DRUG DISCOVERY TODAY TARGETS

Target-based drug discovery: is something wrong?

Frank Sams-Dodd

For the past decade the pharmaceutical industry has experienced a steady decline in productivity and a striking observation is that the decline coincided with the introduction of target-based drug discovery. The target-based approach can very effectively develop novel treatments for a validated target, but the process of target validation is complex and associated with a high degree of uncertainty. The purpose of this paper is to analyse these aspects in detail to determine if weaknesses in this part of the drug discovery path might explain why this paradigm has not resulted in increased productivity over the traditional *in vivo* approach, considering its superiority in screening capacity and its ability to define rational drug discovery programs.

For the past decade, in spite of increasing levels of investments in pharmaceutical R&D, there has been a steady decline in the number of new molecules and biologicals that enter clinical development and reach the market [1–2]. Several reasons have been forwarded to explain this decline, primarily focused on business, competitive and regulatory aspects [2–6]. A striking observation, however, is that the decline in productivity has, to a large extent, coincided with the introduction of target-based drug discovery (Figure 1). This drug discovery paradigm replaced the traditional physiology-based approach ~10–12 years ago, because it allowed an increased screening capacity and the definition of rational drug discovery programs. It was believed that this approach would result in an increased productivity [7–8]; however, the decline in productivity questions whether this assumption was correct. The purpose of this article is to analyse target-based drug discovery to determine if the approach has inherent limitations and to find out whether there are general aspects of the process that can be improved to increase productivity.

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Target-based drug discovery

A target is usually a single gene, gene product or molecular mechanism that has been identified on the basis of genetic analysis or biological observations [9–14]. The literature does not distinguish between target classes, but for the present analysis they will be divided into two classes: genetic or mechanistic targets. Genetic targets represent genes or gene products that, in specific diseases, have been found to carry mutations (e.g. the familial forms of Alzheimer's Disease) or that confer a higher disease risk (e.g. predisposing the individual for developing schizophrenia or depression). By contrast, mechanistic targets represent receptors, genes, enzymes, and so on that usually are not genetically different from the normal population. These latter targets originate from biological observations in the clinical disease state, models of disease, basic biological findings or mechanisms of action of clinically effective drugs.

Genetic targets

A target-based drug discovery program focusing on a genetic target will have the goal of developing a

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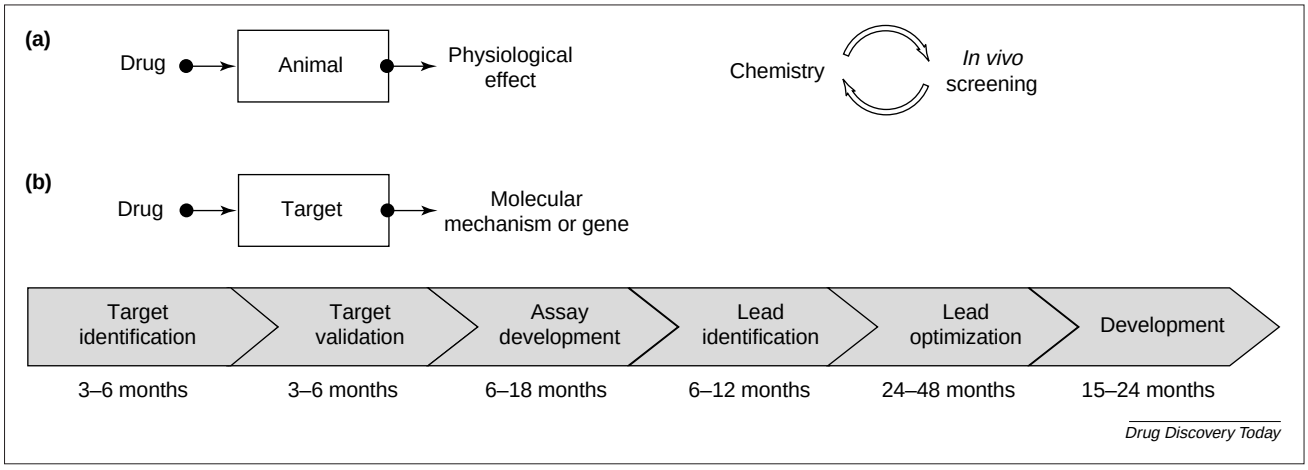

FIGURE 1

Physiology- and target-based drug discovery. (a) Physiology-based drug discovery. The organism is seen as a black box and drugs are characterised on the basis of their physiological effects in complex disease-relevant models (e.g. animal models or isolated organ systems). Assays are developed based on disease knowledge, clinically effective drugs or basic biological knowledge. The approach does not require understanding of the aetiology or the biology of the disease or the mechanism of action of the compound, because the organism is seen as a black box. The weakness of the approach is lack of a clear relationship between the drug mechanism of action and biological effect and low-throughput screening. Its strength is that the only requirement is a disease-relevant model with predictive validity. **(b)** Target-based drug discovery. The organism is seen as a series of genes and pathways and the goal is to develop drugs that affect only one gene or molecular mechanism (i.e. the target) in order to selectively treat the deficit causing the disease without producing side effects. The approach consists of five steps: target Identification, where the exact target and the specific patient population are identified; target validation, where the therapeutic value of the target in the specified patient population is determined; assay development, where the target is expressed in an HTS assay system; lead identification, where compound libraries are screened to identify target-selective compounds; and lead optimization, where lead structures are optimised for target affinity and selectivity. The strengths of the approach is high screening capacity and the ability to formulate simple, clear requirements to the drug, which allows the implementation of 'rational drug design'. Its weakness is that drugs can only be optimised against a small number of targets simultaneously (i.e. this approach is inconsistent with 'dirty' drugs) and the dissociation of physiology from the drug discovery process. Similarly to the physiology-based approach, this also requires access to a validated disease model for proof-of-principle studies (the term proof-of-concept is reserved for clinical proof-of-concept).

drug that selectively modulates the effects of the disease-associated gene or gene product without affecting other genes or molecular mechanisms in the organism. Targets will typically originate from population studies or from the human genome project; an example could be a leptin analogue to compensate for a deficit in leptin production in certain familial forms of obesity (Box 1; Figure 2). Target identification for genetic targets requires identification of the disease-associated gene and the specific patient population to which it is relevant, whereas target validation will frequently involve producing a transgenic animal that carries the mutation to demonstrate that this animal has a phenotype that mimics certain aspects of the clinical condition. *In vivo* proof-of-principle studies as well as drug screening can subsequently be performed in this animal to demonstrate that modulation of the gene or gene product has a therapeutic effect on either the disease process or its symptomatology.

Genetic targets have, in connection with the human genome project, received considerable attention and much hope has been attached to this approach [2,15–17]. They will not be universally applicable to diseases, however, because certain conditions must be fulfilled. First, the disease must be attributed to a genetic mutation or the increased disease-risk must predominantly be attributed to a single gene. Second, the gene or gene product must contribute to the disease process or disease-risk at the time of treatment.

The first condition means that diseases caused by genetic mutations (e.g. Huntington's chorea) fall into this category, however, the size of these patient populations is generally small. The more common diseases that have the highest socioeconomic impact are multifactorial (e.g. depression, anxiety and obesity). For these diseases it will only be possible to target a gene that affects disease-risk if the risk factor is very high, because each treatment may produce side effects and the therapeutic value of lowering only one of many risk factors may therefore not outweigh such negative consequences.

The second condition states that the target must contribute to the disease process at the time of treatment and, although this sounds very logical, it means that developmental diseases like schizophrenia (Box 1; Figure 2) cannot be treated by such an approach, because the gene responsible for the disease might have only exerted its effect at a certain time point during the developmental process. A possibility could of course be prophylactic treatment in the prenatal state, but as any genetic predisposition only confers an increased risk of developing a disorder it seems unlikely that such a treatment will be feasible or welcome.

Owing to these limitations, the impact of genetic targets on disease treatment will most likely be limited, as all the major diseases are multifactorial [9] where specific genes each only contribute with low risk factors. However, an

BOX 1

Complex diseases and target-based drug discovery

Obesity
An increasing problem in industrialised countries and there is an urgent need for pharmacological intervention [31,32]. In 1994, it was discovered that the hormone leptin was released from adipose tissues and that the release was proportional to the size of the storage of fat. A family was identified that carried a mutation in a gene responsible for the production of leptin and family members with this mutation were highly obese. A leptin analogue was developed, but during clinical testing it was discovered that although the drug was extremely effective in people carrying the mutation, the drug did not induce weight loss in obese individuals without this specific mutation. This means that a genetic mutation responsible for a familial form of a disease might not be relevant to sporadic forms and that a treatment developed based on the familial form may only be effective in individuals carrying this specific mutation.

Depression
Characterised by strongly depressed mood, suicidal ideation and loss of initiative and has a life time prevalence of 15% [33–35]. Pharmacological treatments are available that, after 3–6 weeks of administration, can successfully treat the condition in most individuals (e.g. selective or mixed re-uptake inhibitors of serotonin and noradrenalin, monoamine oxidase-B inhibitors, tricyclics and electroconvulsive therapy). This means that a treatment does not have to affect a single, specific receptor, rather that similar clinical benefit can be derived through different mechanisms. The delayed onset of action would tend to suggest that drugs induce a cascade of effects that ultimately result in biological changes capable of mediating therapeutic action (i.e. there is not a clear, direct relationship between target and therapeutic effect).

Schizophrenia
Affects ~1% of the population worldwide [36–38]. The disease has a strong genetic component and the risk-factor is 50% for monozygotic twins. Recent studies suggest schizophrenia is caused by a developmental deficit during the prenatal period or around birth. The cause of the deficit could be a range of factors such as viral infections *in utero* or hypoxia during birth that affect the normal developmental process. This means that the factors that caused the changed development may only have been present for, for example, 30 min around birth and then are gone forever and that the genetic environment only confers a susceptibility to the individual in terms of being extra sensitive towards these external manipulations at the time of the insult. The consequences are that a treatment does not in any manner have to be related to the factors that caused the disease initially or to the genetic predisposition, and that the disease process cannot be reversed in the adult because the brain cannot be rewired back to the connectivity it should have had if the developmental insult had not taken place.

important application of identified disease-associated genes is to permit the production of disease-models in which mechanistic targets can be identified and which can be used to evaluate potential treatments that may be suitable for both familial and sporadic forms of certain diseases. Nevertheless, the problem remains that a familial form of a disorder may not be representative of sporadic forms and access to different disease-relevant models for proof-of-principle will therefore continue to be important. With respect to treatments for genetic disorders or high-risk associated genes, these patient populations are small and it will therefore not be possible to develop specific treatments for each disorder owing to the costs of clinical testing. Instead, it will be necessary to develop general methods (e.g. gene therapy) that permit the treatment of gene deficits on an individual basis. This approach will require that the regulatory authorities approve of the method for treatment based on case studies across indications, but will not require a full clinical trial package for each indication.

Mechanistic targets

Mechanistic targets are identified on the basis of biological observations and the only condition that needs to be fulfilled is that affecting a single molecular mechanism will be sufficient to obtain a significant therapeutic effect. Mechanistic targets avoid the limitations of the one gene, one disease hypothesis and can therefore be applied much more broadly; for example, conditions that have a strong environmental element can be included, such as stroke, concussive injury and spinal cord lesions, as well as genetic diseases where the target is different from the disease-causing mutation.

Following the identification of a receptor, enzyme or gene that is changed in the disease state or that appears promising on the basis of biological knowledge, it is necessary to demonstrate that the target is associated with a therapeutic benefit in the disease. The therapeutic action can be achieved either if the target in a causative manner is involved in producing the pathological state or certain symptomatology or if the target indirectly can alleviate certain consequences of the disease state to produce symptomatic relief or modification of the disease process (see Figure 2). In contrast to genetic targets, where the target validation process is relatively easy because the disease-associated gene has been identified, the validation of a mechanistic target is complex and depends upon the availability of predictive disease models. However, for any mechanistic target it can be stated that, firstly, a drug selective for the target will only act when administered to the animal and, secondly, the drug will only affect a fraction of its targets (i.e. *in vivo* the drug will rarely exhibit 100% target occupancy continuously).

These statements are trivial, but it is common practice for target validation to study knockout animals, where the target has been deleted. If these animals show a different response compared with control animals in a disease-relevant situation, it is often taken as proof that the target has therapeutic benefits. However, knockout animals completely lack the target during development, with the result that the organism might make compensatory changes and adapt to the new situation. This situation is therefore fundamentally different from the case where a drug is given to an adult animal to block a fraction of the

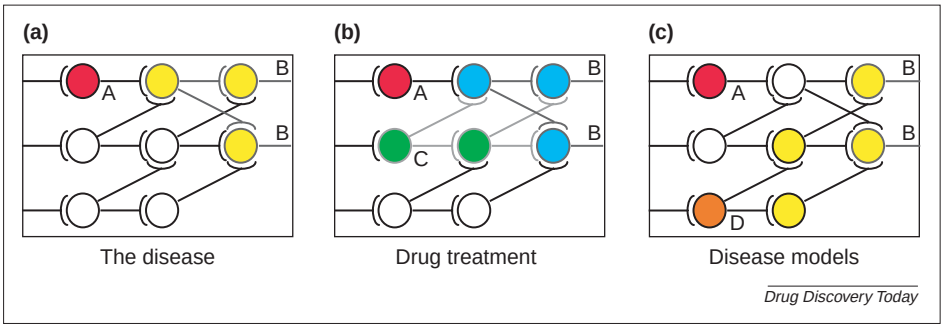

FIGURE 2

Neuronal network models. Simple neuronal network models can be used to simplify and visualize many aspects of diseases and drug treatment [38]. The base condition is the situation where the normal animal analyses information from the environment and makes a behavioural response that serves to increase the chances of survival and reproduction. Any mental disorders can, in this context, be seen as the result of abnormal information processing in the central nervous system (CNS), whereby the individual perceives and responds incorrectly to stimuli and the effects of drug treatment is to normalise this process. **(a)** The disease. A disease has changed the properties of cell A such that it integrates and analyses information incorrectly. The information is distributed to other cells whereby the local network reaches a false decision that is transmitted out of the network by the output cells B. This false information will, through interconnections to other nuclei and cortical areas, spread throughout the CNS and might affect perception and the selection of behavioural responses to external stimuli. The result is that the individual perceives stimuli incorrectly and that an abnormal behaviour is produced, which we call, for example, schizophrenia or depression. A comparable situation can be visualised for neurodegenerative disorders such as Alzheimer's disease or Parkinson's disease, except that for these indications specific cells are lost (e.g. cell A). The model shows how a primary defect can cause secondary changes by spreading across the network and may make it extremely difficult to identify the primary cause. However, it also indicates that other cells within the network might be able to compensate for the abnormal properties of a given cell. **(b)** Drug treatment. The effect of drug treatment is to normalise the function of the network. The drug can affect cell A directly in order to normalise the disease-affected cells or can act through cell C to affect the output cells B to limit the effects of the disease-affected cell (cell A). In either case, the abnormal information originating from cell A will be limited within the network such that cells B can transmit normal or almost normal information out of the network. It shows how drugs affecting different targets can achieve similar therapeutic effects and how they can induce cascades of effects such that the target of drug action and mechanism of therapeutic effect may be different. **(c)** Disease models. Assume cell A corresponds to the true pathological state in a disease. A model of the disease might mimic the true disease condition by introducing the correct disease condition on cell A in which case it is the perfect disease model. However, it is also possible that the model acts at a different site (e.g. cell D), but to the observer this will still change the information processing in such a way that the output of the network resembles the disease state. For a number of diseases (e.g. obesity, Alzheimer's disease and Parkinson's disease), familial forms exist and specific genetic defects have been identified in these families; however, it is also known that these specific genetic deficits are not necessarily shared by the sporadic forms. In terms of our network model, assume cell D corresponds to the genetic mutation of the familial form and cell A corresponds to the sporadic cases. A target-based approach targeting cell D might therefore only be an effective treatment for individuals carrying this familiar mutation, but not for sporadic cases. This situation would correspond to the experience with leptin.

targets. In normal animals the target has contributed to the development of the animal and its partial removal by adding a drug will have completely different consequences to the situation where the target has never been present; for example, the effects seen in Figure 2b cannot be seen in a knockout animal because the target was never present. For this reason, knockout animals provide very little information on how a drug selective for a given target will behave in the clinical setting.

Another common approach to target validation is to examine how the target behaves in the disease state. For example, if the target is specifically expressed in the disease state one possibility is that the target is part of the disease process, in which case we should antagonise the target. However, an equally plausible possibility is that the body is expressing the target to fight the disease, in which case an antagonist would worsen the disease state. Expression patterns, changes in regulation and so on, can provide important information for target identification, but for target validation arguments for or against can always be constructed. For this reason, biological arguments based on associations and correlations to support target validation are weak and should be viewed with caution.

The point is that proper target validation or proof-of-principle requires demonstration of disease modification or symptomatic relief in a disease-relevant model using clinically relevant conditions and using a method of affecting the target that is comparable to the method that ultimately will be used. For early proof-of-principle, alternative approaches such as small interfering RNA (siRNA) techniques, antisense, conditional knockouts and so on, can be used [18–21]. These will be valuable tools when we understand how they compare with standard pharmacological drugs, but unless the treatment will be based on these techniques [22,23] they can only give an indication of whether the target may have therapeutic potential, because off-target activity could be responsible for any observed effects.

Finally, it is necessary that the proof-of-principle studies closely mimic the clinical condition. Often, corners are cut to speed up the development, but this can be an expensive strategy. A good example comes from stroke research [24–26], where compounds were administered to animals before or at the time of inducing a stroke episode even though it was known that the time-to-needle for stroke patients is usually 5–6 h. Furthermore, the ability of the compounds to protect the brain was evaluated using anatomical measures at 24 h after the stroke, in spite of the fact that the recovery of patients is evaluated weeks to months after the stroke and is based on functional recovery. These compounds failed clinical trials and it was subsequently discovered that the clinically observed effects could have been predicted if the animal proof-of-principle studies had mimicked the clinical situation correctly.

Limitations of the target-based approach

An analysis of the key properties of target-based drug discovery approaches (Table 1) indicates that treatments developed for genetic targets will only have limited impact on disease treatment, because of the small size of these patient populations. This in turn raises concerns regarding the impact of the human genome project on disease

TABLE 1

Summary of key properties of target-based and physiology-based drug discovery approaches

	Target-based		Physiology-based
	Genetic targets	**Mechanistic targets**	
Disease type	Diseases or increased disease risks caused by single genes	All	All
Target type	Disease-associated single genes	Any type	Any type
Target number	Single	Up to two to three	Multiple
Main screening method	*In vitro*	*In vitro*	*In vivo*
Read-out	Gene regulation	Target modulation	Physiological parameter
Target identification	Gene analysis/linkage analysis	Physiological observations	Not required
Target validation and proof-of-princple	Phenotype of transgenic animal Reversal of condition in transgenic animal	Drugs, siRNA or antisense in disease-relevant model	Drugs, siRNA or antisense in disease-relevant model
HTS amenable	Yes	Yes	No
Reliance on disease-relevant models	No, it is the model	Yes	Yes
Affected by species differences	Yes	Yes	Yes
Advantages	High validity of disease model Use of transgenic animal for identifying mechanistic targets	High throughput Rational drug design	Screening in disease-relevant model Integrated *in vivo* response
Key problems	Size of population carrying gene Familial versus sporadic forms Relevance of risk-increasing genes Developmental role of gene	Low number of simultaneous targets Target must be identified Reference drugs may have unknown biological effects	Low throughput High reliance on disease models Reference drugs may have unknown biological effects

treatment, unless it becomes possible to treat specific genetic disorders on an individual basis. An important application for identified disease-associated genes is to facilitate the discovery of novel mechanistic targets that might be effective in both familial and sporadic forms of a disorder. The validity of studying familial forms as being representative of sporadic forms is rarely questioned, however, and this raises the concern that new leptin stories may appear. For mechanistic targets, proper target validation requires demonstration of therapeutic benefit of a compound belonging to the chemical class that ultimately will be used for clinical trials in a disease model using a clinically relevant treatment regime. This will almost never be possible early in a drug discovery program, and the consequence is that upon entry into the program the target will rarely have been properly validated [27]. This is an inherent risk of the R&D process, but it means that the level of certainty regarding the therapeutic value of the target is constantly changing, starting at a low level early in the program where, for example, antisense techniques might have been used to validate the approach and finally reaching its highest level at the end of the lead optimisation program where the clinical candidate is tested. In many companies, however, it is a common strategy to assume the target is fully validated after the initial validation trials and only to perform additional proof-of-principle studies at the end of the lead optimisation phase (e.g. [28]), that is, 3–5 years into the program. This is a questionable strategy as many factors could change over this period of time and it increases the risk that the developed drugs may be ineffective when they are finally tested in the selected disease model, meaning that years of resources have been wasted.

Managing uncertainty

Methods for determining a strategy in a complex environment have received considerable attention in the management literature, but they can, in general, be divided into two approaches. One approach [29] recommends first gathering all relevant information, followed by analysis of every possible outcome of every possible decision. On the basis of this complete picture, one can then choose the optimal strategy, plan it in detail and stick to the plan until it has been implemented. This is, of course, not possible in reality, but the approach emphasizes the necessity of obtaining sufficient information to make a reasonably informed decision and to actively plan the strategy. The second approach [30] states that we can never achieve full insight into any complex process and when we make strategic decisions we change the direction of the process and this in itself has consequences that make the outcome even more unpredictable. Because of these conditions, it is recommended to determine a strategy on the basis of information that is accessible through reasonable effort and, instead of making detailed and fixed strategy plans for several months or years ahead, to initiate the strategy, to monitor its progress continuously and to make changes to the strategy as we learn the consequences of our

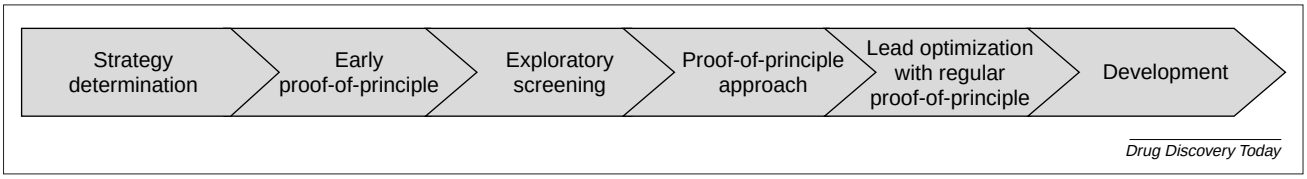

FIGURE 3

Integrated target/physiology-based drug discovery paradigm. The paradigm seeks to combine the advantages of rational drug discovery with a strong physiology/disease-based approach in order to overcome some of the weaknesses of both of the traditional methods. It consists of five steps: strategy determination, where information regarding the biological function of the target, clinical manifestations of the disease, screening strategy and proof-of-principle criteria are determined; early proof-of-principle, where the therapeutic value of the target is determined if suitable reference compounds are available; exploratory screening, where the first screening is conducted using, for example, HTS assays and HTS or disease models together with some exploratory chemistry to determine the feasibility of the approach; proof-of-principle for approach, where the identified lead structures are tested in the chosen disease-model; and lead optimization with regular proof-of-principle studies, where lead structures are optimized for target affinity and selectivity and where they are tested on a regular basis in the chosen disease-model.

introduced changes as well as changes that may occur from the outside. The key points are to take small steps to see the consequences and to learn from the process to be able to improve the decision and strategy process itself.

For the purpose of improving the drug discovery process, it is therefore necessary to consider the more general concepts discussed below as well as the specific issues that were identified earlier. Firstly, target-based drug discovery is reductionistic in concept where the drug–organism interplay is reduced to drug–target interplay, and this enables the definition of a rational drug discovery program and the industrialisation of the drug discovery process (e.g. combinatorial chemistry, HTS etc). However, this also means a dissociation of physiology from the drug discovery process, because compounds are optimised for target selectivity and not for specific physiological responses. Secondly, physiology-based drug discovery has a low throughput and it is difficult to develop drugs in a rational manner, but the approach has the advantage that drugs are optimised for physiological effects in the intact organisms independently of specific mechanisms. Thirdly, our level of understanding of biological and disease mechanisms is limited and it is therefore not possible to predict the physiological consequences of modulating a novel target. This can only be determined through actual experiments and, as a consequence, the target validation process is very important because this determines if resources are allocated to the project. Because of off-target activity, however, the level of certainty regarding target validation is not constant, but changes during the drug discovery process. Lastly, for the design of target validation and proof-of-principle studies, it is necessary to understand the biological role of the target, the clinical manifestations of the disease and current treatment practice.

An integrated target/physiology-based drug discovery paradigm

The optimal approach to drug discovery necessarily depends upon the specific company and its strategy, but a proposal for an approach that integrates the above issues is shown in Figures 3 and 4. The first step is to classify the target according to the criteria in Table 1. Next, to conduct a comprehensive strategy determination that includes collecting information regarding the indication and the biology of the target; setting a clear strategy for proof-of-principle studies and determining the screening strategy based on the properties of the target. This process will be time-consuming, particularly if it is a new indication for a company, but the amount of resources that can be saved by doing this properly makes it worth the investment. An alternative to an in-house process can be the use of advisory boards that include people with drug discovery experience in that particular indication. Several key areas should be considered in the strategy evaluation and are discussed below.

Target evaluation

Clinical information to understand the clinical aspects of the disease should be gathered. This might include current treatments, unmet needs, feasibility of clinical testing, common side effects of medication, and so on. For genetic targets the frequency of the gene in the patient population should also be determined to estimate patient population.

Biological information about the target is required to determine areas of strength (e.g. preclinical or clinical evidence to support its therapeutic effect) and weakness (e.g. prior knowledge of target-related side effects). For genetic targets a transgenic mouse model carrying the mutation should be produced to determine the relationship between the target and the disease.

Screening strategy

The screening system should be the simplest system predictive for the target being investigated. This will depend upon whether it is a single target, multiple targets or a 'dirty' (or non-selective) drug and on whether or not it is an agonist, an antagonist and so on. For single and multiple targets it is often possible to combine HTS assays. For dirty or non-selective drugs or unknown targets, screening using the physiology-based approach in disease-relevant models might be necessary. Possible counter-screens should be considered for off-target activity or specific side-effects. Proof-of-principle criteria should be determined, including choice of disease-relevant models, possible

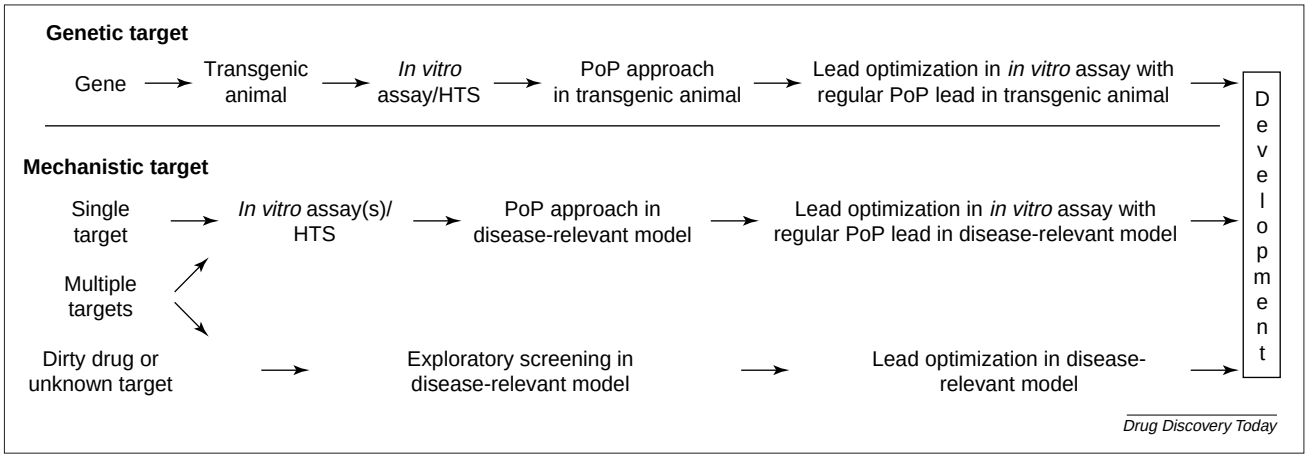

FIGURE 4

Flow-chart for the drug discovery process. Summary of the integrated target/physiology-based drug discovery paradigm outlining the different steps for each type of target. Abbreviation: PoP, proof-of-principle.

limitations of these models, drug administration schedules, inclusion of comparators to determine the therapeutic benefit of the new approach compared with existing treatments, and key side effect tests to determine the therapeutic window.

Compound criteria

What are the minimal criteria for a compound to be used for proof-of-concept? These are difficult to determine in absolute terms, but one approach is to state what the compound must not do (e.g. have affinity for certain receptors), because the disease models in these cases show false positives. Too narrow criteria might mean compounds are never sufficiently selective with the result that the project continues indefinitely, and too broad criteria might mean that off-target activity is responsible for effects in the disease model.

After strategy determination and an early proof-of-principle study, if suitable compounds are available exploratory screening (e.g. assay development, HTS and some initial chemistry) is initiated and a proof-of-principle study is then performed using the identified lead structures. In cases where the compounds are ineffective, there might still be arguments for continuing (e.g. too low affinity, selectivity, etc), but the project should probably be re-evaluated with respect to resource allocation and the requirements for a proof-of-principle study. These criteria should be pragmatic to avoid the project continuing indefinitely. If the outcome is positive, the path ahead is straightforward (i.e. lead optimisation combined with regular proof-of-principle studies and, upon identification of a candidate, entry into the development phase).

This outline is of course very general, but it emphasizes the necessity of understanding the indication in depth and the value of performing validation studies with the actual compounds in development on a regular basis to ensure that the project is on track. The frequency of such studies depends upon their complexity, costs and duration, but these factors should be evaluated relative to the resources allocated to the project, considering that these resources could have been spent on other projects if a proof-of-principle study had shown the approach was not feasible.

The outline presented here has only focused on biological criteria, because of the complexity of the target validation process, but for a complete analysis of the drug discovery pathway, it is equally important to consider the chemical feasibility of developing a selective compound with an acceptable pharmacokinetic and toxicological profile, as well as examining the competitive situation within the market place.

For both genetic and mechanistic targets, where selective compounds are not available for early proof-of-principle studies, it should be considered whether it is faster to do extensive target validation before entering exploratory screening or simply to do a HTS to identify compounds with selectivity for the target followed by *in vivo* proof-of-principle studies in disease-relevant models. The latter approach will provide the project with data supporting the therapeutic benefits of the target and compounds that can be improved in the lead optimization phase, thus placing the project in a good position with minimal use of resources. This strategy could also be superior to the strategy of systematically producing knockout animals for every known gene and testing the animals in a battery of tests. The latter strategy is resource intensive and even if a positive finding is made the process of transforming the knowledge from a knockout animal into a treatment is long and depends upon a multitude of factors. By contrast, a novel target-selective compound resulting from an HTS assay and showing effect in a disease model would represent a very valuable asset that rapidly can be converted into a treatment.

A consistent problem of any drug discovery program is the dependence upon disease-relevant models. For most indications the cause of the disorder is not understood,

and any model can therefore only be an approximation of the clinical condition. For *in vivo* models species differences will also affect our ability to predict clinical outcome. Disease-relevant models can be validated to determine their degree of predictive validity relative to clinically tested drugs, but for a drug affecting a completely novel target it will always be uncertain if the model can correctly determine its therapeutic potential until the drug has been tested in the clinic. These limitations mean that in cases where proper disease-relevant animal models are not available, moving a project into clinical testing should be considered if it is sufficiently attractive and has a side-effect profile that is acceptable within the dose range that demonstrates a high level of target activity. Even considering the costs of clinical trials, this might be a better strategy than years of research that do not deliver a clear answer. An alternative approach to animal models can be to obtain patient tissue material. If the tissue displays physiological abnormalities unique to the patient population then compounds can be screened for their ability to normalize cell or tissue function, using a black-box type approach.

Conclusions

The introduction raised the question whether the shift to target-based drug discovery could be responsible for the decline in the productivity of the pharmaceutical industry. It is not the only explanation, because many factors have changed over the past 10 years [1–10], but during this period it has been the dominating paradigm and we have seen a strong decline in the number of new molecules entering clinical testing, suggesting that it could be a contributing factor. The point of this statement is not to discard the target-based approach, because it has several advantages over the physiology-based approach in terms of screening capacity and the ability to define rational drug discovery programs. However, there has been a tendency to focus narrowly on the target and to underestimate the complexity of the physiological role of the target in the intact organism. As a consequence the validity of the target was not questioned sufficiently, and this meant that programs have continued beyond the point where they could and should have been terminated – and this reduces the productivity of the industry. Another contributing factor is that many companies tend to pursue the same targets, owing to the lack of good drugable and validated targets, with the result that if the target fails the collective loss of resources across the industry is substantial. With the physiology-based approach, this risk is probably lower because companies have different starting points in the chemical structures used, and even if the compounds are screened in the same complex models to obtain the same physiological effects the drug programs in different companies will develop in different directions. This means that across the industry there will be a higher degree of variability in the types of drugs that are developed and the mechanism(s) that they act upon, and this variability could increase the chances of success. An example is the large number of newer atypical antipsychotics that were developed using the same complex disease models, but which show substantial variation in their mechanism of action.

The optimal drug discovery strategy is probably impossible to achieve, but it is relatively simple to reach a drug discovery paradigm that integrates rational drug discovery with a strong physiology and disease focus. The paradigm must not be risk aversive, because pharmaceutical R&D is by definition high-risk, but it should balance a high-risk strategy with proper risk and resource management. The paradigm should be data-driven and should favour a 'try and learn' approach to produce a high turn-over of projects in the early pipeline, because only by trying can we evaluate a new approach to disease treatment.

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