Background: Structure of aspirin.

DESIGNER MEDICINES

Molecules of the Future

JENNY MARTIN describes how the molecular basis of disease is being studied to improve the odds of discovering new drugs.

Drugs can be natural or synthetic chemicals and are used as therapeutic agents for treating disease. Generally they comprise a small number of atoms (~100 or so) but they interact with very much larger biological molecules, usually proteins, that can consist of many thousands of atoms.

The interaction between the relatively small drug molecule and the relatively large protein changes the function of the protein, so that a specific biological effect occurs. For drugs like aspirin, the biological effect is a decrease in pain and inflammation.

Optimally, a drug would have a very selective biological effect, and would have a low incidence of side-effects.

The Drug Pipeline

How are new drugs developed? How do we go from a chemical in a test tube on a laboratory bench to a tablet in a package on the pharmacy shelves?

The process of developing a new drug is called the drug pipeline. The pipeline involves many stages, including identification of candidate drugs, testing in animals and three stages of clinical trials in humans.

The pharmaceutical company Searle has set up a Web site with a "Pipeline Game" that shows the steps involved in developing a new drug. At each stage of the pipeline, candidate drugs are rejected as they fail criteria for effectiveness or toxicity.

It is estimated that for every new drug that passes through the pipeline, 10,000 others are rejected. The time required for a chemical to enter the pipeline and emerge as an approved new drug is approximately 10–20 years and the cost is estimated at US$300–500million.

So how can we be smarter about discovering and developing new drugs? How can we reduce the costs, increase the odds and decrease the time required for chemicals to travel through the drug pipeline?

For many of the later stages in the pipeline it is not possible to radically affect the costs, odds or time, because these steps are strictly regulated by administrative bodies such as the Therapeutic Goods Administration in Australia or the Food and Drug Administration in the USA. This is reasonable because we don't want new drugs on the shelves that are not safe or effective.

But one way in which we can be smarter about developing new drugs is to focus on the early stage of drug development, the stage of drug discovery.

Discovering Candidate Drugs

Drugs that are in common use today have diverse origins. Some have found their way into the 21st century through folklore usage. An example is the discovery by William Withering, an English physician of several centuries ago, that digoxin is useful in the treatment of heart disease. Dr Withering had heard about a concoction of herbs used to treat a condition known as dropsy. He obtained the recipe and identified the active component as foxglove or digitalis. The pure form of the active component, digoxin, is still used today to treat heart conditions.

Another way of finding new drugs is by serendipity, a chance observation meeting a prepared mind. Early in the 20th century, Dr Alexander Fleming in the UK found that a bacterial plate in his laboratory was contaminated with a fungus. Rather than throwing the plate out, he noticed that the bacteria did not grow near the fungus; there was a zone of exclusion around the fungus. Fleming reasoned that the fungus was probably producing a chemical that inhibited the growth of the bacteria. Together with Howard Florey, an Australian scientist working at Oxford University, the chemical was isolated and developed as a drug. This new drug, penicillin, revolutionised the treatment of bacterial infections.

A third way of identifying candidate drugs is to screen thousands of compounds until one is found that has the desired activity. The chances of finding a new drug in this way are about one in 10,000, something like finding a needle in a haystack. Yet there are many drugs that have been identified in this way.

While all these methods are valid and have been used successfully in the past for discovering new drugs, there are newer and smarter means of coming up with candidate drugs that are less risky.

Structure-Based Drug Design

One of these methods is called structure-based drug design. This method identifies new drugs by using knowledge about

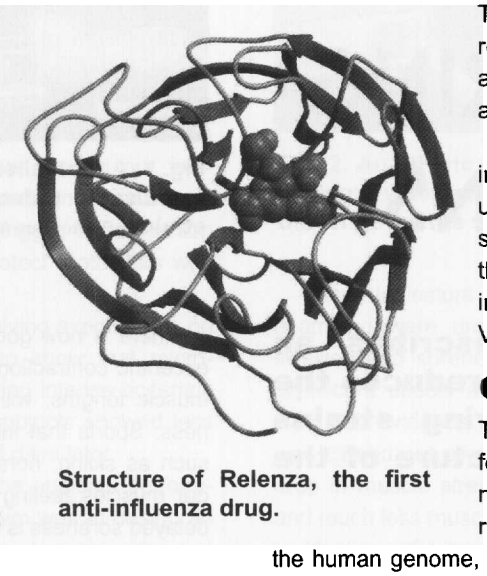
the molecular basis of disease. The odds of finding new drugs by this method are much improved: about one in 300.

So if structure-based design is so much better, why don't we use this method all the time? The reason is that this method requires a lot of background information. We need to know a lot about the biology of the disease, including the identification of the rogue protein that is causing the disease. Once the culprit is identified, we also need to know what it looks like; that is, its three-dimensional structure. Armed with this very detailed information it is possible to identify the weak spot in the disease-causing protein, and then to design a specific chemical to attack the weak spot.

The bad news is that currently this technique is limited to a very few diseases because we only have 3-D structures for a small number of disease-causing proteins.

However, in a decade or so this will no longer be a problem. Genomic information will help us to identify proteins that cause disease, and their 3-D structures will subsequently be determined.

Although only a few diseases can be targeted by this technique at present, some drugs are already appearing on the pharmacists' shelves that owe their origins to structure-based drug design.



Structure of Relenza, the first anti-influenza drug.

Relenza: The First Anti-Influenza Drug

Relenza is an Australian-designed drug that combats the influenza virus. In July 1999 it was approved for use in the treatment of influenza-infected humans. Prior to this, the only treatment was palliative or preventative vaccination.

The research that led to the development of Relenza was a collaboration between the groups of Peter Colman (CSIRO, Melbourne), Mark von Itzstein (Victorian College of Pharmacy, Monash University) and Graeme Laver (Australian National University). A key enzyme in the influenza virus lifecycle, neuraminidase, was identified and characterised, its three-dimensional structure solved and an inhibitor designed to match a critical site on the enzyme structure (Fig. 1).

If Relenza is taken within the first 2 days of influenza symptoms, the duration of the illness is decreased on average by 1.5 days and the severity of the symptoms is decreased for the remainder of the illness.

Improving Arthritis Treatment

Celebrex is a new treatment for arthritis. Its discovery was based on improved knowledge of the biology of arthritis and inflammation.

It was found that the anti-inflammatory effects of aspirin and other non-steroidal anti-inflammatories are due to the inhibition of an enzyme called cyclooxygenase (or COX). However, these older drugs have a number of side-effects because they do not discriminate between two related proteins, COX-1 and COX-2.

COX-1 is a housekeeping enzyme, while COX-2 is inducible and causes the inflammation of arthritis. It is COX-2 that is the real target for anti-inflammatory drugs.

The three-dimensional structures of both COX-1 and COX-2 have been solved, and inhibitors selective for COX-2 were designed on the basis of these structures. These drugs are expected to have reduced side-effects compared with aspirin and the older non-steroidal anti-inflammatories.

The first of these COX-2 selective inhibitors, Celebrex, was approved for use in 1999 and was the most prescribed drug treatment for arthritis in that year. Another COX-2-selective inhibitor due for release this year is Vioxx.

Conclusion

There are tremendous opportunities for drug discovery research over the next decade. First, the biotechnology revolution, particularly the decoding of the human genome, will have an immense impact on our ability to understand disease biology and to identify biological molecules to be targeted for therapeutic intervention.

Second, high-throughput structural biology techniques, using mega-research facilities called synchrotrons, will allow us to build up dossiers of three-dimensional structures of disease-causing proteins so that we can visualise the culprits.

Third, modern structure-based drug design methods provide us with the tools to design better drugs and to combat diseases that are currently untreatable.

Together, these technologies of genomics, structural biology and medicinal chemistry herald a new era in drug discovery: the designer medicine era of smarter, safer and better medicines. There is no doubt that these developments will have an enormous impact on the health and economy of nations that invest in basic biomedical research and that support venture capital investment in the outcomes of this research.

The question is, will this include Australia?

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