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Exploratory toxicology as an integrated part of drug discovery. Part I: Why and how

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Toxicity and clinical safety have major impact on drug development success. Moving toxicological studies into earlier phases of the R&D chain prevents drug candidates with a safety risk from entering clinical development. However, to identify candidates without such risk, safety has to be designed actively. Therefore, we argue that toxicology should be fully integrated into the discovery process. We describe our strategy, including safety assessment of novel targets, selection of chemical series without inherent liabilities, designing out risk factors and profiling of candidates, and we discuss considerations regarding what to screen for. We aim to provide timely go/no-go decisions (fail early) and direction to the discovery teams, by steering away from safety risk (showing what will not fail).

Introduction

Drug development is an increasingly long and costly process: clinical trial and drug approval phases take ~8 years on average, and estimates of out-of-pocket costs to bring a new drug to the market approach ~US$1 billion [1–3]. However, the productivity of pharmaceutical R&D is low because of high attrition rates in clinical development: ~90% of all new drugs fail after first-in-human studies [4]. An analysis of the causes of attrition showed that, in the year 2000, toxicity and lack of clinical safety accounted for ~30% of the failed drug development programs (Fig. 1a). More recent data indicate that safety issues remain a significant hurdle even in late development stages (Fig. 1b,c) [5,6]. An analysis of our own terminated programs showed a similar trend. In addition to their impact on drug development, adverse drug reactions are the cause of the majority of drug withdrawals, restricted use policies or black-box warnings issued by regulatory agencies, and even rank highly as a cause of disease and death [7,8].

In an effort to avoid costly late-stage failures, predictive toxicology assays and models have been implemented in earlier phases of the pharmaceutical R&D value chain [9–11]. A 'fail early' strategy has often been mentioned and is supposed to prevent drug candidates that will induce adverse effects in humans from entering clinical development. However, that does not automatically guide toward identification of drug candidates with no safety liabilities. So, in addition to 'fail early', a successful strategy also has to show the way toward 'what will not fail'. The molecular properties of a drug candidate are finalized at the interface between discovery and development. That means that properties causing mechanism (target)-related toxicity, off-target side effects and compound-chemistry-related toxicity are all fixed. To produce drug candidates without such risks associated, we argue that target- and compound-related risk factors need to be addressed during the drug discovery phase, when discussions on novel drug targets take place and compound series are identified and optimized.

Here, we present our strategy to integrate exploratory toxicology into the drug discovery process for small molecules. The aim is, by means of *in vitro*, *ex vivo* and *in vivo* disciplines, to avoid and steer away from potential liabilities in addition to giving a broader characterization of the development candidates. It is important to emphasize that such a strategy is based on testing 'the right things at the right time' to make a diligent decision instead of testing 'everything early'. The strategy needs to be specific to the organization (resources, risk aversion, etc.) and should also be tailored to the therapeutic indications within the organization.

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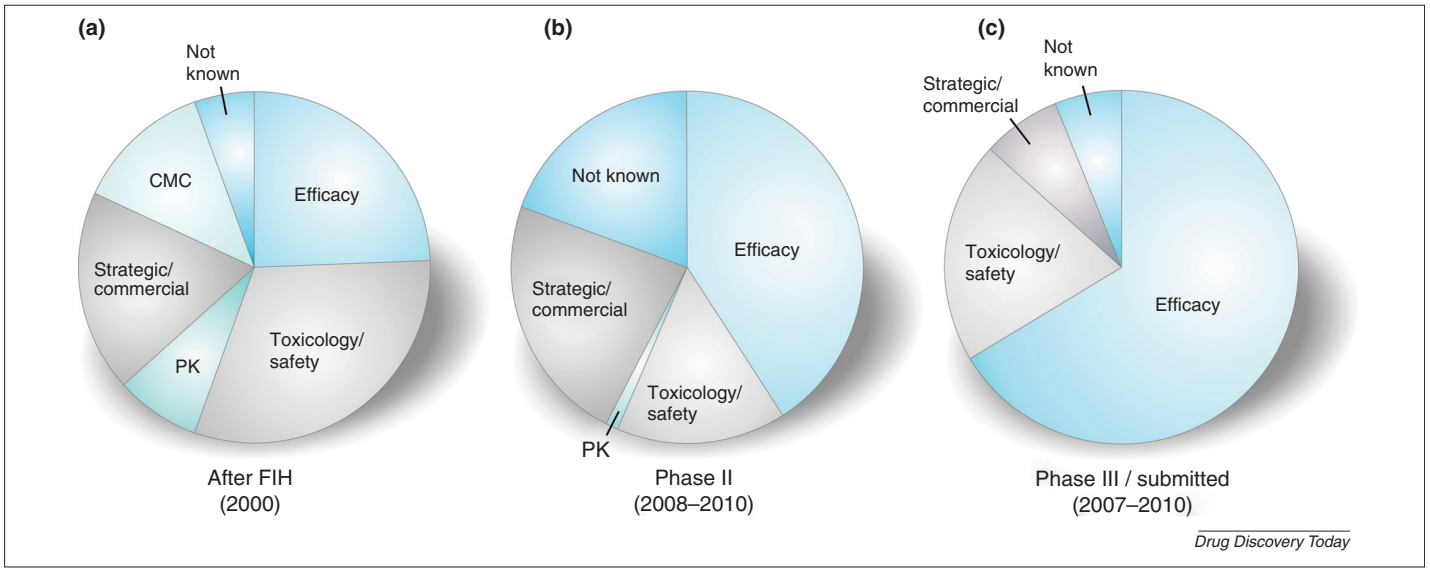

FIGURE 1

Major reasons for the discontinuation of drug development programs. **(a)** Data for projects discontinued in 2000 by ten big pharmaceutical companies [4]. **(b)** Data for projects discontinued in Phase II in 2008–2010 [5]. **(c)** Data for projects discontinued in Phase III and during registration [6]. *Abbreviations*: FIH, first in humans; PK, pharmacokinetics; CMC, chemistry, manufacturing and controls.

Exploratory toxicology as an integrated part of drug discovery

To influence decisions actively in the dialog with other main disciplines (chemistry, pharmacology, metabolism and pharmacokinetics), we find it important that discovery toxicologists are part of the core discovery project teams. They need to have a broad knowledge about the drug discovery disciplines, the targets and indications, working practices and the development-oriented nonclinical safety and clinical research disciplines, including regulatory aspects. To secure optimal knowledge transfer from drug discovery into development – and back – a strong link to regulatory toxicology (including metabolism and pharmacokinetics), clinical research and project management needs to be maintained.

Our integrated toxicology strategy, includes four main activities that are executed in the various stages of the drug discovery process: (i) a safety assessment of novel drug targets as part of target validation; (ii) selection of chemical series without inherent safety issues as part of the hit-to-lead process; (iii) designing out risk factors as part of lead optimization; and (iv) a broader toxicological profiling of potential drug candidates as part of development candidate selection (Fig. 2).

Target safety assessment

Drug discovery projects typically start with the identification of a drug target. Pursuing novel targets has in general been less successful than going after precedential targets [12], but the facts that many drug candidates lack efficacy in the clinic and many indications remain to have a high unmet need, emphasizing the need to aim for novel drug targets or combinations thereof [13–16]. Going after a novel target also implies that the target-related toxicity is unknown. One example of target-related toxicity is the skin toxicity caused by epidermal growth factor receptor (EGFR) inhibitors. Drugs hitting other targets in the Raf/Mek/Erk pathway (i.e. downstream of EGFR) induce similar toxicity [17], which indicates this is indeed mechanism-based. This skin toxicity occurs in ~80% of patients treated with EGFR inhibitors and requires therapy withdrawal in ~32% of patients [18].

To identify potential target-related safety hazards as early as possible, we perform a thorough target safety evaluation as part of target validation efforts. This typically starts with information searches using, for example, the scientific literature, pathway analysis tools (e.g. Ingenuity®, Qiagen, USA), drug approval document databases (e.g. PharmaPendium®, Elsevier, The Netherlands) and wider pharmaceutical data sources (e.g. Pharma and Life Sciences, Thomson Reuters, USA). The aim is to generate an overview of safety aspects that could be associated with the target of interest, the pathway in which the target operates or the cell type or organ in which the target is expressed. The target safety evaluation will cover potential concerns, based on *in vitro* or *in vivo* data in the literature, and known adverse effects, based on clinical trials in which a related mechanism of action was studied. Upon this initial assessment, a follow up plan is generated. This can lead to experiments to assess target safety further, for instance by adding relevant safety readouts to target validation studies or by performing dedicated toxicity studies with tool compounds or in genetically modified animals (if sufficiently relevant tools exist). In most cases, assays or models that assess a particular safety concern are integrated into the project screening tree. These can include simple counterscreen assays on closely related off-targets, specialized models or assessment of *in vivo* safety biomarkers that preferably can be translated into the clinic. In this way, it can be adequately assessed whether target-related safety concerns are actually relevant and, if so, occur with a certain therapeutic index (TI) toward the intended pharmacological effect. It should be noted that generating a target safety assessment can be challenging if the target is truly novel and has not been described extensively in the literature. In such cases, it becomes more important to extend the safety assessment beyond the target itself and include pathway components or specific cellular functions that the target is connected to, as well as to increase the emphasis on safety endpoints as part of the target validation studies.

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