The discovery of first-in-class drugs: origins and evolution

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Abstract | Analysis of the origins of new drugs approved by the US Food and Drug Administration (FDA) from 1999 to 2008 suggested that phenotypic screening strategies had been more productive than target-based approaches in the discovery of first-in-class small-molecule drugs. However, given the relatively recent introduction of target-based approaches in the context of the long time frames of drug development, their full impact might not yet have become apparent. Here, we present an analysis of the origins of all 113 first-in-class drugs approved by the FDA from 1999 to 2013, which shows that the majority (78) were discovered through target-based approaches (45 small-molecule drugs and 33 biologics). In addition, of 33 drugs identified in the absence of a target hypothesis, 25 were found through a chemocentric approach in which compounds with known pharmacology served as the starting point, with only eight coming from what we define here as phenotypic screening: testing a large number of compounds in a target-agnostic assay that monitors phenotypic changes. We also discuss the implications for drug discovery strategies, including viewing phenotypic screening as a novel discipline rather than as a neoclassical approach.

First-in-class drugs
Drugs that modulate an as-yet unprecedented drug target or biological pathway.

Phenotypic screening
The testing of a large number of — in most cases randomly selected — compounds in a systems-based assay.

Target-based approaches
Hypothesis-based approaches that aim to manipulate a biological system by pharmacologically modulating a specific component or target (an enzyme, receptor, and so on).

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Since Drews and Ryser[1] published an analysis on escalating research and development (R&D) costs in the pharmaceutical industry and discussed the consequences if this increase continued, many additional studies and perspectives have been published on the trends, metrics and measures that drive R&D productivity. Several have offered possible solutions to increase R&D efficiency[2–8], but some are rather pessimistic and raise doubts about the sustainability of the current drug discovery model[9–11]. In fact, the numbers are concerning. Over the past six decades the average inflation-adjusted cost of bringing a new drug to market has been increasing constantly and is doubling approximately every 9 years, despite scientific discoveries and technological advances that include modern molecular biology methods, high-throughput screening, structure-based drug design, combinatorial and parallel chemistry, and the sequencing of the human genome[8]. These innovations have allowed a rational, target- and hypothesis-driven approach to drug discovery and were implemented with the promise of greatly enhancing the productivity of R&D. However, so far there has been little apparent impact of these advances on the number of drug approvals by the US Food and Drug Administration (FDA).

An excellent recent analysis of new medicines that were approved by the FDA during the 10-year period from 1999 to 2008 found that, of the first-in-class drugs that are small molecules, 28 were discovered through phenotypic screening, whereas 17 originated from target-based approaches[12]. Given that this was an era in which the focus and investment was heavily biased towards target-based approaches, the apparent greater success of phenotypic screening in the discovery of innovative small-molecule drugs raises several important questions. Has the pharmaceutical industry invested in the wrong technologies for almost three decades? Should the industry return to a 'classical' phenotypic approach to drug discovery, as postulated by some[13–16]? What is the basis for the apparent superiority of phenotypic screening over target-based approaches, and what are the implications for future drug discovery projects?

A definition of phenotypic screening

To try to answer these questions, we analysed the origins of the first-in-class drugs approved by the FDA between 1999 and 2013, an extension of 5 years over the previous analysis[12]. We considered this extension to be important in evaluating the impact of target-based approaches,

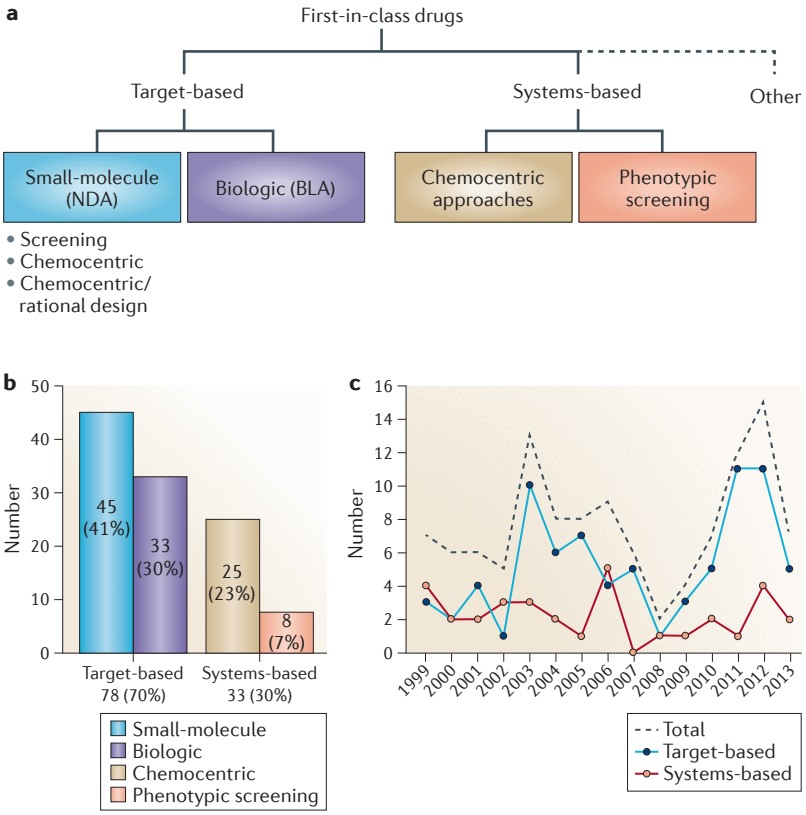


Figure 1 | **Discovery of first-in-class drugs approved by the FDA between 1999 and 2013.** **a** | First-in-class drugs were classified according to whether they were discovered in a systems-based, target-agnostic manner or using a hypothesis-driven, target-based approach. Central to the discovery of systems-based drugs was either a phenotypic screen or a chemocentric approach starting from a known compound or compound class. Target-based drugs were categorized into small-molecule drugs and biologics depending on whether they were approved by the US Food and Drug Administration (FDA) under a new drug application (NDA) or biologics license application (BLA), respectively. **b** | The majority of first-in-class drugs were discovered through target-based approaches with slightly more small-molecule drugs than biologics. Most drugs that were discovered through systems-based approaches originated from a known compound or compound class (that is, a chemocentric approach), and only a few were based on a phenotypic screen as defined in this article. **c** | There is no statistically significant trend over the 15-year period that would indicate a growing superiority of one approach over the other. However, from 2003 onwards (with two exceptions), the number of newly approved target-based first-in-class drugs exceeds that of system-based drugs, and since 1999 the level of systems-based drugs has been constantly low.

given their relatively recent introduction in the context of the long time frames of drug discovery and development. We also realized that the conclusions that can be drawn from the data depend on a clear definition of the drug discovery approaches and on careful use of terminology. The term 'phenotypic screening' in particular appears to be used rather loosely and with different meanings. In the original analysis[12], and also in a subsequent paper focused on first-in-class drugs[17], phenotypic screening was considered to encompass all non-target-based approaches to drug discovery. However, for the purpose of this analysis we define phenotypic screening more specifically as the testing of a large number of (in most cases randomly selected) compounds in a systems-based approach using a target-agnostic assay that monitors phenotypic changes. We believe that this is how the term is understood and used in most research laboratories today.

Using this definition, it is apparent that not all systems-based approaches to drug discovery rely on phenotypic screening. Aspirin, for example, was not discovered through phenotypic screening in this sense, but through the isolation and further derivatization of an active ingredient from a plant extract, the pharmacological activity of which was known for hundreds of years[18]. In fact, before the invention of modern molecular biology tools in the mid-1980s and the technological advances in high-throughput screening in the early 1990s, most drugs were discovered based on studies with a particular compound or compound class in a systems-based and target-agnostic manner[19]. For this approach, we would like to coin the term 'chemocentric drug discovery' and propose to categorize drug discovery approaches as shown in FIG. 1a, with systems-based drug discovery subdivided into two categories: phenotypic screening and chemocentric approaches. The latter approaches typically include the identification of an active ingredient from a plant or microbial extract with known pharmacological activity (for example, aspirin) or the derivatization of a pharmacologically active natural substance (for example, prostaglandins, steroids, nucleosides, amino acids and biogenic amines) or synthetic chemical, often based on serendipitous findings made decades before. We found many such cases in our analysis, and some are highlighted in BOX 1.

With the advent of gene cloning and sophisticated molecular biology techniques in the mid-1980s, it was possible to work in a more hypothesis-based, rational and systematic manner on particular protein targets. Many pharmaceutical companies quickly switched to this new approach, which is typically referred to as target-based drug discovery. High-throughput technologies for screening large compound libraries in target-based assays have been used to discover many new, synthetic or naturally occurring pharmacologically active compounds with low molecular mass[20]. Molecular biology techniques have also enabled the development of therapeutic biologics, such as monoclonal antibodies that are specific for a particular protein target[21]. For our analysis, we have therefore divided target-based drugs into these two categories (FIG. 1a).

Analysis

First-in-class drugs and their origins. Our analysis covers a time frame of 15 years (1999–2013), during which 113 first-in-class drugs were approved by the FDA (see the Drugs@FDA database). The results are shown in FIGS 2,3,4 and the data are listed in Supplementary information S1 (table). Drugs were designated as first-in-class drugs based on their modulation of an — until then — unprecedented target or biological pathway. This was considered to be independent of the mechanism of modulation; that is, if two drugs modulate the same target with the same biological consequence but bind to different sites (for example, the active site versus allosteric

Small-molecule drugs
Drugs with a low molecular mass (typically < 1,000 Da); this includes synthetic drugs, natural products (or derivatives) and natural substances (or derivatives).

Systems-based approach
Hypothesis-agnostic assay or approach that monitors or is based on a phenotypic change *in vitro* or *in vivo*.

Box 1 | **Examples of chemocentric drug discovery**

Ingenol angelate
Plants of the *Euphorbiaceae* family have been used for the treatment of cancers and warts since at least 400 BC. The isolation of ingenol angelate as one of the active principles in 1983 led to the development of a drug that was approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of actinic keratosis[55].

Nitisinone
Nitisinone, which was approved in 2002 for the treatment of hereditary tyrosinaemia type 1, is based on a compound class developed as herbicides in the 1970s (originating from natural products, beta-triketones, which were known for decades). The toxicological profile, together with the subsequently elucidated mechanism of action, led to the therapeutic hypothesis and start of clinical development in 1989 (REF. 56).

Varenicline
Varenicline, another drug derived from a natural product, was approved in 2006 for smoking cessation and is based on cytisine, which has been known since 1912 as a substance with nicotine-like activity[57].

Nelarabine
Nelarabine is an example of a drug derived from a natural substance. It was known since the 1960s that some nucleoside analogues (for example, cytosine arabinoside) have antitumour activity[58]. Later, deoxyguanosine analogues[59] and arabinosyl guanine[60] were found to be selectively toxic for leukaemic T cells. Nelarabine, which was approved in 2005 for the treatment of T cell acute lymphoblastic leukaemia and T cell lymphoblastic lymphoma, is a water-soluble prodrug of arabinosyl guanine[61].

Docosanol
Docosanol is a synthetic low-molecular-mass molecule. Based on the finding that butylated hydroxyl toluene, a food additive, integrates into membranes and disturbs them, the antiviral activity of long-chain unsaturated monoglycerides and alcohols was discovered, and docosanol was thus approved as antiviral agent in 2000 (REF. 62).

Ezogabine
Ezogabine, also known as retigabine, is another synthetic low-molecular-mass molecule and was synthesized as a back-up compound to flupirtine, which was discovered in the 1960s in an effort to find novel analgesics with a mode of action different from opiates. Ezogabine is a 2,3,6-triaminopyridine derived from the known analgesic pyridium (discovered in the 1930s). Later, ezogabine as well as flupirtine were found to possess anti-epileptic activity in addition to their analgesic activity in various animal models, and ezogabine was approved for the treatment of epilepsy in 2011 (REF. 63).

Chemocentric approaches
Drug discovery approaches based around a specific compound or compound class. Chemocentric approaches have made a substantial contribution both to drugs originating from systems-based approaches and to drugs originating from target-based approaches.

Natural substance (or derivative)
A chemical substance (or derivative thereof) produced by a living organism found in nature that usually has pharmacological or biological activity. For this article we arbitrarily excluded natural products from natural substances to keep the former as a separate class of compounds.

Biologics
Defined here as all drugs approved under a biologics license application (BLA) by the US Food and Drug Administration (FDA); usually antibodies and other proteins.

Chemotype
A family of molecules that possess the same core structure or scaffold.

site of an enzyme), only the drug that was approved first has been categorized as first-in-class. For the purpose of our analysis, we excluded diagnostic drugs such as contrast agents.

We searched scientific publications and the patent literature using the chemical structure of the molecule and its mechanism of action to identify the following: the origins of the relevant chemotype; the findings that led to the formulation of the therapeutic hypothesis and the link to the final indication; the methods and technologies that were used for the discovery of the drug, and the first publication on the final drug molecule. We have defined the starting point for drug discovery as the publication of the key finding that, at the time, enabled the initiation of dedicated drug discovery efforts. In many cases, these key initial findings were the identification of the target or chemotype. In our analysis, we have not taken into account the fundamental research that led to these key findings, which in itself often constituted a series of important discoveries. Therefore, our definition of the starting point arbitrarily separates the foundation of scientific studies from drug discovery; however, in reality they are closely linked.

For example, the capacity of tumour cells to stimulate angiogenesis was discovered in 1945 (REF. 22) and the presence of soluble tumour-derived factors was demonstrated in 1968 (REF. 23). This led to the formulation of the 'anti-angiogenesis' therapeutic concept for the treatment of tumours[24]. The subsequent purification of vascular endothelial growth factor (VEGF) in 1983 (REF. 25) and its cloning in 1989 (REF. 26) facilitated the discovery of bevacizumab, the first VEGF-specific antibody[27]. For our analysis, we have chosen the purification of VEGF as the starting point of drug discovery efforts. Another example is the discovery of imatinib for the treatment of chronic myelogenous leukaemia (CML)[28]. A chromosomal abnormality, the Philadelphia chromosome, was discovered in 1960 in white blood cells of patients with CML[29]. In 1973 the Philadelphia chromosome was shown to be a translocation between chromosomes 9 and 22 (REF. 30). A series of subsequent discoveries resulted (in 1985) in the insight that the chromosomal translocation leads to the expression of the BCR–ABL fusion protein and led to the hypothesis that its tyrosine kinase activity drives malignant transformation[31]. Imatinib was subsequently developed as an inhibitor of the BCR–ABL kinase. Given the scope of this analysis, we selected the discovery of the BCR–ABL fusion protein as the starting point for drug discovery.

We also realize that what we have identified as a first publication might not always represent the exact starting point of discovery efforts towards a particular drug. This might pertain more to systems-based drugs, as the first publication of the chemotype — which usually is also the first publication of such projects — may have occurred several years after the initiation of drug discovery activities. In addition, publication intensity was substantially lower before the 1980s. For target-based drugs, however,

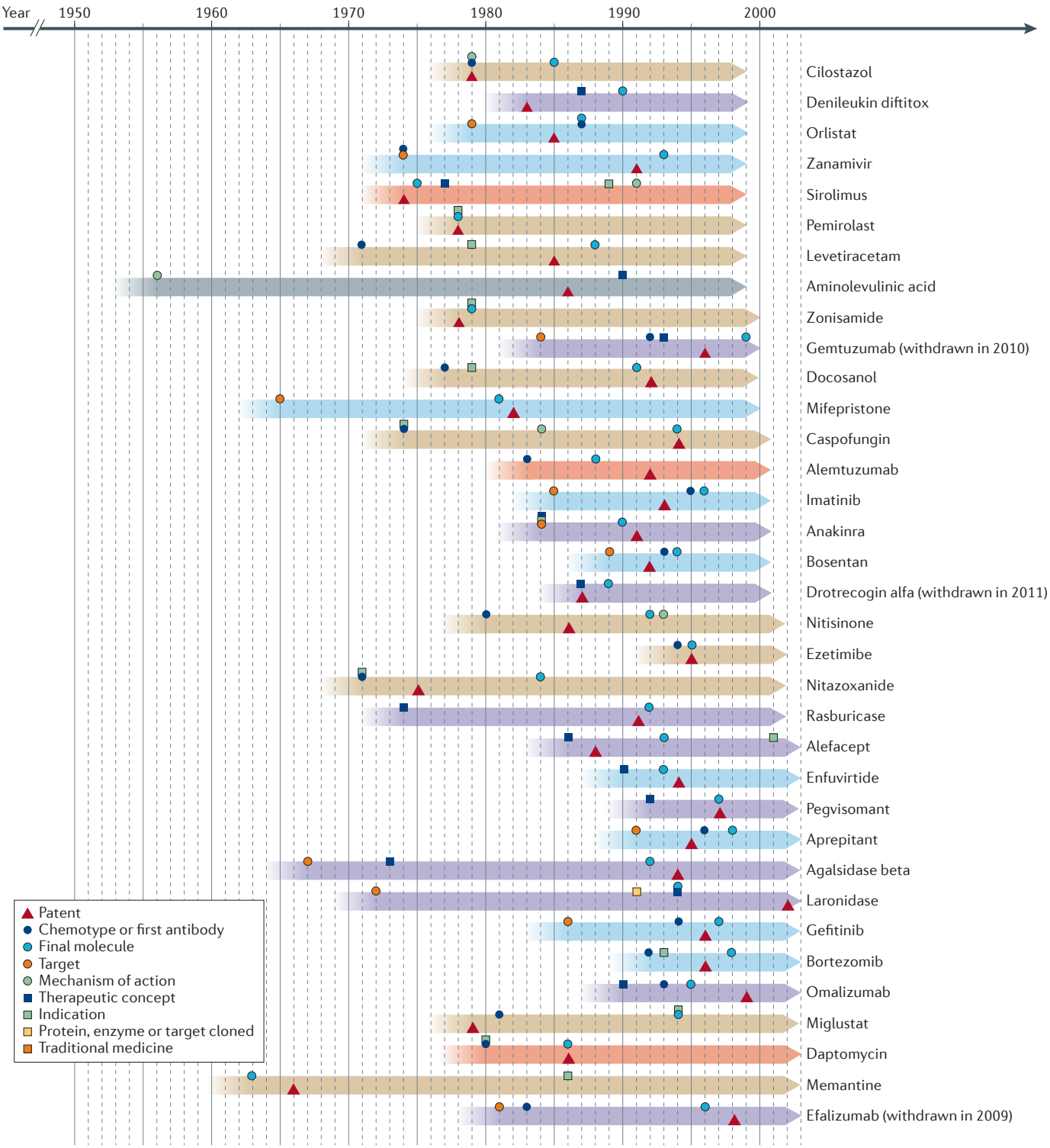


Figure 2 | **Chronology of the discovery of first-in-class drugs approved between 1999 and 2003.** All 113 first-in-class drugs approved by the US Food and Drug Administration (FDA) between 1999 and 2013 are listed in the order of their approval date in FIGS 2,3,4. This figure shows those approved in the 5-year period from 1999 to 2003. The colour coding for the different approaches, systems-based phenotypic screening, systems-based chemocentric, target-based small-molecule drug and target-based biologic, is defined as in FIG. 1. Other drugs are represented by grey arrows. Important points in the discovery chronology of each drug, such as the publication year of the patent covering the final drug molecule and the publication year of the final molecule, are indicated on the arrows using the symbols in the key. The first publication, usually the identification of the chemotype, target or concept, does not necessarily mark the exact starting point of discovery efforts towards a particular drug; this is symbolized by the fading at the beginning of each arrow. For details of each drug, see Supplementary information S1 (table).

we believe that many projects were initiated around the time of the publication of the target hypothesis, which we take as the typical starting point of such projects. In fact, some target-based drug discovery projects might even have started later than that. Despite these uncertainties, we think that our analysis gives a clear picture of the various drug discovery approaches and chronology of events.

Drug types and discovery approaches. According to our analysis and definitions, of the 113 first-in-class drugs, 33 (30%) were discovered through systems-based approaches and 78 (70%) were discovered from target-based approaches (FIG. 1b); the numbers discovered per year from each approach are shown in FIG. 1c. Two drugs were classified as 'other': aminolevulinic

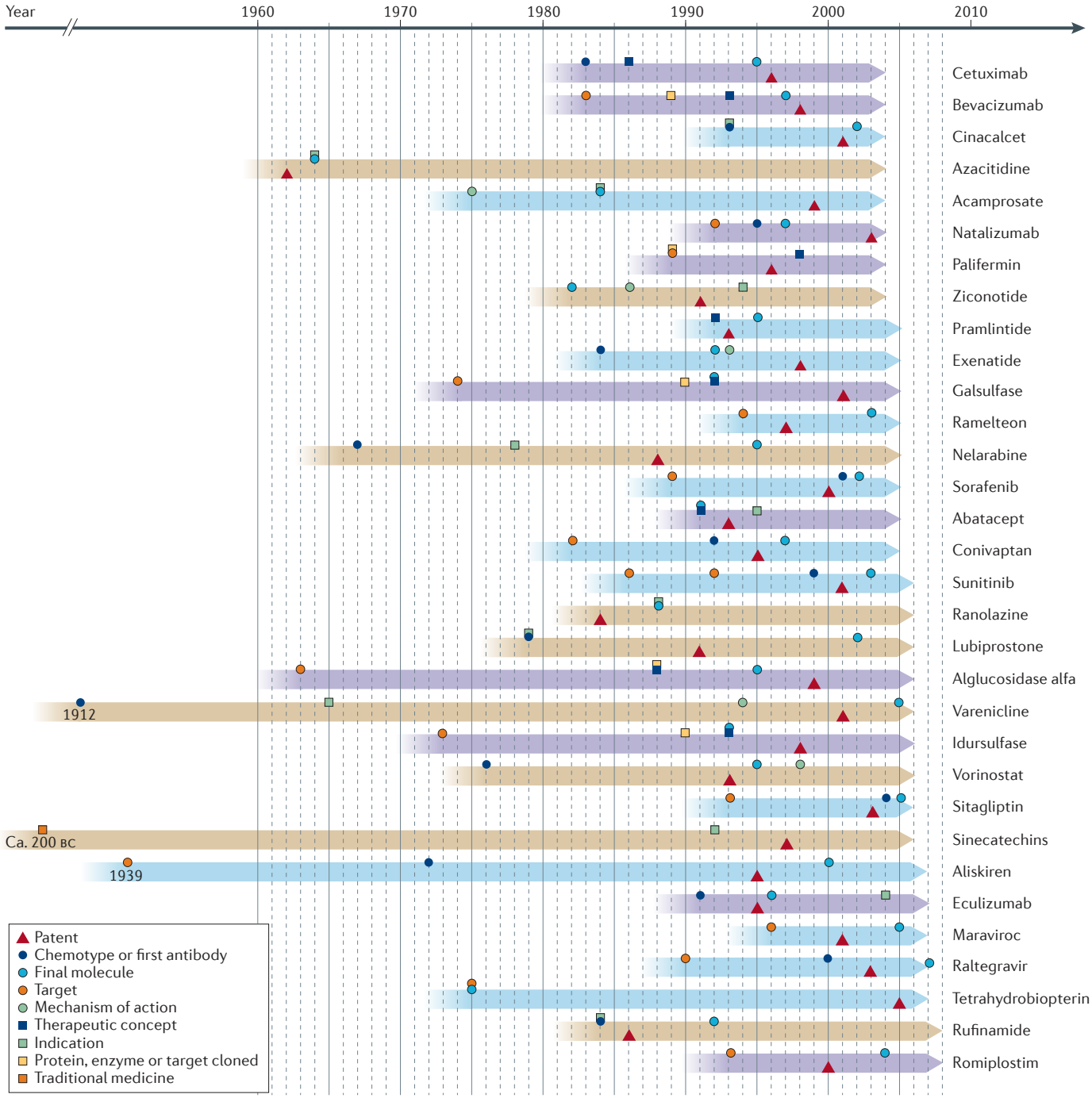
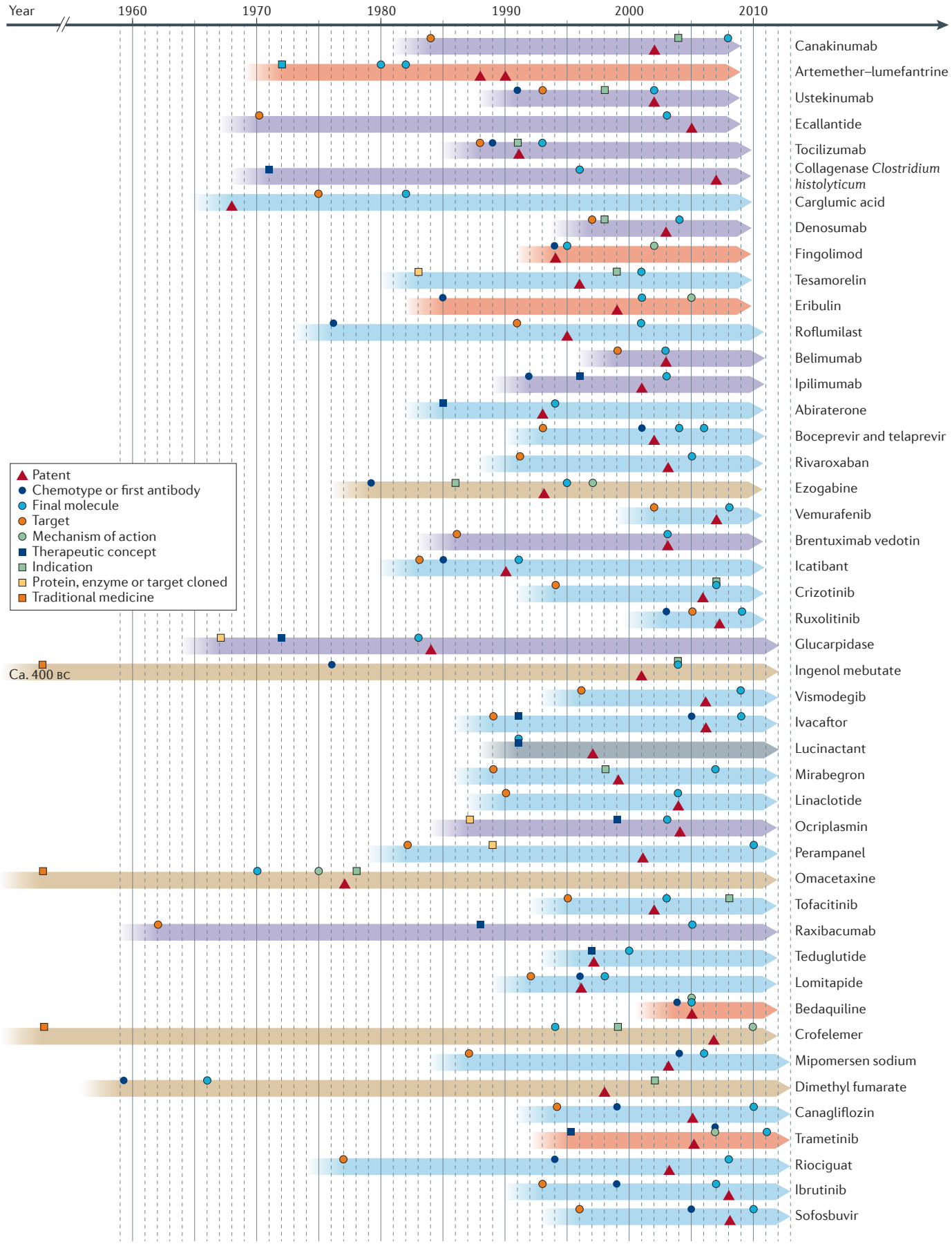


Figure 3 | **Chronology of the discovery of first-in-class drugs approved between 2004 and 2008.** The colour coding for the different approaches, systems-based phenotypic screening, systems-based chemocentric, target-based small-molecule drug and target-based biologic, is defined as in FIG. 1. Important points in the discovery chronology of each drug are indicated on the arrows using the symbols in the key. For details of each drug, see Supplementary information S1 (table).



◂ Figure 4 | **Chronology of the discovery of first-in-class drugs approved between 2009 and 2013.** The colour coding for the different approaches, systems-based phenotypic screening, systems-based chemocentric, target-based small-molecule drug and target-based biologic, is defined as in FIG. 1. Other drugs are represented by grey arrows. Important points in the discovery chronology of each drug are indicated on the arrows using the symbols in the key. For details of each drug, see Supplementary information S1 (table).

acid (a precursor of protoporphyrin, which is used for photodynamic therapy) and lucinactant (a peptide that lowers alveolar surface tension, used for the treatment of respiratory distress syndrome).

Target-based drugs are divided into 45 (41%) small-molecule drugs and 33 (30%) biologics. Biologics were typically found by screening (antibodies) or rational design. The starting points for target-based small-molecule drugs were derived as follows: 21 from various screening methods (18 from high-throughput screening, one from fragment-based screening, one from *in silico* screening and one from low-throughput screening); 18 from chemocentric approaches (for example, the starting points were analogues of known ligands for the target or related targets); and six from rational design, in most cases based on a known substrate.

Of the 33 systems-based drugs, 25 were small-molecule drugs that were discovered through chemocentric approaches (which were considered as a type of phenotypic screening in the previous analysis)[12]. A further seven small-molecule drugs were discovered by phenotypic screening according to the more specific definition we use: sirolimus, daptomycin, artemether–lumefantrine, fingolimod, eribulin, bedaquiline and trametinib. The other drug we classified as being discovered through a phenotypic screening approach was alemtuzumab, an antibody directed against CD52 that was discovered by raising antibodies against human peripheral blood mononuclear cells without knowledge of the target.

Three of the small-molecule drugs originating from phenotypic screening (sirolimus, fingolimod and eribulin) are natural product-derived compounds that were found by analysing a discrete number of extracts for specific biological activity, with some prior knowledge on similar extracts (see Supplementary information S1 (table)). Interestingly, the original phenotypic activity of sirolimus and that of the fingolimod precursor myriocin were unrelated to their therapeutic activity, which only became apparent during follow-up studies. Of the eight drugs discovered through phenotypic screening, three are anti-infective, four are anti-proliferative or cytotoxic molecules, and one — fingolimod — is an immunosuppressive drug.

Natural product (or derivative)
Secondary metabolites (or derivatives thereof) that are extracted from tissues of plants, marine organisms or microorganism fermentation broths.

Pharmacophore
The steric and electronic features of a ligand that are necessary to ensure optimal interactions with a biological target structure and to trigger (or to block) its biological response.

Target- versus systems-based approaches

At first glance, the results of our analysis appear to significantly deviate from the numbers previously published for first-in-class drugs, which reported that of the 75 first-in-class drugs discovered between 1999 and 2008, 28 (37%) were discovered through phenotypic screening, 17 (23%) through target-based approaches, 25 (33%) were biologics and five (7%) came from other approaches[12]. This discrepancy occurs for two reasons. First, we consider biologics to be target-based drugs, as there is little philosophical distinction in the hypothesis-driven approach to drug discovery for small-molecule drugs versus biologics. Second, the past 5 years of our analysis time frame have seen a significant increase in the approval of first-in-class drugs, most of which were discovered in a target-based fashion.

With regard to the second reason, it is interesting to look at the time frame for drug discovery projects. For all the drugs in our data set, we calculated the apparent median time from the first publication of the therapeutic concept, target or chemotype to FDA approval, and found that it was 22 years. There was also a statistically significant difference in the median time frame for drugs that were discovered through systems-based versus target-based approaches: 25 and 20 years, respectively (Supplementary information S2 (box)). Therefore, taking into account the fact that the tools needed to efficiently discover drugs in a hypothesis-driven manner — including modern gene cloning and expression methods, high-throughput screening, crystallography and the sequencing of the human genome — have only become established or sufficiently advanced between 1985 and 2000, it is not surprising that the impact of these tools on target-based drug discovery may only have begun to become apparent in more recent years[12].

Interestingly, all but four systems-based drugs have their beginnings before 1985, and one of those four drugs — ezetimibe — originated from a target-based drug discovery project until it was noticed that the lead molecule had *in vivo* activity independently of, or in addition to, its target-based activity[32]. So, the finding that a considerable number of systems-based drugs have been approved over the past 10 years is likely to be due in part to the length of time these projects took.

The data also suggest that target-based drug discovery might have helped reduce the median time for drug discovery and development. Closer examination of the differences in median times between systems-based approaches and target-based approaches revealed that the 5-year median difference in overall approval time is largely due to statistically significant differences in the period from patent publication to FDA approval, where target-based approaches (taking 8 years) took only half the time as systems-based approaches (taking 16 years) (Supplementary information S2 (box)).

The pharmaceutical industry has often been criticized for not being sufficiently innovative. We think that our analysis indicates otherwise and perhaps even suggests that the best is yet to come as, owing to the length of time between project initiation and launch, new technologies such as high-throughput screening and the sequencing of the human genome may only be starting to have a major impact on drug approvals. Target-based drug discovery, together with modern screening technologies, has also greatly broadened the scope of pharmacophores available for medicinal chemistry[20], and increased the number of 'tool compounds' to use for investigating biological systems, potentially leading to new therapeutic

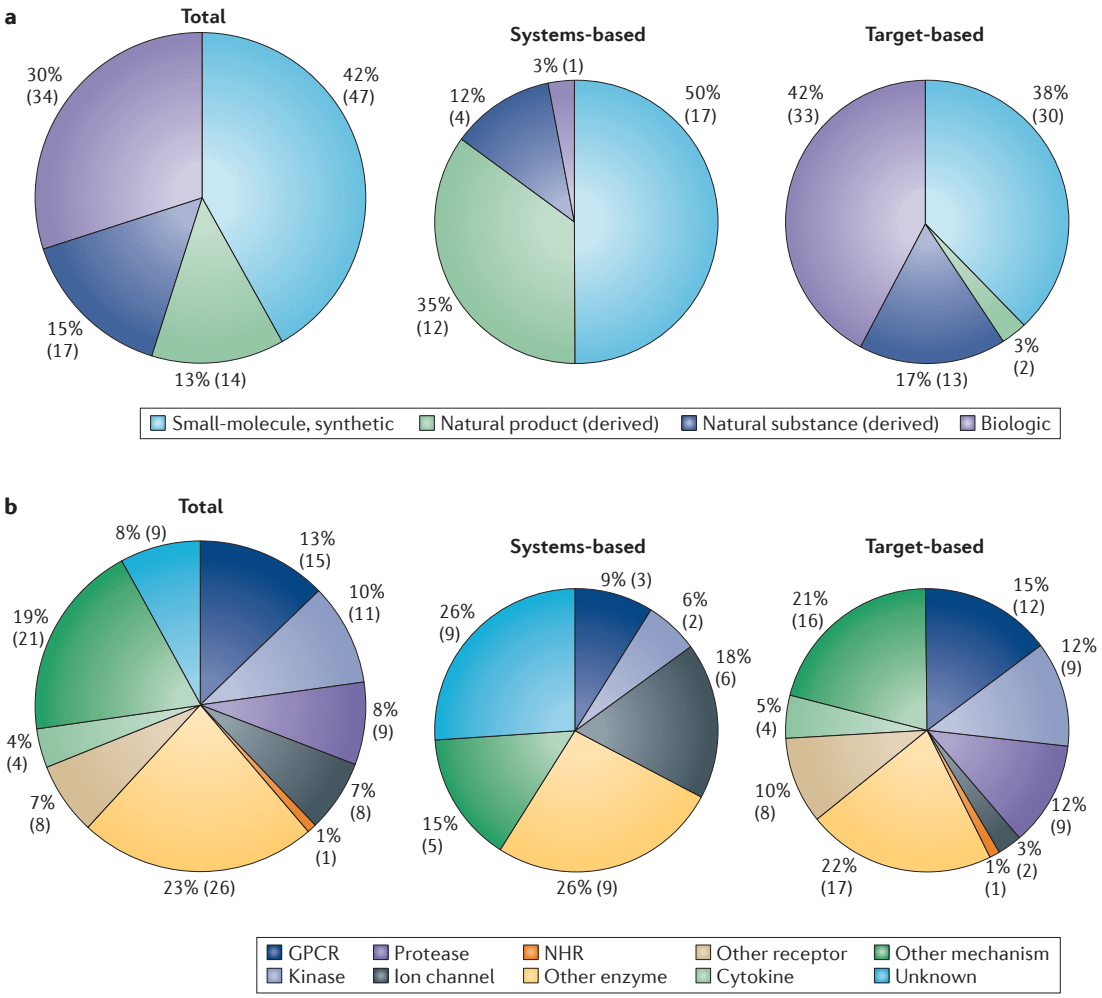


Figure 5 | **Distribution of first-in-class drugs according to the molecule type and target family.** **a** | The distribution according to molecule type (that is, the source of the drug molecule) differs between systems- and target-based approaches. There is a strong bias for the use of natural products for systems-based approaches over target-based approaches, whereas biologics have only had a major impact in the target-based space. Note that artemether–lumefantrine was counted twice as it contains two drugs. **b** | The distribution of drugs across target families. G protein-coupled receptors (GPCRs), kinases, proteases and ion channels constitute the major target families. Kinase and protease inhibitors are prominent in the list of target-based drugs, but under-represented or absent from that of systems-based drugs. By contrast, the fraction of drugs targeting ion channels is significantly higher among systems-based drugs. Note that memantine was counted twice as it modulates GPCRs as well as ion channels. NHR, nuclear hormone receptor.

targets and/or chemical starting points for new drugs. One question that may be asked, although a rather academic one, is what course the industry would have taken in the absence of these innovations: that is, at what point in time would the industry have run out of chemotypes as starting points for the classical chemocentric approach?

Molecules and target families

Of the 113 first-in-class drugs, 34 (30%) are biologics, 14 (13%) are natural products or compounds derived thereof, 17 (15%) are natural substance-derived molecules (including peptides, but arbitrarily excluding natural products to keep this class of compounds separate for the analysis) and 47 (42%) are other small-molecule drugs, mainly low-molecular-mass synthetic compounds (FIG. 5a). Although natural substances appear to be the basis for a similar proportion of the drugs discovered by target- and systems-based approaches (17% and 12% respectively), natural products were the basis for a much more substantial proportion of systems-based approaches. Of the 33 systems-based drugs, 12 (35%) are derived from natural products, whereas only two (3%) of the 78 target-based drugs are derived from natural products: orlistat, which is based on the lipase inhibitor lipstatin; and canagliflozin, which is based on phlorizin. Of the 14 natural product-derived first-in-class drugs approved between 1999 and 2013, five were discovered by screening approaches (four by systems-based phenotypic screening and one by target-based high-throughput

Low-molecular-mass synthetic drug
Low-molecular-mass drugs that are not derived from natural products or natural substances.

screening) and nine were discovered by chemocentric approaches. The latter includes four drugs that were found by ethnobotanical approaches through the isolation and identification of the active ingredients of plant extracts that are used in Chinese and other traditional medicines. Natural products, therefore, have been an important source of chemotypes for systems-based drug discovery approaches and are likely to have an important role in future phenotypic screening as well as in chemocentric approaches.

The distribution of first-in-class drugs across target families is similar to that previously published for all drugs[33], with G protein-coupled receptors (GPCRs), kinases, proteases and ion channels being the major target families in addition to the 'other enzymes' category, which contains a number of smaller target families and singletons (FIG. 5b). Probably based on the lack of suitable chemotypes before the 1980s, kinase and protease inhibitors are under-represented or absent from the list of systems-based drugs, and were predominantly discovered by target-based approaches. By contrast, drugs that target ion channels are over-represented in this list, perhaps reflecting some of the difficulty and complexity in discovering such inhibitors in a target-based, rational manner.

Interestingly, for nine (26%) of the 33 systems-based drugs, the mechanism of action is unclear or even unknown, which highlights that knowledge of the mechanism of action might be helpful but is not mandatory to successfully develop a drug. However, elucidating the mechanism of action of molecules identified through systems-based approaches by using forward chemical genetics, chemoproteomics or other chemical biology methods could access a large untapped potential for the discovery of novel mechanisms and therapeutic principles[34–37]. In this way, systems- and target-based approaches are often interlinked, and what started as a systems-based drug discovery effort might uncover important tool compounds for further target-based approaches. The discovery of the mammalian target of rapamycin (mTOR) pathway, for example, was greatly facilitated by studies with sirolimus[38], and there are numerous other examples.

Phenotypic screening as a new discipline

In the course of almost three decades of target-based drug discovery, a number of evolutionary steps have been taken to improve its efficiency, and some initial problems have been addressed. In particular, there was a widespread trend in the field during the late 1990s and early 2000s to industrialize drug discovery using high-throughput methodologies in biology and chemistry. Consequently, this approach to candidate drug discovery was established as a linear sequence of separate steps — target identification, tool production and assay development, hit finding and validation, hit-to-lead progression, lead optimization and preclinical development — each of which was the focus of optimization efforts with the goal of increasing the throughput and/or efficiency of each step. The assumption was that brute force and ever-larger numbers of projects and high-throughput experiments would increase productivity.

Today, the pharmaceutical industry has largely taken a step back from this 'brute force' approach, realizing that this seemed to instead hamper creativity, innovation and, ultimately, productivity[39]. Despite all the improvements over the past decades towards more effective drug discovery, the productivity challenge remains substantial, particularly with regard to the discovery of first-in-class drugs. In this context, phenotypic screening could be an important contribution as it offers the potential to provide important pharmacological tools to study new biology[34–37] at a faster pace than classical chemocentric systems-based approaches. We would like to emphasize that, in our view, the distinction between phenotypic screening and chemocentric drug discovery is not just a semantic one; rather, phenotypic screening as we define it here is a new discipline. A plea for more phenotypic screening in drug discovery, as has been made frequently during recent years and is being implemented in many groups[40–44], should not be taken as a call to revert to the classical, chemocentric approach to drug discovery.

Phenotypic screening holds the promise to uncover new therapeutic principles and molecular pathways of currently untreatable diseases[45]. Indeed, a number of highly encouraging recent examples of potential drugs derived from phenotypic screening[46–51], such as bromodomain inhibitors[50] and hepatitis C virus NS5A inhibitors[51], are now in late-stage clinical trials. However, so far only a few of the approved drugs were discovered through phenotypic screening, the majority of them either being anti-infective or anti-proliferative compounds (see above).

Reporter gene assays are a specific category of phenotypic screens, although they are somewhat artificial and have limitations[52,53]. Many reporter gene assays have been run in pharmaceutical companies and academic institutions over the past 20 years, with a peak in the mid to late 1990s, apparently with little success in terms of delivering drug candidates. We did not find any example of a first-in-class drug originating from such a screen, but noticed several examples of target-based drugs that could have been identified in such assays.

One of the fundamental challenges of phenotypic screening is the selection of a few interesting compounds from a large list of active substances, which typically contains thousands of compounds and is often heavily dominated by unselective or toxic compounds, substances with unwanted mechanisms of action or false positives. Usually, potency is the sole criterion by which such hit lists are sorted and compounds selected for further studies, but this criterion might be inappropriate for identifying the best chemotypes. It is important to understand that we will require new methodologies and approaches to increase the success rate of phenotypic screens. For example, many diseases today are still difficult to faithfully mirror in test plates and model organisms, and the use of stem cell technology or whole-organism screens might enable the establishment of more physiological assay systems that better reflect the actual disease. Progress here will certainly increase the likelihood of finding disease-relevant pathways, but it may not enable

a more effective selection of interesting compounds, and so more innovation is required. Consequently, in order for phenotypic screening to be successful, it will be important to recognize it as a new discipline that needs new technologies and methods, and for which lessons must be learnt to avoid frustration from unrealistic expectations and premature conclusions if the current investments do not yield quick returns.

Perhaps we are in a phase today similar to the one in the mid-1980s, when systems-based chemocentric drug discovery was largely replaced by target-based approaches. This allowed the field to greatly expand beyond the relatively limited number of scaffolds that had been studied for decades and to gain access to many more pharmacologically active compound classes, providing a boost to innovation. Now, with an increased chemical space, the time might be right to further broaden the target space and open up new avenues. This could well be achieved by investing in phenotypic screening using the compound libraries that have been established in the context of target-based approaches. We therefore consider phenotypic screening not as a neoclassical approach that reverts to a supposedly more successful systems-based method of the past, but instead as a logical evolution of the current target-based activities in drug discovery. Moreover, phenotypic screening is not just dependent on the use of many tools that have been established for target-based approaches; it also requires further technological advancements.

The choice should not be between phenotypic screening or target-based discovery, as both approaches can complement each other, are interconnected and should be run in parallel[54]. Although target or pathway discovery for chemotypes identified from phenotypic screens is not necessarily required for further drug development, it could be an advantage in order to discover additional pathway nodes for target-based therapeutic intervention or to enable the discovery of follow-on drugs. Therefore, the goal will be to screen phenotypically in an efficient and effective manner and to combine phenotypic screening sensibly and productively with target-based drug discovery.

1. Drews, J. & Ryser, S. The role of innovation in drug development. *Nature Biotech.* **15**, 1318–1319 (1997).
2. Garnier, J. P. Rebuilding the R&D engine in big pharma. *Harv. Bus. Rev.* **86**, 68–70 (2008).
3. Douglas, F. L., Narayanan, V. K., Mitchell, L. & Litan, R. E. The case for entrepreneurship in R&D in the pharmaceutical industry. *Nature Rev. Drug Discov.* **9**, 683–689 (2010).
4. David, E., Tramontin, T. & Zemmel, R. Pharmaceutical R&D: the road to positive returns. *Nature Rev. Drug Discov.* **8**, 609–610 (2009).
5. Paul, S. M. *et al.* How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Rev. Drug Discov.* **9**, 203–214 (2010).
6. Kola, I. & Landis, J. Can the pharmaceutical industry reduce attrition rates? *Nature Rev. Drug Discov.* **3**, 711–715 (2004).
7. Ruffolo, R. R. Why has R&D productivity declined in the pharmaceutical industry? *Expert Opin. Drug Discov.* **1**, 99–102 (2006).
8. Scannell, J. W., Blanckley, A., Boldon, H. & Warrington, B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Rev. Drug Discov.* **11**, 191–200 (2012).
This article discusses four factors as the primary causes of the decline in pharmaceutical R&D efficiency.
9. Munos, B. Lessons from 60 years of pharmaceutical innovation. *Nature Rev. Drug Discov.* **8**, 959–968 (2009).
10. Horrobin, D. F. Realism in drug discovery — could Cassandra be right? *Nature Biotech.* **19**, 1099–1100 (2001).
11. Pammolli, F., Magazzini, L. & Riccaboni, M. The productivity crisis in pharmaceutical R&D. *Nature Rev. Drug Discov.* **10**, 428–438 (2011).
12. Swinney, D. C. & Anthony, J. How were new medicines discovered? *Nature Rev. Drug Discov.* **10**, 507–519 (2011).
This article analyses the origins of first-in-class drugs (FDA approvals from 1999 to 2008) and postulates that target-based drug discovery contributes to low productivity in pharmaceutical R&D.
13. Butcher, E. C. Can cell systems biology rescue drug discovery? *Nature Rev. Drug Discov.* **4**, 461–467 (2005).
14. Hellerstein, M. K. A critique of the molecular target-based drug discovery paradigm based on principles of metabolic control: advantages of pathway-based discovery. *Metab. Eng.* **10**, 1–9 (2008).
15. Kell, D. B. Finding novel pharmaceuticals in the systems biology era using multiple effective drug targets, phenotypic screening and knowledge of transporters: where drug discovery went wrong and how to fix it. *FEBS J.* **280**, 5957–5980 (2013).
16. Zheng, W., Thorne, N. & McKew, J. C. Phenotypic screens as a renewed approach for drug discovery. *Drug Discov. Today* **18**, 1067–1073 (2013).
17. Swinney, D. C. Phenotypic versus target-based drug discovery for first-in-class medicines. *Clin. Pharmacol. Ther.* **93**, 299–301 (2013).
18. Schrör, K. *Acetylsalicylic Acid* (Wiley, 2009).
19. Sneader, W. *Drug Discovery: A History* (Wiley, 2005).
20. Macarron, R. *et al.* Impact of high-throughput screening in biomedical research. *Nature Rev. Drug Discov.* **10**, 188–195 (2011).
21. Beck, A., Wurch, T., Bailly, C. & Corvaia, N. Strategies and challenges for the next generation of therapeutic antibodies. *Nature Rev. Immunol.* **10**, 345–352 (2010).
22. Algire, G. H. & Chalkley, H. W. Vascular reactions of normal and malignant tissues *in vivo*.1. Vascular reactions of mice to wounds and to normal and neoplastic transplants. *J. Natl Cancer Inst.* **6**, 73–85 (1945).
23. Greenblatt, M. & Shubk, P. Tumor angiogenesis — transfilter diffusion studies in hamster by transparent chamber technique. *J. Natl Cancer Inst.* **41**, 111–124 (1968).
24. Folkman, J. Tumor angiogenesis — therapeutic implications. *N. Engl. J. Med.* **285**, 1182–1186 (1971).
25. Senger, D. R. *et al.* Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* **219**, 983–985 (1983).
26. Leung, D. W., Cachianes, G., Kuang, W. J., Goeddel, D. V. & Ferrara, N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science* **246**, 1306–1309 (1989).
27. Presta, L. G. *et al.* Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res.* **57**, 4593–4599 (1997).
28. Buchdunger, E. *et al.* Inhibition of the Abl protein-tyrosine kinase *in vitro* and *in vivo* by a 2-phenylaminopyrimidine derivative. *Cancer Res.* **56**, 100–104 (1996).
29. Nowell, P. C. & Hungerford, D. A minute chromosome in human chronic granulocytic leukemia. *Science* **132**, 1497 (1960).
30. Rowley, J. D. New consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. *Nature* **243**, 290–293 (1973).
31. Shtivelman, E., Lifshitz, B., Gale, R. P. & Canaani, E. Fused transcript of abl and bcr genes in chronic myelogenous leukemia. *Nature* **315**, 550–554 (1985).
32. Burnett, D. A. *et al.* 2-Azetidinones as inhibitors of cholesterol absorption. *J. Med. Chem.* **37**, 1733–1736 (1994).
33. Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* **1**, 727–730 (2002).
34. Lokey, R. S. Forward chemical genetics: progress and obstacles on the path to a new pharmacopoeia. *Curr. Opin. Chem. Biol.* **7**, 91–96 (2003).
35. Hall, S. E. Chemoproteomics-driven drug discovery: addressing high attrition rates. *Drug Discov. Today* **11**, 495–502 (2006).
36. Pruss, R. M. Phenotypic screening strategies for neurodegenerative diseases: a pathway to discover novel drug candidates and potential disease targets or mechanisms. *CNS Neurol. Disord. Drug Targets* **9**, 693–700 (2010).
37. St Onge, R., Schlecht, U., Scharfe, C. & Evangelista, M. Forward chemical genetics in yeast for discovery of chemical probes targeting metabolism. *Molecules* **17**, 13098–13115 (2012).
38. Heitman, J., Movva, N. R. & Hall, M. N. Targets for cell cycle arrest by the immuno-suppressant rapamycin in yeast. *Science* **253**, 905–909 (1991).
39. Sams-Dodd, F. Is poor research the cause of the declining productivity of the pharmaceutical industry? An industry in need of a paradigm shift. *Drug Discov. Today* **18**, 211–217 (2013).
This paper discusses potential reasons for the high failure rate of target-based drug discovery and suggests changes to improve productivity.
40. Lee, J. A. & Berg, E. L. Neoclassic drug discovery: the case for lead generation using phenotypic and functional approaches. *J. Biomol. Screen.* **18**, 1143–1155 (2013).
41. Carragher, N. O., Brunton, V. G. & Frame, M. C. Combining imaging and pathway profiling: an alternative approach to cancer drug discovery. *Drug Discov. Today* **17**, 203–214 (2012).
42. Lee, J. A., Uhlik, M. T., Moxham, C. M., Tomandl, D. & Sall, D. J. Modern phenotypic drug discovery is a viable, neoclassic pharma strategy. *J. Med. Chem.* **55**, 4527–4538 (2012).
43. Chatterjee, A. K. & Yeung, B. K. Back to the future: lessons learned in modern target-based and whole-cell lead optimization of antimalarials. *Curr. Top. Med. Chem.* **12**, 473–483 (2012).
44. Payne, D. J., Gwynn, M. N., Holmes, D. J. & Pompliano, D. L. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Rev. Drug Discov.* **6**, 29–40 (2007).
45. Fishman, M. C. & Porter, J. A. Pharmaceuticals: a new grammar for drug discovery. *Nature* **437**, 491–493 (2005).
46. Welch, E. M. *et al.* PTC124 targets genetic disorders caused by nonsense mutations. *Nature* **447**, 87–91 (2007).

47. Rottmann, M. *et al.* Spiroindolones, a potent compound class for the treatment of malaria. *Science* **329**, 1175–1180 (2010).
48. Butchbach, M. E. *et al.* Effects of 2,4-diaminoquinazoline derivatives on SMN expression and phenotype in a mouse model for spinal muscular atrophy. *Hum. Mol. Genet.* **19**, 454–467 (2010).
49. Chen, B. *et al.* Small molecule-mediated disruption of Wnt-dependent signaling in tissue regeneration and cancer. *Nature Chem. Biol.* **5**, 100–107 (2009).
50. Filippakopoulos, P. *et al.* Selective inhibition of BET bromodomains. *Nature* **468**, 1067–1073 (2010).
51. Gao, M. *et al.* Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. *Nature* **465**, 96–100 (2010).
This paper describes the discovery of daclatasvir (BMS-790052) by phenotypic screening and further chemical optimization in the absence of target knowledge.
52. Naylor, L. H. Reporter gene technology: the future looks bright. *Biochem. Pharmacol.* **58**, 749–757 (1999).
53. Chiba, T., Tsuchiya, T., Mori, R. & Shimokawa, I. Protein reporter bioassay systems for the phenotypic screening of candidate drugs: a mouse platform for anti-aging drug screening. *Sensors* **12**, 1648–1656 (2012).
54. Williams, M. Systems and integrative biology as alternative guises for pharmacology: prime time for an iPharm concept? *Biochem. Pharmacol.* **70**, 1707–1716 (2005).
55. Ogbourne, S. M. *et al.* Antitumor activity of 3-ingenyl angelate: plasma membrane and mitochondrial disruption and necrotic cell death. *Cancer Res.* **64**, 2833–2839 (2004).
56. Lock, E. A. *et al.* From toxicological problem to therapeutic use: the discovery of the mode of action of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), its toxicology and development as a drug. *J. Inherit. Metab. Dis.* **21**, 498–506 (1998).
57. Coe, J. W. *et al.* Varenicline: an α4β2 nicotinic receptor partial agonist for smoking cessation. *J. Med. Chem.* **48**, 3474–3477 (2005).
58. Kessel, D., Hall, T. C. & Wodinsky, I. Transport and phosphorylation as factors in the antitumor action of cytosine arabinoside. *Science* **156**, 1240–1241 (1967).
59. Gudas, L. J., Ullman, B., Cohen, A. & Martin, D. W. Jr. Deoxyguanosine toxicity in a mouse T lymphoma: relationship to purine nucleoside phosphorylase-associated immune dysfunction. *Cell* **14**, 531–538 (1978).
60. Cohen, A., Lee, J. W. & Gelfand, E. W. Selective toxicity of deoxyguanosine and arabinosyl guanine for T-leukemic cells. *Blood* **61**, 660–666 (1983).
61. Lambe, C. U. *et al.* 2-amino-6-methoxypurine arabinoside: an agent for T-cell malignancies. *Cancer Res.* **55**, 3352–3356 (1995).
62. Katz, D. H., Marcelletti, J. F., Khalil, M. H., Pope, L. E. & Katz, L. R. Antiviral activity of 1-docosanol, an inhibitor of lipid-enveloped viruses including herpes simplex. *Proc. Natl Acad. Sci. USA* **88**, 10825–10829 (1991).
63. Szelenyi, I. Flupirtine, a re-discovered drug, revisited. *Inflamm. Res.* **62**, 251–258 (2013).

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Competing interests statement
The authors declare competing interests: see Web version for details.

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