Broad Institute Chemical Biology Platform and Novel Therapeutics Platform: Overview of Principles and Processes

OVERVIEW

The Chemical Biology and Novel Therapeutics Platforms have been established at the Broad Institute to accomplish two goals: (1) discover small molecules that impact biology and medicine; and (2) innovate the process through which probes and drugs are discovered and developed. To accomplish these goals effectively, we plan to undertake the most innovative chemical biology screening projects arising from the broader scientific community. We have established two distinct pipelines for investigators to propose and execute projects with the Chemical Biology Platform (Figure 1):

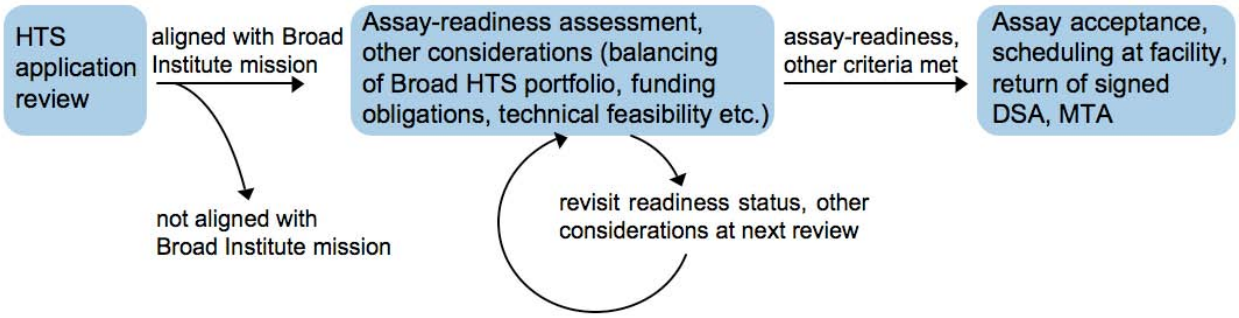
Broad Institute Chemical Biology Pipeline. We have established a process for accepting and reviewing applications *directly* from the community.

Broad Institute 'Molecular Libraries and Probe Production Centers Network' (MLPCN) Pipeline. The Broad Institute has been selected as a Probe Development Center within the MLPCN, and we will perform screens accepted by the NIH for screening by our group ("Broad Institute Probe Development Center" [BIPDeC]).

These pipelines differ in several ways, including the application process, compound collections screened, commitment to follow-up chemistry, and data-sharing policies. Supporting these parallel pipelines requires a high degree of organization and clear communication with our broader community. This document aims to define clearly the differences between the two pipelines, as well as define general principles for working with the Platform effectively.

GENERAL PRINCIPLES

Project Selection. Screens will enter the Broad Institute through two different mechanisms, both of which involve objective scientific review by a broader group for alignment with our missions (Figure 1):



Broad Institute Application for Screening: Project proposals are reviewed for scientific merit and technical feasibility by the Application Review Committee, consisting of a mix of program and platform leadership from within the Broad Institute with expertise in basic biology, disease biology and drug discovery. The scientific review is followed by a review of the overall portfolio of projects and the bandwidth of the platform. If projects are reviewed favorably but lack funding, we will help investigators explore options for support, including consideration for funding through

the NCI's Cancer Target Discovery and Development (CTD²) Network, the Stanley Center's PsychHTS program and endorsement of applications for foundation and NIH grants.

Application for Screening through the NIH MLPCN: We will perform screens accepted by the NIH for execution in our Probe Development Center. Project selection will ultimately be determined by the grant review committee assembled by the NIH to evaluate the full set of applications. All projects accepted by the NIH receive funding for screening and probe optimization by medicinal chemistry efforts. As outlined in Figure 1, the Application Review Committee will endorse some NIH grant applications for acceptance by the MLPCN and assignment to our Center. Individual projects may submit both an NIH grant and a Broad Institute Screening Application.

Additional detail on how to apply to either of these pipelines is provided below.
Screening Process. We are committed to executing screens of high quality in an efficient manner in the Broad Institute's state of the art screening center. All screens entering either pipeline will be assigned a Broad chaperone who will usher the screen through each stage in the process from Assay Development to Data Analysis, and in some cases, to Follow-up Chemistry. Each project will begin with the definition of a project plan, with clearly defined go/no-go criteria for advancement through each stage. We will not advance projects that do not meet the rigorous criteria for quality at each step, but our assay development team is committed to working with investigators to reach these standards in a reasonable time frame.

Compound collections. The Broad Institute maintains a distinct (unique and non-overlapping) compound collection for each of the two screening pipelines:

Broad Institute Screening Collection. All compounds in the Broad Institute Screening Collection are of known structure and high-purity (> 75%), enabling the best possible outcome for our screeners. We currently aim to grow this collection to 300,000 compounds, which include unique compounds resulting from diversity-oriented synthesis pathways developed by the Chemical Biology Platform and elsewhere, FDA-approved drugs, and compounds with known biological activity ("bioactives"). In principle, we can accept new compounds into the screening collection, provided they are of known structure and sufficient purity (>75%), provided their structures can be publicly disclosed, and provided that all compounds are available for screening by all users of the platform. Additionally, they should be in a format compatible with our compound management capabilities, without excessive disruption to our ability to provide our standard services.

The compounds in the Broad Institute Screening Collection are a unique resource assembled to serve the community through the screening process. We will provide screeners with 'cherry-picks' to retest positives from their assay in dose response studies and help prioritize positives for follow-up chemistry. However, given that compounds are limited in quantity, we cannot distribute plates of compounds from the collection for screening at outside institutions.

MLPCN Screening Collection. All compounds in the MLPCN Screening Collection are of known structure and purity. The collection currently comprises 320,000 compounds assembled by the NIH Molecular Libraries Small Molecule Repository (MLSMR) from a variety of sources (natural products, commercial vendor libraries, compounds emanating from national CMLDs). The structures of all compounds included in the collection have been publicly disclosed via the online database *PubChem*. This collection is shared by the screening centers within the

MLPCN, and all assays will be screened against the entire collection. In principle, new compounds can enter the screening collection via submission to the MLSMR, provided they meet the requirements defined by the NIH. All 'cherry-pick' requests for positives resulting from our MLPCN screening projects will be submitted to a third-party, Galapagos NV, which maintains master compound stocks for the entire network of screening centers. Galapagos will provide 'cherry picks' for execution of retest studies.

Follow-up chemistry.
Broad Institute Screening Projects. We cannot provide follow-up chemistry support for all screening projects undertaken by the Chemical Biology Platform. However, we are committed to helping our screeners evaluate their options and to develop a strategy to advance their projects (e.g., outsourcing synthesis). In some cases, there may be circumstances in which we mutually agree to pursue collaborative follow-up chemistry. These probe development projects will be executed by Broad Institute Organic Synthesis Fellows (OSF), a group of highly trained Ph.D. level chemists.

MLPCN Screening Projects. All projects entering the pipeline through the NIH MLPCN will receive support for follow-up chemistry. Probe development projects will be executed by Broad Institute Organic Synthesis Fellows (OSF).

Engagement.
Broad Institute Screening Projects. All projects accepted for screening through the Broad Institute Screening Application will be subject to the Broad Institute Chemical Biology Platform Screening Services Memo of Understanding (MOU) as well as an incoming Materials Transfer Agreement (MTA) for any materials that need to be brought into our facility. Distribution of compounds for further testing in the PI's lab or in our Outreach facility requires execution of an Outgoing (MTA).

MLPCN Screening Projects. All projects accepted for screening by the NIH through the Broad Probe Development Center will be subject to the NIH MLSCN Project Team Position on Data Sharing and IP in the MLPCN Program. Furthermore, the agreement requires public disclosure of early-stage data in PubChem (primary assay, confirmatory screen and 1 – 2 secondary assays) within 2 weeks of data validation. When projects enter late stage and chemistry optimization has begun, data can be held in confidence for up to 1 year **or** until 6 months from the submission of a Probe Report (the goal of every MLPCN Project).

Novel Therapeutics. The Novel Therapeutics Platform at the Broad Institute has been established to advance projects that address unmet medical needs, or transform the process of drug discovery. Investigators collaborating with the Novel Therapeutics Platform will enjoy the unique opportunity to develop their projects further towards clinical application than usually possible in the academic setting (e.g., through extensive medicinal chemistry and ADME/tox).

HOW TO APPLY
Broad Institute Screening Application. Please submit an application for HTS at the Broad. The Application Review Committee will meet every three months to evaluate new applications based on scientific merit and alignment with the Broad mission. The application and the deadlines for submission are available on our web site at: http://www.broadinstitute.org/chembio/pipeline.

MLPCN Screening Center Application. The NIH R03 mechanism provides funding for screening by an MLPCN Screening Center. Furthermore, if you have the development of assays for use in high-throughput screening described as a goal in an existing peer-reviewed grant, you may be eligible for a 'Fast Track' application pathway for screening. To apply for a letter of endorsement from the Broad Institute Probe Development Center, please contact the Manager of our Outreach Facility, Dr. Nicola Tolliday (tolliday@broadinstitute.org).

'SMALL PROJECTS' AND NON-SCREENING ACTIVITIES

We recognize that many members of the community rely on our instruments and staff to support smaller projects and non-screening activities (e.g., early assay exploration; secondary assays to characterize screening hits; SAR studies; chemical biology research projects). We have always attempted to accommodate such needs, and now have formalized a process for providing this support. Our **Outreach Lab** is open to all members of the scientific community for a small, annual user fee. Investigators also have access to a screening collection (1,600 compounds comprised of known "bioactives" and "drug-like" molecules) for assay validation. To discuss access to this facility, please contact Nicky Tolliday (tolliday@broadinstitute.org).

FUNDING SCREENING PROJECTS

We are eager to work with all of our collaborators to identify funding for their screening and probe development projects. For specific disease areas, including cancer and psychiatric disease, we have secured funding sources to support a specific number of projects each year, and all relevant applications would be considered for support. In addition, we are actively exploring mechanisms to fund other areas of research. If your project is not aligned with the missions of our existing granting agencies, we would work with you to obtain alternative funding, for example by endorsing an application for foundation awards, a SPARC proposal, and/or NIH grants. In the event any member of the Broad community is planning to write a grant to fund screening, it is critical that you contact us early enough in the grant writing process to enable us to adequately assist in the strongest application possible. Additionally, it is important to allow us to plan the pipeline of projects.

To enable more effective financial planning, we have transitioned to a service facility cost structure (SSF) which makes the recovery of our costs fair and equitable, allows investment for future process improvements to enable price reduction, and provides more transparency to the Broad community. We are able to provide any investigator writing a grant proposal or planning a project with an estimate of the screening cost on a "per well" and fee basis.

CONTACT US

If you have any questions regarding these principles and processes, please email htsfacility@broadinstitute.org and your request will be directed to the relevant contact.