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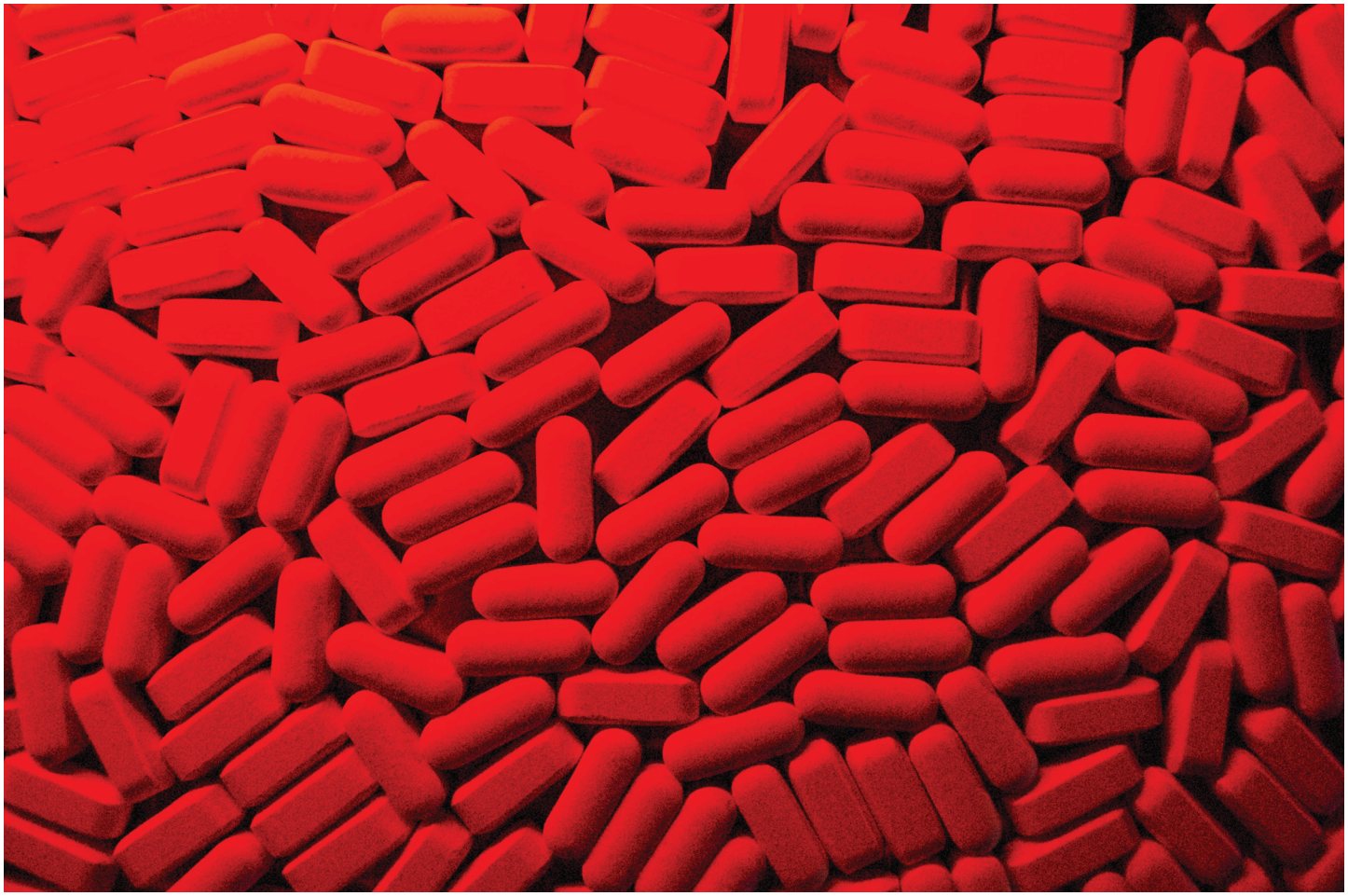
Drug development process: combating pain



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This free course is an adapted extract from the Open University course S827 *Concept to clinic*: www3.open.ac.uk/study/undergraduate/course/a332.htm.

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Intellectual property

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Introduction

Drug discovery, from concept to clinic, is a complex and expensive process involving the work of an escalating number of people and resources over many years. A major component of this cost has been the attrition rate of medicines that reach the development stage but then fail as the result of adverse toxicity or only limited effectiveness against the target disease. In recent years much greater attention has been paid to addressing the problems of attrition at an earlier stage in the discovery process and moving the focus of research away from a strategy based purely on potency against the isolated target protein. It begins with practical, multidisciplinary, laboratory work leading to the identification of candidate molecules that are evaluated in large multinational clinical trials. The escalating costs are mirrored by the increasing demand for supply of the compound as development work proceeds. Typically, a hit is identified from a few milligrams of compound; preliminary pharmacokinetic and efficacy determination will typically require hundreds of milligrams to grams of material, escalating to perhaps kilograms for preclinical safety and pharmacy evaluation. By the time human trials are initiated, tens to hundreds of kilograms are often necessary; production may entail quantities measured in tonnes.

This OpenLearn course is an adapted extract from the Open University course : S827 *Concept to clinic*.

Learning Outcomes

After studying this course, you should be able to:

- appreciate the intrinsic difficulties associated with developing a drug molecule from conception into a medicine suitable for clinical use
- appreciate how molecular modelling can be used in the drug discovery process
- understand the historical background to pain control
- understand that opioids, steroids and NSAIDs all work at the molecular level
- appreciate that anti-inflammation drug discovery requires a detailed understanding of the biochemical processes that constitute the inflammatory response.

1 Drug discovery process

Contemporary lead discovery is usually driven by high-throughput screening of large numbers (millions) of compounds in corporate collections, although this has its problems in the identification of viable leads. Corporate collections are notorious for their tendency to be populated by larger, more lipophilic molecules, which, whilst being a good means of generating active compounds, do not necessarily give the best leads. There is a trend for more focused screening (as compound-handling methods improve) to complement the mass-screening campaigns and also for the high concentration screening of smaller 'fragment' molecules using a range of biophysical techniques. Since the decoding of the human genome, it has also been possible to correlate disease states with previously unidentified gene products (proteins) and to devise potential ligands using computerised modelling.

The goal of all of this is to produce smaller, leaner (i.e. less lipophilic) leads. A 'hit' molecule would be described as a molecule or closely-related series of molecules, which has demonstrable desirable activity in a particular primary screen. The term 'lead' would describe the best of a series of molecules, with established Structure–Activity Relationships (SARs) and, perhaps, activity in secondary assays of some evidence of a desirable pharmacokinetic profile. From such work a 'tool' molecule may arise. This is a term sometimes used to describe a compound with demonstrable activity, which can be used to establish mechanism or prove the concept of a particular target being efficacious in animal models – but without the necessary overall profile to be considered good enough to be a candidate. To produce good drug *candidates*, compounds should not only possess potent action against the target protein, but should also have the appropriate physical properties (solubility, size, lipophilicity) that necessarily accompany effectiveness and selectivity *in vivo*. Much of the *lead optimisation* process, which involves the iterative synthesis of analogue structures to hone the activity of a molecule, balanced with appropriate physicochemical properties required to achieve good pharmacokinetic (what the body does to a drug) and pharmacodynamic (what the drug does to the body) profiles. Combinatorial and/or multiple parallel synthesis techniques can have an impact at many stages in the drug discovery process – although the balance may be shifting to more focused libraries with better properties in the earlier stages – and to compounds designed with the aid of computer graphics in lead optimisation.

Historically, adverse drug metabolism and pharmacokinetic properties have been a major reason for failure in clinical trials. Modern drug design tends to take these factors into account at a much earlier stage, thereby reducing this liability. The fact is that optimising purely for potency in an isolated protein assay has not necessarily resulted in the most effective drugs. Compounds with high lipophilicity can bind strongly to many protein active sites since most proteins have multiple regions with high lipophilicity. One effect is to reduce selectivity for the target; another is for this generally undesirable physical property to confer poor solubility in aqueous media, including body fluids, resulting in sub-optimal ADME outcomes. Thus, the compound with the highest intrinsic activity is almost invariably not the best drug candidate. Improvements in ADME ideally need to be part of the original drug design process, thereby offering improved selectivity and reducing the potential for undesirable side-effects.

(Note that the study and analysis of ADME factors is usually described as 'drug metabolism and pharmacokinetics' or DMPK studies.)

Taking the above factors fully into account improves the chances that any selected candidate will progress through to Phase 1 trials. Even then, at the present time, some 40% of candidates drop out of contention at the preclinical evaluation stage. Success in Phase 1 clinical trials, establishes the tolerability and safety of the compound, and is followed by Phase 2 and Phase 3 clinical trials in which efficacy against the target disease is sought. When these data have been collated, analysed and reviewed by regulatory authorities, the permission to market the drug as a new medicine, as it may now finally be termed, might be granted.

The key stages in the drug development process are:

1 *Disease selection and target identification*
- Unmet medical needs.
- Genomics approaches.
- Reducing a concept to practice to enable a discovery programme.

2 *Lead identification and target validation*
- Methods for discovering chemical leads to enable an optimisation programme to commence.
- Investigative tools may be derived from active compounds.

3 *Lead optimisation: the essence of drug discovery*
- Achieving the best balance between novelty, potency and acceptable pharmacokinetic and pharmacodynamic properties
- The quality of drug candidates and their chance of making it to market depend on originality and good science at this stage.
- Intellectual property rights are essential to protect new discoveries.

4 *Candidate selection*
- Forming a short list of potential development candidates based on preliminary toxicology, ADME studies and efficacy in an animal disease model.

5 *Preclinical evaluation*
- Selection and characterisation of preferred drug candidate.
- Preparation for Phase 1 studies in humans.

6 *Clinical evaluation*
- Assessment of the safety and dosing regimes of the candidate drug in humans.
- Evaluation of the effectiveness of the drug in selected patients in a clinical context.
- Compilation of a data package to enable product registration, prior to manufacturing and sale.

1.1 Use of molecular modelling in drug design

Modern drug discovery has its roots in the detailed investigation of such substances; classically, modification and/or mimicry of natural substances were the basis for drug discovery programmes. As screening technology moved with time from the primary evaluation of single compounds in animal models, through organ baths to modern ultra high-throughput profiling of millions of compounds, the character and appearance of molecules evolved too. Such approaches may provide very many active compounds against the primary target; but to be an effective drug, the experimental molecule must still

have adequate physical properties (especially water solubility), be absorbed and distributed into the body and possess a level of stability that enables it to be delivered effectively to the intended target with an appropriate duration of action. A further challenge for certain therapeutic targets, such as pain and other central nervous system (CNS) associated conditions, is the need to achieve penetration of the blood–brain barrier, a process that has exacting physico-chemical requirements.

A more detailed study would address these issues and illustrate the methods not only for discovering new active compounds, but also optimising these to ensure that they can perform effectively and safely as drugs for the improvement of health and treatment of diseases.

One of the most important tools for drug discovery is molecular modelling. Before high-speed computers became commonplace, medicinal chemists could only build physical models of possible drugs. However, the development of both hardware and software has meant that the medicinal chemist can:

- create visual images of a drug and manipulate them with ease;
- calculate the best geometry for the molecule involving optimum bond lengths, bond angles and torsional angles;
- use crystal structures of proteins to identify drug binding sites and to identify which molecules will bind most effectively to the binding site;
- based on the primary structure of a protein obtained from the genome, predict possible secondary and tertiary structures of a protein and thus possible binding sites;
- without any structural knowledge of the binding site build up an idea of its geometry and functionality based on pharmacokinetic information from a series of drugs and their structures.

If we are reviewing the process of drug discovery from concept to clinic, molecular modelling is an essential area to study, so we will focus on some of the basic tools.

2 Developing anti-inflammatory drugs

The general areas of pain and inflammation illustrate a number of concepts behind the development and use of small-molecule drugs. Historically, experience showed that certain natural substances could have a beneficial effect on disease states having associated pain. This would not have been possible had those substances not, in the first place, had reasonable pharmacokinetic and pharmacodynamic properties, which are perhaps evolutionary consequences of their biosynthesis. Nature is sparing of energy, few natural products are synthesised without some purpose in the life of the producer.

2.1 Understanding pain

Pain has traditionally been perceived as a subjective experience and is usually indicative of some underlying condition, injury or trauma. It is an experience that is crucial for survival since it induces the sufferer to avoid risk of injury and promote well-being. The experience of pain is the single most common reason why people attend surgeries or take self-medication. It is also, in its chronic form, the third greatest problem in human health

after cardiovascular disease and cancer, causing a huge economic burden in absence from work, lost productivity and healthcare costs. Until fairly recently, the mechanisms by which pain was perceived were poorly understood. Its treatment was by means of empirically-derived medicines or by attempting to relieve the underlying cause of the pain with surgery. One visible clinical manifestation that often accompanies pain is inflammation and efforts to reduce this frequently result in a reduction of accompanying symptoms.

Historically, neither inflammation nor pain has been managed using rationally-designed drugs. The agents that were discovered empirically usually provided the starting point for greater understanding. Within the last 20 years an increasing understanding of the mechanisms by which pain itself is experienced has arisen, especially chronic neuropathic pain (that which is not accompanied by visible symptoms) and this has enabled usable models to be set up for testing hypotheses and developing new treatments. It is evident that the immune system plays a central role, eliciting reactions both in the peripheral and central nervous system as well as mediating the classical inflammatory response.

2.2 Opioid drugs

Opioids represent some of the oldest drugs discovered and they are still crucial to medicine today, particularly for the treatment of pain. The story of their discovery and development illustrates the traditional approach to medicinal chemistry before the era of genomics, proteomics, molecular modelling and *in silico* drug design. Traditionally, drug research required the discovery of an active compound (morphine in the case of the opioids), either from the natural world or from synthetic compounds produced in laboratories around the world. This compound would then serve as the ‘lead compound’ for further research. Synthetic chemists would make as many different analogues of the lead compound as possible with the aim of finding a compound which had good activity, a minimum of side-effects and favourable pharmacokinetic properties. In the early days, there were no drug design strategies that could be used to guide the medicinal chemist in these efforts and so structures were usually ‘churned out’ in a trial-and-error process. Nevertheless, the results from all this hard graft gradually led to a growing recognition of the various drug design strategies that are used today. The discovery that the opioids act on receptors within the body came relatively late in opioid research (the 1970s), followed by the isolation of endogenous opioids such as the enkephalins, endorphins and dynorphins. Contrast that with the approach favoured by the pharmaceutical industry today, where the initial goal is to identify a molecular target that may play a role in a disease state and then find a lead compound that will interact with that target. Ideally, the target structure is then crystallised along with the bound lead compound. X-ray crystallography is used to determine the crystal structure which can be studied using molecular modelling software to determine how the lead compound binds to the target site. Such studies can be used to guide the medicinal chemist to the analogues which are most likely to have improved binding interactions, activity and selectivity, thus cutting down the synthetic work from many thousands of analogues to a handful. Having said all that, the opioid story is still an important one. It would be wrong to assume that all drug design follows the ‘ideal route’. The molecular targets for lead compounds discovered today are not always known, and even if they are, it is not always possible to crystallise them to produce the crystal structures that would allow molecular modelling studies to be

carried out. Therefore, the traditional approaches illustrated in opioid research are still of relevance today.

Finally, the opioid story may be an old one but it is far from over. Current research is leading to a better understanding of the opioid receptors and their binding sites. It may well be that the modern approach will eventually succeed where the traditional approaches have failed, namely in the design of an orally active analgesic that is as effective as morphine in relieving pain, but without the risks of addiction and unacceptable side-effects.

2.3 Steroid drugs

Steroids were some of the earliest naturally produced endogenous structures discovered and they play an important part in many fields of medicine, including fertility and contraception, and the treatment of inflammation, asthma and cancer. They also have an important role to play in the treatment of ailments such as cardiovascular disease, infection, osteoporosis, trauma, as well as menstrual disorders and problems during the menopause.

Steroids have also been used as ‘spacer’ molecules in neuromuscular blockers and as carrier molecules for other drugs. The fact that steroids have such a diverse number of applications suggests that they have a ‘privileged scaffold’. This means that the physical and chemical properties of the steroid skeleton are such that there is a good chance that a substance having a similar structure will have the required pharmacokinetic properties to be an effective drug. For example, steroids are generally hydrophobic in nature and so they are able to pass through the cell membrane and reach potential targets such as enzymes and receptors within the cell.

The story of the discovery and development of steroids has similarities with that of the opioids in that it illustrates the traditional approaches used in medicinal chemistry before the era of genomics, proteomics, molecular modelling and *in silico* drug design. As with the opioids, active steroids were discovered long before their molecular targets in the body were identified. Therefore, drug research focused on the structure of the lead compound and concentrated on making various analogues to study how such changes altered the pharmacological properties. As in all areas of medicinal chemistry, modern techniques such as genomics, proteomics, X-ray crystallography and molecular modelling have served to provide new insights into how the steroids interact with receptors and enzymes, and to design new drugs based on that understanding.

Steroids are defined as having a particular tetracyclic skeleton involving three six-member rings and one five-member ring. Different steroids have different functional groups or substituents attached to this skeleton (for example alkyl groups, alcohols, ketones and halogens) or functional groups within the structure itself (for example an aromatic ring and/or alkene groups). Slight modifications in functional groups and substituents can have a dramatic effect on the pharmacological activity and selectivity of these compounds. This is one reason why steroids are such important hormones, and can have such a wide range of effects within the body. They are vital to numerous physiological processes including cell growth, sexual development, maintenance of salt balance and the control of sugar metabolism. Abnormalities in steroid biosynthesis, metabolism and receptor interactions all contribute to a variety of diseases. Steroids are not confined to human biochemistry. They are also found in animals, plants, and fungi. Steroids from other species have the same molecular tetracyclic scaffold as human steroids, but they have quite different functional groups and substituents.

The most common steroid present in the human body is cholesterol, which is crucial to the biosynthesis of the hormonal steroids that are present in much lower quantities. Cholesterol also plays an important structural role in cell membranes. Despite that, high cholesterol levels are a well-known problem that can lead to cardiovascular or cerebrovascular disease, and so cholesterol-lowering drugs such as the statins are some of the most important and profitable drugs produced by the pharmaceutical industry.

Steroids are not without controversy. Like all drugs, they can have unacceptable side-effects. Moreover, they are open to abuse; anabolic steroids were originally designed as a means of building up muscle in patients suffering from muscle-wasting diseases, but they have been a long-running problem in the sporting world, with athletes taking these agents in an attempt to produce better performances, despite the many risks associated with their usage and the doubtful benefits obtained.

The medicinal chemistry research behind steroids is vast, so it is important to concentrate on the steroids that are important, or have the potential to be important, in the treatment of inflammation and asthma. Their design is based on the glucocorticoids, which are produced in the adrenal medulla. Currently, the most common steroids used in medicine are beclometasone dipropionate, budenoside, ciclesonide, fluticasone propionate, mometasone furoate, triamcinolone acetonide, betamethasone, dexamethasone, flumetasone pivalate, flunisolide, deflazacort, methylprednisolone, prednisolone and hydrocortisone.

2.4 NSAIDS

You will already have covered the introduction to pain, earlier in the course, and briefly examined the role of steroids and opioids in controlling pain and inflammation. This part of the course focuses on the physiology of the inflammatory response and how it can be controlled.

Inflammation is the physiological response of the body to tissue damage, whether brought about by infection, irradiation, physical impact, or a malfunction of the immune system. Inflammation, therefore, is not a disease or illness in its own right but a defensive reaction to a problem. When properly deployed, such defences contribute to the healing process; if inappropriately deployed, they can exacerbate the illness. It is for these latter situations that anti-inflammatory drugs are commonly prescribed.

Most of us will have taken an anti-inflammatory drug at some time in our life. Probably the best known drug in this class, and certainly the most widely used in the 20th century, is aspirin, which was introduced into medicine in 1898. A similar, though more selective, drug is ibuprofen, which was first made available commercially in the 1960s.

Ibuprofen was the prototype of an array of ‘profen’ anti-inflammatory drugs, which, together with an increasingly wide variety of drugs with a similar mode of action but a diverse range of molecular structures, have come to be classified as *non-steroidal anti-inflammatory drugs* (NSAIDs). This classification clearly distinguishes them from corticosteroids, the other major class of anti-inflammatory drugs that has already been studied.

Regardless of the type of drug taken or the illness being treated, all anti-inflammatory drugs have a molecular mechanism of action that interferes with one or more steps in the diverse range of biochemical processes that constitute the inflammatory response.

Conclusion

In this course you have had a brief introduction to how the drug-discovery process is conceived and initiated. You should by now have some appreciation of the intrinsic difficulties associated with developing a drug molecule from conception into a medicine suitable for clinical use and of how molecular modelling can be used in the drug discovery process. You should also by now have an elementary appreciation of the concept of pain and some understanding of the historical background to pain control. You should be aware that opioids, steroids and NSAIDs all work at the molecular level. Finally you should appreciate that anti-inflammation drug discovery requires a detailed understanding of the biochemical processes that constitute the inflammatory response.

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