Trans-NIH Genome-Wide RNAi Screening Program
Status and Call for Proposals
July 20, 2010

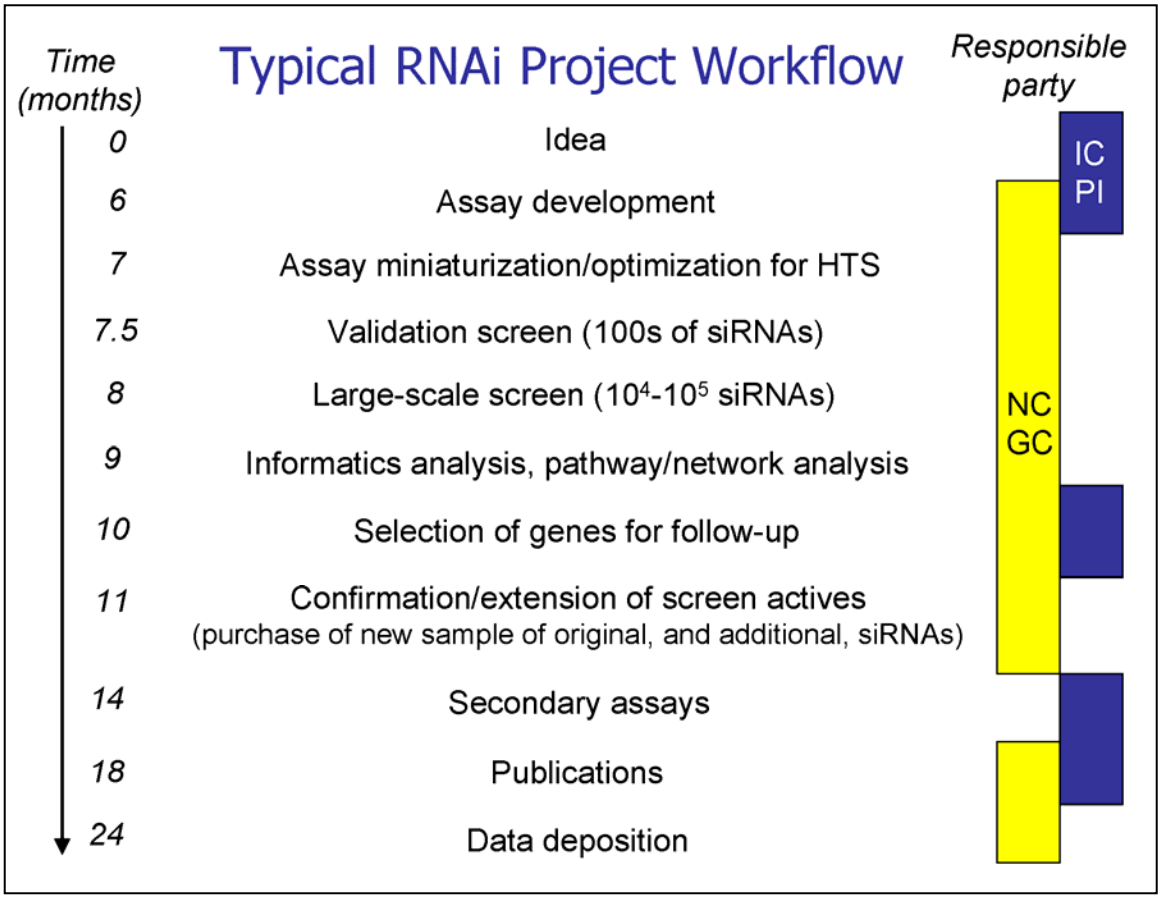
Introduction: Gene silencing through RNAi has emerged as a powerful tool for understanding gene function. Over the past several years, high-throughput RNAi screens have illuminated a wide variety of biology ranging from genes that affect the activity of therapeutic agents to elucidating novel components of signaling pathways. **The NIH has established a state-of-the-art RNAi screening facility that is now soliciting proposals from any intramural researcher.** The Facility assists with all stages of projects beginning with assay development through genome-wide siRNA screens, informatics/pathway analysis, and rigorous follow-up. Considerable emphasis has also been placed on establishing a robust computational infrastructure, as the goal of the Facility is to provide collaborating investigators with highly enriched and validated lead genes. Druggable genome and genome-wide siRNA screens for both human and mouse are available, and miRNA mimic and inhibitor libraries are routinely included in screens. shRNAs and other species capacities may be added depending on demand. See below for specifics. Interested researchers should contact Scott Martin at the NIH Chemical Genomics Center, martinsc@mail.nih.gov, 301-217-1079.

Libraries available: siRNA kinome, siRNA druggable genome (mouse and human), siRNA whole genome (mouse and human), miRNA mimic and inhibitor (human)

Scale of projects to be performed: projects should aim to screen at least the "druggable genome" ≥6,500 genes.

Project scope/deliverables: the desired endpoint of all projects is important insight(s) into a pathway or phenotype, and one or more joint publications. Each project has multiple stages (see Figure below) with varying degrees of shared responsibility between the RNAi Facility and the collaborating PI. The average project lasts 12-24 months, with the screen itself taking up a small part of this time; the most time-consuming, and ultimately most important part of any project is the assay development before, and hit characterization after, the screen.

Given this substantial commitment of time and resources, approval via formal application is required for full-scale screening to be performed (see below). However, since investigators are frequently unfamiliar with the requirements of this type of large-scale screening project, investigators are encouraged to work with the RNAi project team (contact: Scott Martin, martinsc@mail.nih.gov) prior to submission. The RNAi Project Team can assist with all levels of project development.



Once a project is formally accepted, the RNAi Project Team will further refine conditions and conduct pilot screens. Upon completion of the development phase, a full-scale campaign will be conducted and identified genes will be confirmed as hits in rigorous follow-up experiments. The Project Team will apply extensive informatics to rank and enrich hit lists with associated data, such as pathway information and GO term enrichments. Investigators will need to specify robust secondary assays to help prioritize hits identified from the screening efforts. The entire process is intended to be highly collaborative, resulting in joint publications and eventual data release. As such, investigators should identify personnel that will be dedicated to the project.

Application Process: applications will go through three stages of review.

1. IC SD: the investigator should submit the proposal to his/her SD, who will initially review for scientific merit and relevance to IC mission
2. RNAi Proposal Review Committee: will rank proposals based on novelty, importance to one or more fields of science, technical characteristics of the primary screen assay, and available follow-up assays
3. Final selection will be performed by Drs. Wiltrout and Gottesman, as primary funders for the development of the RNAi initiative.

As outlined in the application below, a number of technical criteria need to be addressed prior to approval for large-scale screening. Projects must have cell-based model systems and an assay amenable to high-throughput screening. The RNAi Project Team can accommodate a wide

variety of assay formats, ranging from luminescence and fluorescence-based assays to high content imaging. The Project Team can assist with assay development.

Following internal institute(s) review and approval, the Trans-NIH RNAi Proposal Review Committee will consider whether an application should proceed, or be returned to the applicant for further scientific and/or technical refinement. Key criteria to be considered by the committee are likely scientific impact, novelty, feasibility for high-throughput screening, and the plan for and commitment to follow-up.

FOR FURTHER INFORMATION/INQUIRIES:

Primary contact (project ideas/questions/advice):
Scott Martin, RNAi Project Team Head, NCGC; martinsc@mail.nih.gov; 301-217-1079

NCGC Director: Chris Austin; austinc@mail.nih.gov; 301-217-5733

Project Selection Committee Chair: Natasha Caplen, NCI; ncaplen@mail.nih.gov; 301-451-1844

RNAi Screening Program Governance Heads: Bob Wiltrout, NCI and Michael Gottesman, DDIR

Application for RNAi Project Collaboration

Name:

Title:

IC/Branch:

Date:

Abstract: Less than 250 words.

Target/Pathway/Cellular Phenotype is to be assayed:

Desired scope of screen (e.g., druggable genome, whole genome)

Species:

Prior RNAi screens, of any scale, conducted in similar systems:

Specific Aims/Desired deliverables of Project:

Primary Assay: Describe

- The high-throughput amenable assay
- Reagents necessary for the assay and their availability and cost. Note those that may be difficult or expensive to obtain in sufficient quantities.
- Preliminary data and controls using siRNAs and/or compounds
- Data on cell transfectability and method thereof

Secondary Assays: Describe secondary assays for hit prioritization and follow-up. These should include both assays at the same level of biological complexity with alternative readouts, and more physiological, lower-throughput assays to assess biological robustness and relevance.

Follow-up Plan: Describe follow-up experiments and applications to be conducted, with an endpoint of high quality publications and data useful to the research community

Personnel: Indicate personnel that will be committed to project over the expected two-year duration of the project

Estimated Consumable cost, if known:

Applicants: Submit completed form to your IC SD for review

Indication of scientific review and approval by applicant's SD: