NIH: Steward of Medical and Behavioral Research for the Nation

“Science in pursuit of fundamental knowledge about the nature and behavior of living systems ... and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.”
The mission of the National Institutes of Health (NIH) is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and to reduce the burdens of illness and disability. The power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine. The foundation of success in biomedical research has always been the creative insights of individual investigators. But increasingly those investigators are working in teams, accelerated by interdisciplinary approaches and empowered by open access to tools, databases, and technologies, so a careful balance is needed between investigator-initiated projects and large-scale community resource programs. For both individual and large-scale efforts, it is appropriate to identify areas of particular promise. Here are five such areas that are ripe for major advances that could reap substantial downstream benefits.

**High-Throughput Technologies**

In the past, most biomedical basic science projects required investigators to limit their scope to a single aspect of cell biology or physiology. The revolution now sweeping the field is the ability to be comprehensive—for example, to define all of the genes of the human or a model organism, all of the human proteins and their structures, all of the common variations in the genome, all of the major pathways for signal transduction in the cell, all of the patterns of gene expression in the mouse, the genetic underpinnings of 20 major tumour types. This information will likely force a complete revision of diagnostic categories in cancer and will usher in an era where new treatments in specific tumours will be matched with the known targets of existing therapeutics. Another example is the opportunity to understand how interactions between ourselves and the microbes that live on us and in us (the "microbiome") can influence health and disease (2).

**Translational Medicine**

Critics have complained in the past that NIH is too slow to translate basic discoveries into new diagnostic and treatment advances in the clinic. Some of that criticism may have been deserved, but often the pathway from molecular insight to therapeutic benefit was just not bring them to clinical trials and U.S. Food and Drug Administration (FDA) approval.

As one example, the NIH Therapeutics for Rare and Neglected Diseases (TRND) (3) program will allow certain promising compounds to be taken through the preclinical phase by NIH, in an open environment where the world’s experts on the disease can be involved. Furthermore, as information about common diseases increases, many are being resolved into distinct molecular subsets, and the TRND model will be even more widely applicable.

The first human protocol (for spinal cord injury) involving human embryonic stem cells (hESCs) was approved by the FDA in 2009, and the opening up of federal support for hESC research will bring many investigators into this field. The capability of transforming human skin fibroblasts and other cells into induced pluripotent stem...
Opportunity #2: Translating basic science discoveries into new and better treatments
Despite Greater Pharma R&D Investments, FDA Approvals of NMEs Declined


Sources: Pharmaceutical Research and Manufacturers of America; FDA

*Estimate*
BREAKTHROUGH OF THE YEAR

Human Genetic Variation
2007 1st quarter
2008 1st quarter
A Changing Landscape: Shifting the Paradigm for Therapeutics Discovery

Growing “environmental” pressures on pharmaceutical industry

- Search for ways to increase # and quality of cost effective new medicines w/o unsustainable R&D risks and costs
- Traditional drug development paradigm → proposed alternative paradigm “quick win-fast fail”

FDA
Review
Ph. III
Ph. II
Ph. I
FDA IND
Pre-Clinical
Lead to Probe
HTS
Assay Dev.
Target ID
Disease
NIH Molecular Libraries Initiative
NIH TRND
NIH RAID
Pharma, Biotech, NIH Clinical Center, CTSAs
New NIH FDA Partnerships
NIH RAID
NIH TRND
NIH Supported Basic Research
New NIH-FDA Partnership

- NIH-FDA Joint Leadership Council
  - Meeting: October 28, 2010

- Joint Regulatory Science Initiative
  - 58 applications received
  - 4 projects funded
    - Diverse areas of research: Nanotechnology, heart-lung models for testing safety and efficacy, innovative clinical trial design, innovations in toxicological screening
The Problem of Rare and Neglected Diseases

- ~7,000 diseases affect humankind – but only a small fraction support commercial development of therapeutic agents

- Two types of neglected diseases:
  - Low prevalence, i.e., “rare” (<200,000 diagnosed in U.S.)
    - There are >6000 rare (orphan) diseases
    - Cumulative prevalence in U.S. ~ 25 – 30 million
    - Most are single gene diseases
    - <200 have any pharmacotherapy available
  - High prevalence but “neglected”
    - Occur chiefly among impoverished and marginalized populations in developing nations (treatment costs prohibitive)
    - Most are infectious
THE WALL STREET JOURNAL

NIH Takes On New Role in Fight Against Rare Diseases

By Amy Dockser Marcus

A government program focusing on rare diseases has launched five pilot projects that are taking the National Institutes of Health in a new direction: developing drugs.

The NIH Therapeutics for Rare and Neglected Diseases (TRND) program was established last year with $2.4 million of funding. TRND will work together with scientists, advocates and others to do the required research and testing on drugs before a compound can be tried in humans in a clinical trial.

Promising new drugs discovered through basic research often flounder during this stage of the process, which is expensive, time-consuming and prone to failure.

The pilot projects, three of which were selected this spring, target drug development for sickle-cell disease; chronic lymphocytic leukemia; the fatal neurodegenerative disease Niemann-Pick Type C; the genetic muscle disorder hereditary inclusion body myopathy; and the parasitic diseases schistosomiasis and hookworm.

The projects, which are in various stages of development, were selected because they illustrate a range of problems and issues in the effort to drive drug development.

The problems include the high cost of studies in animals to determine if a drug is too toxic to give to humans, the challenges of meeting regulatory requirements before the Food and Drug Administration allows clinical trials to begin, and the sheer amount of coordination that goes into getting a new drug to market.

"Most of the problems we are addressing are not scientific problems," said Christopher P. Austin, director of the NIH program. "They are operational issues."

For most new drugs, these issues are handled by a pharmaceutical company. Rare diseases, which the NIH defines as diseases that affect fewer than 200,000 people in the U.S., represent a small market.

As a result of the small market, many pharmaceutical companies are reluctant to take on the risks and expense of trying to develop new drugs for these conditions.

TRND is assigning project managers with experience in drug development to the pilot projects to help identify the necessary steps to get to clinical trials.

The sickle-cell disease project, for instance, involves AesRX LLC, a Newton, Mass., biotech company, and needs to complete toxicity studies and regulatory work to launch a trial.

The alternative would be to raise outside capital from venture capitalists," said Steve Seiler, chief executive of AesRX. Mr. Seiler said at this stage of the project it would have been difficult to get the financing. "Once we have human clinical data, it is much different," he said.

With the muscle disorder hereditary inclusion body myopathy, William A. Gahl, clinical director of the National Human Genome Research Institute, said he had been unable to launch a clinical trial to test a promising compound for three years, before the project was taken up by the NIH program.

He said that before he could start a clinical trial with the compound, the FDA wanted toxicology studies conducted in animals, at an estimated cost of $500,000 to $1.5 million—money the small biotech company and patient advocacy group he is working with didn't have. "We were about to give up," Dr. Gahl said.

TRND is getting toxicology studies done and has hired a regulatory consultant to help address any regulatory issues with the FDA to get permission to start a trial.

"TRND has smoothed the way enormously," said Dr. Gahl, who said he hopes to launch the trial this year.

In the case of Niemann-Pick Type C, TRND's Dr. Austin had previously worked with a group of scientists and parent funders called SOAR-NPC to screen already approved FDA compounds to see if they might be effective against the disease. A promising compound was identified, but extensive work will be required to determine whether the drug is safe and effective enough to be tried in patients, Dr. Austin said.

This kind of tinkering with a promising drug—testing it in animals and then going back to the lab for further tweaks—is both time-consuming and expensive, and can be out of the reach of a parent-funded organization like SOAR.

Last week, at the annual conference of the advocacy group Genetic Alliance, Dr. Austin, a parent funder in SOAR, and Steven U. Walkley, a professor at Albert Einstein College of Medicine who is a member of SOAR, gave a joint talk that addressed some of the pressures the NIH program faces.

"There is a lot of promise built into TRND, but there is no guarantee that they will be able to make the science deliver a therapy for a disease," Dr. Walkley said.

Dr. Austin said he recognized that "we have to succeed with these pilot projects, and if we don't, the program won't continue."

Half of the program's budget this year is going to fund the five pilot projects, he said. The other half of the budget is going to setting up TRND. Dr. Austin added that the program plans to solicit additional projects in September.
NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

Creating a Drug Development Pipeline at NIH

- Congressionally-mandated effort to speed development of new drugs for rare and neglected diseases
- Collaboration between NIH-intramural and extramural labs with appropriate expertise
- Projects will:
  - Enter TRND at a variety of stages of development
  - Be taken to phase needed for external organization to adopt for clinical development
  - Not duplicate PhRMA projects
- TRND will encourage creative partnerships; novel approaches to intellectual property
TRND Pilot Projects

Chosen to establish processes in advance of solicitation, with diversity of project stage, type of disease and collaborators

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type</th>
<th>Pathology</th>
<th>Collaborators</th>
<th>Compound type</th>
<th>Stage</th>
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<td>Infectious parasite</td>
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<td>NME</td>
<td>Early (lead optimization)</td>
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<td>Repurposed approved drug</td>
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<td>Muscle</td>
<td>Biotech, Intramural</td>
<td>Intermediate replacement</td>
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<tr>
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<td>Blood</td>
<td>Nonprofit, Intramural, Extramural</td>
<td>NME</td>
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<tr>
<td>Chronic Lymphocytic Leukemia</td>
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<td>Cancer</td>
<td>Disease Fnd, Extramural</td>
<td>Repurposed approved drug</td>
<td>Pre-IND</td>
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Centenary: 1910 Discovery of Sickle Cell Anemia

James B. Herrick

Archives of Internal Medicine (1910) vol. 5

PECULIAR ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES IN A CASE OF SEVERE ANEMIA

JAMES B. HERRICK, M.D.
Therapeutics for Rare and Neglected Diseases (TRND): Pilot Project on SCD

- **Collaborator:** AesRx, Boston-based biotech
- **Compound:** 5-hydroxymethyl-2-furfural (Aes-103)
  - Binds to sickle hemoglobin and increases its oxygen affinity
- **Stage of project:** late preclinical

Aes-103 0mM almost all cells underwent sickling
Aes-103 5mM almost no sickled cells except some ISCs
The New Paradigm for Translation:
*Sickle Cell Anemia*

**NIH Supported Basic Research**

**NIH Molecular Libraries Initiative**

**NIH TRND**

**NIH RAID**

**Pharma, Biotech, NIH Clinical Center, CTSAs**

**New NIH FDA Partnerships**
Therapeutics for Rare and Neglected Diseases (TRND)

- Schistosomiasis is a parasitic disease that affects 250 million people, mostly in Africa
- Currently controlled by praziquantel (PZQ)
  - Cure rates not 100%
  - Evidence that schistosomes could become resistant to PZQ → search for new treatment options
- NIH grantee Dr. David Williams
  - Identified potential new target
  - Collaborated with TRND to identify targeted chemicals for new drugs
Developing Drugs for Schistosomiasis

Identification of oxadiazoles as new drug leads for the control of schistosomiasis

Ahmed A Sayed, Anton Simeonov, Craig J Thomas, James Inglese, Christopher P Austin & David L Williams

1Department of Biological Sciences, Illinois State University, Normal, Illinois 61790, USA. 2NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-3370, USA. Correspondence should be addressed to D.L.W. (dwilli@ilstu.edu) or C.P.A. (austinnc@mail.nih.gov).

Ex vivo worm killing

Livers of treated mice
The application deadline for the first cycle of the program is **December 6th, 2010**.

Submitted research proposals will be reviewed for scientific merit and technical feasibility, as well as program balance and availability of resources. Successful applicants will partner with TRND to create and implement a therapeutic project plan. No grant funds are awarded for this program.

Applications to the TRND Program are evaluated for (criteria and weight of criteria):
H.R. 3590
One Hundred Eleventh Congress of the United States of America

AT THE SECOND SESSION

Began and held at the City of Washington on Tuesday, the fifth day of January, two thousand and ten

An Act

Entitled The Patient Protection and Affordable Care Act.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the “Patient Protection and Affordable Care Act”.
(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:
Sec. 1. Short title; table of contents.

TITLE I—QUALITY, AFFORDABLE HEALTH CARE FOR ALL AMERICANS
Subtitle A—Immediate Improvements in Health Care Coverage for All Americans
Sec. 1001. Amendments to the Public Health Service Act.

“PART A—INDIVIDUAL AND GROUP MARKET REFORMS

“SUBPART II—IMPROVING COVERAGE

“Sec. 2711. No lifetime or annual limits.
“Sec. 2712. Prohibition on rescissions.
“Sec. 2713. Coverage of preventive health services.
“Sec. 2714. Extension of dependent coverage.
“Sec. 2715. Development and utilization of uniform explanation of coverage documents and standardized definitions.
“Sec. 2716. Prohibition of discrimination based on salary.
“Sec. 2717. Ensuring the quality of care.
A Bold New Paradigm: Cures Acceleration Network (CAN)

- Established by the Affordable Care Act
- Authorized $500 M (but not appropriated) for FY10
- House and Senate markups for FY11 include $50M

124 STAT. 978
PUBLIC LAW 111–148—MAR. 23, 2010

SEC. 10409. CURES ACCELERATION NETWORK.

(a) Short Title.—This section may be cited as the “Cures Acceleration Network Act of 2009”.

(b) Requirement for the Director of NIH To Establish a Cures Acceleration Network.—Section 402(b) of the Public Health Service Act (42 U.S.C. 282(b)) is amended—

“(c) Functions.—The functions of the CAN are to—

“(1) conduct and support revolutionary advances in basic research, translating scientific discoveries from bench to bedside;

“(2) award grants and contracts to eligible entities to accelerate the development of high need cures;

“(3) provide the resources necessary for government agencies, independent investigators, research organizations, biotechnology companies, and patient advocacy groups to reduce the barriers between laboratory discoveries and...
Cures Acceleration Network: Funding Mechanisms

- Grant Awards:
  - Up to $15 million per award per fiscal year

- Flexible Research Awards:
  - DARPA-like authority
  - Not to exceed 20% of total appropriated funds in any fiscal year

- Partnership Awards:
  - $1 match for every $3 from NIH
  - Up to $15 million per award per fiscal year
### Cures Acceleration Network

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<th>Disease</th>
<th>Target ID</th>
<th>Assay Dev.</th>
<th>HTS</th>
<th>Probe to Lead</th>
<th>Pre-Clinical</th>
<th>FDA IND</th>
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<th>Ph. II</th>
<th>Ph. III</th>
<th>FDA Review</th>
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- **NIH Supported Basic Research**
- **NIH Molecular Libraries Initiative**
- **NIH TRND**
- **NIH RAID**
- **Pharma, Biotech, NIH Clinical Center, CTSAs**

**New NIH FDA Partnerships**
The NIH Scientific Management Review Board (SMRB)

- **2006 NIH Reform Act**
  - Reauthorizes, reaffirms mission of NIH
  - Authorizes new process to facilitate trans-NIH research
  - Creates the SMRB

- **SMRB**
  - Advises NIH Director
  - Conducts comprehensive organizational reviews of NIH; reports findings to DHHS and Congress
  - 21 members:
    - 9 Institute and Center Directors
    - 12 external research and management experts
Charge to the SMRB: Translational Medicine and Therapeutics

- Identify the attributes, activities, and functional capabilities of an effective translational medicine program for advancing therapeutics development.

- Broadly assess, from a high-level view, the NIH landscape for extant programs, networks, and centers for inclusion in this network and recommend their optimal organization.
To know what has to be done, then do it, comprises the whole philosophy of practical life.

Sir William Osler
NIH...
Turning Discovery Into Health

U.S. Department of Health & Human Services
National Institutes of Health
Legal Challenges to Human Embryonic Stem Cell Research

- 8/23/10: Judge Lamberth issues preliminary injunction blocking federal funding for human embryonic stem cell (hESC) research
- Injunction halted:
  - Continuation of funds for 24 extramural grants ($54M)
  - 8 intramural research grants
  - Funding for 20 promising new hESC applications ($24M)
  - Review of new lines
  - Peer review of hESC research proposals
- Created upheaval, uncertainty, and angst
Legal Challenges to Human Embryonic Stem Cell Research: *Current Status*

- **9/9/10**: U.S. Court of Appeals for the DC Circuit issues a temporary stay of the preliminary injunction
  - NIH resumes hESC activities
- **9/16/10**: Hearing, Senate Subcommittee on Labor, HHS, Education Appropriations
  - **9/28/10**: Court of Appeals issues a stay, pending appeal of preliminary injunction
  - Appeal to be expedited
  - Legal proceedings continue

In both courts…
Opportunity #3: Putting science to work for the benefit of health care
Since Barack Obama became the 44th president of the United States in January 2009, nearly all sectors of society have engaged in intense discussions about the best ways to stimulate the nation’s economy and reform the US health care system. The National Institutes of Health (NIH) has been—and will continue to be—in the middle of such conversations, emphasizing the power of biomedical research to show what health interventions yield the greatest benefits.

Health reform and economic concerns may have moved comparative effectiveness research (CER) from relative obscurity into the public policy spotlight. However, CER is not a new concept to NIH, which has long recognized and supported the value of CER for providing evidence-based, well-validated approaches to medical care.

For instance, nearly 2 decades ago, NIH-supported researchers published results of the Cardiac Arrhythmia Suppression Treatment trial, which compared the benefit and risk of adding beta-blocker medications to the treatment of heart rhythm disorders. The results showed that beta-blockers, while effective, also carried a high risk for death due to a side effect called torsades de pointes. The trial showed that making decisions about medical treatments for cardiac rhythm disorders requires more than just academic knowledge about the disease and its treatments.

NIH’s commitment to comparative effectiveness research is ongoing. The National Institutes of Health recently provided $1.2 billion in funding for comparative effectiveness research, representing 10% of NIH’s total research budget. This funding is intended to support studies that compare the effectiveness of different treatments for the same disease, with the goal of helping clinicians and patients make informed decisions about the best course of treatment.

NIH has also established the Comparative Health Effectiveness Research Collaboratory (CHER), which is a national network of researchers and clinical sites that conducts comparative effectiveness research on a wide range of health conditions. The CHER network includes over 300 hospitals and 400 clinical sites across the United States, and is designed to facilitate collaboration among researchers and increase the efficiency and effectiveness of comparative effectiveness research.

NIH’s commitment to comparative effectiveness research is also reflected in its support of research on the economic outcomes of different treatments. NIH has provided funding for research on the economic consequences of different treatments for a wide range of health conditions, including cardiovascular disease, diabetes, cancer, and mental health disorders.

NIH’s commitment to comparative effectiveness research is driven by the belief that making evidence-based decisions about health interventions is essential for improving health outcomes and reducing health disparities. NIH is committed to continuing to invest in comparative effectiveness research to help healthcare providers and patients make informed decisions about the best course of treatment.
Health Care Legislation and CER: Patient-Centered Outcomes Research Institute (PCORI)

- Non-profit corporation to organize, fund CER
  - Board of Directors announced on September 23, 2010
  - Includes Directors of NIH, AHRQ
  - Standing methodology committee includes NIH, AHRQ

- Charged to identify
  - National research priorities
  - New clinical evidence; evidentiary gaps
  - Relevance; standards; economic correlates

Estimated Funding

- Green bars: Annual per-capita charges
- Orange bars: Appropriated funds

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Health Care Legislation and CER: Patient-Centered Outcomes Research Institute (PCORI)

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  - Board of Directors announced on September 23, 2010
    - A. Eugene Washington, MD, MSc will be Chairman
  - Includes Directors of NIH, AHRQ
  - Standing methodology committee includes NIH, AHRQ

Subtitle D—Patient-Centered Outcomes Research

SEC. 6301. PATIENT-CENTERED OUTCOMES RESEARCH.

(a) IN GENERAL.—Title XI of the Social Security Act (42 U.S.C. 1301 et seq.) is amended by adding at the end the following new part:

"PART D—COMPARATIVE CLINICAL EFFECTIVENESS RESEARCH"

Patient-Centered Outcomes Research Institute: The Intersection of Science and Health Care

Carolyn Clancy¹ and Francis S. Collins²*  
Published 23 June 2010, Volume 2 Issue 37 37cm 18

The Patient Protection and Affordable Care Act created the Patient-Centered Outcomes Research Institute (PCORI), a nonprofit corporation that is neither an agency nor an
Comparative Effectiveness Research at NIH

- Prevention
- Diagnosis
- Treatment
- Behavior change
- Health systems
- Special populations

NIH conducts research in 88 of 100 IOM CER priority areas

Using Science to Improve the Nation's Health System
NIH's Commitment to Comparative Effectiveness Research

Michael S. Lauer, MD
Francis S. Collins, MD, PhD

Since Barack Obama became the 44th President of the United States in January 2009, nearly all sectors of society have engaged in intense discussions about the best ways to stimulate the nation's economy and reform the US health care system. The National Institutes of Health (NIH) has been—and will continue to be—in the middle of such conversations, emphasizing the power of biomedical research to show what health interventions yield the greatest benefits.

Health reform and economic concerns may have moved comparative effectiveness research (CER) from relative obscurity into the public policy spotlight. However, CER is not a new concept to NIH, which has long recognized and supported the value of CER for providing evidence-based, well-validated approaches to medical care.

For instance, nearly 2 decades ago, NIH-supported researchers published results of the Cardiac Arrhythmia Suppression Trial, which was the first randomized trial to demonstrate a major reduction in all-cause mortality. The results of this study were published in the New England Journal of Medicine, and the conclusions were supported by other randomized trials.

Congressional Budget Office cited NIH's comparative effectiveness studies as prime examples of government-sponsored research that could directly inform clinical practice and public policy.

Today, the biomedical research community has an unprecedented opportunity to build on this foundation. The United States urgently needs the evidence to design a system that offers health interventions that are both beneficial and cost-effective. The American Recovery and Reinvestment Act (ARRA) of 2009 appropriated $1.1 billion for CER, with $400 million of that funding allocated to NIH and the remainder to AHRQ and the Office of the Secretary of the Department of Health and Human Services.

While the ARRA-mandated report of the Federal Coordinating Council acknowledged that NIH historically has been the largest source of federal support for CER, NIH has important partners in other government agencies, particularly AHRQ. NIH generally contributes to CER by supporting primary research, including both observational studies and randomized control trials. AHRQ's strength is in conducting secondary comprehensive meta-analyses of multiple studies, seeking to identify overarching conclusions and informing public policy.

NIH conducts research in 88 of 100 IOM CER priority areas.
Apply to TRND

The TRND program is intended for broad use by academic laboratories, not-for-profit organizations, and for-profit companies. Foreign organizations may also apply.

To apply to the TRND program, please see the project solicitation.

The application deadline for the first cycle of the program is December 6th, 2010.
Appropriation History vs. Actual Purchasing Power (BRDPI)
(FY 1998 appropriation – FY 2011 Revised Presidential Budget)
Success Rates: FY 1978 – FY 2012 (estimate)
(Includes Recovery Act Funds)