

Proposals for Collaboration
Therapeutics for Rare and Neglected Diseases (TRND) Program
Division of Pre-Clinical Innovation
National Center for Advancing Translational Sciences
National Institutes of Health

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Introduction to TRND

The NCATS [Therapeutics for Rare and Neglected Diseases \(TRND\) program](#) is an NIH intramural research program focused on pre-clinical and early clinical development of new treatments for [rare conditions](#) and [neglected tropical diseases](#). TRND also aims to develop new technologies, models and paradigms to improve the efficiency of therapeutic development.

The operational model of TRND is collaboration between NIH intramural drug development scientists and external partners from the public and private sectors. TRND partners bring promising investigational therapeutic candidates and disease/target knowledge to the collaboration, but they either lack the expertise or resources to move these candidate molecules into clinical testing.

The minimal starting point for entering into collaboration with TRND is a high-quality chemical or biological lead molecule with validated proof-of-concept in *in vitro* or *in vivo* disease-relevant models. TRND has expertise developing various treatment modalities, including small molecules and large molecule biologics, repurposing approved drugs for new indications, and platform technologies that are applied to a rare or neglected indication with the potential to address a wider range of human disorders or that can enable more efficient future development of other therapeutics. TRND uses a milestone-driven, multi-stakeholder project team approach to drive project execution. Assuming all milestones are met, TRND commits resources to enable completion of an Investigational New Drug (IND) filing with the Food and Drug Administration (FDA). TRND scientific teams bring a range of expertise to the collaboration, including medicinal chemistry, drug metabolism and pharmacokinetics (DMPK), manufacturing of drug substances and drug products, non-clinical toxicology, clinical testing and industry-level project management. On a case-by-case basis, TRND may support proof-of-concept human studies (Phases I and II) to enable successful out-licensing for further commercialization.

Public reporting burden for this collection of information is estimated to average one hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0658). Do not return the completed form to this address.

Proposal Instructions

Overview

This is not a grant application, and no external funding is available. Rather, it is a proposal to collaborate with TRND scientists, with the goal of moving promising small molecules, large molecule synthetic and recombinant biologics, and gene- and cell-based therapies into clinical testing. If accepted into the TRND program, external investigators will partner with TRND scientists to develop and execute a milestone-driven drug development program. TRND scientists will provide drug development expertise and operations and will use TRND funds to complete tasks required to meet program milestones. The external collaborator(s) will provide starting points for the project, ongoing disease-area expertise, and, when appropriate, efficacy or other testing of compounds to support selection of clinical candidate molecule(s).

The primary focus of TRND is to move promising molecules through the pre-clinical phases of drug development for rare and neglected diseases. It is expected that projects will enter TRND at a stage between lead optimization and IND filing with the FDA. The endpoint of TRND projects will be successful clearance of an IND application. On a case-by-case basis, TRND will support continued development of certain rare or neglected diseases with initial safety and proof-of-concept testing in human subjects.

Proposals are meant to identify candidate projects for collaborative development. All rare and neglected diseases are of interest. Proposals to collaborate with TRND will be accepted on a rolling basis.

General Instructions

At this time, TRND is considering small molecules, large molecule synthetic and recombinant biologics, and gene- and cell-based therapies for collaboration. Vaccines, devices, diagnostics and medical procedures are not within program scope and will not be considered.

Proposed projects must target an untreated or poorly treated [rare condition](#) or [neglected tropical disease](#). Data from the most relevant *in vivo* and *in vitro* models available should be obtained before proposing to collaborate. Efficacy should be demonstrated via the intended clinical route of administration and preferably be published in a peer-reviewed journal or independently replicated. If efficacy has been demonstrated by a route that differs from that proposed for initial clinical trials, then additional data obtained by the different routes should be provided to compare exposure levels in target organs.

Projects must be at least at the stage of a validated small molecule lead series (or related stage in biologics development, such as affinity-matured and humanized antibody) in order to be considered for TRND. Projects requiring earlier-stage resources, including assay development, high-throughput screening, initial medicinal chemistry optimization of screening hits, gene-therapy vector codon optimization, and affinity maturation and/or humanization of a therapeutic antibody, are not appropriate for TRND. Researchers interested in these types of resources are encouraged to explore other programs within the [NCATS Division of Pre-Clinical Innovation](#) or consult with extramural program staff at the appropriate NIH Institute or Center to discuss other funding options.

Interested investigators must register with the online [proposalCENTRAL](#) system and provide a project abstract. The abstract must summarize the proposed collaboration in a way suitable for public dissemination. Describe the disease, the proposed therapeutic agent, the current state of the project (i.e., an indication of the available efficacy, pharmacology and safety data), the resources required to advance development, the public health impact and why TRND is the desired partner for collaboration. The abstract should be informative to other scientists working in the same or related fields and understandable to a scientifically or technically literate lay reader. Do not include proprietary, confidential information or trade secrets. Following registration, a mandatory pre-proposal call is required with the TRND program staff to assess project eligibility and orient investigators to the proposal and collaboration processes. Eligible investigators then will be invited to submit a full electronic proposal via [proposalCENTRAL](#).

Required Documents for TRND Program Proposals

A. TRND Proposal

The proposal should not exceed 5 pages (Arial 11pt, single space, 1" margins). Any graphs, pictures or 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 the Proposal Template appendix will not count against the 5-page limit.) The proposal should succinctly define the scientific nature and rationale of the proposed project and the current stage of its development. It should include the following:

- 1. Background and Therapeutic Hypothesis:** Clearly articulate the scientific opportunity presented. Provide a brief summary of the disease to be treated, the current standard of care and need for new therapies, and the rationale for the therapeutic compound or biologic selected, including a brief description of the competitive landscape and any efficacy data on comparator compounds. Provide a clear statement of the therapeutic hypothesis. Briefly summarize the level of consensus in the field supporting the proposed mechanism of disease and how modulation of the target will substantially improve morbidity and/or mortality. Manuscripts and other supporting publications can be uploaded as described in section B. (See "*B. Supporting Documents*" on page 6.)
- 2. Current State of Project:** Investigators can propose TRND collaborative projects at various stages of pre-clinical development, but no earlier than optimization of well-characterized leads, and no later than a new molecular entity (NME), new biologic entity (NBE), gene or cell-based therapy, or repurposed drug in need of IND-enabling studies. Projects of interest will be at one of the following stages:
 - **Lead Optimization:** This stage 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 cellular model if an animal model is not available) of the disease; initial indications of favorable absorption, distribution, metabolism, and excretion (ADME) properties; and favorable head-to-head comparisons with the prior art.
 - **New Molecular/Biologic Entity:** This represents an advanced lead molecule, requiring completion of IND-enabling studies. At minimum, the candidate molecule will include clear efficacy data, good DMPK properties, and initial non-Good Laboratory Practice safety studies demonstrating absence of gross toxicities. Development candidates may require completion of IND-enabling pharmacokinetics (PK), pharmacodynamics (PD), toxicology or formulation studies.
 - **Gene or Cell-Based Therapy:** Gene or cell-based therapies employ technologies to deliver genes or living intact cells to patients to treat or prevent certain diseases. TRND considers only late-stage gene or cell-based therapy projects at this time. At a minimum, a late-stage gene or cell-based therapy project should have the delivery vector identified, the curative gene construct selected and the animal disease model(s) validated.
 - **Repurposing:** A repurposing candidate represents a drug previously approved by the FDA for another indication, which has been shown to have efficacy in an animal model (or a cellular model if an animal model is not available) of a rare condition 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.
 - **Platform Technology:** Investigators will seek to develop a therapeutic candidate directed toward a specific rare or neglected disease indication, but the technology will represent a platform that has 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.

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 or disease to be treated.
- b. Medicinal chemistry optimization performed to date, including questions remaining and potential for further optimization.
- c. Evaluation of 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 the clinically intended route(s) of administration, clearance, volume of distribution, elimination half-life and related studies.
- d. Evaluation of PK, PD and efficacy, including *in vivo* exposure and half-life in serum and other relevant fluids or 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, assessments of immunogenicity and IND-directed toxicology.
- f. Definition or optimization of dose and schedule for *in vivo* activity in animal models.
- g. PD measures in animal studies and their applicability as biomarkers in human studies.
- h. Acquisition of bulk substance (Good Manufacturing Practices [GMP] and non-GMP), process development efforts, 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. For gene therapies: Confirmation of serotype and tropism for the selected viral vector, evaluation of the safety of the vector and toxicity of the expressed protein(s), verification that the route of administration successfully transports the gene of interest to the target site, evaluation of the immune response against the gene therapy product, and evaluation of the biodistribution of the gene of interest.
- n. Determination of clinical endpoints and whether these are acceptable to regulators.
- o. Natural history studies of the disease and their relevance to the proposed target-therapeutic combination.

- p. Status of biobanks and registries of patients with the disease and which organizations maintain them.
- q. Potential clinical trial designs and evidence of feasibility.
- r. Results of prior consultations with the FDA or other regulatory agencies.
- s. Results of assessments received from impartial clinical experts in the field as to why modulation of the target, pathway or phenotype is expected to decrease the morbidity or mortality of the disease.
- t. Results of discussions with or assessments by potential drug development partners that would support this drug candidate through FDA registration and market launch.
- u. For projects with clinical data: 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, inclusion and exclusion criteria, estimated sample size, treatment arms or regimens, statistical endpoints, correlative studies, patient samples required to perform correlative studies). Describe the availability of clinical trial support, infrastructure resources and experts available. If available, the Investigator's Brochure should be uploaded in the supporting documents.

3. **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 to which the project will need to be taken to attract outside development resources. Identify milestones and describe potential challenges and go/no-go decision points. 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.
4. **Justification:** Address how the resulting drug from this collaboration will change the standard of care and affect the practice of medicine for this disease. Describe how the investigator team will engage and collaborate with the TRND scientists, including the expertise and/or resources that will be contributed to the collaboration. Describe the likelihood of the drug candidate being adopted at the completion of pre-clinical development (i.e., once an IND is cleared) and why other organizations (e.g., biotechnology and pharmaceutical companies, venture capital firms) are presently unwilling to fund or develop this project as it currently stands.
5. **Data Tables Appendix:** Tables are provided as an appendix within the TRND Proposal Template to facilitate data collection. Clearly indicate the ID or name of the molecular entity from which data were generated. Provide the 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 the proposal, enter "N/A" or leave the data cell empty. Do not delete any cells from the tables. If there are relevant data specific to the proposal but not included in the provided tables, additional tables/rows may be added. Indicate clearly in the ID field what types 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 readers have access to critical data that may be cited. Compile all reference documents into a single PDF upload, if possible, pending individual file size limits in [proposalCENTRAL](#).
- **Timeline and Milestones:** Provide a clear statement of the development tasks that are proposed for completion. Provide an estimated timeline for conducting the collaborative research with TRND. A simplified timeline chart is acceptable. State all current and applied-for sources of support for the proposed project tasks. This includes a summary of the status of past, ongoing, or planned negotiations with companies related to licensure or future development. Include information on any peer-reviewed grant or contract applications pertaining to the proposed project. Provide a clear statement as to how TRND resources would complement — not duplicate — other sources of support. (**NOTE:** If collaboration with TRND begins, a rigorous gap analysis will be conducted. The team will establish a formal timeline, milestones and go/no-go decision points to govern the project.)
- **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, a detailed description of any key *in vitro* or *in vivo* assay methods is required. Assays and animal models must be commercially available or otherwise readily transferrable to TRND or to a second site (i.e., contract research organization). If lead optimization for further characterization of SARs is a primary request, validated and optimized high-throughput methods are required (i.e., 96-, 384- or 1,536-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, a clear description of the relevant patent space and status of IP is required. This includes a list of any patents issued or pending with respect to either the agent to be developed or any non-commercially available technology or material required for the development of the proposed agent. In the event that a project would require the use of non-commercially available technology or equipment that is patented by a third party, the proposal must include documentation verifying that the patent holder does not object to its use in support of the proposed TRND project.

Each TRND proposal must include the information described below, signed by an authorized staff member overseeing IP and/or technology transfer at the investigator's institution or company. This verifies that he or she has reviewed the TRND proposal 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 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 or freedom to operate around the proposed agent. This is especially important for, 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 knowhow
 - 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 proposal. 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 proposal:
 - 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, including 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 before initiation of TRND collaboration are retained by the investigator/institution as background IP. The potential for development of new IP will depend on 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 U.S. patent law and governed under the collaborative agreements executed at the outset of the formal research partnership.

- **Key Investigators Biosketch:** All key investigators (i.e., all investigators intellectually involved in the project) must provide biosketches following the current [NIH General Biographical Sketch](#) 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 principal investigator (point of contact) should provide additional contact information.
- **Regulatory Communications:** If the investigators have previously consulted with the FDA or other regulatory agencies, complete meeting minutes or other informal written communications should be provided. These documents should not take the place of the summary discussion of any key outcomes within the body of the proposal. (See "*Current State of Project*" on page 3.) Submission of these documents is optional at the time of the initial proposal.
- **Study Report Summaries:** In cases where an investigator has generated significant data (e.g., batch syntheses, *in vivo* toxicology), whether in-house or from outside collaborators or contract organizations, a one-page summary of results may be provided. Full study reports should not be uploaded. Summaries should not take the place of the discussion of any key data within the body of the proposal (e.g., "*Current State of Project*" on page 3) or completion of the provided Data Tables Appendix in the Proposal Template. Submission of this document is optional at the time of initial proposal.

NOTE: Prior to submission, all documents must be converted to searchable PDF format, free of any digital protection or passwords, to allow compilation and handling by the proposalCENTRAL system.

Selection Process

NCATS staff initially assess proposals to TRND for scope and availability of internal resources. TRND staff then seek feedback on select proposals from NIH staff in relevant Institutes and Centers and external drug development experts to measure enthusiasm for the proposed science, competitiveness within the disease research area, and feasibility of drug development. Feedback will be obtained in the following areas:

- Target and therapeutic validation
- Strength of current data package
- Feasibility to reach first-in-human clinical trials
- Medical impact relative to current standard of care
- Likelihood of external adoption

NCATS also will assess the strength of the investigator's IP estate in its consideration of the proposed project. Details of the NIH and external expert deliberations are kept confidential by the TRND program, though investigators will receive written communication regarding the proposal's final outcome. All materials submitted to TRND via [proposalCENTRAL](#) are considered confidential.

Following the scientific assessment, TRND staff will evaluate select proposals further through due diligence and face-to-face meetings with potential collaborators, during which TRND staff may request additional supporting data. Portfolio balance and availability of resources also will impact final decisions.

Post-Submission Communications

NCATS staff will inform investigators of the status of their proposal as soon as is feasible. During the selection process, additional (just-in-time) data may not be submitted. Twelve months after a proposal is deferred or declined, investigators may be given an opportunity to provide new data in support of the proposal. Significant changes to a proposal's scientific direction or available data may require submission of a fully revised proposal document. (See "*Updates to Prior Proposals*" on page 9.)

Collaborative Agreements

Research projects are governed by formal NIH collaborative agreements. When a 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 a collaborative agreement has been executed, a project team will be formed. In consultation with the collaborating investigator, the project team will develop and define the following elements:
 - Project 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 made by the project team based on the Project Plan. If necessary, the project team may consult with the project's Joint Research Committee, which will make recommendations to TRND leadership. TRND leadership makes the final decision regarding changes to project scope or termination.
- **Project Termination:** Upon failure to meet timelines, milestones, and/or deliverables or with the recommendation of the project's Joint Research Committee when needed, TRND will terminate a project. Whenever possible, collaborating investigators will be provided guidance on how to move the project forward.

Updates to Prior Proposals

TRND may accept updates 12 months after a proposal is initially deferred or declined.

Updates may require:

- A summary letter, not to exceed 2 pages.
 - Explain how the proposal has been modified and strengthened.
 - If the prior proposal received a detailed evaluation by TRND, respond to any comments and recommendations, and address any disagreements.

- An amended proposal.
 - The amended proposal should follow the current “Proposal Instructions” governing required documents and page limits.