Overview and Mission

The Small Molecule Discovery Center (SMDC) is located at the California Institute for Quantitative Biomedical Research (QB3) on the Mission Bay Campus of the University of California, San Francisco. The SMDC offers biomedical investigators at UC campuses in San Francisco, Santa Cruz, and Berkeley access to small molecule discovery technologies including high-throughput screening, fragment-based screening, and hit-to-lead medicinal chemistry. High-throughput screening (HTS) is the predominant technology used in the pharmaceutical industry to identify small molecule hits in drug discovery programs. The SMDC screening function is enhanced by the presence of an integrated chemistry group staffed by experienced medicinal chemists from the pharmaceutical industry. The application of medicinal chemistry following screening allows correlations between chemical structure and biological activity (SAR) to be more fully understood and provides a better measure of a target's druggability than does screening alone. By collaborating with UC investigators, the SMDC aims to accelerate the path from new discoveries in biology to validated biological targets that could eventually lead to new small molecule therapeutics.

Capabilities and Workflow

The High-Throughput Screening (HTS) core of the SMDC performs biochemical and cell-based assays utilizing a screening library of more than 150,000 compounds. This compound collection contains diversity libraries (ca. 100K compounds), targeted libraries (>40K compounds), fragment libraries (ca. 12K compounds), and libraries of known drugs/actives (ca. 4k compounds). Collaboration between the SMDC and an investigator lab begins with the development of an assay suitable for a high throughput format. This work is normally performed in the investigator lab with the consultation of the HTS director of the SMDC. When the assay is judged to be robust enough for HTS (e.g., with a Z prime > 0.5) the screen is performed using SMDC instrumentation with the training and supervision of the SMDC screening group. Our HTS instrumentation includes liquid handling robots and automated bulk dispensers to plate-out compounds/reagents and high-throughput plate readers to measure assay readout (e.g., fluorescence polarization, FRET, luminance, etc.). As part of a special arrangement with GE, the SMDC also houses the IN Cell analyzer 1000, a high-content screener used for cell-based phenotypic assays. Data analysis is carried out with a suite of programs in the commercial programming platform Pipeline Pilot. Pipeline Pilot also interfaces with relational databases allowing storage and subsequent retrieval of all assay and compound data deposited in the system. The results of a screen are posted to a website where users can view the data, including preliminary structure-activity relationships (SAR) generated automatically by Pipeline Pilot from the screening data.

Following a screen, the SMDC will cherry-pick the hits (up to 0.3% of the total number of compounds screened) and provide these to the investigator lab. The cherry-picked "hits" can then be scrutinized in more detail for example by determining IC_{50} values, performing mechanism of action studies, and evaluating off-target toxicities. These studies are typically conducted in the investigator lab. In the event that additional quantities of hit compounds are required for these studies, the SMDC will assist users in finding suitable vendor(s) for re-supply. Following hit validation, the SMDC chemistry group will work with investigators to determine which hits are potential candidates for chemistry optimization. Of the approximately 8-10 high-throughput screens performed each year in the SMDC, we expect that only 1-2 (at most 3) will progress into the hit-to-lead chemistry phase.

The goal of the hit-to-lead chemistry effort is to improve potency against the target while minimizing off-target toxicities. This may be accomplished empirically by systematic modification of the chemical structure and/or by structure-based design if crystallographic information is available for the target. Alternate chemical scaffolds are examined that retain key recognition features of the hit but are more drug-like in nature (e.g., constrained systems, peptido-mimetics, etc.). Consideration of the germane patent literature is also advisable during this phase. New analogs are evaluated for target potency, cytotoxicity, and metabolic liabilities. As a project matures, select compounds may be tested for in vivo efficacy in animals, if reliable models are available. The hit-to-lead process requires close collaboration between the SMDC and user laboratories and typically require between 12 and 18 months of effort. When a promising lead series has been identified, composition-of-matter patents may be filed and partners in industry or the non-profit sector are sought out to continue lead optimization studies with the ultimate objective of identifying drug candidate(s).