

High-Throughput Compound Screening and Discovery in an Academic Setting

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ChemCORE at The Johns Hopkins University School of Medicine is an integrated robotics and chemical repository unit. It provides combined access to large chemical libraries and state-of-the-art robotic capability. Its goal is to perform high-throughput screening of assays in search of compounds for scientific investigation, clinical use, and commercialization.

Costs and risks of high-throughput screening are reduced when high-throughput screening is performed by an established laboratory, because it is very expensive for an individual laboratory to acquire compounds independently and set up a robotic facility. A goal of ChemCORE is to use its capabilities to bridge chemistry and medicine, and, at the same time, to position the institution competitively for funding and quality scientific results.

Industry or Academia

A major strength of industry is that it can make a huge investment to develop a drug (i.e., \$700 million on average). Industry's goal is to obtain a return on its investment; thus, it requires a proven target with a clear therapeutic value. The for-profit objective requires secrecy and "labor in isolation."

In the academic environment, funding is provided by federal agencies and collaborations, which nurture an "open system." Because of limited funding, academia may not be able to provide as much financial support as industry, but it does provide unlimited and free knowledge and expertise. Academia allows the pursuit of targets and structures that are unproven and risky with no guarantee of short-term commercial gain, providing significant opportunity for discovery and therapeutics.

Chemical Core or Typical Core Facility

In the typical DNA sequence core, input is very standard—a DNA template and a primer. The technology is essentially a generic sequencer, and the output is an electronic file. With the ChemCORE process, input can include different targets and bio-

logic systems. The technology requires different assays, different detection, and read-outs. The output is diverse, and the compound structures of interest may have different structural features, requiring participation of chemists with widely specialized expertise.

Challenges

First of all, if theoretical predicted diversity is 10^{60} and there are only 10^7 registered compounds, that means that there is a tremendous diversity of chemical structures yet to be explored, that probably will not be explored in the foreseeable future. Our rationale is that we need to start with a reasonable library size with sufficient diversity, tractability, and renewable supply. At ChemCORE, we focus on a diverse set of 20,000 compounds. In particular, we have 3,000 selected known structures and drug structures.

A second challenge relates to the targets. There are 20,000 human genes; 3,000 G-protein-coupled receptors; 400 ion channels; and 160 potassium channels. To meet this challenge, we focus on innovative assays, discovery-oriented content, and model systems in parallel. Current strategies include 1,000 full-length human protein targets.

A third challenge relates to the chemistry in a diverse hit structure. We have established chemical synthesis agreements with small and midsized specialty companies near Johns Hopkins, and we have recruited 18 chemists from various institutions in the mid-Atlantic region. They participate in the projects through mutually beneficial collaboration and maintain confidentiality regarding results.

Informatics and data mining represent an important domain. We intend to provide real-time data acquisition and analysis, library-oriented linear integration, and, most importantly, an institutional database of knowledge. After we screen an assay, we can provide an index factor to indicate whether the identified compound has been identified in other assays or not. That way, we can facilitate communication among investigators who may have a shared interest and may be potential collaborators.

Hopkins ChemCORE is striving for flagship capability. We would like to have content-rich assays, discovery opportunities, and clinical significance. For example, Hopkins has recently developed and patented technology

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that is able to profile a compound for potassium channel activity for its ability to interfere with the activity. Thus, after an assay is screened, we can provide information regarding whether a compound is likely to influence the potassium channel, which is important in the side effects of QT prolongation.

Current Capabilities

ChemCORE personnel include an automation engineer, assay technicians, chemists, and a project manager. Clients can log onto a secured website, commu-

nicate with the project manager, and see the data as they are generated and deposited in their folder. We have various types of hardware and various compound libraries. We receive funding from several sources, including both federal and private sources. Our libraries have produced hits in five assays that were validated with resynthesized compounds. The National Institutes of Health grants were submitted based on the hits. A term sheet has been signed for a state-of-the-art photonics screening platform that is generic for all molecular interaction.