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Drug discovery: selecting the optimal approach

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The target-based drug discovery approach has for the past 10–15 years been the dominating drug discovery paradigm. However, within the past few years, the commercial value of novel targets in licensing deals has fallen dramatically, reflecting that the probability of reaching a clinical drug candidate for a novel target is very low. This has naturally led to questions regarding the success of target-based drug discovery and, more importantly, a search for alternatives. This paper evaluates the strengths and limitations of the main drug discovery approaches, and proposes a novel approach that could offer advantages for the identification of disease-modifying treatments.

In the past few years, the commercial worth of novel targets in licensing deals has fallen dramatically, unless they are accompanied by extensive *in vivo* validation studies and several chemical lead structures. This reflects the fact that the distance between identification of a novel target and entry into preclinical development for a molecule with suitable drug-like properties and with proper target validation is considerable [1]. In a recent report it was estimated that the probability of reaching preclinical development was only 3% for a novel target, compared with 17% for an established target [2].

Since the early 1990s, the target-based drug discovery paradigm has been the dominant approach in the pharmaceutical industry. It takes a rational and scientific approach to the drug discovery process by defining the specific molecular mechanism or mode-of-action (MoA) to be targeted by the treatment based on biological and clinical findings. Selecting MoA allows the use of molecular modelling techniques, SARs and, more importantly, automated screening technologies. However, despite the fact that the target-based approach is highly advantageous from a scientific and practical viewpoint, it does not translate into a high success rate for novel targets, presumably because our level of insight into disease and biological processes is not sufficient to predict the therapeutic value or drugability of a novel target.

From a commercial perspective, a success rate of 3% for reaching preclinical development is not attractive. Each drug discovery project usually lasts 2–4 years, and if 33 targets on average have to be evaluated to identify one target that can proceed into preclinical development, it means that at least 66 years of research is needed to produce one successful drug discovery project for a novel target. Considering that the attrition rates caused by toxicological effects and lack of clinical effects also are substantial, it means that novel unvalidated targets are not attractive for the pharmaceutical industry. Owing to these realities, the pharmaceutical industry is increasingly focusing on known targets and using existing drugs in new indications, but this can only be a temporary solution because the number of such possibilities is limited.

There has, in the past few years, been an increasing focus on the limitations of the target-based approach [3–10], and it is necessary that we learn from our experience with this paradigm. However, a more intriguing question is whether other approaches might be more suitable for the identification of novel treatments – the purpose of this paper is to contribute to this discussion. The paper will analyze the different drug discovery approaches to identify their strengths and limitations from a theoretical viewpoint and, based on this discussion, a novel approach will be presented.

Drug discovery approaches

In principle, a disease can be viewed as an abnormality at the mechanistic level, for example, with a receptor or gene. This abnormality gives rise to a functional deficit (e.g. abnormal function of the mitochondria or the Golgi apparatus) that will cause the cell or the organ to function abnormally. These effects will spread and cause secondary changes in the organism and will result in symptoms and physiological changes that can be observed and that are used for the categorization of diseases. Based

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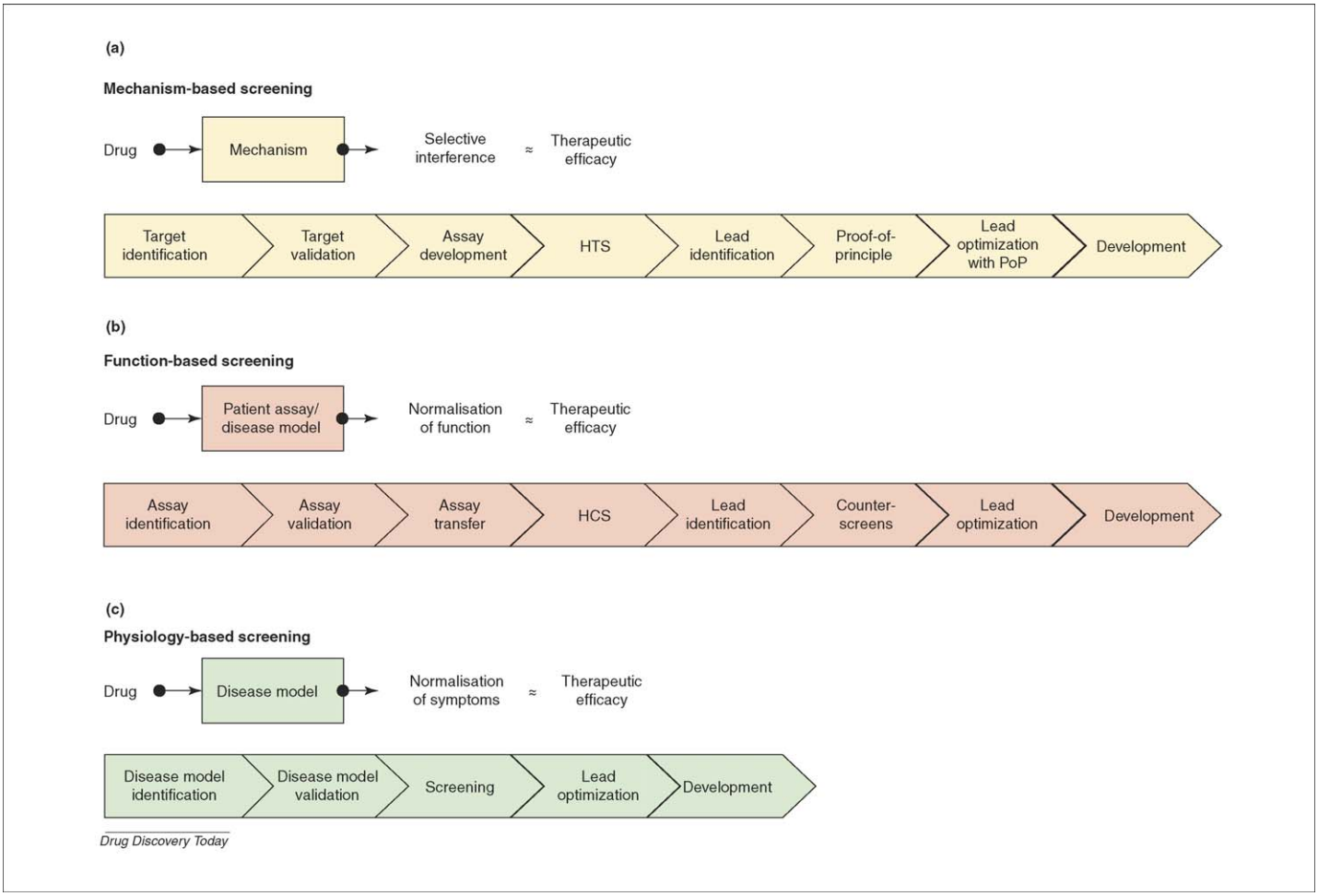

FIGURE 1

Drug discovery approaches. (a) Mechanism-based drug discovery – novel targets are typically identified based on biological and clinical findings and validated based on expression patterns and knockout mice, unless a selective compound is available. After target selection, an HTS-suitable *in vitro* assay is developed to measure the selectivity of compounds to the target, and then the HTS is performed. This normally results in several compounds, preferably belonging to different chemical classes, with medium to high affinity to the target. In the lead identification phase, small-scale analoging around these structure classes are performed to determine feasibility of reaching a selective compound with appropriate drug-like properties. The lead structures can be tested in a disease model to determine if the targeted mechanism has therapeutic potential and if the outcome is positive, the LO programme begins. In this programme, a large number of analogues are produced around the lead structures and are screened for target selectivity, and pharmacokinetic and metabolic properties. At the end of the LO phase, suitable compounds are tested in an *in vivo* disease model for proof-of-principle and, if the study is positive, the compound is selected for development. **(b)** Function-based drug discovery – the first step is to identify a functional deficit at the level of cells or tissue that is unique to the disease state. For example, by comparing cells or tissue from patients, transgenic animals carrying a human mutation or animals that have been exposed to a traumatic event (e.g. hypoxia) with healthy control cells or tissue. The second step is to validate the specificity of the dysfunction for the disease (e.g. by comparing sporadic and familial forms and comparing to other diseases). The predictive validity can be measured if disease-modifying treatments are available, but symptomatic drugs are unlikely to have an effect. The next steps are to transfer the assay to a format suitable for screening, to perform the screening campaign and to select acceptable lead structures. These can be evaluated in side-effect tests to ensure their safety. Finally, the LO programme can be initiated using the function assay to determine compound efficacy in combination with assays for pharmacokinetic and metabolic properties. **(c)** Physiology-based drug discovery – the first step is to develop a disease model that mimics certain symptoms of the disease, and then to demonstrate predictive validity by demonstrating that clinically effective drugs are effective in the disease model. Compounds are screened in the disease model and they are evaluated relative to existing treatments based on their ability to demonstrate increased therapeutic efficacy or equal efficacy, but an improved side effect profile. Following identification of a lead compound, the LO programme is performed using the disease model combined with tests for pharmacokinetic parameters, side effects, and so on.

on this process, drug discovery can be conducted at three different levels – mechanism, function and physiology (Figure 1). The three approaches are clearly different and consequently show different strengths and weaknesses (Table 1).

The mechanism-based approach

The mechanism-based (MB) approach, which corresponds to the target-based approach, seeks to produce a therapeutic effect by targeting a specific mechanism. It screens for compounds with a specific MoA. This drug-discovery process is well known, and numerous examples (e.g. selective serotonin-reuptake inhibitors) are available [11–14].

The function-based approach

The function-based (FB) approach seeks to induce a therapeutic effect by normalizing a disease-specific functional abnormality. It

TABLE 1

Comparison of drug discovery approaches

	Mechanism-based	Function-based		Physiology-based
Mode of action				
Screening goal	Mechanism selectivity	Biological effect		Biological effect
Preselection of mode-of-action	Yes	No		No
Number of mechanisms	1–3	Medium		Large
Combination of mechanisms	No	Yes		Yes
Unknown mechanisms	No	Yes		Yes
Screening system				
Preparation	Cell or cell-free system	Patient	Animal	Non-human
Complexity	Cell component to cell	Cell to tissue	Cell to tissue	Organ to intact animal
Disease	None	True disease	Disease model	Disease model
Proof-of-principle				
System	Disease model	Disease assay		Disease model
Validation	Separate from screening	Part of screening process		Part of screening process
Time to validation	2–4 years	Immediately		Immediately
Screening capacity				
Assay development	Methods well established	Unknown		Difficult
Amount of compound needed	Low	Low		High
Screening capacity	Ultra-high to high	Medium		Low to very low
Key strengths	Selective compounds for validated targets	Disease modification?		Symptomatic treatment
Main limitations	Identifying mode-of-action with therapeutic effect	Access to material		Validity of disease model
	Validity of disease model for Proof-of-principle	Limited experience with approach		Screening capacity
	Compounds might not be drug-like	Technological development needed		Pharmacokinetic profile of compound

screens compounds for their ability to induce or normalize functional parameters in disease-relevant models, such as axonal transport, growth processes, hormone secretion or apoptotic processes. Compared with MB, functional parameters represent a higher level of organism complexity because function requires the integrated action of many mechanisms. However, unlike the physiology-based approach (see below), the parameters cannot be compared directly to the symptoms observed in patients. Examples of the FB approach currently used in drug discovery are microdialysis and whole-cell or extracellular electrophysiology, but the screening capacity of these methods is low and so they cannot be used for library screening. Recently, it has become possible to measure functional parameters at the cellular level with reasonable screening capacity (e.g. high-content screening technologies that can measure dynamic changes in the cytoskeleton) and these new technologies will make it possible to integrate functional screening fully into the drug discovery process.

The physiology-based approach

The physiology-based (PB) approach seeks to induce a therapeutic effect by reducing disease-specific symptoms or physiological changes. It screens compounds for these properties in animal models that usually mimic specific aspects of disease symptomatology, common treatment side-effects or characteristics of clinically effective compounds. The screening is usually conducted in isolated organ systems or in whole animals. The PB approach was the first drug discovery paradigm, and has resulted in many effective treatments. It is still used extensively (e.g. for the development of antipsychotic and antidepressant drugs) but suffers from a very low screening capacity and difficulty in identifying the MoA of compounds.

Mode of Action

The most fundamental difference between the three approaches is that MB selects a specific MoA for the drug, whereas PB and FB screen drugs based on their ability to produce a specific biological effect in the chosen screening system, but do not assume a particular MoA for the drug. This has several implications. As shown in Figure 2, assume that the outer circle represents the biological space of the organism (i.e. all the mechanisms and combinations of mechanisms that can be affected in the body) and that the second outermost circle represents the therapeutic

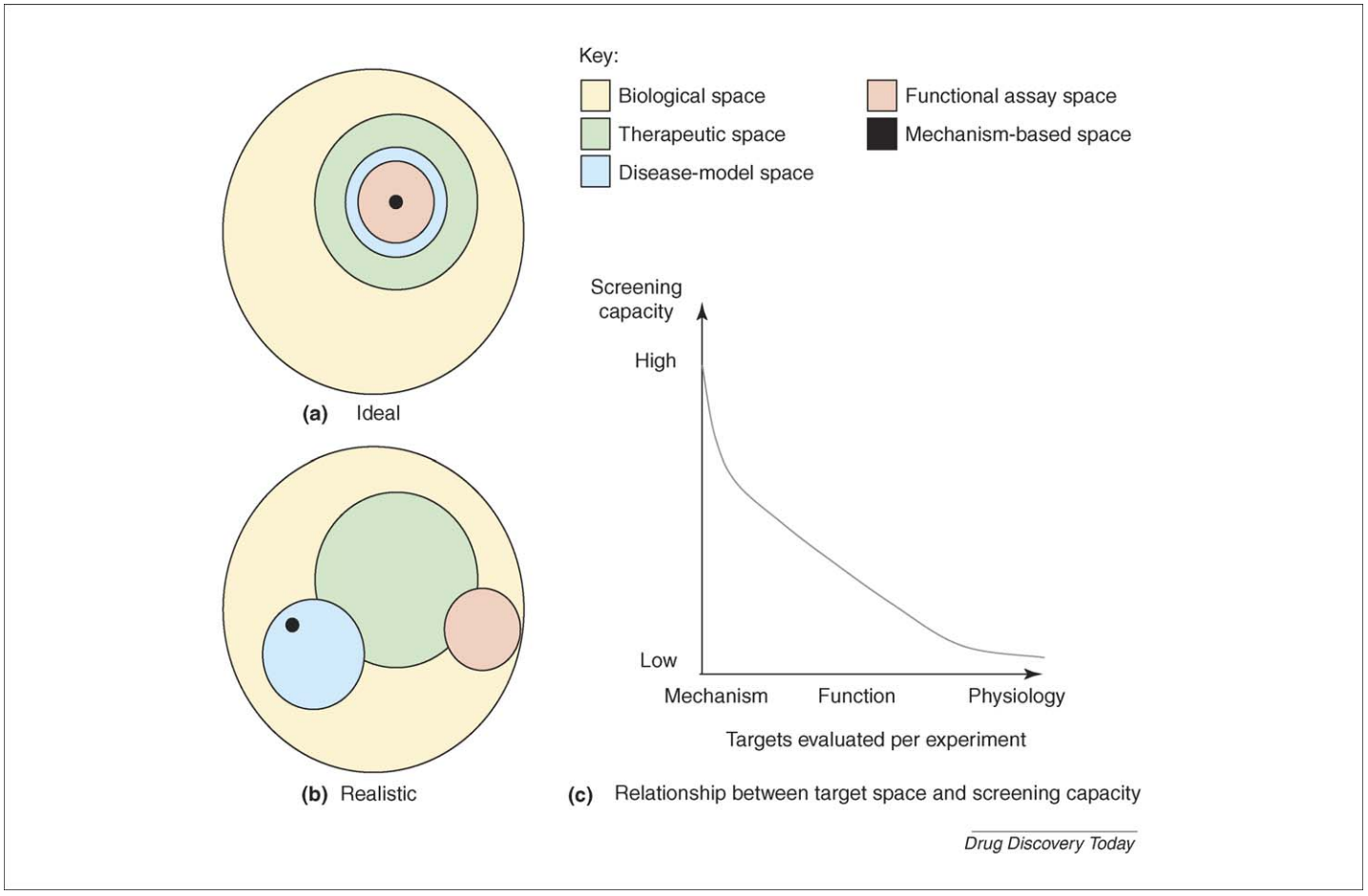

FIGURE 2

Comparison of drug discovery approaches. The outer circle (cream) represents the entire space of biological targets and mechanisms that can be affected by different treatment paradigms in an organism. The inner circle (green) represents the therapeutic space for a given indication (i.e. the subset of targets and mechanisms that can be affected to produce a therapeutic effect in the disease state). The mechanism-based approach selects a single known mechanism and investigates its therapeutic potential, and it will therefore be represented as a single point within the therapeutic space. By contrast, the physiology-based and the function-based approaches do not *a priori* make any assumptions regarding the mechanism the drug has to affect and they can therefore identify any mechanism or combination of mechanisms within their respective disease-model spaces (i.e. the subset of mechanisms the disease-model is able to detect, shown as the inner-most circles). In **(a)** the ideal relationship between the different spaces is shown, whereas **(b)** pictures a more realistic situation, namely that there is only little overlap between the therapeutic space and the disease-model spaces and that the selected target lies outside the therapeutic space, but within the disease-model space such that it pre-clinically will appear validated. **(c)** The screening capacity and the ability to work systematically with the development of a treatment must also be considered. By selecting to focus on a single known mechanism within the biological space it is possible to use HTS techniques, whereas by screening in disease-based models, where specific mechanisms are not selected, the screening capacity is lower but the information content is higher. There is consequently a negative correlation between screening capacity and the number of targets and/or MoAs that can be evaluated simultaneously.

space for a given disease (i.e. the subset of mechanisms or combination of mechanisms that have therapeutic efficacy in the disease – for most diseases, for example, depression, more than one MoA will have therapeutic effects). Comparable to the biological space, there is a chemical space (not shown) that represents all possible chemical structures and where each point represent the subset of structures that can affect a specific mechanism in the biological space. The MB approach selects one mechanism in the biological space – a point space – and identifies from the chemical space the subset of drugs with effect on this mechanism, but at the same time excludes all other options. By contrast, FB and PB screen drugs for a specific biological effect in a disease-relevant screening system, meaning that they can identify any drugs in the subset of the chemical space that act on biological mechanisms in the disease model space. This means that the biological and chemical spaces are not point-spaces, but have specific areas defined by the disease model system, and that chemistry can guide the drug discovery process because compounds are screened in a disease-relevant assay for their ability to induce a specific biological effect, whereby novel MoAs can be identified [15]. The information content resulting from the screening of one compound in the MB system is therefore very low compared with FB and PB but, as discussed later, this must be seen in relation to the screening capacity. However, perhaps more importantly, the possibility of letting biology and chemistry deliver serendipitous discoveries is excluded by the MB approach because the MoA is restricted to known mechanisms and biological processes for which we can provide a theoretical framework for their role in the disease.

MB selects the MoA for the treatment, so the success of a drug discovery programme depends on the ability to predict the ther-

apeutic potential and drugability of a novel target in a disease. By contrast, FB and PB do not place any restrictions on the MoA and can identify completely novel and unknown MoAs, but are limited by the validity of their screening systems. Another aspect is that most MB drug discovery programmes focus on a single target to keep the drug screening and optimization in the lead optimization (LO) phase manageable, whereas FB and PB can identify any combination of mechanisms by screening for a biological effect. Therefore, MB assumes that the therapeutic efficacy that can be achieved by selectively affecting one mechanism is sufficient and can compete with drugs with a broader MoA profile. In several indications, it is known that different MoAs can be used for treating a disease and that added clinical benefits can be obtained by combining MoAs, either in one compound [16,17] or by combining treatments [18]. An important advantage of the MB approach, compared with FB and PB, is that in the LO phase it is much easier to define chemical backup strategies if the lead structures are not suitable. However, the advantage depends upon the specific target, for example, not all D2 dopamine-receptor antagonists have the same binding site on the receptor, which makes it difficult to establish clear SARs.

Screening System

The screening system determines the information that can be learned about the properties of a compound. For MB, the screening system is designed to measure compound effects on a single previously selected mechanism, and can therefore only provide information on the selectivity of the compound for this specific mechanism. By contrast, FB and PB screen drugs for biological effects in disease assays or models and are therefore not limited to identifying specific MoAs or types of drugs, but can identify any compound that can produce the desired biological effect. However, in contrast to MB, it is the validity of the screening system that determines whether drugs and MoAs with clinical therapeutic potential are identified.

The development and validation of disease models are discussed in detail elsewhere in the literature [19]. Generally, the validity of a disease model is affected by three factors: (i) the origin of preparation (e.g. a patient versus a rodent); (ii) the complexity of preparation (e.g. a cell-based system versus an intact organism; and (iii) the induction of disease state, or disease simulation (e.g. the clinical disease versus a drug-induced state). The closer each of these components is to the patient, the higher the validity of the disease model. To quantify the disease process or the symptoms in a disease model, a test is used in a similar way to a diagnostic tool, and it must be validated to ensure it measures disease-relevant parameters.

PB screens drugs in disease models for their ability to produce or normalize specific physiological parameters or symptoms. These models are often *in vivo* systems and the screening system will, therefore, favour compounds with drug-like properties, unlike the MB approach. However, it is often possible to improve pharmacokinetic and blood–brain barrier properties in the LO phase, so compounds might be excluded even if they could have been optimized at a later stage. A more fundamental problem with disease models is that we have little insight into the cause of diseases – except in the case of infectious diseases – and, as a result we do not know how to correctly reproduce the clinical disease state in an animal model. We only have consistent information on symptomatology so most disease models are developed to mimic symptoms. However, as shown in Figure 3, it is known that one disease mechanism can give rise to very variable symptomatology in patients [20,21] and, conversely, that a specific symptomatology can have many different causes [22]. This, in turn, means that

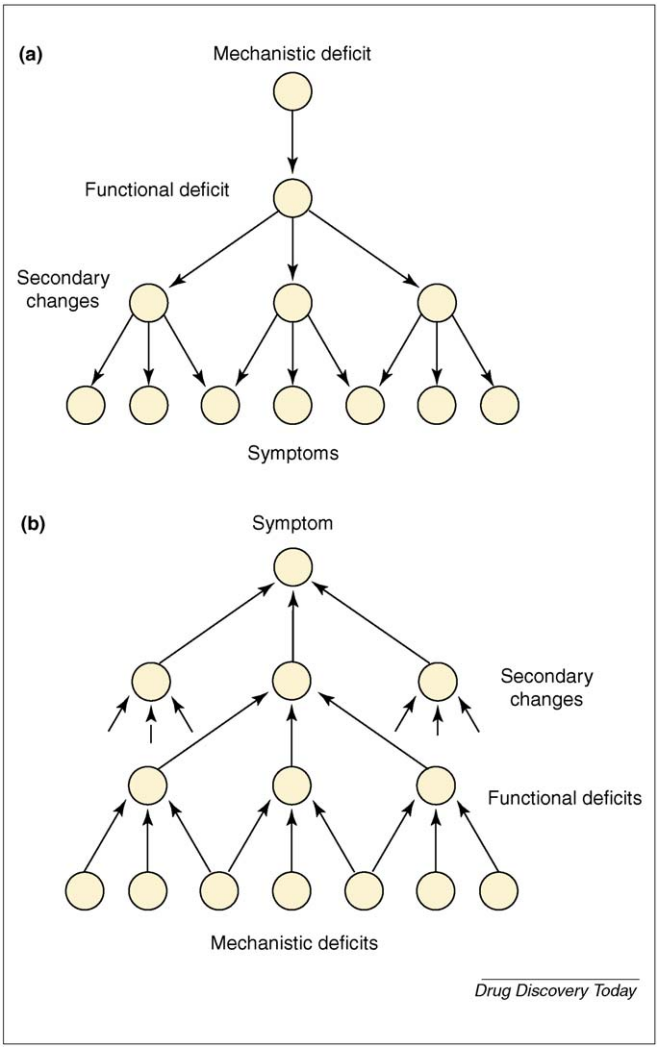

FIGURE 3

Relationship between disease mechanisms and symptoms. **(a)** The cause of the disease is a deficit in a certain mechanism, which leads to functional abnormalities, which again give rise to a number of primary and secondary changes, and which finally result in the symptoms that can be observed in the patient. By comparing patients within a disease group, it is known that the same disease mechanism can induce a very variable symptomatology in different patients and in some diseases it might even be difficult to recognise that the patients suffer from the same disease. Therefore, it is often impossible to establish a clear relationship between disease mechanism and symptomatology. **(b)** A set of symptoms can result from a number of underlying primary and secondary causes and these can again be caused by a wide array of deficits at the mechanistic level. For most diseases, the underlying mechanistic deficit is unknown and it is therefore necessary to develop disease models based on symptom-similarity to the clinical condition. However, because a specific symptom can be caused by an array of different underlying mechanistic deficits, the probability of inducing the disease state in the disease model in the same manner as in the clinic will be low. This might explain why most disease models are primarily predictive for symptomatic and not disease-modifying treatments.

because disease models are developed to mimic symptoms, the likelihood of inducing the disease in a manner corresponding to the clinical condition is low, with the consequence that the disease model will only rarely be valid for disease-modifying approaches. This correlation is supported by the observation that most treatments tend only to be symptomatic and not disease-modifying, except for infectious diseases where the disease-causing agent is known.

FB screens drugs for their ability to affect or normalize a functional parameter in a cell or a tissue-based screening assay. For many diseases, it is possible to obtain material from patients, thereby enabling the study of functional abnormalities in cells that contain the true disease and the correct genetic background. For some conditions, such as central nervous system disorders, it will not be feasible to obtain patient material on a regular basis, but it has been shown that transgenic animals carrying a human familial mutation can express the correct disease mechanism even if they do not show the clinical symptomatology (transgenic mice carrying a human mutation causing Alzheimer's disease show the same deficits in axonal transport mechanisms, but the mice do not show prominent cognitive deficits) [23,24]. These observations suggest that a human mutation in a mouse can cause the same mechanistic and functional changes as in the patient at the cell and tissue level but the overall symptomatic consequences are different [25]. For both screening systems it is necessary to generalize any finding to the broader patient population to avoid the development of treatments that are only effective in one patient or in one familial form, as occurred with leptin for the treatment of obesity [26,27].

Screening capacity

Screening throughput is an important requirement in the early phases of a drug discovery programme because it determines the ability to screen large compound libraries and, thereby, the discovery of new classes of compounds that can be used for pharmaceutical purposes. One key advantage of MB is the screening capacity, but it is also necessary to consider the amount of information that is learned from each screening round (Figure 2b). MB only samples one point in the target space, whereas FB and PB sample larger areas per drug. In order for these approaches to be competitive with MB, they do not have to reach the same screening throughputs as MB.

The focus of MB is on one single mechanism, which permits the use of HTS and ultra-HTS technologies for screening and makes MB a highly effective approach for the identification of target selective compounds. The PB approach uses complex disease models that integrate physiological responses into the screening process and so the amount of information acquired from each experiment is consequently very high. However, the screening process is usually slow and resource intensive and this imposes a significant preselection of the types of compounds that can be evaluated. Technological developments are ongoing to automate *in vivo* characterization of compounds, but even if these problems are solved, *in vivo* disease models require large amounts of compound and compound characteristics, such as pharmacokinetic and blood–brain barrier penetration properties, have significant impact on the types of compounds that can be evaluated, even if these compound properties can often be improved in the LO phase. The result of these limitations is that disease models are primarily useful for screening in the late LO phase or for proof-of-principle studies. However, even if these disease models are slow, they are competitive relative to the MB approach if several targets must be evaluated before identifying a successful candidate.

FB does not yet play a significant role in drug discovery, although there are initiatives being taken in inflammatory and myofibrillary diseases [28,29] primarily in academic laboratories. However, many of the technologies being developed for high-content screening are directly applicable and, for these systems, it is already possible to reach screening rates that allow compound-library screening. On one hand, the capacity will not be as high as for MB but, on the other hand, more information is collected per screening round, thus making the approach competitive.

Proof-of-principle

For any new compound, it is necessary at some point in the discovery process to evaluate it in a system that is believed to be representative for clinical therapeutic efficacy. For PB and FB, this will be the disease model or assay that was used to identify the compounds and this means that the proof-of-principle validation is incorporated into the screening process. For MB, proof-of-principle studies will normally be conducted in the same *in vivo* disease models as those used for PB. Therefore, the MB approach is subject to the same limitations as PB in terms of the validity of disease models; few companies are willing to move a compound into development without *in vivo* proof-of-principle. However, unlike PB, it is necessary for the MB approach to first develop a compound with the desired selectivity profile before it can be tested in the chosen disease model to determine its biological profile (~2–4 years into the programme for a novel target). It is possible to use expression patterns and effects of siRNA and conditional knockouts in relevant tests for the early validation of a novel target but, although these are important tools, they do not correspond to the actions of a drug. A drug will rarely bind irreversibly to its target, but will exhibit a specific on–off rate and rarely occupy all binding sites. By contrast, these genetic tools will affect the expression of the target so that the biological consequences will be different. Consequently, true target validation requires the testing of a compound belonging to the chemical class that will be used.

Summary

The MB approach focuses on the development of compounds that selectively affect one, or at most three, mechanisms and, as a consequence, allows high screening capacity and the ability to optimize the LO programme. This is a superior strategy for properly validated targets, but the risk can be high for novel targets because the time required to reach target validation is ~2–4 years. The PB approach evaluates compounds based on biological efficacy in disease models and can identify compounds with novel modes of action, but the screening rate is low, the compounds must fulfil certain pharmacokinetic requirements to be suitable for testing, and it is difficult to define a backup strategy because the MoA is often unknown. Consequently, the PB approach is mostly suitable for target discovery and validation but will be competitive to the MB approach if several targets must be evaluated to identify one successful candidate. The FB paradigm is new and there is little experience of this approach. FB, like PB, evaluates compounds based on biological efficacy but instead of measuring physiological

responses and symptoms, it quantifies functional parameters at the level of cells and tissue. The screening capacity for this approach will, with the continued development of high-content screening methods, reach levels that allow screening of compound libraries. Many of the disease models used for the PB approach, and for proof-of-principle studies for the MB approach, are developed to mimic the clinical symptoms, probably with the consequence that most of the treatments developed in these models will be symptomatic rather than disease-modifying treatments. By focusing on functional parameters in abnormal patient material or in transgenic animals carrying human disease mutations, FB could have a higher probability of identifying treatments that will prove to be disease-modifying in the patient, but it is also possible that symptomatic treatments can be identified in case the functional deficit is responsible for inducing specific symptoms.

Function-based screening in disease models: an opportunity?

There is considerable experience of the advantages and disadvantages of the MB and PB approaches, whereas the FB approach is new and untested. However, the analysis of the drug discovery approaches suggest that the FB approach could have several advantages: the screening goal is a biological effect that makes it possible to explore fully the chemical and biological spaces (i.e. no restrictions on the MoAs); the screening capacity enables the evaluation of compound libraries within a reasonable time period; the screening system is a clinically valid disease model; and the screening criteria are disease-relevant.

There is currently a trend in the pharmaceutical industry towards the use of more complex systems for drug screening, such as high-content screening, zebra fish and systems biology (e.g. [28–34]), but in most cases the screening goal is still to identify or validate a specific target and the screening systems are usually based on healthy cells or tissues, or on models where a specific mechanism has been manipulated instead of using patient material where the disease state is intrinsic, or on transgenic mice carrying a known disease-causing human mutation. The aetiology of most diseases are not understood and, by choosing to induce a disease state artificially instead of using, where possible, material carrying the clinical disease state (or at least being as close to the clinical state as possible), there is the considerable risk that the disease state in the screening system does not correctly reflect the clinical situation, with the consequence that a treatment might not be effective in patients. These approaches only tackle one problem in the drug screening process (the ability to identify novel MoA) but do not address the issues of the validity of the screening system or the disease relevance of the parameters being tested.

The FB approach avoids these limitations by screening for normalization of disease-specific functional deficits in cells and tissue from patients or transgenic animals carrying human disease mutations. For material originating from patients, this screening system has the highest level of validity that can be realistically obtained. The material contains the clinical disease state and the genetic background is not only human, but also from patient who has developed the condition. For some diseases, it might not be possible to patient disease-relevant material from patients. In these cases, screening can make use of transgenic animals carrying a familial mutation.

The assay itself would be developed by comparing cells from patients with cells from healthy controls or, alternatively, comparing transgenic animals carrying a disease mutation to control animals, to identify functional differences. When a functional abnormality is identified, it must first be generalized to the disease state by testing cells from different patients and, if possible, by comparing familial and sporadic forms to healthy controls and to patients with other diseases. In transgenic animals, generalization can be addressed by demonstrating that different familial mutations cause the same functional deficits, whereas familial mutations in other diseases have different effects. Most studies of disease conditions focus on mechanistic or physiological changes and not function, but because a change in mechanism necessarily must result in a functional abnormality in order to produce symptoms, it is clear that functional abnormalities will be identified once we start looking for them.

For FB, the goal of a treatment is to reverse or reduce the consequences of a disease-specific functional deficit and the approach is therefore based on the assumption that a drug with these effects will enable the body better to compensate for the disease condition and that this will lead to a therapeutic improvement. The advantages of focusing on function instead of mechanism are first that each screening will evaluate drug effects on many mechanisms instead of one; second that drugs acting directly as well as indirectly with the underlying mechanistic deficits can be detected because the readout is an improvement in function, irrespectively of how it is achieved; and third, it increases the likelihood of identifying treatments that are effective in larger groups of patients since different disease mechanisms may produce the same functional consequences. This approach may be more likely to detect disease-modifying treatments, but depending upon the assay it may also be sensitive to secondary consequences of a disease process and may be able to identify treatments that primarily have symptomatic effects.

Conclusion: balancing drug discovery approaches

The analysis of mechanistic-, functional- and physiological-based screening has clearly demonstrated that each approach has its specific strengths and limitations, and that the choice of approach – not surprisingly – depends on the actual indication being pursued. The MB approach is clearly superior for well-validated targets and will, in most cases, also be the choice for novel targets where the supporting biological and medical evidence is strong. However, the risk associated with MB for novel targets is considerable because it takes 2–4 years to identify a selective compound that can be used for target validation and, for this reason, alternative approaches should be considered when entering a new programme. The PB approach has significant limitations because of its low screening capacity, but it is probably the superior approach for developing symptomatic treatments in indications where an obvious disease-related target is not available and where it can be expected that many targets will need to be evaluated before a target with therapeutic value is identified. The FB approach is a novel approach for which little experience is available but it holds promise as a new method for identifying disease-modifying treatments that combines the screening capacity of the MB approach with the disease-focus of the PB approach. Because the necessary technology for studying functional processes in cells at a rate that allows library screening is only in the process of being developed, it

will be several years before the FB approach can be fully implemented. However, it is currently possible to identify disease-specific functional deficits in transgenic animal or human tissue and to use these observations for implementing drug discovery programmes based on the MB approach.

In summary, the above analysis did not show a clear advantage of one drug discovery paradigm over the others, but that all drug discovery approaches have their specific strengths and weaknesses. The choice of paradigm must depend on the specific disease and the type of treatment being sought and for this reason any drug discovery programme should begin with an open strategic analysis of which drug discovery paradigm is most likely to be suitable for the current project [35].

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