CONSORTIUM FOR NEUROPSYCHIATRIC PHENOMICS
Request for Proposals
Pilot Projects 2010

Overview:

The UCLA ***Consortium for Neuropsychiatric Phenomics (CNP)***, supported by the NIH Roadmap Initiative, is requesting proposals for "proof of concept" pilot projects. This unique mechanism aims to foster transdisciplinary research using novel approaches to bypass obstacles that usually impede scientific discovery relevant to the understanding and treatment of neuropsychiatric disorders. A two-stage submission process includes:
(1) "White Papers" (due March 30, 2010);
(2) Final Proposals (due May 15, 2010).
The final review of applications and funding decisions will be made on June 2, 2010 at the CNP Annual Retreat. A total of $60,000 is available to support two or three awards For further information contact Dr. Fred Sabb (UCLAphenomics@gmail.com) and/or see the website (www.phenomics.ucla.edu <http://www.phenomics.ucla.edu/>).

Details:

The UCLA *Consortium for Neuropsychiatric Phenomics (CNP)* is requesting proposals for innovative "proof of concept" projects. The CNP, founded in September 2007 to advance trans-disciplinary research on cognitive phenotypes for neuropsychiatric disorders, is one of nine new Interdisciplinary Research Consortia across the nation. The CNP comprises 8 awards supported by the National Institutes of Health (NIH) "Roadmap Initiative", specifically as part of the program "Research Teams of the Future", which aims to generate breakthroughs by fostering creative approaches to complex, interdisciplinary research questions that so far have been refractory to solution through conventional strategies. The CNP's long-term goal is to serve as a national resource for the identification, representation, and measurement of phenotypes that will advance the understanding and treatment of complex neuropsychiatric syndromes.

The CNP pilot project program has the following Aims:

- To attract new faculty participation and research avenues to the CNP;
- Create new transdisciplinary collaborative activities;
- Educate CNP faculty, trainees and staff in new research areas relevant to the CNP mission;
- To provide UCLA faculty with intellectual and financial resources, reagents, and core facilities that will facilitate their obtaining preliminary data for the development of new NIH funded programs;
- To increase the impact of the CNP on the scientific community.

The program will involve a two-stage submission process that starts with a brief "White Paper" (no more than one page describing Specific Aims) that summarizes the overall concept.

This white paper will undergo preliminary review by the CNP Executive Operations Team, and will be referred also to other CNP members, or other faculty outside the CNP if appropriate, for further development. This development process will take place in collaboration with CNP faculty and staff, and a subset of final proposals will be submitted for review and final recommendations by our Executive Operations Team (which will function similarly in this way as a combination of "Initial Review Group" and "Scientific Program" at NIH, assigning priority scores and making recommendations for funding. The final recommendations will be reviewed by our CNP Steering Committee at the Annual Retreat on June 2, 2010, where the Steering Committee members can meet with potential applicants (who will be invited to attend whether or not they are CNP members) to address questions, and also solicit the input of our External Advisory Board.

In its initial "exploratory" phase, the CNP has assembled an interdisciplinary team of experts at UCLA to tackle obstacles faced in treatment development for complex neuropsychiatric disorders. One problem is that the conventional diagnostic boundaries of neuropsychiatric disorders, which are based largely on behavioral symptoms, may not only fail to reflect underlying neurobiological processes, but also *impede* discovery of basic mechanisms by reifying invalid distinctions. To approach this problem the CNP is interested in identifying and refining phenotype definitions across conventional diagnostic boundaries. Another problem is the lack of adequate tools for translational investigation. While it is widely acknowledged that research must be conducted at multiple levels, from molecular to ecological, to understand complex neuropsychiatric disorders, there are many gaps in knowledge making it difficult to bridge clinical and basic approaches. The CNP thus aims to refine measurement of phenotypes specifically across species. CNP workgroups already have generated catalogs of phenotypes at many levels, including measures derived from behavioral, cognitive, neuroimaging, and neuropsychopharmacological investigations, to accelerate discovery of genes and drugs for neuropsychiatric illnesses. The CNP Hypothesis Web project is helping to organize these catalogs into a phenomics knowledgebase that can be used for queries about phenotypes and their relations to other sources of biological knowledge. The next step in the work of the CNP is to help support one or more "Proof of Concept" pilot projects, which will help serve as an example of how these ideas for advancing interdisciplinary investigation can be harnessed in specific scientific investigations. Further information about the CNP goals and structure is available at www.phenomics.ucla.edu <http://www.phenomics.ucla.edu/> .

Applicants should be aware of the following goals and priorities of the CNP Pilot Project Program:

- The CNP currently prioritizes two broad cognitive phenotypic domains as areas of interest for identifying neuropsychiatric phenotype/genotype relationships, specifically those associated with **memory** (including declarative and working memory) and **response inhibition** (including "impulse control"); but other phenotypic areas may be considered. To the extent that new phenotypic domains are examined, this departure from the current CNP themes would need to be well argued.

- Translational studies will be encouraged at T1 (translation from "bench to bedside," or in other words, from basic to clinical science) or T2 (translation from "bedside to trench", or in other words from clinical science to community and public health) levels of investigation, and those that provide added value or insights into ongoing CNP research projects will be of highest priority. Despite the implied direction of translation (e.g., "bench TO trench"), the CNP specifically acknowledges bidirectionality of translational research and welcomes research insights from public health that influence clinical research and clinical insights that inform basic science.

- The CNP can provide laboratory and human resources usually not readily available to individual investigators. These resources will be provided through core services available under the aegis of the CNP P30 Core components, including:

The *Human Translational Applications Core* includes the services of:

(1) The Human Recruitment & Phenotyping Unit, which possesses a range of expertise and resources for human recruitment, clinical diagnosis, clinical, personality, and neurocognitive assessment, along with computerized and web-based data acquisition;

(2) The Neuroimaging Unit, which maintains a wealth of expertise in multimodal neuroimaging, including expertise in design, implementation, and technical development for structural, functional and neurochemical imaging using MRI, PET, and/or electrophysiology); and

(3) The Statistics and Database Management Unit, which offers statistical expertise across many areas, including study design, power analysis, consultative expertise in modern psychometric methods including item response theory, multivariate methods for construct validation including covariance structure analysis, latent class analysis, and hierarchical linear modeling.

The *Translational Methods/Facilities Core* which includes the services of:

(1) The Genetic Studies Unit, which provides processing and storage of biological samples for genetic analysis, high throughput genotyping of human and vervet samples; and genetic study design and statistical genetic analyses;

(2) The BAC Transgenic Unit, which provides a complete service to generate BAC transgenic mice and provides mice stably expressing BAC constructs driving cell-specific expression of fluorescent proteins or Cre; and

(3) The Rodent Phenotyping Unit, which provides rodent behavioral assays to determine sensory, motivational and motor competencies, validation of existing assays designed to assess specific functional capacities, and development of new behavioral assays designed to assess functions that are hypothesized to be compromised as well as those hypothesized to be spared.

Applicants will also have access to CNP informatics resources to develop their proposals. For example, given that the CNP already has generated catalogs of phenotypes at many levels, including measures derived from behavioral, cognitive, neuroimaging, and neuropsychopharmacological investigations, applicants will be encouraged to survey these knowledge-bases to determine how their ideas may fit with existing concepts and hypotheses. These tools are available from our homepage.

Projects may focus on any topic but it is anticipate that most will involve the study of specific phenotypes, genotype-phenotype relationships, or develop methods that may be useful in advancing the study of neuropsychiatric phenomics more generally.

Following selection of the most meritorious POC projects for support, additional staff and resources will be committed to work under the direct supervision of the collaborative research team. In terms of scope and duration, the proposed work is expected to occupy one year, but applicants may request a second year of support on a competitive basis. The overall value of awards is anticipated to be in the range of $20,000 to $30,000 in direct support, but of much higher value considering the in-kind support from faculty, staff, and other resources committed to the project by the CNP.

While not a requirement it is anticipated that successful pilot projects may include some combination of the following example elements:

(1) Refinement and/or extension of promising phenotype measurements, assays, or tasks to improve their ability to be used in large-scale studies (such as genomic association studies or clinical trials);

(2) Functional or neurochemical imaging studies in humans or non-human species that will help refine neural system-level hypotheses for the phenotype of interest;

(3) Basic neuropsychopharmacology studies in non-human species that enable translation to the human condition or have clear links to putative treatment mechanisms;

(4) Studies of molecular expression in selected animal models or human tissues to elucidate the functional significance and molecular or cellular pathways that may be impacted by genetic variations; and/or;

(5) General methods development (e.g., development of bioinformatics approaches or modeling strategies for the representation and analysis of phenomics knowledge and relations to other sources of biological knowledge).

Application Process

"White Paper" (March 30, 2010)
We are using a two-stage application process. An initial "White Paper" (less than one page, representing the fundamental idea of the proposal) is due on **March 30, 2010**.
Applicants are further encouraged to contact the CNP Director Robert Bilder (rbilder@mednet.ucla.edu), or any of the other CNP investigators (complete listing is available on the website (www.phenomics.ucla.edu <http://www.phenomics.ucla.edu/>).

The Concept Sheets will be reviewed by the CNP Executive Committee, which will conduct a preliminary prioritization of proposals for further development. Applicants will then be encouraged to work with relevant CNP investigators or others to refine these applications for a final submission deadline of Friday May 15, 2010.

Final Proposals (May 15 , 2010)

The final submissions will undergo review and priority scoring by the CNP Executive Operations Team, who will also make recommendations for funding. Final funding decisions will be made by the CNP Steering Committee at the CNP Annual Retreat (6/2/2010) and after short presentations by the pilot finalists. Notification of awards will be made immediately following the Retreat, and funds will be allocated in the following month.

The final applications should not exceed 5 pages in length, and should include the following sections:

(1) Specific Aims

(2) Background & Significance (outlining the rationale)

(3) Outline of proposed Methods

(4) Proposed interaction with and use of CNP resources, estimated budget and justification for additional resources needed for project implementation.

Draft Criteria for Evaluation of Pilot Projects

1. Consistency with CNP goals (focus on translational research across syndromes and species);
2. Feasibility and likelihood of leading to application for independent extramural support;
3. If the project is for the study of a specific phenotype, there should be a focus on phenotype(s) of high merit for translational research on neuropsychiatric phenomics, with attention to phenotype selection criteria, including:

a. Reliability (internal consistency), test-retest reliability (at least within a particular state, and preferably across states in illnesses which have an episodic pattern), and other desirable psychometric properties (e.g., discriminating power across a broad range of individual differences);
b. Concurrent validity (convergent and divergent validity) with respect to hypothesized endophenotypes;
c. Relevance to higher level constructs in humans, enabling possible links to clinical effectiveness and outcomes;
d. Homologies of expression across species enabling both basic and clinical investigation;
e. Relevance to known genomic variation, and this genetic variation is relatively common in human populations;
f. Associated with neuropsychiatric morbidity;
g. High heritability, or be detectable in family members of individuals with disorders associated with that phenotype;
h. Suitable for application in high-throughput genome-wide association studies or clinical trials;
i. Latent endophenotype constructs should relate to neural systems models sufficiently well studied that physiologically plausible manipulations can be effected and measured using currently available techniques;
j. Implicated neural systems should already be targets of known partially effective treatments for existing disorders, or these systems are the targets of new chemical entities.

While it is not anticipated that any given phenotype would earn high marks on all of these criteria, applicant may use these as a starting point to help justify their selection based at least on these criteria or other strong justification.

All application documents (concept sheets and final proposals) should be submitted in electronic form (Adobe Acrobat PDF files only) by email attachment to Dr. Fred Sabb

(UCLAphenomics@gmail.com). Please download face page at www.phenomics.ucla.edu and include with application.