Form Approved
OMB NO. 0925-0658
Exp. Date 06/30/2015

Name & Degrees:
Institution:
Address:
E-mail:
Proposal Title:

Proposal should outline the scientific nature and rationale of the project. **Proposal is limited to a MAXIMUM of 5 pages** (Arial 11pt, single-spaced, 1" margins). The Data Collection Tables Appendix (provided) does not count against the 5-page maximum. **Any additional figures / tables must be placed in-line with your text, and WILL COUNT AGAINST the 5-page maximum.** Refer to the TRND Application Instructions for detailed descriptions of information requested in each section of this application. Required supporting materials are to be uploaded as described in the instructions.

Background

Replace text with the information requested in the Instructions. 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.

Therapeutic Hypothesis

Replace text with the information requested. Include a clear statement of the therapeutic hypothesis and the clinical indication to be targeted for FDA approval. Summarize the evidence that validates the selected therapeutic-target combination. Review the level of consensus in the field supporting the proposed mechanism of disease and hypothesis that modulation of the target will substantially improve morbidity and/or mortality in the disease. Assess feasibility to reach first in human studies.

Current State of Project

Replace text with the information requested. Identify the project as either (1) Lead Optimization; (2) New Molecular / Biologic Entity (NME / NBE); (3) Repurposing; or (4) Platform Technology, as appropriate.

As outlined in the Instructions, provide all relevant available data, including – but not limited to – the MINIMAL KEY DATA suggested for the four general project categories. Specific information is requested in the Appendix data collection tables and in the uploaded Supporting Documents.

Proposed Development Strategy

Replace text with requested information. 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.

Justification

Replace text with requested information. 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. 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.

Timeline and Milestones

Replace text with requested information. 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.

REMINDER: There is a 5-page maximum to the written portion of the proposal, inclusive of any ancillary figures / tables you have included in-line with the above text. The Data Collection Tables in the following Appendix do not count against the 5-page maximum, and are meant to facilitate orderly data collection across a range of important values. Judicious use of the following tables and required uploaded Reference PDFs can allow provision of key data (e.g., supplemental figures) that otherwise may not fit into the page limits above.

Appendix: Data Collection Tables

Provide data on the proposed lead compound (specify Compound ID) using the following tables. Provide ALL data requested, as available. If there are no data for a particular parameter, or the data do not apply to your molecule, leave the value field blank, or enter "N/A". **DO NOT DELETE EMPTY CELLS.** For compound series, clearly identify structures, compound IDs, and corresponding data. Additional data may be provided in supplemental tables, as appropriate.

I. Compound Properties Profile:

Provide structure or composition of lead compound in box below.

Lead Compound

Structure or Composition

Calculated Properties	Value	Goal
Compound ID		
MW		< 500
Log $D_{7.4}$, cLog P		1-3, 1-4.5
TPSA		< 140 (oral), < 90 (CNS)
Ligand Efficiency (LE, LELP)		> 0.29, <10
Rotatable Bonds		≤ 10
N + O (HBA)		≤ 10
NH + OH (HBD)		≤ 5

In Vitro Properties	Units	Value & Class	Goal
Solubility (pH, media)	(μg/mL)		> 60
Stability – Microsomes (species)	$t_{1/2}$ (min)		> 30
	CL_{int} (mL/min/mg)		< 10
Stability – Hepatocytes (species)	$t_{1/2}$ (min)		> 120
	CL_{int}, μL/min/10^6 cells		< 5
Stability – Plasma (species)	% Remaining at 3 hr		> 80%
Stability – Solution (media)	% Remaining at 24 hr		> 80%
CYP450 Inhibition (isozymes)	% Inhibition at 3 μM		< 15%
	IC_{50} (μM)		> 10
	$C_{max\ at\ MED}$ / K_i		< 0.1
Plasma Protein & Tissue Binding (species)	$F_{u,\ plasma}$ (%)		
	$F_{u,\ tissue}$ (%)		
Permeability – PAMPA	P_e (10^{-6} cm/s)		> 1
Permeability – PAMPA-BBB	P_e (10^{-6} cm/s)		> 4
Permeability – Caco-2	P_{app} (a-b, 10^{-6} cm/s)		> 10
	Efflux Ratio		< 3
Permeability – MDR1-MDCKII	P_{app} (a-b, 10^{-6} cm/s)		> 20
	Pgp Efflux Ratio		< 2
hERG (method)	IC_{50} (μM)		> 10
	IC_{50} / Free C_{max}		> 30
Free C_{max} – Plasma	Total C_{max} (μM) * $F_{u,\ plasma}$		
Free C_{max} – Tissue	Total C_{max} (μM) * $F_{u,\ plasma}$		
Screening Ames	Positive / Negative		Negative

II. Compound Efficacy Profile:

In Vitro Biology	Units	Value & Class	Goal
Activity			
(Assay 1) – IC_{50}	nM		< 1000
(Assay 1) – K_i	nM		< 1000
(Assay 2) – IC_{50}	nM		< 1000
(Assay 2) – K_i	nM		< 1000
Selectivity			
(Assay 1) – IC_{50} / Fold selectivity	nM		> 100
(Assay 2) – IC_{50} / Fold selectivity	nM		> 100

In Vivo Biology	Units	Value & Class
(Species, dose, route) – MED	nM	
(Species, dose, route) – MED	nM	
(Species, dose, route) – MED	nM	

PK Properties	Units	Dose (mpk), Route, Species	Dose (mpk), Route, Species	Goal
$t_{1/2}$	hr			> 3
$AUC_{0\text{-}\infty,\ total'\ unbound}$	hr*ng/mL			> 500 (PO)
CL	mL/min/kg			< 25% HBF
$C_{max,\ total'\ unbound}$	ng/mL (nM)			
T_{max}	hr			
V_d	L/kg			
F	%			> 20%

III. Chemistry, Manufacturing, and Controls:

Provide complete synthetic scheme, including details of isolation and purification, and yield for each step.

Synthetic Scheme

Representative Largest-Scale Batches

Batch	Quantity	Solid State, Salt Form, Polymorphs	Purity (%)	Major Impurities (%)

Late-Stage Formulation

Study	Formulation	Solubility	Stability	Recommended Storage Condition
Rodent Toxicity				
Non-Rodent Toxicity				
Phase I Human Trial				