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What makes a good drug target?

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Novel therapeutics in areas with a high unmet medical need are based on innovative drug targets. Although 'biologicals' have enlarged the space of druggable molecules, the number of appropriate drug targets is still limited. Discovering and assessing the potential therapeutic benefit of a drug target is based not only on experimental, mechanistic and pharmacological studies but also on a theoretical molecular druggability assessment, an early evaluation of potential side effects and considerations regarding opportunities for commercialization. This article defines key properties of a good drug target from the perspective of a pharmaceutical company.

Introduction

Recent analyses of discontinued drug development products and clinical trial failures point to the fact that an increasing number of compounds do not meet the efficacy endpoints [1–3]. The success rates for new development projects in Phase II clinical trials have fallen from 28% (2006–2007) to 18% (2008–2009) [1]. Thomson Reuters Life Science Consulting analyzed the 108 reported Phase II failures from 2008 to 2010 for new drugs and major new indications of existing drugs and observed that 51% of all failures occurred because of insufficient efficacy [1]. Furthermore, an analysis of Phase III and submission failures from 2007 to 2010 demonstrated that two-thirds of the failures across all therapeutic areas were attributable to a lack of efficacy [2]. Thus, novel, promising drug targets with a likelihood of clinical efficacy, as shown in predictive *in vitro* and *in vivo* models, are key for drug discovery success.

In 2009, Bayer HealthCare launched the 'Grants4Targets' initiative [4,5]. The basic idea behind this campaign was to provide bridging grants as well as drug discovery know-how for academia to support the evaluation and validation of novel drug targets. Although we received multiple high quality proposals suggesting interesting new drug targets, it became clear that the key properties of a good drug target had not been discussed sufficiently or well-defined.

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Therefore, in this review, we aim to define the requirements of an innovative and promising drug target from the perspective of a pharmaceutical company (Box 1). We will highlight some important aspects for the identification, selection, evaluation and experimental validation of a drug target. In addition, we aim to point out that 'druggability' and 'assayability' are aspects that have to be taken into account early on in the process. Furthermore, an outlook will be provided on emerging technologies by which the space of druggable target classes will increase in the future. Importantly, we hope to demonstrate that the definition of a good drug target largely depends on the therapeutic area and the specific indications considered, with divergent medical needs and different drug safety requirements.

Target definition and target classes

Although addressing multiple pathways is becoming a topic for target discovery and has already led to some remarkable successes [6], it is considered that the greater the number of molecular targets hit by a single drug then the more probable it is that more adverse events will be expected. Thus, highly selective targeting governs the drug discovery process.

A 'druggable' target is a protein, peptide or nucleic acid with activity that can be modulated by a drug, which can consist of a small molecular weight chemical compound (SMOL) or a biologic (BIOL), such as an antibody or a recombinant protein (Table 1). In 2006, a consensus number of 324 drug targets had been proposed

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BOX 1

Properties of an ideal drug target:

- Target is disease-modifying and/or has a proven function in the pathophysiology of a disease.
- Modulation of the target is less important under physiological conditions or in other diseases.
- If the druggability is not obvious (e.g. as for kinases) a 3D-structure for the target protein or a close homolog should be available for a druggability assessment.
- Target has a favorable 'assayability' enabling high throughput screening.
- Target expression is not uniformly distributed throughout the body.
- A target/disease-specific biomarker exists to monitor therapeutic efficacy.
- Favorable prediction of potential side effects according to phenotype data (e.g. in k.o. mice or genetic mutation databases).
- Target has a favorable IP situation (no competitors on target, freedom to operate).

for all classes of approved therapeutic drugs [7]. Using bioinformatics approaches, Bakheet and Doig identified 668 proteins in the non-target set of 3573 molecules that have target-like properties [8] thereby having the potential to become innovative targets. However, although the vast majority of targets being currently addressed by drug discovery are proteins, in the future nucleic acids could gain more and more importance as drug targets [9,10]. Currently addressed target classes and the mode of action for therapeutics are summarized in Table 1.

Target classes 'hit' by small molecular weight binders

SMOL drug targets mainly belong to the protein classes of enzymes, extracellular and nuclear receptors, ion channels, and transporters [9]. The overall growth of drug target families has recently been analyzed applying the DrugBank database [11]. The DrugBank database is considered one of the most important sources of information for drugs and drug targets [12]. Rask-Andersen *et al*. identified 435 effect-mediating drug targets in the human genome that are modulated by 989 unique drugs, through 2242 drug–target interactions [11]. Receptors make up the largest group of drug targets with 193 proteins accounting for 44% of human drug targets. G-protein-coupled receptors (GPCRs) have been commonly targeted by antihypertensive and anti-allergy drugs, and represent about 36% of drug targets [11].

Despite those established drug target classes, innovative approaches are addressing previously undruggable target classes such as protein–protein interactions (Table 1) [13]. Moellering *et al*. demonstrated that direct binding of the stapled peptide SAHM1 prevents assembly of the active NOTCH–oncoprotein complex [14]. More recently, the interaction between histones and a bromodomain (BRD)-containing protein was successfully inhibited by competitive binding and displacing the BRD4 fusion oncoprotein from chromatin, thus controlling tumor growth or modulating inflammatory processes [15,16]. Cutting-edge chemical approaches have identified novel mechanisms where SMOL can activate enzyme function [17]. Hence, by applying novel technologies the druggable space can be further broadened, which promises additional SMOL targets in the future.

Target classes 'hit' by biologics

Extracellular proteins and cell surface receptors can serve as suitable targets for BIOL approaches (Table 1), which are represented mainly by antibodies and recombinant proteins that usually do not penetrate the cell. Most of the launched antibodies were developed for cancer and inflammatory disease treatment. Antibody–drug conjugates (ADCs) belong to a complementary strategy for the development of new BIOLs [18,19]. Trastuzumab-emtasine (T-DM1, Genentech) has been developed to combine the clinical benefits of trastuzumab (Herceptin®, Roche) with a potent microtubule-disrupting drug, and is currently being tested in multiple clinical trials [20]. For the ADC strategy, it is not necessary that the target itself modulates the physiology of the affected cell because the cytotoxic agent will instigate cell killing. Thus, the idea of this

TABLE 1

Target classes addressed by SMOLs, BIOLs and nucleic acids and their modes of action

Drug	Covered target classes	Mode of action
Small molecular weight chemical compound (SMOL)	Enzymes	Inhibitors, activators[a]
	Receptors	Agonists, antagonists, modulators, allosteric activators, sensitizers
	Transcription factors	Inhibitors, activators
	Ion channels	Inhibitors, openers
	Transport proteins	Inhibitors
	Protein–protein interface	Inhibitors of protein–protein interaction[a]
	Nucleic acids	Alkylation, complexation, intercalation
Biologics (BIOL)	(Extracellular) proteins	Antibodies
	Transmembrane receptors, extracellular proteins	Recombinant proteins
	Cell surface receptors	Antibody–drug conjugates (ADCs)
	Substrates and metabolites	Enzymatic cleavage
Nucleic acids	RNA	RNA interference

[a] Novel approaches.

approach is that the antibody guides the cytotoxic agent to the selected location on the disease tissue where the antigen is expressed.

Target assessment

The target evaluation process at Bayer HealthCare is detailed in Fig. 1. The successful identification of a novel drug target is followed by detailed molecular target assessments consisting of experimental studies on pharmacodynamic properties according to disease hypothesis and theoretical assessments of molecular druggability, as well as initial ideas for potential target-related biomarkers (Fig. 1).

Target identification

The identification of a novel drug target is the first step (Fig. 2a). One valuable source of novel targets is relevant literature because thousands of scientists all over the world are working to unravel novel molecular pathways and the function of genes and proteins. Beside literature, the first hints for target properties come from descriptive studies on RNA and/or protein expression in target tissues or from a comparison of disease versus healthy tissue. When combined with pathway analyses and powerful data integration, expression data can provide information on potential targets beyond those regulated by RNA or protein levels. Focused proteomics, such as activity-based protein profiling (ABPP) [21], enable the identification of targets based on differential enzymatic activity in diseased versus normal tissue, further opening up the target space. Other sources of novel target ideas are information on genetic alterations and phenotypes of knockout mice, as well as on somatic mutations, gene fusions and copy number variation, especially for cancer targets.

For targets to be addressed by inhibitors or agonists, functional genomics approaches combined with phenotypic screening are advantageous because targets are identified in a cellular model system and selected or engineered to reflect the disease model more closely. The perturbation of expression of a gene (e.g. by siRNAs or shRNAs, overexpression of cDNAs, or the inhibition of gene function by a chemical compound) combined with

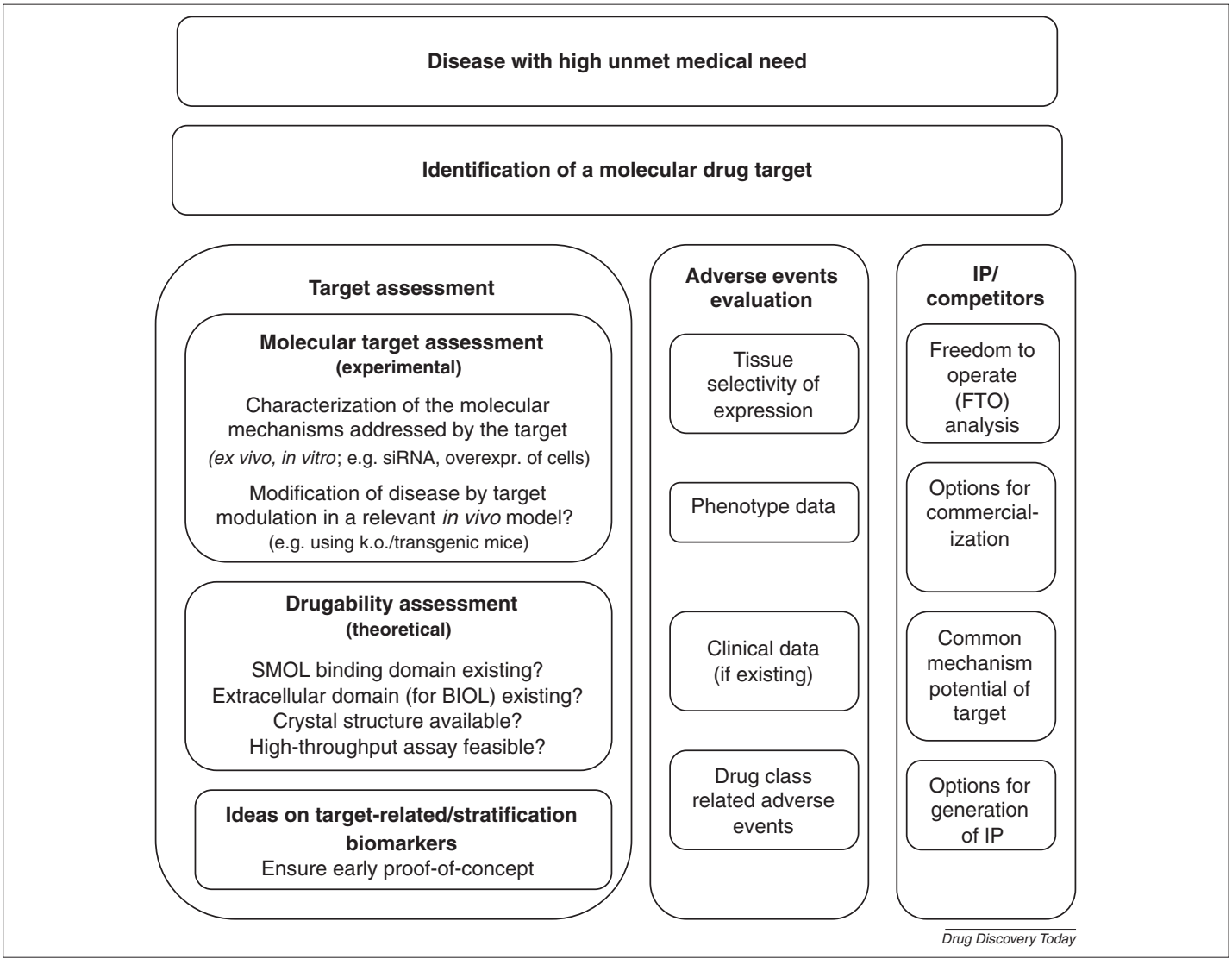

FIGURE 1

The pillars of the target evaluation process at Bayer HealthCare.

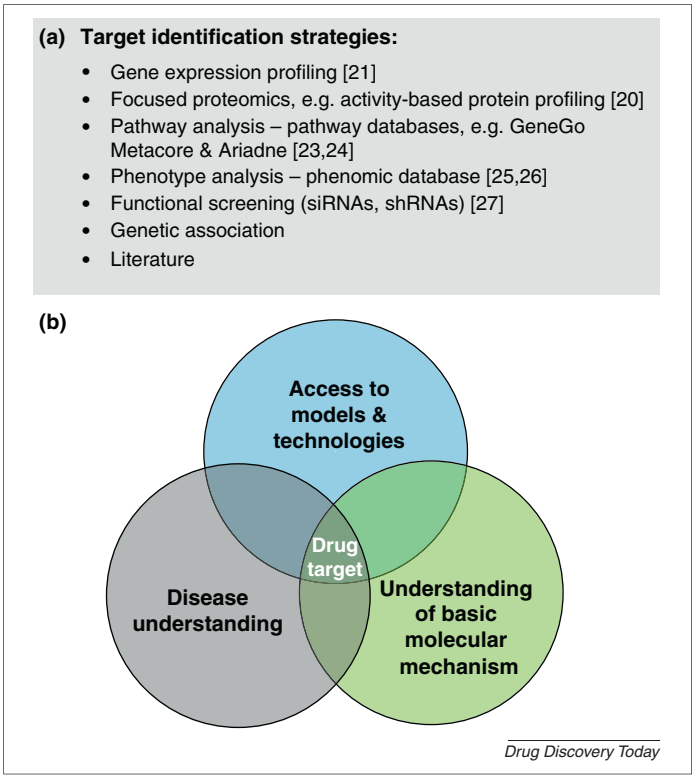

FIGURE 2

Key factors contributing to a successful target identification strategy. **(a)** Target identification strategies applied at Bayer HealthCare. **(b)** The relationship of disease understanding, suitable models and technologies with basic molecular mechanisms leading to a successful identification of a promising drug target.

appropriate phenotypic readout systems in cellular model systems is a powerful method. Of these examples, high-throughput RNAi screening technology has already contributed successfully to target identification [22,23]. Chemical genomics approaches are usually not as straightforward, because they require target decoding after phenotypic screening. Sophisticated databases that have been described previously in more detail, see Refs [21,22,24–28], support the identification of a drug target. At Bayer HealthCare, we integrate publicly and internally available information on targets in the Phylosopher database (GeneData, Basel, Switzerland) and make this database available to all scientists at Bayer HealthCare. The targets are then prioritized based on complementary evidence from the integrated set of data. However, when relying on published data, key results should be replicated internally because a generally low rate of reproducibility, about 30%, of published *in vitro* and *in vivo* studies has been experienced in-house [29].

Figure 2b lists three key factors contributing to successful target identification: profound disease understanding, knowledge on molecular mechanisms and the availability of predictive models and supporting technologies. The better the disease understanding the more support is given by predictive models. We believe that the identification of a promising drug target results from a deep pathophysiological understanding and its causative molecular mechanisms and the application of relevant target identification and target validation technologies.

Target validation

The drug target has to be validated experimentally according to the proposed mode of action. Here data link directly to the probability of clinical efficacy (i.e. experiments in human cells/tissues of eminent importance). Functional studies can apply genetic knockdown, knockout or, using target specific tools, if SMOL compounds or tool antibodies are available. *In vitro* cell-based mechanistic studies can be used to reveal regulative characteristics of targets and the pathways in which they are involved. Finally, depending on the disease, it can be necessary to evaluate the relevance of a particular target for the disease in appropriate animal models. Assuming that functional orthology between mice and humans is given, and suitable disease models exist, knockout or transgenic animals can be used for target validation. In general, however, the translation of *in vivo* validation into humans is not risk-free. Whereas some models promise to be highly predictive for the situation in humans, others show strong discrepancies [30,31]. Moreover, some diseases are restricted to higher primates, whereas most mechanistic animal studies are carried out in rodents. Hence, not all indication-specific challenges can be addressed at this early stage of drug discovery.

Translating these considerations into real drug discovery terms, the interleukin (IL)-2-inducible tyrosine kinase (Itk) could be an innovative concept for the therapy of inflammatory skin diseases [32]. Itk is expressed selectively in diseased tissues. It is present mainly in T cells and is increased in lesional skin from patients with dermatitis. RNA silencing was applied as a target-validation strategy and was followed by *in vivo* studies (i.e. in an Itk knockout mouse model). Moreover, a SMOL inhibitor was identified that confirmed the role of this kinase in disease models.

Druggability assessment

Current approaches to evaluate protein druggability (Fig. 1) consist of methods exploring sequence-related properties of proteins as well as methods exploring the 3D-structures of proteins, and are described elsewhere [24,33]. Drug targets with known 3D-structures can be located in the Potential Drug Target Database (http://www.dddc.ac.cn/pdtd/), currently containing 1207 entries covering 841 known and potential drug targets with structures from the Protein Data Bank (PDB) [34]. Knowing the 3D-structure is an advantage for a drug target evaluation because it enables the prediction of potential binding sites for SMOLs, as done by the structure-based druggability search engine provided by EMBL-EBI (https://www.ebi.ac.uk/chembl/drugebility).

In addition to the prediction of druggability, for a potential SMOL target the assessment comprises the analysis of catalytic and/or functional aspects and an analysis of selectivity issues compared to other proteins with similar binding niches [24]. Given the 3D-structure of a protein, computational approaches, described elsewhere [35], have been developed to estimate protein-binding sites for ligand design that are also described elsewhere [35].

Assayability assessment

To support a later screening program for a suitable lead compound, biochemical and/or cellular assays for binding and function need to be provided, which we address under the term 'assayability' of a drug target. The probability of establishing a meaningful assay

depends on target class and the information on the target. Because the activity status of many GPCRs can be monitored easily by measurements of second messenger levels, a de-orphaned GPCR target can be expected to have a favorable assayability, whereas, by contrast, an orphan GPCR will probably yield a low assayability despite the fact that the druggability is not questionable. In this case, functional studies need to be provided and formatted into pharmacologically relevant assays.

Definition of a good drug target depends on the indication

An important aspect used to judge the validity of a given target depends on the indication for which the target is considered. A good example is kinase inhibitors such as Bayer's anticancer drug sorafenib (Nexavar®) which gains its success, at least in part, from the multikinase inhibitory properties including serine/threonine kinase Raf and ERK signaling [36,37]. Existing literature data [38] also emphasize the role of Raf/MEK/ERK1/2 activation in the process of cardiac hypertrophy [39], a major risk factor for the development of arrhythmias, heart failure and sudden death. However, cardiac hypertrophy is a maladaptive process initiated early in the development of heart failure (e.g. after myocardial infarction or by sustained elevation of blood pressure). Thus, prevention of cardiac hypertrophy by treatment with kinase inhibitors requires an early onset of therapy and probably a life-long treatment to prevent disease progression.

Obviously, the requirements in terms of safety and tolerability for such a drug in a preventive setting are more challenging than for the use of kinase inhibitors in the therapy of a life-threatening disease such as cancer. In this respect, a PubMed search (status June 2011) linking the search terms 'kinase & inhibitor & cardiac & toxicity' yielded 200 publications referring to cardiotoxicity as a clinically important adverse event of kinase inhibitors when administered as anticancer drugs. Consequently, seven FDA-approved kinase inhibitors have FDA label warnings regarding possible cardiotoxicity. The adverse effects might be explained by a dual role of multiple kinases in signaling pathways involved in hypertrophy, and also in maintenance of normal cardiomyocyte function or by lack of target specificity of small molecule anticancer kinase inhibitors [40]. Because the ATP-binding site is well conserved across the kinome, it is still difficult to develop highly specific kinase inhibitors – even with sophisticated structure biology tools. The limitations in target specificity of SMOL drugs, as revealed for kinase inhibitors, might lead to the conclusions that a BIOL approach – being generally more specific – could be an attractive treatment alternative, independent of whether an antibody, a recombinant protein or even a nucleic-acid-based antisense or RNAi approach is considered. However, these three approaches have the disadvantage that oral delivery is so far impossible, which might be an issue for certain indications. Finally, the costs involved for a BIOL approach exceed those of a SMOL treatment. This could represent a higher hurdle to jump if long-term treatment is necessary to achieve a therapeutic benefit.

Taken together, most therapeutic conditions require a specific therapeutic option and, according to current disease understanding, it needs a careful evaluation whether a multiple target approach is to be preferred or whether the one-drug-one-target guidance needs to be followed [11].

Clinical and commercial needs

Key aspects to be considered are a high unmet medical need (no drug is available or existing therapies have serious limitations with regard to efficacy or safety or both) and there is a reasonable market size.

The full therapeutic potential of many drug targets is often not obvious at the time of their discovery. A good example is the rate-limiting enzyme of the cholesterol biosynthetic pathway, HMG-CoA reductase, the target that the pharmaceutical industry has generated its highest sales from all drug targets until today [41]. During early research on this enzyme, some investigators were led astray by the fact that the first inhibitor, compactin, did not lower plasma cholesterol in the rat, which was later shown to result from massive induction of HMG-CoA in rat liver by inhibitors of the enzyme. It took more than 20 years from the idea conception regarding inhibition of HMG-CoA reductase for cholesterol lowering until the first clinical results confirmed the validity of this drug target [42]. Sometimes favoring 'fail early – fail cheap' modulation of a target should reveal, early in the process of target validation, that a therapeutic effect can be achieved, ideally already by phenotypic assays *in vitro* or at the latest by *in vivo* experiments.

Even if a target has been successfully validated for an indication, it might be necessary to broaden its therapeutic use by looking for additional indications in which it might also have a role, a term we refer to as 'common mechanism potential' (Fig. 1). This allows for broadening of the therapeutic landscape of a drug or to shift a target if, in later phases of development, difficulties arise for the anticipated indication.

The intellectual property situation

As described by others [43,44], the contribution of a pharmaceutical company to the value chain is a patentable chemical compound (or BIOL) that becomes a drug rather than the target itself. The ideal – but often not achievable – is the combination of both: a patent-protected compound (be it a BIOL or a SMOL) and a patent for the use of modulators against a target for the treatment of specified diseases.

An early analysis of 'freedom-to-operate' (FTO) ensures that a particular action, such as development of an assay to identify modulators for the target, can be done without infringing the valid intellectual property rights of others.

A novel target promises that there is an opportunity – if chemical space allows – to file a new patent on the SMOL compound interfering with the target and thereby generating intellectual property. The full return on investment can only be achieved if the company has the exclusive rights for the commercial use of a modulator against the target, accompanied by the payment of royalties to external inventors for their contribution to the marketed drug. The same is true for the protection of compounds and/or antibodies that modulate the target: If we do not have a patent-protected SMOL or BIOL we cannot defend ourselves against competitors.

Generally, because many targets are initially identified in scientific literature, there is a direct relationship between the degree of validation and the competition around a given target. Some companies are more risk averse in selecting targets and are willing to accept greater competition, whereas other companies are willing to accept more scientific risk to reduce competition in the hope of developing a first-in-class drug.

Early evaluation of potential adverse events

Owing to pleiotropic effects, the same target might have different functions in different organ systems or at different time points during development and adulthood. It is therefore helpful to have a look at the expression level of the desired target throughout the human body. Although there are some exceptions, it can be assumed that the broader the expression the higher the risk for adverse events when the drug has to be administered systemically. Differential expression in samples representing human disease versus healthy controls is an additional parameter contributing to an early assessment of putative target-related adverse events. As an example, the extremely high tolerability of proton pump inhibitors for the treatment of gastric reflux diseases is largely explained by the near exclusive expression of their molecular target – the gastric H^+/K^+ ATPase – in gastric mucosa. The relative importance of these descriptive criteria, however, varies between the individual indications. Obviously, the tolerability for target-related undesired effects is considerably higher in life-threatening oncologic conditions than in less devastating diseases.

Further hints for potential adverse events can be obtained from data on knockout mice and from genetic deficiencies in humans. For example, the inhibitors of the mitochondrial enzyme dihydroorotate-dehydrogenase (DHODH) that are being developed for rheumatoid arthritis are known for their teratogenic potential, as demonstrated in mice [45]. Recent studies applying the new technology of exome sequencing identified that mutations in the DHODH gene are the cause for Miller syndrome, a rare Mendelian disorder, which is characterized by severe craniofacial and limb anomalies [46]. Thus, early access to those human gene-disease-association data could contribute to the early awareness of potential undesired target-related effects.

Known phenotypes can be easily discovered in the database provided by Jackson laboratories (http://www.informatics.jax.org/). To overcome embryonic lethality of the homozygous null animal tissue, restricted and/or inducible knockouts can be produced. To evaluate the phenotype of mutant mouse lines, the German Mouse Clinic (GMC) has been established at Helmholtz Zentrum München as a phenotyping platform with open access for the scientific community [47]. Such phenotyping studies on knockout mice are useful to evaluate potential target-related adverse events that can arise when the drug target is strongly or irreversibly inhibited.

Detailed studies of existing clinical data are helpful when considering a new indication for a known target. For example, the Therapeutic Target Database (TTD) has been developed to provide information about therapeutic targets and corresponding drugs [48].

From bench to bedside and *vice versa*

A major drawback in target validation arises from the fact that the validity of a given target in a specific disease can only finally be judged after a clinical 'proof-of-concept' trial. As mentioned above, only 18% of Phase II studies from 2008 to 2010 for new drugs and major new indications of existing drugs were successful and more than 50% of Phase II failures occurred as a result of insufficient efficacy [1]. In this respect, early considerations for mechanistic biomarkers confirming the mode of action are of crucial interest to validate a target:

If the mechanistic biomarker reveals that the target was insufficiently 'hit' by the drug, this might favor the search for better lead structures. However, if the biomarker confirms a sufficient modulation of the target/pathway – but without any net clinical benefit – the questions arise as to whether the target/pathway is valid at all. A good example how such a mechanistic biomarker can help to judge the validity of a target is the development of angiotensin-II receptor antagonists for the treatment of hypertension: In Phase I trials, no blood-pressure-lowering effect after compound treatment can be expected in healthy volunteers but a compensatory increase of plasma renin activity could already be observed in healthy volunteers ensuring that the pathway was also affected in humans [49]. Thus, the risk that the compound cannot achieve the therapeutic goal in a later Phase II trial because the pathway is irrelevant in humans is reduced. Therefore, we recommend to consider putative mechanistic biomarkers for the validation of a target as early as possible, ideally in preclinical animal experiments. The potential of biomarkers and their use has been recently reviewed elsewhere [50].

All *in vivo* target validation approaches should, whenever possible, also incorporate available tool compounds or established drug treatments. As an example, a new drug target in cancer should not only be validated by examination of its effect on tumor weight in either transgenic or knockout mice but it should also be evaluated if the effect is still observed on top of treatment with established anticancer drugs; a situation that a modulator of the respective target has to face in the clinical setting as well. Box 1 summarizes the key properties of a good drug target.

Concluding remarks

The present manuscript provides the point of view on target selection criteria and target validation options from the perspective of scientists at Bayer HealthCare. However, there are different perspectives on target selection that relate to the degree of validation, clinical area, unmet need, competition and intellectual property, particularly across small, medium and large companies.

We believe that a thoroughly performed target validation should help to reduce attrition rates in the later stages of drug development. In this respect, the best SMOL or BIOL against a new drug target is dispensable if the initial disease hypothesis is invalid.

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