NIH Blueprint Neurotherapeutics Network (BPN): Funding and Resources for the Discovery of Novel Drug Candidates for the Treatment of Neurological Disorders

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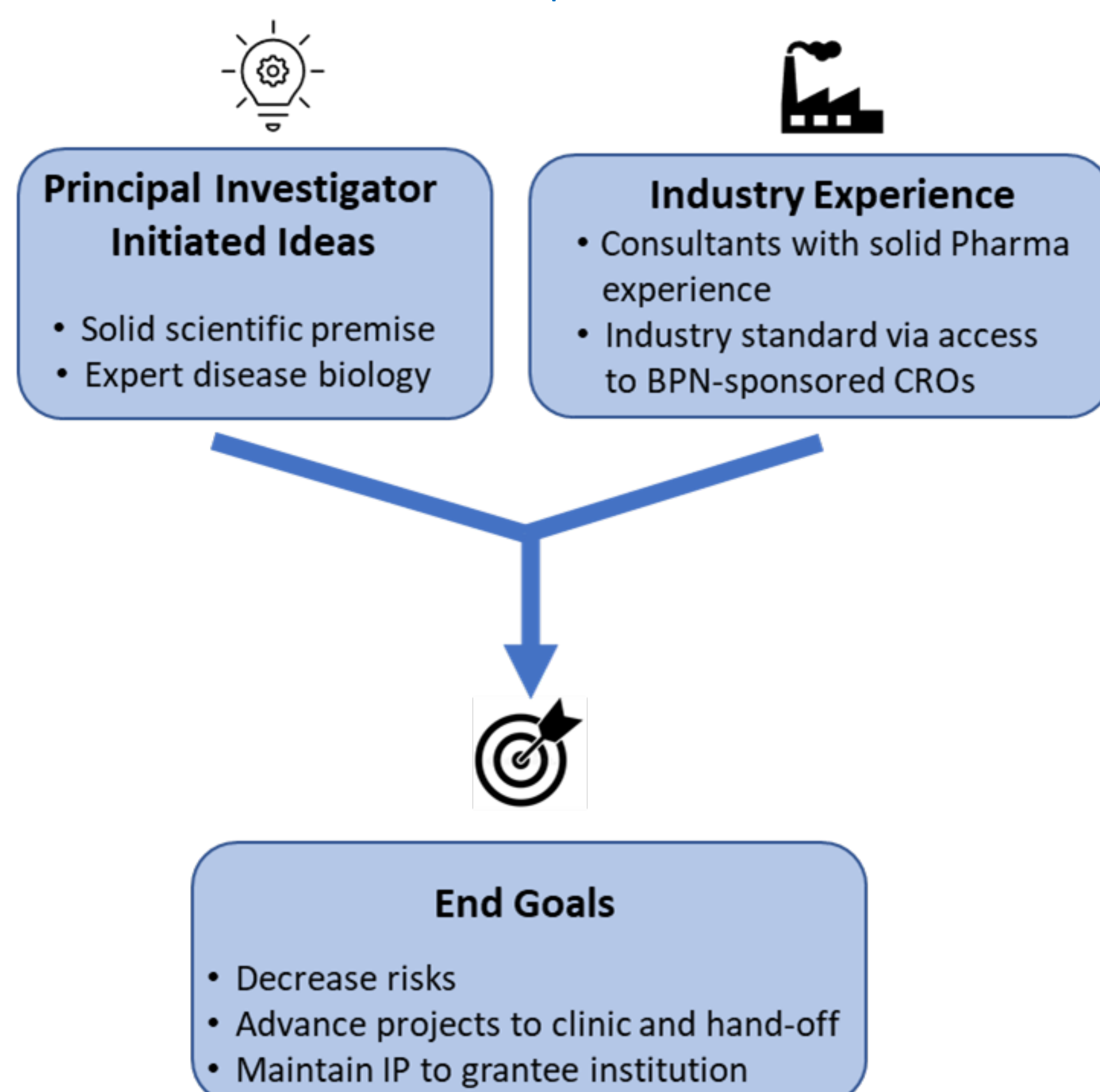
ABSTRACT

There remains a high unmet need for novel treatments for CNS diseases. Many academic and industry scientists are eager to undertake novel drug discovery approaches for the treatment of neurological disorders but lack some of the drug discovery infrastructure. To boost and de-risk drug discovery and development in the neuroscience field, NIH Blueprint for Neuroscience Research introduced a series of translational programs to promote neuroscience drug discovery and development efforts to mitigate the current pipeline gaps.
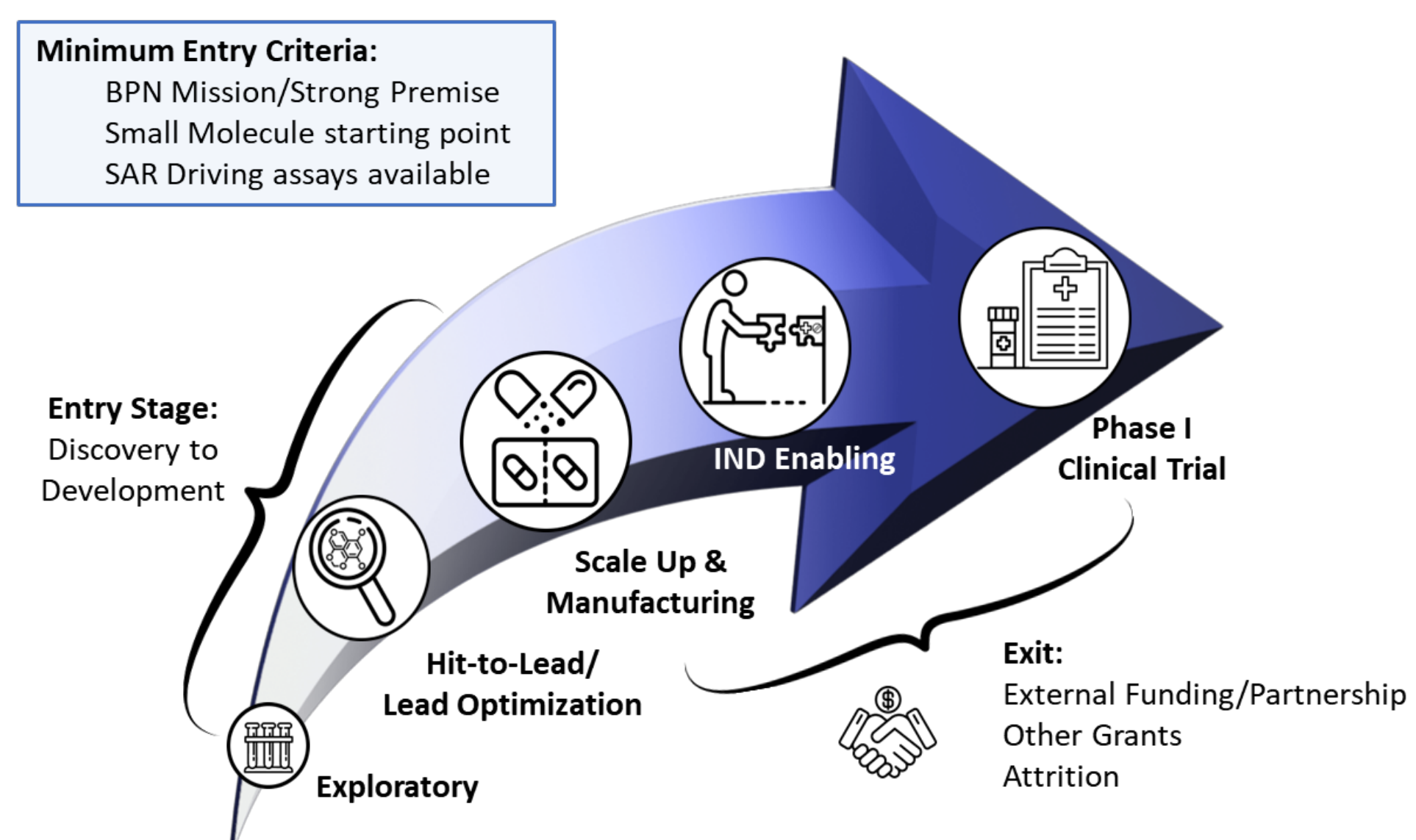
In this presentation, we demonstrate how NIH Blueprint Neurotherapeutics Network (BPN), by providing funding, resources (contract access to medicinal chemistry, DMPK, toxicology, drug manufacturing and formulation, as well as contract access to perform the Phase I clinical study) and expertise, have contributed to the successful translation of academic and industry discoveries in basic disease biology into novel drug candidates in clinical testing.

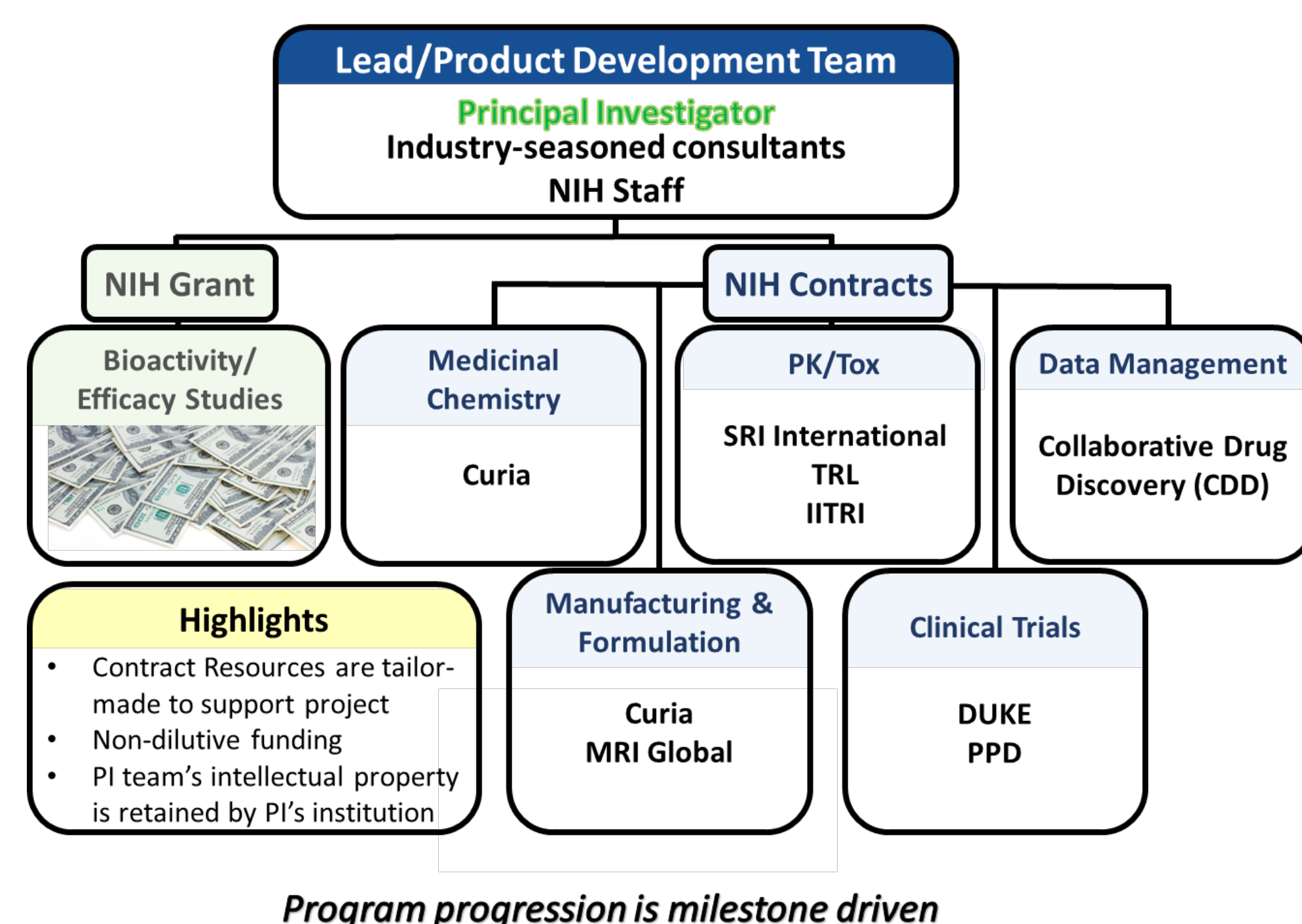## BLUEPRINT NEUROTHERAPEUTICS (BPN) PROGRAM VISION

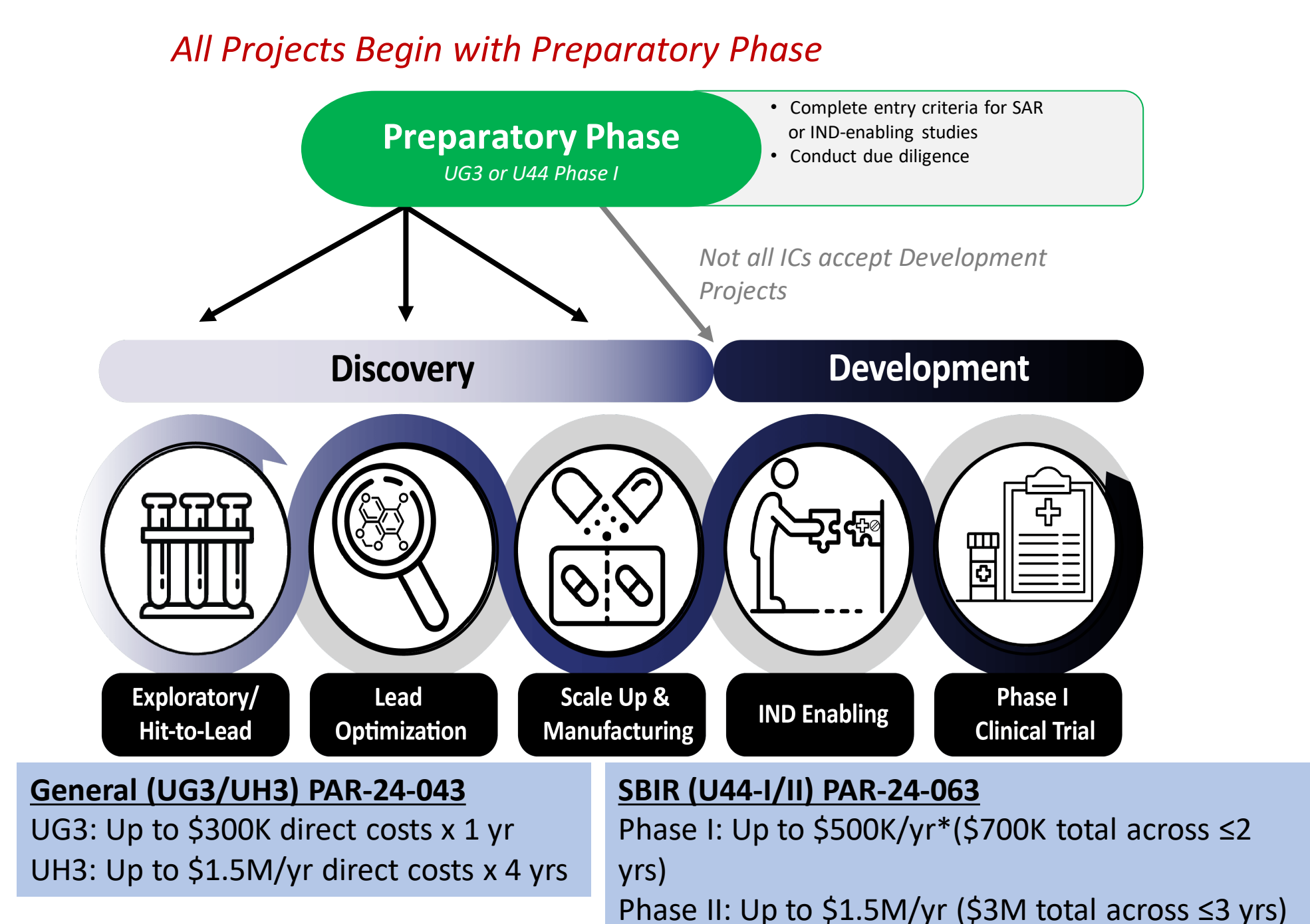"Combine Strengths of NIH and Industry Expertise for Small Molecule Neuroscience Drug Discovery & Development·

Principal Investigator Initiated Ideas
- Solid scientific premise
- Expert disease biology

Industry Experience
- Consultants with solid Pharma experience
- Industry standard via access to BPN-sponsored CROs

End Goals
- Decrease risks
- Advance projects to clinic and hand-off
- Maintain IP to grantee institution

BPN PROGRAM- SCOPE

Minimum Entry Criteria:
BPN Mission/Strong Premise
Small Molecule starting point
SAR Driving assays available

Entry Stage: Discovery to Development

IND Enabling

Hit-to-Lead/Lead Optimization

Scale Up & Manufacturing

Exploratory

Phase I Clinical Trial

Exit: External Funding/Partnership
Other Grants
Attrition

BPN PROJECT ORGANIZATION

Lead/Product Development Team
Principal Investigator
Industry-seasoned consultants
NIH Staff

NIH Grant
- Bioactivity/ Efficacy Studies

NIH Contracts
- Medicinal Chemistry — Curia
- PK/Tox — SRI International, TRL, IITRI
- Data Management — Collaborative Drug Discovery (CDD)

Highlights
- Contract Resources are tailor-made to support project
- Non-dilutive funding
- PI team's intellectual property is retained by PI's institution

Manufacturing & Formulation — Curia, MRI Global

Clinical Trials — DUKE, PPD

Program progression is milestone driven

BPN – PROJECT CAN ENTER AT ANY PRE-CLINICAL STAGE

All Projects Begin with Preparatory Phase

Preparatory Phase UG3 or U44 Phase I
- Complete entry criteria for SAR or IND-enabling studies
- Conduct due diligence

Not all ICs accept Development Projects

Discovery | Development

Exploratory/ Hit-to-Lead | Lead Optimization | Scale Up & Manufacturing | IND Enabling | Phase I Clinical Trial

General (UG3/UH3) PAR-24-043
UG3: Up to $300K direct costs x 1 yr
UH3: Up to $1.5M/yr direct costs x 4 yrs

SBIR (U44-I/II) PAR-24-063
Phase I: Up to $500K/yr*($700K total across ≤2 yrs)
Phase II: Up to $1.5M/yr ($3M total across ≤3 yrs)
*NINDS rules check specific IC rules if no vertebrate animal work $225K/yr

Next application due dates for BPN: February 9, 2024 & July 15, 2024

MILESTONE PROGRESSION BY STAGE

UG3 6-12 months (entry permitted along spectrum)
UH3 1-4 yrs depending on entry point

| Exploratory 6-12 months | Hit to Lead ~12 months | Lead Optimization ~12 months | Predevelopment 6 months | IND enabling 12 months | Ph I SAD study ~8 months |

MS1a-In-vitro assays
MS1b-Funnel/TPP
MS2-Chemistry

MS4a-candidate selection
MS4b-PK-PD established
MS4c-acceptable rodent DRF

MS6a-Pre-IND
MS6b-Acceptable TI est.
MS6c-GMP enabled
MS6d-CTM produced

MS3a-pharmacology
MS3b-chemistry

MS5a-Acceptable LA DRF
MS5b-stable form ID.
MS5c-Tractable route
MS5d-Clinical specialist
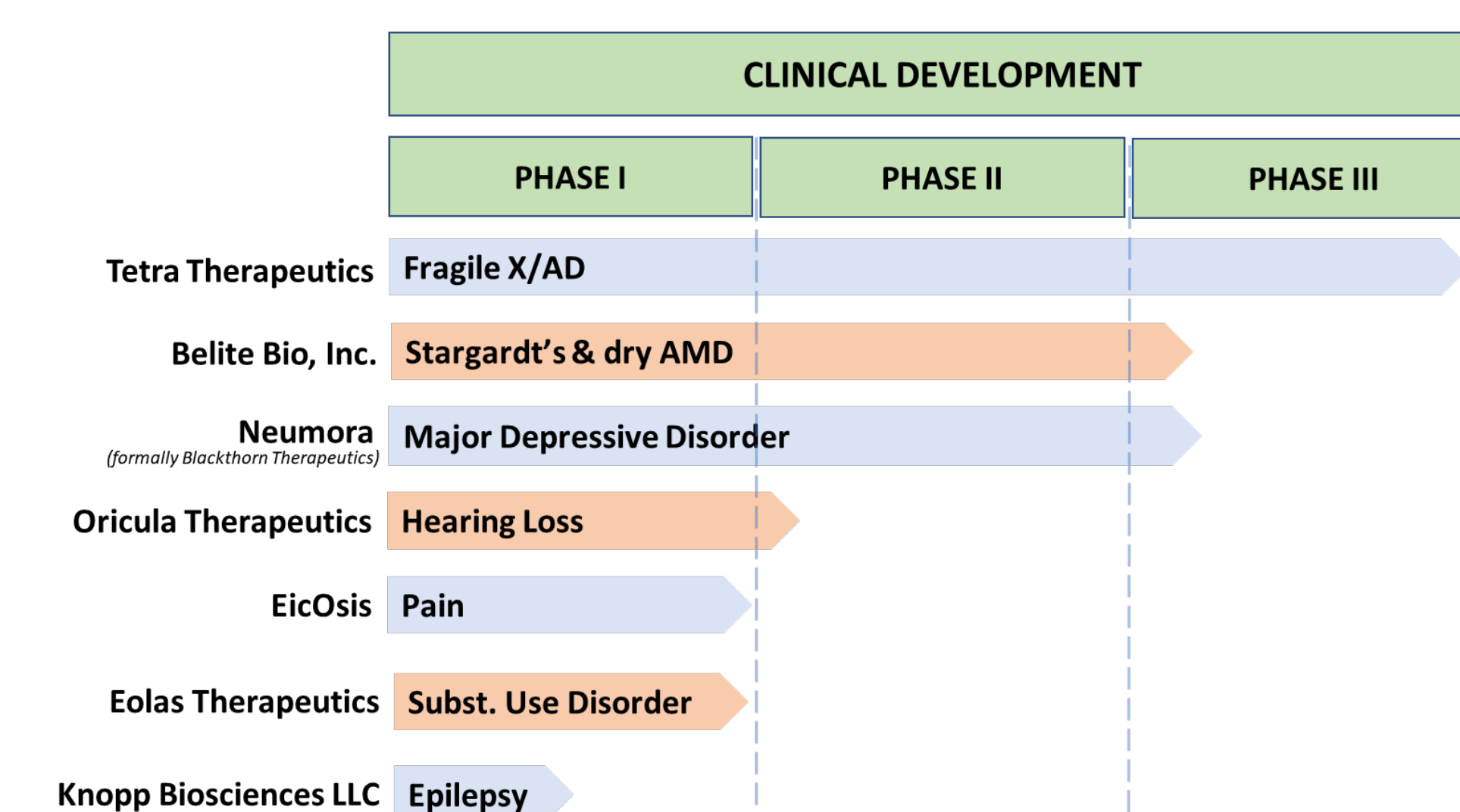
MS7a-Open IND
MS7b-Human PK acceptable

ENTRY CRITERIA

Discovery

Disease Biology
- Novel target for the disease
- Strong biological validation
- Feasible path to the clinic

Assays
- Robust in-vitro assay for optimization
- Strong confirmatory assays

Compounds
- Project must require medicinal chemistry
- Amenable to chemistry
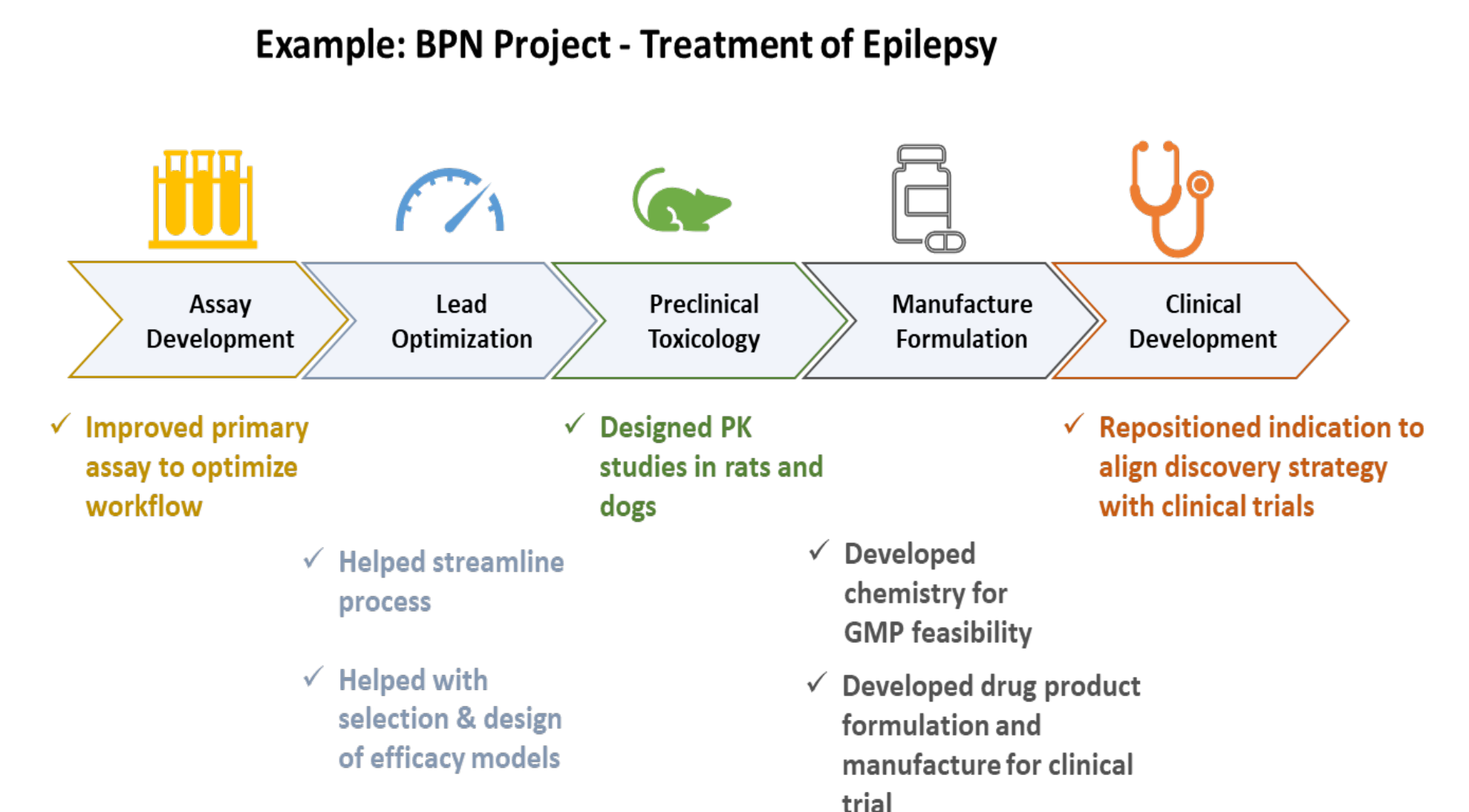- IP free of obvious roadblocks

Development

Fully Optimized Compound
- Strong data linking target to disease
- Biological & ADMET activity appropriate for intended clinical use
  - Efficacy/PD when delivered by clinically intended route
  - Fully profiled, defensible ADMET results
- Feasible path to the clinic
- IP free of obvious roadblocks

BPN PROJECTS SUCCESSFUL POST-PROGRAM PROGRESSION

	CLINICAL DEVELOPMENT		
	PHASE I	PHASE II	PHASE III
Tetra Therapeutics	Fragile X/AD		
Belite Bio, Inc.	Stargardt's & dry AMD		
Neumora (formally Blackthorn Therapeutics)	Major Depressive Disorder		
Oricula Therapeutics	Hearing Loss		
EicOsis	Pain		
Eolas Therapeutics	Subst. Use Disorder		
Knopp Biosciences LLC	Epilepsy		

10 projects have announced additional industry funding since utilizing the BPN

KNOW HOW AND EXPERTISE PROVIDED

Example: BPN Project - Treatment of Epilepsy

Assay Development | Lead Optimization | Preclinical Toxicology | Manufacture Formulation | Clinical Development

- Improved primary assay to optimize workflow
- Helped streamline process
- Helped with selection & design of efficacy models
- Designed PK studies in rats and dogs
- Developed chemistry for GMP feasibility
- Developed drug product formulation and manufacture for clinical trial
- Repositioned indication to align discovery strategy with clinical trials

A CROSS-NIH INSTITUTES EFFORT

National Institute of Neurological Disorders and Stroke — Charles Cywin, PhD — charles.cywin@nih.gov

National Institute on Aging — Lorenzo Refolo, PhD — refolol@mail.nih.gov

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Visit the BPN Webpage