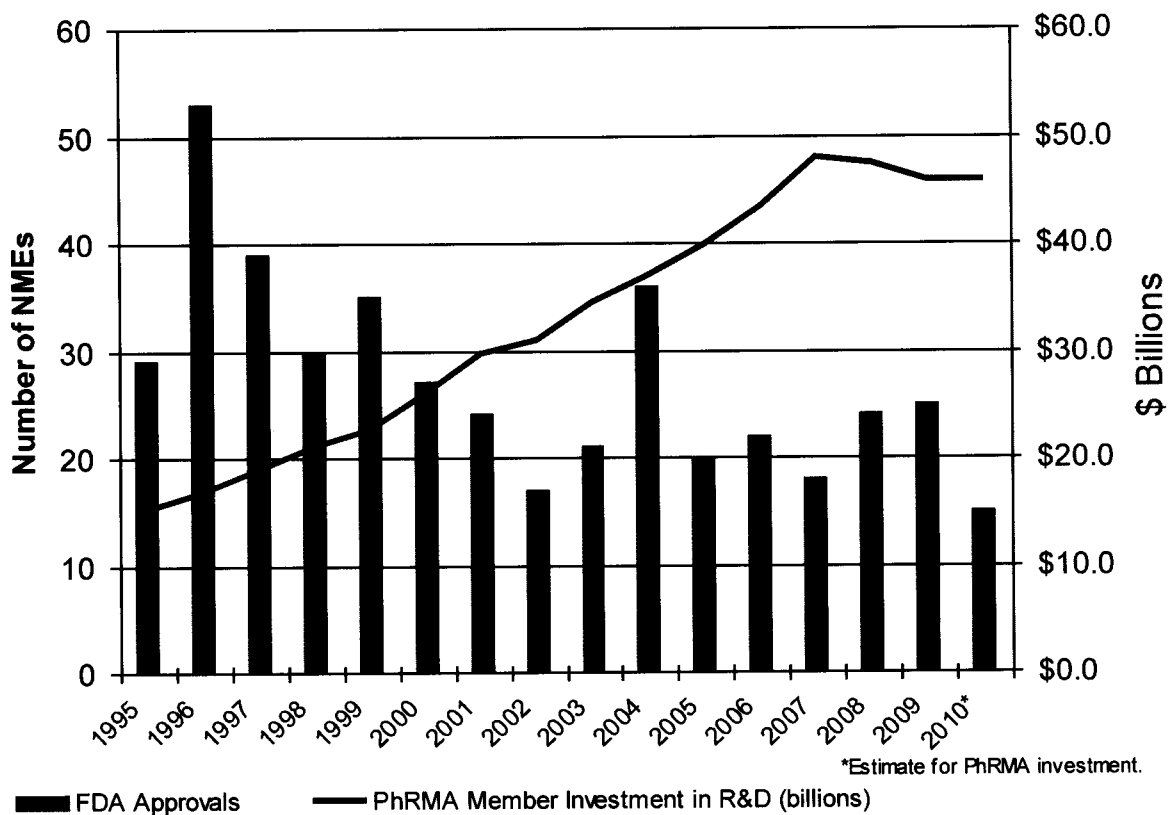
### **Priority Initiatives**

Within the FY 2012 Budget Request, NIH plans to emphasize a groundbreaking new program to optimize and accelerate translational sciences and therapeutics development and three other themes that are exceptionally ripe for investment – technologies to accelerate discovery; the evidence base for health care decisions; and new investigators and new ideas. These four critical areas hold promise for advancing the health of the American people.

#### **\* Optimizing and Accelerating Translational Sciences and Therapeutics Development: The National Center for Advancing Translational Sciences (NCATS)**

***Opportunities:*** NIH-supported basic biomedical research has been successful in deciphering the physiological processes that underpin health and disease. For example, we now understand—at the molecular level—the basis for thousands of diseases, both common and rare. This knowledge, combined with advanced technologies for rapidly screening thousands of molecules for therapeutic potential, has generated a rich inventory of potential new targets and candidates for therapeutic drug development.

***Challenges:*** Translating basic discoveries into new and better diagnostics and treatments has historically been the province of the private sector. Developing new therapeutics, however, has become an exceedingly complex, costly, and risk-laden endeavor. Only a few compounds out of hundreds or thousands will ultimately prove safe and effective and make it to the medicine cabinet. According to research in 2004 and 2008 on the drug discovery process, 90-95 percent of new compounds entering clinical testing do not succeed. The cost of developing a new drug is estimated to range from \$500 million to \$2 billion, when all of the failures are taken into account. Moreover, in spite of significant investments in research and development, the number of FDA-approved new molecular entities (NMEs) has declined by 49 percent in recent years—from an average of 37 per year between 1995 and 1999 to an average of 21 per year between 2000 and 2010. These two trends are illustrated below in a chart that maps investments by pharmaceutical companies in drug research and development against the annual number of FDA approvals for NME drugs, excluding new biologic approvals, in the period from 1995 to 2010.



Note: Data on FDA approvals obtained from: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121136.htm>. Data on Pharma Investment from the Pharmaceutical Research and Manufacturers of America, Profile 2010, pages 24-25 ([http://www.phrma.org/sites/default/files/159/2010\\_phrma\\_annual\\_report.pdf](http://www.phrma.org/sites/default/files/159/2010_phrma_annual_report.pdf))

The staggering development costs and failure rates have become a potent disincentive for pharmaceutical and biotechnology companies. In the last decade, for example, industry efforts to develop new antibiotics for multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* have declined significantly. According to 2007 research on the drug market, since 1999, 10 of the 15 largest companies have fully abandoned, or cut down significantly, discovery efforts in this field. In 2010, two pharmaceutical companies decided to end drug discovery work on pain, depression, anxiety, schizophrenia, and bipolar disorder. As another potential missed opportunity of significant consequence, the genetic bases of more than 2,000 rare diseases have now been identified, but effective therapies are available for only about 200 of those diseases. The limited economic incentive for such small markets means that roughly 20 million Americans affected by these rare diseases may have little hope of a new therapeutic – unless NIH gets involved.

**A New Role for NIH in Therapeutics Development:** The cost and amount of time required for developing new therapies has increased the risk associated with this research in the private sector. NIH is uniquely positioned to catalyze progress in therapeutics development by capitalizing on new and emerging scientific opportunities, leveraging new biomedical discoveries and existing scientific resources, and forging new partnerships with diverse organizations and sectors.

To do so, however, certain translational sciences programs at NIH must be more effectively organized in order to maximize synergy and efficiency. Although not yet reflected in the present FY 2012 Budget Justification documents, NIH is proposing to establish the National Center for Advancing Translational Sciences (NCATS) at the beginning of FY 2012 to catalyze improvements in therapeutics discovery and speed the development of new, urgently needed diagnostics and drugs. In December 2010, the Scientific Management Review Board (SMRB), which was established by Congress to advise the NIH Director on organizational issues, recommended the creation of a new NIH Center with the mission of supporting and strengthening translational medicine and therapeutics development. The SMRB reached its conclusions about the need for a new center after considering the views of internal and external experts and stakeholders, and analyzing a range of organizational alternatives. NIH's proposal is consistent with the advice of the SMRB. Budget details for transitioning to this new Center will be provided this spring.

NCATS would be responsive to the need for innovative strategies for therapeutics development, a need recognized as never before—by the public, government, academic institutions, pharmaceutical and biotechnology companies, and venture capitalists. The recognition of this need and the mounting interest in these strategies are outgrowths of several forces. One is intense interest from the public, whom NIH serves, in development of new treatments for both rare and common diseases. Another is investor-generated pressures on the private sector to speed the pace of therapeutics discovery and reap more rapid returns on the billions of dollars that pharmaceutical and biotechnology companies invest in R&D. Another force is widespread dissatisfaction with the traditional model of therapeutics discovery and its low success rate. Every quarter of the enterprise is calling for approaches that are both *modular* and *integrative*,

#### **A Bird's Eye View of Drug Development**

**Therapeutics development involves many phases, beginning with basic research to illuminate the cause and natural history of disease and preclinical studies to identify a disease target i.e. an aspect of the disease process that might be discoverable for diagnostic purposes and susceptible to intervention for therapeutic purposes. The target must then be validated, another complex and pivotal process. Compounds that hit the target are screened to identify promising candidates for further assessment of their therapeutic potential. The most promising candidates will undergo painstaking preclinical research involving animal models of disease to assess the safety, toxicity, pharmacokinetics, and metabolic properties of the candidate compounds, only a few of which will ultimately prove to be safe or promising enough for clinical studies in humans. Such studies are conducted in a three-phase process of clinical trials, which are expensive and laden with challenges. A final step is FDA approval.**

that enable each sector to deploy its strengths to the component of the process at which it excels, and that foster coordination by bringing the efforts and strengths of the sectors together through public-private partnerships.

An illustrative example of how productive these approaches can be is the recent collaborative effort between several components of NIH (including the National Heart, Lung, and Blood Institute; the NIH Clinical Center; and the Therapeutics for Rare and Neglected Diseases Program) and a private sector company (AesRx) to develop a new therapy for sickle cell disease (SCD). Sickle cell disease is the most common inherited blood disorder in the United States, affecting approximately 70,000 to 100,000 Americans, primarily those of African descent. It affects 1 in every 500 African American newborns.

Sickle cell disease is caused by a defect in the oxygen carrying capacity of red blood cells. Affected individuals face a lifetime of episodes of pain, chronic anemia, severe infections, and multi-organ damage, usually beginning in early childhood. As yet, there is no cure for SCD; a combination of fluids, painkillers, antibiotics and transfusions are used to treat symptoms and complications. The new investigational sickle cell drug acts by increasing the red cell oxygen carrying capacity. It has been designated by the FDA as an orphan drug for the treatment of sickle cell disease. The collaborative effort between NIH and AesRx will carry out both the pre-clinical development activities necessary for Investigational New Drug (IND) application, as well as the clinical trials following IND approval. The result will potentially lead to a major advance toward a safe and effective therapy for SCD -- a disease affecting approximately 13 million people worldwide.

NIH has the capacity to conduct and to support research in the early, preclinical stages of therapeutics discovery and development—research that industry and venture capital are increasingly reluctant to pursue. NIH also has a key role to play in identifying new techniques and technologies that enhance the predictive value of work done at the preclinical stages of therapeutics discovery. As such, NIH can both conduct the essential preclinical work and help prevent the attrition of compounds and failure at later, more expensive, stages of clinical testing by discovering and disseminating innovative approaches to preclinical development.

By establishing NCATS, NIH is positioning itself to assume a greater and more focused role in the therapeutics discovery and development enterprise. The intent is not to assume a role more appropriate for the private sector, rather, through the marshalling and concentration of expertise, technologies, and resources, to fill gaps in the early developmental phases that biotechnology and pharmaceutical corporations are not equipped to fill, and to “de-risk” projects for future commercial investment. NCATS will work synergistically with the private sector and enable NIH to help bridge the translational divide by accelerating, improving, and streamlining a newly collaborative process for realizing the promise of translational medicine and science.

### **Components, Functions, and Focus of the New Center**

NCATS will align and bring together in one organization a number of trans-NIH programs that are inherently cross-cutting (i.e. they do not have a specific disease focus) and are ideally suited for incorporation into the new Center. NCATS programs are expected to include the following components:

The ***Molecular Libraries Program (MLP)*** provides academic researchers with access to technology for assay development, so that the discovery of a new drug target can be developed into an assay amenable to high throughput screening of chemical libraries. More than 100 potential lead compounds relevant to a long list of rare and common diseases have been identified, and many of these are poised for further development. Under the auspices of the new Center, MLP will continue to grow and gain more attention from potential investigators engaged in a wide variety of research areas. One program funded by MLP is the ***NIH Chemical Genomics Center (NCGC)***, which provides robotic high-throughput screening services and a library of more than 350,000 compounds for use in basic discoveries and as probes of cellular pathways, and provides medicinal chemistry support to identify initial hits and lead compounds for preclinical testing.

The ***Therapeutics for Rare and Neglected Diseases (TRND)*** program is designed to bridge the gap that often exists between basic research discovery and the testing of a new drug in humans, as in the example of SCA mentioned above. Leveraging expertise and investments from both the public and the private sectors, TRND strives to encourage and speed the development of drugs for rare and neglected diseases—an area where limited market and commercial potential may discourage others from pursuing critical, life-saving research. This unique program moves candidate drug compounds forward until they meet FDA requirements for an Investigational New Drug (IND) application, at which point they will be attractive to biotechnology and pharmaceutical companies willing to carry them through clinical development and subsequent commercialization. In addition, the TRND program also offers a laboratory for research on the development process itself with a specific focus on improving success rates in the crucial preclinical stage.

The ***NIH Rapid Access to Interventional Development (RAID)*** program helps fill the gap and reduces some of the common barriers that block progress of therapeutic discoveries from the bench to the bedside. The program makes available critical resources that are needed to develop new therapeutic agents, including ones that can generate bulk amounts of the drug candidate or test its stability or toxic effects. It also provides researchers with access to expertise at the FDA on document preparation and submission.

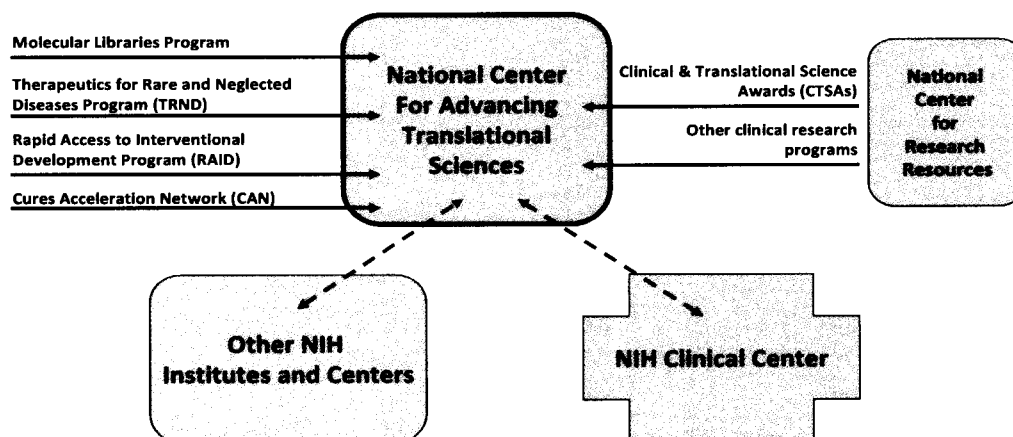
NCATS will be involved in a new ***NIH-FDA Partnership*** formed in 2010 to foster regulatory science, a specialized and interdisciplinary area of biomedical research that generates new knowledge and tools for assessing experimental therapies, preventatives, and diagnostics. A key goal of the partnership is to accelerate the development and use of new tools, standards, and approaches to enhance the efficiency of product development and the effectiveness of product review for safety, efficacy, and quality. Through a funding initiative begun in FY 2010, *Advancing Regulatory Science through Novel Research and Science-Based Technologies*, the agencies are supporting four regulatory science grants to advance nanoparticle characterization, adaptive trial design, development of a heart-lung micromachine for safety and efficacy testing, and toxicology testing strategies that will reduce dependency on the use of animals in toxicology testing.

The ***Cures Acceleration Network (CAN)*** will also be part of NCATS. CAN will advance the development of “high need cures” through the reduction of barriers between research discovery and clinical trials. Authorized by the Affordable Care Act of 2010 (P.L. 111-148), CAN includes flexible authorities to conceptualize and execute projects that will enable transactions other than contracts, grants, and cooperative agreements to achieve the goals and objectives of CAN, where, in the Director’s determination, these standard mechanisms are not adequate. Contracts require the agency to envision and establish the project at the beginning, direct the project, and receive a deliverable. Grants require the recipient to envision and direct the project and report results after completion of the project. NIH will use the flexible research authority to work collaboratively with individual experts and teams in order to envision and identify new opportunities, and then fund exactly what is needed to overcome scientific and developmental hurdles. The authority allows NIH, on a project-by-project basis, to act quickly to capitalize on scientific opportunities and to direct the project, set and monitor specific milestones, and stay involved from both the scientific and administrative aspects, as well as to terminate the project as

necessary. This sort of flexibility has been essential to the success of DARPA, and will also be critical in translational medicine, where product development is the goal and where the exact needs to meet this specific goal cannot be fully anticipated in advance.

NCATS will become the new home of the *Clinical and Translational Science Awards (CTSAs)*. Originally administered under the auspices of the National Center for Research Resources, the CTSAs provide funding for a nationwide consortium of biomedical research institutions. Consortium members are united around the goals of accelerating therapeutics development, engaging communities in clinical research efforts and training clinical and translational investigators. Launched in 2006, the CTA program now includes 55 medical research institutions in 28 states and the District of Columbia.

## NCATS



These programs and other components will enable NCATS to perform a range of critical functions in translational science and medicine. These include:

- Conducting and supporting translational research throughout the process of therapeutics development, but especially in the early phases of fundamental discovery and application;
- Providing a visible, central focus for broader access to scientific and technological resources, tools, and expertise in translational science and medicine;
- Streamlining and improving therapeutics development by facilitating effective handoffs between steps; learning from successes and failures of each project, enhancing the feedback loop; and designing innovative approaches to product development;

- Serving as a resource for NIH by augmenting the strengths and experience of current Institute/Center (IC)-based activities providing services and expertise to ICs, and informing the development of trans-NIH strategies and initiatives;
- Serving as a catalyst, resource, and convener for collaborative interactions by developing and providing scientific resources (e.g., assay development, chemical libraries, high-throughput screening, databases, repositories, data-sharing infrastructures, unique research facilities); promoting and facilitating open exchange of information; supporting novel and innovative partnerships; providing a means of “de-risking” projects that currently seem economically unattractive to the private sector; and developing creative intellectual property frameworks that provide a “win-win” outcome for public-private partnerships;
- Addressing the needs for education and training in translational science and medicine;
- Enhancing communication among all stakeholders in the enterprise of translational medicine.

NCATS will focus research efforts in high-need areas that attract insufficient commercial interest, areas that will not detract from the agency’s emphasis on fundamental knowledge but rather stimulate the pursuit of new avenues of scientific inquiry. The scientific agenda of the new Center will evolve to meet the emerging needs of the field, but initial opportunities will include the rescue of abandoned drug products that have not been approved but hold promise, and the repurposing of approved products for new indications (i.e. applying them for other preventative, diagnostic, and therapeutic purposes). Rescue and repurposing offer a major short cut in getting a product into clinical trials, saving years of work and hundreds of millions of dollars.

NCATS will move quickly to conceptualize, incubate, and launch new partnerships among the various sectors engaged in therapeutics discovery and development. As previously noted, no one entity or sector can pursue all the opportunities available in translational medicine, nor can any single organization or sector tackle the myriad, inherent challenges and risks. A model that relies to a greater extent on cross-sector and interdisciplinary collaborations will distribute risks and capitalize on diverse perspectives and expertise. Public-private partnerships to advance biomedical science and translational medicine are not new. There is, however, a growing recognition on the part of all those involved in translational medicine that the current model for development is not sustainable and that novel partnerships and collaborations are critical to progress. Especially in this tight budget climate, the limits of any one sector are well recognized, as is the need for approaches that integrate and coordinate the respective strengths of multiple sectors.

By virtue of its role in funding biomedical research and training—and thereby shaping the landscape of biomedical science and public health in the U.S.—NIH has the singular capacity to convene government, academia, and industry around common goals in translational medicine and science, in ways that would not have been possible a few years ago. The agency can develop and provide platforms for sharing data, including both positive and negative results, and it is