Yale Center for Molecular Discovery

Request for Proposals - 2013 Pilot Project Program

Due Date: 15 July 2013, 5:00 PM EST
Email: michael.kinch@yale.edu
Award Decisions: 15 August, 2013
Award Start Date: 1 September, 2013
End Date: 30 August 2014

SCOPE

The Yale Center for Molecular Discovery is announcing a new round of its Pilot Project Program to underwrite most costs required for target discovery and/or early proof-of-concept to identify molecules that alter key biological behaviors. The Center normally supplements at least 50% of the costs (with a 1:1 match) for the Yale community. The Pilot Project Program increases this supplement to 2:1) for projects selected using a peer-review system.

Services provided include but are not limited to biology (assay development or optimization, screening small molecules, antibodies or siRNA, high-content imaging), chemistry (structure and/or ligand-based design), and natural products.

Project selection by the Pilot Grant Review Committee, a panel comprised of faculty and Center staff. All activities will be confidential. Projects will be selected for their assay goal, research impact, methods, availability of reagents, and innovation.

Goal: The goal of the project should be clearly articulated. What will define success?
Research Impact: How will the project further your research? How may it facilitate new knowledge?
Methods: What are the methods? Are assays amenable to high-throughput screening.
Availability of Reagents: Are unique reagents required? How will they be procured?
Innovation: Are the goals or methods novel? Could they lead to new ideas or applications?

ELIGIBILITY & PREPARATION

All Yale investigators are eligible. Collaborative proposals are highly encouraged.

Potential applicants are strongly encouraged to interact with Center personnel, who can help assess study design, costs, and timelines and to evaluate project suitability.

FUNDING AND PROJECT PERIOD

Projects will be selected to receive a subsidy for Center activities of $2 for each $1 committed by the Applicant. The Awardee is responsible for reagent costs.

For exceptional opportunities, the Center will determine the potential for "nano-grant" to provide small-scale loans to support projects. Investigators considering this exceptional circumstance must contact the Center prior to submission.

Each project will receive its subsidy through monthly invoices, with a copy sent to the project PI. Any changes in rate structure during the course of the project will be communicated in writing at least one month before the new rates are enacted.

The subsidy provided by the Center may be utilized for the Award period (1 September to 30 August). Awards will not be renewable or transferable.

The Pilot Project Programs is intended to initiate new lines of investigation. Simple project continuations will not be considered although new lines of investigation that arose from past activities will be considered.

ELIGIBLE ACTIVITIES

Center services are listed below. Applications can include activities from more than one service as appropriate to the project. Those interested in additional or alternative services are encouraged to contact the Center to determine availability.

Biology Services:

Assay Development/Optimization: Activities include development and/or optimization of cell or molecule-based assays. Activities include but are not necessarily limited to assessments of enzymatic activity, protein-protein interactions, cell-based measurements of growth, differentiation, signaling, metabolism, survival and migration.

Imaging: The Center has capabilities in high content screening using fixed or live cultures. The assay formats emphasizes throughput screening (96 or 384 well).

Small Molecule Screening: The Center has more than 140,000 small molecules that span a large molecular space. These can be used to screen for desired activities in robust molecule- or cell-based assays.

siRNA Screening: The Center has libraries of human siRNAs, sets of biological targets and genome-wide sets.

Chemistry Services:

Compound Synthesis and Analogs: The center can develop routes for synthesis of compounds and facilitate preparation. We will also devise a chemistry strategy to analog hits and optimize properties to meet research objectives. Compounds may be optimized for potency and pharmacokinetics.

Structure-Activity Modeling: We offer a variety of computational and analytical methods to identify the essential molecular features driving compound biological activity. Techniques employed include computer generated Macromolecule Ligand Docking, Ligand-based Virtual Screening and quantitative structure-based activity relationships, QSAR.

Pharmacokinetic Prediction and Testing: The Center can model cell permeability, metabolic stability and other properties. We can also identify molecular features associated with adverse toxicological outcomes.

We also serve as a hub and resource for getting experimental data on the measured cell permeability, plasma and liver microsome half-life, plasma protein binding, solubility and other critical pharmacokinetic characteristics.

Compound Novelty and Literature Review: The Center can assist with searches of scientific and patent literature. This information can provide guidance into the best synthetic routes, reported uses and claims surrounding your chemical matter.

Natural Products:

Source Material: The Center will work with our customers to develop a strategy to generate source material from novel biomass provided by internal and external partners. These services encompass both direct and consultative activities.

Extraction and Partial Fractionation: Center personnel can develop strategies and perform partial fractionations to provide material for screening

Library Generation: The Center will help create and maintain searchable databases, both electronic and physical samples of fractions and individual compounds to facilitate proper archiving and information retrieval.

Informatics:

Screen Robustness Assessment: Robustness statistics are generated at the plate, run, replicate and/or screen level. These statistics determine the quality and reliability of the results.

Data Normalization: Center staff will perform data normalization services to transform raw plate readouts for comparison across screen runs and replicates. Numerous data normalization methods can be applied based on the assay characteristics.

Hit Selection: The Center will analyze genes or compounds producing the desired phenotype and select hits via various methods, such as rank-based selection or threshold based selection.

Gene Clustering and Annotation: Center personnel can analyze canonical pathways, broad interactive gene and protein networks, and other data, and use the associated gene annotations to inform hit selection of siRNA screens. These techniques can produce final hit lists of genes with increased relevance to the specific biological process under investigation.

Image analysis algorithm development: The Center develops robust image analysis scripts customized to the specific needs of each project. Analysis can include quantification of phenotypes per well and/or per cell.

CENTER & FUNDING MECHANISM BACKGROUND:

Mission

The Yale Center for Molecular Discovery identifies and validates targets through screening and molecular design. The Center is a steward of University resources for access, optimal use and benefit to the Yale community. We apply innovative technologies in a collaborative and educational environment.

Our mission is accomplished using a mix of internal laboratory expertise with consultative services to provide customized solutions for unique challenges.

YCMD Background

The Mission of the Yale Center for Molecular Discovery is to identify and validate targets by providing expertise in compound screening and molecular design. We apply innovative technologies in a collaborative and educational environment to advance understanding in the development of new tools or to probe new opportunities for drug development.

The Center performs an average of 90 projects per year. This project load is facilitated by a team approach working together with our partners. This approach emphasizes bottom line results and educational opportunities for participants.

The Center is staffed biomedical scientists with experience in academia and the industry. These diverse experiences provide unique insights to advance projects through hurdles that sometimes limit promising research in academic settings.

The range of services includes all aspects of project development, from early stage planning through later stage preclinical development. Center staff routinely assist in the design and writing of grant applications and manuscripts.

Each project is tailored to meet the needs of our customers. Key considerations include time, cost, and probability of meeting the researcher's goal. Significant resources are spent training Yale researchers, analyzing data and developing cost-effective solutions to promote their needs.

The Pilot Project awards are a credit to be used exclusively for Center activities.

All projects must be biosafety level 2 or lower. No projects requiring radioactivity are allowed. Awardees are responsible for all compliance and regulatory approvals.

Pilot Project Awards

It is estimated 5 projects will be selected to receive a Pilot Project award.

This funding mechanism is intended to provide seed resources for new programs. Timelines and milestones will guide project advancement and decision making.

Project Implementation

PIs will provide background information, protocols and assay guidance upon transfer of the assay to the Center. A point person in the PI's laboratory, typically a postdoctoral fellow, student or research associate, will work with Center staff member to transfer experience-based knowledge about the assay and its reagents. The point person will participate in all of the screening activities and PIs will make final decisions regarding assay conditions for screening.

Deliverables

The Center will provide a brief quarterly summary. This summary will include data and brief statements regarding project progress.

A closeout meeting will be conducted to review results, opportunities for future improvement and next steps. All data and images will be transferred to the awardee. Data will be archived at the Center for a period no less than one year.

Intellectual Property

The Center follows the policies of Yale University. All questions should be referred to the Office of Cooperative Research (OCR).