

Name:
Institution:
Address:
E-mail:
Title:

This application should not exceed five pages (Arial 11pt, single space, 1" margins). Graphs, pictures and tables should be included in the text. The text should explain the rationale behind the development of the proposed therapeutic agent and summarize the current stage of its development. Manuscripts and supporting publications may be uploaded in the appendix as described in the Application Instructions.

Background

Replace text with the requested information. Provide a brief summary of the disease to be treated. Discuss the current standard of care for the disease and why new therapies are needed. Explain the selection of, and level of agreement in the field, regarding the therapeutic target and its potential clinical relevance. Describe the proposed agent, its impact on the target and the rationale for selecting the agent over similar entities. Briefly describe the competitive landscape and the effectiveness of comparator compounds, if any.

Available Data

Replace text with requested information. As appropriate for the stage of the program, please describe data obtained in the following areas:

Chemistry

- Medicinal chemistry optimization performed to date, including identified issues with the proposed molecule*
- Acquisition of bulk substance (GMP and non-GMP) and availability of protocols for scale-up production and analytical methods*
- Development of suitable formulations*
- Production and stability assurance of dosage forms*

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.

PK/PD/Toxicology

- *Evaluation of PK and pharmacodynamics (PD), including oral bioavailability and half-life in serum and other relevant fluids/tissues*
- *The applicability of PD measures in animals as biomarkers in human studies*
- *Evaluation of ADME properties in vitro and in vivo, including routes and products of metabolism, microsomal stability, and related studies*
- *In vivo efficacy evaluation, including dosing and schedule*
- *Toxicology studies in rodents and non-rodents, including IND-directed toxicology, with correlative pharmacology and histopathology*

Regulatory Affairs and Clinical Trial Information

- *Potential clinical trial designs, including projected dose, dose regimen, length of treatment and duration of therapeutic response in humans, if known*
- *Determination of clinical endpoints and whether these are accepted by regulatory agencies*
- *Results of consultations with FDA or other regulatory agencies, if any, on the project*
- *For repurposing projects in which clinical data are available:*
 - *Provide a summary of clinical efficacy, safety and PK/PD data.*
 - *Describe the clinical trial strategy, such as 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. If available, the Investigator's Brochure should be uploaded in the appendix.*

Development plans

Replace text with requested information. Provide a clear statement of the tasks that are proposed for completion by BrIDGs contractors. If the investigator or a collaborator intends to conduct tasks that may impact research supported by the program (e.g., the investigator will provide the drug material to the NIH for use in BrIDGs-supported studies), then the investigator should indicate how those tasks will be conducted and funded.

State all current and applied-for sources of support for the project. This includes a summary of the status of past, planned or ongoing negotiations with companies related to licensure or future development of the product. Include information on any peer-reviewed grants or grant applications pertaining to the project. The applicant should indicate how BrIDGs support would complement, not

duplicate, other sources of support. For projects close to clinical application, the investigator should document the strategy for obtaining funding for early phase clinical testing. Include potential collaborators and institutional arrangements for oversight and institutional review board review, if applicable.

Justification

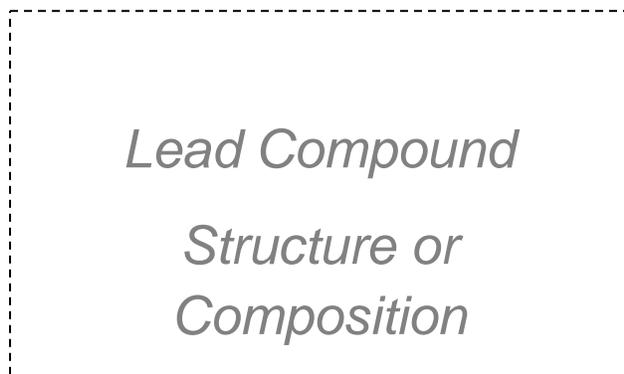
Indicate why private funding for the project is not currently available. Describe the likelihood of the adoption of the therapeutic agent once an IND is approved, and why organizations (biotechnology companies, venture capital firms, pharmaceutical companies) are presently unwilling to fund or develop this project as it currently stands.

Timeline and Milestones

Replace text with requested information. Outline a potential timeline for the conduct of studies needed to file the IND application. The timeline should highlight potential milestones and go/no-go decision points. A timeline chart is acceptable. Following acceptance of a project, NIH staff may modify the timeline, milestones and go/no-go decisions points based on review recommendations and contract availability.

Appendix 1:

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

I. Compound Properties Profile:

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

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

II. Compound Efficacy Profile:

| <i>In Vitro</i> Biology | Units | Value & Class | Goal |
|---|-------|---------------------|--------|
| Compound ID | N/A | | N/A |
| Activity | | | |
| (Assay 1) - IC ₅₀ | nM | <i>Provide data</i> | < 1000 |
| (Assay 1) - K _i | nM | <i>Provide data</i> | < 1000 |
| (Assay 2) - IC ₅₀ | nM | <i>Provide data</i> | < 1000 |
| (Assay 2) - K _i | nM | <i>Provide data</i> | < 1000 |
| Selectivity | | | |
| (Assay 1) - IC ₅₀ / Fold selectivity | nM | <i>Provide data</i> | > 100 |
| | | | |

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

| 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 | <i>Provide data</i> | <i>Provide data</i> | > 3 |
| $AUC_{0-\infty, \text{total}^{\dagger}}$ unbound | hr*ng/mL | <i>Provide data</i> | <i>Provide data</i> | > 500 (PO) |
| CL | mL/min/kg | <i>Provide data</i> | <i>Provide data</i> | < 25% HBF |
| $C_{\text{max, total}^{\dagger}}$ unbound | ng/mL (nM) | <i>Provide data</i> | <i>Provide data</i> | |
| T_{max} | hr | <i>Provide data</i> | <i>Provide data</i> | |
| V_d | L/kg | <i>Provide data</i> | <i>Provide data</i> | |
| F | % | <i>Provide data</i> | <i>Provide data</i> | > 20% |