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

Name:
Institution:
Address:
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Title:

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

Background

Replace text with the requested information…

Therapeutic Hypothesis

Replace text with the requested information…

Current State of Project

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Proposed Development Strategy

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Justification

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Timeline and Milestones

Replace text with requested information…

Appendix 1:

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

I. Compound Properties Profile:

5.1

5.2 Lead Compound

5.3 Structure or

Calculated Properties	Value	Goal
Compound ID	*Provide data*	**N/A**
MW	*Provide data*	**< 500**
Log D7.4, 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%**

Appendix 2: 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.