National Institute of Neurological Disorders and Stroke

URGenT
Ultra-Rare Gene-based Therapy

NINDS URGenT Program

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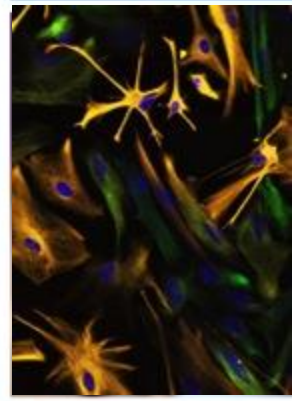
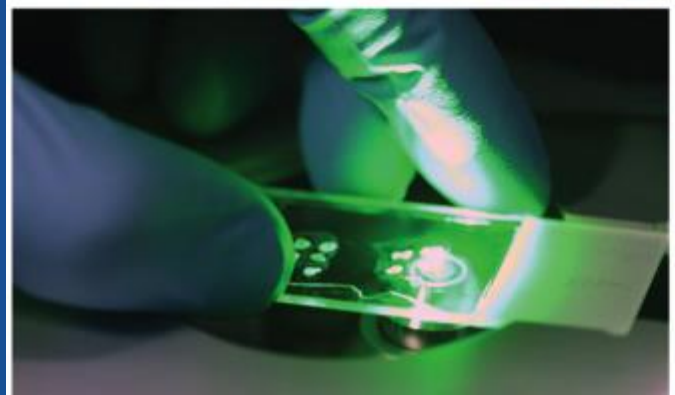
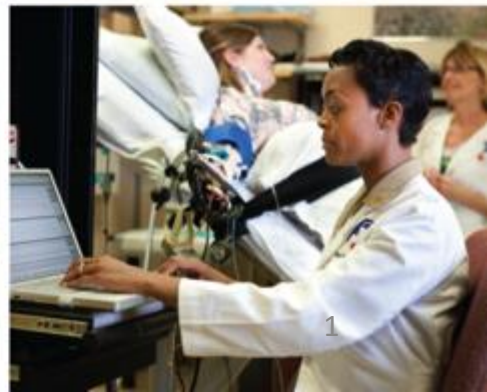
Program Director

Date: Dec 19th, 2023







Background

- Biotherapeutics make up an **estimated 25 to 30 percent** of therapeutic agents on the market and expected to increase.

- Promising recent developments for nervous system disorders include:
  - **Spinraza**™: ASO treatment for SMA approved in 2016
  - **Luxterna**™: Gene therapy for rare retinal eye disease approved in 2017
  - **Zolgensma**™: Gene Therapy for SMA approved in 2019

- Future Expectations: New designs and platforms poised to accelerate research, clinical development, and facilitate approvals

Mila's Story

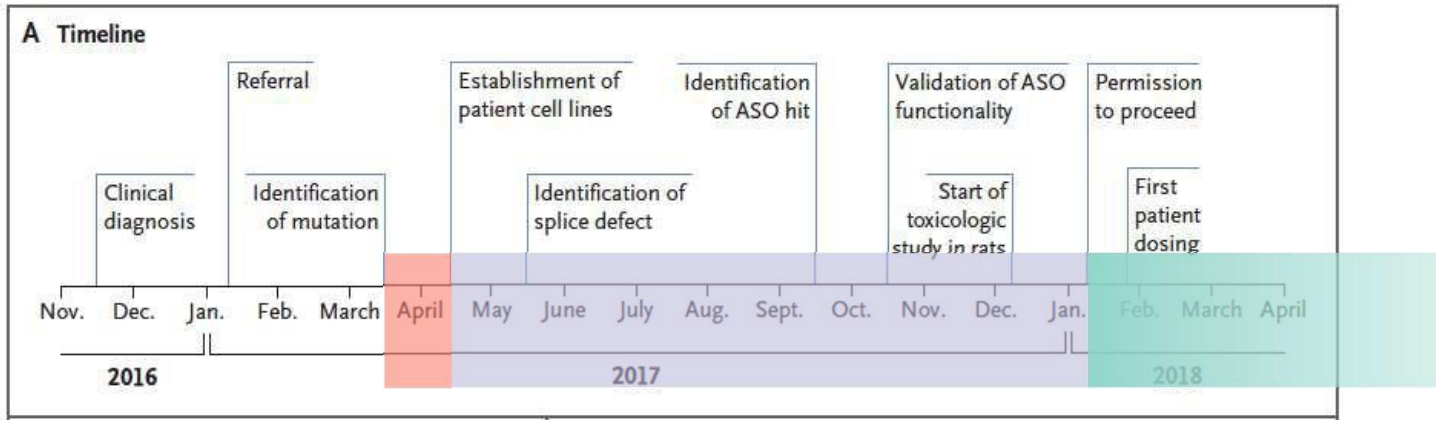
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu

N Engl J Med. 2019 Oct 24;381(17):1644-1652.



Planning Therapeutic development Clinical treatment

What are the Major Challenges?

- **Lack of access to manufacturing capacity**, therapy development expertise, and regulatory guidance

- **Lack of available infrastructure** for academics and small businesses to facilitate translation of biopharmaceuticals from manufacturing, PK/PD, toxicology, to clinical testing

- There **is no commercial incentive to develop gene-targeted therapies** for many rare central nervous system disorders

Why Now?

- **Many of disease**s within the mission of NINDS are monogenic and amenable to personalized therapy approaches
- Recent scientific advances suggest **great promise for using oligonucleotides, genome editing and gene therapy** as a personalized medicine for rare diseases
- **No current program available** to provide support for this modality beyond funding alone
- Majority of investigators **lack the multidisciplinary support** to advance ideas from discovery to clinical testing
- **Favorable regulatory environment** for implementing personalized medicine strategies

Strategy

The mission of the network is to provide resources and funding for the scientific community to develop gene-targeted therapies from bench to bedside for rare diseases

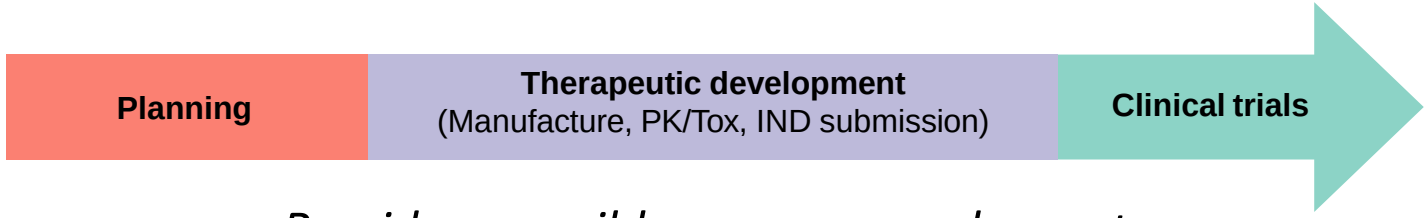
Build an infrastructure that includes:

- **Access to contract resources** e.g. contracts for modality specific biotherapeutics manufacturing, toxicology, pharmacology and animal model development
- **External Oversight Committee (EOC)**
- **Centralized Data Management**
- Consultants for **toxicology, drug metabolism, clinical pharmacology, regulatory and assay development, IND enabling toxicology, phase I clinical trials**
- **Facilitate** the formation of a network of clinical sites to execute first-in human clinical trials.

URGenT Goals

Goals:

- **Accelerate** advancement of discoveries into the clinic.
- **Provide** resources and expertise not available to applicants.
- **Deliver** therapeutics to patients with ultra-rare neurological diseases.
- **Standardize** and **harmonize** best practices and protocols for the development of gene-based therapies for ultra-rare diseases.



Provide accessible resources and experts
*for **rapid** development of **tailored** gene-based therapies.*

URGenT will support PIs with a lead gene therapy from start-to-finish over 3 years through planning, manufacture, IND-enabling PK/toxicology studies, and IND submission into clinical trials.

Scope

Ultra-rare Disease affect substantially fewer people, less than or equal to 6,000; in the U.S., this equates to as few or fewer than one in 50,000 people

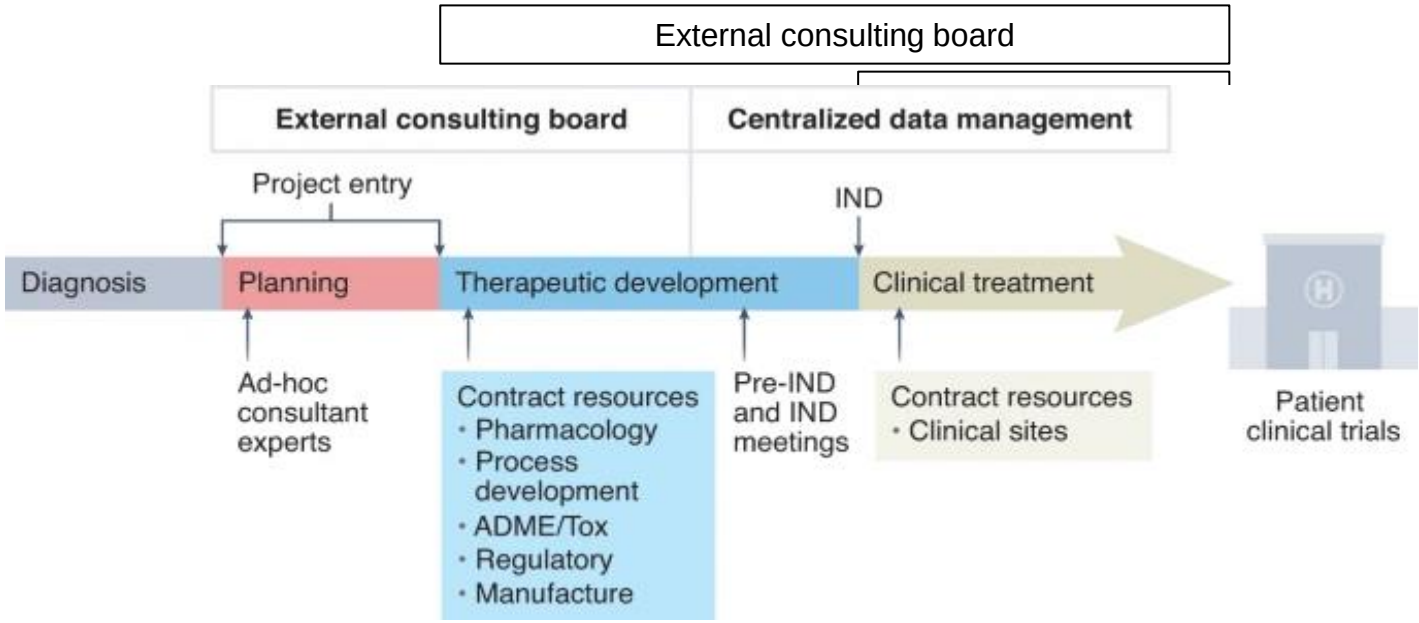
Gene-based or transcript-directed therapeutics include but are not limited to:

- Oligonucleotide-based approaches
- Viral vector-based approaches
- Genome editing-based approaches
- Other gene-based therapeutic approaches

Ultra-Rare Gene Therapy (URGenT) Network

URGenT Network provides support for the development of gene-based and transcript directed therapies for ultra-rare neurological and neuromuscular diseases.

- ✓ Phased funding mechanism with multiple entry points
- ✓ In kind access to R&D contract and expert consultant resources from late-stage nonclinical development to clinical testing
- ✓ Accelerated development timeline – 3 years start to finish



Correspondence | Published: 04 November 2021

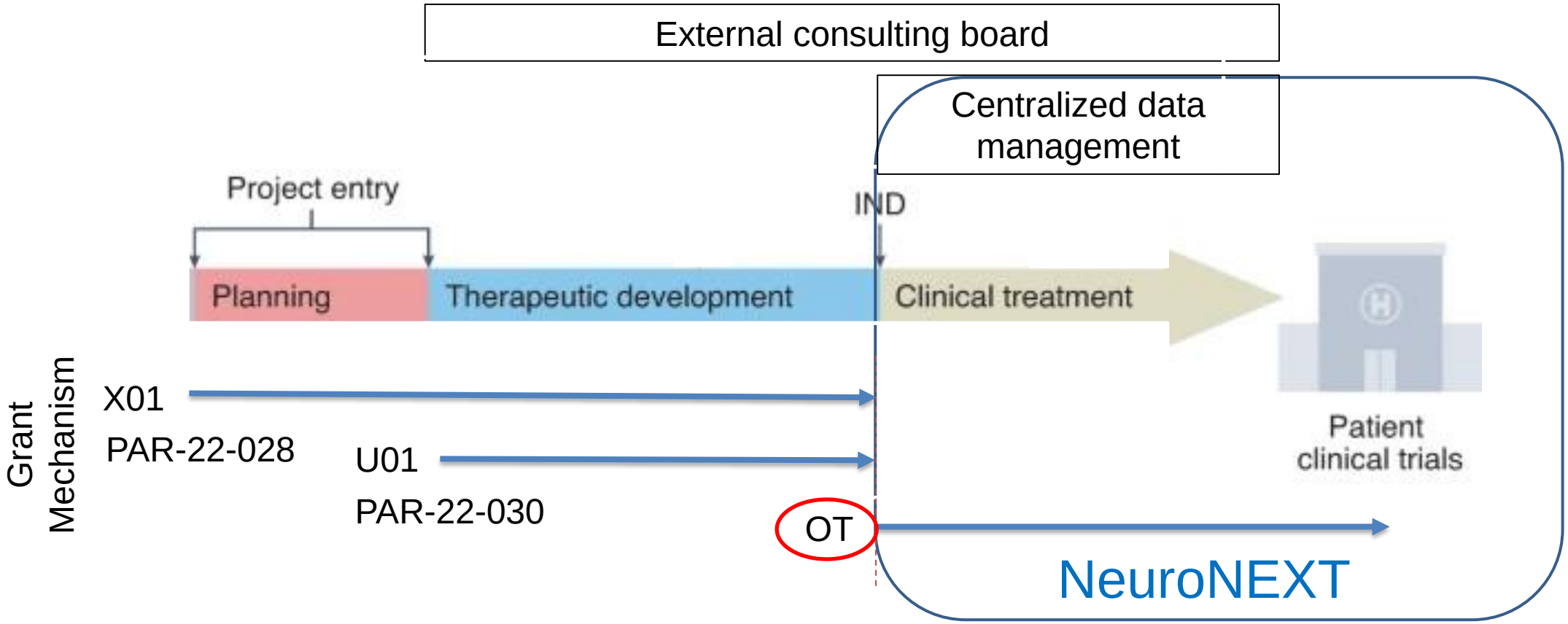
NINDS launches network to develop treatments for ultra-rare neurological diseases

Nature Biotechnology **39**, 1497–1499 (2021) | Cite this article

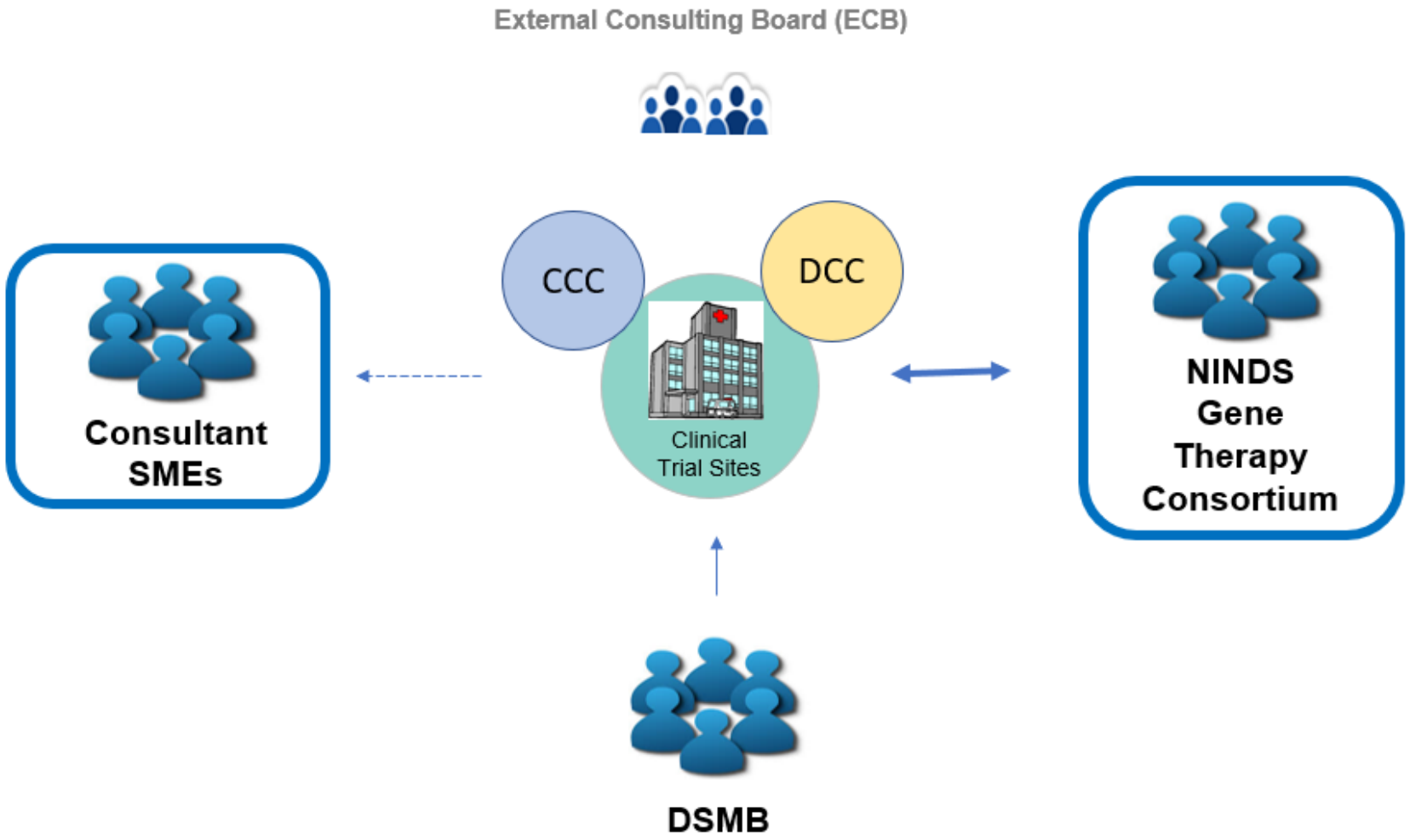
882 Accesses | **15** Altmetric | Metrics

National Institute of Neurological Disorders and Stroke

Clinical Trials Network within NeuroNEXT



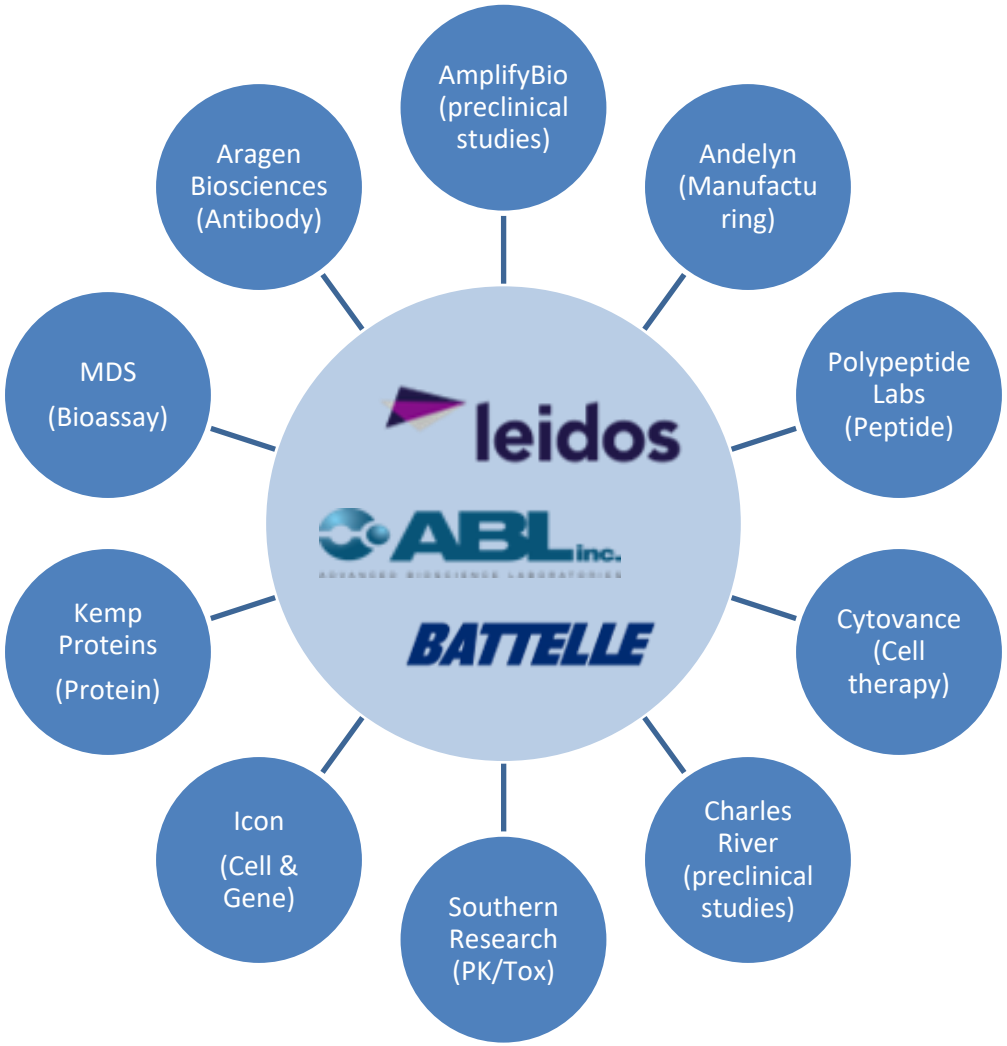
Clinical Trials within NeuroNEXT



Established R&D Contract Resource Network

Multi-Disciplinary Teams	Prime Contractors
• Build and manage project teams • Coordinate activities of PIs and contractors • Provide technical direction and guidance to NIH	• Task orders are written specific to project needs • Provide inhouse project management services • Can subcontract with specialty providers

Bioassays, PK/PD, ADME, Toxicology + Scale up and Manufacture, Formulation, Fill finish → Clinical Trials

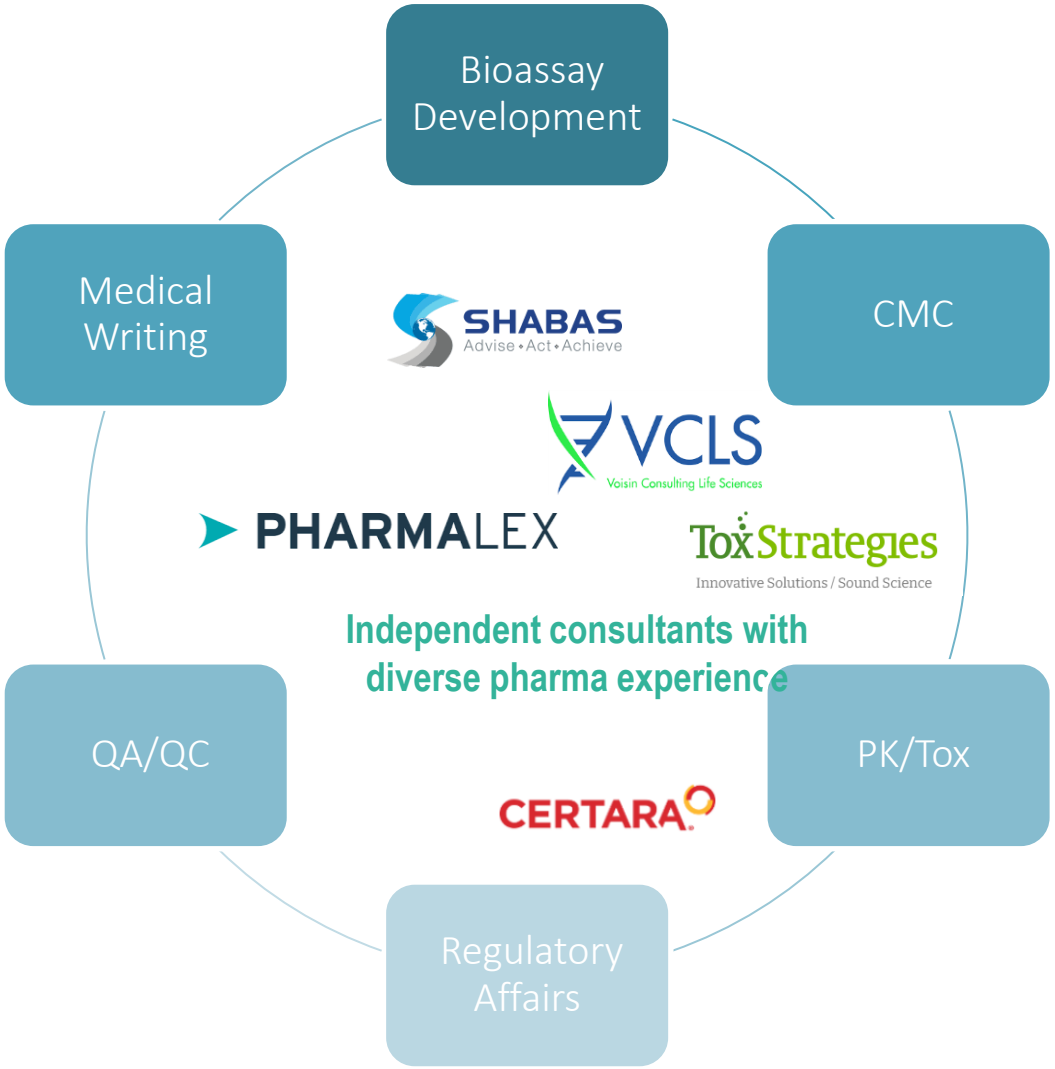


Established Consultant Network

<u>25 consultants</u> are available to provide in-kind support to awarded projects

Currently recruiting experts in:

- Oligonucleotides
- AAV Gene Therapy
- Assay development



Entry Requirements

- The **POC data** establishes the **feasibility** and rationale for candidate use with effective dose range using appropriate assays.
- The Program Director/Principal Investigator (PD/PI**) identified a gene-based or transcript-directed therapeutic clinical candidate** supported by *in vivo* and/or *in vitro* data (efficacy and preliminary safety).
- The PD/PI **has held formal pre-IND discussions**
- The PD/PI **can provide an outline** of the future clinical trial

Supports Late-Stage Nonclinical Development

Applications proposing plans for nonclinical development in parallel with clinical planning activities, including, but not limited to:

- **Manufacturing** (i.e., technology transfer, process development etc. and clinical scale cGMP manufacturing)
- **Qualification and/or validation** of any bioassays for IND-enabling nonclinical and clinical studies
- IND-enabling **efficacy studies** with intended clinical grade product and **safety and toxicology** testing in relevant animal model(s)
- Assessment of off-target affects
- Evaluation utility of **pharmacodynamic/target engagement biomarkers** associated with the therapeutic target or disease
- Completion of all clinical trial planning activities (IRB)
- Preparation and submission of an **IND package**

Cooperative Agreement

Structure

- For each project provided access to the network, the NINDS will assemble a customized **Multi-disciplinary Project Team (MPT)**.
- The MPT will include members of the **Program Director/Principal Investigator's (PD/PI) team** and additional **SME consultants**.
- The MPT will establish **an overall strategy** for the project with milestones, including **a plan and timeline**, and will develop and coordinate activities across different URGenT contract resources.

URGenT: Current Project Portfolio

Title	PI	Institution	Sector	Mechanism	Indication	Modality	Date of Award
IND-enabling studies for Aspartylglucosaminuria (AGU) to support the initiation of an AAV9/AGA gene transfer clinical trial	GRAY, STEVEN J (contact); I ANNACCONE , SUSAN T	UT SOUTHWESTERN MEDICAL CENTER	Academic	U01	Aspartylglucosaminuria	Viral vector-(AAV9)	Launched
Viral gene therapy for Menkes disease	KALER, STEPHEN GE RARD	RESEARCH INST NATIONWIDE CHILDR EN'S HOSP	Academic	U01	Menkes Disease	Viral vector-(AAv9)	Launched
Advancement of Prion Protein-Lowering Divalent siRNA Therapy for Prion Disease	MINIKEL, ERIC VALLAB H	BROAD INSTITUTE, INC.	Academic	U01	Prion Disease	Oligonucleotide-(siRNA)	Launched
Silence ALS: A Platform for the Discovery and Development of Antisense Therapeutics for Patients with Ultra-Rare Forms of ALS	SCHNEIDER, NEIL ALAN	COLUMBIA UNIVERSITY HEALTH SCIENCES	Academic	U01	ALS	Antisense Oligonucleotides (ASOs)	To Be Launched Soon

URGenT Website

URGenT
Ultra-Rare Gene-based Therapy

RESEARCH FUNDED BY NINDS

- Clinical Research
- Neuroscience Research
- Translational Research

LATEST UPDATES

NINDS Strategic Plan 2021-2026

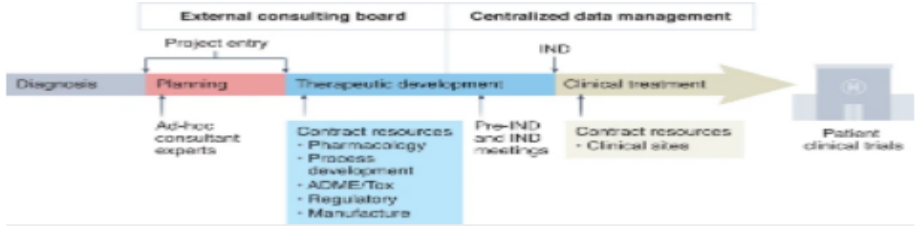
Read more

Ultra-rare Gene-based Therapy (URGenT) Network

The Ultra-rare Gene-based Therapy (URGenT) program will support the development of state-of-the-art gene-based therapies for ultra-rare neurological diseases, which affect as few or fewer than one in fifty thousand people. Altogether, around 7,000 known rare and ultra-rare diseases affect 30 million people in the US. Many are life-threatening and few have FDA-approved treatments. About 45% of rare diseases, including ultra-rare diseases, are neurological disorders, and 90% of rare childhood disorders have major neurological effects. 85% of rare and ultra-rare diseases are single gene disorders, making them excellent candidates for gene therapy. The URGenT program will provide funding and resources to advance gene-based therapies for ultra-rare neurological diseases from late-stage pre-clinical development into first-in-human clinical testing.

The goals of the URGenT program are to:

1. **Accelerate** advancement of discoveries into the clinic.
2. **Provide** resources and expertise not currently available to applicants.
3. **Deliver** therapeutics to patients with ultra-rare neurological diseases.
4. **Standardize** and **harmonize** best practices and protocols for the development of gene-based therapies for ultra-rare diseases.



Overview of the URGenT network - URGenT will support PIs with a lead gene therapy candidate from start-to-finish over a 3-year period. Projects enter before or after the planning stage, during which access to specialized consultants is available as needed. Appropriate contract partners are provided to aid with different stages of therapeutic development (including manufacturing, IND-enabling PK/toxicology studies, and IND submission), and transition to clinical trials. All aspects will be overseen by an external consulting board. Centralized data management ensures facilitative sharing of data, resources and practices with other projects in the network. ADME, absorption, distribution, metabolism and excretion; IND, Investigational New Drug; tox, toxicology.

URGenT Funding Opportunities

PAR-22-030: Translational Efforts to Advance Gene-based Therapies for Ultra-Rare Neurological and Neuromuscular Disorders (U01 - Clinical Trial Optional)

PAR-22-028: Ultra-Rare Gene-based Therapy (URGenT) Network Resource Access (X01, Clinical Trial Not Allowed)

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Related Funding Announcements

URGenT Funding Opportunities

View All Funding Opportunities

News & Events

URGenT Network Information Session
April 21, 2022 | 3PM EST

NINDS launches network to develop treatments for ultra-rare neurological diseases
November 4, 2021

Contact information

Future webinars

FOA information

Program Contacts

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