Alzheimer's Disease Translational Research Initiatives at the National Institute on Aging

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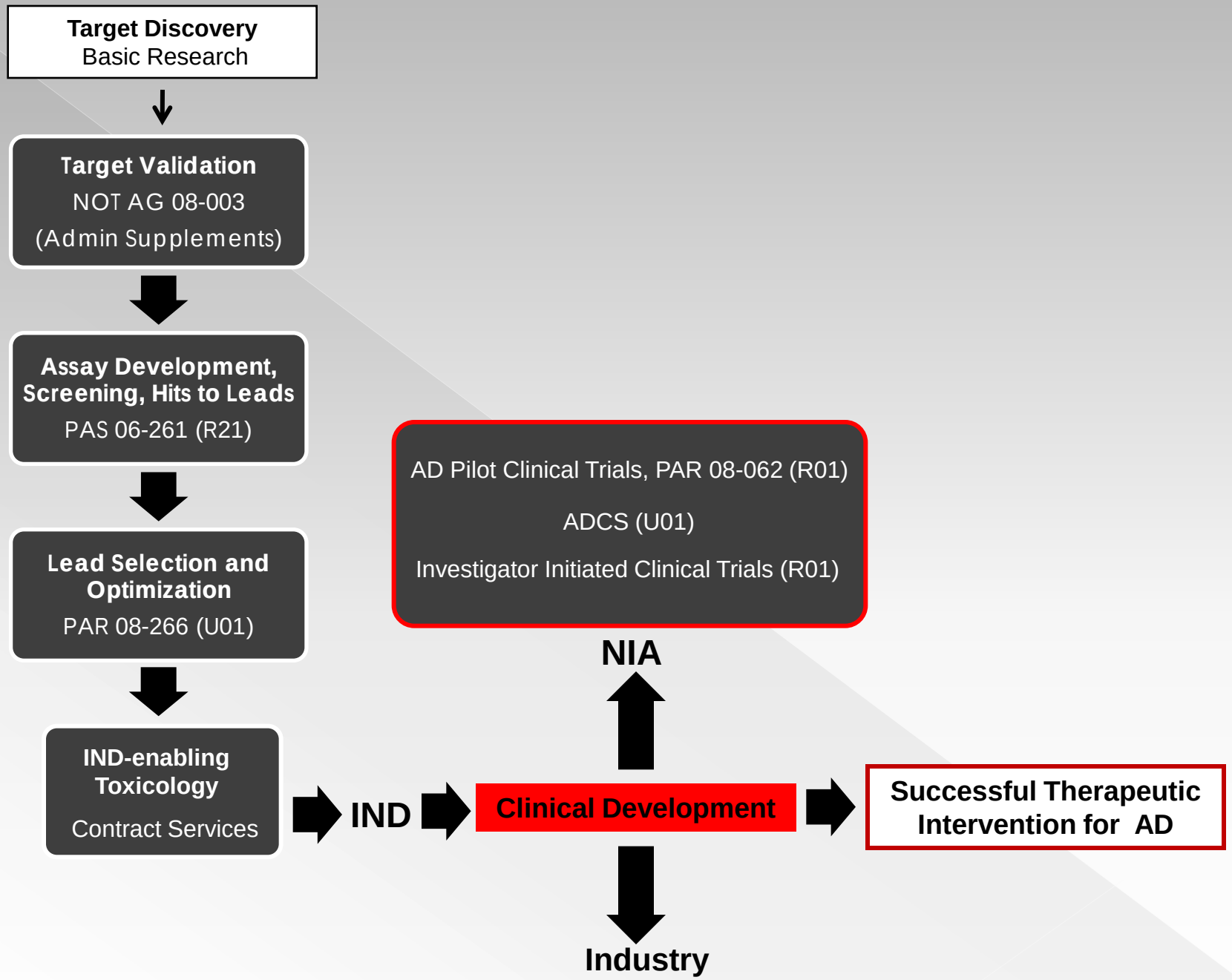
Overall Goal of NIA's AD Translational Research Program

To seed early drug discovery and preclinical drug development projects in academia and the small business community and in doing so increase the number of drug candidates that can then be clinically developed by industry or through various clinical trial programs at the NIH.

Drug Discovery Groups for Alzheimer's Disease RFA 1991-Program Projects

- **Gage** (Tuszynski): neurotrophins, genetically modified cells.
- **Greengard** (Frangione, Price, Bartfai, Gandy): APP cell biology and processing, cholinergic systems and amyloidosis, galanin.
- **Krafft** (Klein, Frail): neural proteases
- **Simpkins** (Meyer, Crews, Kozikowski): PI modulation, calcium, TRH, estrogen analogs.
- **Parker** (Eaton, Wilcox): NGF, mitochondrial function, free radicals.
- **Hefti** (Nikolics, Price): neurotrophins


Target Discovery
Basic Research
Target Validation
NOT AG 08-003
(Admin Supplements)
Assay Development, Screening, Hits to Leads
PAS 06-261 (R21)
Lead Selection and Optimization
PAR 08-266 (U01)
IND-enabling Toxicology
Contract Services
IND
Clinical Development
AD Pilot Clinical Trials, PAR 08-062 (R01)
ADCS (U01)
Investigator Initiated Clinical Trials (R01)
NIA
Industry
Successful Therapeutic Intervention for AD

NIA's AD Translational Research Funding Initiatives

Early Drug Discovery (R21)

- In 2004 the NIA partnered with the ISOA/ADDF and in 2005 released a program announcement for early drug discovery for AD (PAS 06-261). This mechanism provides up to 275K (direct costs) over 2 years.

- These R21 applications are reviewed by a Special Emphasis Panel at CSR, directed by Mary Custer.

- R21 portfolio

- 35 projects funded to date by the NIA
- 17 additional projects have been funded by the ADDF
- multiple anti –Amyloid beta approaches
- many non-Amyloid beta targets

NIA's AD translational Research Funding Initiatives

Preclinical Drug Development (U01)

- In 2005 NIA released a program announcement for cooperative agreement applications (U01) focused on preclinical drug development for AD (PAR 08-266). This mechanism provides 300K-800K per year (direct cost) for up to 5 years.

- The projects are not hypotheses driven and quantitative milestones are used as measures of progress.

- The U01 applications are reviewed by a Special Emphasis Panel at NIA's Scientific Review Office.

- U01 portfolio

-12 projects funded to date

-development of new chemical entities and reformulation/repurposing of existing drugs or natural products

-3 of the U1 projects are from investigators who received R21 support

U01 Drug Development Program

- Provides support for proof of concept of efficacy in animal models relevant to AD; medicinal chemistry and formulation; PK/PD profiling; and initial toxicological evaluation.

- The U01 program in conjunction with NIA's toxicology contract will facilitate the preclinical drug development and testing necessary for an IND submission.

- **These R21 and U01 programs have been sponsored by set-aside funds from NIA's Director's reserve through FY2009.**

Other grant mechanisms for funding drug discovery

- SBIR, STTR
- RPG: R03, R01, P01
- Training: F, K, T

Other Translational Research Announcements:

"Drug Discovery for Nervous System Disorders": PAR-10-001, PAR-10-002

Participating Institutes: NIMH, NIA, NIDA, NINDS, NIAAA

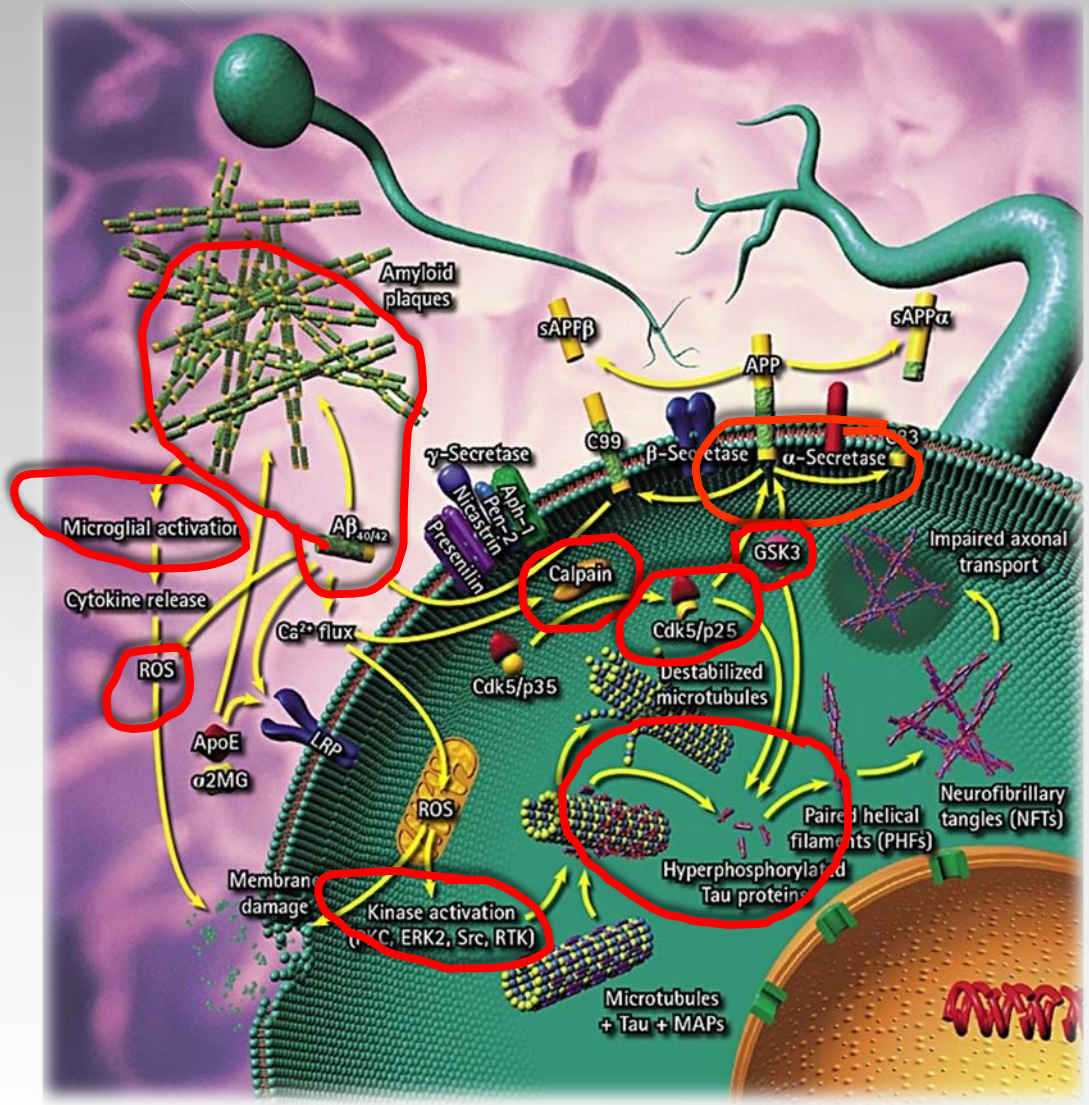
R01 and R21 mechanisms

- **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 <u>are not covered</u> under this announcement.**

Portfolio Summary



Other targets:

P75NTR

TGFBeta Receptor

NO/cGMP/CREB pathway

Phosphodiesterase 4E

GABA-A Receptors

Nicotinic receptors

Neurogenesis

NIA's AD translational Research Funding Initiatives

IND-Enabling Toxicology

NIA contract with SRI

NIA Project Officer: Neil Buckholtz PhD
SRI Principal Investigator: Karen Steinmetz PhD, DABT

National Institute on Aging

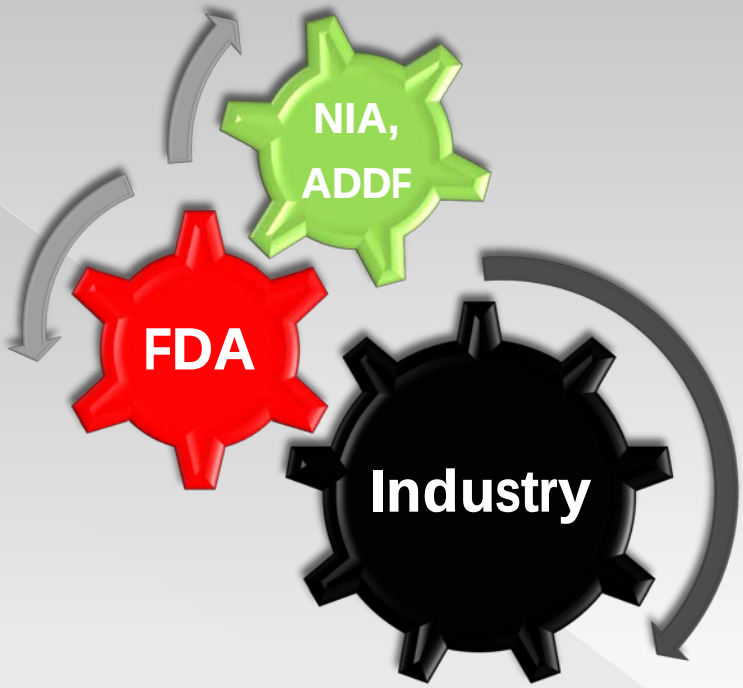
2nd Alzheimer's Disease Translational Research Investigators Meeting

September 10– September 11, 2009
Bethesda, MD

Purpose: To enable more hands-on oversight of the progress on the funded projects, to provide guidance and foster interactions among investigators funded by these initiatives, to provide a venue for the investigators to interact with drug discovery experts from academia, industry and the FDA.

Future Goals:

- To extend, expand and refine the current translational programs.
- To continue to recruit academic scientists to participate in drug discovery for AD, MCI and age-related cognitive decline.
- To establish a strategic working relationship with industry and the FDA.



"The scope of discovering, developing and delivering a drug for neurodegenerative disease is routinely under-appreciated by those who have not been directly involved in pre-clinical research and clinical development. Success requires an extremely broad and coordinated multidisciplinary effort." Jeffrey Neye, Vice President, Experimental Medicine, Johnson and Johnson Pharmaceutical

Complementary NIH Programs

Molecular Libraries Screening Centers Network

- **The Molecular Libraries Roadmap offers public sector biomedical researchers access to the large-scale screening capacity necessary to identify small molecules that can be optimized as chemical probes to study the functions of genes. This will lead to new ways to explore the functions of genes and signaling pathways in health and disease.**

- **These projects will also facilitate the development of new drugs, by providing early stage chemical compounds that will enable researchers in the public and private sectors to validate new drug targets, which could then move into the drug-development pipeline. This is particularly true for rare diseases, which may not be attractive for development by the private sector.**

MLSCN Components

Molecular Libraries Probe Production Centers Network (MLPCN). This is a nationwide consortium of small molecule screening centers that has been recently funded to produce innovative chemical tools for use in biological research. The MLPCN performs HTS on assays provided by the research community, against a large library of small molecules maintained in a central molecule repository.

PubChem. A new and comprehensive database of chemical structures and their biological activities has been developed by the National Center for Biotechnology Information at NIH. PubChem houses both compound information from the scientific literature as well as screening and probe data from the MLPCN.

Technology Development. 30 percent of the Molecular Libraries Roadmap budget is devoted to technology development in the following three areas:

-Chemical Diversity
-Assay diversity
-Instrumentation

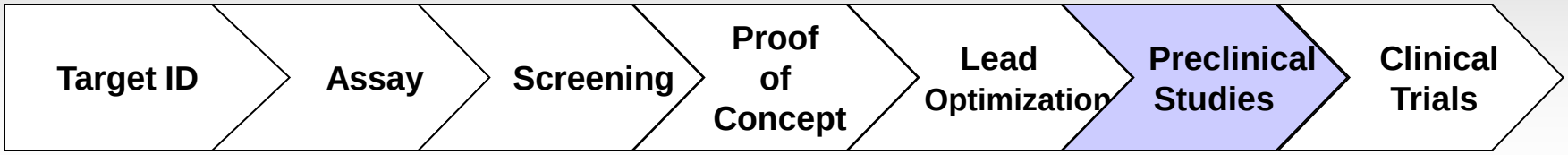
MLSCN - Current Funding opportunities

Solicitation of Assays for High Throughput Screening (HTS) in the Molecular Libraries Probe Production Centers Network (MLPCN) (R03)
PAR-09-129

Assay Development for High Throughput Molecular Screening (R21)
PAR-08-024

NIH-RAID

(Rapid Access to Interventional Development)



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Program Overview

- NIH Roadmap Initiative – program designed to address trans-NIH programmatic needs.
- NIH-RAID was established to make available, on a competitive basis, certain critical resources needed for the development of new therapeutic agents.
- Applications for the development of therapies for all diseases are accepted.
- Hands-on approach

NIH-RAID Eligibility

- Open to domestic and foreign academic and non-profit institutions, as well as SBIR-eligible businesses, and NIH Intramural programs.
- X01 Resource Access Award (**PAR-09-027).**
- Approved projects are provided access to the expertise and contract resources of NCI and NHLBI programs.
- IP retained by principal investigator.
- Small molecules, peptides, oligonucleotides, natural products, gene vectors, monoclonal antibodies and recombinant proteins are eligible for development.
- X01 Applications accepted through Sept 2011.

Entry Points

- Lead agent is identified
  - NIH-RAID X01 does not provide lead optimization or animal efficacy services
- Lead molecule not identified

When a Lead is Identified

For small molecules, natural products, peptides, oligonucleotides, and gene vectors

- Synthesis
- Scale-up production
- Development of analytical methods
- Development of suitable formulations
- Isolation and purification of natural products
- Pharmacokinetic/ADME studies including bioanalytical method development
- Range-finding initial toxicology
- IND-directed toxicology
- Manufacture of clinical trial supplies
- Product development planning and advice in IND preparation

When a Lead Is Identifed

For recombinant proteins and monoclonal antibodies

- Pharmacokinetic/ADME studies including bioanalytical method development
- Range-finding initial toxicology
- IND-directed toxicology
- Product development planning and advice in IND preparation

When a Lead Is Not Identified

- *For small molecules, natural products, peptides, oligonucleotides, and gene vectors*
  - Synthesis
  - Development of analytical methods
  - Isolation and purification of natural products
  - Preliminary Pharmacokinetic/ADME studies, including bioanalytical method development
  - Preliminary toxicology
- *For recombinant proteins and monoclonal antibodies*
  - Preliminary Pharmacokinetic/ADME studies, including bioanalytical method development
  - Preliminary toxicology

Application & Approval Process

- Three receipts per year: January, May and September.
- 25 page maximum research plan.
- Programmatic assessment of responsiveness.
- CSR review (Special Emphasis Panel).
- Preliminary cost estimate prepared by NIH.
- Investigator seminar, if warranted.
- Preparation of tasks, timeline, milestones, and costs by NIH.
- Funding decisions by co-sponsoring Institutes
- Independent Product Development Plans available

Project Management

- Projects typically completed over two years.
- Monthly progress meetings and reports.
- Meetings at decision points.
- Reports and material and sent to PI.

Administrative Supplements

- In vitro or in vivo efficacy studies
  - New agent in same model
  - Same agent in new model
  - Not model development or clinical support
- Studies completed by PI or collaborator/contractor
- $2M Budget
  - 50K direct costs
  - One year award
  - Up to 25 awards made
- Efficacy Supplements accepted in FY10 and FY11
- Five page request. Notice will be released after Oct. 1 with details.

Program Contacts:

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