ESSAY

Case histories, magic bullets and the state of drug discovery

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Abstract | The case histories of five modern drugs are taken as a basis for reflection on the state of drug discovery. Two issues intimately associated with drug research are highlighted: the nature of the intellectual process leading to new discoveries; and the possibility that the principle of selective efficacy, which has guided drug research from its beginnings, might need modification, at least in some areas of pharmacotherapy.

'Learning by doing' is an established principle of scientific research. We start with a question, provide a hypothetical framework within which this question can be answered and, finally, design experiments to allow us to either confirm, modify or reject our hypothetical assumptions. A further aspect of learning by doing is that of retrospective analysis, in which critical ideas and actions taken are related to success or failure.

In recent decades, advances in molecular biology have transformed the research underlying drug discovery, and have made this interdisciplinary endeavour increasingly amenable to hypothetico-deductive reasoning as described above. The identification and evaluation of molecular targets for new drugs has led to new 'rational' strategies for drug discovery, and highly target-specific recombinant proteins, monoclonal antibodies and peptides have emerged as important new types of drug. Given such considerable changes, could the retrospective analysis of case histories of particular drugs help us to understand factors or events that relate to success or failure in modern drug research? And can such analyses be used to improve research and development strategies in order to avoid failures and to increase the probability of success?

Such questions were the catalyst for a meeting in June 2005, organized by *Nature Reviews Drug Discovery* and *Nature Biotechnology*, to discuss the case histories of five prominent innovative drugs. The drugs included cyclooxygenase 2 (COX2) inhibitors and imatinib (Gleevec; Novartis), two monoclonal antibodies — natalizumab (Tysabri; Elan/Biogen-Idec) and bevacizumab (Avastin; Genentech/Roche)— and the peptide enfuvirtide (Fuzeon; Roche). Two of the drugs that were analysed and discussed, rofecoxib (Vioxx; Merck) and natalizumab, were subsequently withdrawn from the market after successful launches, although findings obtained during the past few months have mitigated some of the initial fears with some of these agents, and natalizumab has now been reapproved for marketing, albeit with a special restricted distribution programme. The other three drugs — imatinib, bevacizumab and enfuvirtide — continue to be highly successful medicines in the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours, colorectal carcinoma and HIV, respectively. In this article, drawing on the discussions at the meeting, I consider each drug in turn, with the aim of discussing factors that might underly the success of imatinib, bevacizumab and enfuvirtide, and also the major problems with rofecoxib and natalizumab after their initial success, and suggest general lessons for drug discovery research.

COX2 inhibitors

The enzyme cyclooxygenase (COX) has a key role in the production of prostaglandins (FIG. 1). It was established as the target of a range of important anti-inflammatory drugs, such as aspirin, by the end of the 1970s, although some puzzling differences in the effects of such drugs remained unexplained (for a review, see REF. 1). Between 1989 and 1993, a potential explanation emerged: a second COX gene, dubbed *COX2,* was discovered[2–5]. In contrast to COX1, the COX2 enzyme turned out to be inducible[1,6,7], and seemed to be the mediator of inflammatory responses, whereas COX1, which is expressed ubiquitously, could be assigned a protective function for the mucosa of the gastrointestinal tract[8].

It was therefore anticipated that compounds that selectively inhibited COX2, but spared COX1, might have the desirable anti-inflammatory properties of drugs such as aspirin, but with reduced potential for gastrointestinal problems resulting from COX1 inhibition. Despite the high similarity between the COX1 and COX2 proteins, a replacement of isoleucine in COX1 at positions 434 and 523 by valine in COX2 results in a larger and more flexible substrate channel in the COX2 protein, which opened the possibility of identifying selective COX2 inhibitors. So, the development of selective inhibitors of COX2 seemed both desirable and feasible, and was actively pursued, resulting in compounds such as celecoxib (Celebrex; Pfizer) and rofecoxib that were capable of suppressing inflammatory responses in experimental animals without affecting their gastrointestinal mucosa[1]. Therefore, two elements of hypothetico-deductive reasoning existed: first, it was possible to synthesize selective COX2 inhibitors; and second, the pharmacological results seemed to confirm the hypothesis that such drugs could have beneficial anti-inflammatory effects with reduced gastrointestinal toxicity[1,7,9].

On the basis of large-scale clinical trials, both celecoxib and rofecoxib were licensed in the late 1990s as anti-inflammatory drugs for conditions such as rheumatoid arthritis, and rapidly became very popular. But in late 2004, rofecoxib was withdrawn from the market following the discovery that it significantly increased the risks of adverse cardiovascular events in a trial assessing its potential to protect against the development of colon cancer (which has been linked to overexpression of COX2). This withdrawal

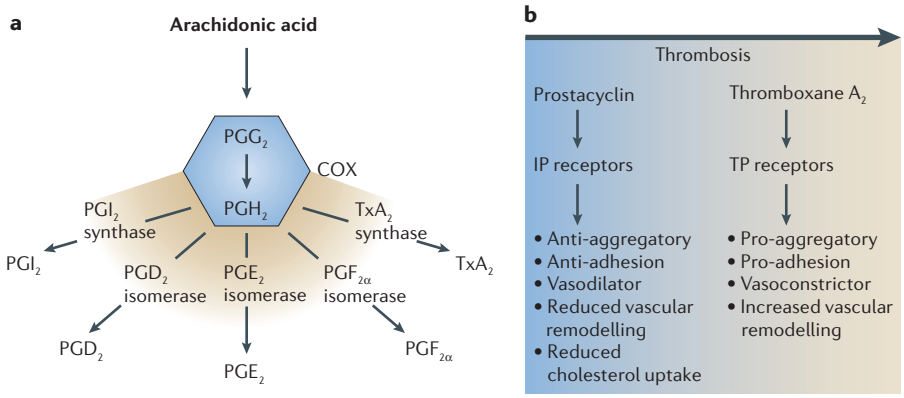

Figure 1 | **Cyclooxygenases and prostanoid synthesis. a** | Arachidonic acid is converted by cyclooxygenase (COX) in a two-step process to prostaglandin H_2, which is converted by other enzymes to prostanoids including prostaglandin E_2 (PGE_2), prostacyclin (PGI_2) and thromboxane A_2 (TxA_2). The levels of these enzymes vary widely in different tissues; for example, platelets have high levels of thromboxane A_2 synthase, and endothelial cells have high levels of PGI_2 synthase. PGE_2 is important in inflammation and pain, and the therapeutic actions of non-steroidal anti-inflammatory drugs that inhibit COX enzymes are thought to be the result of inhibition of PGE_2 production. **b** | Prostacyclin has antithrombotic effects, whereas thromboxane A_2 has pro-thrombotic effects, and disruption of this balance is one proposal that has been put forward to explain the adverse cardiovascular effects of selective COX2 inhibition. Adapted from REF. 16. IP receptor, prostacyclin receptor; TP, thromboxane receptor.

stimulated ongoing and widespread debate about the risks and benefits of COX2 inhibitors in particular, and drug safety and post-marketing surveillance in general.

Rofecoxib had been tested in a large-scale controlled clinical trial (known as VIGOR) against naproxen. As expected, the COX2 inhibitor caused fewer gastrointestinal side effects than naproxen[10], but the number of myocardial infarctions occurring in the rofecoxib group was five times higher than the corresponding figure for the naproxen group. At the time, this difference was attributed to the protective effect of naproxen against cardiovascular incidents, comparable to the effects elicited by low doses of aspirin, an interpretation that was plausible because the VIGOR study did not have a placebo arm. Other selective COX2 inhibitors such as celecoxib and lumiracoxib were also tested against conventional nonsteroidal anti-inflammatory drugs (NSAIDs) in large, controlled clinical trials. Although these studies (CLASS for celecoxib and TARGET for lumiracoxib) confirmed the much-reduced incidence of gastrointestinal complications for the selective COX2 inhibitors versus conventional NSAIDs, they did not show an increased cardiovascular risk associated with any of the COX2 inhibitors[11,12]. Subsequent studies, however, in which celecoxib was compared with placebo for the prevention of colorectal adenomas, did show a greater incidence of thrombotic events in the celecoxib group as compared with placebo[13].

Further studies with newer COX2 inhibitors, such as parecoxib and valdecoxib, also indicated a small but significant increase in cardiovascular events when compared with placebo[14]. The available data, however, do not allow the ranking of COX2 inhibitors and non-selective NSAIDs with respect to their cardiovascular risks. Consequently, celecoxib and some traditional NSAIDs have been allowed to remain on the market, but carry a black-box warning against gastrointestinal bleeding as well as cardiovascular incidents. A clinical study that is about to be undertaken, known as the PRECISION trial, might bring much needed clarity to our understanding of the precise gastrointestinal as well as cardiovascular risks posed by conventional NSAIDs and COX2 inhibitors in a large and fairly typical patient population. Ibuprofen, naproxen and celecoxib will be compared in 21,000 patients with rheumatoid arthritis over 2 years with respect to efficacy and safety parameters[15].

The story of the COX2 inhibitors shows that it is risky to identify and develop drugs on the basis of incomplete and insufficiently validated hypotheses. At the initiation of the COX2 projects, the function of the two COXs and their relative physiological roles had not been elucidated in sufficient detail to allow the formulation of a robust hypothesis. Various explanations have been put forward to explain the increased cardiovascular risk associated with COX2 inhibitors, including the effect of selective inhibition of COX2 on the prostacyclin:thromboxane A_2 ratio, which is dependent on the two enzymes[16]. As prostacyclin dilates blood vessels and inhibits blood clotting whereas thromboxane helps to form blood clots, changes in this ratio might make the formation of pathological blood clots more likely. Another possibility is that NSAIDs and COX2 inhibitors increase blood pressure and that even a small but chronic elevation of mean arterial pressure could lead to changes in vascular architecture and, subsequently, to adverse cardiovascular events (R. Temple, personal communication).

It has also been suggested that COX2 is expressed in blood vessels that are damaged or which have been exposed to bacteria. The inhibition of COX2 under these conditions could lead to a lowering of local prostacyclin concentrations, and thereby induce a prothrombotic state[16,17]. Highly selective COX2 inhibitors do not seem to inhibit thromboxane A_2 production in megakaryocytes, but they do affect the generation of prostacyclin in the kidney[16]. Again, such a disparity in effects could tip the balance between pro- and anti-coagulatory factors in favour of blood coagulation and thrombotic events. None of these suggested mechanisms have actually been shown to be responsible for cardiovascular events in patients treated with COX2 inhibitors, and much more research will have to be conducted before a more coherent picture emerges.

The rates at which COX2 inhibitors induce serious gastrointestinal side effects amount to only 20–40% of those observed with non-selective NSAIDS. On the other hand, COX2 inhibitors taken as a group seem to carry the same risk — or, in the case of rofecoxib, a higher risk — of adverse cardiovascular events. So, where is the progress? Will one advantage be neutralized by an equally important disadvantage?

Of course, we must remember that most patients taking NSAIDs do not experience any serious adverse events at all, be they gastrointestinal or cardiovascular in origin. But what about those individuals who do? Do these patients carry any genetic markers that are predictive of either gastrointestinal or cardiovascular complications that could be used diagnostically? The optimization of therapeutic drug responses, including the reduction of unwanted effects, cannot be achieved by chemistry and pharmacology alone. Increasingly, such strategies will have to take into account the genotype, as well as the immunological or metabolic characteristics, of the person that is being treated. Drug discovery and drug treatment are becoming

ever more target-oriented. This development will force scientists and physicians to understand the genetic variability of drug targets and the phenotypic drug responses associated with them.

Natalizumab

In the early 1990s, Lawrence Steinman and his collaborators were instrumental in demonstrating the key role of the cell-adhesion molecule α4β1 integrin in the homing of immune cells to the central nervous system (CNS)[18,19]. The interaction of the α4β1 receptor on the surface of immune-system cells with the vascular cell-adhesion molecule 1 (VCAM1) ligand on endothelial cells allows immune-system cells to enter the brain[19]. Given this, a monoclonal antibody to the α4β1 molecule that prevented its interaction with VCAM1 might be expected to have a therapeutic effect in CNS autoimmune disorders by inhibiting the passage of pathogenic immune-system cells into the CNS (FIG. 2). And indeed, in rats, an anti-α4 antibody blocked the development of experimental autoimmune encephalitis (EAE)[19], an animal model of multiple sclerosis, and even reversed paralysis that had occurred after the onset of the disease[20].

Such encouraging results provided the basis for the development of natalizumab (Tsyabri), a humanized monoclonal antibody against the α4 subunit of the α4β1 integrin[18,21]. In clinical trials, natalizumab reduced relapses in patients with multiple sclerosis by 66 %, compared with the typical reduction of 33% described for existing therapies[18,22]. In other words, the drug looked extremely promising and, against this background, it received accelerated approval by the FDA late in 2004.

However, only 3 months after its introduction came the shock: natalizumab was linked to two cases of fatal progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis who had been taking the drug, leading to its withdrawal from the market. A third case of fatal PML was subsequently reported in a patient with Crohn's disease receiving natalizumab in a clinical trial.

So what were the reasons underlying such serious complications of natalizumab treatment? A major hypothesis is that the observed PML cases were due to reactivation of the common JC virus, a polyoma virus that causes PML, raising the possibility that natalizumab was leaving at least some patients dangerously susceptible to opportunistic infections[23]. But during the development of natalizumab, animals had been deliberately infected with various viruses to investigate whether antibody treatment would make them prone to opportunistic infections, and according to these experiments natalizumab had not seemed to carry much risk of doing so, if any.

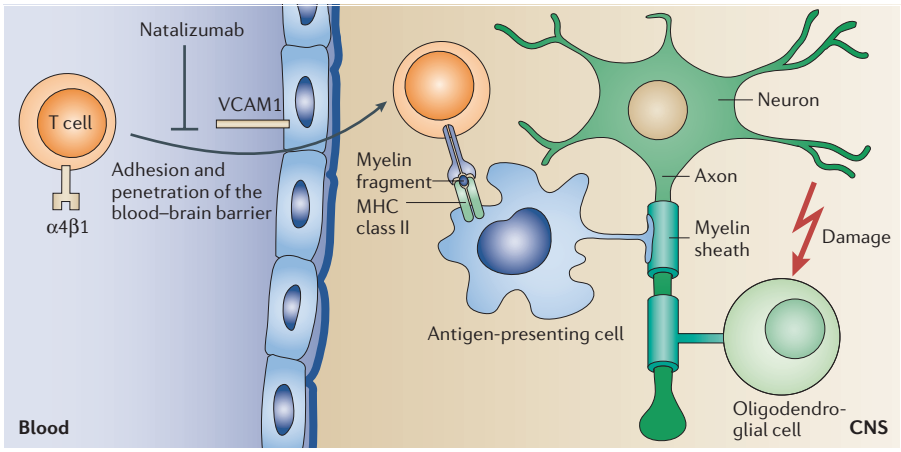

Figure 2 | **Multiple sclerosis and the role of α4β1 integrin.** The interaction between the integrin and vascular cell adhesion molecule 1 (VCAM1) is important in the entry of leukocytes, including T cells, into the central nervous system. In multiple sclerosis, these cells are thought to contribute to the damage of the myelin sheath and possibly the axon through several complex mechanisms. Natalizumab, a humanized anti-α4 antibody, blocks the interaction between α4β1 integrin and VCAM1, and is thereby thought to inhibit the entry of pathogenic immune-system cells into the central nervous system (CNS). Adapted from REF. 42 © Macmillan Magazines Ltd (2005). MHC, major histocompatability complex.

Such serious and surprising problems clearly show that our knowledge about the way in which natalizumab would affect the immune system was limited, and raise many pressing questions. Why did the drastic reduction in the number of T cells entering the CNS not lead to activation of other dormant viruses, such as herpes? Why did so few patients experience the reactivation of a dormant virus that is ubiquitous? Are there different strains of the JC virus, some of which are activated when immune surveillance by T cells is minimized? Or is there a more specific relationship between the α4β1 integrin and certain viruses? Indeed, it was suggested that α4β1, which is known to be an attachment protein for polyoma viruses in mice, might in some way be connected with the reactivation of dormant JC virus. These issues are now being actively investigated.

In view of the clear benefits that natalizumab brought to many MS patients, natalizumab has very recently been re-approved for marketing subject to a special restricted distribution programme. However, the findings with natalizumab obviously raise concerns about other anti-α4 antibodies presently in development, and about the safety of novel immunomodulators more generally, particularly those that might affect immune surveillance in the CNS. At this stage, it seems that our knowledge of immune mechanisms in the CNS is still incomplete. Efforts to develop novel therapeutics for immune disorders that affect the CNS will therefore have to be pursued with the utmost caution. Future efforts should also take into account more detailed knowledge of the mechanisms that are crucial for keeping dormant viruses in their inactive state.

Imatinib

The elucidation of the genetic basis of cancer transformed anticancer drug discovery in the 1980s[24]. In particular, growing evidence that deregulated protein kinases are often at the core of malignancies stimulated efforts to develop drugs that inhibit these enzymes in the hope that by specifically targeting aberrant signalling pathways in cancer cells, greater efficacy might be achieved with fewer side effects than with traditional cytotoxic chemotherapies[24–26].

Imatinib (FIG. 3) resulted from a drug discovery programme to develop kinase inhibitors. It was found to be a potent inhibitor of the BCR–ABL kinase — a fusion protein that originates from a chromosomal translocation event and has been known for some time to be the driving force behind cellular proliferation in chronic myeloid leukaemia (CML) — by an academic laboratory that collaborated with Novartis[24]. CML is not a very common disease and, taken by itself, was thought to only represent a small market. Nevertheless, Novartis made the courageous

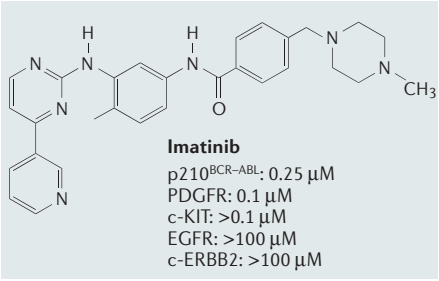

Figure 3 | **Chemical structure of imatinib.** As well as inhibiting the BCR–ABL kinase, imatinib is a potent inhibitor of c-KIT and the platelet-derived growth factor receptor. IC_{50}s for inhibition of auto-phosphorylation are given. Data from REF. 24.

and wise decision to pursue development of the compound for this indication. And like many other drugs that started with an 'orphan drug' perspective, imatinib now represents a landmark in drug discovery and development. First, it has dramatically changed the prognosis of CML, and the attitude of physicians and patients to this disease. Although the drug does not cure CML, it can induce complete cytological remission. However, resistance does occur, although it is not a frequent event (16% of patients after 40 months of exposure to the drug).

Interestingly, imatinib is not entirely selective for the BCR–ABL kinase. It also inhibits c-KIT, platelet-derived growth factor (PDGF) receptor and a stem-cell receptor[25], and these additional activities have provided the basis for its use in other cancers. For example, c-KIT is important in many gastrointestinal stromal tumours (GIST), and the drug has been also approved for the treatment of these cancers. Overall, the dramatic treatment effects of imatinib have demonstrated the power of a targeted approach, and acted as a catalyst for the development of many other therapies affecting protein kinases involved in cancer, a few of which have also already proved to be important advances in cancer therapy, with many more in various stages of development[27].

Bevacizumab

Like imatinib, bevacizumab is a targeted anticancer drug. Its origins could be considered to stretch back to the early 1970s, when Folkman proposed that targeting tumour angiogenesis might be an effective anti-cancer strategy. Efforts to identify diffusible factors that stimulated tumour angiogenesis led to the isolation and cloning of VEGF in the late 1980s[28]. It was subsequently demonstrated that a mouse monoclonal antibody against VEGF could suppress tumour growth *in vivo*[29]. Clinical trials with bevacizumab, a humanized form of this antibody, as a single agent, and in combination with various cytotoxic drugs, began in 1997 in a broad range of cancers, including renal-cell carcinomas, breast cancer, non-small-cell lung cancer (NSCLC) and colorectal cancers (CRC)[28].

The breakthrough occurred when bevacizumab was combined with 5-fluorouracil/leucovorin in CRC[30]; the results of large-scale trials were so encouraging that the antibody was approved for this indication in 2004. Other combinations involving bevacizumab have since been successfully tested, not only in CRC, but also in breast cancer and NSCLC. Like imatinib, this targeted anticancer drug has few side effects, the most important being a rise in blood pressure and arterial thromboembolic events. Both risks seem to be manageable with appropriate treatment[31].

Bevacizumab can still be regarded as a drug at the beginning of its 'career', and much remains to be learned about the mechanisms underlying its efficacy (FIG. 4), and how its clinical use might be optimized. For example, it is yet not fully understood why bevacizumab is synergistic with cytotoxic drugs. One possibility is that 'normalization' of the tumour vasculature by bevacizumab improves the delivery of cytotoxic drugs to the tumour[32]. Encouraging initial results have also been seen in combination with other targeted anticancer drugs, such as cetuximab (Erbitux; ImClone)[31]. Another issue is how beneficial bevacizumab might be at different stages of disease; most studies so far have been in patients with advanced disease, but further studies should clarify its potential in the neo-adjuvant and adjuvant settings[31].

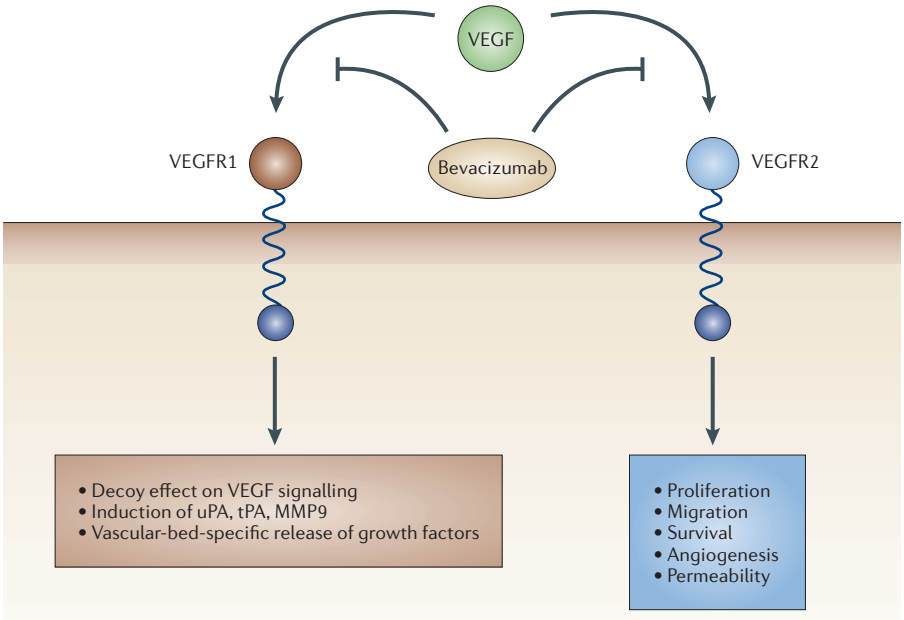

Figure 4 | **VEGF signalling and cancer: a simplified view.** VEGFR1 and VEGFR2, the receptors for vascular endothelial growth factor (VEGF), are expressed on the surface of blood endothelial cells. VEGFR2 is thought to be the major mediator of endothelial cell mitogenesis, survival and microvascular permeability, and VEGFR1 has other activities that can be important in cancer, including induction of matrix metalloproteinases (MMPs). Bevacizumab, a humanized anti-VEGF antibody, blocks the interaction of VEGF with its receptors. Reproduced, with permission, from REF. 31 © Macmillan Magazines Ltd (2005). tPA, tissue plasminogen activator; uPA, urokinase-type plasminogen activator.

Enfuvirtide

Elucidation of the life cycle of human immunodeficiency virus (HIV) in the 1980s revealed a number of targets for therapeutic intervention, leading to the development of several classes of drugs that have revolutionized the treatment of HIV. There have also been considerable efforts to develop anti-HIV vaccines. Indeed, the discoveries that led to the development of enfuvirtide (Fuzeon) — the first member of the most recent class of anti-HIV drugs to be approved, known as HIV entry enhibitors — were serendipitously made during such efforts. Synthetic peptides derived from the HIV glycoprotein gp41 were investigated as part of an epitope-mapping experiment in preparation for developing an anti-HIV-1 vaccine; when some of these peptides were incubated with human T cells, an antiviral effect was observed. Further study of the fusion process between HIV-1 and CD4 cells

showed that these peptides acted as decoys of their natural analogues and inhibited the entry of HIV-1 into T cells[34] (FIG. 5). The pursuit of this line of research eventually led to the identification of several peptides derived from gp41, of which enfuvirtide, a peptide corresponding to positions 643–678 in gp160, had the greatest antiviral activity, leading to its selection for development.

However, chemically manufacturing a peptide of 36 amino acids posed a considerable challenge, with the synthesis requiring 106 steps[33]. But overcoming this hurdle, and achieving a production capacity of several tonnes per year, turned out to be very rewarding. The drug was investigated in large-scale trials that enrolled heavily treatment-experienced patients with multi-drug-resistant HIV infections. The trials also used an innovative, but challenging, design in which the drug was either added or not to a background regimen that was individually optimized to each patient. In these trials, the addition of enfuvirtide provided significant antiretroviral and immunological benefits[33,35,36], and it received accelerated approval in 2003, providing a much-needed new treatment option. Enfuvirtide has contributed significantly to the goal of suppressing HIV RNA to the largest possible extent and of preventing the selection of resistant viral mutants[37]. And apart from its own role, enfuvirtide exemplifies a new mechanistic principle — viral entry inhibition — that will undoubtedly be exploited further in HIV therapy, and also in the treatment of other viral infections.

Discussion: the concept of magic bullets

This article has so far briefly touched on the different scientific paradigms that have influenced drug discovery. Independently of these changes, one vision — that of the 'magic bullet' — has inspired scientific drug discovery from its very beginnings and has remained with this multidisciplinary endeavour ever since. Paul Ehrlich, who first used this term to describe the specific action of antibodies, might have taken it from the romantic opera 'Der Freischütz', which became hugely popular during the nineteenth century. In it a young man sells his soul to the devil for a number of magic bullets, so as to prevail in a marksmanship contest in which he is expected to win the hand and heart of the lady he loves. Fortunately, the young hero not only wins the contest and the hand of his lady, but also regains his soul — an ideal ending. And in drug research, with the growth of chemistry, pharmacology and other disciplines, the ideal of generating 'magic bullets' or achieving exclusive and absolute specificity has been a constant aim. The switch from mechanism- to target-oriented drug discovery brought about by molecular genetics and genomics has recently re-established this ideal in a strict molecular context.

So far, our efforts to find and develop novel drugs have been largely guided by this 'puritan' ideal of specificity and exclusivity. Ideally, an agent should interact with one selected target, elicit a premeditated or intended response, disengage from the target and be metabolized and excreted without any further effects on the organism in question. Indeed, the five drugs briefly discussed above all reflect this vision. Exclusive inhibition of COX2 was considered to be desirable, because this enzyme, and not COX1 or any other target, was seen as the initiator of inflammatory responses and of pain connected with inflammation. The blockade of one integrin by an antibody to its α4 subunit — natalizumab — was pursued because this protein seems to be particularly crucial in the control of the traffic of T cells into the brain. Imatinib was chosen from a series of compounds for its almost selective activity against a deregulated tyrosine kinase (BCR–ABL) that drives the proliferation of immature myelocytes in CML. In this case, the additional efficacy of imatinib against other kinases involved in cancerous growth might have been regarded desirable at a relatively early stage of development.

Bevacizumab also reflects the principle of selectivity, although with a more generous rationale. By eliminating a crucial ligand, the activity of two receptors that are stimulated by VEGF and the respective downstream events (FIG. 4) are inhibited (the more selective inactivation of each of the two receptors would have represented a less effective and a more time-consuming and expensive strategy). Finally, enfuvirtide represents a pure example of a 'magic bullet', afforded by the creation of a decoy that mimics one crucial structure in the fusion process between an HIV-1 virus and a T cell (FIG. 5).

In summary, drug discoverers have recently been able to generate molecules that fulfill the demands of the 'magic bullet' concept to a considerable degree. The visionary request made by Moshe Talpaz during the meeting that conventional cancer chemotherapy should be replaced step by step by targeted therapy illustrates what has already been achieved and indicates how drug therapy against cancer should develop over the coming years. However, two open issues remain. In spite of a growing sophistication in describing the molecular details of a particular target — for example, HIV protease — the ideal of designing drugs *de novo* or synthesizing tailor-made chemicals that fulfill all requirements of efficacy, tolerance and absorption, distribution, metabolism and excretion (ADME) characteristics has remained elusive. We have made progress in molecular modelling and in defining 'chemical spaces' related to particular targets. Apart from monoclonal antibodies, however, we cannot create magic bullets on the basis of science alone. We must still rely on contributions that one could classify as semi-rational. Personal experience,

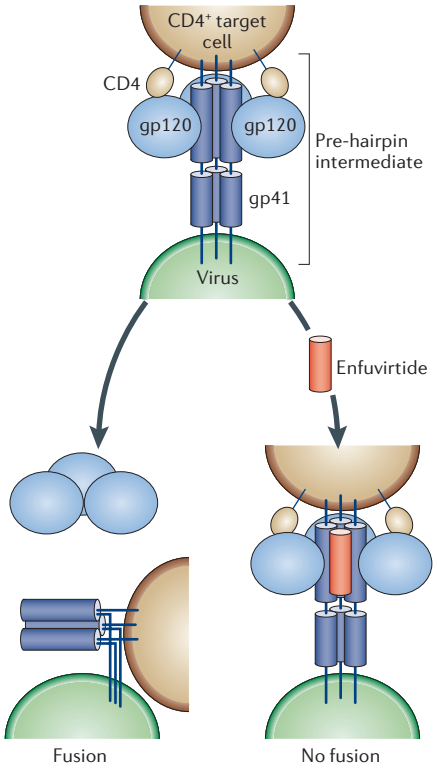

Figure 5 | **Viral entry in the HIV life cycle.** The figure gives a simplified view of the mechanism of entry of HIV-1 into host cells. The envelope glycoprotein of HIV-1 consists of two subunits, gp120 and gp41. After attachment of the virus to host cells that carry the CD4 receptor, gp120 interacts with the CD4 receptor, initiating a series of conformational changes in gp41 and gp120 that lead to the insertion of the hydrophobic amino terminus of gp41 into the host-cell membrane, and the formation of the fusion intermediate at the top of the figure. Subsequent conformational changes in gp41 bring the viral and cellular membranes close enough for membrane fusion to occur (a process known as gp41 zipping)[33]. By binding to gp41, enfuvirtide prevents the successful completion of gp41 zipping and subsequent viral entry. Adapted, with permission, from REF. 43 © Macmillan Magazines Ltd (1998).

intuition, serendipity and luck still play a role alongside rigorous science and rational thinking, and they probably always will.

The second, and perhaps more serious, comment concerns the principle of the 'magic bullet' itself — or, as we would say today, the concept of exclusivity in which a drug interacts with only one target. In any therapy with drugs that inhibit protein kinases or other elements of signal transduction, compounds that address a few selected targets could hold greater promise than medicines that are entirely exclusive in their target interactions. Cancer therapy might be the first area in which this supposition is substantiated. In fact, imatinib might already be the prototype of a drug with 'intended' multiple specificities. At least in some multifactorial diseases, a drug with multiple well-chosen points of attack might be preferable to a drug with only one target, even if that target is crucial and its engagement by the drug in question absolutely specific. In searching for and developing such compounds, we should bear in mind that physiological regulatory mechanisms are not always strictly hierarchical, but can also function in parallel. After all, physiological redundancies and pleiotropic mechanisms have represented successful evolutionary strategies to many organisms. Although it can be difficult to find drugs that interact specifically with one target molecule, the identification of molecules that will address several desired targets will be even harder. Eventually, however, drug discovery must not only identify single, crucial points of attack, but must take into account the evolutionary complexities of biological systems.

So far, target-oriented drug discovery has been tantamount to aiming chemically at a single molecular entity[38]. Overall, the outcome of this widely hailed approach has been disappointing. Some authors have therefore advocated a return to biology-driven strategies that expose drug candidates to more complex test systems[39,40]. This does not mean a return to crude empirical techniques of the past, but should rather entail the generation of test systems that combine molecular detail with the interactiveness of a biological system. Such a system could, for instance, be composed of several cell types that are crucial for a physiological or pathological reaction such as inflammation, and could allow several relevant read-outs. Approaches of this type might indeed help to select compounds that address a typical combination of targets, rather than a single molecular entity[41]. The continued systematic review of recently developed and/or marketed drugs in the form of carefully studied case histories could soon offer us further clues with respect to the relative advantages or disadvantages of classical 'magic bullets' as opposed to such 'magic bullets of the second order'.

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Competing interests statement
The author declares no competing financial interests.

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