**Request for Applications**

**Presentation to the Drug Evaluation Committee**

**Announcement Date: Monday, March 9, 2020**

**Proposal Deadline: Friday, April 10, 2020**

**Introduction**

To accelerate the rate of translation of Purdue discoveries into clinical applications, the Purdue Institute for Drug Discovery (PIDD) is inviting applications for presentation from faculty who want to obtain input on their drug discovery project from our Drug Evaluation Committee (DEC). Presentations at all stages of drug discovery/development are welcomed, including target identification, target validation, hit identification, hit to lead maturation, lead optimization and preclinical development. The committee will evaluate your project and provide you feedback on both the clinical potential for your therapeutic/diagnostic agent and the critical path forward for moving your drug into the clinic. Additionally, for those selected to present, PIDD will provide funding to perform research activities recommended by the DEC to move your project forward. The DEC will be meeting to evaluate faculty projects during the morning of **Friday, May 22, 2020**. Presentations are expected to last ~15 minutes followed by ~15 minutes of discussion.

The newly formed DEC is comprised of a panel of external drug discovery/development experts from both industry and academia with a broad understanding and experience of the drug discovery and development process. The mission of this new DEC has been expanded to provide guidance to Purdue faculty at any stage of the drug discovery process along with serving as an external advisory board to the Institute for Drug Discovery. A list of participating members can be found at the end of this document.

**General Guidelines**:

1. **Qualification** – Presenter must currently be or become a member of the Institute for Drug Discovery.
2. **Proposal Length** – Proposal should be single-spaced and a maximum of3pages in length (Calibri or similar font at 11pt) with no less than 0.5 inch page margins. References are not part of the page limit. Please see application format section for more information.
3. **Timeline** – Read-ahead materials will be sent to DEC by May 8th, 2020. Presentations to the DEC will be made on Friday, May 22, 2020. Any funding provided after presentation should be expended by the end of FY21 (June 30th 2021).
4. **File format** – Only .doc, .docx, .ppt, .pptx or .pdf files will be accepted. Any figures should be embedded in the document and must fit within the maximum page limit.
5. **Deadline** – Applications must be received by Karson Putt ([puttk@purdue.edu](mailto:puttk@purdue.edu)) by 5:00 pm on Friday, April 10th, 2020. Applicants **do not** need to work with pre-award/SPS to submit an application for this internal RFA.

**Award**:

Selected projects will have the opportunity to present to and receive advice from the DEC on May 22nd, 2020. Based upon feedback from the DEC regarding the most optimal studies to perform to advance the project, PIDD will provide funds to perform these activities.

For example, if the DEC recommends that a PK study is necessary to advance the project, PIDD will provide support for that PK study to be ran at Purdue or by an external 3rd party.

Funds can only be used for S&E, core facility expenses, external 3rd party (i.e. CRO) expenses or grad/post-doctoral student salaries depending on DEC recommendations.

**Application Format:**

The following information must be included within the maximum 3-page limit

1. Project Title
2. Medical need/Disease (e.g. therapy for colon cancer, diagnostic test for Alzheimer’s disease)
3. Stage of research (e.g. target identification, lead optimization, etc.; please see Stages of Drug Discovery section below for more information)
4. Background and overview of current project
5. Current experimental activities and supporting data
6. Goals/Future directions of project

Additional information that can be included (does not apply to page limit requirements)

1. References

**Review Criteria**:

1. Potential for the proposed project raising the prominence of Purdue and the Institute for Drug Discovery
2. Scientific merit
3. Potential for subsequent external follow-on funding (R01s, etc.)
4. Potential impact on patient care via feasibility of translating academic discoveries into the clinic

Publications resulting from Drug Discovery support should be acknowledged as follows:

“The authors gratefully acknowledge support from the Purdue University Institute for Drug Discovery”

**Stages of Drug Discovery**

**Target Identification**

During this first stage of drug discovery a disease relevant biological target(s) (e.g. receptor, protein, enzyme, DNA, RNA, ribosome) is identified. Common approaches involve the use of bioinformatics, gene associations or phenotypic screening. Key questions addressed during this stage of discovery include:

* Rationale for efficacy in the disease
* Safety of modulating the target
* Clinical need
* Druggability of the target

**Target Validation**

During this phase of discovery, a correlation of the target to the pathophysiology of a disease needs to be demonstrated. One can use, an in vitro tool, a whole animal model, or by modulation of a desired target in disease patients. While each approach is valid, the confidence in the observed outcome is significantly increased by a multi-validation approach. Some criteria for assessing the viability of a target include:

* Disease modifying and/or proven function in the pathophysiology of a disease.
* Target expression is not uniformly distributed throughout the body.
* If druggability is not obvious, a 3D structure for the target or close homolog should be available for
* druggability assessment.
* Target has favorable biochemical and/or cellular assay for binding and function to enable high-throughput screening
* A mechanistic biomarker exists to monitor efficacy
* Target has a favorable IP situation

**Hit Identification**

A Hit is a compound which has the desired activity in a compound screen and whose activity is confirmed upon retesting. During the hit identification stage, attention should be placed on the robustness of the compound screening approach (HTS, focused screen, fragment screen, structural-aided design, virtual screen, physiological screen, NMR screen). The questions to be addressed during the hit identification stage include:

* Are the screening methods robust for covering the chemical space
* Is there sufficient chemical diversity in the hits obtained to develop a robust SAR
* Are the hits in a chemical space that is covered by existing IP.

**Lead identification**

The aim of this stage of the work is to refine each hit series in order to produce more potent and selective compounds. The questions to be considered when identifying a lead include:

* Do the leads being pursued allow for sufficient modification to optimize for selectivity and potency
* Are there clear functional liabilities in the lead structures that will present a roadblock to future PK optimization work

**Lead Optimization & Preclinical Evaluation**

The object of this final drug discovery phase is to maintain favorable potency and selectivity properties while now optimizing the PK properties. (For example, to modify the structure to minimize hERG liability and to improve the absorption of the compound). Common methods for evaluating a lead at this stage include; aqueous solubility, Log D7, Microsomal stability Clint, CYP450 inhibition, Caco-2 permeability, MDR1-MDCK permeability, Hep G2 hepatotoxicity and cytotoxicity in a suitable cell line. The 1 or 2 optimized leads are the evaluated for their suitability as a clinical candidate based on the following criteria:

*In vitro*

* Appropriate in vitro target and cell based activity.
  + IC50 < 100 nM
  + EC50/LD50
* Appropriate in vitro selectivity that bears positively on hypothesis, safety, and differentiation criteria.

*In vivo*

* Potent, profound in vivo effects that are proportional to measurable target engagement and are amenable to PK/PD modeling of desired responses in man
  + F > 30%

*ADME*

* Acceptable human dose/regiment that can fully support the testing of the hypothesis in man, and the properties of the molecule (or enabled formulation if necessary) support the absorption of the proposed dose. Potential for drug-drug interactions has been minimized.

*Tox*

* Acceptable exposure multiples appropriate for the target disease state that supports safe testing of the hypothesis in man. Best case is that the pre-clinical findings portend monitorable and reversible clinical signs.

**PIDD Drug Evaluation Committee**

*Members Attending May 22nd meeting*:

**Dennis Liotta**

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