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One target – multiple indications: a call for an integrated common mechanisms strategy

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Ever-increasing research and development costs are putting constant pressure on the pharmaceutical industry to improve their efficiency. Efforts to increase the output of the research pipeline have yielded limited success. Traditionally, maximization of the value of a drug is attempted through life-cycle management, which is initiated late in development, or when the drug is already on the market. Validated targets can be exploited further through development of a follow-up drug, which may offer advantages regarding safety or convenience.

In this article, we propose to systematically evaluate the full therapeutic potential of a drug target, proprietary chemical lead structure, or drug candidate as broad and as early as possible and we call this the 'common mechanism' approach.

Attrition rates in R&D are very high and costs to bring drugs to the market are rising significantly. It is estimated that the success rates from first dose in man to registration is only approximately 11% across indications [1]. As a result, the total cost to launch a product has been estimated to be US$ 800 million [2] and probably exceeds that figure today. The main reasons for drug failure are efficacy (30%), toxicity (20%) and pharmacokinetic issues (10%) [3]. Pharmaceutical companies have implemented different measures to improve early clinical decision making and to increase development success rates. To this end, early evaluation of on target effects by drug treatment can be obtained as part of phase 0 [4] or phase I trials. In addition, proof-of-concept (POC) trials can be used as a cost-effective way to generate information about clinical efficacy. An alternative strategy is to modify the balance between the level of innovation and development risk: the traditional drug discovery process develops novel chemical compounds for novel targets that have not been clinically validated. This approach is frequently referred to as first-in-class approach. Clearly, this process has the potential to produce highly innovative drugs and, if the drug reaches the market, the returns are frequently very high. Numerous medicines have been developed by this route and this strategy remains the cornerstone of drug development. However, this approach carries the combined risks associated with new compounds and the risk that the target mechanism may not produce the expected therapeutic effect. Consequently, overall attrition rates can be reduced by pursuing clinically validated drug targets, rather than novel targets with new chemical matter. This approach is often referred to as best-in-class approach. Here the risks are mainly compound-related, as target-related risks have been largely excluded. Although this approach frequently produces only incremental innovation, this strategy has turned out to be commercially very attractive. Indeed, later market entrants can generate higher sales than their first-in-class competitors as illustrated by the cholesterol synthesis inhibitor atorvastatin and the calcium channel blocker amlodipine, two of the top ten best selling drugs worldwide.

An alternative strategy to reduce attrition rates is to use existing proprietary compounds to target additional indications. For successfully marketed products, these activities can be part of line extension activities during life-cycle management; a recent example of this is the anti-CD20 antibody rituximab, which was originally launched for the treatment of B-cell non-Hodgkin's lymphoma [5] and later also developed for the treatment of refractory rheumatoid arthritis [6]. The search for new indications

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.10.004

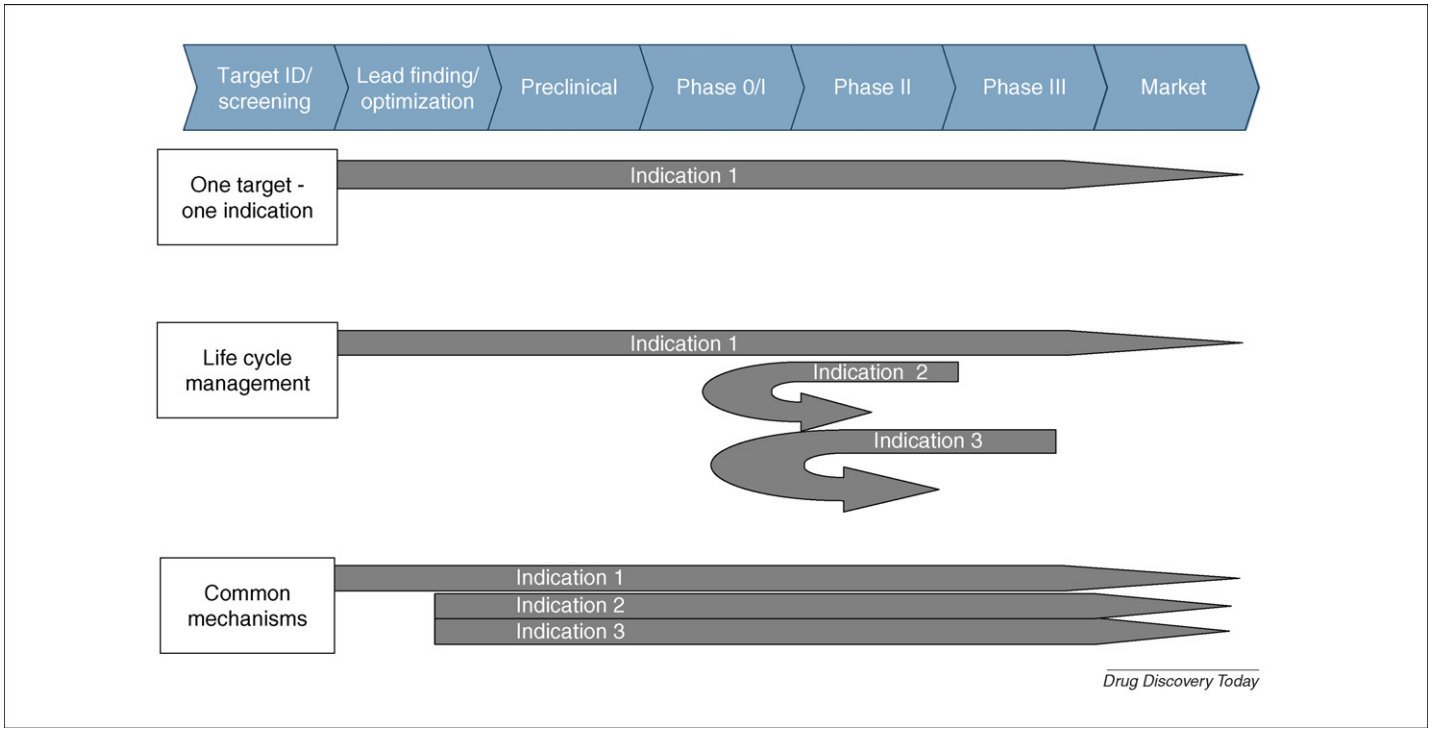

FIGURE 1

A schematic representation of three approaches to research and development along the value chain, as discussed in the text. Traditionally, and most simply, one target will lead to one drug candidate, which is profiled in one indication (top panel). Life-cycle management is usually initiated when a drug is in its advanced development stage or on the market, leading to novel projects exploring the value of the drug in additional indications (middle panel). The common mechanisms approach aims to explore the potential of a validated target, a novel and proprietary lead structure, or drug candidate as early and as broadly as possible (lower panel).

can even rescue projects that have failed in clinical trials for reasons other than safety. These activities are pursued by many companies and are often referred to as drug repurposing [7], repositioning [8] or indication switch [9]. Phosphodiesterase 5 (PDE5) inhibitors are an example of this, where preclinical data in animal models suggested that PDE5 inhibitors increase coronary blood flow. Consequently, clinical development was initially aimed at patients with angina pectoris. However, the primary indication was dropped, and subsequently erectile dysfunction became the target indication. As part of life-cycle management, sildenafil was additionally developed for the treatment of pulmonary hypertension, and vardenafil is currently under investigation in the treatment of symptomatic benign prostatic hyperplasia [10]. These examples illustrate that the search for additional indications leads to highly innovative products with a reduced development risk, because the availability of toxicological and human data results in lower attrition rates [9].

However, a strategy which simultaneously reduces the target-related risks of the best-in-class approach and optimizes the market opportunities in several indications has not yet been implemented. Since target-related risks are largely a consequence of focus on a single lead indication, it is crucial to evaluate the importance of a target in multiple diseases. Although most companies will, at some stage, evaluate the utility of their compounds in different diseases, these activities usually begin relatively late in development. A potential reason for this is the organization of research units according to distinct therapeutic areas, resulting in silo mentality, unhealthy competition and limited interaction between research groups. To overcome this, we propose a systematic strategy that we call the 'common mechanisms' concept. As part of this approach, drug targets are evaluated across different indications in the beginning stages of the R&D process. Early knowledge of the relevance of a drug target in different indications can guide clinical development (Fig. 1). To increase the probability that targets are relevant for multiple diseases, a portion of the project portfolio should address mechanisms that are therapeutically relevant in several diseases simultaneously, based on common pathophysiological processes.

Common mechanisms

Many diseases ultimately share the same underlying pathological processes and we refer to these as common mechanisms. There are a number of pathological processes that play a particularly prominent role and are involved in multiple, yet diverse, diseases. These common mechanisms include inflammation, angiogenesis, fibrosis and cellular proliferation, amongst others (Fig. 2). Although inflammation is a defense mechanism, an inappropriate inflammatory response is the cause of many diseases, including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, endometriosis, arteriosclerosis and psoriasis. Therefore, an understanding of the cellular effectors and mediators that play a key role in the different inflammatory diseases can guide the ultimate positioning of anti-inflammatory agents. Similarly, angiogenesis is a key disease process in multiple indications [11], including tumor development and metastasis, age-related macular disease, arthritis, endometriosis and psoriasis. More than one common mechanism may have an impact on a particular disease, as seen in arthritis, endometriosis and psoriasis, and this

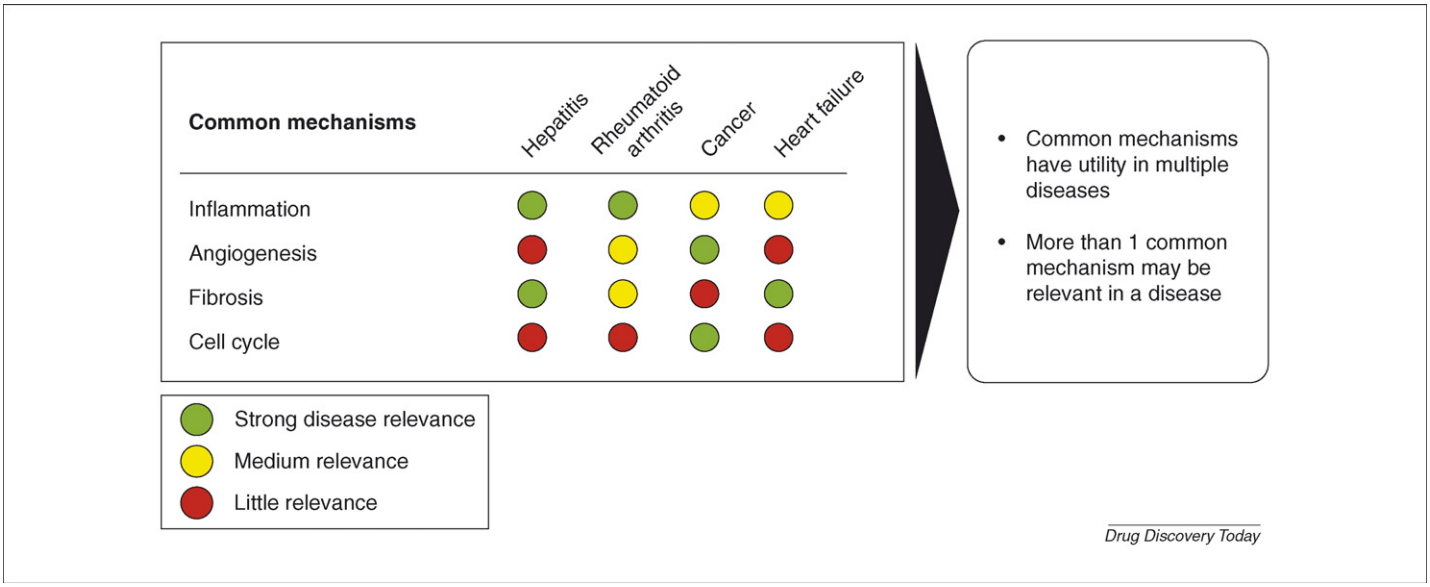

FIGURE 2

Common mechanisms represent key pathological disease processes that play an important role in multiple diseases. Therefore, drug targets that modulate common mechanisms have therapeutic potential in multiple diseases.

may provide opportunities for combination therapies with synergistic effects. Fibrosis is another common mechanism that encompasses diseases with prominent fibrotic etiology, such as lung fibrosis, liver cirrhosis, renal failure and tissue scarring. Because fibrotic processes are often downstream of inflammatory processes, inflammation and fibrosis may represent optimal drug targets for the same disease at different stages of clinical disease progression.

The common mechanisms strategy also addresses a key problem emerging from an aging patient population. As the average age of patients increases, comorbidities will increase and a higher proportion of patients will require concurrent treatment for several chronic diseases. This will shift the therapeutic needs from treatment of a single disease to simultaneous treatment of multiple illnesses in multimorbid patients. Consequently, our understanding of which common pathological processes are the driving force of comorbidity in patients will become increasingly important. Targets of common mechanisms that, by definition, interfere with very fundamental disease processes are ideally positioned to serve this increasing medical need to treat multimorbid patients.

Targets of common mechanisms: case studies

TNFα

As defined above, common mechanisms represent fundamental pathological processes that potentially play an etiological role in multiple diseases. Therefore, these target mechanisms are expected to show therapeutic effects in multiple indications. The development of anti-TNFα antibodies highlights how a common mechanistic approach may overcome target-related risks and how this ultimately increases the probability of reaching the market. During early preclinical studies, TNFα was recognized as a key immunologic/inflammatory mechanism. However, administration of TNFα itself was initially evaluated as an antitumor agent. Conversely, interfering with TNFα signaling was evaluated in multiple diseases with initial focus on sepsis [12,13], graft rejection [14], rheumatoid arthritis [15,16] and Crohn's disease [17]. Subsequently, the list of potential indications of therapeutics targeting TNFα steadily increased and data emerged for a range of diseases, including heart failure [18] and psoriasis [19]. Multiple clinical trials were initiated targeting TNFα using either anti-TNFα antibodies or fusion proteins of the soluble TNF receptors and the Fc portion of IgG. The predominant focus for clinical development was initially on sepsis and graft versus host disease; however, no clinical benefits could be demonstrated in these indications. Initial safety evidence of anti-TNFα therapy was, however, provided by these early trials and clinical development continued in rheumatoid arthritis. Anti-TNFα therapy proved efficacious in rheumatoid arthritis and was soon demonstrated to be useful in several other indications, including Crohn's disease, ankylosing spondylitis and psoriasis. Today there are three marketed anti-TNFα therapeutics: the anti-TNFα antibodies, infliximab and adalimunab, and the p75TNFR-IgG fusion protein, etanercept. Although preclinical evidence suggested involvement of anti-TNFα therapy in multiple diseases, the risk of failure for any particular indications remained high, as was demonstrated in the failed sepsis [20] and heart failure trials [21]. Ultimately, the potential of anti-TNFα therapies to target common mechanisms ensured the survival and accessibility of these drugs into the market for several indications. Consequently, anti-TNFα drugs have become commercially highly successful therapeutics.

Vascular endothelial growth factor (VEGF)

VEGF plays a crucial role in regulating angiogenesis and inhibitors of VEGF have therapeutic potential in the treatment of multiple diseases, including cancer, age-related macular degeneration, diabetic macular edema, rheumatoid arthritis, endometriosis and psoriasis, amongst others [11]. Diverse strategies have been pursued to inhibit VEGF specifically, including antibodies and aptamers. Bevacizumab is an antibody that neutralizes the effects of VEGF and was initially developed for the treatment of metastatic

colorectal cancer. A high-affinity Fab fragment, ranibizumab, was successfully tested in macular degeneration, and the first anti-VEGF drug to receive FDA approval was the anti-VEGF aptamer pegaptamib for the treatment of age-related macular degeneration. Both pegaptamib and ranibizumab stopped or slowed disease progression in macular degeneration and demonstrated beneficial effects on visual acuity. Clinical efficacy of anti-VEGF therapy has been demonstrated in very diverse indications and more are likely to follow, highlighting the common mechanism potential of this target.

Soluble guanylate cyclase (sGC)

sGC is the intracellular downstream target of nitric oxide (NO) and represents the major effector of NO-mediated physiological effects, and was originally identified as a potent vasodilator [22]. NO has subsequently been demonstrated to regulate a wide variety of physiological and pathophysiological processes that play a crucial role in cardiovascular, renal, hepatic and inflammatory diseases. Starting in the mid-1990s, a variety of compounds have been identified, which can be classified according to their molecular mode of action into the NO-independent but haem-dependent stimulators, and the NO- and haem-independent activators [23]. Based on the assumption that activation or stimulation of the sGC has the potential to avoid the limitations associated with NO donors, a variety of potential indications are currently being explored in preclinical and clinical studies. Stimulators of sGC can potentially be used for the treatment of arterial hypertension, as has been demonstrated in spontaneous hypertensive rats [24]. Interestingly, sGC stimulation not only normalizes blood pressure in hypertensive animal models, but also restores the sensitivity of the sGC to NO [25] and prevents cardiac and renal end organ damage [26]. Stimulation or activation of the sGC also provides a significant benefit in pulmonary hypertension, as has been indicated in acute, as well as chronic, models of pulmonary hypertension [27,28].

The efficacy of the inhibitors of PDE5 in erectile dysfunction has initiated an increasing interest in the NO-sGC pathway for the treatment of this disease. The sGC stimulator BAY41-2272 has demonstrated efficacy *in vivo*, even under conditions where endogenous NO-mediated erection is impaired, such as in diabetes mellitus [29]. In congestive heart failure, sGC activators have been shown to provide favorable hemodynamic effects, because of their balanced venous, as well as arterial, unloading effects. In a dog model of pacing-induced heart failure, the sGC activator BAY58-2667 reduced cardiac pre- and afterload, resulting in an increase in cardiac output with no neuro-humoral activation [30], whereas stimulation of the sGC did not significantly reduce cardiac preload [31]. The anti-inflammatory and antifibrotic effects of the NO-sGC pathway have been addressed in a number of studies in renal or hepatic fibrosis. Stimulation of the sGC can decrease the renal production of transforming growth factor β (TGFβ), and reduce proteinuria in a model of acute glomerulonephritis [32] and the sGC activator BAY58-2667 slowed the progression of renal disease in a model of subtotal nephrectomy [33], while the sGC activator BAY60-2770 has been shown to reduce collagen accumulation in different rodent models of liver cirrhosis [34].

Based on the fundamental role of the NO-sGC pathway in a large variety of diseases, the potential to exploit common disease mechanisms via activators or stimulators of sGC seems enormous. The early preclinical profiling of different compounds (sGC activators and stimulators) has helped identify promising clinical target indication for each compound. Accordingly, the sGC activators are in clinical phase in patients with heart failure and angina pectoris, while the sGC stimulator BAY63-2521 is being profiled in pulmonary hypertension. Moreover, additional indications will probably be pursued based on the outcome of these clinical studies and preclinical data.

Common mechanisms strategy

The common mechanisms strategy aims to identify the therapeutic potential of the target portfolio across indications, early in the research process, so that a drug development strategy can be set up that considers the full therapeutic potential for any given drug candidate. Choice of drug targets can be divided into two subsets. The first is strategically selected, because these targets are aimed at common mechanisms and have clinical utility beyond the initial lead indication. During early phases of research, a project should be spearheaded by a lead indication, where the target mechanism shows greatest promise. However, the therapeutic potential should also be broadly evaluated preclinically across multiple disease areas in animal models. The research goal is to provide a compound for clinical development that has supporting *in vivo* data in disease models for several indications, allowing for the opportunity to follow different clinical development paths. POC trials should also provide some guidance on which indications may be most appropriate for late stage development. The other subset of targets is primarily aimed at a single lead indication with little or no knowledge of the target's potential in other indications at the onset of the project. The goal for these targets is to evaluate whether the targets are largely disease-specific or whether they encompass a variety of other indications. Therefore, the potential of a particular target to have an effect on other indications should constantly be evaluated and tested experimentally.

Common mechanisms process

Implementation of the common mechanisms strategy requires that a process be put in place for the entire target portfolio that allows the early identification of therapeutic opportunities across indications. The approach for revealing the potential common mechanisms of a target differ, depending on the stage of a particular project. During the early stages, before identification of more advanced compounds, the therapeutic opportunities are evaluated in terms of potential target–disease relationships. Once compounds are available, compound characteristics, such as target specificity and pharmacokinetic parameters, like route of administration or half-life, have a major impact on the utility of a drug candidate across indications, because indications may have different compound requirements. In some cases, the optimal approach to exploit fully a lead series across multiple indications is to develop different compounds with different characteristics to meet the indication-specific needs.

The common mechanism approach is highly crossfunctional in nature and a key component is to bring together expertise from different areas of the R&D organization, including target validation, research expertise from the disease areas, biomarker groups, as well as early and late stage clinical development.

There are a number of key components to the common mechanisms strategy:

(1) target validation and target selection
(2) *in silico* data mining to establish target–disease relationships
(3) *in vitro* evaluation of the target/lead compounds
(4) *in vivo* evaluation of compounds across indications in animal models
(5) POC trials

Target validation and target selection

One of the most crucial stages in building the portfolio is target selection. This decision will ultimately define the therapeutic potential of the future pipeline. Therefore, it is paramount to obtain early information if a target is largely disease-specific, or if it has potential across multiple indications. When no pharmacological tool compound is available, overexpression of the target gene by transfection or gene transfer, downregulation of expression by siRNA or interfering with the target with antibodies may be used to investigate the therapeutic potential of a target across indications. At this stage, it is also important to decide whether a target mechanism has multi-indication potential, or if diverse mechanism-based effects may become mechanism-based side effects that limit the utility of the target.

In silico data mining

Once a target is actively pursued, it is essential to review target–disease relationships and to provide a target-centric view of all available information on a target and its potential role in different indications, including publications, genetic or phenotypic databases, expression data, patents, competitor pipeline databases and in-house experimental data. To achieve this, an appropriate IT-structure has to be put in place that establishes the required links and provides easy access to the wealth of data. This information provides an early view of the current knowledge of the involvement of a target in different diseases and points toward potential safety issues. Since, in most cases, the goal is not to identify proven target–disease relationships, but rather, collect early signals for emerging disease relevance, sophisticated text and database analysis tools are required to reveal novel information and minimize the noise associated with large sets of data.

In many cases, our knowledge of target relevance across indications is very limited and relevant target information is often obscure, thereby restricting the value of database mining. Therefore, in addition to *in silico* capabilities, it is essential to implement approaches for experimentally evaluating the utility of compounds across indications.

In vitro evaluation of compounds

Often, the full potential of a target is not apparent at the onset of a project, but emerges at a much later stage. Although studies on target relevance often start in knockout (KO) animals, the ability of these models to predict the pharmacological potential of a drug target remain a challenge, especially in classic KO murine models. For many targets, *in vitro* and *in vivo* pharmacological studies are essential for understanding target relevance and potential as a future drug target, even though compound specificity may limit interpretation of the data. In order to capture the full spectrum of activity across indications, advanced compounds should be evaluated in a wide range of functional cell- or tissue-based assays that can provide new links to additional diseases. Phenotypic cellular disease models are particularly suited, because compounds can be tested cost-effectively across a diverse set of assays. In addition, the external evaluation of compounds by academic collaborations or contract research organizations (CROs) should always be considered in order to cover those methods and assays that are not available in-house.

In vivo testing of compounds

In vitro testing should be complemented with *in vivo* testing in animal models. Short-term animal models are particularly interesting in this context, because a compound can be evaluated broadly at an acceptable cost. To obtain a rapid readout for the effectiveness of a compound, biomarkers provide readouts for chronic processes like inflammation or fibrosis. To conserve compound requirements, particularly at the early stages of the drug development process, mice and rats are the preferred species for evaluating different diseases.

Proof-of-concept (POC) trials

One of the main aspects of the common mechanisms strategy is to exploit the potential of a target in multiple indications. Although this approach can increase the probability of a compound reaching the market, the risk of failure associated with any particular indication remains high. It is important to obtain evidence as to which indication has the highest probability of success from small POC clinical trials in order to move forward cost-effectively. Ideally, by looking at multiple parameters in small sets of different patient collections, relevant information can be generated to help guide the decision process during early stage development (POC/phase II).

Pros and cons of the common mechanisms strategy

The common mechanisms approach can be implemented in a cost-effective manner, provided that infrastructure or assay systems are not replicated in multiple places. If a lead indication initially drives the compound optimization process, additional testing in other indication models will only add marginal costs. Even if different indications require different clinical candidates to serve the indication-specific needs, the approach remains cost-effective, because infrastructure and assays to evaluate the mechanism-based properties can still be performed at the site, where testing for the lead indication is taking place. Although investment in POC studies increases, because more potential clinical opportunities exist for common mechanism targets, the risk of late stage failure decreases, resulting in overall reduction in cost and an increased probability of ultimately reaching the market (Fig. 3).

As discussed earlier, it is essential to perform an in-depth target analysis before a target enters the portfolio for lead identification and optimization. In particular, it is essential to balance the potential of a target as a therapeutic for several indications against the potential risks from target-based side effects. Beneficial effects in one disease may be an issue in another disease. The risk benefit profile of common mechanism targets has to be carefully evaluated so that the broad activity in multiple indications does not become a liability.

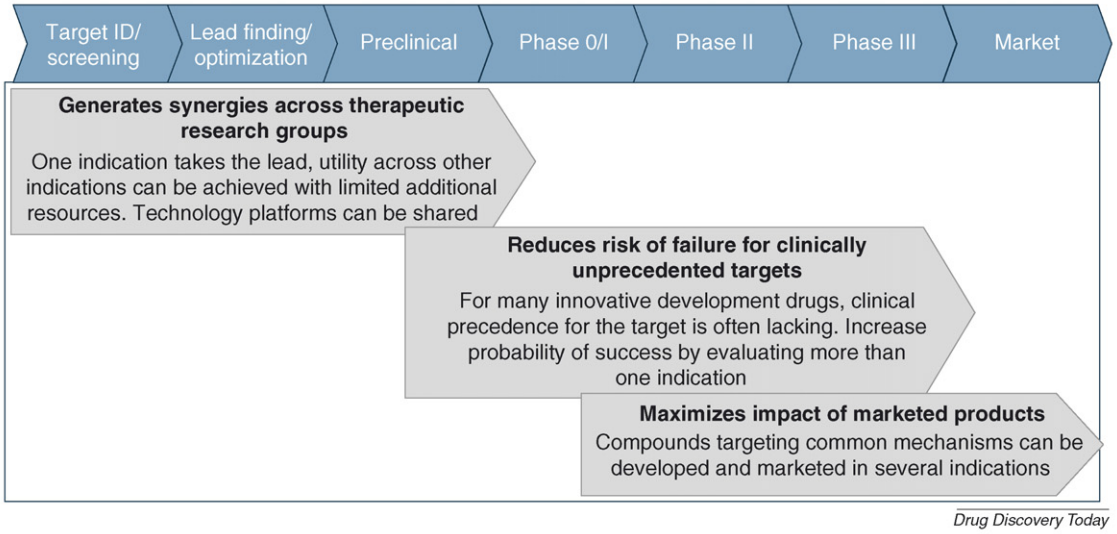

FIGURE 3

The common mechanism strategy generates synergies at all stages of R&D and marketing.

The common mechanisms strategy provides a framework for developing innovative therapeutics while reducing attrition rates in the R&D process and increasing the opportunities for positioning successful compounds into the market place. A key aspect of the common mechanisms strategy is to move drug development from the concept of one target for one disease to one target mechanism for multiple diseases. To this end, we propose a broad discovery strategy that evaluates the potential of a target in multiple indications followed by clinical development in those indications with promising preclinical results. In some cases, it may be apparent from the onset that therapeutic options exist in several indications, while for other targets only the continued search for new indications will reveal their full potential. The search for new indications should be initiated as early as possible after a compound is available. Thus, the evaluation process across indications will lead the way to an optimized design of early clinical trials. In some cases, more than one compound may be needed for the treatment of different diseases, because the required compound characteristics may be disease-specific, for example, pharmacokinetics and formulation, amongst others. In summary, the common mechanism strategy can help to develop novel medications successfully and in a cost-effective manner.

Disclosure statement

All authors are currently full time employees of Bayer HealthCare. All authors hold stocks in Bayer AG. AB and SS were full time employees of Sanofi Aventis Deutschland until 2005.

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