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Understanding drug targets: no such thing as bad news

Ruth A. Roberts[1,2]

How can small-to-medium pharma and biotech companies enhance the chances of running a successful drug project and maximise the return on a limited number of assets? Having a full appreciation of the safety risks associated with proposed drug targets is a crucial element in understanding the unwanted side-effects that might stop a project in its tracks. Having this information is necessary to complement knowledge about the probable efficacy of a future drug. However, the lack of data-rich insight into drug-target safety is one of the major causes of drug-project failure today. Conducting comprehensive target-safety reviews early in the drug discovery process enables project teams to make the right decisions about which drug targets to take forward.

Introduction

Understanding the unwanted effects of engaging a potential target is a piece of news that – seemingly – some pharma companies do not wish to read. And, yet, target-related safety issues are responsible for many drug project failures. Around 10 years ago, large pharmaceutical companies started a process of self-analysis for project failures, looking particularly at safety and toxicology in discovery and early drug development. They established the two major safety reasons for project failure.

- Chemistry-related reasons. In other words, the drug itself would have unwanted side effects.
- Target reasons. There could be unwanted consequences of interacting with a particular target.

As a result, large pharma recognised that a systematic, early review of potential safety issues associated with a drug target made sense [1]; implementation of this strategy has since reduced rates of project loss substantially [2–4]. However, among medium and smaller pharma companies – where it can be argued there is less experience than at their larger counterparts – the focus of attention is on the potential efficacy of hitting a drug target and less on safety aspects. This can lead to a lack of consideration of the unintended consequences of working with a specific drug target.

Aside from what might be a lack of knowledge at the smaller end of the pharma sector, there is also a fear factor based on the way they are funded. Many biotech and small companies are largely reliant on venture capital funding and, to retain their commercial attractiveness to investors, they can be reluctant to generate data and information about a drug target that would expose its poor investment potential. This is not necessarily a deliberate move to mislead but a genuine desire to focus on generating positive data to reassure and persuade everyone involved in the project that hitting this target is a great idea and is important for addressing a particular disease. Smaller companies are often constrained because they focus on a relatively small number of targets and try to maximise the choices available to them, where larger companies have the option to review a greater number and choose the targets with the fewest risks.

Where the reliance on enthusiasm and passion over facts and data can fall down is where investors back a project but then, further down the line, discover the toxicology data have killed the project which will, therefore, never deliver a financial return (Fig. 1). Surely it is better to present investors with a full picture – including any issues – early on in a project, which will allow

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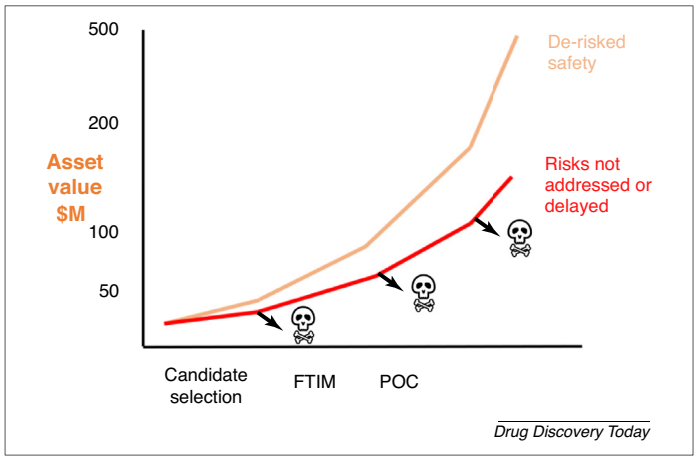

FIGURE 1

A schematic depicting drug project value. A drug project increases in value as it progresses through candidate selection towards first-time-in-man (FTIM) and towards proof-of-concept (POC) in the clinic. Inflection points reflect key decision points where positive data cause a step up in value. The orange line depicts a project where careful re-risking drives a more rapid increase in value compared with a project where risks are not adequately evaluated (red line). The emergence of unexpected, unfavourable data can cause project failure owing to toxicological risks that could have been identified and mitigated earlier in discovery and development.

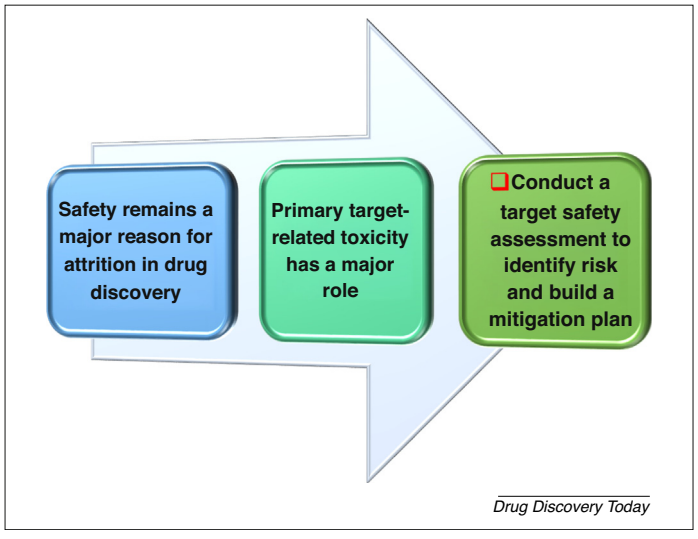

FIGURE 2

The role of target safety assessments in drug discovery and development. How well do we understand the role of the intended drug target in normal physiology and the toxicological consequences of its modulation? Expert assessment and interpretation literature and available databases is invaluable in identifying and mitigating target-related risk.

all concerned to continue moving forward, either with a different drug target or with full knowledge of the risks involved. Of course, this is preferable to reaching the point where you are ready to dose the first human volunteers – which is governed by various regulatory guidelines – and the toxicology package delivers bad news. By that point, it is too late to change direction. However, acting earlier in the project by taking a closer look at a target means you have more chance to mitigate the risks, perhaps by assessing whether the toxicity identified in animal studies is relevant to humans.

Some companies will treat the toxicology element of drug development as a box-ticking exercise to complete before initiating clinical trials. However, they should understand that early assessment of risks provides a cost-effective way of identifying whether what they have got is really a good idea or not. That is why, in assessing a potential drug target, there really is no such thing as bad news: the information you gain before investing seriously in a target helps companies to prioritise and conclude whether a particular target is a good idea and, if not, move their resources elsewhere (Fig. 2). It is far better to know this upfront than to go forward into toxicology studies with issues that will affect the long-term viability of the project.

Target safety assessments: addressing drug target issues early in drug discovery

For almost all drug projects it is normal to come forward with a well-characterised view of the function of individual protein molecules and the efficacy of the drug target. However, what you rarely see is a characterisation of the risks associated with the specific drug target. Drug discovery has a tendency to concentrate on the disease biology and pursue a target without stopping to think of the unintended consequences. What is the approach and the output of a target safety assessment (Table 1)?

Assessing risk

Undertaking a target safety assessment early in the process allows you to create a table of risks and an understanding of how likely it is that each risk will occur, what the probable impact of the risk is and to devise an integrated risk assessment plan.

Summarising the target biology

The background information you need to collate and summarise includes the target biology, listing alternative names, paralogs and homology in common preclinical species compared to humans. You also need the distribution and expression information in humans and preclinical species where possible; this means identifying which tissues contain the target and how prevalent they are in humans and other species so you can extrapolate between the two. This is important in understanding the relevance of preclinical safety species choices, as well as in the likelihood of translation of preclinical observations to the clinic.

Effects of loss- or gain-of-function within human and mouse phenotypes

Looking at human and transgenic mouse phenotypes is about understanding what effect the target has on the tissue of interest. For example, what would happen by inhibiting target X? This involves reviewing transgenic mouse phenotypes to see what effects modifying the target has on model species and also the human genetic database for known mutations or familiar lines where a gene is mutated. Overall, this helps to understand what effect inhibiting a

TABLE 1

Typical content of a target safety assessment

1	**Executive summary**	☑
2	**Background** (aim, nomenclature, homology, distribution and expression, summary of target biology, human mutation phenotype, transgenic mouse phenotype)	☑
3	**Potential safety risks** (including nervous, respiratory, cardiovascular, reproductive, liver, immune and gastrointestinal systems plus others relevant for the target)	☑
4	**Competitor compounds**[a]	☑
5	**Suggested risk assessment plan** (*in silico*, *in vitro*, *in vivo* and biomarker including staging)	☑
6	**References**	☑

At early stages when building confidence in a target, or selecting between targets, a shorter, more-focused review might be optimal. At more advanced stages, a more-extensive examination of target risks and a potential mitigation plan might be required. Every project also has its own unique features that will need additional consideration.
[a] From publicly available information.

target might have on humans. If the intention is to activate the target then data from *in vitro* and *in vivo* gene knock-in experiments could also be valuable. In weighing up the overall risk, it is key to take into account the strengths and limitations of these different data sources. It is a significant extrapolation from gene knockout in a transgenic mouse to partial or transient inhibition of a target in humans.

Identifying safety risks by organ system

A target safety assessment also tests the potential safety risks by organ system including bone, cardiovascular, endocrine, gastrointestinal, haematopoietic, immune, kidney, liver, muscle, nervous, reproductive, respiratory, skin and special senses.

Competitor compound information

Reviewing competitor compound information reveals whether any previous drug used to inhibit the target or a related pathway resulted in toxicity. This gives you important insight into what might happen in animals or in people with your chosen target – useful information to have while the project still has choices and has not invested too much money. The availability and value of preclinical and clinical data can vary considerably – if a compound has stopped before registration it can be hard to find data. However, if a drug is registered then extensive preclinical and clinical data could be readily available.

Other considerations such as modality and target patient population

Knowledge of the intended modality (such as small molecules, antibodies or oligonucleotides) can influence risk. For example, an antibody approach could be used for a target present at the cell membrane without necessarily triggering activation or inhibition of the intracellular target. Similarly, the risk profile could support inhibiting or activating a drug target in certain diseases and patient groups but not in others.

Target safety assessment: understanding the risk:benefit ratio

Conducting target safety assessments early in the drug discovery process means a company might conclude that it has a suitable target to start developing a drug while, equally, pinpointing relevant risks. The project can then assess whether those risks have manifested themselves in the preclinical animal studies and are real risks or not. The target safety assessment should grow with the project and become a comprehensive document. This is extremely valuable because, as the project progresses, you are trying to understand the risk:benefit ratio – what is the likely benefit to patients and are the risks acceptable to this patient population?

Having a live assessment document means you can call upon it at different stages and answer questions including: did the risk identified in the *in silico* research manifest itself? How severe was it? If the risk did not manifest itself, it might be downgraded in terms of what is monitored in the clinic. For example, if the target safety assessment highlighted a potential risk is bone marrow, you could take bone marrow from early efficacy or toxicology studies in animals and see whether the predictions were correct and build them into the overall target assessment. This allows the project team to have data-driven, risk:benefit assessments at all times. And, it could start to inform the clinical trial monitoring and identify exclusions for certain patient groups. This is about taking the long view, looking ahead to creating the environment for a successful clinical programme by being aware of the risks and mitigating them where possible.

Target safety reviews: de-risking projects early

In his chapter *Drug Safety and Evaluation – Methods and Protocols,* Richard J. Brennan says, ``Modern approaches to drug discovery and development increasingly demand a comprehensive understanding of the biological functions of the proposed target and its relationship to the projected indications. From the perspective of the project team toxicologist, understanding target function must go beyond 'normal' biology and disease relationship and take into account possible unintended adverse consequences of target engagement by whatever modality is chosen" [5]. He also states that, ``The goal of a target safety evaluation is to identify potential unintended consequences of target modulation and to propose a risk evaluation and mitigation strategy to shepherd compounds through the discovery and development pipeline, to confirm and characterize unavoidable on-target toxicities in a timely manner to assist in early program advancement decisions and to anticipate, monitor and manage potential clinical adverse events" [5]. In addition, the summary of a joint workshop held by the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry reported, ``Robust target identification and validation is critical to ensuring that the right target is selected – and helping to 'de-risk' the R&D process . . . overall, improving the quality of targets and subsequent compounds entering clinical development, and developing robust biomarkers in parallel for 'go' or 'no go' decisions, offers efficiency gains in R&D by reducing the number of failures seen in clinical trials" [6].

Concluding remarks: taking the right risk in drug discovery and development

It is acceptable in drug discovery and development to take risks but companies need to ensure they have all the necessary information to take the right risks. Smaller and medium-sized pharma companies do not have the luxury to take the wrong risk. With resources only for one or two targets it is vital to make the right choice. Therefore, decisions should be made based on having all the information. A target assessment is a vital part of that.

Having a passionate target or project champion who is convinced that a particular drug target is the right way to go is laudable. However, it also needs a member of the project team – perhaps the one responsible for funding the project – to provide a check and balance on decisions driven by enthusiasm alone. Drug

discovery is difficult and it is important to have people guided by passion and a belief that what they are doing can make a difference to patients. However, it also needs a more rational view to counterbalance, with people who are willing to ask the difficult questions early and be willing to listen to the answers. Biology provides us with clues about what might happen to humans with certain targets, therefore target safety assessments are essential to help those in drug discovery and development to take the right risk.

Conflicts of interest

Ruth Roberts is co-founder and co-director of ApconiX, an integrated toxicology and ion channel research company that provides expert advice on nonclinical aspects of drug discovery and drug development to academia, industry, government and not-for-profit organisations.

References

1 Cook, D. *et al.* (2014) Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nat. Rev. Drug Discov.* 13, 419
2 Atienzar, F.A. *et al.* (2016) Key challenges and opportunities associated with the use of *in vitro* models to detect human DILI: integrated risk assessment and mitigation plans. *BioMed Res. Int.* 2016, 20
3 Hornberg, J.J. *et al.* (2014) Exploratory toxicology as an integrated part of drug discovery. Part I: why and how. *Drug Discov. Today* 19, 1131–1136
4 Hornberg, J.J. *et al.* (2014) Exploratory toxicology as an integrated part of drug discovery. Part II: screening strategies. *Drug Discov. Today* 19, 1137–1144
5 Brennan, R.J. (2017) Target safety assessment: strategies and resources. In *Drug Safety Evaluation Methods in Molecular Biology*, (vol. 1641) (Gautier, J.C., ed.), pp. 213–228, Humana Press, New York
6 The Changing UK Drug Discovery Landscape. The Academy of Medical Sciences & ABPI 2016: 16. Available at: http://www.abpi.org.uk/about-us/resources/publications-library/the-changing-uk-drug-discovery-landscape

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