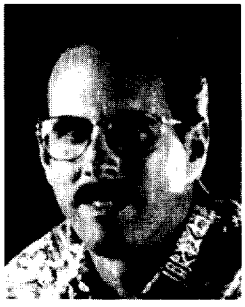
Accelerating drug discovery



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Over the years, screening for identification of drugs or drug leads has been the most successful approach for bringing new therapies to market. In the past decade, however, 'evolutionary pressures' have dramatically changed the process of screening. To accomplish the current lead identification goals, investigators are combining new molecular targets with fully automated assays and large sample libraries. These tools have resulted in a significant increase in the number of hits, but not necessarily in the number of clinical candidates (on a per researcher basis). As a result, the overall process of drug discovery has not been appreciably accelerated; instead, we have simply shifted the bottleneck from primary screening for hit identification to follow-up evaluation and validation of the resulting hits. In order to help increase the chances for success in the future, it is first useful to review a brief historical example of successful drug discovery using the screening approach.

Looking to history

In the 1970s, investigators at Merck Research Laboratories (West Point, PA, USA) conducted screening assays to identify novel CNS-active compounds. Each day, hundreds of mice were treated orally with compounds for screening (one compound per 'well') and a series of behavioral parameters were assessed over six hours. Many interesting molecules were identified from this program. MK801, for example, was found to possess anti-epileptic properties in animal models and eventually in humans. More than a decade after its initial synthesis, the molecular mechanism of action of MK801 was identified, which led to further clinical applications of the compound. Unlike current drug discovery efforts, the arcane Merck approach allowed researchers to capture a great deal of functional information from the primary assay, including multiple pharmacological endpoints, oral bioavailability, time dependence and toxicity. This information allowed the scientists to move rapidly to the later stages of the drug development process.

As a consequence of being able to test 100,000 or more samples very rapidly, modern molecular screening approaches have alleviated the problem of hit identification. Unfortunately, the testing of large chemical libraries with high-capacity screens has created a new bottleneck at the stage of characterizing and validating each hit because these downstream activities do not keep pace with the rate of primary screening.

Many of the causes of bottlenecks in the drug discovery process are simply related to the identification of a plethora of hits that are often false positives or 'garbage' molecules, which are eliminated slowly during follow-up. Other bottlenecks, however, are related to the lack of pharmaceutical relevance of the hits. Some of these problems that modern drug discoverers are forced to face, typically in very late stages of lead optimization, include short duration of action, poor oral bioavailability, limited aqueous solubility and lack of specificity.

Utilizing old concepts

It is now essential to make rapid and full use of our primary screening efforts by resolving such bottlenecks as early as possible. To accomplish this goal, drug discovery researchers need to test more pharmaceutically relevant molecules and consider, as early as possible, the parameters that made the previous generation of researchers successful in bringing new molecules to the clinic. Clearly, this will require the utilization of old concepts, such as determining oral activity or safety, albeit in a new high-throughput cultured cell mode, as well as implementation of sophisticated data-mining tools to enable assimilation of all of the relevant information.

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In order to keep up with primary screening capabilities, investigators are purchasing and synthesizing large sample libraries. Many scientists believe that the sheer size of a library will guarantee sufficient diversity while other groups employ sophisticated computer algorithms to maximize diversity when populating the library. Unfortunately, in most cases, these

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approaches are focusing on *chemical* diversity rather than on *pharmaceutically relevant* diversity. Many researchers now believe that more effort should be spent on populating the library with molecules that look 'drug-like' from prior experience. At the very least, resource-wasting molecules (such as chelators, intercalators and nonspecific protein binders) should be minimized in the collection. In addition, each new screen should be pretested with a small library of diverse samples. This process could give valuable information about the quality of the assay and allow it to be modified, if necessary, to minimize the chances of identifying false positives and wasting time in follow-up studies.

For each primary screening hit, thousands of assays may be conducted in the typical follow-up scheme. These expensive and time-consuming efforts include dose–response studies to quantify potencies against many related and non-related assays. While this information is very helpful, there are other parameters that are critical to making an intelligent decision, including cytotoxicity, metabolism and oral absorption indicators, as well as various physicochemical indices, such as water solubility, log P and stability. To the extent possible, these parameters should be predetermined so that the most appropriate lead molecules can be progressed rapidly through the drug development process.

While in each institution many compounds are chosen for testing in a specific library (directed screening), it is becoming increasingly common to test a large portion of the total set of libraries against many targets. Comparison of the biological and chemical information can help to guide scientists to the best hits/leads for further studies. In addition to searching for all prior pharmacological, pharmacokinetic and physicochemical information, the ideal database would allow substructure searching to assess structure–activity relationships rapidly.

Ultimate goal

In summary, significant progress has been made towards the goal of rapid drug discovery. As functional genomics and other basic research advances increase the number of important therapeutic targets, it is becoming more critical to accelerate the whole process, not just to move the bottleneck to someone else's responsibility. Remember, the goal is to rapidly find drugs to treat people, not just to identify inhibitors of molecular events.

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