Drug development: what drugs do

What are drugs made from?

Most drugs are small organic chemicals

Many drugs are small molecules that bind to specific structures in or on our cells. Our cells have numerous specialist functions, regulated by instructions from our genes. The drug molecules alter these processes, subtly changing cell biochemistry.

In ancient cultures, natural products such as herbs, tree bark and minerals were used as drugs. Many of these would have contained small molecules that acted on cells in similar ways to modern drugs. During the European Renaissance, apothecaries experimented with plants retrieved from the Americas by explorers, including the bark of the 'quina-quina' (cinchona) tree. The Peruvians were using it to treat malaria. As it turned out, the bark contained the active ingredient quinine, still used today to treat malaria, in some parts of the world.

Even when an active ingredient had been identified, doctors rarely knew how it actually worked. A profound change came when researchers began to use an understanding of the molecular basis of human physiology to develop new drugs – so-called rational drug design.

Sir James Black was behind two major drug families: beta-blockers, to treat coronary heart disease, and drugs that block histamine receptors, which are used to treat stomach ulcers. He introduced a new way of thinking to drug development. Black's approach involved understanding how cells use messenger molecules to communicate with each other. By adapting these natural processes, he was able to develop analogues that bound to the same targets but stopped them working.

Is small better?

Drug companies have preferred to create drugs from small molecules. This should make them easy to synthesise, modify and characterise, as well as more likely to reach their targets in the body. They can generally be given in pill form. A small, stable molecule is easier to quality assure, and scaling up to full production is more straightforward.

However, large molecules have their uses too. Antibodies and other proteins are increasingly used, mimicking molecules produced in body. The first 'biologic' drug was the humanized insulin produced in 1982 to treat diabetics. Proposed advantages of biologics are that they are more specifically targeted and less toxic.

Monoclonal antibodies

Monoclonal antibodies are being used to treat a host of different diseases

A crucial part of drug development is getting a therapeutic agent binding specifically to its target. But, as usual, nature is several steps ahead of us, and has already created highly targeted molecules: antibodies.

Monoclonal antibodies – in effect, cloned antibodies all recognising the same structure – are now entering the clinic in increasing numbers. Many monoclonal antibody therapies have been developed for cancers, as cancer cells have distinctive structures on their surfaces that can be specifically recognised by an antibody. If a toxin is attached to the antibody, it can be delivered directly to a tumour.

Other monoclonal antibodies are similar to small-chemical drugs, in that they target receptors or ligands, blocking biochemical signalling. Trastuzumab (Herceptin), for example, targets 'HER-2 positive' breast cancer cells, which carry high levels of HER2 receptors. Patients can be tested for the presence of HER2, to determine whether trastuzumab might be a beneficial treatment for them. Infliximab (Remicade) and adalimumab (Humira) block a molecule that promotes inflammation (tumour necrosis factor-α, or TNF-α) and are used to treat rheumatoid arthritis, Crohn's disease and ulcerative colitis.

How do drugs work?

What do pharmaceuticals do to the targets of disease?

Drugs interfere with our biochemistry. Usually, they stop something happening (inhibitors); sometimes they kick a biochemical process into life (activators).

The molecule that a drug acts on is its target. Targets need to be accessible, so they are commonly molecules on the surface of cells, such as receptors for signalling molecules. Binding of the drug prevents it being activated by its natural ligand.

Drugs may also bind to ion channels (pores in the cell membrane that traffic ions into or out of the cell) or target molecules that transmit signals between cells.

The magic bullet?

Ever since Paul Ehrlich proposed the idea of a 'magic bullet', drug development has sought compounds with the ability to hit their targets and nothing else. Such cleanly acting drugs would be highly specific, binding only a single type of receptor or channel, meaning fewer unexpected side-effects. Drugs that bind multiple different receptors or channels have traditionally been considered undesirable therapeutically, but there are indications that less selective compounds might also be useful.

Part of the rationale comes from studies of antipsychotic drugs. Early anti-psychotic drugs targeted dopamine receptors in the brain non-specifically, resulting in them hitting targets all over the central nervous system and causing a raft of side effects including dyskinesia (unwanted movements), tremors and rigidity. Now it is known which receptors antipsychotics recognise, they have been refined chemically to try to reduce side-effects. However, it has become clear that too narrow a focus on specific targets can be a bad thing – antipsychotics that target single receptors are of very limited use. Current thinking is that drugs should act on multiple targets to maximise effectiveness, which means designing molecules with structures that can recognise multiple targets.

Drugs of the future

The future may bring alternatives to the treatments we know today

Small-chemical drugs are the principal pharmaceutical tools for current medicine, although monoclonal antibodies and proteins are having an increasing impact.

Other approaches are also in development:

Gene therapy

In the 1980s, there were high hopes that gene therapy would open up a wealth of new treatments, particularly for inherited conditions. The idea behind gene therapy is that a gene is delivered into cells and begins to make a therapeutic protein; for example, people with cystic fibrosis, who lack a working version of a protein known as CFTR, would receive a copy of the CFTR gene.

Whilst gene therapies have not quite reached the heights that some imagined just yet, massive progress has been made. In 2012, Glybera, a treatment for a very rare form of hereditary pancreatitis became the first gene therapy treatment to be recommended by the European Medicines Agency. It allowed cells to produce a missing enzyme for digesting fats. Unfortunately, it was withdrawn in 2017 due to low patient demand and soaring costs. However, there are now hundreds of ongoing gene therapy trials in the US alone and a slowly increasing number of approvals by the Food and Drug Administration (FDA). In 2017, it approved Kymriah and Yescarta, gene therapies for leukaemia, as well as Luxturna, to treat a form of inherited blindness.

RNAi

RNA interference (RNAi), which gained a Nobel Prize in Physiology or Medicine for its discoverers in 2006, is starting to see its first successes. RNAi is used to eliminate (or 'knock down') specific proteins from a

cell, such as those causing a disease. It is based on an unusual phenomenon: short double-stranded RNA molecules triggering highly specific destruction of messenger RNA molecules containing the same RNA sequence. Its normal role is probably to protect against viruses invading the cell.

The medical possibilities are very broad. Examples include knocking down the receptor for a virus, or an overactive protein causing cancer or messenger molecules promoting inflammation.

As in gene therapy, it is difficult to deliver the RNA and there are worries that other, useful proteins might be eliminated. However, in 2018, the first RNAi therapy, Onpattro (patisiran), was approved by the FDA for treatment of a genetic disease called hereditary transthyretin amyloidosis, which causes toxic proteins to build up in the heart and nervous system. Patisiran targets the proteins for destruction by double-stranded DNA.

In March 2019, it was reported that a second RNAi drug was entering the approval phase with the same company, Alnylam. The new drug, givosiran would be used to treat acute hepatic porphyria, an inherited disease affecting the body's production of heme, the iron-containing protein in blood.

Nanotechnology

Nanotechnologies involve the engineering of nanoscale systems – those at the same scale as biological molecules themselves. Nanotechnology-based solutions are being tested for a variety of conditions.

Some applications depend on the unusual properties of materials at the nanoscale. Silver has been used since the 19th century in antibacterial applications and silver sulfadiazine treatment of burns began in the 1970s. However, silver nanoparticles are now being used in wound dressings to prevent infection. The nanosized particles provide a greater surface area and make better contact with bacteria cells, which they are able to enter and destroy from the inside.

Gold nanoparticles, meanwhile, have been used medicinally for centuries in the form of colloidal gold – nanoparticles in a fluid – to treat diseases such as syphilis, but with no knowledge of its mechanisms. Today, researchers are using nanoscale gold to generate heat inside cancer cells, in order to destroy tumours.

Targeting is and will be crucial for many new applications. Antibodies and other proteins can be used to target a toxin-linked nanoparticle to a cancer cell, for example. The targeting molecules bind to specific cell surface receptors that mark out diseased cells, enabling the drugs to bypass healthy cells.

Nanoparticles are also being explored as molecular scaffolds for tissue repair. Some potential applications combine a physical support role for nanomaterials with bioactive molecules attached to a nanoscale scaffold. This approach could be used to encourage tissue regrowth after damage. Gold nanoparticles, for example, have shown good biocompatibility as candidates for bone tissue regeneration in the test tube.

Nanotechnologies also show promise in diagnostics, for example, through 'lab-on-a-chip' technologies, or the detection of very low concentrations of key molecules involved in disease, and medical imaging. Another exciting possibility is to link detection to treatment, so a diagnostic device automatically delivers the required medication. In animal studies, nanoparticles have been used both to detect blood glucose levels and to release insulin.

Nanotechnologies could have a profound impact on healthcare. However, they also raise challenging regulatory issues. If the properties of nanomaterials differ fundamentally from their everyday counterparts, can they be considered the same substance? There are concerns about the possible environmental impact of engineered nanomaterials, as they are shed into water systems and soil, and are easily taken up by cells. Some nanoparticles have been shown to have negative impacts on wildlife, but because the range of different materials is so broad, it is difficult to come to any conclusions about these materials as a whole.

Living medicine

How leeches, worms and maggots help cure disease

As well as chemically produced agents, researchers are looking at living organisms for their medicinal benefits. In doing so, they are reviving a long and colourful medical history.

Leeches may not be everyone's cup of tea, but they produce a very useful anti-blood-clotting agent (hirudin) and are very effective at draining blood. They are used clinically in microsurgery, helping to improve blood flow when digits are reattached.

Maggots may be similarly repellent to most, but they have long been medicinally useful. In World War I, wounds infested with maggots kept bacterial infections in check –surgeon William Baer noticed they healed faster than uninfested wounds and proved less fatal. Experiments have been carried out with maggots to clean wounds; they seem to secrete enzymes that break down bacteria and dead cells, and they have been shown to be just as effective as the traditional method of clearing out wounds with a scalpel. Greenbottle larvae are also commercially available for use in medicine. The main obstacle to their wider use is patient (and doctor) squeamishness.

An area of growing interest is the use of parasites or their secretions or eggs to manipulate the immune response. There is a school of thought that the current high incidence of asthma, inflammation and allergy in the West is due to a lower parasite burden. In parts of the world where parasites are common, asthma is rare. One 2017 study by UK researchers found that roundworms, which live in the human gut, produce a protein that dampens allergic responses. They hope this knowledge could be used to develop a treatment for asthma.

Much effort is being put into identifying the active substances produced by parasites, so that they can be given medicinally without a patient having to be infected with the real thing.