BROAD INSTITUTE

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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").

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.

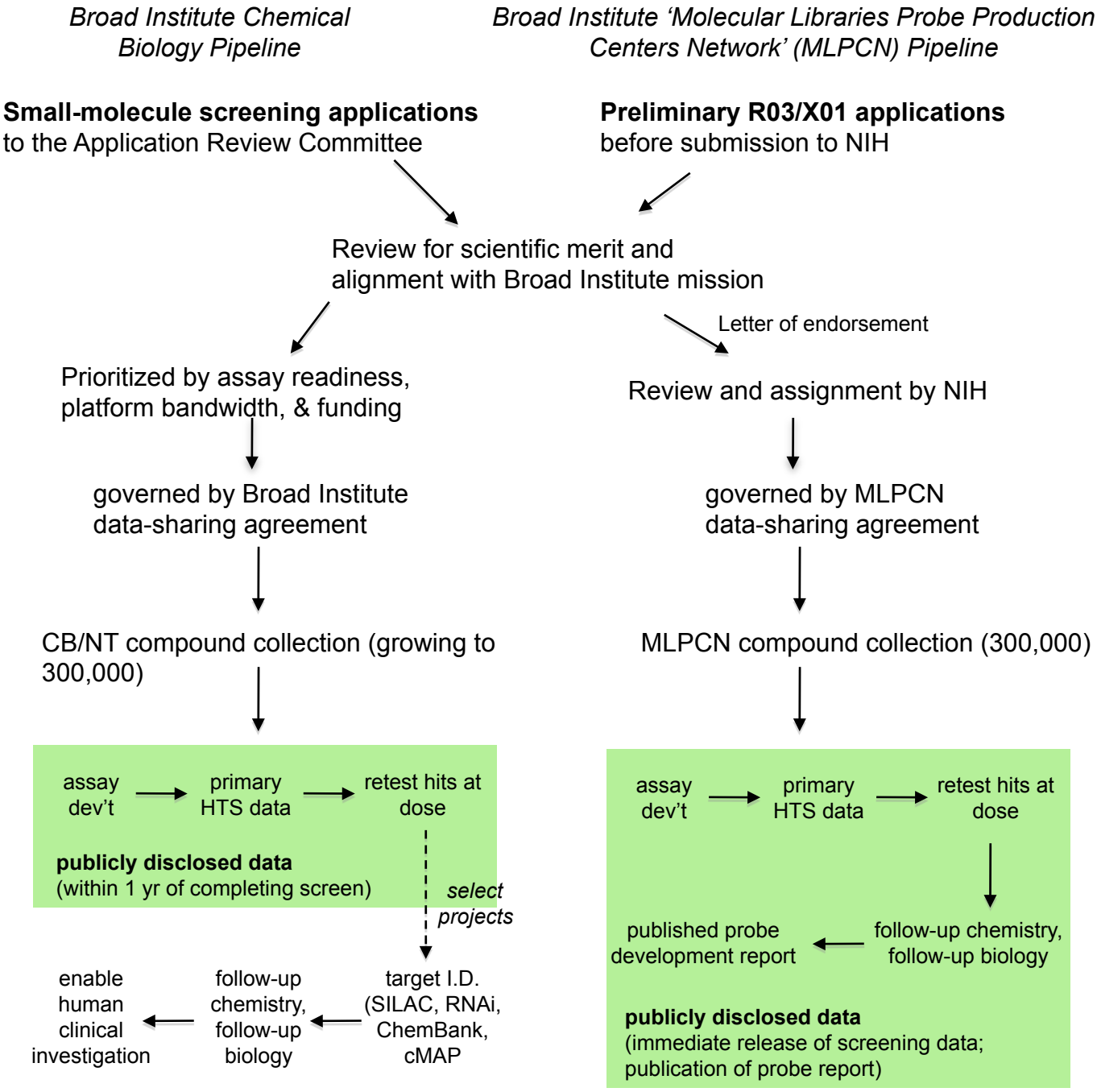
GENERAL PRINCIPLES

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 Initiative for Chemical Genetics 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 by 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. As outlined in Figure 1, the Application Review Committee will endorse some NIH grant applications projects 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.



- each compound collection is unique and non-overlapping
- the two screening paths are NOT mutually exclusive
- the funding mechanisms are distinct: (A) Broad Institute Chemical Biology screens are supported by individual investigator grants or by Broad Institute funding mechanisms (e.g., ICG, JDRF, Starr CC, SPARC, U54, R24, etc.); (B) MLPCN screens are supported indirectly via the R03 or X01 mechanisms – the Broad Probe Development Center is encouraged to develop its pipeline within the constraints of its MLPCN funding obligations.

Figure 1. Small-molecule screening and probe/therapeutic discovery flow chart

Screening Process. We are committed to executing screens of high quality in an efficient manner in the Broad Institute's new 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 recently expanded 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"). The structures of all compounds included in the collection will be publicly disclosed via the online database *ChemBank*. 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 300,000 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).

Data-sharing.
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 and Data-Sharing Agreement (DSA). By signing the DSA, you gain access to a non-public database containing the screening data of all members of this screening community, including that generated in your project. The agreement also requires inclusion of follow-up data associated with compounds in the screening collection, *but not data associated with compounds resulting from follow-up and medicinal chemistry* (green box, Figure 1). The contents of this database allow the generation of biological hypotheses from apparently unrelated biological problems, possibly sparking new collaborations. The contents of this database are then released to the public ~1 year after completion of the screen.

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 MLSCN Program. The agreement requires that all screening data be made publicly available immediately through PubChem. Furthermore, the agreement requires public disclosure of follow-up data associated with compounds in the screening collection, *as well as data associated with compounds resulting from follow-up and medicinal chemistry*, in the form of a published probe development report (green box, Figure 1). The MLPCN provides for a 60-day grace period before disclosure during which investigators can file provisional patents.

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 at our web site at http://www.broad.mit.edu/science/platforms/chemical-biology/screening-application.

MLPCN Screening Center Application. The NIH R03 and X01 mechanisms provide funding for screening by an MLPCN Screening Center. Furthermore, if you have existing R01 funding for your assay development, 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, submit a preliminary version of the grant three weeks before the due date to the screening facility (htsfacility@broad.mit.edu). The Screening Review Committee will review these before each grant cycle and decide which to support with letters of endorsement. The guidelines for the preliminary grant submission and specific application deadlines are available

on our web site at http://www.broad.mit.edu/science/programs/chemical-biology/bipdec-probe-development-collaboration. For projects not ready for high-throughput screening, the NIH provides the R21 mechanism which provides funds for assay development. Further detail on these procedures can be obtained from Stacey Donnelly (sdonnell@broad.mit.edu) in the Office for Sponsored Research.

EXCEPTIONAL REQUESTS AND OUTSIDE COMMITTMENTS

If an investigator has a need that is inconsistent with the general principles outlined above, we may be able to accommodate the request under exceptional circumstances (e.g., the project addresses an unmet medical need). The investigator should discuss the proposal with the Chemical Biology/Novel Therapeutics Steering Committee, a group that meets weekly and has been empowered to make such decisions for the Platform. Please contact Robert Gould (rgould@broad.mit.edu), Committee Chair, to secure time with the Committee if you have such a request.

We understand that investigators rely on the Platform capabilities to meet commitments to granting agencies and outside collaborators. We are committed to working with Investigators to succeed in their ambitious scientific goals. However, to accomplish this effectively, the Platform needs to be engaged at an early stage to assess the feasibility of potential commitments involving its resources. We again request that investigators requiring the support of the Platform (e.g., when drafting a new grant application) contact the Chemical Biology/Novel Therapeutics Steering Committee to discuss their proposal. Where appropriate, we can then provide a letter of endorsement and commit to the activity.

'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, however the increase in screening volume associated with the new MLPCN pipeline both limits our bandwidth and forces us to become more organized in how we handle such requests. As such, we have initiated a project aimed at determining the resources required (equipment, personnel, funding, space) to establish a dedicated research environment to support such activities.

The general question of how to support such non-large scale projects in any of the Broad Institute platforms is currently under discussion by the Broad Institute Leadership Council. As we work towards a more general solution, if you have a request, please submit a project plan to Michelle Palmer (mpalmer@broad.mit.edu), Director of Screening, describing the goal of the activity as well as detailing the resource needs (instruments, people). *Where possible,* we will work to accommodate the request and appreciate your patience during this time.

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" basis.

CONTACT US

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