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Solicitation for Collaborative Projects

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

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Introduction to TRND

The Therapeutics for Rare and Neglected Diseases (TRND) program, part of the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH), performs preclinical and early clinical development of new treatments for rare and neglected tropical 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 NIH intramural drug development scientists and partners having promising leads and disease / target knowledge, but who lack the expertise and resources to develop these projects into clinical stage programs attractive to biopharmaceutical or other suitable organizations.

The TRND program is an NIH intramural activity, through which partnerships are established with collaborators in the public and private sectors. The goal of the program is to work together to “de-risk” candidate rare and neglected tropical disease (RND) drug development projects. TRND scientists will be responsible for the development process, while collaborators with well-validated targets, efficacy models, starting-point lead compounds, and deep target and disease expertise are sought through public solicitation.

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. Other starting points include a repurposed, marketed therapeutic with sufficient data to support its use in an RND indication, or a platform technology addressing an RND indication, but with the potential to address a wider range of disorders and that can enable more efficient future development of other therapeutics. 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) application clearance. In limited cases, TRND may support proof-of-concept human studies (Phase I-IIa), if necessary to enable successful licensing.

TRND Program Application Instructions

Overview

This is not a grant application, and no external funding is available. 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 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-area expertise, and when appropriate and with the support of TRND, efficacy or other testing of compounds developed in the course of the project.

The primary focus of TRND is the preclinical phase of small molecule and biologic drug development for rare and neglected diseases. 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 a new molecular entity (NME), new biologic entity (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 / clearance, or when required, when initial safety and efficacy studies in humans have been completed.

The purpose of this solicitation is to select candidate programs for collaborative development. All rare and neglected diseases are of interest.

General Instructions

At this time, TRND is considering only small molecule or biologic therapeutic development projects for collaboration. Gene therapies, devices, diagnostics, and medical procedures are not within program scope, and will not be considered responsive to this solicitation.

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

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 types of resources are directed to other NIH resources including the Molecular Libraries Program, the NCI Chemical Biology Consortium/NExT Program, and the NIAID Microbiology and Infectious Diseases Resources.

Proposals are made using the electronic grant-making system, proposalCENTRAL. The written "TRND Concept Application" includes seven (7) major sections as described in detail below, with specific additional supporting materials required. Prior to submission, all documents must be converted to searchable PDF format (i.e., free of any digital protection or passwords), to allow compilation and handling by the proposalCENTRAL system. The review and evaluation process is kept confidential by the TRND program. All materials submitted to TRND via proposalCENTRAL are considered confidential, pursuant to review guidelines in accordance with 42 CFR Part 52h. All reviewers sign conflict of interest and confidentiality agreements before being given access to applications.

TRND employs a Letter of Intent process, and requires applicants to contact the TRND Solicitation Coordinator 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). Any graphs, pictures, and data tables must be included in the body of the text, and will count against the 5-page limit. (**NOTE:** The specific TRND-developed data collection tables provided in *Appendix 1* will not count against the 5-page limit.) 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, as well as the rationale for the type of small molecule compound or biologic therapeutic selected, in order to provide the reviewers with an understanding of the scientific opportunity presented. Include data on rare or neglected tropical 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:** Provide a clear statement of the therapeutic hypothesis and the clinical indication targeted for FDA approval. This can include the projected reduction of symptoms, slowing of disease progression, or the feasibility of treating the disease. Clearly summarize the evidence that validates the selected therapeutic-target combination, including mechanism of action and data from cellular or animal models and/or clinical studies. Appropriate targets may include pathways or phenotypes clearly related to 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. Assess feasibility to reach first in human studies. Manuscripts and other supporting publications can be uploaded as described (See *"B. Supporting Documents"*, below).

3. **Current State of Project:** TRND collaborative projects will be initiated at various stages of preclinical development, but ***no earlier than*** optimization of well-characterized leads, and ***no later than*** a new molecular entity (NME), new biologic entity (NBE), or repurposed drug in need of IND-enabling studies. Projects of interest will be at one of the following stages:

   (1) **Lead Optimization:** Lead Op aims to identify and develop a potent, specific development candidate from among the preliminary series through initial medicinal chemistry. These early-stage candidates must include clear structure-activity relationships (SAR) in at least two structurally distinct chemical series or a 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; initial indications of favorable Absorption, Distribution, Metabolism, and Excretion (ADME) properties; and favorable head-to-head comparisons versus the prior art.

   (2) **New Molecular / Biologic Entity (NME / NBE):** This will represent an advanced lead molecule, requiring completion of IND-enabling studies. At minimum, the selected candidate molecule will include clear efficacy data, good drug metabolism and pharmacokinetic (DMPK) properties, and initial non-GLP safety studies demonstrating absence of gross toxicities. Development candidates may require completion of IND-enabling pharmacokinetic / pharmacodynamic / toxicology / formulation studies.

   (3) **Repurposing:** A repurposing candidate represents a drug previously approved by FDA for another indication, which has been shown to have efficacy in an animal model (or when not available, cellular model) of a rare or neglected tropical disease. Relying heavily on the previous indication data package, a repurposing candidate will be more advanced, in need of formulation, dose-finding, disease-specific toxicology, or other studies to allow clinical testing to commence.

   (4) **Platform Technology:** These programs will seek development support for a therapeutic candidate directed toward a specific rare or neglected tropical disease indication, but will represent a technology platform with the potential to address a wider range of additional disorders and that

can enable more efficient future development of other therapeutics. Both early- and later-stage projects will be considered, as described above

Depending upon the current stage of your project, and the support you are seeking from TRND, provide as much of the below data as are available:

a. Compound or biologic optimization status and strategy, including the assays and efficacy studies used to guide medicinal chemistry optimization and define structure-activity, structure-selectivity, and structure-property relationships. Include evidence of their robustness, reproducibility, and relevance to the human disease or symptom. Provide results of molecular pharmacology assays (e.g., in vitro functional activity, potency), 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 microsomal or hepatocyte stability, species comparison of in vitro metabolic pathways, CYP inhibition / induction potential evaluation, plasma or tissue protein binding, inhibition of major transporters, in vivo bioavailability at clinically-intended route(s) of administration, clearance, volume of distribution, elimination half-life, and related studies

d. Evaluation of pharmacokinetics (PK), pharmacodynamics (PD), and efficacy, including in vivo exposure and half-life in serum and other relevant fluids / tissues, ED50 or minimal efficacious dose in animal models

e. In vitro and in vivo toxicology studies in rodents and non-rodents, including Ames and hERG tests, 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 animal studies, 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 clinic

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

n. Natural history studies of the disease and their relevance to the proposed target-therapeutic combination

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 prior consultations with FDA or other regulatory agencies

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

s. Results of discussions with, or assessments by, potential drug development partners that would support this drug candidate through 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 supporting documents.

NOTE: TRND provides the following list of MINIMAL KEY DATA (from the above lettered list) for inclusion in your proposal in support of the four general project categories:

- Lead Optimization: A, B, C, D
- NME/NBE Candidates: A, C, D, G, H
- Repurposing: A, F, G, H, I, J, L
- Platform Technology: A, C, D, I, J

4. **Proposed Development Strategy:** Describe what is needed to advance the program to IND status for the rare or neglected tropical disease indication. Identify the current roadblocks to development 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, indicate this explicitly. Include specific details as necessary to demonstrate that the project has been well thought-out (e.g., 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 / 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 tropical disease. Describe how the applicant team will engage and collaborate with TRND for the length of this drug development project, including the 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 cleared), and why other organizations (e.g., biotechnology companies, venture capital firms, pharmaceutical companies) are presently unwilling to fund or develop this drug project as it currently stands.

6. **Timeline and Milestones:** Outline a timeline for conducting the collaborative research with TRND. Identify potential milestones, and describe potential challenges, go/no-go decision points, and costs of related tasks / studies (if known). A simplified timeline chart is acceptable. (**NOTE:** Following acceptance into TRND, a rigorous gap analysis will be conducted. The collaborative TRND and applicant investigator team will establish a new timeline, milestones, and go/no-go decision points to govern the project.)

7. **Appendix:** Tables are provided as *Appendix 1* of the TRND Concept Application to facilitate data collection. Clearly indicate the ID / name of the molecular entity from which data were generated. Provide structure(s) of the chemical lead compound (for NME) or composition (for NBE). Populate

the tables with any current physical property, in vitro and in vivo efficacy, and PK data on the proposed lead compound(s). If there are no data generated for a particular property, or if not applicable to your proposal, leave the data cell empty or enter "N/A". **Do not delete any cells from the tables.** If there are relevant data specific to your proposal, but not included in the provided tables, you may add additional tables / rows and indicate clearly in the ID field what type of data are being included. (**NOTE:** Populated tables in the Appendix are REQUIRED to be included in the uploaded proposal, but are NOT COUNTED TOWARD the 5-page limit.)

B. Supporting Documents

- **References:** References should NOT be exhaustive. Provide a list of no more than 15 references relating directly to the proposal. Provide PDFs of any key papers, to ensure that all reviewers have access to critical data you wish to cite. Compile all Reference documents into a single PDF upload, if possible, pending individual file-size limits in proposalCENTRAL.

- **Scientific Abstracts:** Two (2) summary abstracts are required: 1) a non-confidential general audience summary and 2) a scientific abstract. The non-confidential summary (4,000 characters maximum) is submitted via text field in the proposalCENTRAL portal. This general summary should describe the disease, the proposed development project, the medical treatment goals, the current state of the project, and the projected timeline. The more in-depth scientific abstract (1-page maximum, Arial 11-pt, single-spaced, 1" margins) should be written for a more sophisticated audience, and may contain more sensitive data drawn from the body of the proposal. The detailed abstract must be submitted as a separate supporting document in PDF format.

- **Key Methods and Models:** To assess the current state of the project and strength of the data package, and to enable conduct of necessary validation and follow-on studies upon adoption into the portfolio, applicants must provide a detailed description of any key in vitro / in vivo assay methods. Assays and animal models must be commercially available or otherwise readily transferrable to TRND or to a second site (i.e., contract research organization, CRO) for required validation studies. If lead optimization for further characterization of structure-activity relationships (SAR) is a primary request, validated and optimized high-throughput methods are required (i.e., 96/384/1536-well plate format). Secondary and orthogonal assays for validation of compound efficacy may be of lower-throughput.

- **Intellectual Property (IP) Information:** To ensure sufficient freedom to operate on the proposed agent, the applicant must provide a clear description of the relevant patent space and status of IP. This includes a list of any patents issued or pending with respect to either the agent to be developed, or to any non-commercially available technology / material required for the development of the proposed agent. In the event that a project would require 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 in support of the proposed TRND 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.

  The following information is REQUIRED. If any of the following are not applicable to your project, state so explicitly (e.g., "There are no confidentiality agreements in place with a third party"):

- **Description of the patent space / freedom to operate around the proposed agent. This is especially important, though not limited to, lead optimization projects likely to require significant medicinal chemistry support.**

- **Details of all the following rights that are owned by your institution and that 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. If there are contributors from outside the institution, describe 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

NOTE: Any IP generated PRIOR to initiation of TRND collaboration are retained by the applicant / institution as background IP. The potential for development of new, multi-party IP will depend upon the stage at which the project enters into collaboration with TRND. However, all collaborators should anticipate that there WILL BE joint IP development with TRND / NCATS employees. Inventorship of any new, multi-party IP created from this collaboration will be determined according to United States patent law, and governed under the collaborative agreements executed at the outset of the partnership.

- **Key Investigators Biosketch:** All Key Investigators (i.e., all investigators intellectually involved in the project) must provide biosketches following the NIH standard format. In the list of publications, please highlight any that are directly related to the 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 panel consisting of non-NIH experts in drug development. The applications will be evaluated according to the following major criteria (by relative weight):

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 adoption (10%)

The strength of the development project will be rated in the following areas (as 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

In addition to the non-NIH panel, applications will be discussed by NIH staff in relevant Institutes and Centers to identify synergy and overlap. TRND also considers program balance, workload distribution, and availability of resources. The evaluation process will be kept confidential.

Collaborative Agreements

Once selected applicants are notified, NCATS / TRND 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. More information about the available standard model agreements may be found on the NCATS website.

Project Initiation, Planning, Termination

- **Project Team:** Once the project is selected for collaboration and the collaborative agreement has been executed, a project team will be formed of both TRND and applicant investigators. The project team will develop a formal 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 TRND leadership. Any changes to the Project Plan will need to be approved by TRND leadership. Go/no-go decisions will be evaluated by the project's Research Committee, which will make recommendations to TRND leadership regarding project termination, if necessary.

- **Project Termination**: Upon failure to meet timeline, milestones, and/or deliverables, or with the recommendation of the project's Research Committee, TRND will terminate a project. Whenever possible, the applicant investigators will be provided guidance on how to move the project forward. Applicants may submit a new application if barriers are overcome.

TRND Proposal Resubmission Instructions

Resubmission guidelines pertain to: A) submission of an application that has previously been evaluated by TRND but not selected for adoption; or B) submission of an amended proposal concerning a project which was previously terminated by TRND but has overcome its key barriers. TRND will accept only two (2) resubmissions, for a total of three (3) submissions for a specific 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. As applicable, respond to any comments and recommendations from the scientific reviews, and address any disagreements with reviewers' comments.

2. An amended version of the concept application to highlight substantial scientific changes.
    a. The amended application should follow the current "TRND Program Application Instructions" governing required documents and page limits.
    b. Substantial scientific changes should be clearly marked (e.g., underlining, *italics*, **bold**, or other formatting) for ease of reference. However, if the changes are so extensive that essentially all of the text would be marked, explain this in the Resubmission Summary, and forgo any special call-out formatting.

Reviewers will have access to the original application through proposalCENTRAL, so it is not necessary to resubmit the original as an addendum. Resubmissions are considered according to the published TRND submission cycle.