

Drug Target Research

One of the most interesting fields of study in today's medical world is prescription drug discovery; it certainly is also one of the most important. This branch of medicine has always offered a noble calling and of course, after a successful discovery, an immense feeling of satisfaction. Today, however, with the rise of technology and the invention of such fields as genomics, bioinformatics, and combinatorial chemistry, drug discovery has been able to really take off...we are witnessing an unparalleled expansion of investment in prescription drugs. Furthermore, since the new technology offers several more efficient modes of research, there is a potential to develop more drugs in less time, with less money being devoted to research.

Before Genomics

In the traditional method of drug discovery, which was used by most companies in the pharmaceutical industry until the early 1980s, an "initial lead compound was found by isolating a molecule with a certain biological activity"¹ This could occur in one of two ways: by intense scientific research (a process called "ethanobotany", or by pure chance, which was the case with the discovery of penicillin). The "lead compound" was modified based on the results of a structure-activity relationship (SAR) which was, in a sense, the predecessor of drug target analysis. An important and difficult process was that of synthesizing the compound, and then retesting it. (Even if the compound was

¹ <http://www.cr.org/publications/MSM99/html/T23.0.html>

successful, if it could not be reproduced synthetically, and it was not naturally abundant, it could not realistically be made into a drug). While this process was (obviously) eventually successful, it was painstaking and enormously expensive. The average time span from initial research to the pre-clinical phase was five to six years.²

After Genomics

With genomics and other new biomedical technologies, the way researchers worked to discover new drugs changed dramatically; drug research became more of a science than ever. With the identification of a drug target, the drug development industry, taking advantage of advances in related fields of medicine, (namely genomics) was able to focus more specifically on *where* diseases act in the body and at which stages the development of a disease could be hindered or eliminated. This changed the field dramatically in that with this new technology, a “biological target molecule is chosen before any drug discovery project is begun. The biological target is a macromolecule which is crucial for the biological activity or process which is to be inhibited”.³ So genomics, it seemed, would help researchers to virtually eliminate the guess factor and allow them to *scientifically* determine at which crucial step (in the life cycle of a disease) some interference could be introduced and hopefully, eliminate the reproductive capability of the disease.

According to a leading European drug research company, Organon, there are several challenging steps involved in drug discovery. The first step (made possible by genomics) is to “identify a biological drug target. This is typically a receptor, enzyme, or ion channel that can be manipulated to prevent the development of a disease or to

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alleviate symptoms. Organon boasts, “the advent of genomics means the number of drug targets available is on the verge of a colossal expansion”.⁴ After successfully identifying a potential drug target, the researchers conduct what is called an “assay test” to see if there are any compounds in existence that have any affect on the drug target. This is, arguably, the most difficult step in the process, and coincidentally, the one for which cutting-edge technology has not yet been developed. In this stage, scientists revert to traditional organic chemistry; however, more and more often, combinatorial chemists employing newer techniques are assisting these organic chemists. At Organon “...compounds likely to show activity on the target are synthesized... [they] are then screened to investigate their action on the assay, and potential drug candidates are identified for further research and development”.⁵ If a molecule is successfully identified, (which is to say, proven to interact in some productive way with the enzyme, ion channel, etc.) the next step is to develop a computer simulation which allows the researchers to investigate this interaction more closely and to consider the molecules’ properties.

Often there are three separate research units in a company such as Organon, which interact closely with each other. For example, the “Target Discovery” department is responsible for closely following the rapid advances in the human genome project as well as identifying “genes coding for potential drug targets of interest”.⁶ The “Lead Discovery” branch takes the research done by the scientists working on target discovery, and works to find possible “lead compounds” or potential drug candidates that have a desirable effect on the target site. Finally, the “Lead Optimization” sector works

⁴ Organon International <http://www.organon.com/innovations/discovery/index.asp> Reference Date: 12/6/02

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exclusively with the compound identified in the previous step and concentrates its efforts on producing a compound that can be used in pre-clinical trials, with the ultimate goal of producing a safe, effective drug.

The Case with Tuberculosis

In April of 2000, researchers found what they hoped would be an enormously beneficial drug target: “a mutant strain of a deadly bacterium that was produced by eliminating a single ring-like component of a molecule on the surface of *Mycobacterium tuberculosis*”.⁷ After eliminating this component, the researchers noticed that the bacterium was subsequently unable to form “braided, serpentine colonies that signify virulence”.⁸ A great deal of new research is concentrating on the creation of drugs that could cut the treatment time of tuberculosis, an affliction which affects 32% of the world’s population and causes two million deaths each year, according to Howard Hughes Medical Institute (HHMI)! Tuberculosis is a unique disease, according to William Jacobs, Jr., a researcher at HHMI, “because of its remarkable ability to persist in the body”.⁹ The aim of the drug target research is to devise a new therapy that would cut the treatment time from more than six months to just a couple of weeks. Scientists like Jacobs discovered this promising drug target by trying to find what properties of tuberculosis made it so hearty.

Other Questions and the Future of Drug Target Research

It seems that fashioning prescription drugs by finding targets to inhibit some crucial process in the development of a disease is indeed the way of the future. Some interesting proof – just last week the biopharmaceutical company “Mercury Therapeutics

⁷ <http://www.hhmi.org/news/jacobs2.html>

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Inc.” announced that it had acquired worldwide rights to an oncology-drug technology which it bought from Massachusetts General Hospital. A spokesman for Mercury said the company plans to use the technology to “develop small-molecule inhibitors to the Ras-Raf protein interaction”, which, according to Mercury, is “a completely unexploited oncology drug target”. It seems extraordinarily promising when private industry begins to become more involved and invest in new technologies such as this one. This means, of course, that there is a profit to be made, but more importantly, that lives can be saved and treatment of diseases can be revolutionized. According to Mercury’s CEO Neal Brinberg, “30 percent of all human tumors harbor mutant Ras-Raf proteins”.¹⁰ If this new drug target turns out to be something around which a treatment can be produced, it would “revolutionize the treatment of the majority of human cancers” Birnberg said.

Researchers at Stanford University recently developed a new approach that they hope will speed up the discovery of drug targets. One of the biggest hindrances in the quest to discover new drug targets was the “requirement of prior knowledge of the defective gene or protein that is being targeted”.¹¹ In the laboratory of biochemistry professor Ron Davis, researchers developed a new and improved method that allows scientists to choose a drug target without having to rely on existing literature or the prevailing medical opinion (both of which can be rare), but more importantly, without knowing much about the genes or proteins involved in the disease. According to Guri Giaever, who works in Professor Davis’ lab, “the key to the new method is the construction of strains of bakers’ yeast that have a single gene deleted”¹². Utilization of this method is much less expensive and much simpler than using genes from higher

¹⁰ <http://www.boston.bizjournals.com/boston/stories/2002/12/02/daily6.html>

¹¹ <http://www.stanford.edu/dept/news/report/news/march10/drugres310.html> - 3/10/99

¹² IBID

organisms. Also, since yeast is such a simple organism, all of its genes have been sequenced, making it a prime candidate for drug target research. Since some genes in yeast and humans are similar, researchers are optimistic that a suitable drug target found on yeast may be comparable in humans, and can be applied toward treatments for a whole range of diseases, including cancer!

It seems that in the press genomics sometimes gets a bad rap; the word invokes immediately a connotation of “science playing God”, which in the most extreme cases seems a reasonable enough position. However, in the majority of situations genomics affects, it is adding an exciting new technology and opening doors to research that before genomics was either impossible or needlessly rigorous. Genomics is revealing so many crucial parts of how we humans are put together, how we interact with the world around us, and its most important practical application: helping us to understand how disease attacks the human body and how it can be stopped. The application of genomics, bioinformatics, and combinatorial chemistry (all three recent technological wonders) should be taken advantage of to the fullest extent in finding specific targets to inhibit disease in the human body. These fields have a mind-boggling potential to increase the quality of human life.