National Institute of Neurological Disorders and Stroke

NINDS Programs for Translational Research

ICARE

April 12, 2018

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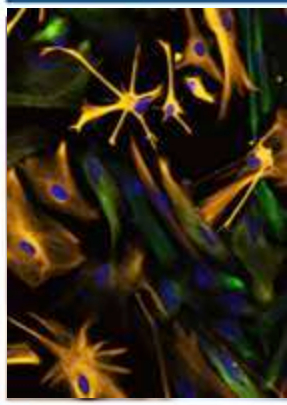
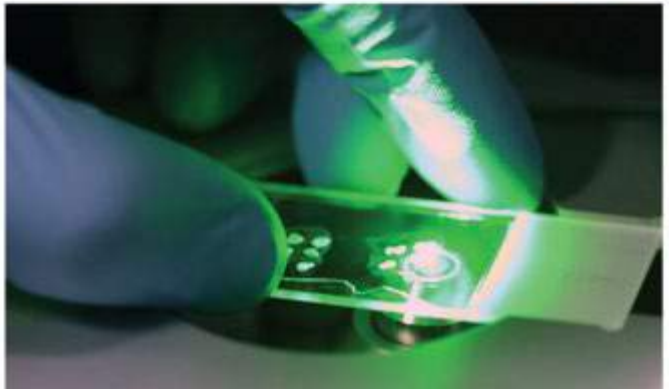




The National Institutes of Health

There are **27** different Institutes and Centers (ICs), **24** of which award grants.

Each one has:

- Different missions
- Different funding priorities
- Different budgets
- Different types of grants they support
- Different procedures for making funding decisions
- Different funding strategies

NINDS/DTR Mission

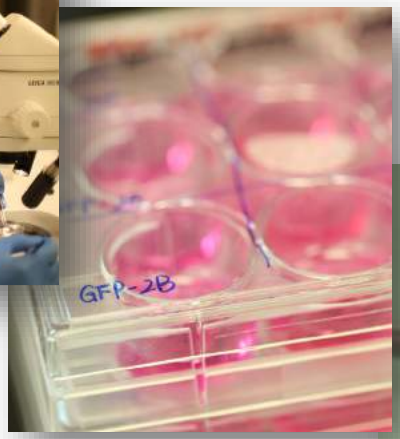
The Mission of NINDS

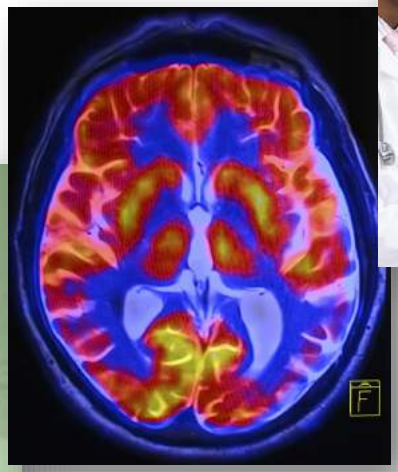
…is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

The Mission of NINDS DTR

To accelerate basic research findings towards patient use for neurological disorders and stroke by providing funding, expertise, and resources to the research community

NINDS Is Investing Across the Research Spectrum

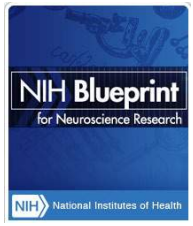




Basic	Translational	Clinical
Disease-Focused Research	*Assay Development*	*Phase I, II, III Trials*
Identify Targets	*Pre-Clinical Research*	*FDA Review*

Investing Across the Translational Spectrum

Grants



Resources

Training

Epilepsy Therapy Screening Program (ETSP)

Contracts

ADME/Tox.

Chemistry

Manufacturing

Clinical

Preclinical and Early Clinical Trials

Grants

Dissemination and Implementation Research in Health (R01)

NeuroNEXT Clinical Trial (U01)

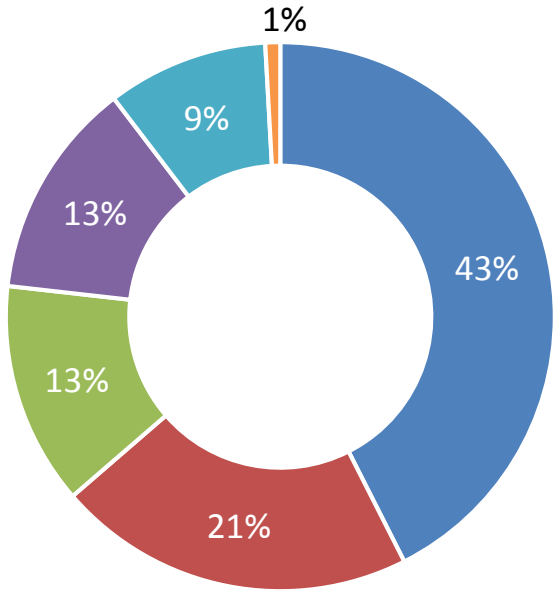
StrokeNet Clinical trials & Biomarkers (X01)

Neurological Emergencies Treatment Trials (NETT)

Clinical Trials and Infrastructure Resource

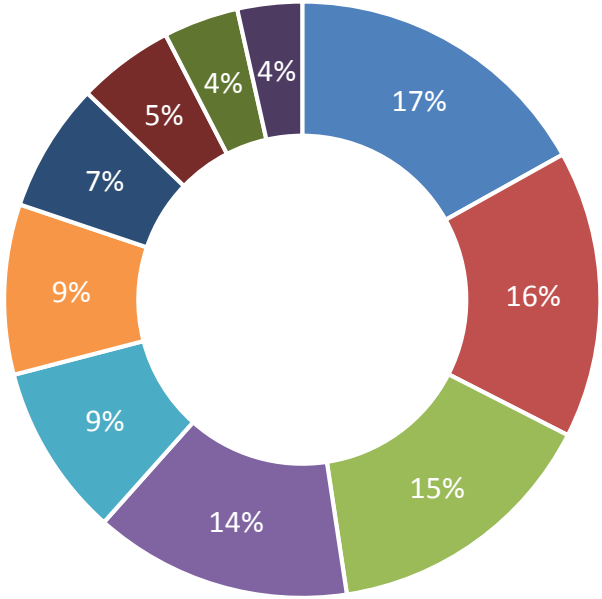
2017 Portfolio – >200 Projects

Funding by Research Area



- Therapeutic small molecule, $47 M
- Therapeutic biologic, $23.4 M
- Research tool/animal model, $14.5 M
- Therapeutic/prevention device, $14.2 M
- Diagnostic device/ biomarker, $10.5 M
- Other (contracts, etc), $1 M

Funding by Indication



- Stroke, $18.7 M
- Countermeasure, $17.3 M
- Neurodegeneration, $16.7 M
- Genetic/rare disease, $15.5 M
- Injury, $10.4 M
- Epilepsy, $10.2 M
- Neuroscience research tools, $7.8 M
- Multiple/other, $5.8 M
- Pain, $4.5 M
- Brain tumor, $3.9 M

Total: $111 M

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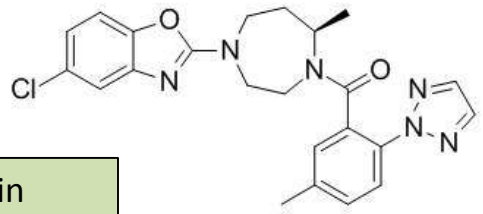
Funding for Basic Research

Funding

At least partial NINDS or NIH support

Other

Suvorexant for Insomnia



Discovery of orexin peptide and receptor family

Canine narcolepsy caused by mutations in orexin receptors

Narcoleptic patients have profound decrease in CSF orexin

Dirunal variation of CSF orexin levels in humans

Both orexin receptors are required for wakefulness

Dual orexin receptor antagonist (suvorexant) induces sleep in rats, dogs, humans

Clinical trials demonstrate safety and efficacy of suvorexant

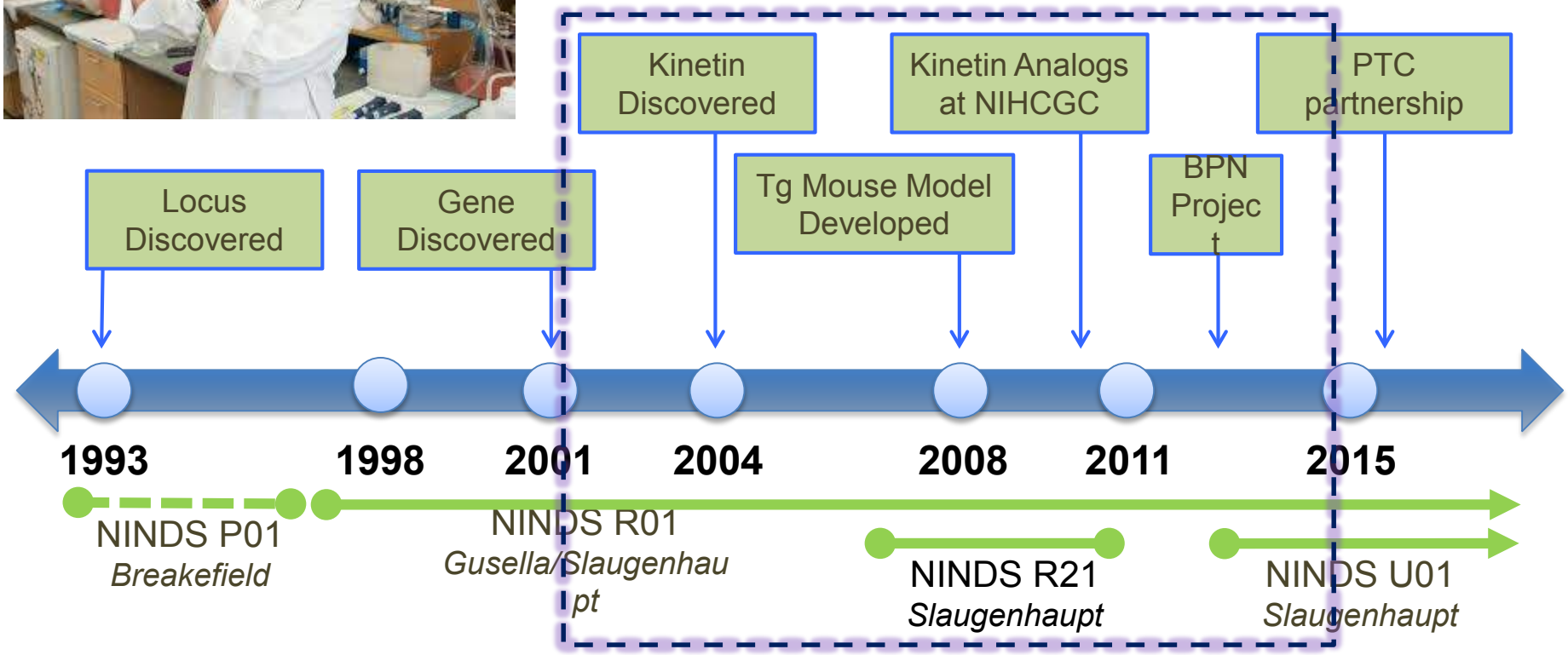
FDA approves suvorexant for insomnia

2000s

2010s

Funding to Bridge Bench to Bedside

NINDS Support for Familial Dysautonomia Research



Additional Public/Private Funding

Dysautonomia Foundation
Israeli Science Ministry
Harvard Center for Neurodegeneration and Repair
US Israel Binational Science Foundation

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Epilepsy Therapy Screening Program (ETSP)

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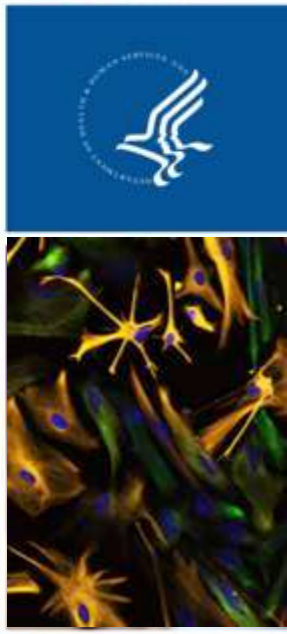

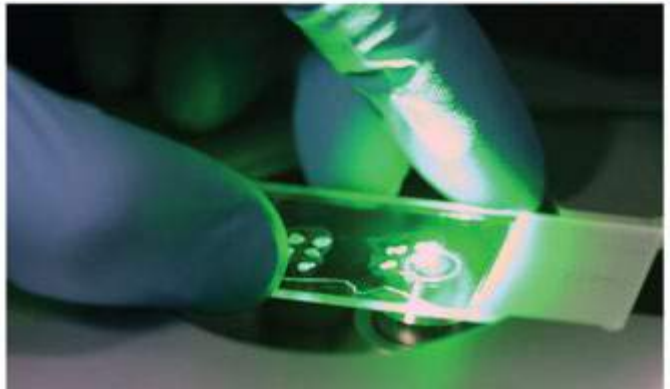

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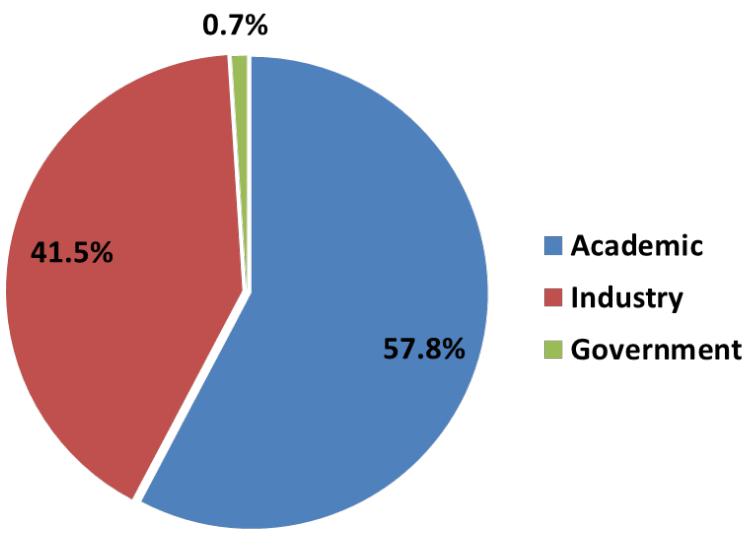
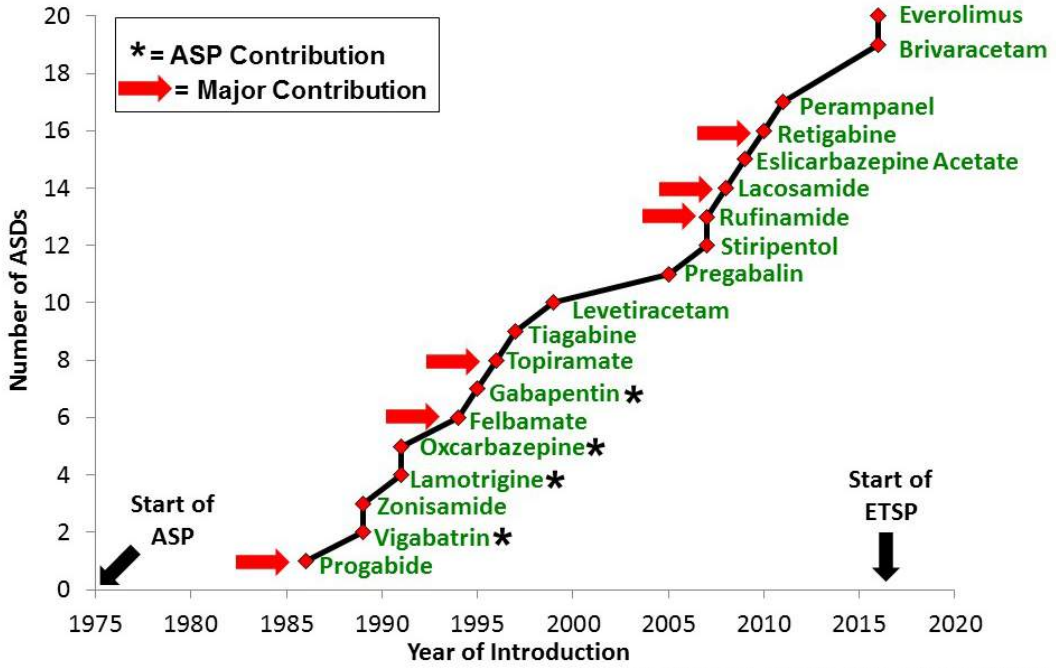
ETSP Mission

To facilitate the discovery of new therapeutic agents addressing the unmet medical needs in epilepsy

A Strong Foundation: Anticonvulsant Screening Program(ASP)





Adapted from: Loscher & Schmidt , 2011, Epilepsia, 52:657

- Established in 1975 to facilitate the discovery of new antiseizure drugs
- Free testing in rodent antiseizure screens (University of Utah)
- >600 total participants, academia/industry, from 38 countries
- 32,000 compounds tested
- Contributed to advancement of 9 antiseizure drugs to the market

ETSP is the "Next Generation"

New name reflects expanded mission

- Pharmacoresistant epilepsy
- Disease prevention and modification

External Consultant Board established

- Feedback on testing strategy, model development and program direction
- Members: Amy Brooks-Kayal, M.D.; Henrik Klitgaard, Ph.D., Wolfgang Loescher, Ph.D., Steve Perrin, Ph.D.

➔ ***ETSP continues to offer screening services free of charge to qualified applicants from around the world***

Current Contract

Current Contract Cycle: Sept 2015 to Sept 2020

- Awarded after open competition

Prime Contract site: University of Utah

- Principal Investigator: Karen Wilcox, Ph.D.
- Two subcontract sites perform additional specialized studies
  - SynapCell (France)
  - University of Washington (Seattle WA)

Administrative Staff (NINDS)

- John Kehne, Ph.D. (Program Director)
- Brian Klein, Ph.D. (Scientific Project Manager)
- Shamsi Raeissi, Ph.D. (Scientific Project Manager)
- Shalini Sharma, M.S. (Program Analyst, Chemist Specialist)
- Ana Garcia, B.S. (Program Coordinator)
- Dhananjaya Kempegowda, B.E. (IT Specialist)

Key Principles of ETSP Testing

Ensure that compound submissions are high quality

- Strict criteria for identity and purity
- Chemical/biological rationale and other supporting data used to evaluate suitability for compound entry into the program

Align screening with specific goals for different types of treatments

- Generate separate screening flows
- Incorporate etiologic models relevant to human pathophysiology
- Build comparative pharmacology databases
- Monitor the effectiveness of screening flows and decision trees, and make modifications as needed

Pharmacoresistance Epilepsy Workflow

IDENTIFICATION

Acute Seizure Models

- *6 Hz Electrical Stimulation (mouse, rat)*
- *Maximal Electroshock Test (mouse, rat)*

Behavioral Toxicity Screens

- *Rotarod (mouse)*
- *Neurological Impairment (rat)*
- *Locomotor Activity (rat)*

Chronic Seizure Models

- *Corneal Kindled Seizure Test (mouse)*
- *Spontaneous Bursting Slice from Post-kainate Status Epilepticus Rat (in vitro)*

DIFFERENTIATION

Mesial Temporal Lobe Epilepsy Model *(mouse)*

Lamotrigine-Resistant Amygdala Kindling *(rat)*

Post-Kainate Status Epilepticus-Induced Spontaneous Recurrent Seizures *(rat)*

Video-EEG monitoring

Other ETSP Performance Areas

Special Populations

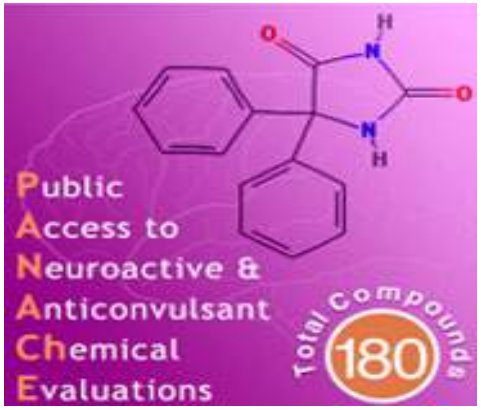
- Viral-induced epilepsy
  - Theiler's murine encephalitis virus (TMEV) induces seizures in C57Bl/6 mice
  - Strong inflammatory signal → seizures and epileptogenesis
  - Potential value for evaluating novel drug interventions
- Acute benzodiazepine-resistant status epilepticus
  - Lithium/Pilocarpine model (rat)

Antiepileptogenesis & Disease Modification

- Mouse mTLE model (focal hippocampal kainic acid injection)
- Mouse mTLE model (focal amygdala kainic acid injection; in development)
- Rat chronic epilepsy model (spontaneous recurring seizures in rats previously exposed to kainic acid induced status epilepticus)

Learn More about ETSP Testing

- **PANAChE (Public Access to Neuroactive and Anticonvulsant Chemical Evaluations) Website** http://panache.ninds.nih.gov
- Publicly-accessible database for *non-confidential data* on compounds tested by the ETSP
- Include non-proprietary compounds that probe specific mechanisms of action
- Provides detailed information on test data, test protocols & flowcharts
- 180 total compounds in database to date, more coming
- Goal: become increasingly useful as an epilepsy drug discovery tool



National Institute of Neurological Disorders and Stroke

Innovation Grants to Nurture Initial Translational Efforts (IGNITE)

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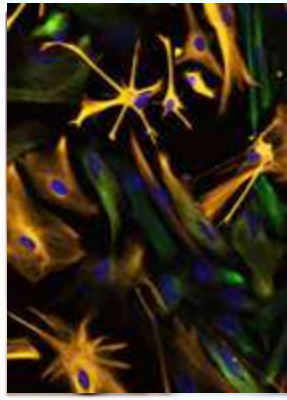
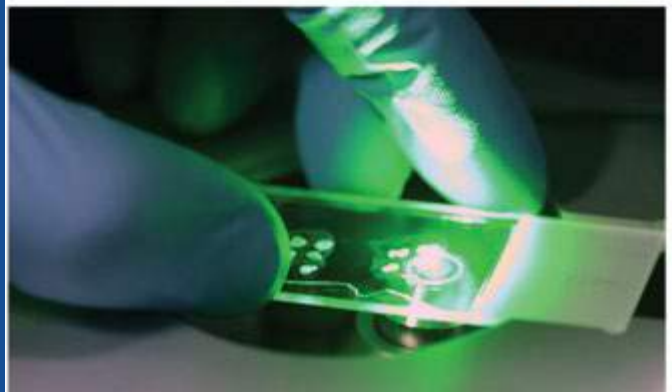
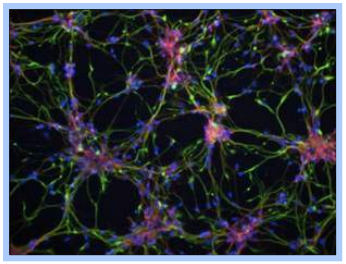


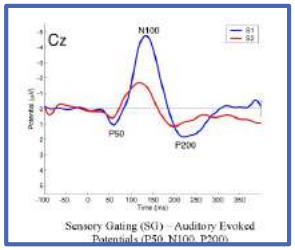


IGNITE: A Suite of Early Translational Funding Opportunities

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

Uses a Phased R61/R33 Milestone-Driven Grant Mechanism

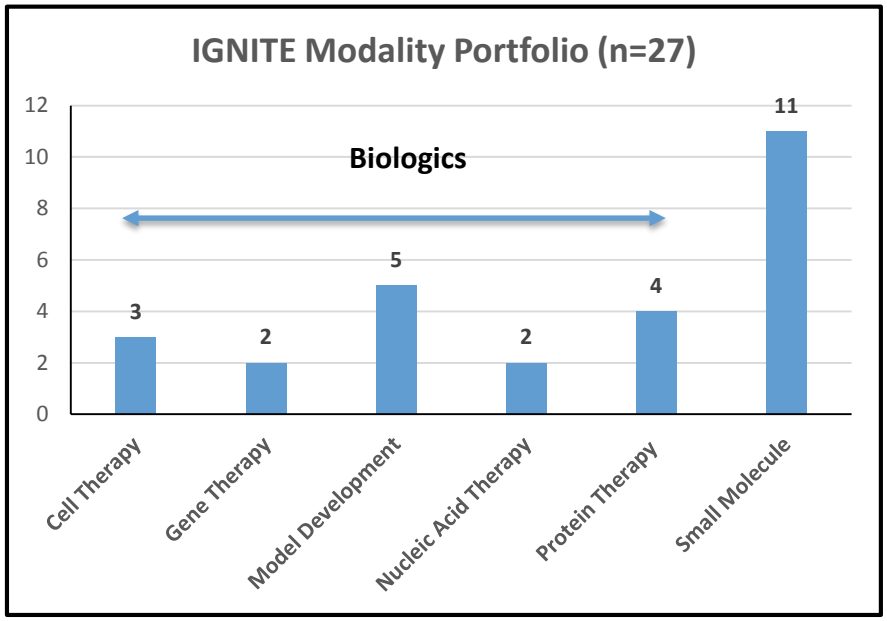


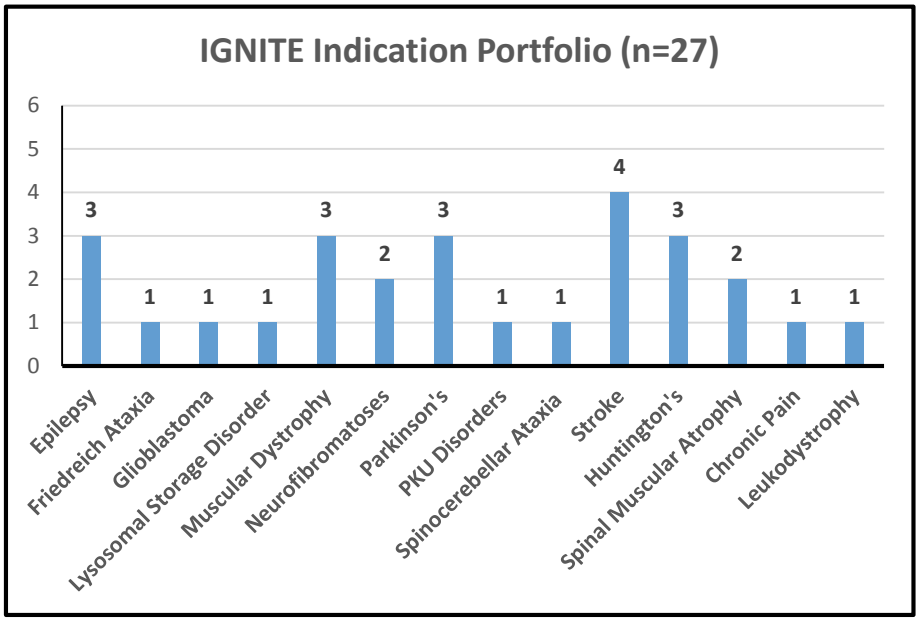


Budget: ≤$499,000 in Any One Year; ≤$750,000 for Entire Project

Re-Issued FOAs: Next Application Due Date: Early Summer, 2018

Snapshot of IGNITE Portfolio





Awarded Epilepsy IGNITE Projects

Project Title	Indication	Awardee Institution	IGNITE Funding Opportunity	Project Completion Year
Inhibitors of TrkB Signaling	Temporal Lobe Epilepsy	Duke University	PAR-15-070 Assay Development and Hit Identification	2019
Anti-Convulsant Screening Using Chronic Epilepsy Models	Chronic Epilepsy	Massachusetts General Hospital	PAR-15-070 Assay Development and Hit Identification	2020
EP2 Antagonists as Novel Anti-Epileptogenic Agents	Post-Traumatic Epilepsy	Emory University	PAR-15-071 In Vivo Efficacy	2020

NIH Natio Neur and S

Most Advanced Project: Small Molecule Inhibitors of TrkB Activation of PLCγ1

James McNamara, Duke University

- Temporal lobe epilepsy (TLE): a common form of epilepsy that lacks preventive and disease modifying therapy
- Extensive target validation with genetic evidence: uncoupling TrkB from PLCγ1 (with a peptide) *transiently following* status epilepticus prevents TLE in animal model > 1 month later
- Developed a high throughput screen that identified multiple small molecule chemotypes that inhibit TrkB interaction with PLCγ1
- Currently identifying hits that satisfy potency and selectivity criteria
- Exploring entry into BPN program for lead identification and optimization

PAR-15-070: Assay Development and Hit Identification

Goals

- To develop and validate primary and secondary screening assays
- To utilize these screening assays to identify new therapeutic agents
- To conduct focused optimization of these new therapeutic agents

Supported Activities

- Assay Development and Validation
- Screening (including HTS) and Hit Identification
- Focused *in vitro* Hit Characterization and Optimization

PAR-15-071: Hit Characterization and In Vivo Efficacy

Goal

To demonstrate that early-stage neurotherapeutics (novel or re-purposed) have sufficient biological activity to warrant investment in later stage discovery and development, such as CREATE, BPN or alternative funding programs

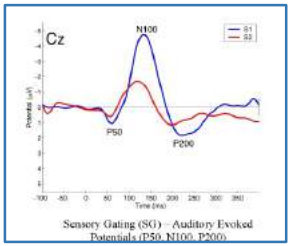
Supported Activities

- Physicochemical/biophysical characterization
- Pharmacokinetic evaluation
- Proof of concept: In vivo efficacy and pharmacodynamic evaluation

RFA-NS-16-013: Development of Model Systems and Pharmacodynamic Markers

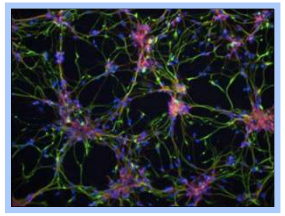
Goals

- To develop a fully validated model system, testing paradigm or PD marker that can be used in both preclinical and clinical settings to test the biological effects of a candidate neurotherapeutic agent
- To promote early development of pharmacodynamic markers (PD) used in the discovery of neurotherapeutics
- To promote a significant improvement in the translational relevance of preclinical models and tools used in the discovery of neurotherapeutics



Supported Activities

- Development of animal models, ex vivo model systems and pharmacodynamic markers for use in drug discovery and development
- Internal and external validation of animal models, ex vivo model systems and pharmacodynamic markers



New Neuroscience Biomarker Program: Quick Summary

Goal : *Facilitate the development of high quality biomarkers to improve the quality and efficiency of clinical research (Phase II and beyond)*

- **Four NINDS Funding Opportunities Supporting a "Fit For Purpose" Validation Process**

Analytical Validation of a Candidate Biomarker For Neurological Disease
***PAR-NS-18-549, *PAR-18-550**

Rigorous validation of biomarker measurement performance characteristics (precision, accuracy, sensitivity, etc.)

Clinical Validation of a Candidate Biomarker For Neurological Disease
***PAR-NS-18-548, **PAR-NS-18-664**

Rigorous, fit for purpose clinical validation of a candidate biomarker for use in clinical trials and/or clinical practice (sensitivity, specificity, prevalence, etc)

Cooperative Agreement Grant Mechanisms
U01 (Academic) and U44 (SBIR)

- **Workshop: "Best Practices in Neuroscience Biomarker Discovery Planned for Early 2019**

- **Centralized NINDS "one-stop" Resource Web Page Tissue/data repositories, funding, information**

**Application Due Date: July 18, 2018*
***Application Due Date: July 18, 2018*

NIH National Institute of Neurological Disorders and Stroke

Questions?

Thank you for your interest!

https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/Funding-Programs-Researchers/IGNITE

The R61/R33 Grant Mechanism

R61: Assay/Model Development and Preparation for R33 (≤2 Years for R61; ≤3 Years for the Project)

Go/No-Go Milestones Each Year
Does This Warrant Further Investment?

R33: The Main Event.
(≤2 Years R33; ≤3 Years for the Project)

Extremely Clear, Quantitative and Definitive Milestones are *Essential*.
Milestones Evaluated Each Year with Only 1 Go/No-Go Point
Transition to R33 via Administrative Review

Definitions: PAR-18-XXX

- Pharmacodynamic (PD) Marker
  - Component of the molecular pathway mediating the biological effects of therapeutic target modulation (direct or indirect)
  - Component of disease etiology that is involved in drug target modulation
- Internal Validation
  - Precision, reliability, analytical sensitivity, accuracy and dynamic range of endpoints utilized in the model system of PD marker measurements
- External Validation
  - Similarity between model or model system and clinical manifestation of the disease ("face" validity)
  - Similarity between model or model system and physiological basis of the disorder ("construct" validity)
  - Similarity between the effect of a validated therapeutic intervention in the model or model system and in the clinical disease population ("predictive" validity)

National Institute of Neurological Disorders and Stroke

NINDS CREATE Bio Program

April 12, 2018

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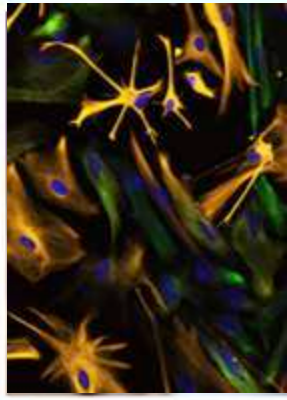
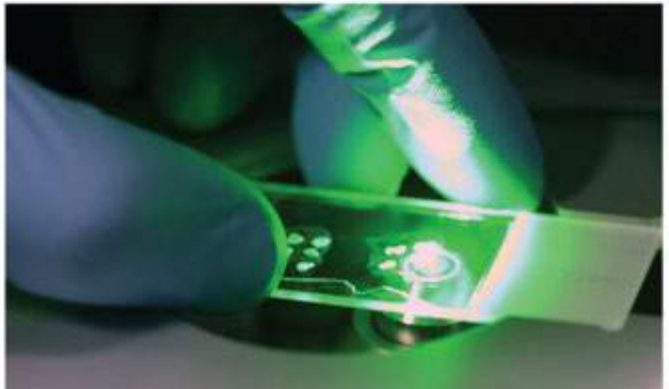




Cooperative Research to Enable and Advance Translational Enterprises Biotechnology Products and Biologics (CREATE Bio)

Funding Translation Promising Therapeutic Biologics

Modalities: Peptides, Proteins, Oligonucleotides, Gene and Cell Therapies

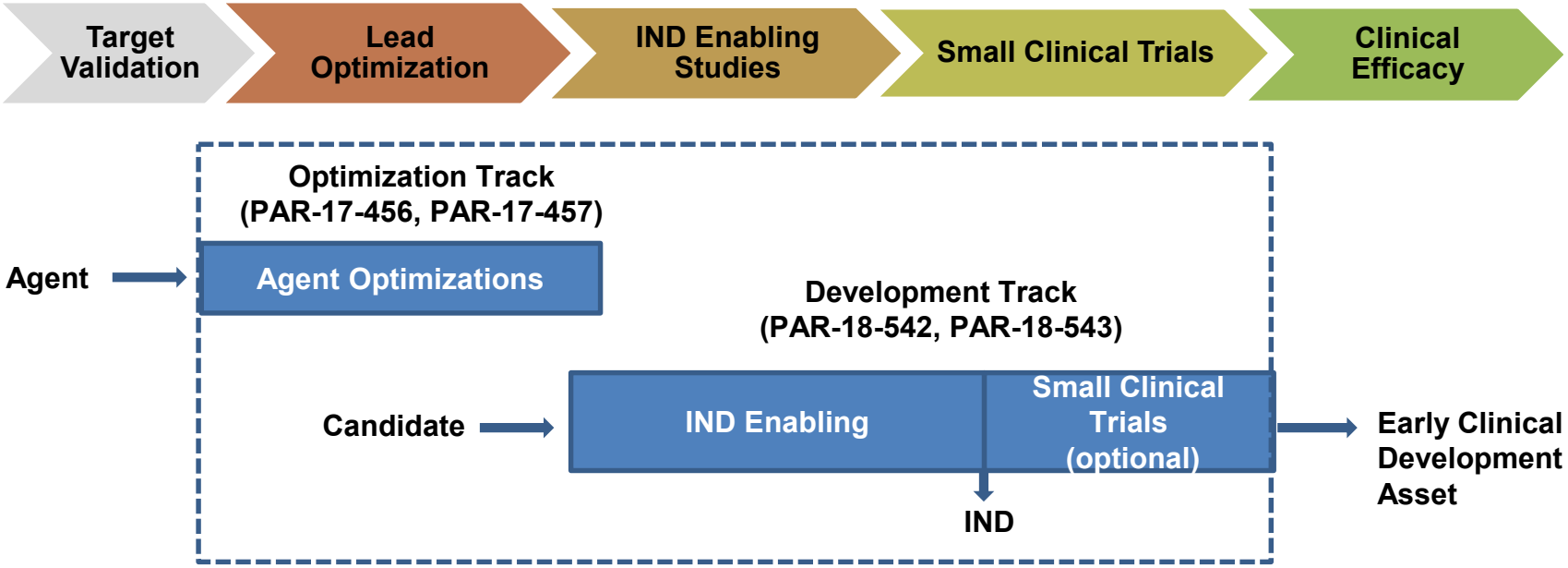
Purpose

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

End Goals

- Optimization: Characterize and select a lead candidate
- Development: Submit an IND application and/or conduct Phase I Trials

CREATE Bio Program



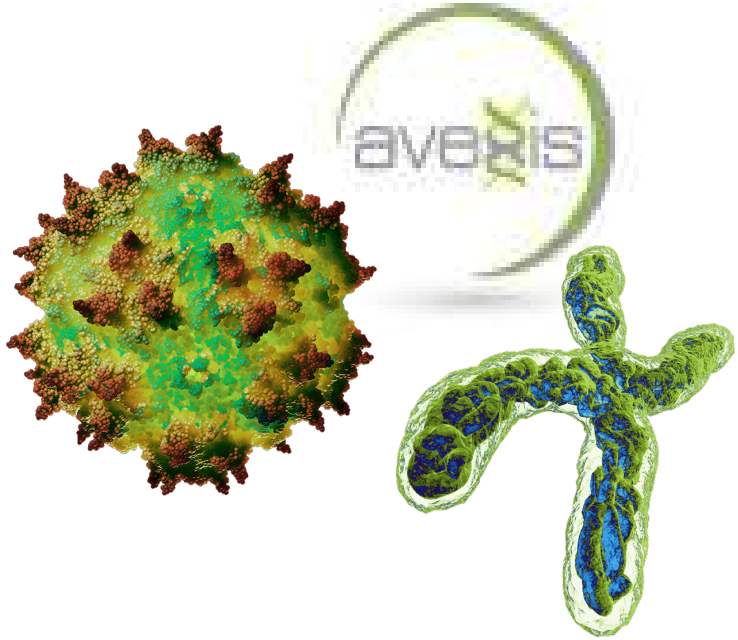
- Cooperative agreement mechanism
- Technical assistance:
  - Consultants: Statistics, Regulatory, CMC

Optimization Track Next Application Date: July 18, 2018
Development Track Next Application Date: July 18, 2018

Expectations of Applications to CREATE Bio Programs

- Comprehensive background and data package
  - Sufficient information for evaluation
  - Confidential (only abstract is publicly available if funded)
- A clear target product profile (TPP) and plans for clinical proof-of-concept study
- Milestones
- Multidisciplinary team
- Emphasis on rigorous study design and reporting
- Intellectual property plans

NINDS U01 Gene Therapy Project Moves into Phase-I Clinical Trial by AveXis for SMA Type 2



- AveXis reports SMA Type 1 Patients who received a single IV dose of AVXS-101 are alive and event-free at 20 months of age
- AveXis Announces Plan to Initiate Phase 1 Trial in SMA Type 2 Utilizing Intrathecal Delivery of AVXS-101

CREATE Bio Website

https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/CREATE-BIO

CREATE BIO

Home » Current Research » Research Funded by NINDS » Translational Research

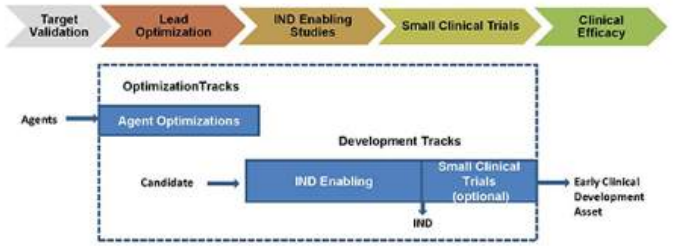
RESEARCH FUNDED BY NINDS

- Basic Neuroscience
- Clinical Research
- Translational Research

CREATE BIO

Cooperative Research to Enable and Advance Translational Enterprises for Biologics

CREATE Bio Program Overview



The NINDS Cooperative Research to Enable and Advance Translational Enterprises for Biotechnology Products and Biologics (CREATE Bio) program is dedicated to biotechnology product- and biologics-based therapies, which broadly include modalities such as peptides, proteins, oligonucleotides, gene therapies, cell therapies, and novel emerging modalities. The program includes two tracks: the Optimization Track supports optimization in order to obtain a candidate appropriate for entering the Development Track, and the Development Track supports IND-enabling studies for the candidate, as well as early-phase clinical trials.

For a quick look to determine the differences between the CREATE Bio FOA tracks such as grant mechanism, FOA number, purpose, and entry criteria

Compare the CREATE Bio Optimization and Development Tracks

The CREATE Bio program has contracts for consultants to advise NIH staff and offer investigators assistance on an ad hoc basis.

CREATE Bio Contract Resources/Consultants

Contact

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Related Funding Opportunities

CREATE BIO Opportunities

Translational Research Opportunities

Related Resources

Application Support Library

NIH Stem Cell Information

FDA CBER guidance documents

FDA CDER guidance documents

FDA Clinical guidance documents

NIH National Institute of Neurological Disorders and Stroke

National Institute of Neurological Disorders and Stroke

NIH Blueprint Neurotherapeutics Network (BPN)

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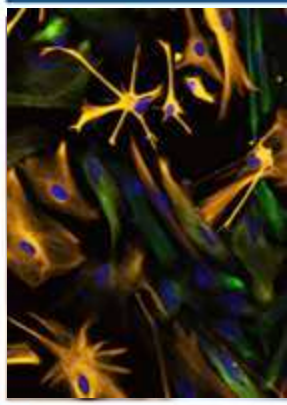
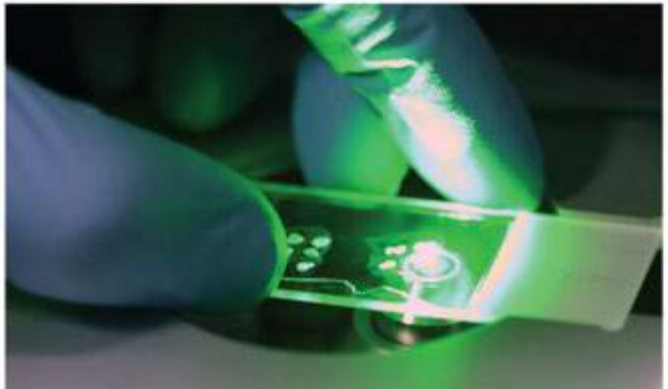
Charles.Cywin@nih.gov





BPN Vision: Combine the Strengths of NIH and Industry Resources

NIH investigator-initiated ideas

- Small molecule starting point
- Strong disease assays and models
- Novel drug targets

Industry expertise

- Advisors with extensive pharma experience
- Industry-standard contract services

National Institute of Neurological Disorders and Stroke

https://neuroscienceblueprint.nih.gov/bpdrugs/

Small Molecule Drug Discovery and Development for Disorders of the Nervous System

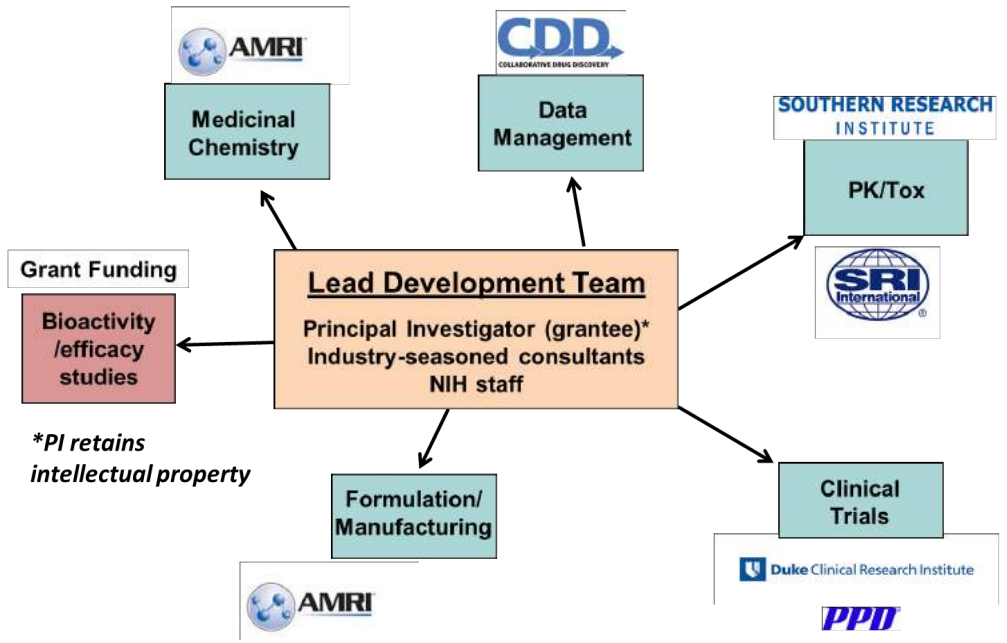
Program Goals:

- To de-risk potential therapeutics to the point that industry will invest in them, allowing potential new drugs to reach patients efficiently.
- To identify the best ideas for translation in the NIH research community through this funding opportunity and associated infrastructure.
- To provide grant (PAR) funding and necessary resources (contracts, consultants, etc.) that are typically lacking in our research community.
- Preserve PI/Institution's Intellectual Property to facilitate licensing

Identify the best ideas and de-risk the projects to promote investment

Blueprint Neurotherapeutics Network

Offers Infrastructure, Expertise, and Grant Funding



BPN14770 capsules for Phase I

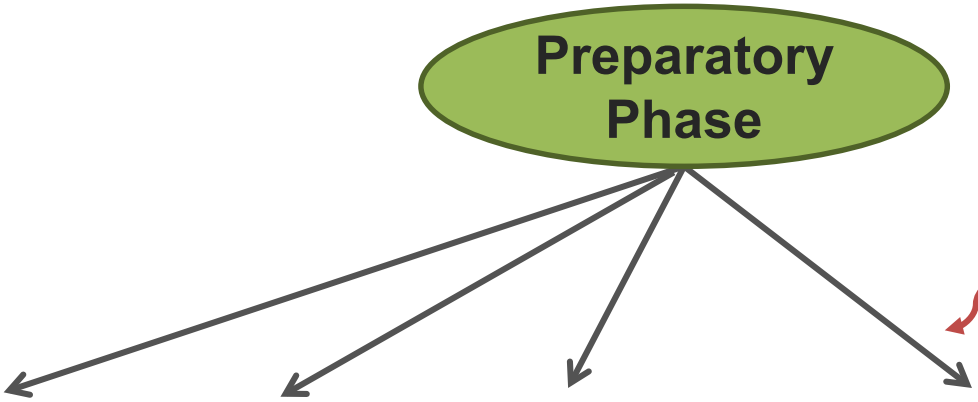
tetra
TETRA DISCOVERY PARTNERS

* Contract resources are tailor-made to support PI teams

Tetra Discovery Partners Announces Positive Results from Phase 1 Studies of Cognition Drug Candidate, BPN14770

Projects Can Enter at Any Preclinical Stage

All Projects Begin with Preparatory Phase



- **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	IND Enabling	Phase I Trial

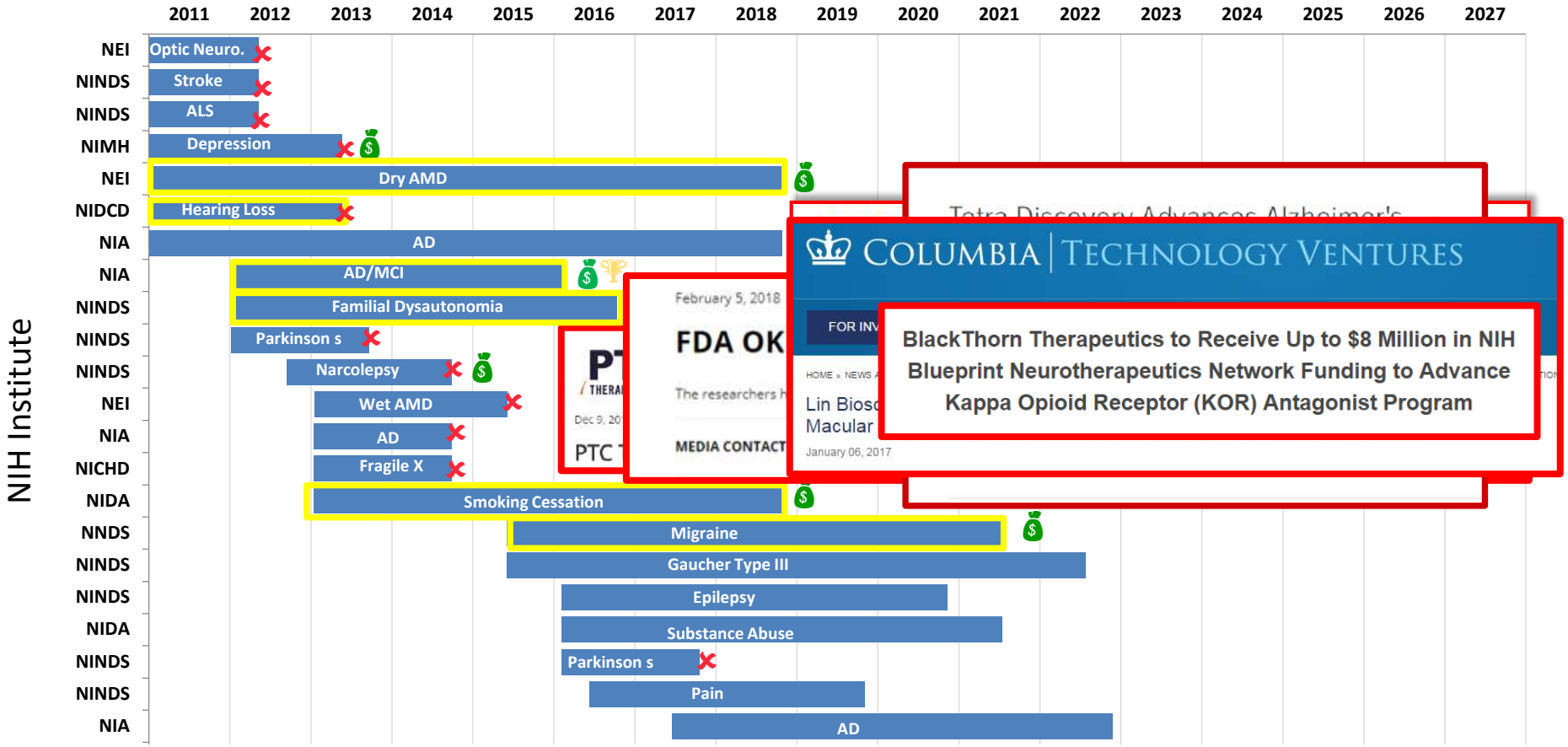
General (UG3/UH3) PAR-18-546
UG3: Up to $300K direct costs x 1 yr
UH3: Up to $1.5M/yr direct costs x 4 yrs

SBIR (U44-I/II) PAR-18-541
Phase I: Up to $500K/yr*($700K total across ≤2 yrs)
Phase II: Up to $1.5M/yr ($3M total across ≤3 yrs)

Next Application Date: August 9, 2018

*If no vertebrate animal work $225K/yr

BPN Success



= Graduated = Licensing and outside investment deal announced = Exited

National Institute of Neurological Disorders and Stroke

Bright past, brighter future with you...

Investigator's Reflection on the BPN program

Professor of Neurology,
Harvard Medical School
Department of Neurology,
Molecular Neurogenetics Unit
Center for Human Genetic Research
Massachusetts General Hospital

https://youtu.be/NPFpI5HoGrA

Professor and Chair Pharmacology and Systems Therapeutics
Experimental Therapeutics Institute
Icahn School of Medicine at Mount Sinai,
Eolas Therapeutics

https://youtu.be/MTd6BhdCKIE

Produced by Josie Anderson
Audio Visual Production Specialist
National Institute on Drug Abuse
National Institutes of Health

NIH National Institute of Neurological Disorders and Stroke

Thank You

BPN info:

https://neurosciencebluepr int.nih.gov/bpdrugs

Please contact me to discuss your project's fit to BPN:

charles.cywin@nih.gov

Next Receipt Date is August 9th.

(PAR-18-546, PAR18-541(SBIR))

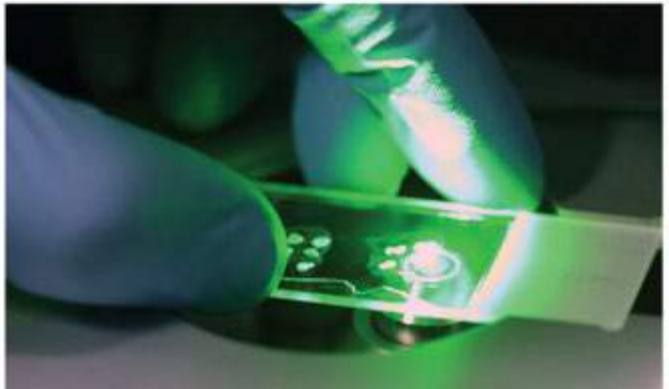
National Institute of Neurological Disorders and Stroke

Devices

ICARE

April 12, 2018

Kari R Ashmont, PhD
Program Specialist
NIH/NINDS
kari.ashmont@nih.gov



Device Development Pipeline

- NINDS Exploratory Research (R21) (PA 18 358)
- NSF NIH Smart and Connected Health (NSF 18 541)
- Bioengineering Research Grants (R01) (PAR 18 206)
- BRAIN New Concepts (R21) (RFA EY 18 001)
- Bioengineering Research Partnerships (U01) (PAR 18 208)
- BRAIN New Technologies (R01) (RFA NS 18 020)
- Translational Neural Devices (UG3 / UH3 / U44) (RFA NS 18 011 / RFA NS 18 012)
- BRAIN Device Optimization (U01) (RFA NS 18 019)
- BRAIN Next Generation Devices (UG3 / UH3 / U44) (RFA NS 18 021 / RFA NS 18 022)
- BRAIN Next Gen Devices (UH3) (RFA NS 18 023)

GOAL:

Support development, optimization, and translational activities and small clinical studies involving therapeutic and diagnostic devices for disorders that affect the nervous or neuromuscular systems

Exploratory CTs
(U01 / R42 / R44)
(PAR 18 420 / PAR 15 277 / PAR 15 278)

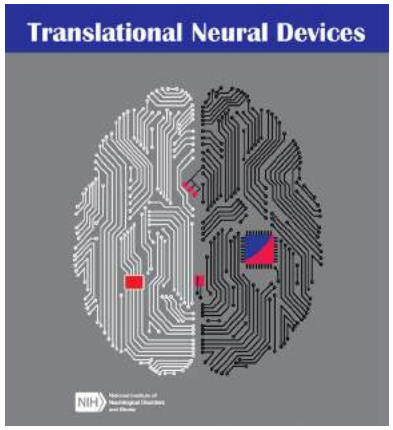
Clinical Trial Networks:

NeuroNext (R01/U01)
(PAR 18 528 / PAR 18 268)

StrokeNET (R01/U01)
(PAR 18 561 / PAR 18 563)

NIH National Institute of Neurological Disorders and Stroke

Translational Opportunities



SBIR · STTR
America's Seed Fund

BRAIN Initiative

Legacy Programs

- NINDS Cooperative Program in Translational Research (2002-2014)
- Advanced Neural Prosthetics Program (2009-2015)
- CREATE Devices (2014-2017)

General Information

- BRAIN: Invasive, CNS required, UH3, Public Private Partnership Program
- SBIR Fast-Track versions available
- Clinical Trials Required
- Delayed onset NOT allowed
- Budget Guidelines (no hard cap)
  - $1M/year (UG3/SBIR Phase I)
  - $1.5M/year (UH3/SBIR Phase II)
- Phased Mechanism
- Cooperative Agreements

NEXT DUE DATES

Translational Neural Devices: June 21, 2018

BRAIN: June 23, 2018

Phased Mechanisms

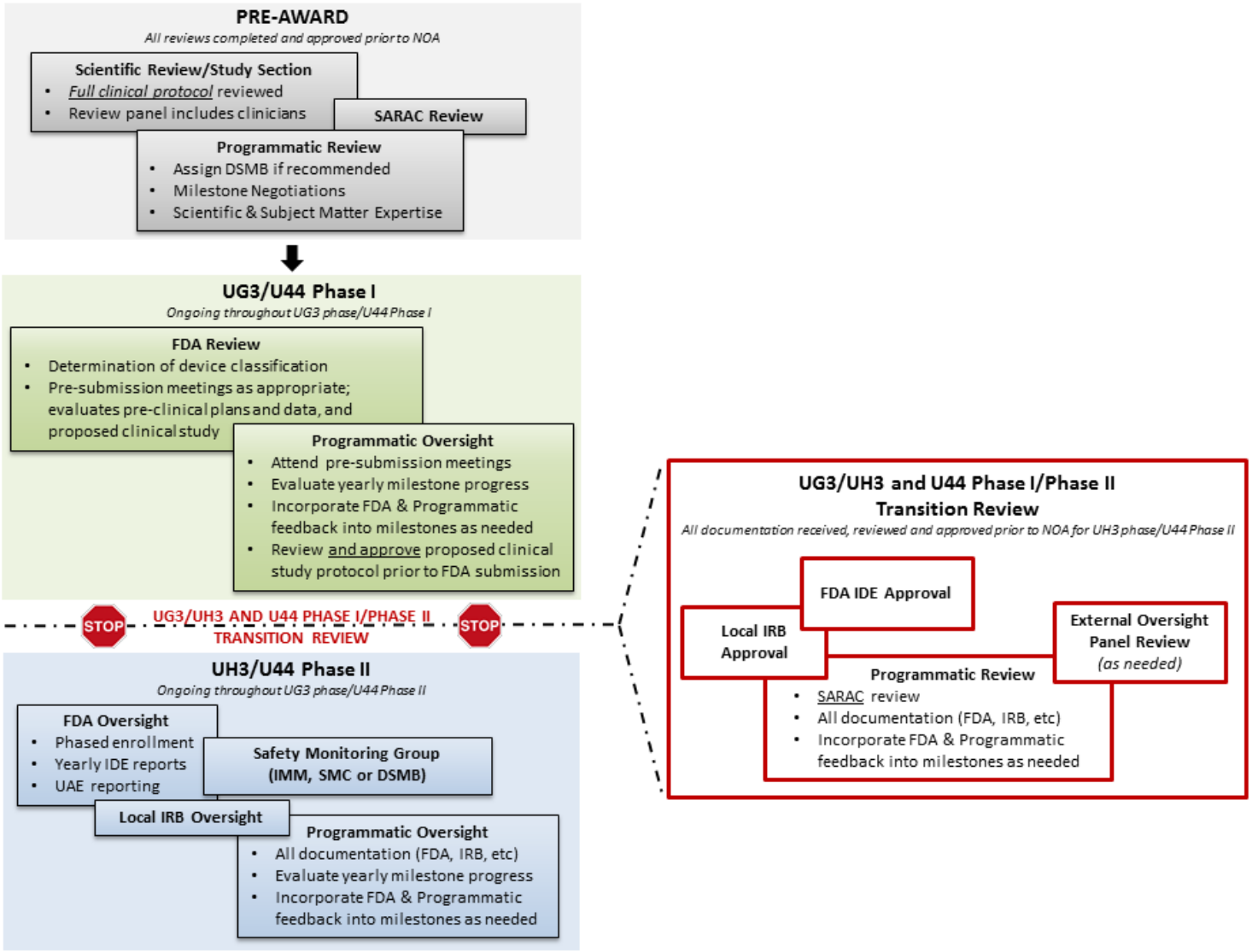
UH2/UG3/SBIR Phase I

- IDE enabling pre-clinical
- Good Laboratory Practices (GLP)
- Good Manufacturing Practices (GMP)
- Software testing and validation
- Biocompatibility
- Quality Systems
- Regulatory activities
- Acute human studies

UH3/SBIR Phase II

- Clinical study
- Marketing application
- Clinical experience to inform final device design

Cooperative Agreement Oversight



Current Portfolio

- **23 Actively Managed Awards**

Program	Mechanism				Approx. Yearly Costs
	U01	UG3/UH2	U44	UH3	
Bioengineering Research Partnership	1	-	-	-	$1.2M
Advanced Neural Prosthetics Program	3	-	-	-	$2.7M
Translational Neural Devices (CREATE)	-	1	2	-	$3.6M
BRAIN	-	4	-	12	$21.2M

Yearly Total: ~ $29 Million!

Indications: OCD (2), Depression (2), Essential Tremor, Locked-in Syndrome, TBI, PD (4), Visual Prosthesis (2), SCI / Phantom Pain, Stroke (3), SCI (4), **Epilepsy (3)**

Neurophysiological Brain State Tracking & Modulation in Epilepsy

PI: Worrell (UH2 NS095495)

Goal: Develop Next Generation Epilepsy Therapeutics Platform based on Medtronic Summit

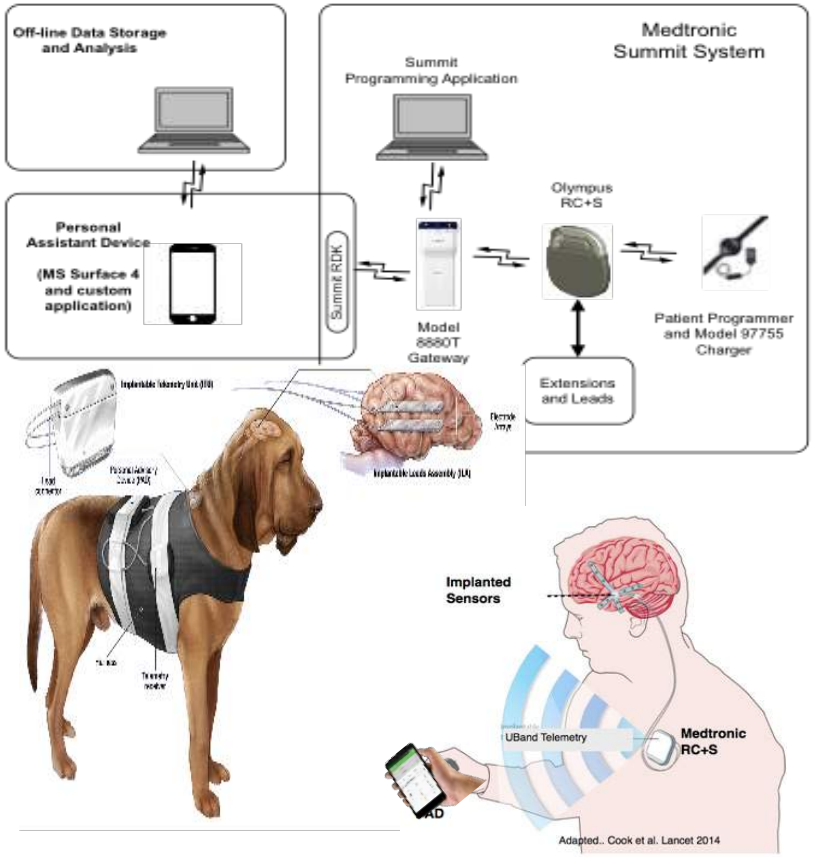
RC+S telemetry & stimulation in dogs
- Cortex, hippocampus, thalamus
- 3% packet loss (97% data transmitted & analyzable)

Automated Seizure Detection & Catalogs
- Legacy data: human & dog (98% Sens. & FP 0.06/hr)
- Prospective detection in implanted dogs ongoing

Responsive Stimulation in Canine Epilepsy
- Evoked related potentials
- Brain state related stimulation

Seizure Forecasting Dog & Human Epilepsy
- Legacy data: human & dog (82% Sensitivity & 75% Specificity)

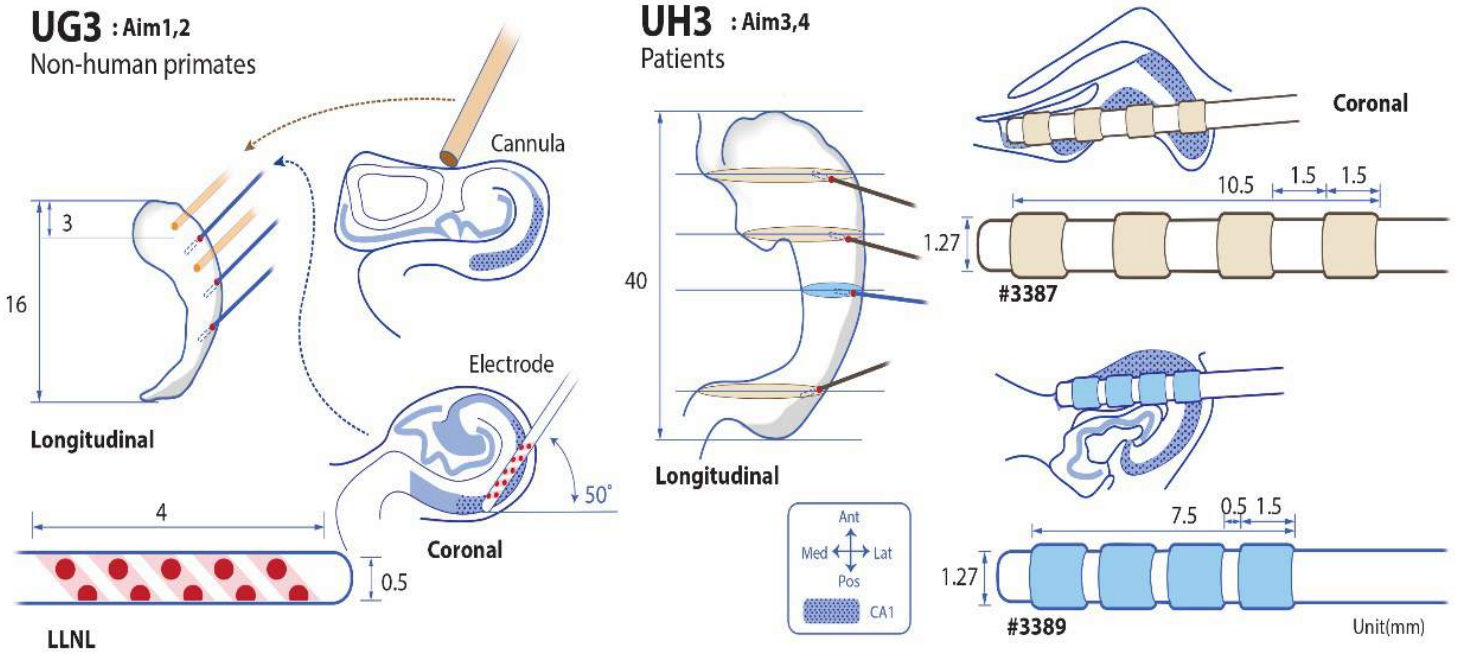
Pilot Trail in Human Focal Epilepsy (UH3)



Asynchronous Distributed Multielectrode Neuromodulation for Epilepsy

PI: Gross, et al (UG3 NS100559)

Goal: To improve the outcome of neuromodulation therapy for drug-resistant epilepsy patients using *distributed bidirectional recording and stimulation.*



National Institute of Neurological Disorders and Stroke

Development of an Implantable TNS System

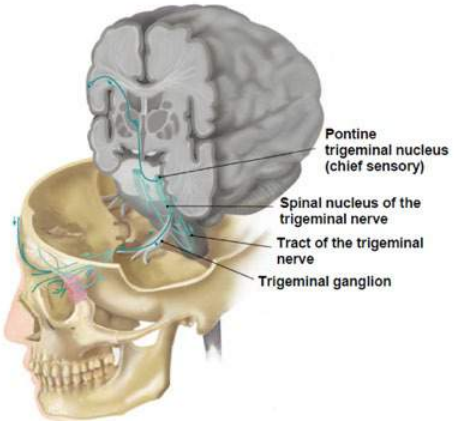
PI: Kealey/Cook (U44 NS081840)

Goal: To develop an implantable subcutaneous Trigeminal Nerve Stimulation System (sTNSTM) for the treatment of DRE.

NeuroSigma

TNS- A New DRE Treatment Paradigm

- Patients with DRE screen for treatment efficacy with non-invasive external TNS (eTNS) prior to implant of minimally-invasive subcutaneous TNS (sTNS)
- Avoids complications and costs of unnecessary procedures



Non-Invasive eTNS

DRE patients can screen prior to implant

Minimally-Invasive sTNS

TNS Product Development Status

- eTNS screening device completed and used for multiple clinical trials
- prototype sTNS system now complete and undergoing benchtop testing
- sTNS system uses thinnest known neurostimulation lead (<0.4mm thick)
- GLP animal tests planned for 2018/2019
- First-in-human implants 2019/2020

NIH National Institute of Neurological Disorders and Stroke

Questions?

Thank you!

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Stephanie Fertig, MBA
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Matthew Raymond, PhD
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Doe Kumsa, PhD
doe.kumsa@nih.gov

National Institute of Neurological Disorders and Stroke

Small Business Programs (SBIR/STTR)

April 2018

Stephanie Fertig, MBA
Director, NINDS Small Business Programs
Division of Translational Research, NINDS
fertigs@ninds.nih.gov

Investing Across the Translational Spectrum

Grants

GNITE Innovation Grants to Nurture Initial Translational Efforts

NIH Blueprint for Neuroscience Research

CREATE Bio

Translational Neural Devices

National Institutes of Health CounterACT Countermeasures Against Chemical Threats

SBIR·STTR America's Seed Fund

Resources

Training 

Epilepsy Therapy Screening Program (ETSP)

Contracts

ADME/Tox. 

Chemistry 

Manufacturing 

Clinical 

Preclinical and Early Clinical Trials

Grants

Dissemination and Implementation Research in Health (R01)

SBIR·STTR America's Seed Fund

NeuroNEXT Clinical Trial (U01)

NeuroNEXT

StrokeNet Clinical trials & Biomarkers (X01)

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

Neurological Emergencies Treatment Trials (NETT)

NETT Neurological Emergencies Treatment Trials

Clinical Trials and Infrastructure Resource

NIH Small Business Programs

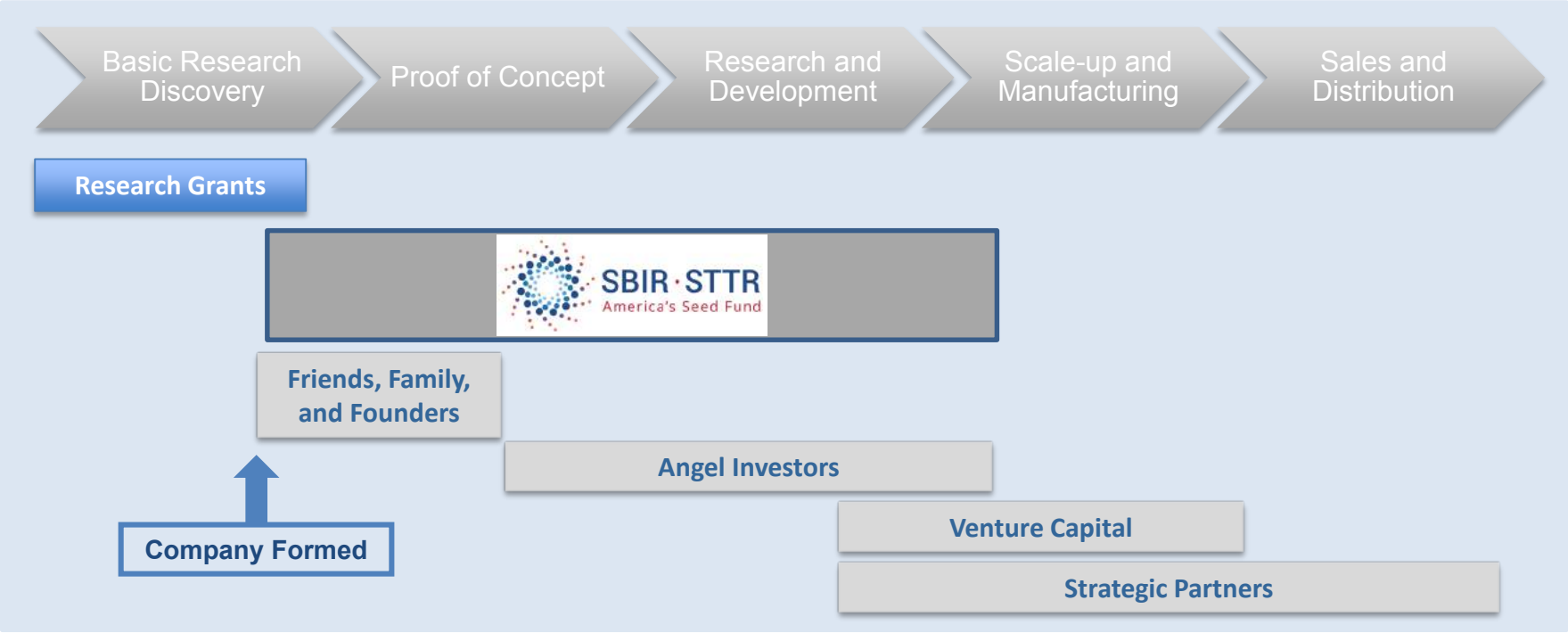
Small Business Innovation Research
Small Business Technology Transfer

- Congressionally mandated set-aside (3.65%)
  - FY 2017: $980M NIH and $55M NINDS
- For R&D with potential for commercialization
- Broad scope:
  - Therapeutics, diagnostics, tools for research
  - Bench research, translational research, early stage clinical trials
- A majority of our applications are investigator-initiated and come in through the omnibus solicitations

https://www.ninds.nih.gov/Funding/Small-Business-Grants

Benefits

- One of the largest funding sources **of early stage life sciences in the US**
- Not a loan, non-dilutive **capital**
- IP rights **are** normally retained by the small business
- Awardees can **leverage to attract other funding and**



SBIR and STTR Critical Differences

	SBIR (Small Business Innovation Research)	STTR (Small Business Technology Transfer)
Set-Aside	3.2%	0.45%
Partnering Requirement	Permits partnering	Requires a non-profit research institution partner (e.g. university)
Work Requirement	Guidelines: May outsource 33% (Phase I) 50% (Phase II)	Minimum Work Requirements: 40% small business 30% research institution partner
Principal Investigator	Primary employment (>50%) must be with the small business	PI may be employed by either the research institution partner or small business

Award is always made to the small business

Phases of SBIR/STTR

Discovery
Phase I

Feasibility

Development
Phase II

Full R/D

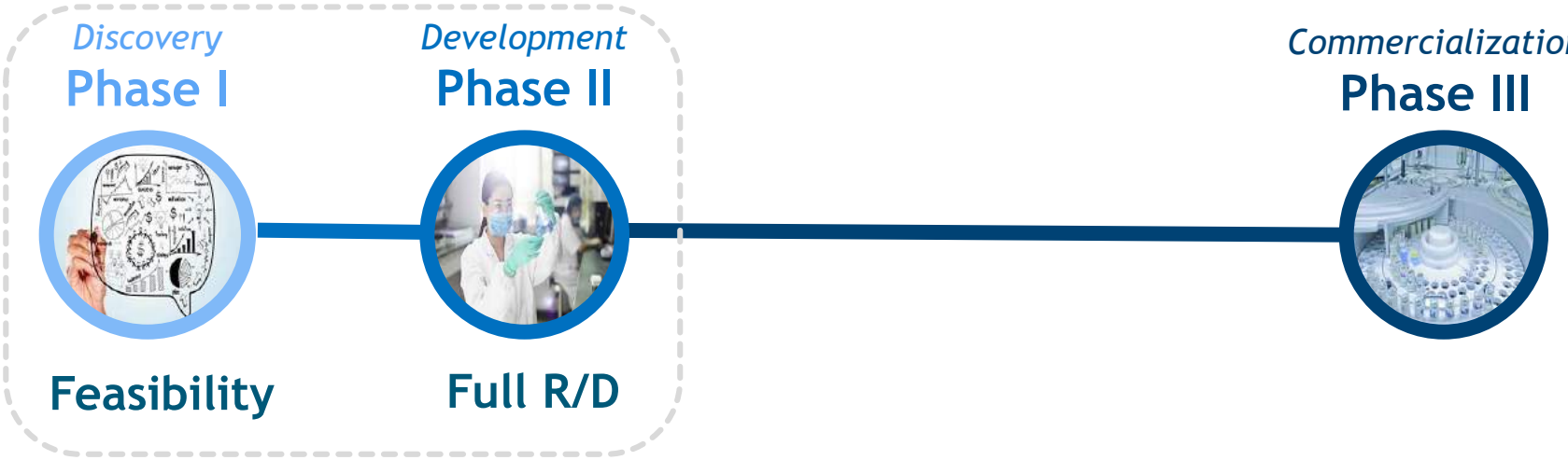
Commercialization
Phase III

Phase I:
Guidelines: $150K/6 months
Hard Cap*: $225K/1-2 years
NINDS Waiver Guidelines:
$700K (not more than $500K/yr)

Phase II:
Guidelines: $1M/1 year
Hard Cap*: $1.5M/1-3 years
NINDS Waiver Guidelines:
$3M (not more than $1.5M/yr)

***NIH has a wavier from the Small Business Administration to exceed these Hard Caps for specific topics**
SBIR/STTR budgets are in total cost (direct + indirect + fee)

Phases of SBIR/STTR: Fast-Track



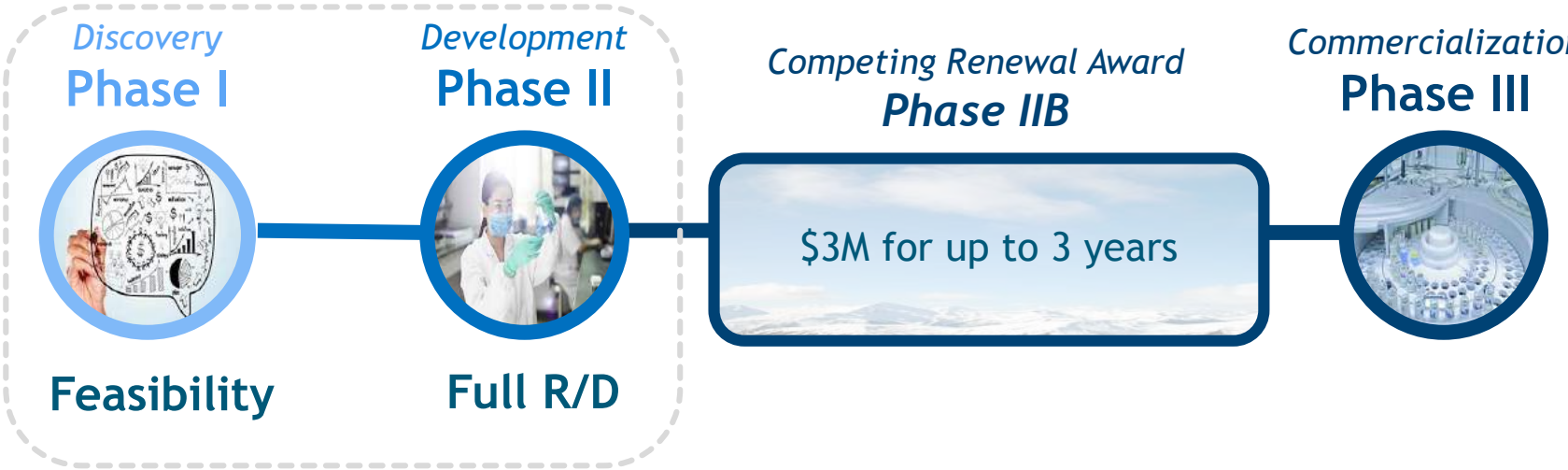
Fast-Track

Phase I → Phase II

- Simultaneous submission and review of Phase I and II
- Phase I is awarded
- Milestones/aims of Phase I are assessed by program staff BEFORE Phase II is awarded

***Across NIH all new application types (Phase I, Fast-Track) have roughly the same success rate**

Phases of SBIR/STTR



- SBIR/STTR Phase II awardees
- Specific Phase IIB program announcements
- Awards up to **$1M/year for up to 3 years**
- Some “strongly encourage” matching funding

- ***Contact NIH Program Staff to discuss!***

Commercialization Support

Pre-SBIR/STTR:

Entrepreneurial Assistance/ Training

NIH I-Corps™ (pilot) and C3i Programs

- Open to current awardees of participating NIH Institutes/Centers
- Administrative Supplements: **PA-18-702** and **PA-18-517**

NIH Applicant Assistance Program (AAP)

- PILOT: **NOT-CA-18-031**; **www.dawnbreaker.com/aap**
- Companies who have not previously won an SBIR/STTR award from NIH
- NCI, NINDS or NHLBI mission
- **Provide free services**: application preparation, needs assessment, etc.

Phase I:

Market Analysis:

Niche Assessment Program (NAP)

Entrepreneurial Assistance/ Training

NIH I-Corps™ and C3i Programs

Phase II/IIB:

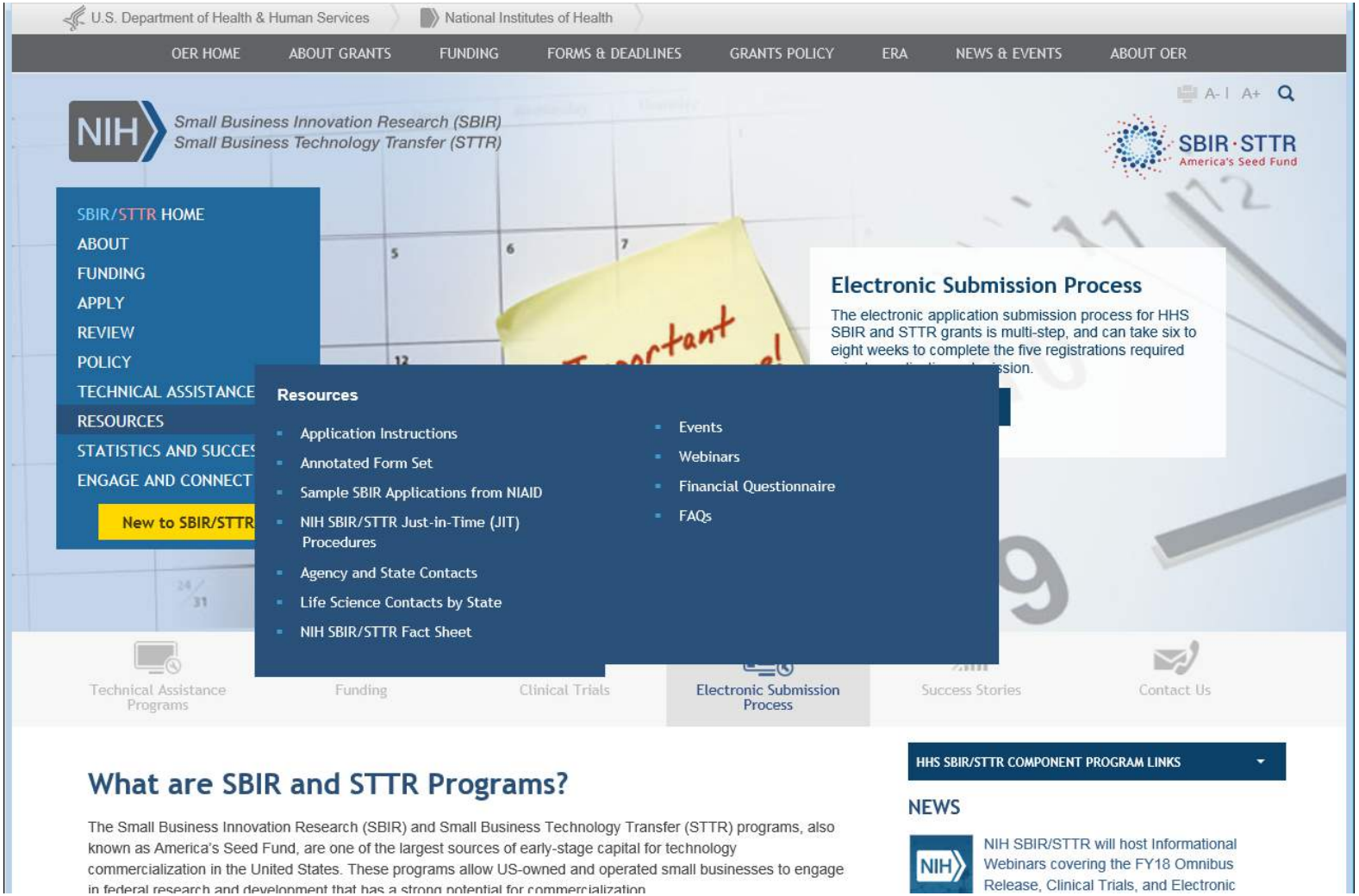
Technical Assistance/Training:

Commercialization Accelerator Program (CAP)

https://www.ninds.nih.gov/Funding/Small-Business-Grants

NIH National Institute of Neurological Disorders and Stroke

NIH Small Business Programs Website



https://sbir.nih.gov/

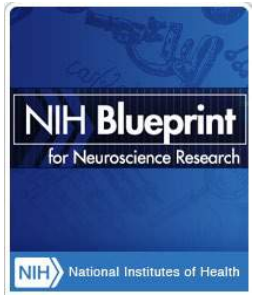
NINDS Small Business Priorities

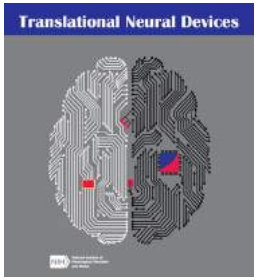
NOT-NS-18-002

- NINDS gives priority to **meritorious research proposals with the greatest potential to advance the NINDS mission**
  - We are especially interested in:
    - Novel and innovative technologies that are new to the SBIR or STTR programs.
    - Technologies coming to the SBIR or STTR programs for their first indication or market opportunity.
    - Companies and applicants that are new to the SBIR and STTR programs.
    - NINDS Cooperative Agreement (U44) Translational Programs

https://www.ninds.nih.gov/Funding/Small-Business-Grants

NINDS Cooperative Translational Programs





Small Molecules (PAR-18-541):

Charles Cywin, Ph.D.
(charles.cywin@nih.gov)

Biologics (PAR-17-457/PAR-18-543):

Chris Boshoff, Ph.D.
(chris.boshoff@nih.gov)

Neural Devices (RFA-NS-18-012):

Nick Langhals, Ph.D.
(nick.Langhals@nih.gov)

Biomarkers (PAR-18-549/PAR-18-548)

Mary Ann Pelleymounter, Ph.D.
(mary.pelleymounter@nih.gov)

NINDS Support for Clinical Studies

- Clinical Research (e.g. diagnostics) are accepted through the general solicitations (clinical trials not allowed)
- NINDS does NOT participate in the Clinical Trials SBIR/STTR omnibus solicitations
- Clinical Trials are accepted through specific program announcements (clinical trials optional or required)

NINDS Exploratory Clinical Trials NINDS Renewal Awards of SBIR Phase II Grants (Phase IIB) Clinical Trials and Clinical Research	**PAR-18-618** (SBIR) **PAR-18-617** (STTR) **PAR-18-665** (Phase IIB)	Stephanie Fertig fertigs@ninds.nih.gov
Neurology Network of Excellence in Clinical Trials	**PAR-18-628**	Codrin Lungu lunguci@ninds.nih.gov

Currently Active SBIR/STTR Epilepsy Grants

SBIR Phase II	R44NS100235	EPITEL, INC.	LEHMKUHLE, MARK J	EEG Patch
SBIR Fast track, Phase II	R44NS086229	XERIS PHARMACEUTICALS, INC.	PRESTRELSKI, STEVEN (c); CLOYD, JAMES C	Auto-Injectable Diazepam Formulation for Rapid Treatment of Uncontrolled Seizures
SBIR Phase I	R43NS105291	LIFESPLICE PHARMA, LLC	TALLENT, MELANIE K	Preclinical Testing of Splice Modulating Oligonucleotides Targeting SCN8A to Treat Dravet Syndrome
SBIR Phase I	R43NS093714	BMSEED, LLC	GRAUDEJUS, OLIVER	Development of a large area high resolution micro ECoG electrode array
Phase IIB	R44NS064647	OPTIMA NEUROSCIENCE, INC.	SHIAU, DENG-SHAN	High Performance Seizure Monitoring and Alert System
SBIR Fast track, Phase II	R44NS093889	ELECTRICAL GEODESICS, INC.	LUU, PHAN (c); PAPADEMETRIS, XENOPHON	Multimodal Image Analysis Software for Epilepsy
SBIR Phase II	R44NS083101	CORTICOMETRICS, LLC	SCHMANSKY, NICHOLAS JOHN (c); FISCHL, BRUCE	Computer-aided detection of focal cortical dysplasias
SBIR Phase I	R43NS102067	MICRO-LEADS, INC.	MCLAUGHLIN, BRYAN L	An Implantable and High-Density, Multiplexed Micro-ECoG System

Funded FY2017: $3.6M

NINDS Small Business Successes

NeuroSigma

R41NS76014

Monarch™ eTMS system

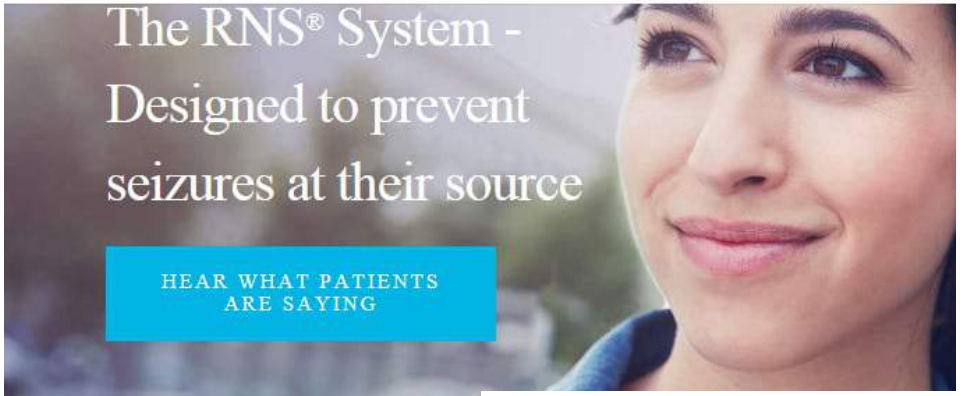
- "External Trigeminal Nerve Stimulation for the Treatment of Epilepsy"
- Available as an adjunctive treatment of epilepsy in the EU, Canada and Australia
- eTMS is an investigational device in the US

Supporting the company to develop an implantable trigeminal nerve stimulation system for drug resistant epilepsy

NIH National Institute of Neurological Disorders and Stroke

NINDS Small Business Successes

NEUROPACE



Epilepsy treatment just got a lot smarter with the RNS® System.

"These studies demonstrated that closed-loop responsive stimulation was feasible and provided preliminary evidence that responsive stimulation could reduce seizures."

Sun FT, Morrell MJ. Closed-loop Neurostimulation: The Clinical Experience. Neurotherapeutics (2014) 11: 553

R44NS034630

NIH Small Business Conference

- Save the Date -

20th Annual HHS SBIR/STTR Conference

October 30 - November 1, 2018
Dallas, Texas

Stay connected for updates!
@NIHsbir | https://sbir.nih.gov/

Eligibility Criteria

- Organized as for-profit US business
- Small: 500 or fewer employees, including affiliates
- Work must be done in the US (with few exceptions)
- Individual Ownership:
  - Greater than 50% US-owned by individuals and independently operated OR
  - Greater than 50% owned and controlled by other business concern/s that is/are greater than 50% owned and controlled by one or more individuals OR
  - Be a concern which is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these

Determined at Time of Award