Multimodal Therapies for Brain Disorders

De-Risking Multimodal Therapy Development

Keck center
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Washington, DC

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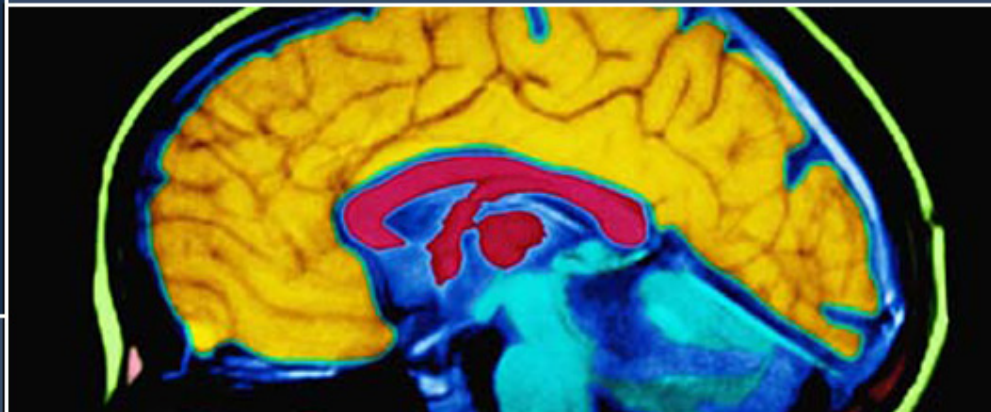
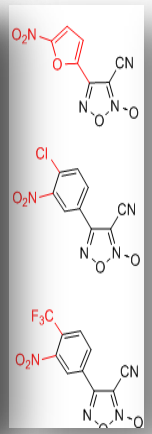
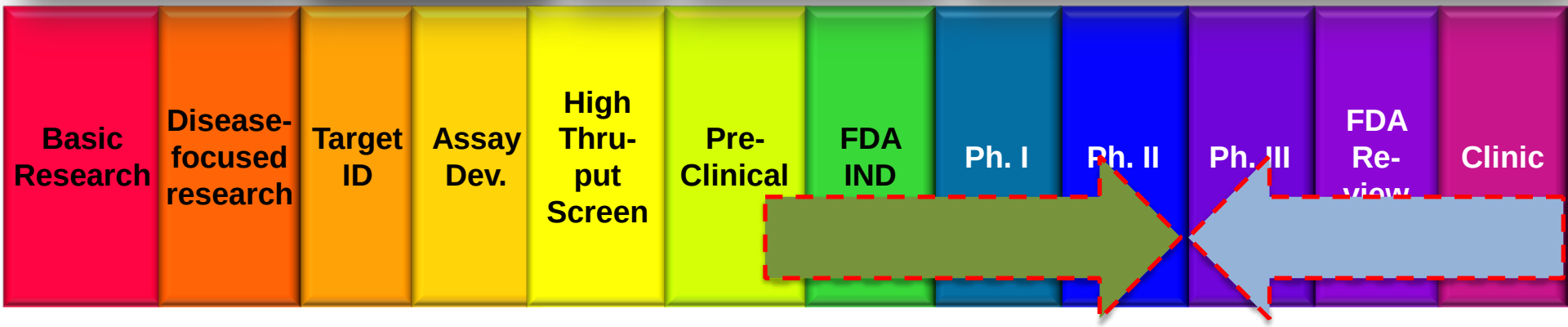


NINDS Is Investing Across the Spectrum



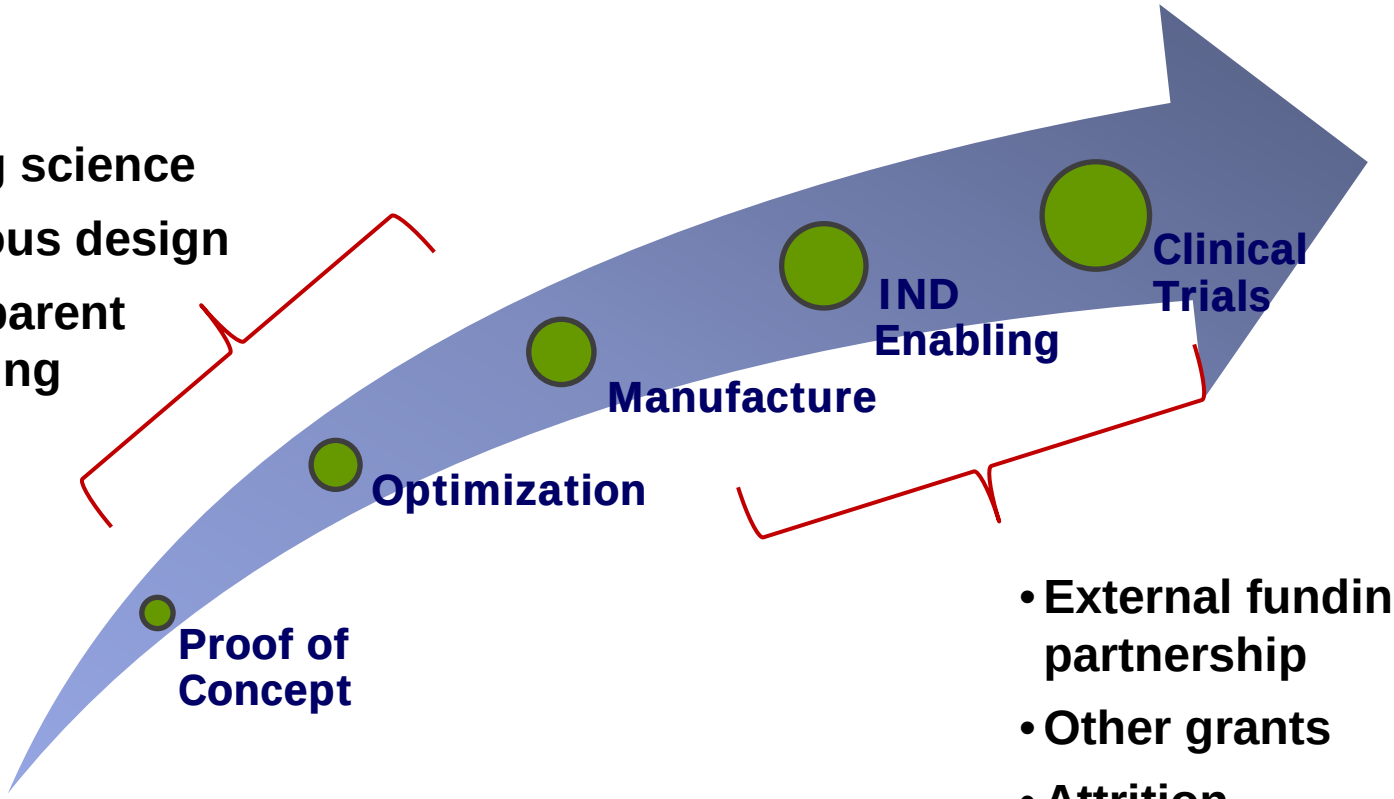


The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

NIH National Institute of Neurological Disorders and Stroke

De-Risking - Advance Projects for Hand-Off

- Strong science
- Rigorous design
- Transparent reporting

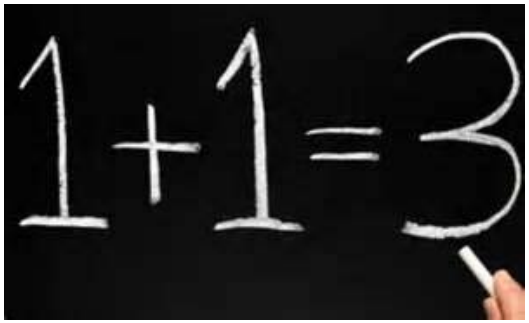


- External funding/ partnership
- Other grants
- Attrition

Decreases risk as projects successfully advance development stages

Combination Approaches Provide Pronounced Promise

- Improved efficacy and safety
- Compliance
- Reduced development of drug resistance
- lower treatment failure rate
- Significant long term savings



- Commercial considerations
- Intellectual property - life cycle management

Acetaminophen,
Chlorpheniramine,
Dextromethorphan,
Pseudoephedrine

Aspirin
Caffeine

We are Seeing Early Promising Products

- Many psychiatric and neurologic disorders are polygenic
- Multiple targets play a role
- Symptoms are complex and heterogenic
- Tools to study disease progression remain scares
- Prevalence of CNS polypharmacy:
  1. Rationale mostly based on symptoms, metabolism, side effects
  2. Few are based on a good understanding of disease mechanism(s)

Improve Side Effect Profile

Opiate dependence
FDA 2002
Buprenorphine (mu opioid partial agonist)
Naloxone (mu opioid antagonist)

Improve Brain Exposure

Parkinson's disease
FDA 2003
Levodopa
Carbidopa
Entacapone

Improve Efficacy/Side Effects Profile

Bipolar I with depression
FDA 2003
Olanzapine (atypical antipsychotic)
Fluoxetine (SSRI)

Challenging Strategies Remain

- Is the effect synergistic or additive?
- Experimental design will remain complicated
- Preclinical models are only models

<u>Preclinical Considerations</u>

- In vivo pharmacology and proof of concept studies
- Route of administration considerations
- Drug-drug interaction and contraindication
- Metabolism
- Manufacture process
- Intellectual property

NINDS Funded Project (1)

Karen Aboody, M.D.

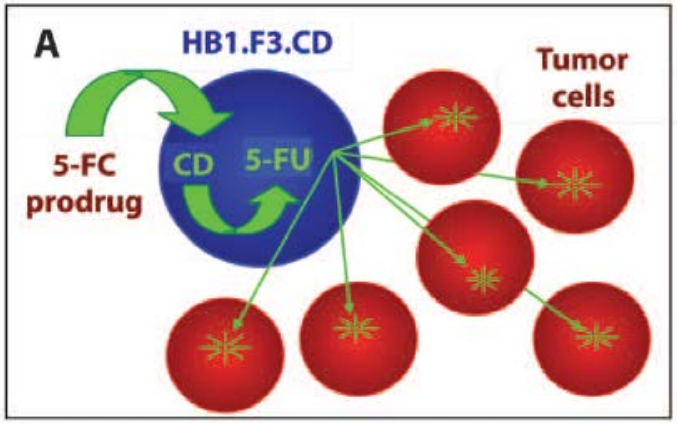
- Professor, Department of Developmental & Stem Cell Biology and Division of Neurosurgery

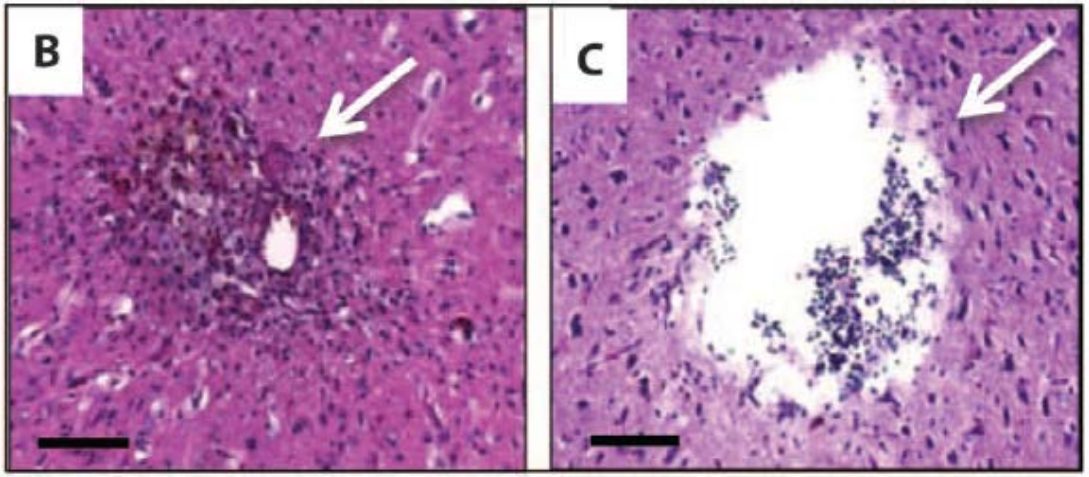
City of Hope™

National Institute of Neurological Disorders and Stroke

Neural Stem Cell–Mediated Enzyme/Prodrug Therapy for Glioma: Preclinical Studies.

Science Translational Medicine 08 May 2013

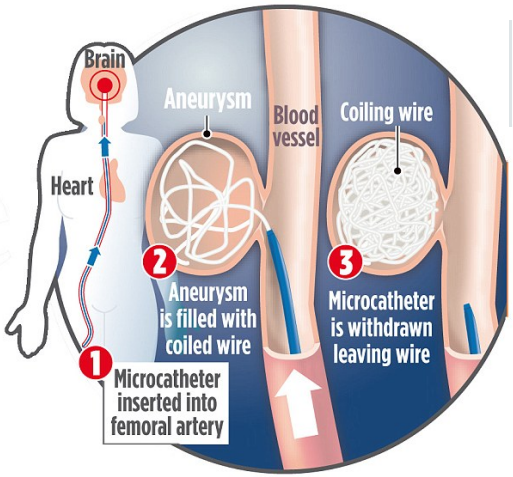




NINDS Funded Project (2)

Drug Eluting Coils for Improved Treatment of Brain Aneurysms

Current treatment options for both ruptured and unruptured aneurysms include surgical clipping (exovascular therapy) and catheter-based intervention (endovascular therapy)



ancure

1. Match kinetics of genipin release and crosslinking with rate of thrombolysis
2. Measure in vitro efficacy using a simulated coil embolization procedure
3. Assess in vitro and in vivo toxicity of genipin

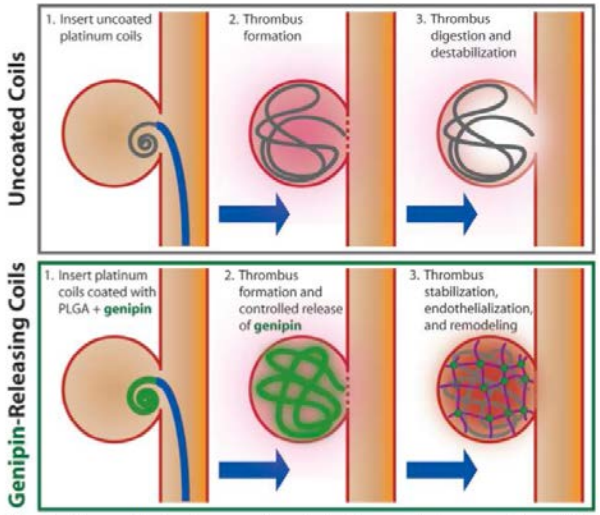
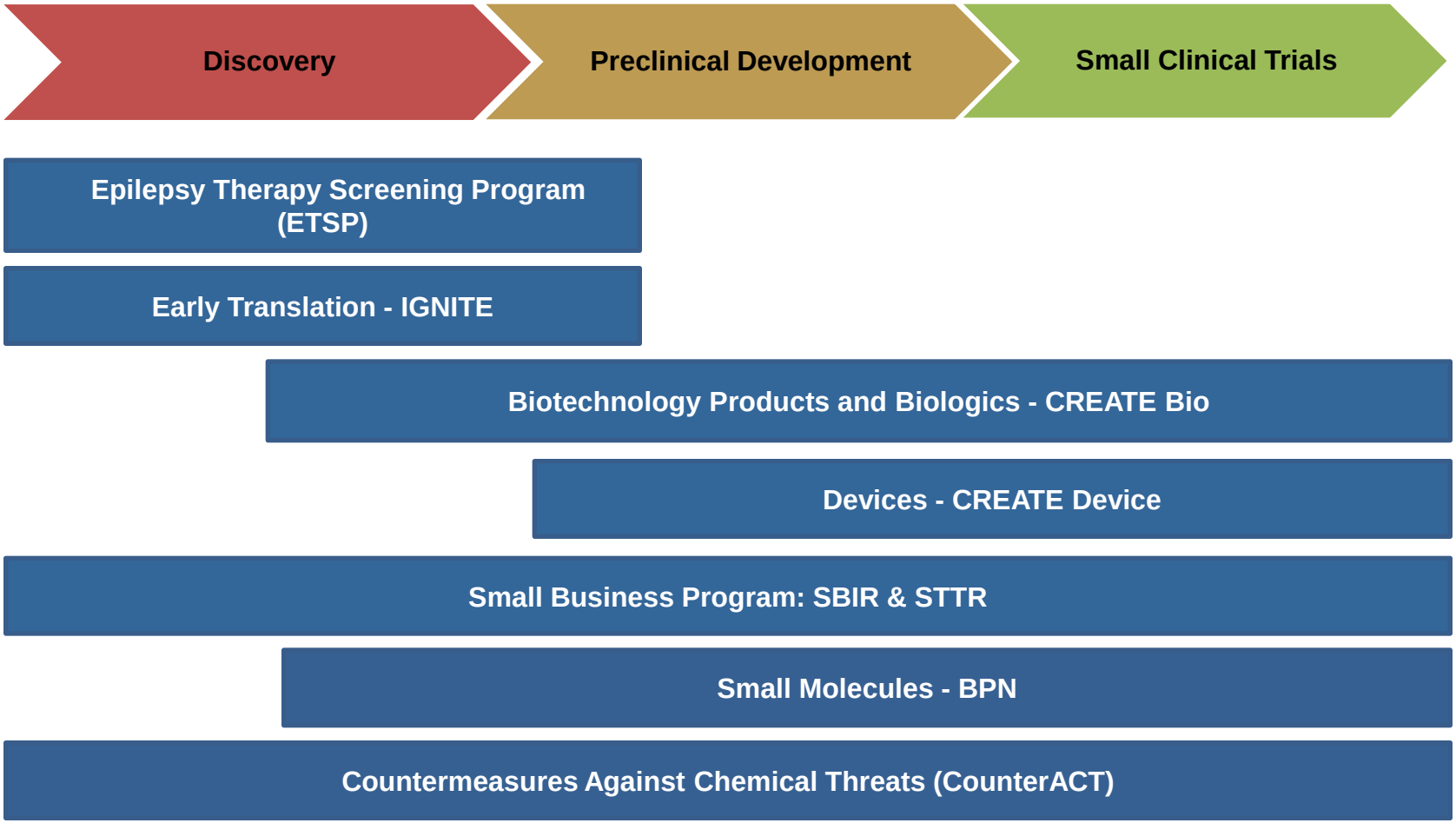


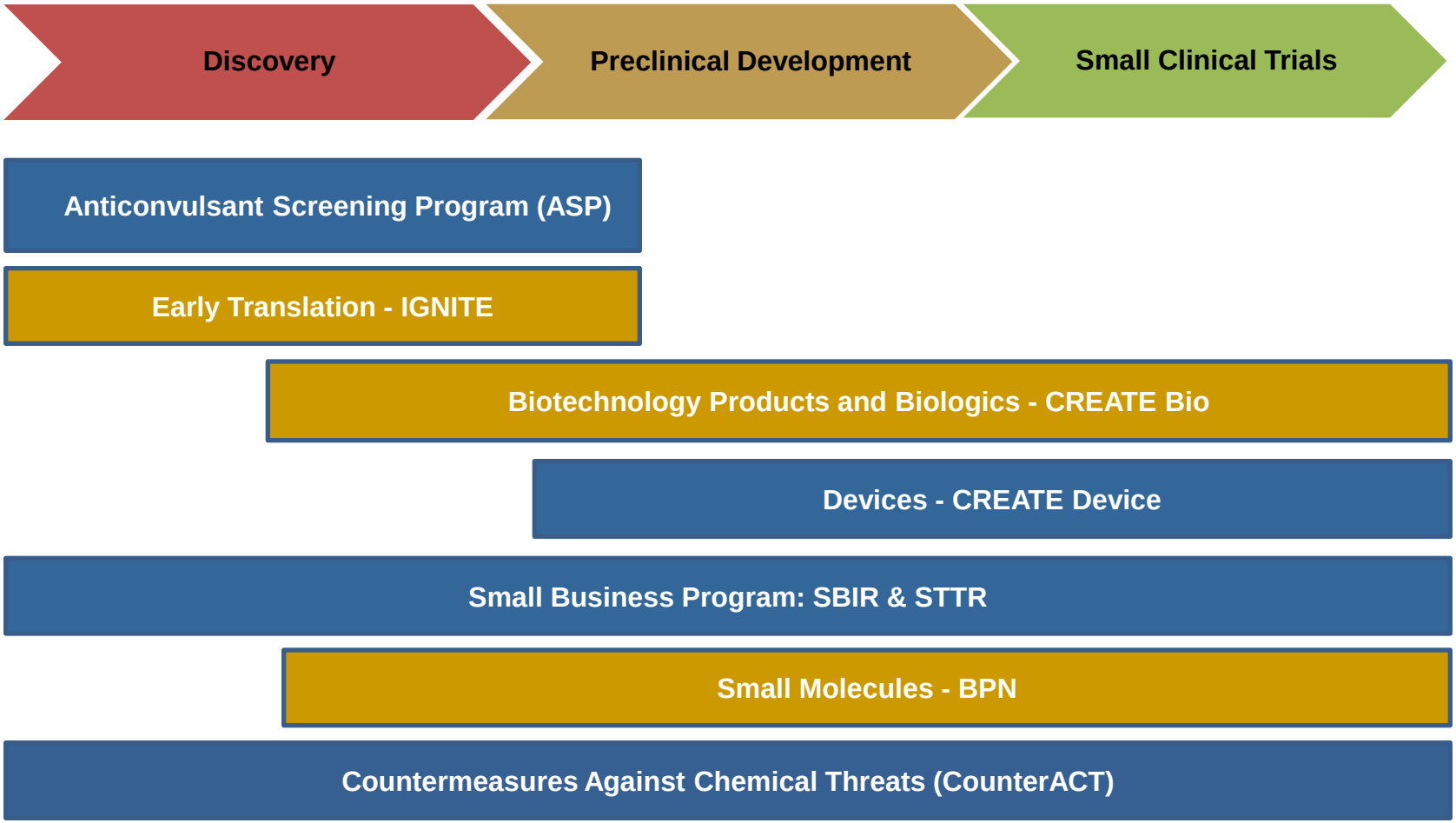
Fig. 1. Controlled release of genipin from platinum coils within intracranial aneurysms to stabilize nascent clots, prevent remodeling/disgestion, and reduce the rate of recurrence.

Translational Funding Opportunities



IGNITE: Innovation Grants to Nurture Initial Translational Efforts
CREATE: Cooperative Research to Enable and Advance Translational Enterprises
BPN: Blueprint Neurotherapeutics Network

Translational Funding Opportunities



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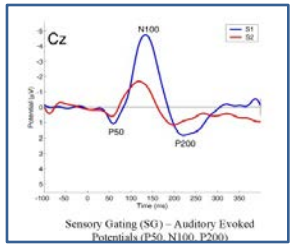
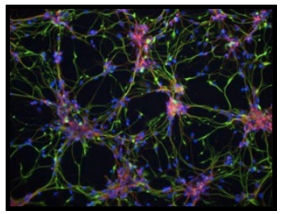
Currently Accepting Proposals

- ✓ PAR-15-070: Assay Development and Therapeutic Agent Identification and Characterization
- ✓ PAR-15-071: Pharmacodynamics and In vivo Efficacy Studies
- ✓ RFA-NS-16-013: Development and Validation of Translational Model Systems for Drug Discovery





Funding to Advance Potential Therapeutics (Devices) into Clinical Development

Modality: Therapeutic Devices

- Translational and Clinical Studies to Inform Final Device Design
- Translational and Clinical Studies on the Path to 510(k)
- Translational and Early Feasibility Studies on the Path to Pre-Market Approval (PMA) or Humanitarian Device Exemption (HDE)

Stephanie Fertig, MBA

Cooperative Research to Enable and Advance Translational Enterprises Biotechnology Products and Biologics (CREATE Bio)

Funding to Advance Potential Large Molecule Therapeutics into Clinical Development

Peptides, Proteins, Oligonucleotides, and Gene and Cell Therapies

- Optimization of therapeutic leads
- IND-enabling studies/Early phase clinical trials

End Goals

- Characterize and select a lead candidate
- Submit an IND application and conduct phase I trails

Hao Wang, PhD
Program Director

NIH National Institute of Neurological Disorders and Stroke

CREATE
Cooperative Research to Enable and Advance Translational Enterprises

Blueprint Neurotherapeutics Network (BPN)

Grand Challenge to Provide Grant Funding and Resources to Facilitate Small Molecule Drug Discovery and Development to Treat CNS Disorders

Entry Stages

- Discovery: Hit-to-lead and lead optimization
- Development: Formulation, scale up and manufacture, IND-enabling studies, and first-in-man clinical trials

End Goals

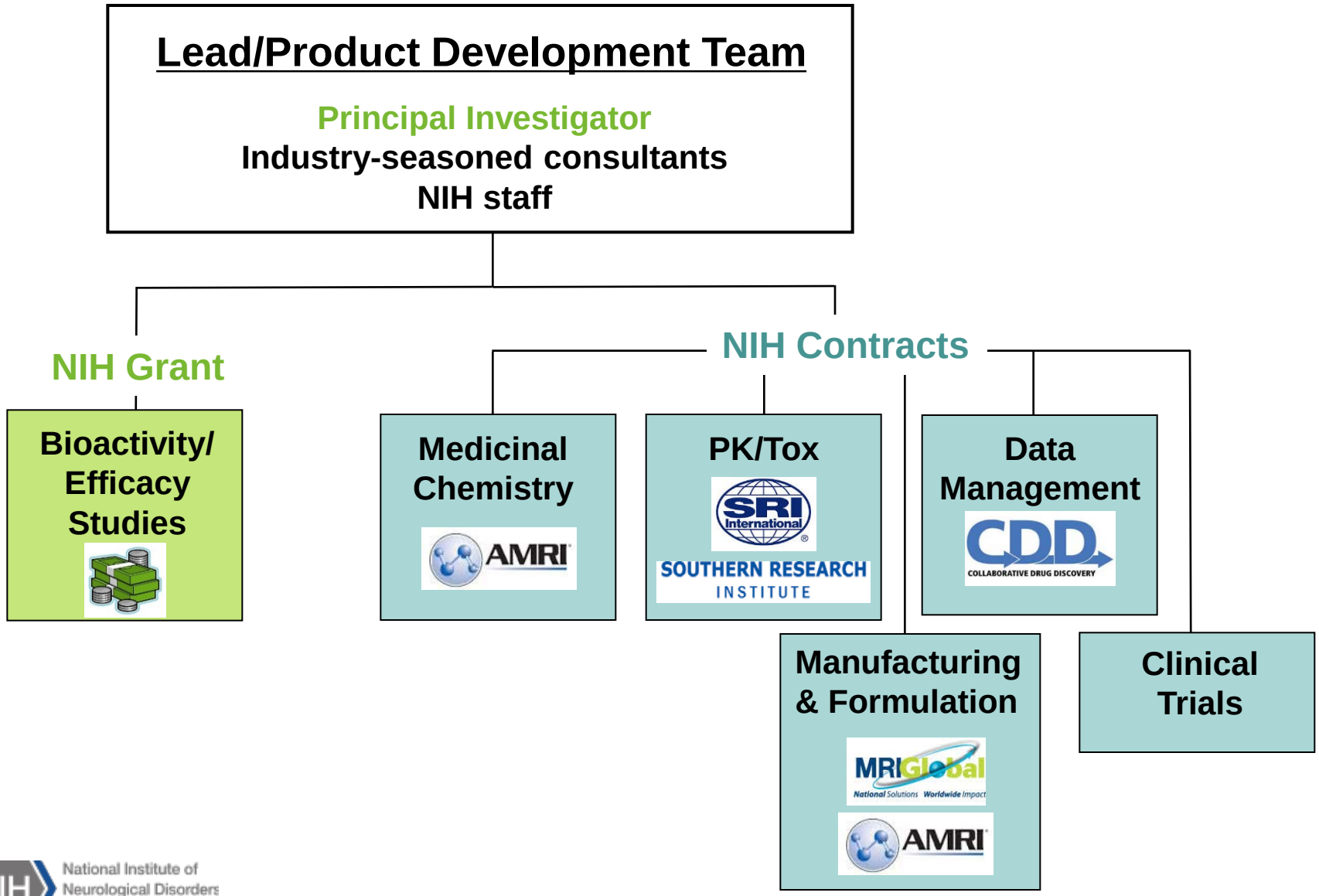
- select and characterize a preclinical candidate
- Complete IND-enabling studies, file an IND, and complete first-in-man trial
- Advance projects for hand-off

Participating Institutes and Centers:

NINDS, NIA, NIAAA, NIDA, NIMH, NICHD, NIDCR, NCCIH

National Institute of Neurological Disorders and Stroke

Infrastructure, Expertise, and Funding
Blueprint Neurotherapeutics Network (BPN) Model



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http://www.ninds.nih.gov/OTR