Form Approved
OMB NO. 0925-XXXX
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Name:
Institution:
Address:
E-mail:
Title:

This 5-page document should outline the scientific nature and rationale of the proposed project. For additional information, please refer to the TRND Solicitation Instructions. Additional material can be uploaded as appendices described in the instructions.

Background

Replace text with the requested information. 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 requested information. 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.

Current State of Project

1. *Replace text with the requested information 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.

Proposed Development Strategy

Replace text with requested information. 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.

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. 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.

Timeline and Milestones

Replace text with requested information. Outline a potential timeline for conducting the collaborative research with NCTT. 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 NCTT investigators and applicant investigators will establish a new timeline, milestones, and go/no go decisions points based on the evaluation recommendations.)

Appendix 1:

Provide data on the proposed lead compound using the following tables:

I. Compound Properties Profile:

Lead Compound Structure or Composition

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

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

II. Compound Efficacy Profile:

In Vitro Biology	Units	Value & Class	Goal
Compound ID	N/A		N/A
Activity			
(Assay 1) - IC_{50}	nM	*Provide data*	< 1000
(Assay 1) - K_i	nM	*Provide data*	< 1000
(Assay 2) - IC_{50}	nM	*Provide data*	< 1000
(Assay 2) – K_i	nM	*Provide data*	< 1000
Selectivity			
(Assay 1) - IC_{50} / Fold selectivity	nM	*Provide data*	> 100

In Vivo Biology	Units	Value & Class	Goal
Compound ID	N/A		
(Species, dose, route) – MED	nM	*Provide data*	
(Species, dose, route) - MED	nM	*Provide data*	
(Species, dose, route) - MED	nM	*Provide data*	

Other Biology	Units	Value & Class	Goal

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

Appendix2:

References for *In Vitro* ADME Assays and *In Vivo* Pharmacokinetics

General References

1. "*Drug-Like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*", E. H. Kerns, L. Di (2008), Elsevier.
2. *"Pharmacokinetics and Metabolism in Drug Design"*, Smith, D.A., et al., (2001), Wiley-VCH
3. "Experimental and computational approaches to estimate solubility and permeability in drug disc. and development settings." Lipiniski, C.A., *et al.*, (1997), *Adv. Drug Delivery Rev. 23*, 3-25.
4. "Application of pharmaceutical profiling assays for optimization of drug-like properties." Di, Li; et al., Current Opinion in Drug Discovery & Development (2005), 8(4), 495-504.
5. "High Throughput Physicochemical Profiling for Drug Discovery", E.H. Kerns; *J. Pharm. Sci.* (2001) 90, 1838-1858.

Solubility

1. "Solution Stability – Plasma, Gastrointestinal, Bioassay", Li Di, *et al.*, *Current Drug Metabolism* (2008), 9(9), 860-868.
2. "In Vitro Solubility Assays in Drug Discovery", Edward H. Kerns, *et al., Current Drug Metabolism* (2008), 9(9), 879-885.

Stability – Microsomes, Hepatocytes, Plasma, Solution

1. "High Throughput Microsomal Stability Assay for Insoluble Compounds"; L. Di, *et al.*, *International Journal of Pharmaceutics* (2006) 317(1), 54-60.
2. "Metabolic Stability: Main Enzymes Involved and Best Tools to Assess It", R. Laine, *Current Drug Metabolism* (2008), 9(9), 9210-927.
3. "Development and Application of High Throughput Plasma Stability Assay for Drug Discovery", L. Di, *et al.*, *International Journal of Pharmaceutics* (2005) 297(1-2) 110-119.
4. "Development and Application of an Automated Solution Stability Assay for Drug Discovery", L. Di, *et al.*, *Journal of Biomolecular Screening* (2006) 11(1), 40-47.

CYP450 Inhibition

1. "Comparison of Cytochrome P450 Inhibition Assays for Drug Discovery Using Human Liver Microsomes with LC-MS, rhCYP450 Isozymes with Fluorescence, and Double Cocktail with LC-MS"; L. Di, *et al.*, *International Journal of Pharmaceutics* (2007), 335(1-2), 1-11.
2. "In Vitro Cytochrome P450 Inhibition and Induction", R.L. Walsky, *et al*., *Current Drug Metabolism* (2008), 9(9), 928-939.

Plasma Protein, Tissue Binding, and Free Cmax – Plasma, Tissue

1. "Plasma / Serum Protein Binding Determinations", M.J. Banker, *et al.*, *Current Drug Metabolism* (2008), 9(9), 854-859.
2. "The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery", Dennis A. Smith, Li Di, Edward H. Kerns, *Nature Reviews Drug Discovery* (2010), 9(12), 929-39.

Permeability – PAMPA

1. "Physicochemical high throughput screening: Parallel artificial membrane permeability assay in the desc. of passive absorp. processes", Kansy, M., *et al.,* (1998), *J. Med. Chem. 41*, 1007-1010.
2. "High-throughput permeability pH profile and high-throughput alkane/water log P with artificial membranes." Wohnsland, F.; Faller, B. (2001), *J. Med. Chem*. *44*, 923-930.

Permeability – PAMPA-BBB

1. "High Throughput Artificial Membrane Permeability Assay for Blood-Brain Barrier", L. Di, *et al.*, *Eur. J. Med. Chem.* (2003) 38, 223-232.
2. "Comparison of blood-brain barrier permeability assays: in situ brain perfusion, MDR1-MDCKII and PAMPA-BBB", Li Di, *et al.*, *Journal of Pharmaceutical Sciences* (2009) 98(6):1980-1991.

Permeability – Caco-2

1. "Caco-2 monolayers in experimental and theoretical predictions of drug transport", Artursson, P., *et al.,* (2001) *Adv. Drug Deliv. Rev.*, 46, 27-43.
2. "Assessing the absorption of new pharmaceuticals", Hidalgo, I.J., (2001), *Curr. Topics Med. Chem.,* 1, 385-401.

Permeability – MDR1-MDCKII

1. "Rational use of in in vitro P-glycoprotein assays in drug discovery", Polli JW, et al. (2001), J Pharmacol. Exper. Therapeutics 299, 620-628.
2. "Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs", Schinkel, A.H., *et al.,* (1994), Cell 77, 491-502.

hERG

1. "Relationship between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development", Redfern, W.S. (2003), *Cardiovascular Res.* 58, 32-45.
2. "Patch clamping by the numbers", Wood, C., *et al*., (2004), Drug Discovery Today, 9, 434-441.

Ames Test

1. "Methods for detecting carcinogens and mutagens with the salmonella/mammalian-microscope mutagenicity test", Ames, B.N., *et al*., (1975), Mutation Research 31, 347-363.
2. "Improvement of the Ames test using human liver S9 preparation", In: Yan, Z. and Caldwell, G.W. (eds.), *Optimization in Drug Discovery: In vitro Methods",* Totowa, Humana Press, pp. 325-336.

In vivo Pharmacokinetics

1. "Rapid determination of pharmacokinetic properties of new chemical entities: *in vivo* approaches", Cox, K.A., *et al.*, (2002), Combinatorial Chem. and H.T.S., 5, 29-37.
2. The simultaneous determ. of mixtures of drug candidates by liquid chrom./APCI mass spectrum. as an in vivo drug screening procedure", (1997), Rapid Comm. Mass Spectrom., 11, 17-23.