A New Emphasis for Drug Discovery, Development and Combinatorial Chemistry

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Keywords:
Drug Discovery
Combinatorial Chemistry
ADMET
Natural and Synthetic Compounds

創薬
コンビナトリアル・ケミストリー
ADMET
天然化合物と合成化合物

Summary

It is well recognized that the enterprise of discovery and development of new drugs is expensive and time consuming. The estimated cost of taking a drug from discovery to market is estimated to be about USD 750 million and can take between ten and twelve years. Furthermore, during the last 10 years the annual R&D expenses for drug discovery have tripled while the number of New Chemical Entities launched has remained at the same level of 50 per year, as stated by George Milne, VP of R&D at Pfizer, during a lecture at the Drug Discovery Technologies 2001 conference.

新規医薬品の創製，開発事業にはコストと時間がかかるということは，十分認識されている。医薬品一品目の創薬から上市までにかかるコストは，約7億5,000万USドルと推定されており，期間は10~12年要している。さらに，Drug Technologies 2001 Conferenceの講演で，ファイザー社のR&D担当副社長George Milne氏は，過去10年間上市された新規化合物数は年間50品目と変化していないにもかかわらず，創薬における年間のR&Dコストは3倍になっていると報告している。

The process of discovery and to bring a drug to market is a complex maze as depicted in figure 1.

Drug discovery begins with testing compounds usually by High Throughput Screening (HTS) and ends with selection of candidates for further study and development. Statistics show that approximately 40% of the research costs are charged to the drug discovery effort as compared to 60% for drug development. A reasonable objective for the pharmaceutical and biotechnology companies should be to concentrate on reducing the costs and shortening the time of the initial step in the drug discovery process. This can only occur if more attention and money are placed in the very first step of drug discovery, which is the selection of screening compounds and/or building blocks for combinatorial libraries. Compounds and libraries for screening must be examined from a chemical point of view that encompasses more than the "Lipinski Rules of Five" listed below:

1. Molecular weights less than 500
2. Log P less than 5
3. Number of hydrogen bond donors less than 5
4. Number of hydrogen bond acceptors less than 5
5. No more than five fused rings

In recent years, a significant portion of the R&D budget has been invested in biology and biology related areas such as genomics and proteomics; and in technology platforms designed to increase the number of compounds assayed. However, some significant problems, such as development time, patent position and attrition rate in clinical trials, remain unchanged, despite these investments. Can a bigger investment in chemistry make positive contributions to drug development and in particular combinatorial chemistry?
The problems encountered with each of three areas of development time, patent position and attrition are described below.

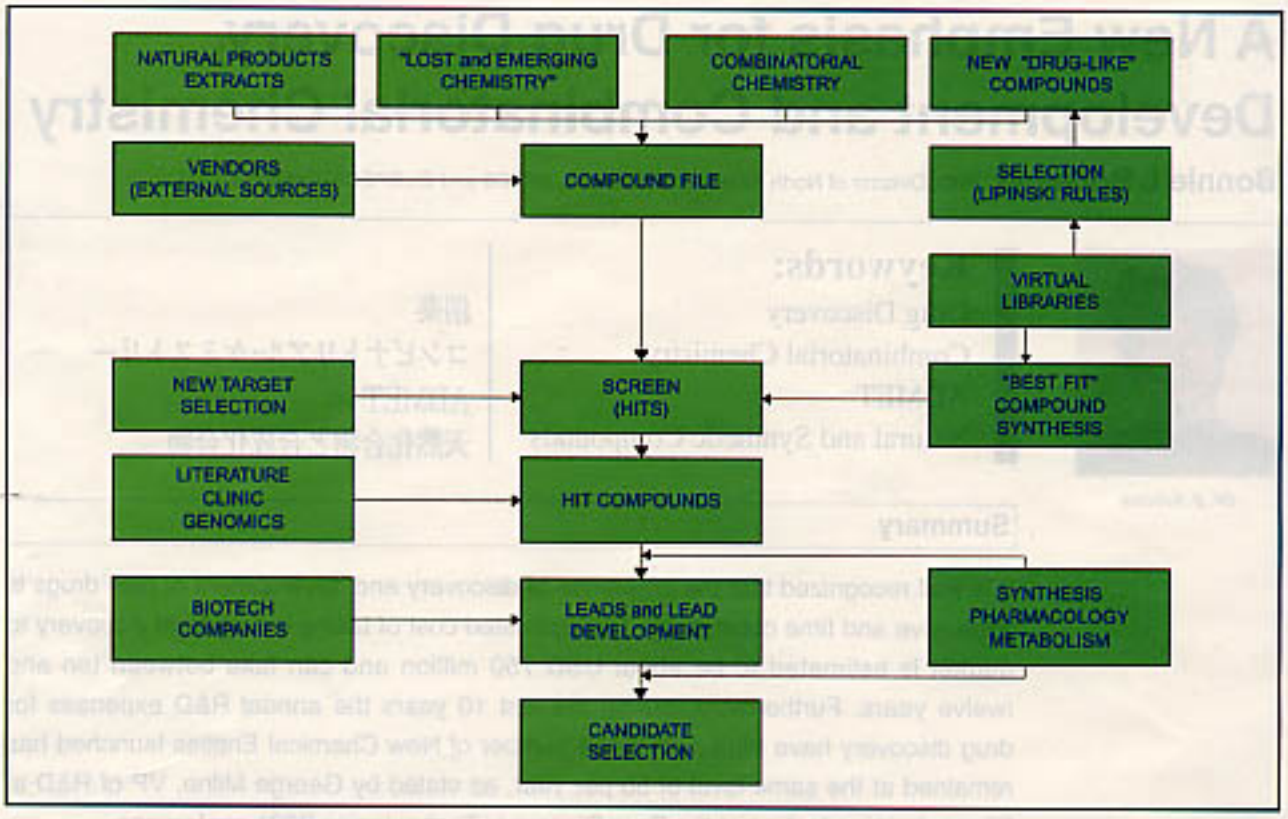

Figure 1: The Drug Discovery Process

- The development time after filing a patent and before a drug reaches the market, is still unacceptably long. This results in a limited period to cash-in from the patent protection. The faster a drug is on the market, and the longer the patent lifetime, the better the investment will be. For a billion dollar per year drug, every month of extended patent life brings an extra $80 million.

- Patent positions are often weak due to the fact that that many companies pursue the same targets and use the same or similar chemical libraries acquired from commercial vendors and/or libraries synthesized using combinatorial or parallel synthesis. This reduces the likelihood of obtaining a patent because known compounds and analogs of known compounds are all being tested.

- The attrition rate is unacceptable high, only 1 out of 12 compounds entered into clinical trials becomes a new drug.

Chemistry can assist in addressing the issues stated above. The pharmaceutical and biotechnology companies must start with better screening compounds and more unique building blocks. If pharmaceutical and biotechnology companies invest in unique areas of chemistry and study their relationship to biology, then the likelihood that companies are pursuing the same targets and the same chemistry will be reduced. Therefore, the starting points (hits) identified in the lead discovery should be as unique as possible, thus reducing the risk that a compound class already has been patented.

When selecting starting materials for combinatorial chemistry unique building blocks and chemical handles need special consideration. Making variations on the same themes over and over again will not add to the knowledge base or produce new chemical entities with characteristics to qualify for patents.

Characteristics of a good building block are:

- Molecular weights less than 350 Daltons,
- Small fused ring heterocycles,
- Interesting core structures,
- Chemical handles.

Interesting core structures include the following:

- Pyridines, diazines and triazines,
- (Iso)quinolines
- (Iso)indoles, benzofurances and benzothiophenses
- Tri-and tetrazoles, (di)thia(di)azoles
- Imidazoles and pyrazoles
- Pteridines, naphtheridines and purines
- Phthalazines, quinazolines and quinoxalines
- Acridines, phenazines and phenothiazines

Qualifying chemical handles are:

- Cargoxylic acids, aldehydes and (stable) acid chlorides
- Sulfonic acids, sulfonic amines/secondary amides
- Halogens, methyl and acyl groups
- Hydroxy-,thio-and nitro groups
- Amines and secondary amides
- Hydrazines, imines and oximes

In addition, chemistry software programs should be utilized effectively. Predictive software can assist in the following areas:

1. Selection of targeted sets of compounds of existing compound repositories using known structure activity relationships. Sophisticated programs are available that combine a number of databases to create a knowledge based system composed of chemical functional groups and a number of biological activities associated with specific compounds.
2. Selection of special sets of compounds using software that correlates chemical structures.
3. Selection of compounds using specified and well-thought-out sets of descriptors such as Lipinski parameters, PSA's, and electro(topological) descriptors.
4. Selection of compounds that display desired toxicological properties
5. Selection of "diverse" sets of compounds from large databases already possessing structural features characteristic of biologically active compounds.
6. Generation of new chemical entities with biological features.
7. Analysis of an organization's chemical repository for diversity.

Let's consider the last two points in more detail. Analysis has shown that synthetic organic chemists more often than not specialize in certain synthetic areas and often do not venture very far a field. In order to achieve more chemical diversity there are two approaches. One approach is to acquire synthetic compounds from as many global sources as possible. The second approach is to explore software programs that generate new chemical entities and scaffolds. The path of least resistance is to continue to do what has been done in the past. Under these conditions, new chemical scaffolds and new chemical entities are not as likely to be generated. This lack of diverse structural types can be demonstrated by the fact that when the three-dimensional shapes and molecular frameworks were examined for the more than 5,000 entries in the Comprehensive Medicinal Chemistry database, only about 20 scaffolds were represented. Pharmaceutical companies should consider analyzing their in-house database for diversity. Then they should consider ways to fill the holes with new chemical entities with biological features. Starting with virtual libraries and then refining the process to generate compounds with biological functionalities can help with this issue. In addition, the compounds must be able to be synthesized in a reasonable number of steps with sufficient yields.

Organic and medicinal chemists unfortunately are not as creative as nature.

This is demonstrated by a 2-dimensional plot of a Natural Product database of 2,661 compounds (see figure 2) and a synthetic products database of 2,000 compounds (figure 3). The axes are defined as the ring descriptor and heteroatom descriptor. The ring descriptor counts all possible size rings from largest to smallest in a compound. The heteroatom descriptor is all the possible ways to count between the heteratoms, from longest to shortest. The Natural Products are much more evenly dispersed throughout the space, whereas the synthetic organic compounds cluster in specific areas, mainly the bins for five and six-membered ring systems. It would be good to examine the spaces where no referenced compounds are located. However, there are limitations here. The virtual chemical world is approximately 10^{9} compounds. Another example slightly more easily comprehended is that if 1,700 different diamines were to be reacted with 26,700 halides, it would take 30,000 years to screen the products at a screening rate of 100,000 per day. This task is even more mind-boggling when we realized the number of targets now identified to assay. Therefore, an

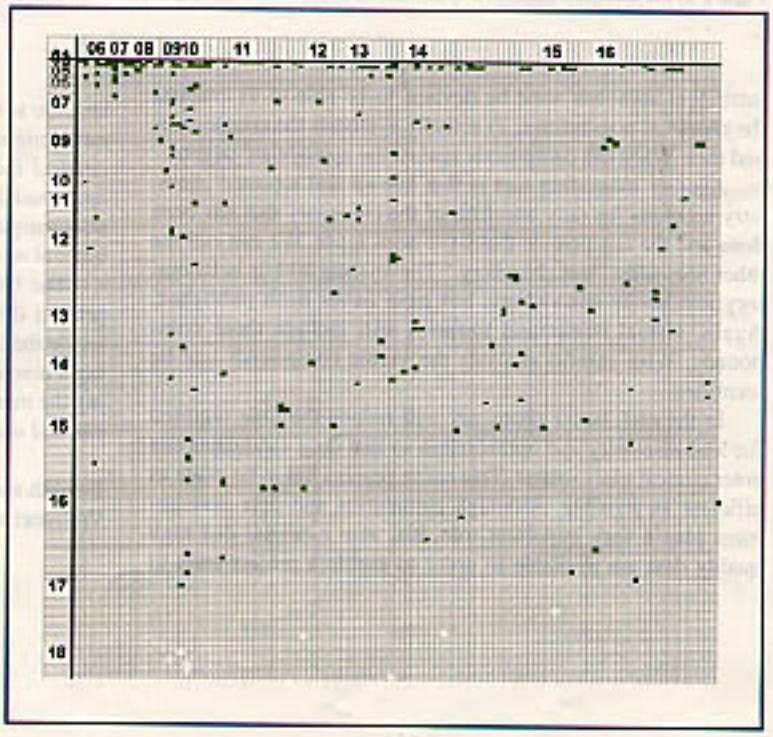

Figure 2: 2D Scaffold Space for Natural Products Database (2,661 Compounds)

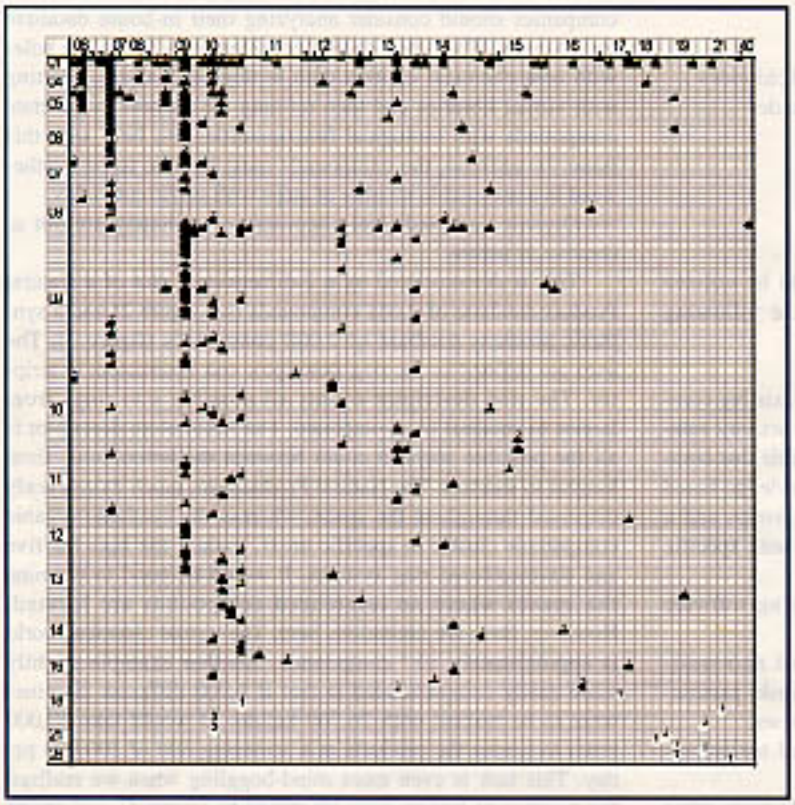

Figure 3: 2D Scaffold Space for Natural Products Database (2,000 Compounds)

intelligent approach must be devised to be able to 1) evaluate the chemical possibilities; 2) actually synthesis the compounds; and then 3) test the compounds against the appropriate targets.

Another interesting fact is that known and reported chemistry accounts for only one-fifth of the chemistry that has been done and the compounds that have been made. We can call the other four-fifths "lost chemistry." The missing 80% is in laboratory notebooks somewhere, but have never been published. Again, virtual compound libraries will include these compounds. With careful analysis the viable compounds can be identified.

In the end, better chemistry will reduce the time required for lead discovery and optimization so that drug candidates can enter clinical trials sooner. This entire process has to be made as efficient as possible. Although automation and data management play a very important role, it is also essential that high quality data are available in order to enable a project team to make sensible decisions. Drug development decisions must be made on the basis of reliable data. Also the quality of the compounds requires close scrutiny in the effort to capture and apply reliable data.

The attrition rate of one in twelve indicates that "designing" a compound with the right pharmacological profile needs much more attention. The important features to be considered are Absorption, Distribution, Metabolism, Excretion and Toxicology (ADMET); all associated with the molecular structure. A much better understanding of this structure/performance relationship is needed to develop predictive algorithms that will increase the survival rate of compounds in clinical trials. Investment in the chemistry upfront should reduce this attrition rate, thus increasing the success rate and perhaps more importantly by reducing at the same time the development costs.

Conclusion

Returning to the drug discovery process illustrated in figure 1, areas where chemists can make fundamental contributions to make drug discovery more efficient are in three main areas. The creation of virtual libraries will expand the chemists' thinking out of the box. The use of high quality predictive software will help to make better initial selections of screening compounds. The medicinal and organic synthetic chemists should more diligently investigate emerging chemistry not immediately available to the pharmaceutical industry. The role of the heterocyclic chemist is clear and crucial in these three areas. Heterocyclic chemistry is the cornerstone of the pharmaceutical industry and there is a vast amount of new chemistry to be done.

The biologists initiated a revolution in the drug discovery process during the nineties. Now it is time for the chemists to tackle the crucial issues that can be solved by chemistry, initiating a revolution by the chemists this decade. Better drugs reaching the market faster with reduced costs - that is what chemistry can and must deliver.

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