Optimization of Small Molecule Probes for the Nervous System

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The official link for this solicitation is: http://grants.nih.gov/grants/guide/pa-files/PAR-09-260.html

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Description:

The purpose of this funding opportunity is to facilitate the development of small molecule probes that will add a pharmacological dimension to basic neuroscience work, and enable proof-of-principle studies linking nervous system therapeutic targets, mechanisms or phenotypes to disease onset or progression.

NIH has made a significant commitment to probe development via Institute-specific and Blueprint for Neuroscience (http://neuroscienceblueprint.nih.gov/) support, and via Roadmap Programs associated with the Molecular Libraries Initiative (http://nihroadmap.nih.gov/molecularlibraries/). For example, Molecular Libraries Programs fund the development of novel in vitro screening assays (see: http://grants.nih.gov/grants/guide/pa-files/PAR-08-024.html). These assays can then be used to identify small molecule interactors (hits) in automated, high-throughput screening (HTS) of large, small molecule collections such as the Molecular Libraries Small Molecule Repository (http://mlsmr.glpg.com). These screening projects are performed in centers belonging to the Molecular Libraries Probe Production Centers Network (http://www.mli.nih.gov), as well as in a variety of screening centers established in recent years to address the need to develop small molecule probes as aids to hypothesis-driven research investigation, as imaging agents, and as therapeutic leads. This effort by the scientific community to automate and screen novel assays against small molecule diversity collections has created a large portfolio of neuroscience-related small molecule probe development projects. This FOA will provide a bridging step between these medium and high-throughput automated screening efforts to find small molecule interactors, and the

insertion of optimized probes derived from these compounds into pharmacological studies aimed at gaining a better understanding of nervous system function, and dysfunction leading to disease states.

Successful compound screening efforts to identify small molecules typically progress to early chemistry optimization work (the generation of analogues) in order to identify features of these template molecules that contribute to the useful attributes needed in a small molecule probe, such as affinity and selectivity for a target. At the completion of this step of early structure-activity-relationship (SAR) studies SBCs will have employed distinct small molecule hits that interact with their biological target to generate and test some small molecule analogues, with the aim of identifying structural features of the hit that are important to its activity. As a result, plans can be proposed for further chemical synthesis to create advanced analogues in which the biological attributes needed in a useful probe are improved. In vitro screening assays available in the SBC principal investigators laboratory that have been miniaturized and optimized could be used to support a medium-throughput screening effort aimed at rapidly characterizing the properties of these compounds.

Many probe development projects that have succeeded in identifying chemicals possessing the basic attributes of the small molecule probe(s) they are seeking will require a continued biological screening and chemistry effort over 1-2 years to optimize these molecules so that useful probes are the end result. This FOA will provide the resources that allow a SBC to successfully identify the small molecule probe (and/or lead compound series) that is the goal of their assay development, screening, and SAR study effort. The Program specifically funds completion of the small molecule probe development when additional time and resources are needed, aims to facilitate the formation of biology and medicinal chemistry partnerships to achieve this, and encourages the use of efficient cheminformatic strategies for compound acquisition and semi-custom synthesis. At the end of the project the investigator should be able to insert these pharmacological tools into their ongoing research Program as investigative tools and pharmacological imaging agents. An emphasis will be placed on the funding of small molecule probe development projects that are focused on novel nervous system targets and mechanisms for which small molecule probes and therapeutic leads are not currently available, or, projects where the currently available compounds are not optimal for the proposed use.

Applications should include both a biological and chemical component. The biological component should include a plan of in vitro and, when appropriate, limited in vivo assays, each capable of measuring the activity of a test compound towards an attribute that the hit compound proposed as a starting point for modification possesses, and that needs to be further enhanced or eliminated by redesign of the hit. Examples of possible biological test activities are listed below. Applications are expected to provide a description of the final small molecule probe that is the target of design, including a detailed description of needed attributes such as affinity, activity and/or selectivity, and a description of how this will be measured (for example: the use of measures of affinity or activity such as Ki or IC50 and/or fold-selectivity comparing two target affinity or activity values). The chemistry component should include a description of the hit scaffold molecules that will be the starting point of design, as well as information about known structure-activity relationships for these hits and the needed values for key compound attributes. A plan for the design of analogues of these small molecule hits should be provided that includes a description of the strategy and approach for optimizing molecules, and decision-making criteria for continuing, or stopping, work on a compound series. An appropriate biological component of a project that could be candidate for the Program might address (but is not limited to) the following topic areas in neurobiology, and would be expected to fit within the interests of the participating NIH Institutes:

- Molecular targets expressed in the nervous system and measured via biochemical or cell-based assays of activity, or, via cell-based assays of cellular signaling or biosynthetic pathway activation.
- Cellular or molecular phenotypes relevant to nervous system function.
- Gene expression in the nervous system, including effects on transcription, translation or RNA splicing.
- Protein:protein interactions important to neural or glial cell signaling.

- Nervous system function modeled in organisms such as yeast, drosophila, C. elegans and zebrafish.
- Potential therapeutic targets associated with the pathophysiology and/or treatment of neurological disorders, aging disorders, alcohol and substance abuse disorders, mental disorders (to include: disorders of mood, anxiety, eating or obsessive-compulsive behavior; schizophrenia; fragile x; autism) and eye disorders involving nervous system impairment.

The in vitro testing methodologies proposed would be expected to have already been developed, characterized and implemented in a medium or high-throughput screening (HTS) Program in which hit compounds to the proposed target were identified and characterized. Investigators can refer to the Assay Development for HTS Program announcement (http://grants.nih.gov/grants/guide/pa-files/PAR-08-024.html) for a description of performance criteria useful in developing assays that would be suitable for use in a small molecule probe optimization plan. The investigator should be capable of running these assays at a throughput that would support the proposed chemical analogue testing program. An appropriate tier of screening assays should be proposed and prioritized (both in terms of sequence and frequency) such as to provide test information (eg; IC50, Ki) about chemical analogues for the different attributes to be encompassed in the probe design. It is generally expected that project applications will have the ability to test 20-40 compounds every two months. A further, small molecule probe confirmation assay can be proposed as a final validation step to demonstrate its utility in the system in which it will be used.

The proposed medicinal chemistry design for the Program would be expected to address (but is not limited to) the following components:

- One or more distinct small molecules that have been identified via a medium or high-throughput screening effort as possessing the principal probe attribute, as measured by interaction in the primary biological screening assay and further confirmed via repeat dose-response testing (or, testing of the same activity but in an alternative format), testing of previously undissolved compound, and physical-chemical structural confirmation. Test values for additional attributes to be included in the probe improvement plan should also be provided in the hit profile.
- A design plan proposing small molecule chemical analogues of the hit structure that is based upon structure-activity-relationship (SAR) information, obtained from an initial effort to acquire chemical analogues that relate discrete changes in structure of the molecule to changes in its important biological properties. This plan can include proposals to further explore structure-activity relationships of the hit molecule and its related structures, as well as the SAR of related chemical scaffolds which resemble, yet are different from the original hit structure. However, the aim of the planning should be to improve the requisite biological attributes of the starting hit molecule to meet the design objectives for developing a useful molecular probe. It is expected that this will require the iterative design and testing of chemical analogues. A model for such a design plan could be based on biased array design and synthesis, and require the design, acquisition and testing of ~20-40 chemical analogues every 2 months.
- A small molecule probe design capability: It is expected that expert medicinal chemistry will be included in the proposal for the design of small molecule analogues in support of SAR studies and compound optimization, but not to a significant extent for the support of synthesis, which is expected to be guided substantially by external procurement as described in the text that follows. The NIH Institutes participating in this Program acknowledge the importance of medicinal chemistry expertise in design and optimization as a critical component of the research proposal, and will therefore support funding allowance within the proposal for attaining such expertise. Some potential applicants may be in need of, or seeking, medicinal chemistry expertise. For those applicants needing assistance in identifying experts to work with, upon request, the Program Director will provide a listing, of medicinal chemists that have expressed interest in providing this design support service under this program as an active participant in both the application planning and proposed studies. The applicant would be responsible for contacting consultants from the list to develop a detailed plan for expert involvement in chemical design. Applicants that have already identified and have access to appropriate medicinal chemical expertise to guide

probe development are not required or otherwise obligated to obtain the list or to consult with anyone on the list to develop their proposal.

- A small molecule acquisition strategy: The use of cheminformatic strategies to search for and acquire small molecule analogues identified in the design effort is highly encouraged as a means of efficient and inexpensive compound acquisition from commercial suppliers. Investigators can include in their applications the use of cheminformatic systems currently in use. One such web-based capability are chemical procurement resources provided by the company ChemNavigator, some of which have been newly developed with support of the National Cancer Institute and now available to NIH-funded investigators without cost (http://www.chemnavigator.com/nih.asp). These resources include capabilities for searching currently available analogues, and for semi-custom synthesis and procurement of compounds (SCSORS: Semi-Custom Synthesis On-line Request System). It is expected that procurement and testing of newly designed analogues will be obtained from sources such as ChemNavigator and, for the most part, will not involve de novo synthesis.

Small molecule probe optimization supported through the R43 mechanism will be funded with up to $150,000 in direct costs each year for a period of up to two years. Projects funded with the R43 mechanism will emphasize the development of highly innovative small molecule probes and therapeutic leads that are not currently available. Some degree of risk is acceptable, particularly if innovation is high. It is expected that preliminary data will be provided in the application demonstrating that the small molecule probe candidate(s) can be developed within the project period. In addition, experimental plans aimed at the design, acquisition and testing of chemical analogues, leading to the development of small molecule probes, must be well defined in the project proposal. Applicants may propose limited follow-up studies to assess the utility of a potential probe or advanced probe candidates in the system of interest, including in vivo models.

Applicants proposing a broader program of discovery, development and preclinical testing of novel compounds (to include small molecule probes developed in the current program) are directed to the PAR-07-049 (R21) and PAR-07-048 (R01) announcements. These links are: http://grants1.nih.gov/grants/guide/pa-files/PAR-07-049.html and http://grants1.nih.gov/grants/guide/pa-files/PAR-07-048.html.