Solicitation for Collaborative Projects

Therapeutics for Rare and Neglected Diseases (TRND) Program
National Center for Advancing Translational Sciences
National Institutes of Health

Introduction to TRND

The National Center for Advancing Translational Therapeutics' Therapeutics for Rare and Neglected Diseases (TRND) program performs preclinical and early clinical development of new drugs for rare and neglected diseases, and develops new technologies and paradigms to improve the efficiency of therapeutic development for these diseases. The operational model of TRND is collaboration between intramural NIH drug development scientists and partners having promising leads and disease/target knowledge but lacking the expertise and resources to develop these projects into clinical stage programs attractive to biopharmaceutical or other suitable organizations.

The last several decades of research have produced unprecedented understanding of the genetics and pathobiology of many rare and neglected diseases, but the vast majority of these disorders have no drug treatment available. Of the approximately 7,000 human diseases, fewer than 500 are of interest to the biopharmaceutical industry, due to limited commercial potential and high perceived development risk. High-throughput screening centers in the private and public sectors, including those supported by the NIH Molecular Libraries Program, have produced a large number of chemical probes useful for the understanding and validation of novel targets for many rare and neglected diseases (RND). However, the difficulty, expense, time, and expertise and resource requirements of the development process required to transform a promising probe or lead into a clinical candidate molecule have prevented all but a few RND programs from reaching clinical testing or approval. This process, encompassing what is sometimes referred to as the "Valley of Death" because of its difficulty and risk of failure, is preventing the realization of the promise of basic biomedical research from reaching patients with rare and neglected diseases, and is what the TRND was specifically created to address.

The minimal starting point for TRND, and the subject of this solicitation, is a high-quality chemical or biological lead with validated biology and efficacy models that can support preclinical and early clinical development. Another starting point is a repurposed, marketed therapeutic with sufficient data to support its use in an RND indication. The exit point for TRND projects adopted from this solicitation will be licensing to an organization outside TRND that will carry the program forward to regulatory approval. It is expected that in most cases, TRND will perform the medicinal chemistry, drug metabolism and pharmacokinetics (DMPK), toxicology, formulation, and other studies required to create compounds that meet Food and Drug Administration (FDA) requirements for Investigational New Drug (IND) approval. TRND will perform proof-of-concept human studies (Phase I-IIa) only as needed to enable successful licensing.

The TRND program is an NIH Intramural activity, part of the newly-established National Center for Advancing Translational Sciences (NCATS). NIH TRND scientists will be responsible for the development

process. However, well-validated targets, efficacy models, starting point lead compounds, and deep target and disease expertise are critical for success, and are sought in this solicitation. TRND will establish collaborations with researchers in the public and private sectors to together "de-risk" RND drug development projects by accomplishing lead optimization through IND and proof-of-concept human studies.

TRND Program Application Instructions

Overview

This is not a grant application. Rather, it is an application to collaborate with the scientific capabilities, expertise, and resources of TRND, with the goal of moving promising small molecules and biologics into clinical testing. If successful, you will partner with the TRND to develop and execute a milestone-driven drug development program. TRND will provide drug development expertise and operations. The applicant collaborator(s) will provide starting points for the project, ongoing biological/disease expertise, and when appropriate and with the support of TRND funding, efficacy or other testing of compounds developed in the course of the project.

As discussed above, the primary focus of TRND is the preclinical phase of small molecule and biologic drug development for rare and neglected disease. It is expected that projects will enter TRND at a variety of stages, but no earlier than the stage of optimization of well-characterized leads, and no later than an NME, NBE, or repurposed drug in need of IND-enabling studies. The endpoint of TRND projects will be their adoption by organizations outside TRND, which will complete clinical development and registration. While these endpoints will be project-specific, it is expected that most projects will exit TRND at the stage of IND application/approval, or when required, when initial safety and efficacy studies in humans have been completed.

The purpose of this solicitation, the first of the newly-initiated TRND program, is to select initial drug development programs for collaborative development. All rare/orphan and neglected diseases are of interest. It is anticipated that TRND will issue two solicitations for this type of project per year.

General Instructions

At this time, TRND is considering only small molecule or biologic therapeutic development projects for collaboration. Gene therapy, devices, diagnostics, and medical procedures are not responsive at this time.

Proposed projects must target an untreated or poorly treated rare or neglected disease.

Special consideration will be given to projects with the potential to address more than one rare or neglected disease by virtue of shared pathophysiology, and projects with a well-developed strategy to exit TRND and complete clinical development, registration, and marketing.

Projects must be at least at the stage of a validated lead series in order to be considered for TRND. Projects requiring earlier-stage resources, including assay development, high-throughput screening, and initial medicinal chemistry optimization of screening hits, are not appropriate for TRND; researchers interested in these resources are directed to other NIH resources including the Molecular Libraries Program and the NCI Chemical Biology Consortium/NExT program.

This "TRND Concept Application" includes eight (8) sections as described in detail below; additional material can be uploaded as an appendix. Please use the TRND Concept Application Template, available only when the solicitation is open, at proposalCENTRAL. Please convert all documents to searchable PDF files before submission. All materials submitted to proposalCENTRAL are considered confidential. All reviewers will sign conflict of interest and confidentiality agreements before being given access to applications.

TRND encourages potential applicants to contact TRND prior to submitting a proposal in response to this solicitation.

Required Documents for TRND Program Applications

A. TRND Concept Application

The concept application document should not exceed 5 pages (Arial 11pt, single space, 1" margins, not including the pages that contain tables provided to collect data on lead compounds). Graphs, pictures and tables should be included in the text. The application should succinctly define the scientific nature and rationale of the proposed project and the current stage of its development, and should include the following:

1. **Background:** Provide a brief summary of the disease to be treated and the rationale for the type of small molecule compound or biologic therapeutic in order to provide the reviewers an understanding of the opportunity. Include data on rare or neglected disease status, the current standard of care for the disease, and why new therapies are needed. Very briefly describe the competitive landscape and efficacy data on comparator compounds, if any.
2. **Therapeutic Hypothesis:** Include a clear statement on the therapeutic hypothesis and the clinical indication to be targeted for FDA approval. This can include the projected reduction of symptoms, slowing of disease progression, or the feasibility of treating the disease. Review the level of consensus in the field supporting the proposed mechanism of disease and hypothesis that modulation of the proposed target will substantially improve morbidity and/or mortality in the disease. Summarize the evidence that validates the drug target from cellular or animal models and clinical studies. Assess feasibility to reach first in human studies. Manuscripts and supporting publications can be uploaded in the appendix.
3. **Current State of Project:** Projects of interest will be at one of the following stages: (1) lead optimization including clear structure-activity relationships (SAR) in at least two structurally distinct chemical series or well defined biological lead, reproducible activity in primary and orthogonal assays, efficacy in an accepted animal model (or when not available, cellular model) of the disease, and initial indications of favorable Absorption, Distribution, Metabolism, and Excretion (ADME) properties, (2) high-quality New Molecular Entity (NME) lead(s) with clear efficacy, good DMPK properties and initial non-GLP safety studies demonstrating absence of gross toxicities, (3) NME clinical candidates with incomplete IND-enabling PK/PD/toxicology/formulation studies; or (4) a drug previously approved for another indication by FDA with efficacy in an animal (or when not available, cellular) model of a rare or neglected disease, making it a candidate for repurposing but in need of formulation, dose-finding, disease-specific toxicology, or other studies to allow clinical testing to commence. As appropriate for the stage of the program, please describe:
    a. Compound or biologic optimization status and strategy, including the assays and efficacy studies used to guide medicinal chemistry optimization and define structure-activity relationships (SAR), including evidence of their robustness, reproducibility, and relevance to the human disease or symptom. Include results of molecular pharmacology assays, including in vitro functional activity, potency, and pharmacology, including evaluation of efficacy in biochemical, cellular, and model organism assays, and justification of the relevance of those assays to the human symptom/disease to be treated
    b. Medicinal chemistry optimization performed to date, including questions remaining and potential for further optimization.
    c. Evaluation of Absorption, Distribution, Metabolism, and Excretion (ADME) properties in vitro and in vivo, including routes and products of metabolism, microsomal stability, and related studies
    d. Evaluation of pharmacokinetics (PK), pharmacodynamics (PD), and efficacy, including oral bioavailability and half-life in serum and other relevant fluids/tissues
    e. Toxicology studies in rodents and non-rodents, including IND-directed toxicology, with correlative pharmacology and histopathology
    f. Definition or optimization of dose and schedule for in vivo activity in animal models

g. Pharmacodynamic measures in animals, and their applicability as biomarkers in human studies

h. Acquisition of bulk substance (Good Manufacturing Practices - GMP and non-GMP), and availability of protocols for scale-up production from lab-scale to clinical-trials lot scale, and analytical methods

i. Development of suitable formulations

j. Production and stability assurance of dosage forms

k. Projected dose, dose regimen, length of treatment and duration of therapeutic response in humans, if known

l. Biomarkers developed, and evidence of their utility and predictive value in the clinical setting

m. Determination of clinical endpoints, and whether these are accepted by regulatory agencies

n. Describe natural history studies of the disease and their relevance to the indication of the candidate therapy

o. Status of biobanks and registries of patients with the disease and which organizations maintain them

p. Potential clinical trial designs and evidence of feasibility

q. Results of consultations with FDA or other regulatory agencies, if any, on the project

r. Results of assessments you have received from impartial clinical experts in the field on why modulation of the target/pathway/phenotype is expected to decrease the morbidity or mortality of the disease.

s. Results of discussions and assessments with potential drug development partners that would support this drug candidate to FDA registration and market launch.

t. For projects with clinical data: provide a summary of clinical efficacy, safety, and PK/PD data. Describe the clinical trial strategy (e.g., primary and secondary study objectives, endpoints, patient population, eligibility criteria, estimated sample size, treatment arms/regimens, statistical endpoints, correlative studies, and patient samples required to perform correlative studies). Describe availability of clinical trial support, infrastructure resources, and experts available. If available, the Investigator's Brochure should be uploaded in the appendix.

4. **Proposed Development Strategy:** Describe what is needed to advance the program to IND status for the rare or neglected disease indication, what the current roadblocks to development are, and the stage that the project will need to be taken to in order to attract outside development resources. If the development plans are not established or clear, please indicate this. Include specific details as necessary to demonstrate that the project has been well thought out (for example, the availability of appropriate cellular and animal models, patent searches on the compounds and components of the assays used to evaluate efficacy, etc.). Address the scientific feasibility of the proposed development strategy, and whether and why proof-of-concept human studies are likely to be needed for the project to be licensed.

5. **Justification:** Address how the resulting drug from this collaboration will change standard of care and impact the practice of medicine for this rare or neglected disease. Provide a statement that the applicant team will engage and collaborate for the length of this drug development project and what expertise and/or resources the applicant will bring to the project team. Describe the likelihood of the drug candidate being adopted at the completion of preclinical development (i.e., once an IND is approved), and why another organization (biotechnology companies, venture capital firms, pharmaceutical companies) is presently unwilling to fund or develop this drug project as it currently stands.

6. **Timeline and Milestones:** Outline a potential timeline for conducting the collaborative research with TRND. Include potential milestones. Describe potential challenges and go/no go decision points (a timeline chart is acceptable). (Note: Following acceptance the project, a project team of TRND

investigators and applicant investigators will establish a new timeline, milestones, and go/no go decisions points based on the evaluation recommendations.)

7. **Appendix 1:** Tables are provided in the appendix 1 to facilitate data collection on proposed lead compound or compound series. In each table, clearly indicate the ID/name of the molecular entity of which the data were generated. In the first group of tables, provide the structure (s) of the chemical lead compound for NME or composition for NBE; populate the tables with any current physical property data, in vitro and in vivo efficacy data, and PK data on the proposed lead compound(s). If there is no data generated for a particular property, leave the data cell empty or enter N/A if not applicable to your proposal. Do not delete any cells in the tables. If there are relevant data specific to your proposal, but not included in the tables, add rows and indicate clearly in the ID , what type of data are included. Populated tables in appendix 1 are REQUIRED to be included in the uploaded proposal, but are not counted towards the 5 page limit of the proposal.
8. **Appendix 2:** References are provided to applicants for in vitro ADME assays and in vivo pharmacokinetics assays. This portion of the template need not be included in uploaded proposal.

B. Appendices

- **References:** Please provide no more than 15 references that relate directly to the project. Upload at least 5 key reference papers as PDF files to accompany the proposal.
- **Public Abstract:** The selected drug development projects that put collaborative agreements into place with TRND will have a public abstract and timeline posted on the TRND website. Please provide a non-confidential abstract that describes the disease, the projects, the medical treatment goals, and the timeline.
- **Intellectual Property (IP) Information:** The applicant should include a list of any patents issued or pending with respect to either the agent or to any non-commercially available technology/material required for the development of the agent. In the event that an application requires the use of non-commercially available technology/equipment that is patented by a third party, the applicant must provide documentation that the patent holder does not object to the applicant's use with the proposed project.

  Each TRND application must include the information described below signed by an authorized staff member overseeing IP and/or technology transfer at the applicant's institution or company. This verifies that he/she has reviewed the TRND request and that the technology is eligible for consideration by the TRND program. If the technology is found not to be eligible for use as outlined in the TRND application, and it is central to the investigator's proposal, submission to the TRND program is not encouraged.

  If available, the following information is requested:

  - **Details of all the following rights that are owned by your institution and will be used in the project (the "institution's IP"):**
    - Patents and patent applications
    - Significant know-how
    - Registered trademarks, applications for registered trademarks, and other marks
    - Registered designs, applications for registered designs, and significant other designs
    - Significant copyright works and other IP rights
  - **Details of all employees, consultants, and other parties involved in the development of the institution's IP related to the TRND project submission. (Are there contributors outside the institution, and if so, what was their role in development?)**
  - **A complete list and brief description of all agreements with third parties related to the TRND project submission:**
    - Granting rights to those third parties under the institution's IP
    - Granting rights under third-party IP to the institution

- **A complete list and brief description of all confidentiality agreements with third parties related to the TRND project proposal**
- **Details of any:**
    - Claims made by third parties against the institution related to the project proposal that the institution has infringed a third party's IP rights
    - Circumstances where a third party has or may have infringed the institution's IP or other IP used in the institutions' business related to the project proposal

  Institution IP constitutes background IP. Inventorship of new IP created from this partnership/collaboration will be determined according to patent law.

- **Key Investigators Biosketch:** All Key Investigator (all investigators intellectually involved in the project) bio-sketches should follow the NIH standard format. In the list of publications, please highlight any that are directly related to proposed project by preceding them with a double asterisk (**). All Key Investigators should list all current external sources of research funds. The lead PI (point of contact) should provide additional contact information.

Evaluation Process

Applications to the TRND Program are evaluated by a Technical Evaluation Panel (TEP) consisting of non-NIH experts in drug development. The applications will be evaluated according to the following criteria.

Criteria (weight of criteria):
1. Target and therapeutic validation (30%),
2. Strength of current data package (30%)
3. Feasibility to reach First in Human clinical trials (20%),
4. Medical impact relative to current Standard of Care (10%),
5. Likelihood of external adaption (10%).

In addition, the TEP will rate the strength of the development project in (where applicable):
1. Medicinal Chemistry
2. ADME
3. PK/PD
4. Toxicology
5. In vivo models
6. Secondary and tertiary assays
7. Formulation
8. Chemical Manufacturing and Controls (CMC) for small molecule projects
9. Expression/Purification for biologics projects
10. IP Status

Following the TEP evaluation, the top applications will be discussed by NIH staff in relevant Institutes and Centers for synergy and overlap. A second level of evaluation for program balance, workload distribution and resources will be conducted by TRND program staff. The NCATS Advisory Council will make final decisions on projects to be adopted by TRND.

Collaborative Agreements

Once selected applicants are notified, NCATS/TNRD and the applicant will initiate an NIH collaborative agreement. When the collaborative agreement is agreed to and signed by all parties, the collaborative project will start. Please see the TRND website (http://trnd.nih.gov) for more information on this topic.

Projects Selected by NCATS/TRND

- **Project Team:** Once the project is selected for collaboration (and as the collaborative agreement is being discussed), a project team will be formed of both TRND and applicant investigators. The project team will develop a Project Plan and define the:
    - Development Plan
    - Timeline
    - Milestones and Deliverables
    - Go/No Go decision points
- **Project Plan:** The Project Plan will be approved by NCATS leadership. Any changes to the Project Plan will need to be approved by the NCATS leadership. Go/No Go decisions will be evaluated by an NCATS advisory panel for recommendations to NCATS leadership in stopping a project.
- **Project Termination**: Upon not meeting timeline, milestones, and/or deliverables, or with the recommendation of an NCATS advisory panel, NCATS will terminate a project. Whenever possible, the applicant investigators will be provided guidance on how to move the project forward. Applicants will be encouraged to submit a new application if barriers are outcome.

TRND Proposal Resubmission Instructions

A resubmission is submission of an application that has previously been reviewed and not selected. TRND will accept only two (2) resubmissions, for a total of three (3) submissions for a specific application.

The resubmission consists of a Resubmission Summary, not to exceed 2 pages, and an amended concept application in which changes are marked. Reviewers will have access to the original application.

The resubmission should include the following:

1. A Resubmission Summary not to exceed 2 pages.
    a. Explain how the application has been modified and strengthened.
    b. Respond to the comments and recommendations from the scientific reviews. Address any disagreements with reviewers' comments.
2. An amended version of the original concept application to highlight substantial scientific changes.
    a. The amended application should follow the current "TRND Proposal Instructions" as described under "Required Documents for Therapeutics for Rare and Neglected Diseases Applications" and should not exceed 5 pages.
    b. Substantial scientific changes must be clearly marked with underlining, *italics*, bold, or other formatting. However, if the changes are so extensive that essentially all of the text would be marked, explain this in the Resubmission Summary.

Applications should be resubmitted according to the published TRND submission cycle.