14 Innovation and Industry Context

CASE STUDY 5: ROCHE–SAQUINAVIR

1995 – A NEW CLASS OF HIV ANTIVIRAL

On 6th December 1995 the US Food and Drug Administration (FDA) cleared Roche's new HIV drug, Invirase ® (saquinavir), for use in combination with approved nucleoside analogues for selected individuals with advanced HIV. This decision to approve Invirase as quickly as possible was addressed in the US media as, 'Some of the most hopeful news in years for people living with AIDS. This approval introduces a new class of drugs for treating AIDS.' Until 1995, HIV therapy had been limited to the use of combination regimens comprising two drugs that were designed to prevent the virus from infecting the cell. The introduction of Invirase enabled the use of new combination regimens that would target the virus at two steps in the replication cycle – providing a 'one-two punch' approach. Like many other infectious agents, immunodeficiency viruses have an unfortunate tendency to mutate in such a way that they become resistant to individual substances used to attack them. As many as 40% of HIV/AIDS patients had failed multiple treatment regimens or had developed resistance to existing options.

While AIDS-related deaths had declined since the introduction of Invirase and subsequent HIV protease inhibitors, the number of people living with HIV continued to grow. The use of triple combination therapy, pioneered in Roche's Phase III clinical trials, became known as HAART (Highly Active Antiretroviral Therapy). The use of HAART therapy has been shown to significantly prolong the survival of people living with HIV, and reduce the incidence of opportunistic infections.

While Invirase provided significant clinical benefits, full potential (antiviral effect) could not be realized due to limited bioavailability of this formulation. When Merck launched Crixivan in late spring 1996, a third protease inhibitor, they focused their marketing activities against Invirase upon the greater viral load reductions achieved with their drug.

Criteria for selecting an ideal antiretroviral combination

- Synergistic or additive anti-HIV activity
- No cross-resistance between drugs
- No overlapping toxicities
- Antiviral activity in multiple cellular and tissue reservoirs of HIV
- Lack of adverse interaction between component drugs and other commonly used agents
- Ease of administration

In addition, a company called Agouron had picked up Roche's patent and had managed to develop a similar compound in just five years with the advantage of achieving higher drug concentrations, and showing a unique drug resistance profile that allowed other protease inhibitors to be used following failure of a Viracept-containing treatment regimen.

MOVING INTO HIV DRUG RESEARCH – THE SITUATION IN 1986

In 1982 an unusual collection of clinical symptoms observed in a small number of homosexual men in urban areas of San Francisco was recognized and classified as Acquired ImmunoDeficiency Syndrome (AIDS). Thereafter, the number of individuals diagnosed with AIDS increased rapidly, and it became apparent that AIDS was widespread in many Western countries and sub-Saharan Africa, and had evolved into a worldwide epidemic. AIDS manifests itself as a severe impairment of the human immune system, leaving those affected vulnerable to a wide range of opportunistic infections, resulting in a dramatic loss of weight and ultimately death. At this early stage in the history of AIDS, the life expectancy of an infected individual was around two years.

The search for the infectious agent responsible for AIDS attracted the attention of scientists around the world. In 1983 two research groups, one in the USA the other in France, independently isolated the same retrovirus, which later became known as Human Immunodeficiency Virus (HIV), the causative agent of AIDS.

Molecular cloning and gene sequencing elucidated the composition of the HIV genome. From this data, it was proposed that much of the genetic information required for replication of the virus was contained in just three distinct genes: *gag*, *pol* and *env*. From the nucleotide sequence of these three genes, a number of enzymes were proposed to be encoded by the HIV, giving scientists the first indication that it may be possible to design specific chemotherapeutic agents capable of inhibiting the replication of this deadly virus.

The sheer scale of the problem and the potentially devastating threat to world health mobilized worldwide cooperation. In 1986, six United Nations' organizations took the unprecedented step of joining forces to form the 'Joint United Nations Programme on HIV and AIDS' (UNIAIDS). Its role is to monitor, facilitate exchange and spread knowledge related to HIV and AIDS. The organization also publishes annual estimates on the spread and scope of HIV infection, as well as mortality rates, with the objective to help direct efforts to control the spread of the virus and those infected by it. From a

Scientific background

HIV is a retrovirus. Like all retroviruses, the genetic material of HIV is RNA rather than DNA. When HIV infects a cell, the viral RNA is transcribed by a specific enzyme, called reverse transcriptase (RT) into DNA which is then integrated into the host cell genome. After that viral DNA is copied to produce components of new viral particles, which are assembled at the cell membrane where budding and maturation result in the formation of a new HIV particle.

Scientists continued to isolate and study HIV from infected individuals in those areas where the disease was of epidemic proportions. It became apparent that two significantly different strains of the virus existed, which were classified as HIV-1 and HIV-2. The latter, most predominant in Africa, is less virulent.

Scientists were comparing the genetic composition of HIV with other closely related viruses in an attempt not only to trace its origin but to better understand its replication and also to identify possible model systems to facilitate the evaluation of potential inhibitory agents. The transmission of viruses from animals to humans is known but is not common and is an inefficient process. Most notable is the transmission of influenza from avian species to man, which until the 1997–8 Hong Kong outbreak was thought to require the intermediacy of hogs. Since HIV infects the chimpanzee attention turned to other primates and viruses that infected primates. There is a high degree of homology between HIV and Simian Immunodeficiency Virus (SIV) which infects the African green monkey. This led to the suggestion that HIV may be derived from SIV that may have crossed the species barrier as early as the 17th century and emerged as HIV in the 1930s.

few known cases in the early 1980s, the number of people living with HIV and AIDS was estimated by UNIAIDS and the World Health Organization (WHO) to have grown to 36.1 million worldwide by the end of 2000, with 1.4 million of them being children. This equates to approximately 15,000 new infections every day. The geographic region most affected by HIV is sub-Saharan Africa, with about 70% of all known cases. A further 16%, or 5.8 million, live in South and South-east Asia.

The first two drugs on the market, Retrovir® (or ATZ) introduced in 1987 by Burroughs Wellcome and Hivid® introduced in 1992 by Roche, were both designed to hinder the viral RNA from being transcribed and integrated into the cell. However, they could not prevent the virus from reproducing once the cell had been infected. Other concerns were that these drugs could only be taken in relatively small quantities, as they tended to interfere with the metabolism of human cells, causing side effects such as diarrhoea, vomiting, nausea, fatigue and headaches. In addition, problems started to occur with strains of the HIV that had mutated in such a way that they had become resistant to the drug.

ROCHE TAKES UP THE GAUNTLET

Even in the mid-1980s the speed with which the virus was spreading focused pharmaceutical companies' attention on the problem. All major pharmaceutical companies seemed to be racing against time and each other to find an angle that would allow them to be first in bringing an HIV drug to market. In late 1985, around the same time Glaxo and SmithKline started to engage in research into HIV, Roche's antiviral chemotherapy group in Welwyn, UK, initiated a programme to develop a drug that would prevent the virus from entering the cell. There were also rumours that Burroughs Wellcome was about to introduce an HIV drug.

In May 1986 the current status of the AIDS pandemic was discussed in Roche Nutley with a call for a corporate commitment to AIDS research and the formation of an AIDS task force. Various aspects of research into AIDS therapy and diagnosis were assigned to different Roche research centres. It was decided that Roche Discovery in Welwyn would take on the HIV protease and reverse transcriptase as therapeutic targets. The prior Rick Kramer, a Roche scientist working in collaboration with the American health authorities performed experiments into which parts of HIV could be produced in yeast cells. In these experiments he deleted parts of the virus to see what effect that had on the other components. He showed that deletions in one gene, suspected of being a protease by analogy with the SIV gene, prevented proteolytic processing of the *gag* and *pol* gene products. This confirmed that the virus encoded a protease which had an essential function in virus maturation and he proposed that this protease could therefore represent a target for an anti-HIV drug.

Protease acts like a pair of scissors cutting into pieces the long protein chains produced by the cell under the influence of the virus. These pieces are needed for the production of a new virus that bursts out of the host cell and then infests new cells. If the protease fails to do its job the resulting immature virus particles are non-infectious.

experience of many Welwyn chemists and biologists in the inhibition of proteases from sources other than HIV underpinned this decision.

Chemist Joe Martin, who had set-up Roche's virology department in the early 1980s, remembers, 'Management told us to drop everything else, I guess about 80% of the virology team were working on or were even dedicated to this project.' It was clear that the input of both chemists and biologist, both located in the same building, would be essential. The first task of the chemistry group, headed by Joe, was to review all molecules to identify possible targets that would allow preventing the virus either from entering the cell or from reproducing. One problem when developing a drug is to find an area for attack that is as specific as possible. If a sequence of events is targeted that can be found in aspects of human biology, then healthy cells will be attacked along with the targeted ones, leading to high levels of toxicity.

Information about the structure and function of HIV protease was far from complete when the inhibitor programme began in 1986. The virology team in Welwyn had little prior experience with protease biochemistry, although there was considerable experience in Welwyn in related areas. Some clues could be obtained from a study of similar viruses in birds and Ian Duncan, a senior virologist at Welwyn, was able to suggest potential cleavage sites, including one that was particularly unusual.

It was the unusual one that caught the imagination of the scientists. From Ian's perspective, the enzyme responsible for splitting the viral proteins up into building blocks for a new virus seemed a good starting point, but he felt that he needed input from a colleague to assess biological aspects. Scientists from all backgrounds had been discussing their work on HIV all the time, and from their internal networking they knew that biologist Noel Roberts had worked for the past 12 years on the biochemistry and inhibition of proteases other than HIV. Noel was invited to join the team to advise and participate on that aspect of the work.

Noel recalls, 'I started by investigating the literature and did some thinking and then gave my thoughts to management. In my view it was essential to get the

The protease had been provisionally classified as an aspartic protease on the basis of an Asp-Thr-Gly amino acid motif in its sequence but this was not confirmed and there was a problem in that all previous aspartic proteases contained two such motifs and this contained only one. The possibility of the enzyme being formed from two identical subunits was proposed and later confirmed by x-ray crystallography.

The cleavage site specificity of the enzyme was also unknown, i.e. between which amino acids did the enzyme cleave the *gag* and *pol* proteins? One of the cleavage sites suggested by Ian Duncan was the unusual cleavage between the amino acid pairs Phe-Pro and Tyr-Pro. (The cleavage sites that Ian Duncan speculatively proposed were later confirmed by researchers in Roche Basle directed by Jan Mous.)

They had no HIV protease in a test tube to inhibit (no one had achieved that at the time), there was no assay to test for the inhibition of the enzyme once they got it, and no test for the inhibition of whole HIV replication (a special high containment laboratory would have been required to work with whole HIV and Welwyn did not have such a facility at that time).

enzyme into the test tube so we could start working on it.' He observed that the unusual cleavage sites, between Phe and Try-Pro, were unique for HIV and similar virus proteases, and that no human proteases, including the mechanistically similar human aspartic proteases, could make such cleavages. Thus, an inhibitor of HIV designed using chemistry based on the amino acids Phe-Pro should be able to produce an inhibitor of HIV protease which would not inhibit the human proteases. This was important as unwanted inhibition of human proteases could result in drug toxicities.

Thus the strategy was set. However, it was largely based on hypothesis, and on the belief that they would be able to achieve a number of significant scientific challenges. When the teams presented to the Hoffman La Roche Senior Research Management Team in October 1986, the project was fully approved. The timing of the programme was very tight and required simultaneous working on several aspects at once, each group working on the assumption that all the other groups would be successful. The programme that was agreed to in November 1986 read as follows:

1. Clone and express enzyme (protease) and demonstrate cleavage of Phe-Pro in a peptide (short piece of protein) substrate (mid-1987).
2. Purify enzyme; develop a rapid assay; achieve a potent and selective inhibitor (mid-1988).
3. Demonstrate antiviral activity (end 1988).
4. Select a drug candidate (end 1990).

After that a method for the large scale production of the compound would need to be found and clinical trials would be the final testbed for the quality of the drug.

TACKLING THE CHALLENGES

> 'In 83 the virus had been completely unknown and by 89 it was probably the best understood virus in the world. To be part of this activity was exciting, to make headway even more so.'

To take their investigations further they needed the enzyme. But as it was not possible at the time to grow HIV to get the enzyme – not least because no one Attempts to clone and express the HIV protease in a bacterium (E coli) using molecular biology techniques were pursued simultaneously by Jan Mous in Basle and by Mary Graves and her group in Nutley; Noel Roberts with help from peptide chemist Raj Handa, set about devising an assay to first detect the activity of the protease and then to assay its inhibition; Ian Duncan established a collaboration with St Mary's Hospital Paddington which had the facilities to set-up an antiviral assay using HIV and Joe Martin and his chemistry team started to make at first relatively simple compounds which could provide the basis for an inhibitor.

Employing some very old chemistry from the 1930s, Noel showed that proline (the Pro part of Phe-Pro) at the end of a peptide would react with a compound called isatin to give a blue colour, but while in the middle of the peptide it would not. Thus, if a peptide were made with a Phe-Pro bond in the middle and this were then cleaved by HIV protease a blue colour could be formed with isatin and the resultant smaller peptide. Soon, bacterial cultures potentially containing genetically engineered HIV protease were coming from the Basle and Nutley labs. In September 1987 a bacterial lysate (broken-up bacteria) added to a Phe-Pro containing peptide, incubated and then reacted with isatin turned blue. They had active HIV protease in the test tube! This assay then needed further refinement to make it both sensitive and quantitative so that they could use it to assay for HIV protease inhibition with the compounds Joe's team were already making. That took about another two months.

The concept of transition-state analogues is that short peptides containing a stable dipeptide mimetics should bind competitively to the active site of the protease, thus preventing the natural substrates (*gag* and *gag-pol* polyproteins) access to the active site of the enzyme and therefore from being processed. The use of crystal structures of enzymes, with and without inhibitors bound in the active site, had been used successfully to aid the design of enzyme inhibitors in other therapeutic areas. Unfortunately, at this early stage there were no crystal structures of HIV protease. Therefore, to assist in their search for novel structures that may bind in the active site of the HIV enzyme, the team began studies to produce crystals of the protein and determining

wanted to get anywhere near large quantities of live HIV – they would have to synthesize it by getting bacteria to produce it, which was a complicated process in which both Basle and Nutley were involved. After the cloning of the HIV protease had been achieved successfully, an assay was needed to prove firstly the activity of the enzyme and then the effectiveness of inhibition.

Noel decided to try to devise a colorimetric assay for the protease, i.e. one in which a colour change in the test tube would indicate the presence of the active enzyme. That would enable rapid assessment of results at least semi-quantitatively, by eye. Noel remembered about his first breakthrough, 'Between Christmas and New Year 1986 I spent three days in the lab, when it was nice and quiet and no phone would ring. It was then that I first managed to observe the formation of a blue colour in the test tube which could be used to detect the presence of the enzyme.' By November 1987 they had a working assay (test) that allowed visual assessment which meant that they could tell within a few hours whether a compound was inhibiting or not. But even nine months before Noel got the assay working Joe had developed compounds based on the link identified, and the first proteinase inhibitors had been synthesized as early as spring 1987.

When working on compounds, past experience came in handy again. Roche had applied a process, called Transition State Mimetics (TSM), before. What this means is making a chemical compound which looks to the target protease to be like molecules that it usually binds to and cleaves but which cannot be cleaved. Thus the mimetic (inhibitor) binds to the enzyme and gets stuck there – 'the wrong key in the right lock'. The challenge was to find a key that would fit the HIV protease without fitting other locks, leading to toxic side effects. In the search for such a key, the computer-based modelling tool developed by the Physics Methods Department at Roche Welwyn was of great help.

A systematic approach to lead generation and lead optimization was adopted. Some of the structures were inhibitive, but not all of them were selective, meaning that they would interfere with other processes too, leading to undesired side effects.

its three-dimensional structure. Meanwhile, homology modelling of the HIV protease active site was initiated using computer graphics which had been developed in the Physics Methods Department at Roche Welwyn. The use of homology modelling enabled the team to look at a three-dimensional structure of the enzyme, from all angles, but also to dock structures of potential inhibitors into the putative structure of HIV protease. This is an extension of the early concept of the 'lock and key' approach to the design of enzyme inhibitors.

In the lead generation process a series of transition-state mimetics was prepared and incorporated into small peptide-like molecules and evaluated as inhibitors of HIV protease. Very rapidly, a range of molecules from different structural classes were identified that had modest inhibitory activity. One of these which was of particular interest because of its novelty and small size (a tripeptide analogue) was considered a lead structure.

The next step was to begin the lead optimization phase. First, six key structural features were identified in the lead structure; each of these were considered essential for activity. Next, each of the six key elements was modified separately keeping the other five constant. Thus, in this first round of optimization a number of preferred structural fragments at each of the six critical sites in the lead structure was identified. The next phase of lead optimization was to assemble individual molecules each containing permutations of all of the best fragments into individual molecules. It was very satisfying to find that the contribution of each of the

A systematic process of chemical modification to the lead Phe-Pro mimetic structure was guided by assaying the potency of the compounds to inhibit HIV protease and their activity against whole HIV. Potent inhibitors were rapidly achieved and, to a large degree, potency against the enzyme was accompanied by potency against the virus. Potency as an antiviral in the test tube is only part way to identifying a drug candidate. The compound must also have an acceptable pharmacokinetic profile (i.e. if you take it by mouth does it get to the parts of the body where it needs to act in sufficient concentrations to be effective), and it needs to have low (ideally no) toxicity. Two or three potential development compounds had been identified by the autumn of 1989.

To get to this point the team had synthesized about 250 compounds; normally they would have expected to have made thousands. From the decision to commence the project to this point it had taken the team only about three years though Joe points out, 'At that time is was incredibly fast and we were even three months ahead of schedule but today things can be done even quicker, mainly due to advances in technology.'

Patenting, of course, was a critical activity, but it also presented some difficult decisions. A patent can be filed immediately after the discovery has been made, but this sets the clock ticking. Alternatively, one can delay filing which will give a longer protection period after marketing. Also, the longer patent filing can be delayed, the stronger the patent can be made by inclusion of additional examples. The downside of delaying is that the competition might file a patent first, which means they would have sole rights to the invented compounds. As competition was fierce in this field, a patent was filed in 1988, covering the genetic aspects of the Roche inhibitors, but the team's preferred compound was specifically claimed in a new patent filed in December 1989.

During the entire research phase less than 10 g of material had been available, with most of the in vitro studies having been completed with no more than 25 mg.

optimized fragments was additive when incorporated into a final molecule. We then had a number of compounds that were very potent inhibitors of the HIV protease. This was the first step towards finding a medicine to inhibit HIV infection.

The next stage involved evaluation for antiviral activity in a cell-based assay that had been set up in collaboration with scientists at St Mary's Hospital, Paddington, London. Again, it was very gratifying to find that the very potent inhibitors of the HIV protease display excellent activity in the antiviral assay. Furthermore, there was a good Structure–Activity Relationship (SAR), that is, the level of activity in the antiviral assay followed in parallel the potencies in the enzyme assay. This was another major advance in the project. Next, it was important to assess the compounds for selectivity and hence potential toxicity. Since there were no animal models available to assess the toxicity of these inhibitors the team took a different approach to assess the toxicity potential. Collaboration was established with Prof John Kay, an expert on mammalian aspartic proteases, at the University of Cardiff. Prof Kay measured the potency of the optimized compounds against a panel of important human aspartic proteases, which gave the Welwyn group a measure of the toxicity potential of their inhibitors. Yet again, they were delighted to find that their potential development candidates were totally selective for the viral enzyme. Thus, none of the compounds inhibited any of the key enzymes in Prof Kay's panel of important human enzymes.

The next step was to select one of the compounds to be the development candidate. A key step was to determine whether any of these compounds had sufficient oral bioavailability to enable the molecule to be taken in tablet form and achieve adequate levels of substance in the blood to be an effective anti-HIV agent. A number of studies were carried out in rats, dogs and monkeys from which it was concluded that these compounds did achieve adequate blood levels to be an effective drug. At this point the compound whose code number was Ro 31-8959 was considered to be the likely development candidate.

DEVELOPMENT – FROM TEST TUBE TO MASS PRODUCTION

Noel recalls, 'In autumn 1989 we had two or three components but one seemed to work best, it was more potent than the others. The problem with that compound, Ro 31-8959, was that it was the chemically most difficult to produce. We had a meeting, myself, Joe, Ian Duncan, David Clough (director of research who had given the project unlimited support throughout) and Peter Machin, director of chemistry. Intuitively we all wanted to go for the most difficult one, but it was really for Peter to decide whether it could be produced on a large scale. Most of the building blocks were able to be purchased or readily prepared, but the decahydroisoquinoline moiety that replaced the proline residue found in the substrate was extremely difficult to make.'

Even though the synthetic tractability was not proven at that time and, on the contrary, it was expected to be rather difficult if not impossible, nevertheless, and despite the fact that only one out of ten drugs that enter development makes it to market, Peter felt quite confident that they would be able to produce the compound in the quantities required and the decision was made to follow gut feelings. The compound, later to become known as saquinavir, was handed over from the research team to an International Project Team (IPT). The IPT was responsible for the development of the compound into a product and also for taking that product to market. The stages involved were: pre-clinical development and formulation, toxicity studies in animals, evaluation in healthy volunteers (Phase I), clinical studies (Phase II and Phase III), registration and marketing (see also Appendix II).

In 1990 experts in chemical process research and production chemistry found themselves confronted with the difficult task of producing the complex molecule on an industrial scale. The elements of the molecule had to be assembled in a specific order to afford the correct molecular structure. Only one out of 64 possible scenarios was wanted, which meant that ways of detecting the one desired outcome were needed. Dieter Krimmer, a development chemist based in Basle, had the task to develop a viable synthetic process that could produce saquinavir on a much larger scale than had previously been undertaken. At the time many competitors knew the compound and its structure, but all of them had declared that it would be impossible to manufacture the compound on production scale and at an acceptable cost to be profitable. If choosing the Phe-Pro mimetic as the core of inhibitors had already been considered very risky, developing a production process was now seen as an outstandingly difficult challenge.

At the same time, other companies such as Merck and Abbott had much larger teams working on similar products. Abbott had chosen to focus on symmetrical inhibitors, whereas Merck and SB were working on renin-like molecules. In fact, Roche had looked at these options as well but had, in the end, decided to focus on protease inhibition based on the more difficult but potentially more selective Phe-Pro moiety. Separately, a group of scientists in Roche at the Nutley site in New Jersey were studying TAT antagonists as an approach to HIV therapy. Both project teams identified development candidates at approximately the same time but because the protease inhibitor had a higher chance of success the decision was made to concentrate on that approach.

The challenge facing the development chemist is not simply a matter of producing material on a larger scale, but also to improve the synthesis to be more efficient by reducing the number of steps in the process. The initial synthetic route deployed in the research phase involved 26 steps, but by the time early clinical studies were being initiated, batches of 30 kg of bulk material were being prepared using a process that had been improved to involve just 17 steps. Another advantage arising from the shortened synthesis was that the time required to produce a batch of saquinavir was reduced by a third, from 15 months to 10 months.

In the early phases of research and development, the physical characteristics of the active substance does not affect the outcome of experimental studies, but by the time large scale manufacture is reached the final product has to be made available in a physical form that is suitable for the preparation of capsules and/or tablets. The physical

characteristics of early batches of saquinavir were such that it was very difficult to fill capsules needed to conduct the early clinical studies. Fortunately, the problem was easily overcome and in 1991 when the production process had been optimized the final compound was obtained as a free-flowing crystalline powder.

CLINICAL TRIALS AND INTRODUCTION

Another challenge was to determine the right dose. The question was, how much needs to be given to ensure that the patient receives enough of the drug for it to be active, but not so much of the drug for the patient to experience unacceptable levels of side effects. Phase I clinical trials were undertaken with healthy volunteers, and took place in 1990.

Following the completion of Phases II and III, a daily dose of three times 600 mg was recommended, and Invirase, as the product based on saquinavir was called, was brought to market in 1995, creating the first of a new class of HIV drug.

The fact that Roche was in the process of creating a new class of HIV drug had also put the company into the limelight early in what was a whole new ball game in the pharmaceutical industry. One of the first groups hit by the HIV epidemic was the gay community. The gay community had established advocacy networks and lobbying experience, and soon began to focus on HIV. HIV treatment advocacy groups began to gain strength, their intention being to reduce the negative stigma associated with HIV, to initiate public awareness to halt the spread of the virus through education about safe-sex practices, and to pressure pharmaceutical companies and regulatory authorities for early access to life-saving medications. Initially, there was a lot of anger. The advocates were literally fighting for their lives, and there was not an established basis for communications between the advocates and the industry. As a result, there were often public displays of anger. All of the drug companies involved in HIV in the early days experienced such action, as did the regulatory authorities and leading HIV physicians.

There was considerable public pressure on Roche to make its new drug available before all clinical trials had been completed. After first hints on the development of a new class of drug had been published in 1993, demands were made to make saquinavir freely available to HIV sufferers by allowing them to participate in Compassionate Use Programmes. Compassionate Use Programmes pushed companies outside their comfort zone, as these programmes required that companies make their drugs available before clinical studies had been completed and evaluated, while at the same time maintaining full responsibility for the

In the Phase II clinical trials the drug was given to HIV-infected individuals, providing the first indications for the product's efficacy. Phase II involved double-blind studies with a total of 200 patients in the UK, France and Italy. The results were good; the number of CD4 cells (the cells of the immune system, which HIV destroys) increased. It seemed to work even better in combination with AZT (the first anti-HIV drug available for clinical use which inhibited another enzyme in the virus, reverse transcriptase). A further study took place in the US with 300 trial participants, exploring three different drug combinations. Finally, in Phase III, which began in the US in 1994, the aim was to detect clinical improvements as well as changes in surrogate HIV markers. In this study 978 patients were involved who were given either saquinavir, or Hivid (another AIDS drug from the first class of compounds – the reverse transcriptase inhibitors) or both. A second part of Phase III began in August 1994 in 200 centres in 24 countries around the world with 3500 patients (the largest combination drug study ever to be carried out in the HIV area). In this study triple drug therapy for HIV was used for the first time. This is now the treatment norm. Side effects were detected in less than 4%, indicating very low levels of toxicity. The Phase III studies showed that Invirase significantly improved the patients' clinical status by delaying the progression of AIDS and improving survival.

consequences. In addition, the usage of the drug in such programmes tends to be less well controlled and monitored than in clinical trials. Compassionate Use Programmes often include patients with more advanced stage of HIV who may suffer more acutely from adverse drug reactions. Roche was initially cautious in agreeing to such a programme. In 1993 AIDS activists had demanded that a different HIV drug Roche had been working on, based on TAT inhibition, should be released. However, Roche had refused – and later clinical trials revealed unacceptable levels of toxicity in the drug, which eventually led to the discontinuation of development of the TAT inhibitor. However, in the case of saquinavir, Roche agreed to set-up a Compassionate Use Programme ahead of approval, and the programme got under way in July 1995. By the end of August 1996 some 12,000 patients had been included.

Thanks to the close cooperation of the teams at Roche with various authorities in relevant countries from an early stage, approval of the drug was more rapid than could normally have been expected. The NDA (New Drug Application) Dossier delivered to the Food and Drug Administration (FDA) on 31st August 1995, consisting of 600 volumes and 160,000 pages, was approved in record time. Approved in the US in December 1995, by the end of 1996 the drug had been approved in North and South America, Australia and several countries in Europe and Asia.

Recognition

1995
- Roche International Research Prize
- Prix Galien (UK)

1997
- Prix Galien (Spain)
- Prix Galien (Portugal)
- SMR Drug Discovery Award
- Innovation Award (Pharmazeutische Zeitung)

1999
- International Prix Galien
- PhRMA Discovers Award (USA)

QUESTIONS

1. Drug development normally takes up to 15 years; Invirase was developed much faster. What enabled the speedy and successful execution of the project?
2. Given the situation in 1996, how would you have taken this part of the company forward?

Additional information on AIDS can be found:

http://www.medicalfutures.co.uk/

Comment: This is the website of *Medical Futures*, a venture aimed at promoting innovation amongst healthcare professionals and facilitating the successful commercialization of these innovations. Medical Futures operates through three main channels: innovative events, a high-quality magazine and database-driven websites

http://www.aidsmeds.com/

Comment: This website, run by people infected with HIV, offers up-to-date information on treatment, developments, readings, conferences, etc.

APPENDIX I: TEAM MEMBERS

Chemistry

JA Martin	AC Freeman	WC Spurden	MP Gunn
BK Handa	RA Hopkins	S Redshaw	JH Merrett
C Kay	KEB Parkes	JC Gilbert	IR Johns
RW Lambert			

Biology

NA Roberts IB Duncan
AV Broadhurst JC Craig
AJ Ritchie L Whittaker

Virology (Roche, Basle)

J Mous

Molecular Biology (Roche, Nutley)

M Graves

Virology (MRC Collaborative Centre)

AS Tyms
DL Taylor

X-Ray Crystallography (Roche, Nutley)

B Graves

Biochemistry (University of Cardiff)

J Kay
AD Richards

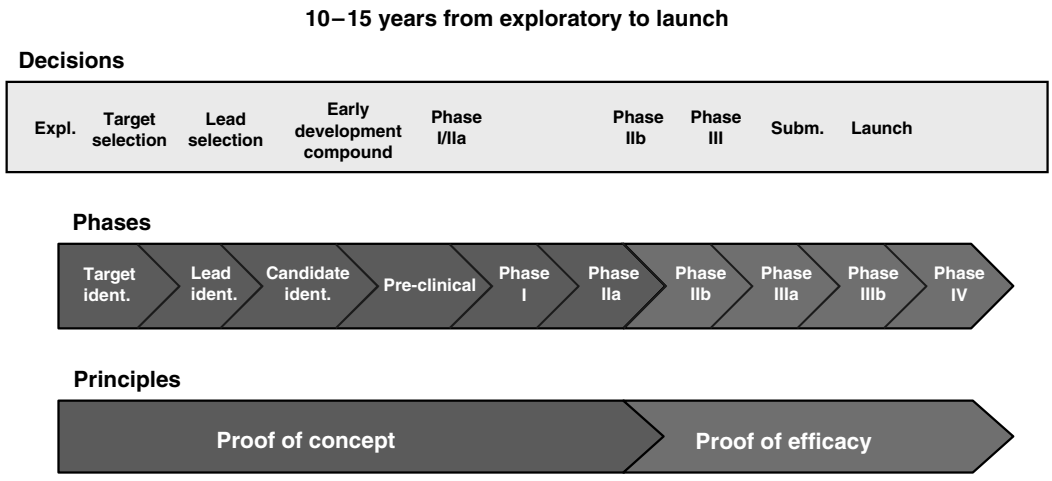
Pharmacokinetics

SL Malcolm
AF Clarke
A James

Molecular Modelling

WA Thomas
A Kroehn

APPENDIX II: DRUG DISCOVERY VALUE CHAIN



NOTES ON CHAPTER 14

[1] Primarily based on the *Oxford Dictionary* and the *Encyclopaedia Britannica*.