UCI Center for Neurotherapeutics

Request for Proposals: Early phase Drug Development support program

The UCI Institute for Neurotherapeutics (UCI CNT) is pleased to announce its second call for applications focused on the discovery and development of small molecules intended to therapeutically modulate targets or pathways implicated in neurological diseases (i.e. any disorder affecting the brain, spinal cord, neuromuscular system, or retina). Applications will be selected for entry into the UCI CNT's Drug Discovery unit, which consists of three distinct, complementary service cores:

a) High-throughput assay development

- Collaborative development of reliable and reproducible assays that can be deployed for identification of novel chemical matter in high-throughput screens
  [Note that we will not perform high-throughput screens as part of this program. Rather, we will be positioning the PI to apply for support for performance of the HTS at an affiliated UC institution, another academic institute, or the NIH (NCATS)]

b) Computational chemistry

- Expertise to set the stage for *in silico* screening work via structural modeling
- *In silico* screening to identify novel chemical matter for entry into a therapy development pipeline, and support for obtaining and/or synthesizing "hits"

c) Medicinal "hit-to-lead"

- Ability to pursue SAR to derive compound series from "hits"
- Prioritization of leads based upon issues of predicted toxicity and BBB penetration

To be eligible, the applicant must have compelling preliminary data to support target or pathway selection, or have already identified small molecules which they wish to advance from "hits" to "leads". The PI will indicate the specific core of the three divisions of the UCI CNT Drug Discovery unit for which they are seeking this translational research support.

Background:

When a PI identifies an attractive pathway or target central to the initiation or progression of a neurological disease, the next step in therapy development involves identification of compounds that modulate the target or pathway. The process of moving from target / pathway to small molecule drug compounds that can ultimately be used in human patients is daunting to most PIs working in an academic environment. One standard approach is to perform a **high-throughput screen** (HTS) to identify potentially promising compounds. HTS assays need to be extremely rigorous and highly reproducible, with assay quality dictated by parameters such as the Z-factor score, in order to successfully identify small molecules for entry into a drug development campaign. In addition to HTS assay expertise, small molecule identification can alternatively be pursued by **computational chemistry** strategies involving *in silico* docking screens to identify compounds that may act on a given target, based upon structural information for the presumed "druggable" domain. Upon completion of HTS work or *in silico* screening, researchers are often left with a list of potential molecules for further study. It is the exceptional compound coming out of a HTS experiment that will advance to becoming a meaningful therapeutic, as there are numerous considerations that determine whether or not a compound has potential for use in humans. Hence, further development requires the expertise of medicinal chemists and structural chemists who consider a range of issues and through structure-activity-relationship (SAR) analysis, and can design? sets of compounds based upon promising leads. Other

considerations, including toxicity, predicted biodistribution, metabolism, and blood-brain barrier penetrability, are also taken into account to prioritize the most promising "hits".

Application Process:
To be considered for Drug Discovery unit support, a PI must hold a full-time faculty position at UCI and submit a **three-page proposal** (Arial 11 font with ½" margins). The required elements of the proposal are as follows:

1. **Title** of the Project (not to exceed 200 characters)
2. **Background/Significance** – Describe the target / pathway upon which the project is focused, and provide the context of existing knowledge for the target / pathway. State the intended disease indication, explaining the current therapeutic landscape and rationale for developing a new treatment modality.
3. **Preliminary Results** – Present the experimental findings that implicate the target / pathway in the initiation and/or progression of the disease of interest. Delineate results that support why successful modulation of the target / pathway would be expected to achieve the desired therapeutic benefit. Indicate efforts thus far to develop an assay(s) to monitor the function of the target / pathway. **Figures with legends** are encouraged and should be included in the three-page main proposal.
4. **Research Strategy** – State which of the three Drug Discovery unit service cores that you would like to utilize for your project. Explain the rationale for selecting the indicated service core.
5. **Literature cited** – This section will not be counted as part of the 3-page proposal
6. **Time expected to external funding** – Provide an addendum of up to one page describing anticipated timing and potential expected sources for external funding.
7. **Biosketch** – NIH style, 5-page limit is required for all PIs and Co-PIs

Selection Process:
The UCI CNT will rank proposals based upon the strength of the scientific premise for target / pathway selection, the level of unmet need for the disease indication, the likelihood of success for the proposed translational research campaign, and the potential for securing follow-on funding upon completion of the project. Before making an award, UCI CNT leadership will contact highly competitive applicants to arrange a brief interview to clarify the rationale for drug development unit support and to discuss the potential plan for follow-on funding. Prospective applicants are encouraged to confer with UCI CNT staff and leadership if they are uncertain as to which Drug Discovery unit service core would be most appropriate for their research program.

PLEASE NOTE: Funds are not being provided to applicants (hence, there is no Budget section requirement.) Rather, all research experimentation performed at the UCI CNT will be fully supported for the duration of the project period. The goal of this Research Proposal program is to support research projects and further integrate talented CNT staff with PI projects. Projects selected for funding will enter into a partnership with the UCI Center for Neurotherapeutics, wherein Center personnel will work with the project team to understand the project's specific needs, design cellular and molecular assays for screening and/or perform in silico computational screening, and pursue medicinal chemistry, in order to expedite the generation of key results that will position the PI, working closely with CNT leadership, to apply for external funding. Consequently, we seek promising partnerships which can leverage Center resources to drug development. Successful applicants will thus be expected to work closely with UCI CNT leadership and staff throughout the performance of the project. Failure to do so may result in termination of service core activities.

PLEASE NOTE: The PI and UCI will retain full control of the intellectual property (IP) of any novel chemical matter and potential therapeutic agents that are identified. We will also facilitate consultation with the Beall Applied Innovation Center for advice on navigating the IP landscape under these circumstances.

Proposal due date: February 2, 2024 @ 5 PM

Submit proposal to: rspitale@uci.edu