Guidelines

Mission

The Molecular Targets Program (MTP) provides leadership for the translation of basic science advances into drug leads, bioprobes and reagents for molecular target evaluation. We exploit chemical and biodiversity repositories, including the NCI Natural Products Repository, for molecularly-targeted lead discovery. The goal is to facilitate the discovery of natural products and synthetic compounds that may serve as bioprobes for chemical genetics, proteomics, target validation and potential lead compounds for clinical development. Compounds of interest include not only classical, "drug-like" organic small molecules, but also peptides, proteins, and other bioactive chemical classes.

A. Interaction of MTP and Principal Investigator(s) with MTP Steering Committee

- Initial contact with MTP is informal and may come through any MTP or MTP Steering Committee member; MTP will organize introductory seminar.
- After an introductory seminar and exchange of ideas, MTP Director will appoint a project manager for initial exploration of feasibility, if appropriate.
- Principal investigator(s) will provide MTP with necessary materials and expertise for initial assay evaluation and optimization.
- After project initiation, Principal investigator(s) and MTP staff will present project status to the MTP Steering Committee for questions and review.
- Pending MTP Steering Committee approval and sufficient progress, MTP will optimize assay system for HTS and prepare cost and time estimates for Steering Committee.
- MTP staff will present potential HTS programs to Steering Committee for approval to proceed with HTS.

B. Interaction of Principal Investigator(s) with MTP Staff

1. General considerations for project evaluation

- Is the molecular target relevant to cancer or to other human diseases?
- Are secondary and tertiary assays available to further evaluate primary screen actives?
- Has it been established that modulation of the molecular target produces a measurable and predictable \textit{in vitro} or \textit{in vivo} effect?
- Have any modulators of the target been identified?
- Are sufficient reagents (cell lines, purified proteins, controls, substrates, detection reagents, etc.) available to support assay development, assay validation, and screening?
- What is the potential assay format and is there a suitable assay platform present in the MTDP to match?
- Is the assay particularly time or temperature sensitive and does the assay generate a stable endpoint?
- Are there concurrent screening efforts in industry or other NCI divisions?
- What is known to non-specifically affect the proposed assay or detection reagents (e.g., solvents, impurities, classes of compounds, etc.)?
- Are positive and negative assay controls available and validated?

2. Cell-based assay requirements - principal investigator(s) should be able to provide:

- Detailed protocol for maintenance and assay conditions for cell lines
- Documentation that cells are mycoplasma free
- Information on passage stability of cell line
- Applicability to growth in a 96-well plate format
- Growth curve data that covers potential assay interval
- If growth factor dependent, provide dose-response curve with applicable growth factor
- Evidence of cell line compatibility with DMSO levels necessary for screening

3. Protein-ligand assay requirements - Principal Investigator(s) should be able to provide:

- Written protocol defining initial assay: reagents, pH, co-factors, other assay components, order of addition, acceptable ranges for time and temperature
- Sufficient supply of target proteins and ligands to allow initial analysis of reagents, binding interaction and assay conditions
- Possible mechanism for re-supply of reagents in quantities necessary for HTS
- Information on reagent stability and optimal handling of reagents
- Willingness to co-perform initial experiments with MTP personnel

4. Phage-display assay requirements - principal investigator(s) will provide one of the following target sources, and/or one of the following library sources:
**Target**

- 500 µg of highly purified target protein, with fusion partner, preferably with biotin acceptor domain, or
- A pair of cell lines: one of which expresses target membrane protein, the other does not, or
- For construction of paramagnetic proteoliposomes, detergents which can be used for cell lysis of pull-down experiments, or
- Biotinylated small molecule for small molecule-binding protein

**Library Construction**

- 10 µg of good quality of poly(A)^+^RNA for cDNA library
- cDNA for target protein fragment library for binding site mapping

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