Drugs and drug development: Making a drug

Developing a novel drug

Drug development is a long and expensive process

A drug can be developed in a whole host of different ways. Constant improvement in technology has transformed drug design over the past few decades. Now, many laboratories in both universities and pharmaceutical companies make use of computers, robotics and artificial intelligence to aid in drug design. These techniques coupled with more traditional methods are becoming increasingly successful in designing novel drugs.

One commonality between all the methods of drug design is that they are fraught with challenges. A pharmaceutical company may start with thousands of chemical compounds as potential drug candidates. Rigorous testing will whittle this down to a single chemical compound that can then be licensed to treat patients. Developing drugs is a risky and expensive business, but the potential profits are huge.

The following step-by-step process provides a guide to how a compound in the laboratory becomes a disease-fighting drug. Option 1 explains the process of transforming initial research in a university lab (or biotechnology company) into a potential drug – about a quarter of drugs approved by the FDA between 1998 and 2007 began in this way. The remaining three-quarters began in pharmaceutical companies, as explained in option 2.

STEP 1 – OPTION 1: Origins in the research lab

In universities and research institutes all over the globe, many scientists dedicate their lives to understanding the molecular details of disease – how disease works. By using animal models, usually mice, they are able to identify specific biochemical pathways that are altered by the disease.

A small team of scientists will study a pathway and identify a potential therapeutic target, usually a protein. To effectively target this protein, they require a detailed 3D structure, often determined by a method known as crystallography, which records the pattern of X-ray scattering by atoms when a compound is exposed to a beam of X-rays. This field, known as structural biology, allows us to analyse the complex structure of the molecule and find areas that a drug could target. Their findings will be published in scientific literature.

By using the detailed structure, the scientists can use computational techniques to predict how a chemical compound might bind to the target protein. Computational techniques are cheaper than high-throughput screening – testing real interactions between large numbers of compounds and targets – but still allow the scientists to test a range of different compound structures. However, computational techniques are not without fault. The technology still lacks the ability to predict perfectly how a compound will bind. Chemical experiments called assays can confirm binding *in vitro* and structural biology can show how well a compound binds to the target.

This initial drug structure is then ready to be fine-tuned into a final structure – but this requires money and resources that the scientists probably do not have.

At this stage, the scientists may decide to set up a ‘spin-out’ company. To do this, the researchers would often have to leave their normal jobs to work in a commercial environment. They would then work solely on developing a drug to target the protein. They would also be required to seek investment from venture capitalists, investors who put money into high-risk projects, to fund their company.

Alternatively, the scientists could remain at their jobs and team up with a small biotech firm. At this point, it is too early for pharmaceutical companies to be interested. The biotech firm will apply for ‘seed’ funding to provide the money required for the scientists to test their agent further.

Whether they set up a spin-out company or team up with a biotech firm, the process of fine-tuning will be similar. They will use a combination of computational techniques, assays and structural biology to determine how the compound is binding. They will then change small aspects of the compound so it will act

more efficiently on the target protein. At the end of all of this they will have a final structure, but there is still a very small chance that this agent will make it to market.

The biotech firm or spin-off company has gone as far as they can go. They require the monetary resources for expensive research and clinical trials that a pharmaceutical company can provide. They therefore often decide to enter a partnership with a large pharmaceutical company.

STEP 1 – OPTION 2: Origins in pharma

Pharmaceutical companies also employ large teams of scientists to carry out research of their own, similar to that of the work done in universities or research institutes. However, their work often focuses directly on potential therapeutic targets from the outset. This differs from research lab work, which might at first just aim to better understand a disease.

Importantly, pharma has access to far more resources, allowing them to carry out much larger studies. They often use automated high-throughput screening (HTS) to identify initial potential compounds. This involves testing a vast number of different compounds' abilities to bind the target protein. Today's most advanced HTS technology platforms use fully articulated robot arms to carry out tens of thousands of tiny experiments and can cost upwards of $1 million (£0.8 million). Once candidate drug compounds have been identified, the company will carry out further tests to reduce this library to a single compound.

Pharmaceutical companies are also beginning to use artificial intelligence, or machine learning, to aid drug discovery. This means they use powerful computer programs to make sense of large amounts of data. Being able to rapidly analyse data from multiple sources (including research papers and clinical trials) could give companies new ideas about the kinds of molecules they screen for certain conditions and help narrow down the search faster. Pharmaceutical company Pfizer is already using this method to look for potential cancer drugs.

STEP 2: Toxicity and animal testing

The pharmaceutical company can run many tests to find out how the agent might behave in the body, initially checking in animal studies for signs of toxicity and characterising further effects on the target. The company's scientists will assess how the agent is metabolised, how long it stays in the animal and where it goes.

Often, compounds that seem to work very well in the lab, behave very differently when they are transferred to live animals. There may be problems associated with delivering the compound to the right tissues or in getting it to bind specifically to its molecular targets and only those targets.

After more chemical refinement, the agent will finally be ready to be tested in people.

STEP 3: Trials and tribulations

Once the agent has passed its toxicity tests and animal models have confirmed that it should tackle the disease in people, phase I clinical trials can begin. A small number of usually healthy volunteers receive the drug in low doses. Volunteers could also be very ill patients who have not responded to other treatments. The volunteers are monitored carefully for any ill effects. If the drug proves to be safe at this stage, it can advance to phase II trials.

Phase II trials involve a small group of patients – up to a few hundred. These trials ensure that the drug is safe for people with the disease to take and that it does have beneficial effects. Any drug that fails here will be an expensive loss. After phase II, around a third of drugs move on to phase III trials. Phase III trials test the drug in larger numbers of patients, potentially thousands, and confirm the beneficial effects. The greater the number of patients used in phase III, the more accurate the results of the study will be. Ideally, phase III trials involve comparing the drug's effects to a placebo or standard treatment and are double-blinded, meaning that neither the person administering the drug, nor the person receiving it, know whether the drug or a placebo is being given.

STEP 4: Convince the regulator and then the doctors

Once a drug has progressed successfully through the first three stages of clinical testing, the company can apply for regulatory approval. Approval may take up to a year, or longer. All of the data collected during the

research and clinical trials is submitted to the licensing body. In the UK, this is the Medicines and Healthcare Products Regulatory Agency, although most novel drugs currently come to market via a centralised EU process under the European Medicine Agency. In the US, it is the Food and Drug Administration. The licensing body may request more research in response to any concerns they might have – for example, if there is an indication of any potentially harmful side-effects – before issuing a license.

If the drug finally gains a license, the pharmaceutical company must then convince health providers that it is worth making available to their patients. Central to this process in the UK is the National Institute for Health and Clinical Excellence (NICE). They will decide whether the drug offers good value for money; without their seal of approval, the drug will never make it to patients.

After NICE's approval, the pharmaceutical company can begin marketing the drug to doctors. Unlike in the US, pharma are not allowed to market directly to patients in the UK. Convincing doctors to prescribe the drug is the final step in the process. It may still take years for the drug to reach every patient.

Clinical trials also continue post-approval and marketing as new drugs become available to more people. As in phase III testing, the gold standard is a randomised controlled trial (RCT), which compares the drug's safety and effectiveness in two groups of patients – one taking the drug and another taking a placebo or receiving standard treatment. In RCTs, patients are randomly assigned to one of these groups. Many different RCTs may be carried out over many years and in different types of patients and settings, to continue establishing the safety and efficacy. Periodic reviews of collections of these trials may eventually bring to light issues that were not raised during the pre-approval process.

Priming the pipeline

New methods are being used to speed up the time it takes to for a new drug to reach the market

The drugs that a company has in development are known as its pipeline. Ideally, a company wants to have a good flow of drugs through its pipeline, launching new products as old ones lose their patent protection. Since the 1990s, this flow has become a trickle across the industry. Many new approaches are being adopted to replenish the pipeline with high-quality drug candidates and get more drugs to market more rapidly.

The study of genomes, or genomics, has become crucial in drug development. Sequencing technologies that were once prohibitively expensive and took years to produce results are now more widely accessible, allowing whole genomes to be sequenced at a fraction of the cost. This has allowed researchers to more rapidly identify genes involved in disease processes and the proteins they produce. Cancer treatment, for example, has benefited from a deeper understanding of the disease's genetic components.

As for the agents that might act on potential targets, high-throughput screening (HTS) can accelerate the search for chemical entities with a possible biological effect. Automated techniques can now rapidly assess tens of thousands of compounds built from combinatorial chemistry building blocks, and the most promising can be selected for more specific analysis. It is also possible to gather more data from each screen, by looking for changes in the activities of thousands of genes (transcriptomics), proteins (proteomics) or metabolites (metabolomics). One approach, high-content screening, uses automated high-throughput microscopy to record the effects of compounds on living cells. As well as robotic handling of samples, image analysis is also automated.

New assays have been developed, using stem cells and genome-editing technologies. Using the CRISPR-Cas technique, for example, it is possible to rapidly and precisely edit DNA to turn specific genes on or off, in order to determine which genes and proteins are involved in a certain disease. The technique can also be used to create better animal models for human diseases, so that researchers can get a more accurate idea of how the drug candidates they are testing might fare in clinical trials later on.

Meanwhile, big pharmaceutical companies are increasingly pairing up with small biotechnology companies and academic researchers early on in the discovery process, helping to increase the likelihood that research breakthroughs will lead to marketable drugs.

Although these techniques have greatly increased the numbers of targets and potential drug compounds, all the other time-consuming stages of drug development are still necessary for candidate drugs.

At all stages, drugs will fall by the wayside. But a lot of work will have gone into characterising a compound, and it would be better to rescue a partly developed drug than to start again from scratch. One approach is to take drugs that were developed for one disease and screen them for effects in another – so-called 'off-target' effects. Several drugs, including Viagra and the anti-HIV drug zidovudine, were developed for one use but repurposed. This is one of the approaches that drug developers in the area of neuropsychiatric disorders are now considering to refill the pipeline, in the hope of providing new treatments for diseases like Alzheimer's and Parkinson's.

Further reading

How CRISPR is transforming drug discovery

https://www.nature.com/articles/d41586-018-02477-1

Does serendipity play an important role in drug discovery?

Drug development is hard work but a little bit of luck never goes amiss

During the 1950s, many new drugs were developed for treating bacterial infections. Iproniazid was developed to target *Mycobacterium tuberculosis*, the agent that causes tuberculosis (TB). Strangely, after taking it, tuberculosis patients sometimes became unusually happy. Iproniazid turned out to inhibit an enzyme, now known as monoamine oxidase, which breaks down serotonin and other neurotransmitters. This led to the monoamine oxidase inhibitors class of antidepressants.

In the first half of the 20th century, valproic acid was a common solvent used by the pharmaceutical industry. Then, in 1963, French researcher George Carraz made a discovery whilst carrying out screens for anticonvulsant properties on a range of compounds. He had dissolved all his compounds in valproic acid – and it turned out they all had anticonvulsant properties. Valproic acid was subsequently developed for treating seizures and epilepsy and is still used today.

The cancer treatment cisplatin was discovered when researchers began studying the effects of electric currents on the growth of bacteria. The bacteria grew to great sizes but never divided. Further studies revealed that it was not the electric field having an effect but the action of ammonium and chloride ions on the platinum electrode, forming cisplatin.

Dedicated staff at the German pharmaceutical company Sandoz were instrumental in the discovery of cyclosporin, which is used to help prevent organ rejection. Staff were encouraged to collect soil samples when on holidays or trips, as part of the search for new antimicrobial agents. An unusual fungus discovered this way, *Tolypocladium inflatum*, produced interesting chemicals, but none looked suitable for further development; however, extracts were later sent for a general screening programme and turned out to be very good at suppressing the immune system.

The blood thinner warfarin famously began life as a rat poison. Its use as a blood thinner originated in a failed suicide attempt made by a US army cadet.

The use of lithium as a treatment for depression arose from a study of uric acid metabolism. A water-soluble salt, lithium urate, was used, and it was the lithium rather than the urate that actually had medical benefits.

Many scientists do not like the idea that luck plays a role in making new discoveries. Drug development is a rational, scientific endeavour and it takes many years of hard work and dedication to produce a successful drug. So, even when luck seems to provide a lead, it still takes insight and experience to spot a good opportunity and a great deal of work to take advantage of it. As Louis Pasteur put it: "Fortune favours the prepared mind."

Drug delivery

It can sometimes be challenging to develop ways to administer drugs

In parallel with research on the medical properties of a potential drug, a company has to ensure it can be given to a patient in a suitable form.

In addition to an active ingredient, all drugs contain other compounds that contribute to their stable delivery. Part of the drug testing process is to ensure that these compounds do not adversely affect the drug in the body.

Pills also include inactive ingredients – on average about nine, but up to 35, according to a Harvard University study published in 2019. Its other constituents bind the ingredients together, mask a bitter taste or help the drug be absorbed by the body. The composition of the pill is usually finalised by the time phase III trials are run.

Other possible routes of administration include suspensions, nasal sprays (e.g. albuterol for asthma), patches and rectal suppositories. The latter might be used for local effects (e.g. haemorrhoid treatment) or because patients are having convulsions or vomiting. In a 2019 study, scientists even tried pumping a potential treatment for Parkinson's disease directly into trial participants' brains using tiny tubes. Although the results were not clear cut, the method itself could be tested for other neurodegenerative conditions that depend on targeting structures within the brain.

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The risk of inactive ingredients in everyday drugs

https://www.health.harvard.edu/staying-healthy/the-risk-of-inactive-ingredients-in-everyday-drugs

Parkinson's drug pumped directly into brain fails to pass key tests

https://www.newscientist.com/article/2194999-parkinsons-drug-pumped-directly-into-brain-fails-to-pass-key-tests/

Bioproduction

Some researchers are looking to biology to make drugs

Most drug production is based on chemical synthesis. But some drugs are produced through biological routes – such as erythropoietin (EPO), which is made by genetically modified mammalian cells grown in culture. Inserting genes in animals or plants to produce drugs has coined the term 'pharming'.

Proteins are large, chemically complex molecules that would not be easy to make synthetically. But nature has been making them for millions of years, by interpreting the information stored in DNA.

It was originally hoped that genetically engineered bacteria might be able to produce therapeutically useful proteins. Unfortunately, it is hard to get mammalian proteins folded properly in bacteria, and they cannot add the multitude of sugars that many proteins have attached to them to form glycoproteins. Yeast cells and cultured mammalian cells have been used instead.

The antimalarial drug artemisinin is now made in yeast. Previously, it could only be produced by extraction from the sweet wormwood plant. Researchers successfully re-engineered yeast with sweet wormwood genes to create an altered yeast that produces artemisinic acid, which is relatively easy to convert into artemisinin. This semi-synthetic antimalarial is now in the process of being produced on a large scale.

A neat biological solution to making drugs would be to engineer animals so they produced medicines in their milk. This could be extracted easily, and the animal could go on making the medicine throughout its life. There are very few successful examples, however. Atryn – antithrombin, a protein that inhibits blood clotting – is produced in genetically modified goats. The European Medicines Agency approved the product in 2006 to treat patients with antithrombin deficiency. Meanwhile, milk from transgenic rabbits is used for producing conestat alfa, to treat people with inherited angioedema – a skin-swelling condition – and more

recently, transgenic chickens were approved to produce sebelipase alfa, a hereditary disease of fat accumulation, in their eggs.

Companies are also exploring the use of genetically modified plants to produce therapeutic proteins. Of particular interest are plants that can be grown within bioreactors rather than expansive fields. Several vaccines are currently being grown experimentally in plants – most notably, perhaps, tobacco plants that produce polio vaccine hit headlines in 2017. However, as yet, no commercial vaccines are ‘pharmed’ in plants.

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Approaches and recent developments for the commercial production of semi-synthetic artemisinin

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FDA approves second transgenic milk drug

https://www.nature.com/articles/nrd4426

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https://www.nature.com/news/us-government-approves-transgenic-chicken-1.18985