



# Translational Research Initiatives for Neurodegeneration at the NIH

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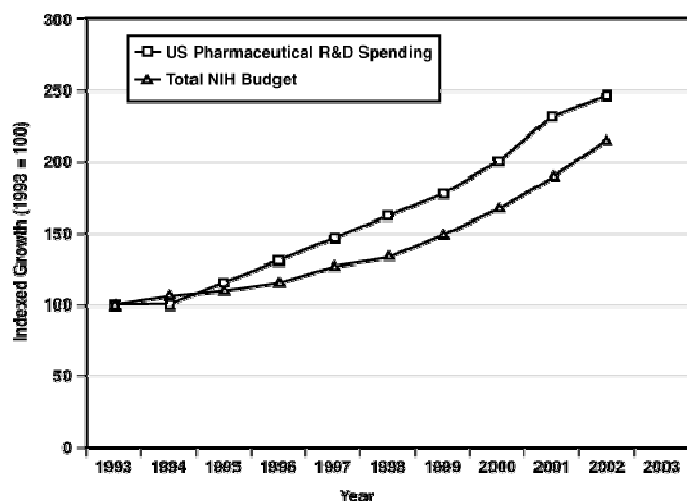


## Overview:

- ❑ **NIH Roadmap translational initiatives:**
  - Molecular Libraries
  - RAID Pilot Program
  
- ❑ **Translational research initiatives at the NIA**
  
- ❑ **Translational research initiatives at the NINDS**
  
- ❑ **Other funding opportunities for translational research for CNS disorders**

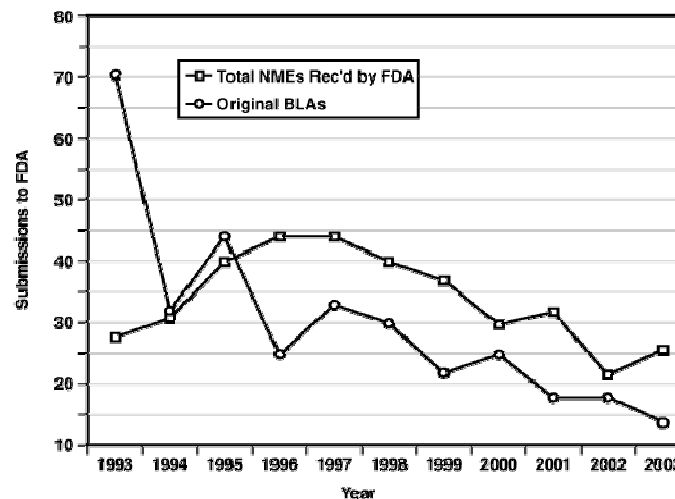
# Lost in Translation

Figure 1: 10-Year Trends in Biomedical Research Spending



The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993-2003) and by pharmaceutical companies' research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2002/2003).

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA



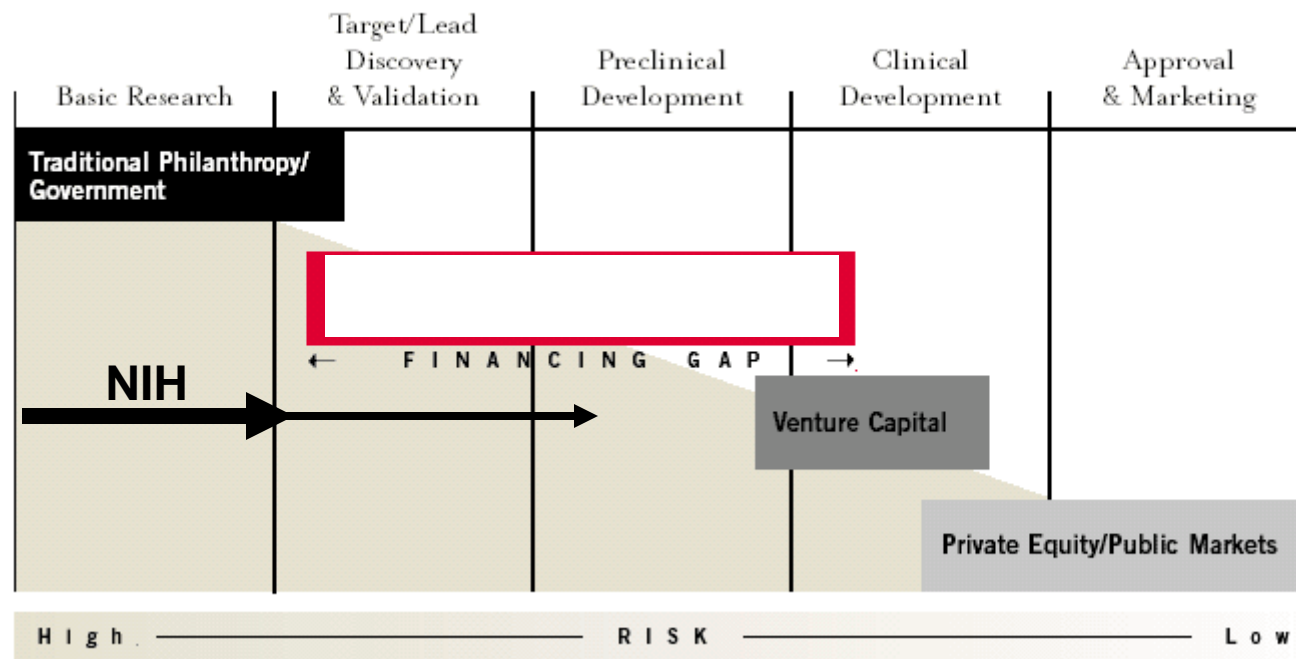
The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

**The applied sciences have not kept pace with the tremendous advances in the basic sciences (*FDA White paper: Stagnation or Innovation; 2004*)**

**Key factors responsible for this disconnect:**

- funding**
- infrastructure**
- expertise**

# The Translation of Basic Research to Therapeutic Interventions is Underfunded



# **NIH Roadmap**

**Since 2002, NIH has begun a series of far-reaching initiatives, the NIH Roadmap, that provide a strategic plan and guidelines for medical research in the 21st century.**

**<http://nihroadmap.nih.gov>**

# Molecular Libraries and Imaging

**Goal:** To empower the research community to use small molecule compounds in their research, whether as tools to perturb genes and pathways, as imaging probes in basic or clinical applications, or as starting points to the development of new therapeutics for human disease.

☐ <http://nihroadmap.nih.gov/molecularlibraries/index.asp>

# Molecular Libraries Roadmap Components

## ❑ Molecular Libraries Screening Center Network (MLSCN)

Small Molecule Repository (SMR)

NIH Chemical Genomics Center (NCGC, intramural)

Extramural Screening Centers

## ❑ Cheminformatics

PubChem

Cheminformatics Research Centers

## ❑ Technology Development

Chemical diversity

Assay development

HTS instrumentation

## Goals of the MLSCN

**Establish a national HTS resource in the academic environment to improve the understanding of biology and disease mechanisms.**

- Provide HTS approaches for identification of small organic molecules that are active in biological assays.
- Synthetic chemistry to improve the utility of small molecules as bioactive probes.
- Make HTS data publicly available in PubChem.
- Stimulate collaborations among biologists and chemists, assay providers, compound providers, and the MLSCN centers.
- Stimulate technology development.
- Provide outreach to the academic community.

**All data generated by the MLSCN are deposited promptly upon data verification into PubChem.**

PubChem is a public sector chemical database developed by the NIH National Center for Biomedical Informatics.

Fully linked to other NCBI Entrez databases of genes, proteins, Medline.

Coordinates bioassay data deposition from the MLSCN.

# Molecular Libraries Small Molecule Repository (MLSMR)

## Initial set of 80,000 compounds purchased from commercial vendors

- Targeted Libraries

  - Active ingredients of FDA approved drugs

- Diverse compounds

- Natural products

## Expanding the compound collection

- Solicitation of compounds from academia, biotech companies, and Pharma

- NIGMS Chemical Methodologies Library Development (CMLD) centers

- Molecular Libraries Chemical Diversity initiatives

- Strategy being developed for acquisition of second 100,000 compounds

## Current MLSCN Program Announcements:

- Solicitation of Assays for High Throughput Screening (HTS) in the Molecular Libraries Screening Centers Network (R03) **PAR-06-545**
- Solicitation of Assays for High Throughput Screening (HTS) in the Molecular Libraries Screening Centers Network (X01) **PAR-06-259**
- Solicitation of Compounds for High Throughput Screening (HTS) in the Molecular Libraries Screening Centers Network (MLSCN) **NOT-RM-06-017**

# **RAID Pilot Program**

**<http://nihroadmap.nih.gov/raid>**

- ❑ The NIH-RAID Pilot is an NIH Roadmap initiative intended to reduce some of the common barriers between laboratory discoveries and clinical trials of new therapeutic entities.**
- ❑ Projects in both the early and late stages of pre-clinical development are suitable for NIH-RAID proposals.**
- ❑ The NIH-RAID Pilot will accept requests over a two year period, with four submission dates.**

# **The RAID-Pilot Program Aims to Support:**

- ❑ Synthesis in bulk of small molecules and oligonucleotides, chemical synthesis of small peptides (GMP and non-GMP).**
- ❑ Scale-up production from lab-scale to clinical-trials lot scale.**
- ❑ Development of analytical methods for bulk substances.**
- ❑ Isolation and purification of pharmacologically active entities from natural sources.**

- **Pharmacology studies with a pre-determined assay.**
- **Development of suitable formulations.**
- **Physicochemical characterization of formulations developed, including tests of stability, disintegration, dissolution, and lot-to-lot variability.**
- **Range-finding initial toxicology.**
- **IND-directed toxicology, with correlative pharmacology and histopathology.**
- **Product development planning and advice in IND preparation**

# **What the RAID-Pilot Program is Not**

- **The NIH-RAID Pilot is not a complete drug development program or an unconditional commitment to develop a particular compound for the clinic.**
- **The NIH-RAID Pilot does not support either in vitro or animal efficacy testing or human subject research.**
- **The NIH-RAID Pilot is not meant to assist industry in its development projects in the absence of an academic partner. However, academic investigators may have collaborations with for-profit partners and qualify for NIH-RAID Pilot funding.**
- **The NIH-RAID Pilot is not intended to support provision of materials for Phase II and III clinical trials.**
- **The NIH-RAID Pilot is not intended to yield NIH-held INDs. It is anticipated that the clinical phases of testing will generally occur under investigator-held INDs within the originating (or collaborating) institution or by partnership with an industry partner.**

# **Critical Dates**

## **Full Proposal and Request submission dates:**

**-Cycle 5** January 5, 2007

**-Cycle 6** June 1, 2007

**-Cycle 7** January 4, 2008

**-Cycle 8** June 6, 2008

**“CNS disorders will become the major medical need of the 21<sup>st</sup> century.”**  
***The World Health Organization***

- ❑ **The driving force of this trend will be the rise in age-related neurodegenerative disorders such as Alzheimer’s and Parkinson’s.**
- ❑ **By 2050 there will be ~1.4 billion people over 65 years of age compared to ~420 million people over 65 in 2000.**
- ❑ **CNS is the fastest growing therapeutic segment on the market with sales of above \$50 billion.**

## **CNS is the Most Challenging Therapeutic Area**

- ❑ Complexity of the CNS.**
- ❑ Insufficient understanding of the pathogenic pathways and the drug targets.**
- ❑ Liability of CNS drugs to cause side effects.**
- ❑ Requirement for CNS drugs to cross the BBB.**
  
- ✓ Bringing a CNS drug to the market takes longer (12-16 years compared to 10-12 years for non-CNS drugs) and costs significantly more.**
  
- ✓ Drug development for CNS disorders is characterized by very high attrition rate.**

## **Bridging the Translational Funding Gap: -NIA initiatives-**

- ❑ In 2004 the NNA partnered with the ISOA and in 2005 launched a program announcement for early drug discovery for AD using an R21 funding mechanism.**
  - ❑ In 2005 the NNA released a program announcement for a U01 cooperative agreement program for preclinical drug development for AD.**
- 
- ✓ Funding for these programs was provided from the NIA's Director's reserve.**
  - ✓ The programs aim to facilitate drug discovery and preclinical drug development in academia and in the biotech industry.**

Basic Research

Target Discovery



Target Validation



Assay Development



Screening Hits to Leads



Lead Optimization



Development



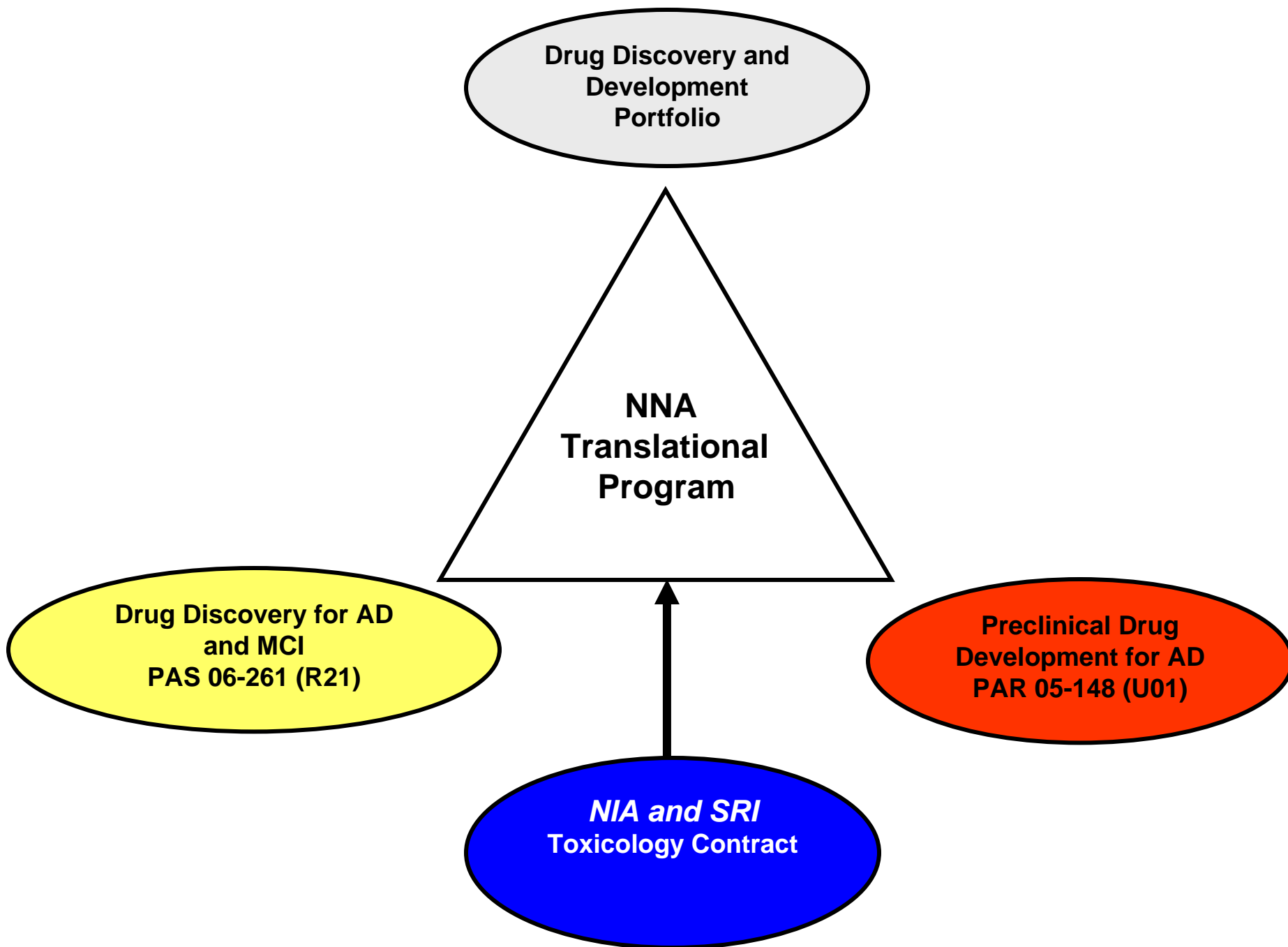
IND

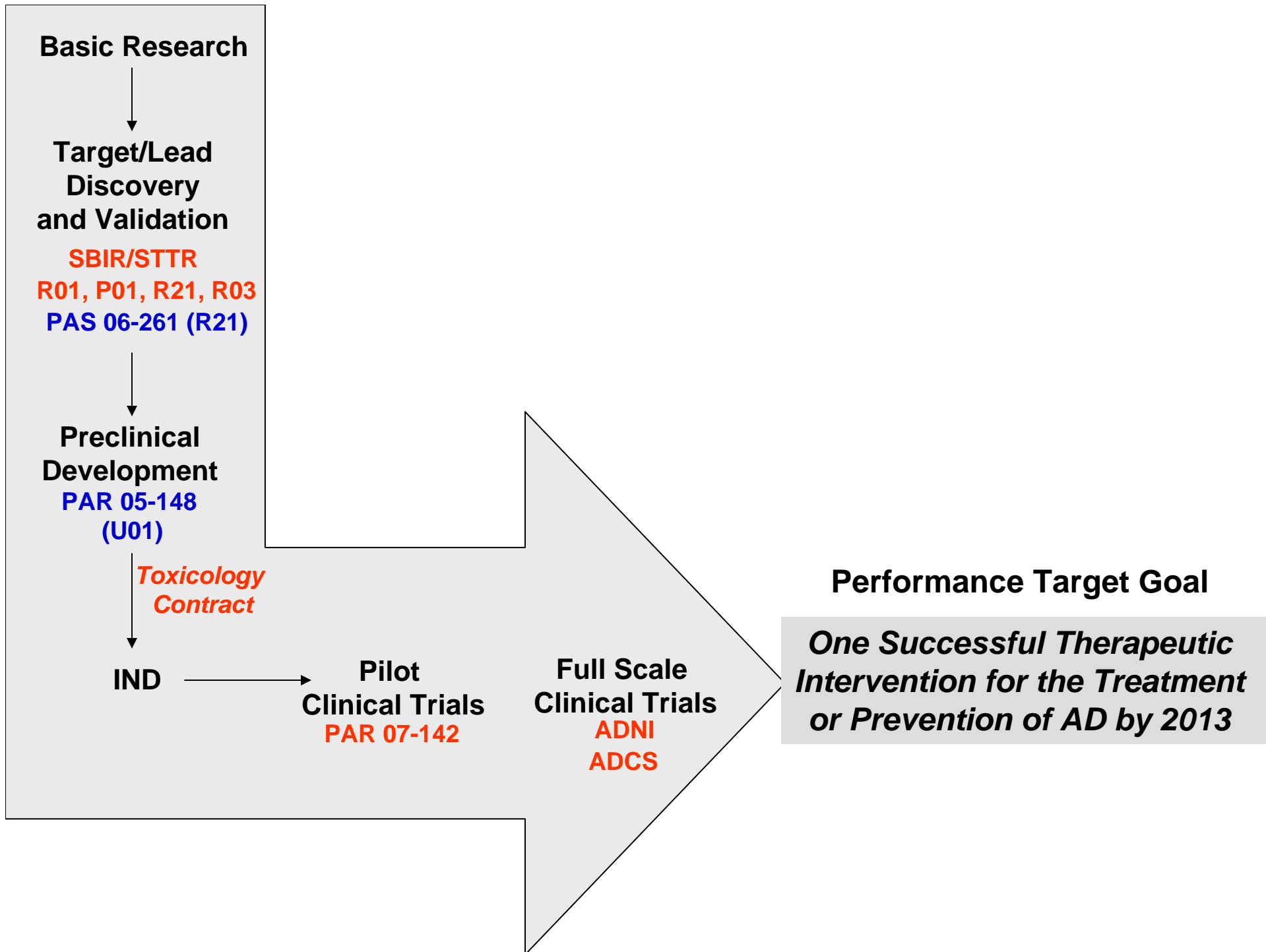


Clinical Trials

PAS 06-261  
Early Drug Discovery

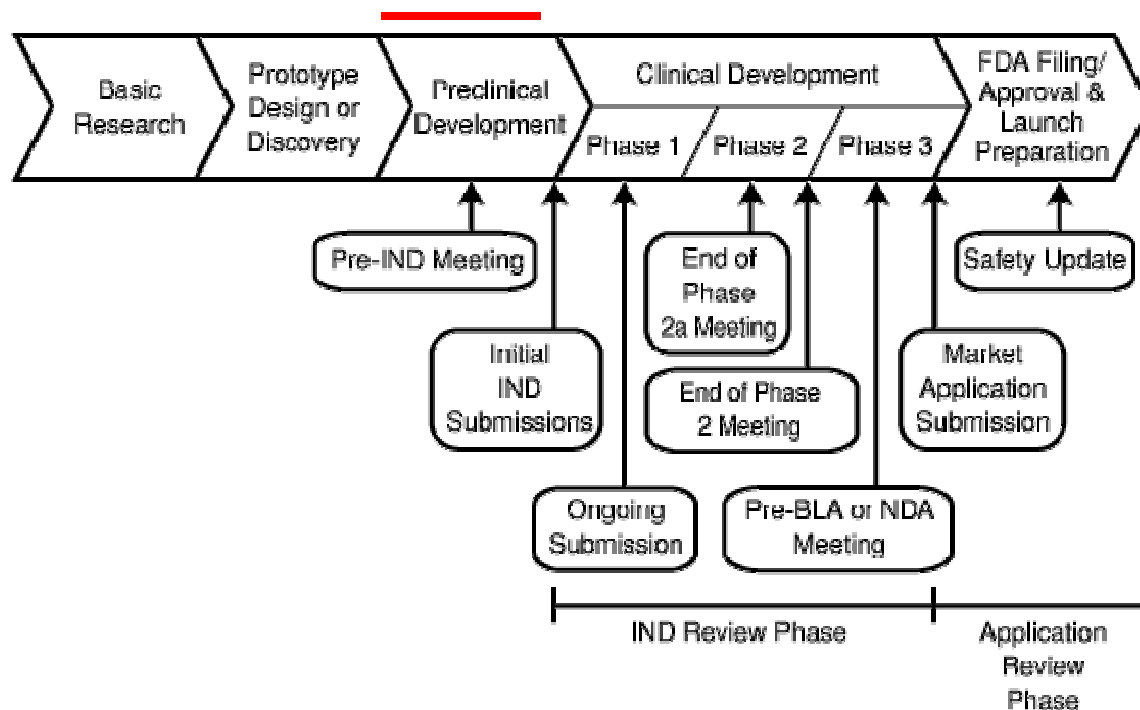
PAR 05-148  
Preclinical Drug Development





# U01 Drug Development Program (PAR 05-148)

The U01 programs in conjunction with NIA's toxicology contract aim to facilitate preclinical drug development necessary for IND submission.



## The NIA U01 program supports:

- 1) Chemical optimization of a lead compound.
- 2) Proof of concept of efficacy in an animal model relevant to AD.
- 3) Pharmacokinetic profiling.
- 4) Toxicology evaluation.
- 5) GMP synthesis.

**The projects must not be hypothesis driven.**

**Quantitative milestones are used as measures of progress and criteria for continued funding.**

**Level of support: \$300,000-\$800,000 in direct costs/year for 3-5 years**

## **NINDS Program for Translational Research**

- **Encourages therapy development projects that focus on neurological disorders germane to the mission on the NINDS (ie. Parkinson's, ALS, HD, AD).**
- **Supports the pre-clinical development of drugs, biologics, and devices.**
- **Does not support mechanistic or basic studies or clinical trials.**

# **Components of the NINDS Translational Research Program**

➤ **Exploratory/Developmental Projects in Translational Research  
-R21 mechanism (PAR-05-157)-**

➤ **NINDS Cooperative Program in Translational Research  
-U01, U54, U24 Mechanism (PAR-05-158)-**

## **Exploratory/Developmental Projects in Translational Research**

**-R21 mechanism-  
(PAR-05-157)**

**Project goals can include:**

- target identification and validation**
- assay and animal model development**
- screening for candidate therapeutics**
- development of tools and technologies used for therapy development**
- acquisition of preliminary efficacy data**

## **NINDS Cooperative Program in Translational Research**

**PAR-05-158**

- **Supports stages of preclinical therapy development through an IND or IDE application to the FDA.**
- **Milestone-driven projects focused on the identification and pre-clinical testing of new therapeutics (e.g. drugs biologics, devices).**
- **Specific milestones of progress toward therapy development must be met prior to funding of next budget period.**

# Cooperative Program Mechanisms

## ➤ U01: Single-Component Translational Research Projects

- supports therapy development projects that are focused on a single therapeutic approach for a disease entity (e.g. beta-secretase inhibitor for AD).
- level of support up to \$1M/yr in direct costs for 5 yrs.

## U54: Multiple Component Research Projects

- supports research programs that take a multidimensional approach to therapy development (e.g. anti-inflammatory, anti-oxidant, anti-amyloid and beta-secretase inhibitor for AD).
- typically U54 programs include a minimum of 3 projects and at least 1 core.
- level of support is up to \$2M/yr in direct costs for 5 yrs.

➤ **U24: Translational Resource Centers**

-support for centers providing essential pre-clinical development services to investigators engaged in therapy development.

-the center would include a pipeline of services that are necessary for moving candidate therapeutics from point of discovery to clinical testing in humans.

-level of support is up to \$2M/yr in direct costs for 5 yrs.

## **Other Relevant Translational Research Announcements:**

### **Drug Discovery for Nervous System Disorders: [PAR-07-048](#), [PAR-07-049](#)**

Participating Institutes: NIMH, NIA, NIDA, NIAAA  
R01 and R21 mechanisms

- Objective of this solicitation is to stimulate preclinical research in the discovery, design, development and testing of novel compounds aimed at prevention or treatment of nervous system disorders.**
  
- Studies aimed at the development and testing of compounds for novel targets are encouraged.**
  
- Projects designed for target identification are not covered under this announcement.**