



Medicinal chemistry strategies in follow-on drug discovery

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Drug discovery targeting novel mechanisms has become extremely expensive and risky. The annual first-in-class drug approvals have not been satisfactory in the past decade (two to six per year) despite an increased R&D budget. Follow-on programs targeting proven mechanisms are less risky and costly but can produce drugs with meaningful differentiations and thus can play an important supporting role. This article will discuss the medicinal chemistry strategies that have been utilized by the pharmaceutical industry to exploit validated therapeutic targets.

Introduction

Drug discovery is a risky and expensive endeavor, which is unlikely to be sustained with the current R&D spending [1,2]. A small fraction of drug discovery programs produce clinical candidates and it is estimated that less than 10% of clinical candidates successfully reach the market [3]. Much of the risk resides in the unproven therapeutic correlations between the biological target that a drug modulates and the disease that it attempts to manage [4]. In the most crucial and expensive phase 3 trials, drugs that use a novel mechanism have more than double the attrition rate of drugs targeting validated mechanisms even after evaluation in phase 2 trials [5]. Therapeutically useful targets are rare commodities and only a small number of drugs targeting novel mechanisms are discovered every year [6] (between two and six per year in the past ten years [7]). These factors have prompted the pharmaceutical industry to exploit validated targets thoroughly to manage risk and, as a result, most approved new chemical entities target known mechanisms [8]. It is worth mentioning that many drugs targeting the same mechanism are developed in parallel and the differentiations are achieved through different optimization protocols and chemotypes of the drug molecule. Several related approaches, such as drug repositioning [9], product-related research [10], platform drugs [11], analog-based drug discovery [12,13] and integrated common mechanism strategies [14] have

been employed by the industry to capitalize the value of the proven mechanisms. A significant proportion of R&D resource has been devoted to, the so-called, follow-on drug discovery. In this article, follow-on discovery is loosely defined as any program that targets a mechanism with proven therapeutic relevance to the disease in question and in some cases a significant level of innovation is involved in developing the product. Several medicinal chemistry strategies in small molecule follow-on drug discovery are discussed here.

Strategies in follow-on drug discovery

Follow-on drug discovery has a long history and there has been much debate about its merits in comparison to the pioneering drug discovery targeting novel mechanisms [15,16–18]. Scientifically, both pioneering and follow-on approaches need a sound hypothesis, or a conception [19], to succeed. Targeting a proven mechanism carries less risk in producing an efficacious and safe drug, but it is more challenging to invent a drug with clinically meaningful differentiation from the pioneering drug targeting the same mechanism. As a result, lack of differentiation is frequently cited as a reason for discontinuation in the development of new drugs [20]. First-in-class drugs could possess a more favorable market position, but the market exclusivity enjoyed by the pioneering drugs has been reduced significantly in recent years [21]. Although novel mechanisms can potentially bring true breakthroughs, it is very difficult to achieve as reflected in the high

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attrition rate in pharmaceutical R&D. Meanwhile, targeting validated pathways can also produce significantly differentiated drugs as shown by some of the examples provided in this article.

A follow-on program can be initiated under a variety of circumstances. Obviously, if a pioneering drug has not been adequately optimized, it creates an opportunity for competitors to design better follow-on drugs. Alternatively, if the optimization and development paths are sufficiently straightforward to allow the production of a noninferior product with a lower budget and risk, some companies might find the follow-on approach economically attractive. This is especially true for companies in emerging markets where price can be the deciding factor for market performance. Serendipity is an important component in drug discovery and a follow-on product may prove superior owing to poorly understood reasons. The emergence of bacterial, viral and tumor resistance renders old drugs less effective and creates a need for better follow-on products. Generations of antibiotics in the same class are prime examples. New knowledge and technologies that were not available when the pioneering drugs were discovered may provide a powerful platform to develop significantly improved products. New animal models and biomarkers that more accurately predict human efficacy and safety are particularly powerful in the lead optimization process.

When a follow-on drug discovery program is initiated, much information about the pioneering drug and its target is frequently available. One needs to analyze what key factors have made the pioneering drug a safe and efficacious medicine *vis-à-vis* the related approaches that have failed and what new information has become available after the development of the pioneering drug. A judgment can then be made about the probability of discovering a significantly improved drug targeting the mechanism of interest. The traditional ways of achieving differentiation (e.g. increase half-life, pro-drug and soft-drug) becomes less useful if the pioneering drug is launched recently because most modern drugs are sufficiently optimized. Drugs with poorly understood mechanisms are more difficult to follow on, owing to the lack of efficacy and safety markers in development [22]. For example, the pioneering drug, clozapine, proved significantly more effective than later second-generation antipsychotics in recent clinical trials [23,24]. The same is true for drugs modulating a chemically difficult target with stringent requirements for its ligands. An example in this category is renin inhibitors. The pharmacokinetic (PK) profile of aliskiren is marginal (oral bioavailability = 3%) but it represents the best effort of decades of research with many programs failing to produce marketed drugs [25]. The quality of the patent protection of the pioneering drug determines the freedom of operation and, thus, must be analyzed carefully. With the advances in synthetic chemistry and *in vitro* biological assays, a large number of analogs can be synthesized, tested and patented by the pioneering team. In today's environment, superior medicinal chemistry insight is essential to find new IP grounds in heavily claimed patents. New synthetic methodologies may enable access to analogs that were previously difficult to make. Medicinal chemistry techniques such as scaffold hopping can also help the follow-on team to identify proprietary chemical matters [26]. Other factors, such as the cost of clinical trials, market shift, available resources, the skills of the scientific team, portfolio maintenance and competitive landscape are all important considerations in

evaluating a program but are beyond the discussion of this article [27]. Several examples are provided to demonstrate different medicinal chemistry strategies adopted by the pharmaceutical industry to exploit the validated mechanisms.

Atorvastatin

Atorvastatin (**1**, Fig. 1) was the 5th statin to be approved by the FDA ten years after the pioneering drug Lovastatin (**2**, Fig. 1), but it became the best-selling drug in history. Besides the definitive therapeutic value of inhibiting 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR), other useful information emerged around the same time that atorvastatin was invented. Lovastatin is a fungal metabolite with a complex molecular skeleton, but by the time the atorvastatin project had been initiated, a more optimization-friendly scaffold (i.e. **3**, Fig. 1) discovered by Merck was known [28]. A pyrrole ring (**4**, Fig. 1) was utilized to replace the phenyl ring in **3**, primarily due to its synthetic accessibility [29]. The first potent compound (**5**, Fig. 1) showed considerable toxicity, but it has been shown that the toxicity of other HMGR inhibitors was either rodent-specific or an exaggeration of the mechanism-based biological effects at high doses. Armed with this knowledge, the team proceeded to make more synthetically challenging analogs and atorvastatin was among the 20 analogs synthesized. Much effort was spent on finding an efficient enantioselective synthesis to maximize the potency. A chronic efficacy study of atorvastatin with a large number of animals demonstrated that atorvastatin was superior to lovastatin [30]. This differentiation prompted the clinical development of atorvastatin and later human clinical trials confirmed that atorvastatin reduces LDL levels more effectively than the previously launched statins [31]. The atorvastatin story showcased several advantages of the

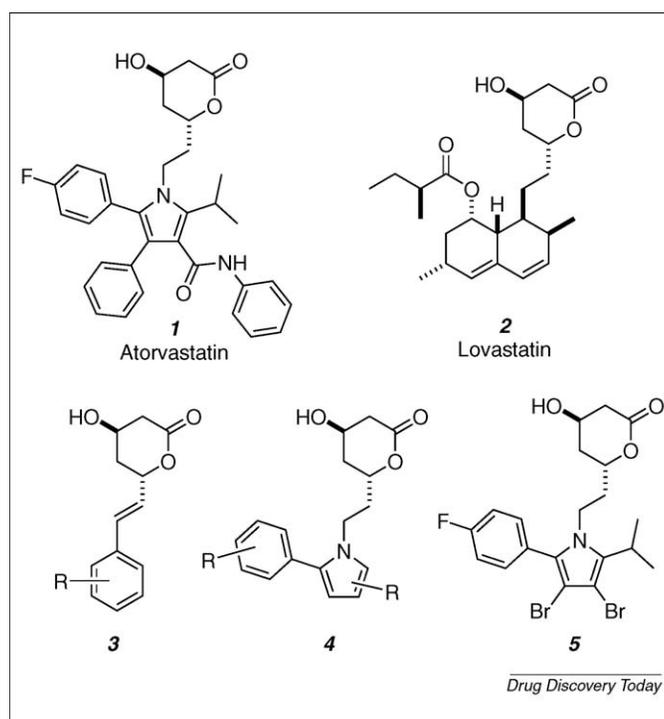


FIGURE 1

Key compounds leading to the discovery of atorvastatin.

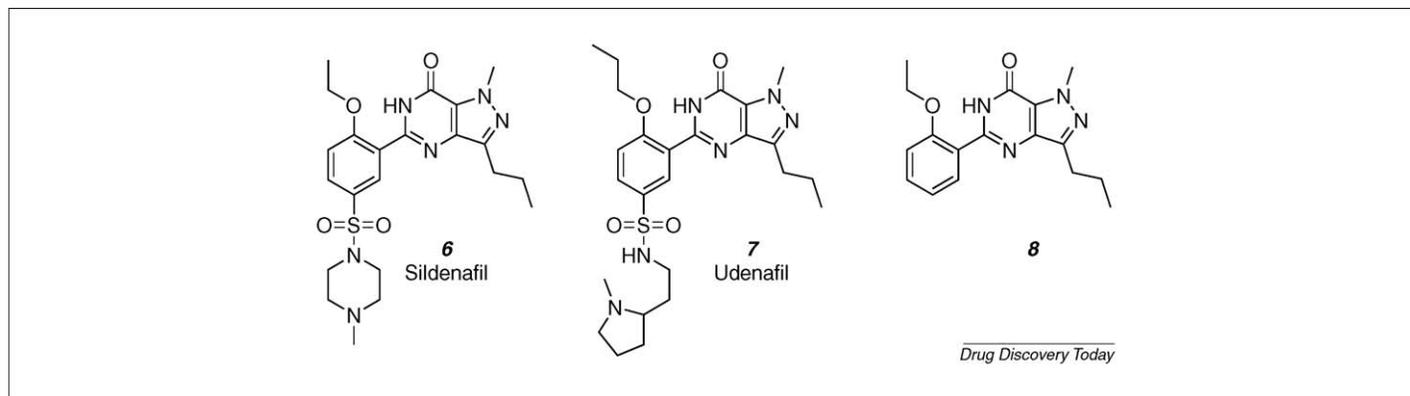


FIGURE 2

Modification of side chains in sildenafil leads to udenafil.

follow-on approach. For example, a chemical lead is known and the optimization path is relatively clear. Because the validity of the mechanism of action is proven, a riskier optimization path can be taken. Specifically for this case, difficult synthetic routes were pursued to produce analogs and investment was made to identify an enantioselective synthesis of atorvastatin. The toxicity shown by the initial candidate was attributed to the specific compounds rather than the targeted mechanism. Chronic and expensive animal experiments were conducted to establish the differentiation. In comparison, the development of the first statin (compactin) suffered several setbacks [32]. In the primary rat model, compactin induced the expression of HMGCR and thus failed to show any efficacy. It was not until compactin was shown to lower LDL in hen model that confidence in the approach resumed. High dose of compactin caused lymphomas in dogs and this observation halted the development of compactin, which also triggered the temporary discontinuation of the lovastatin development. Atorvastatin demonstrated that follow-on products can provide meaningful differentiations and significant commercial returns.

Udenafil

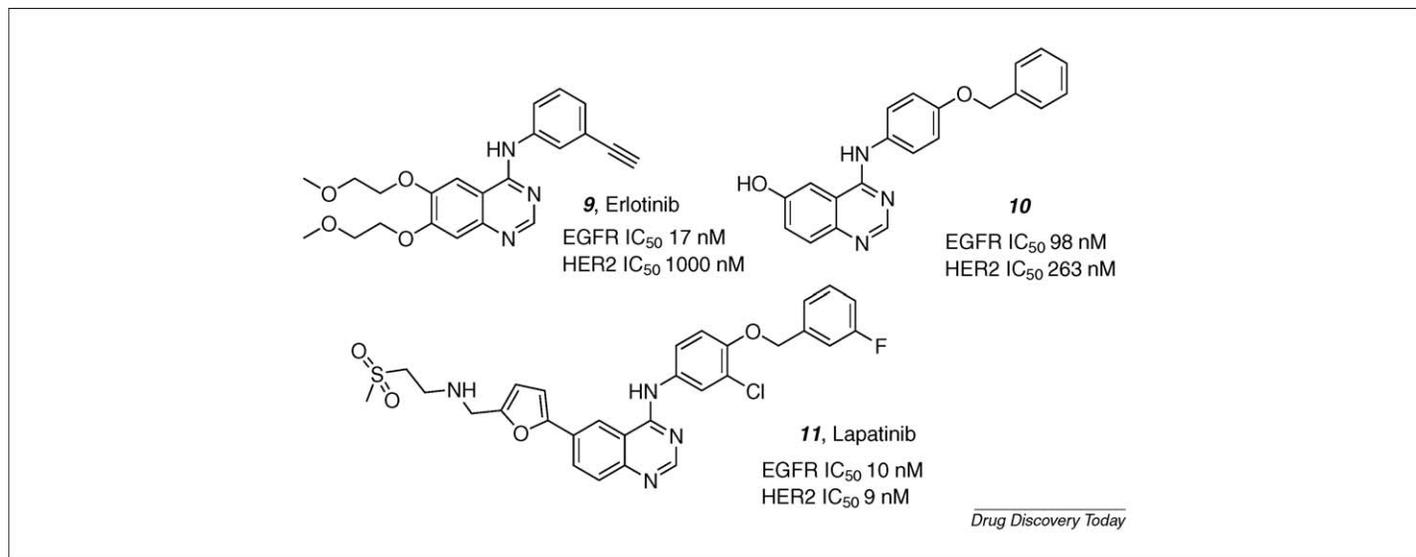
The launch of sildenafil (**6**, Fig. 2) opened the field of phosphodiesterase type 5 (PDE5) inhibitors as male erectile dysfunction (ED) therapeutics. The high degree of structural similarity between udenafil (**7**, Fig. 2) and sildenafil implies a clear medicinal chemistry strategy in designing udenafil. A patent-busting approach was probably adopted to produce proprietary analogs that were closely related to the pioneering drug. It has been reported that the entire sulfonamide portion in sildenafil produces only an approximate 7.5-fold increase in potency (i.e. **6** is 7.5 times more potent than **8**) [33], which suggests that this group could be drastically modified without significantly effecting activity. Modest structural changes (i.e. from **6** to **7**) proved adequate to produce analogs outside patent protection and udenafil was launched in Korea in 2005. Although udenafil has been reported to possess better potency, selectivity, a longer half-life and faster onset action than sildenafil, no head-to-head comparisons have been conducted in large clinical trials to demonstrate such differentiations [34]. The lower development cost, however, allows udenafil to be sold at a discounted price and gain a significant portion of the Korean market. This model is particularly popular for product-oriented companies in emerging markets. Even though such follow-on drugs exhibit

minimum levels of differentiation, they can drive down the prices and thus benefit the patients.

Lapatinib and bendamustine

Many drugs exert their biological effects via multiple effector systems [35], but most of these drugs were not rationally designed and optimized against more than one biological target. Conceptually, intentionally targeting two validated mechanisms with one molecule could lead to improved efficacy and a larger responding population. Although a fixed-dose combination of existing drugs may be a quicker approach targeting multiple mechanisms, such combinations face challenges of obtaining parallel PK and patentability. Recently, rational design of multiple ligands has attracted much attention [36,37]. Several anticancer agents were rationally designed to target more than one mechanism, two of which are highlighted here. Lapatinib was discovered by optimizing a chemical lead against two related targets [38] while bendamustine was invented by combining the essential features of two known drugs targeting two different mechanisms [39].

The inhibition of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) has been validated in cancer therapy. Marketed drugs targeting EGFR, such as erlotinib (**9**, Fig. 3) and HER2, such as trastuzumab, have demonstrated impressive clinical efficacy. The design of lapatinib (**11**, Fig. 3) took advantage of the homology between EGFR and HER2 and the optimization used a common pharmacophore so that the final dual ligands would not be so large as to pose PK liabilities. Structural requirements for potent EGFR inhibition are well defined. Molecular modeling suggested additional hydrophobic groups on the anilino group on the core structure (**10**, Fig. 3) would increase HER2 potency and structure-activity relationship (SAR) studies driven by EGFR and HER2 overexpressing cell lines led to the discovery of lapatinib [40]. Lapatinib has been approved by the FDA for the treatment of breast cancer in patients whose tumors overexpress HER2. An ongoing large clinical trial (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimization, ALTTO) involving 8000 HER2 positive breast cancer patients will provide a head-to-head comparison of lapatinib and trastuzumab in efficacy and tolerability (<http://www.clinicaltrials.gov/ct2/show/NCT00490139?term=ALTTO&rank=2>). Also, several clinical trials are being conducted to study the efficacy of lapatinib in other tumors either as a single agent or a component of combination therapy [41].

**FIGURE 3**

Lapatinib possesses both the EGFR and HER2 binding elements.

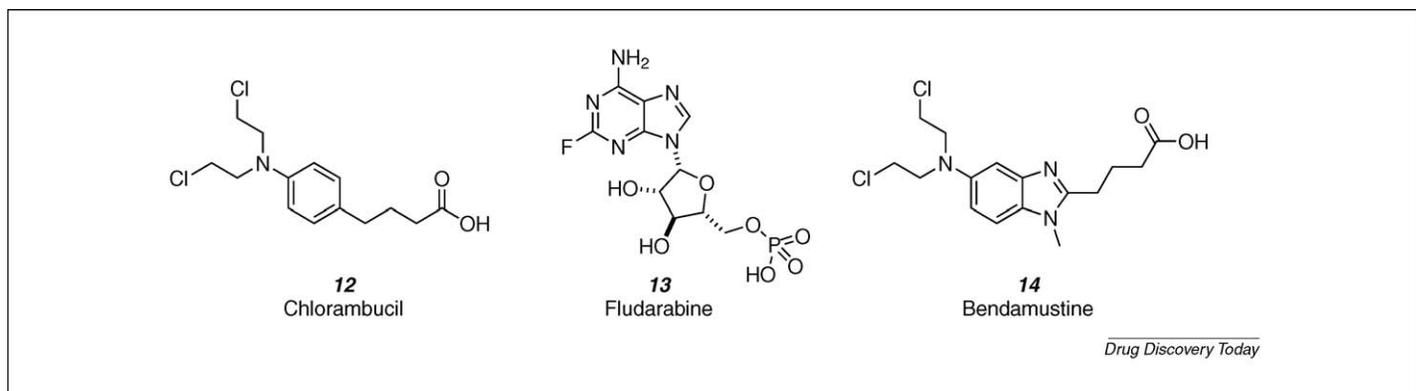
Both chlorambucil and fludarabine are effective in treating chronic lymphocytic leukemia (CLL) [42]. These two drugs share less structural similarity than those in the lapatinib case, but the alkylating agent chlorambucil possesses a small pharmacophore. This is advantageous in designing multiple ligands with drug-like properties. Containing the features of both parent drugs [43], bendamustine induces cytotoxicity through more mechanisms, including apoptosis and mitotic catastrophe, than other alkylating agents *in vitro* [44]. In human clinical trials for CLL, bendamustine caused a higher overall response rate and a longer median progression-free survival time than chlorambucil [45]. Bendamustine also showed low cross-resistance with other alkylating agents and fludarabine in a phase I/II trial [46]. Because some structural features of fludarabine are missing in bendamustine, it is primarily an alkylating agent and its antimetabolite activity has yet to be confirmed [47]. Bendamustine has not been compared with fludarabine in clinical trials (Fig. 4).

Pregabalin and lorcaserin

New knowledge can be a major driver for both pioneering and follow-on drug discovery. Technical advances after the launch of

a drug, such as new synthetic methods, more accurate molecular modeling, availability of X-ray crystal structures of drug targets, better understanding of the target-related pharmacology and toxicology, more predictive assays/biomarkers/PK/PD relationships, novel delivery technologies and clinical knowledge accumulated could all enable more efficient optimization and development process for follow-on programs compared to the discovery of first-in-class drugs when these technical supports were not available. Two recent drugs will be discussed in this section. The first example highlighted the importance of the clinical knowledge gained on an older drug, gabapentin, in the development of pregabalin. The second case involved the removal of a nonmechanism-based toxicity of dexfenfluramine leading to the discovery of lorcaserin.

Pregabalin (**15**, Fig. 5) was originally designed as a γ -aminobutyric acid aminotransferase inhibitor to treat epilepsy. Its actual mechanism of action later proved to be the inhibition of L-glutamate release through binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, a mechanism shared by an older epilepsy drug, gabapentin (**16**, Fig. 5) [48]. As shown in Fig. 5, the two drugs share substantial structural similarities. Clinical use of gabapentin suggested it might be efficacious in managing neuropathic pain and most of the

**FIGURE 4**

Bendamustine contains the features of both chlorambucil and fludarabine.

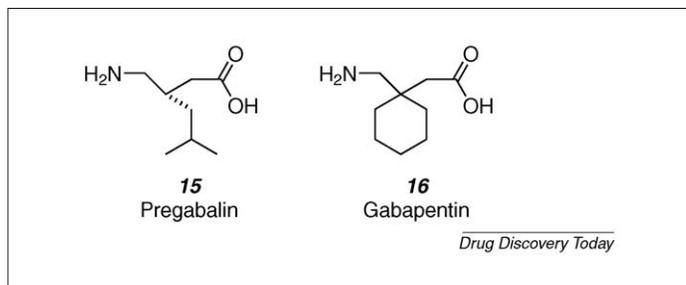


FIGURE 5

Two generations of ion channel blockers.

gabapentin prescriptions are for off-label use on pain. So on the basis of clinical knowledge gained on gabapentin, pregabalin was tested for several broader indications and became the first approved drug for fibromyalgia. Pregabalin is more orally available than gabapentin in humans so lower doses can be used to reduce side effects. It has been advocated that drugs targeting well defined, albeit rare, diseases can be developed preferentially and broader indications pursued on a later date [49]. If this indeed becomes a trend, one can expect the pregabalin model to become more prevalent in the future.

Dexfenfluramine (**17**, Fig. 6) is a 5-HT_{2C} receptor agonist that was approved for antiobesity therapy. It induced 2.7 kg more weight loss than placebo over one year and became the first approved long-term (>3 months) drug for weight loss in 1996 [50]. However, the drug was withdrawn from the market in 1997 because of side effects (i.e. heart valve malformation) [51]. Because 5HT_{2C} is almost exclusively expressed in the CNS system, it seemed unlikely that the cardiac

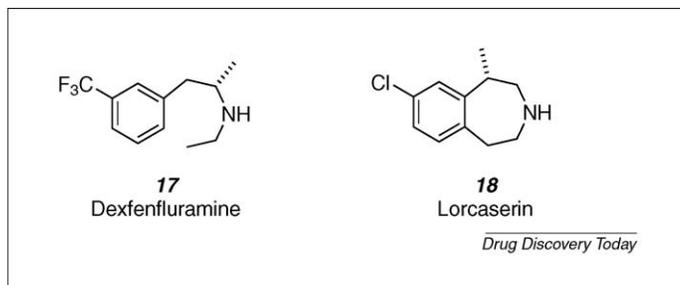


FIGURE 6

Increased rigidity improves selectivity.

toxicity was associated with 5HT_{2C} agonism. The valvulopathy side effect of dexfenfluramine was later linked to its potent agonistic activity toward a related 5HT receptor, 5HT_{2B}, which is expressed in the heart [52]. Selective 5HT_{2C} agonists thus represent an attractive therapeutic hypothesis for obesity. Lorcaserin (**18**, Fig. 6) was developed as a potent 5HT_{2C} agonist with 100-fold selectivity over 5HT_{2B} [53] and found to produce 3.6 kg body weight reduction versus placebo at 10 mg (*b.i.d*) in a phase 2 trial [54]. One year dosing of lorcaserin did not result in a significant number of cases to reach a predetermined stopping criteria for valvulopathy and, as a result, it is now being evaluated in phase 3 trials [55]. Lorcaserin is a conformationally restricted analog of dexfenfluramine and the increased complexity of lorcaserin apparently provided the desired selectivity. This case demonstrated that new knowledge can help further optimize old drugs with safety liabilities that prevent or limit their clinical uses. Common side effects of many drugs can be engineered

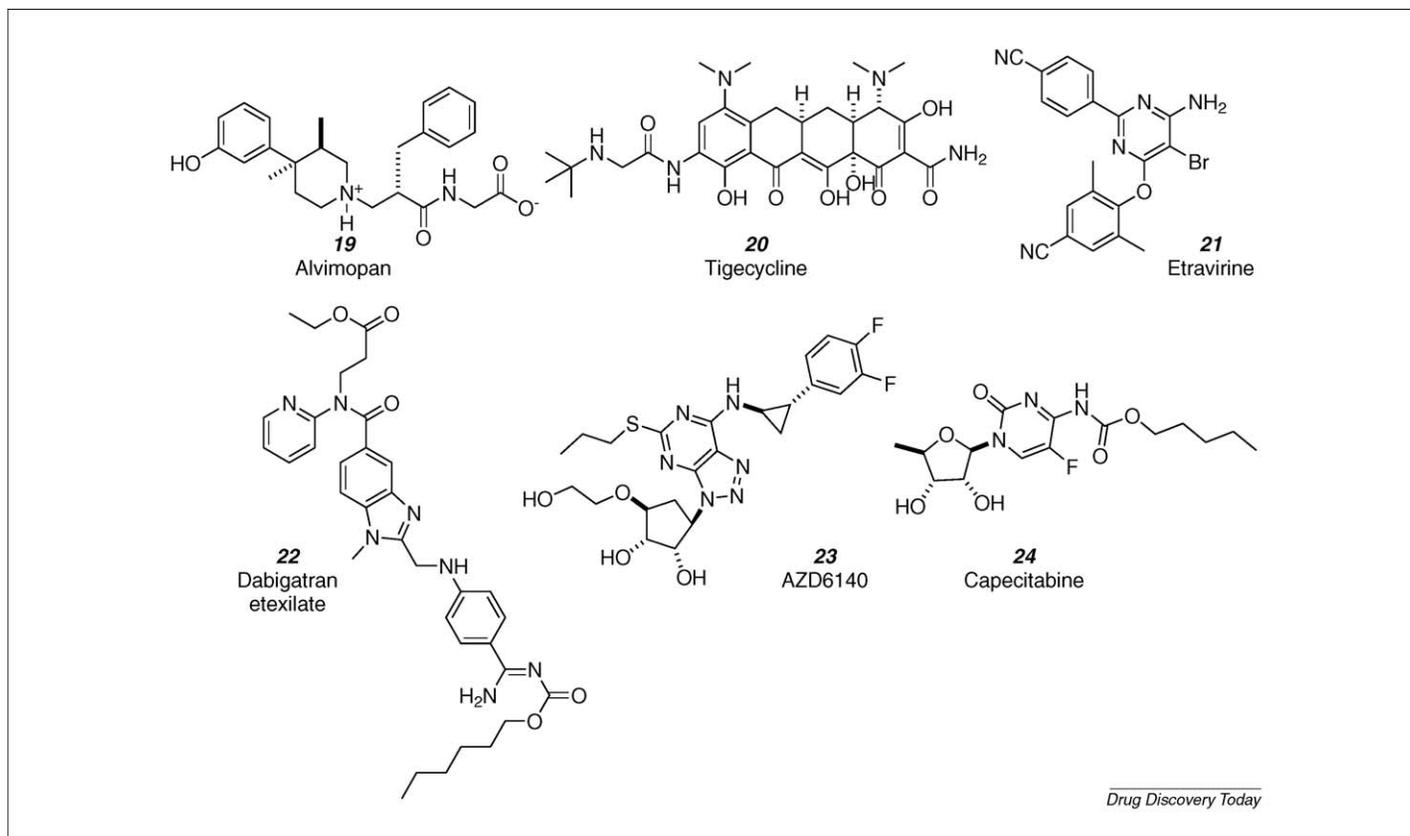


FIGURE 7

Drugs or drug candidates targeting validated mechanisms.

TABLE 1

Preclinical and clinical differentiations achieved by some representative follow-on products.

Follow-on drugs	Preclinical differentiations	Clinical differentiations
Atorvastatin	More efficacious	More efficacious
Udenafil	Faster onset action	To be determined
Lapatinib	HER2/EGFR dual agent	Trial ongoing
Bendamustine	More modes of action	More efficacious
Pregabalin	Similar potency, PK	Expanded indication
Lorcaserin	More selective	Less side effects
Alvimopan	GI selective distribution	Less side effects
Tigecycline	Evades bacteria efflux pump	Efficacious for resistant bacteria
Etravirine	Potent for mutants	Efficacious for resistant HIV virus
Dabigatran etexilate	Orally available	Orally available
AZD6140	Reversible binding, faster onset/offset rate	Trial ongoing
Capecitabine	Orally available, selectively activated in cancer cells	Orally available, less toxic

out, guided by modern preclinical assays. For example, drug–drug interactions mediated by cytochrome P450 inhibition or activation and *torsade de pointe* associated with hERG inhibition can be reduced to minimal levels using current medicinal chemistry techniques thus several old drugs can potentially be made safer.

Miscellaneous

A variety of different approaches to exploit validated targets have been employed in addition to the strategies discussed above. For examples, the zwitterion alvimopan **19** (Fig. 7) was designed to be a GI-selective opioid receptor antagonist devoid of CNS side effects. Both tigecycline (**20**, Fig. 7) and etravirine (**21**, Fig. 7) were developed, targeting mechanisms proven to be effective in treating infections caused by resistant microorganisms. Tigecycline evades the efflux pumps of the bacteria mutants while etravirine was optimized to kill HIV strains carrying clinically relevant mutations. Dabigatran etexilate (**22**, Fig. 7) is an orally available small molecule anticoagulant drug that directly inhibits thrombin, a target validated by a biological drug, desirudin, which is only bioavailable by the i.v. route. Clopidogrel is an irreversible adenosine diphosphate receptor (ADP) antagonist that has proven to be highly useful in reducing clotting events. Reversible ADP antagonists such as AZD6140 (**23**, Fig. 7) with faster on and off rates, are now in advanced clinical development (<http://clinicaltrials.gov/ct2/show/NCT00528411>). Capecitabine (**24**, Fig. 7) is a prodrug that is preferentially metabolized to 5FU in tumor cells and is orally bioavailable and less systemically toxic [56]. Pioneering drugs establish the validity of the mechanism, but these chemical entities often can be further optimized in many aspects. Since novel, therapeutically relevant targets are very difficult to find, they should be exploited thoroughly. The preclinical and clinical differentiations achieved by the examples included in this review are summarized in Table 1.

Conclusion

Drugs targeting novel mechanisms will always be the main driver for pharmaceutical innovation, but follow-on research can play an important supporting role, although with some limitations. Follow-on programs need an innovative drug as lead and cannot be conducted on diseases without any effective treatment. They also carry significant risk because real differentiations can be only confirmed late in the development process. The regulatory agencies and consumers are more and more reluctant to embrace follow-on products. Market can absorb only a finite number of products from a given class and this approach is more applicable for big pharma with more marketing resources. Nonetheless, the mechanism of action of a drug means little to the patients as long as the drug provides real benefit. Consequently, the commercial success of a drug is not related to the novelty of the mechanism upon which it is based, but the differentiation that it provides [57,58]. Finding a new therapeutically relevant target is extremely difficult and pioneering drug discovery has become prohibitively expensive. In the meantime, many validated targets can be further exploited to provide better products with lower risk and cost and a variety of strategies have proven useful as described in this article. Nineteen β -blockers have reached the marketplace, but lung selective β -blockers are still being developed 44 years after the introduction of the pioneering drug propranolol (<http://www.wellcome.ac.uk/News/News-archive/Browse-by-date/2008/News/WTX050304.htm>). Incidentally, it was the inventor of propranolol, Sir James Black who once said ‘the most fruitful basis of the discovery of a new drug is to start with an old drug’ [59].

Conflict of interest disclosure

HZ is employed by Abbott Laboratories and ZG receives lecture fees from Xuanzhu Pharma, Shanghai Central Institute and Hengrui Pharmaceuticals.

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