Guidelines for running small-molecule high-throughput screens (HTS) at the SMDC

Welcome to the SMDC! This document outlines the policies and procedures for running HTS with the Center. These projects tend to be highly collaborative and generally warrant co-authorship; we are also happy to help with grant submissions. Please do not hesitate to contact us with any questions.

Screening process

1. ***Consultation***. Potential users are invited to discuss a screening idea with any member of the SMDC HTS group. Once assay development is underway, the project will be matched with an HTS liaison, who will consult during assay development and help run the HTS.

2. ***Assay development***. The assay is developed by the initiating lab, usually in their laboratory. Clients are welcome to use SMDC instrumentation to test their assay development. A typical use of instrumentation is included in the recharge, and there are hourly rates for extensive development or other project-related use.

3. ***Dry-run***. The proposed HTS assay is tested using positive and negative controls to determine the Z' for the assay. The dry run should use the HTS protocol, including SMDC robotics and plate readers where appropriate. When Z' is consistently > 0.5, pilot screening can proceed.

4. ***Pilot screen***. Approximately 2000 compounds are run using the HTS protocol. All aspects of the screen, including data analysis, are tested. When the Z' and Z-factors are >0.5, HTS can proceed. The pilot set can be a focused library (eg drug set) or the first few plates of the desired screen set. *A typical screen is run in 50 µl, at a final concentration of 10 µM compound, in 0.1% DMSO.*

5. ***HTS***. Screening begins in earnest, working at the fastest pace appropriate for the assay. A full diversity screen is 177,000 compounds, though more or fewer are also possible. See "Available Compounds."

6. ***Data analysis***. Each day of screening, results are uploaded to the SMDC database and are accessible via the HiTS web interface (hits.ucsf.edu). C*ollaborators are encouraged to sign up for a free account to HiTS.* Data will be kept confidential and each project is accessible only to approved users. Z' and Z-factors determine whether a run is interpretable. "Active" wells are those with signals > 3 stdev from the mean of the baseline signal.

7. ***Rescreen***. Actives are cherry-picked for rescreening, usually at multiple doses. Typically, 320 compounds screened are cherry-picked at 10 µL and are plated at 8 concentrations.

8. ***Preliminary SAR***. HTS data are analyzed by substructure or other similarity algorithm to determine preliminary structure-activity relationships (SAR). SAR can be used to focus compounds for repurchase and/or for generating hypotheses about the binding site. At this stage, the SMDC will also provide available information about which actives are nonselective, cytotoxic, and/or covalent modifiers. *Data for screens, cherry-picks, and chemical structures are available via HiTS.*

9. ***Repurchase***. The SMDC will provide information on repurchasing the active compounds. The initiating lab then purchase the compound for their own use. Sometimes, it is not possible to purchase the compound from commercial sources; in these cases, the SMDC will suggest alternatives, such as close analogs that are commercially available.

After repurchase, the screening services are complete, but there are avenues to continue working with the SMDC. If equipment is needed, we will provide the instrument recharge policy. Further collaboration is often encouraged, and begins with a discussion of long-term goals and strategy.

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