Designing small molecules for therapeutic success: A contemporary perspective

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Successful small-molecule drug design requires a molecular target with inherent therapeutic potential and a molecule with the right properties to unlock its potential. Present-day drug design strategies have evolved to leave little room for improvement in drug-like properties. As a result, inadequate safety or efficacy associated with molecular targets now constitutes the primary cause of attrition in preclinical development through Phase II. This finding has led to a deeper focus on target selection. In this current reality, design tactics that enable rapid identification of risk-balanced clinical candidates, translation of clinical experience into meaningful differentiation strategies, and expansion of the druggable proteome represent significant levers by which drug designers can accelerate the discovery of the next generation of medicines.

Keywords: Drug design; Attrition; Lead optimization; Pharmaceutical research; Small molecule; Decision making

Introduction

Reducing the high rates of attrition through Phase II is the most important and difficult challenge facing the pharmaceutical industry as it endeavors to sustain the flow of transformational medicines to patients.[1] Success requires the identification of molecular targets with therapeutic potential and candidate molecules capable of unlocking this potential, the combination of which largely determines the probability of technical success through Phase II. Historically, suboptimal molecular properties conferring pharmacokinetic (PK) and safety issues have been a major source of attrition and opportunity for drug design solutions.[2] In that environment, best-in-class design strategies to improve upon drug properties of first-in-class agents brought value to patients. The design of the best-in-class calcium channel blocker, amlodipine, through drug-property optimization of the first-in-class agent, nifedipine, is one example. Incorporation of a basic nitrogen, increasing volume of distribution without having an unfavorable impact on clearance, created a molecule suitable for once-daily administration, improving compliance, and providing better blood pressure control and fewer adverse events.[3]

However, over the past few decades, substantial progress has been made in the understanding of optimal molecular properties and the inclusion of associated principles in design.[4–8] As a result, recent first-in-class molecules frequently leave little room for improvement and issues related to molecule quality represent a minor source of attrition in preclinical development through Phase II. This is supported by an analysis of Pfizer oral small molecules undergoing attrition in the 5-year period from 2015 to 2019 (Fig. 1a). In this recent cohort, issues related to the molecular target comprised the largest source of attrition (47%), most of which was related to insufficient efficacy (Fig. 1b) and not realized until the later, more-costly, stages of development (Fig. 1c). By contrast, issues related to molecule quality accounted for only 19% of attrition overall, most of which were related to safety issues (Fig. 1d) and realized in the least-costly preclinical development phase, in which underlying

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https://doi.org/10.1016/j.drudis.2021.09.017

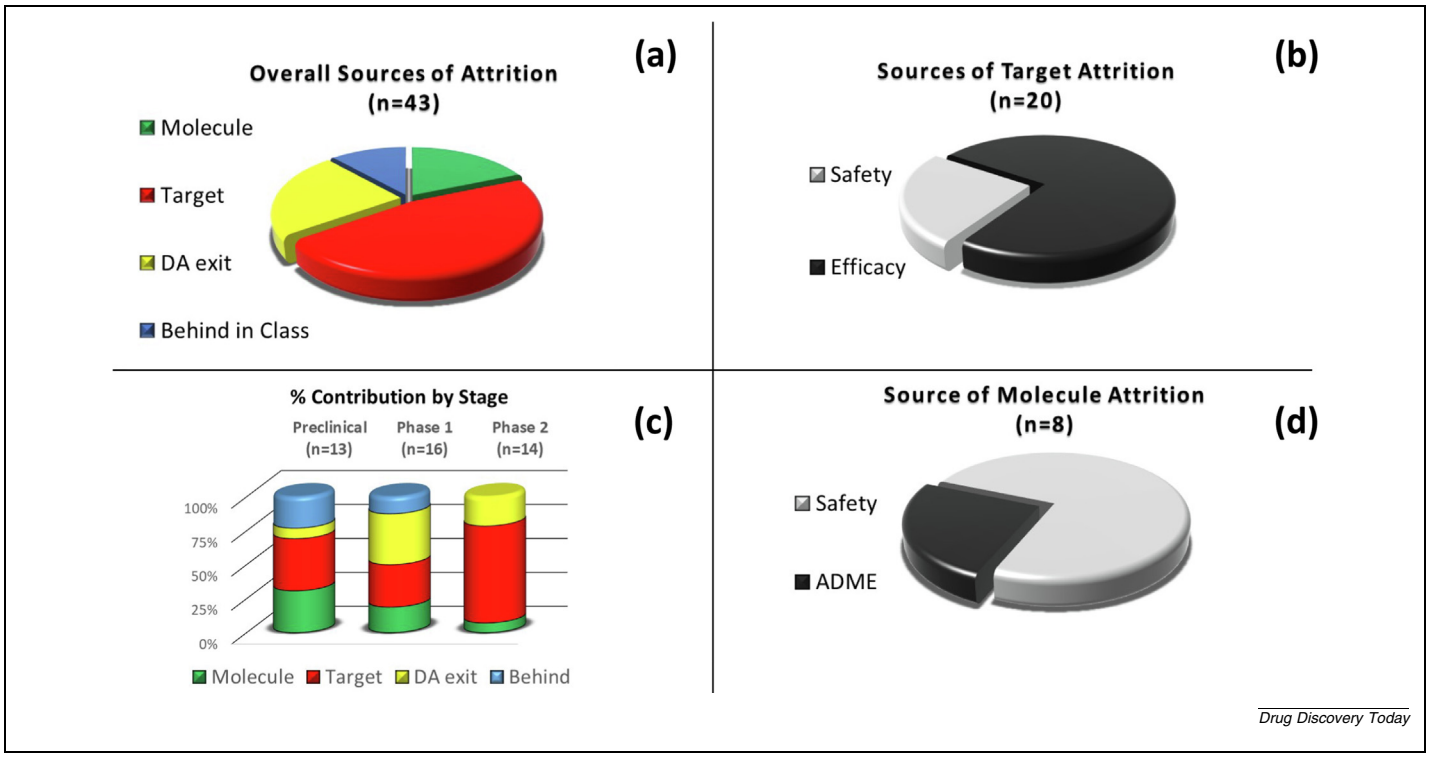


FIGURE 1

Retrospective analysis of oral, small-molecule attrition from 2015 to 2019. **(a)** Sources of attrition among 43 programs completing preclinical development, Phase I, or Phase II. **(b)** Sources of target-based attrition. **(c)** Sources of attrition by stage of development. **(d)** Sources of molecule-based attrition. Target-based attrition is defined as that resulting from the loss of confidence in efficacy or safety despite evidence of adequate target engagement. Molecule-based attrition is defined as that resulting from inadequate pharmacokinetics or safety of the candidate molecule. Disease area (DA) exit is defined as attrition resulting from divestment in the associated therapeutic area. Behind-in-class represents attrition resulting from being behind in class without a compelling differentiation hypothesis.

issues can often be rapidly addressed in follow-on design efforts (Fig. 1c). Consistent with these findings, several retrospective analyses over the past 2 decades indicate that issues related to the PK properties of molecules (e.g. absorption, distribution, and clearance) represent a relatively minor source of attrition relative to those related to efficacy and safety.[2,9–11] No other retrospective attrition analysis to date has clearly discerned between molecule and target-based attrition. Although this precludes a quantitative head-to-head comparison with prior scholarship, AstraZeneca have also reported a relative enrichment in target-based attrition in the later, more-costly stages of drug development and a particularly high overall attrition risk in disease areas in which target confidence has historically been considered lowest (e.g. neurosciences and oncology).[10] The preeminent issue of target-based attrition is also highlighted by other reports indicating that, among the various phases of development, the probability of technical success is lowest in Phase II proof-of-concept studies and that overall productivity is most sensitive to this metric.[1,12]

Accordingly, these findings suggest that design strategies aimed at improving the molecular properties of first-in-class molecules no longer represent a transformational lever in improving productivity across a portfolio of drug discovery programs. Rather, first-in-class design strategies of today should address the overriding risk of late-stage, target-based attrition by enabling improved efficiency in the clinical evaluation of novel molecular targets. Doing so is expected to accelerate the realization of patient value and, in some cases, could provide clinically relevant insights that can be leveraged in the rational design of meaningfully differentiated follow-on molecules. To this end, drug designers of today must also develop new capabilities that enable prosecution of the most promising molecular targets, many of which are currently considered 'undruggable'.

Accelerating the realization of patient value

Given the challenge of target-based attrition through Phase II, the rapid identification and progression of clinical candidates capable of testing therapeutic hypotheses at a well-tolerated and developable dose early during clinical development has become a crucial part of enhancing R&D productivity.[13,14] In addition, risks related to potential candidate molecules must be considered relative to other overarching risks, such as target efficacy, to avoid delays that are ultimately counterproductive to realizing patient value.

Rapid identification of a clinical candidate

Recently reported cycle times between first synthesis and nomination of a candidate for clinical development suggest that there is ample opportunity to improve the efficiency with which candidate-quality molecules are recognized.[13] There are many scientific and operational enablers to rapidly discover and advance clinical candidate molecules, including high-

throughput analog synthesis; early investment in drug supplies for clinical trials and regulatory toxicology studies; selecting chemical structures with readily scalable syntheses; and early investment in exploratory toxicology studies. However, the greatest enabler of overall project speed is perhaps the early identification of the molecular property space aligned with evaluating the therapeutic hypothesis at a well-tolerated and developable dose in the clinic. Such context will necessarily provide the requisite balance of pharmacological, toxicological, and PK properties.

To this end, empirical metrics describing the balance of molecular properties required to achieve 'drug-like' molecules have effectively guided design strategies. Such metrics (e.g. LipE and LipMetE) provide valuable direction to molecular design and delineate the molecular property space previously associated with extant drugs (e.g. Ro5 for oral ADME properties).[5,7,8] However, recent analyses suggest that the molecular properties space within which success has been achieved has expanded.[15] Thus, strict adherence to historical metrics believed to define 'drug-like space' might unnecessarily restrict design efforts, particularly given the shift toward target space previously considered 'undruggable'.[15,16] As such, approaches that further delineate this expanded property space and enable the simultaneous optimization of the multiple parameters contributing to orally efficacious drug molecules will further improve the efficiency by which compounds with the right balance of properties are identified

Given that compounds able to demonstrably modulate target activity in early clinical trials have improved survival in Phase II,[17] design strategies aligned with achieving adequate target engagement will enable efficient decision-making and expedite the delivery of effective molecules into clinical development. Increasingly, desirable target modulation profiles are being defined by genetic information, patient profiling, and systems biology at stages preceding lead optimization. Such profiles are being integrated with desirable drug properties through translational PK and PK/pharmacodynamic (PK/PD) models to facilitate the efficient design, identification, and development of clinical candidates.[18,19] Specifically, PK and PK/PD models are providing increasingly robust translational context to drive drug design through predictions of clinically relevant endpoints, such as effective concentration profiles and dose from chemical structures and *in vitro* data.[19] These approaches provide a means for defining clear objectives against which an effective molecule can be designed and assessed more efficiently. In addition, methods in cheminformatics, machine learning, artificial intelligence, and mechanism-based translational modeling are increasingly accelerating design by providing a clinically relevant line of sight into the generation and prioritization of design ideas.[20–22] One example is the integration of machine learning (ML) and physiologically based PK (PBPK) modeling to support the design of brain penetrant molecules (Fig. 2).[23–27] The use of such computationally enabled approaches for multiple clinically relevant endpoints (e.g. potency, selectivity, clearance, and absorption) provides a means of rapidly designing clinical candidates with the right balance of properties to evaluate therapeutic hypotheses at a reasonable dose regimen. An example of such a multiparametric optimization approach was recently illustrated by scientists at IKTOS and Servier, whereby computational approaches were used to provide virtual structures based on 11 design objectives covering aspects related to pharmacological activity, selectivity against other targets associated with safety issues, and ADME properties. Informed by a data set of 880 molecules (none of which met all of the objectives), the computational approach provided 150 virtual structures, 20 of which were made and three of which met all 11 design objectives.[28]

Beyond enabling multiparametric lead optimization, computational approaches are being developed to expedite almost every step in the drug discovery process, from choice of biological target, to hit identification and chemical synthesis. An area of particular focus is in the development of more predictive models and ML/AI methods to identify real screening hits from virtual screening campaigns searching extremely large virtual libraries of synthetically tractable chemical space.[29] Finally, although current examples are limited, integration of computational approaches for hit identification, lead optimization, and synthesis with hardware technologies that enable facile experimentation (e.g. robotics, microfluidics, and analysis) provide increasingly automated drug design platforms.[30,31] Although beyond the scope of this review, Schneider *et al.* recently provided a more detailed review and perspective on the potential of computationally informed drug design.[32]

Since drug safety is a key component to success, design strategies aimed at delivering molecules with an adequate therapeutic index are also crucial to the rapid identification of clinical candidates. Given the range of potential mechanisms involved in toxicity, a focus on low dose requirements is perhaps the most generally effective means of ensuring safety.[33] The construction of predictive safety models based on prior data and linkage to structural or physiochemical properties is potentially transformational to expedite the identification of safe clinical candidates. Historically, this has been achievable where an understanding of mechanism translates a toxicology finding into quantitative 'safety pharmacology' (e.g. QTc prolongation), thereby allowing for screening and the establishment of safety margins with an acceptable level of risk.[34]

Finally, the role of target tissue exposure in toxicity is being increasingly recognized and exploited in drug design strategies. Design strategies aimed at avoiding untoward accumulation of drugs in end organs of toxicity has proven beneficial in expanding therapeutic index and further efforts in this space are warranted.[35,36] Likewise, strategies aimed at overcoming physiological barriers to drug distribution or exploiting mechanisms for drug accumulation to the desired site of action within tissues are increasingly being leveraged to enhance safety (e.g. through the application of nanoparticles, conjugates, and transporter-mediated disposition).[37–40] Finally, emerging knowledge regarding the differential expression of possible drug targets across tissues could provide additional opportunities for the design of drugs with enhanced safety.[41]

Risk-balanced decision making

In selecting clinical candidates for advancement, priority should be placed on those with the potential to provide meaningful new

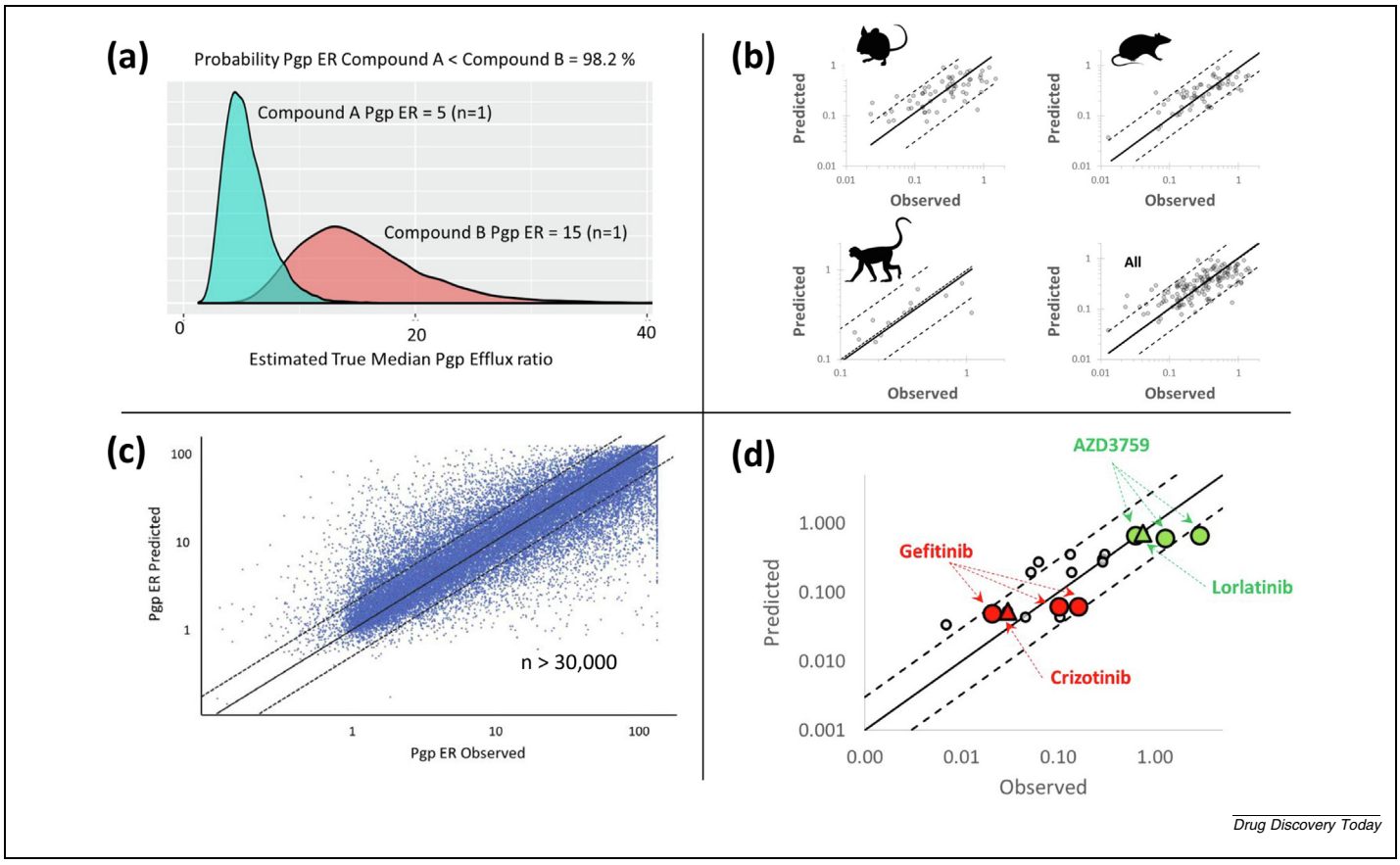


FIGURE 2

A previously described translational platform to enable the design of brain-penetrant compounds.[23] **(a)** High-throughput *in vitro* assays enable a statistically robust discernment of efflux activity between compounds. **(b)** *In vivo* translation of in-house *in vitro* data across species is accomplished via a physiologically based pharmacokinetics (PBPK) model. **(c)** Machine-learning models allow prediction of *in vitro* inputs based on the chemical structure. **(d)** Case example of model-based predictions of brain penetration for a series of EGFR ($N = 6$) and ALK ($N = 2$) inhibitors in humans (triangles) and rodents (circles). Highlighted compounds illustrate the ability to discern first-generation agents (gefitinib and crizotinib) from those that were later designed for improved brain penetration (AZD3759 and lorlatinib). Data in (d) from[24–27].

treatment options to patients and retain or establish a leader advantage. To this end, designers should avoid incurring delays for the sake of identifying a molecule with a 'perfect' profile without considering the broader balance of opportunities and risks facing the program. In many cases, even 'imperfect' first-in-class molecules have provided value to both patients and innovator companies. A retrospective look at the class of Bruton's tyrosine kinase (BTK) inhibitors provides an excellent example. The first-in-class covalent inhibitor, ibrutinib, was discovered through optimization of a nonselective, noncovalent lead and first approved by the US Food and Drug Administration (FDA) in 2013 for the treatment of mantle cell lymphoma, with subsequent approvals for other B cell-related cancers, including European Medicines Agency (EMA) and FDA approval in 2016 as a first-line treatment for chronic lymphocytic leukemia.[42] Although ibrutinib has been associated with adverse effects, such as platelet dysfunction, bleeding, atrial fibrillation, diarrhea, and skin rash, it has brought value to patients by replacing less well-tolerated immunosuppressive and cytotoxic therapies and providing options for patients with refractory/resistant disease years ahead of follow-on agents. More than 30 covalent and noncovalent BTK inhibitors, designed in part to improve the safety profile and treatment experience for patients in these and additional indications through greater selectivity, have entered clinical development, with only four additional inhibitors receiving regulatory approval to date (acalabrutinib, orelabrutinib, tirabrutinib, and zanubrutinib). Despite this substantial investment across the industry and some reports of better tolerability in follow-on agents, ibrutinib remains for now the market leader, having delivered an acceptable risk–benefit profile for its approved indications years ahead of follow-on agents. Although the potential for many of the follow-on BTK inhibitors in oncology or other indications remains to be determined, this example illustrates the importance of understanding the acceptable risk–benefit profile within a disease, and how a market leader can provide a high bar for differentiation in design.

To facilitate risk-balanced decision-making, a clear assessment of molecule-based risks is necessary. Given that most molecule-based risks (e.g. dose regimen, safety, and drug–drug interactions) can only be understood in relation to the exposure required for efficacy, first-in-class approaches without clinical benchmarks to enable translation will carry more uncertainty and require caution to avoid excessive efforts toward identifying perfect molecules preclinically. Accepted risks should never lead to an unfavorable risk–benefit profile for patients, but could include those in which the associated uncertainty can be cost-effectively assessed in Phase I,

or those outweighed by the upside of being leader in class and providing patient access to medicines sooner (e.g. drug–drug interaction potential in the drug label). Finally, full transparency of the risks of a molecule in relation to the evolving knowledge of its effective concentration as it progresses through the phases of development is required to facilitate effective risk management of projects by drug development organizations.

Accessing transformational efficacy

Design strategies aimed at either enabling the prosecution of novel targets or patient-relevant differentiation within established targets can lead to transformational efficacy for patients. Novel design strategies for meaningful differentiation within established targets are best informed by clinical experience with lead molecules, thereby providing a competitive advantage to innovator companies able to effectively leverage such information. Furthermore, investments aimed at increasing the 'druggable' proteome are expected to enable the pursuit of the most promising new targets emerging from genetic analyses, phenotypic screens, and other contemporary biology approaches informed by human disease.

Therapeutic differentiation

Clinical experience with lead molecules and first-in-class drugs can not only establish the therapeutic potential of a molecular target, but also reveal characteristics of the molecular target that limit realization of the full therapeutic potential. Novel strategies designed to overcome such limitations can provide transformational benefits to patients through clinically meaningful improvements in safety and efficacy. Examples include osimertinib, a third-generation EGFR inhibitor for the treatment of non-small cell lung cancer (NSCLC) with improved activity against the T790M gatekeeper mutation, and second-generation antihistamines with reduced sedation owing to limited distribution across the blood–brain barrier.[43,44] More recent examples include lorlatinib, a third-generation EML4-ALK inhibitor with improved efficacy in NSCLC owing to significantly improved brain penetration and activity against resistance mutations,[45,46] and the investigational ACC inhibitor, clesacostat, with an improved safety profile in Phase II owing to hepatoselective distribution (Box 1).[47,48]

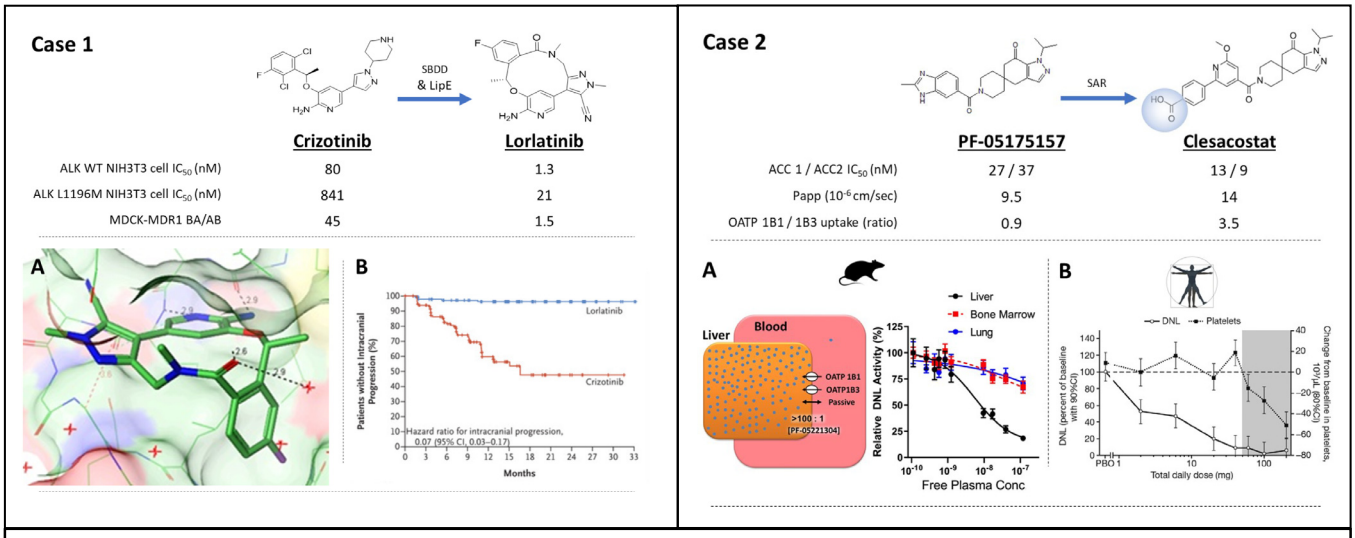
To ensure success, taking a novel design approach to an established target requires an objective assessment of the likelihood of achieving patient-relevant differentiated therapeutic benefit, rather than incremental improvement. The latter can lead to follower molecules, including internal 'back-up' molecules nominated to address a preconceived risk, with a high risk of attrition because of incremental patient value relative to the timing of access. As suggested previously, such back-up molecules carry a significant risk of attrition unless informed by clinical learnings to drive meaningful differentiation via novel design.[10] This is supported in our data set by a closer look at the cohort of programs suffering attrition by being behind in class without a viable point of differentiation. Within this cohort, two of five molecules (40%) were 'back-up' molecules nominated ahead of clinical learnings from the front runner, both of which were discontinued because of a lack of meaningful differentiation from the lead candidate (Fig. 1).

Novel approaches to expand the 'druggable' proteome

Achieving transformational efficacy for patients will increasingly require a focus on novel targets, which will include gene classes that have historically been considered 'undruggable'. Many such targets are known or believed to be fundamental to human disease but have been therapeutically elusive to more traditional small-molecule approaches because of the challenges of identifying functionally relevant binding pockets with physical properties considered to render them 'druggable'.[49,50] Innovative approaches being applied across the industry include: screening larger compound collections (>10^9) than traditional high-throughput screening (HTS) (e.g. DNA-encoded library technologies); computational screening of large virtual libraries of compounds; novel (e.g. label-free) screening methodologies that allow identification of allosteric binding sites on proteins that might offer 'druggability' opportunities not afforded by the active site; screening of compounds in cells, lysates, or protein complexes more reflective of their native environment than traditional biochemical assays; and screening of compounds distinct from those in most traditional HTS screening collections, such as compounds capable of covalent reactions, macrocycles, and natural products.[29,51–53]

Recent examples in this space include sotorasib, a small-molecule KRAS G12C inhibitor recently approved for the treatment of non-small cell lung cancer, which targets a ligandable cryptic pocket identified by a novel covalent-first approach,[54–57] and danuglipron, a small-molecule agonist of the class B GPCR, GLP-1R, for the treatment of diabetes and obesity that was derived from a lead molecule with activity in a novel sensitized high throughput assay (Box 2).[58,59]

Particular challenges and opportunities exist for target proteins that affect multiple cellular processes through interactions with other proteins or complexes thereof (e.g. scaffolds, chaperones, or transcription factors). In these cases, 'druggability' is further complicated by a complex relationship between drug binding and a potentially broad range of altered protein–protein interactions involved in a diversity of cellular processes (e.g. proliferation, differentiation, apoptosis, metabolism, immune response, protein transcription and translation, and DNA repair). Examples in this space include some of the most genetically relevant target proteins in cancer against which no approved drug currently exists (e.g. C-MYC, p53, and RAS)[60] and also clinically precedented targets in which the therapeutic potential has yet to be fully realized (e.g. androgen and estrogen receptors).[61] For such targets, expanding the breadth of small-molecule approaches to affect function through altered protein expression (e.g. molecular glues, chimeric protein degraders, protein stabilizers, and RNA modulators) and modulation of protein–protein interactions provides additional options in delivering potentially transformative efficacy to patients.[62,63] To this end, significant parallel investments will be necessary to understand and exploit the unique biological determinants of safety, efficacy, and PK/PD associated with such novel molecular mechanisms of action.[64,65] Such an understanding will also be crucial in navigating the chal-



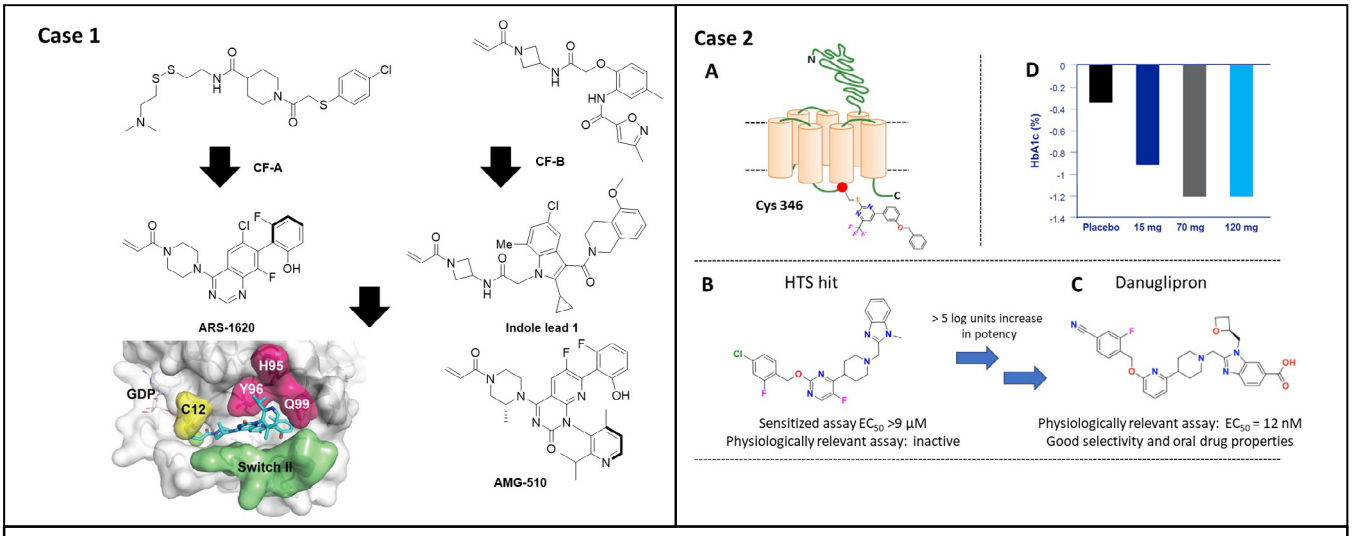
Box 1: Examples of novel design approaches informed by clinical experience.

Case 1: Design of lorlatinib, approved as first-line treatment for EML4-ALK positive non-small cell lung cancer.[45] **A:** Starting from the first in class EML4-ALK inhibitor, crizotinib, the macrocycle lorlatinib was created using structure-based drug design and multiparameter optimization guided by lipophilic efficiency to achieve good brain penetration via reduced Pgp efflux and extraordinary potency against wild-type and clinically resistant ALK mutants. **B:** Recent data from the Crown Trial demonstrated a clinically meaningful improvement of progression free survival over crizotinib treatment. Figure reprinted from Shaw AT et al Copyright © 2020 Massachusetts Medical Society.[46] Reprinted with permission from Massachusetts Medical Society.

Case 2: Design of clesacostat, a liver-targeted ACC inhibitor currently in phase 2b for the treatment of NAFDL/NASH.[47-48] Starting from a clinical candidate that showed unexpected thrombocytopenia secondary to ACC inhibition in the bone marrow, a carboxylic acid was incorporated in order to achieve hepatoselectivity via OATP uptake. **A:** Preclinically, clesacostat displayed significant liver accumulation and liver selective pharmacology in rodents. Figure from Huard et al reprinted with permission Copyright 2020 American Chemical Society.[48] **B:** Clinically, negligible effects on platelets were observed at clesacostat doses that produced near maximal inhibition of hepatic de novo lipogenesis. Figure reprinted from Bergman et al under a Creative Commons attribution license DOI: 10.1002/cpdd.782.[47]

lenging physiochemical properties that are associated with some of these approaches via a more nuanced understanding of what constitutes drug-like space.[66]

In addition to novel target-based interventional approaches, phenotypic screens, in which the assay endpoint is aligned to a disease or validated pathway-relevant endpoint, also provide a promising means by which to expand the 'druggable' proteome by identifying novel targets with the potential to lead to meaningful medicines. Given that phenotypic screens reflect a broader target space, they can also enable multitarget strategies in which the desired phenotypic response results from activity across multiple targets achieved either serendipitously or by design.[67] This alternative approach can offer increased confidence in patient efficacy through a focus on human translation, although significant downstream investments are frequently required to ensure sufficient understanding of mechanism of action and safety of molecules emerging from such screens.[68] Medicinal chemistry follow-up on phenotypic screening hits provides different challenges because the target or targets being modulated are often unknown, at least initially. Drug discovery teams must either invest in, and succeed with, target deconvolution methodologies (e.g. chemical biology approaches)[69] or be prepared to use more empirical approaches to potency optimization and toxicology evaluation. Even when deconvolution methodologies are successful, the targets and mechanisms of action that emerge are frequently not those that would have been considered 'druggable' in advance (e.g. 'dark targets').[70] Recently approved drugs for the treatment of cystic fibrosis in which cell-based phenotypic screening[71] first gave rise to CFTR potentiators, such as ivacaftor,[72] and then CFTR correctors, such as lumacaftor, tezacaftor, and elexacaftor, exemplify this approach.[73] The antiviral HCV NS5a inhibitors provide another example in which original chemical matter emerged from a cell-based HCV replicon screen leading to daclatasvir,[74] which fueled further NS5a inhibitors, such as ledipasvir and veltpasvir, to cover additional HCV genotypes. The TYK2 inhibitor deucravacitinib (BMS-986165), currently in development for psoriasis and other autoimmune diseases, is another recent example, in which the initial chemical leads were identified from a phenotypic screen for inhibitors of the validated IL-23 signal transduction pathway and subsequent mechanistic evaluation demonstrated allosteric inhibition of TYK2 as the mode of action.[75,76]



Box 2: Novel design approaches to expand the druggable proteome.

Case 1: Design of the oral, KRAS G12C inhibitor AMG510 currently in phase 2 for advanced colorectal cancer. In attempting to drug the challenging target, KRAS, Shokat and a group from Amgen applied covalent fragment screening techniques to inhibit the activating G12C mutant form of the protein, leading to hits CF-A and CF-B, respectively.[56-57] Hits were elaborated by structure-based drug design into ARS-1610 by a group at Wellspring Biosciences, and Indole Lead 1 by the Amgen team.[54,57] Knowledge gained from each of these leads, particularly the induction of a cryptic pocket induced by the rotation of the H95 residue by Indole Lead 1, led to AMG510 – a very potent and selective inhibitor of KRAS G12C.[55] X-ray crystal structure reprinted with permission, Copyright 2020 American Chemical Society.[55]

Case 2: Design of danuglipron (PF-06882961), an oral, small molecule GLP-1 receptor (GLP-1R) agonist in clinical development for the treatment of type 2 diabetes.[58-59] Design of a sensitized GLP-1R agonist screen (A) led to the identification of a weak lead compound (B) through HTS screening, which was subsequently optimized to the clinical candidate, danuglipron (C) that recently demonstrated HbA1c lowering in type 2 diabetics treated for 4 weeks (D) and is now undergoing phase 2 trials.

Concluding remarks

Advances in small-molecule drug design have reduced molecule-based attrition and revealed the overarching risk of late-stage target-based attrition. Although drug design cannot change the intrinsic therapeutic potential of molecular targets, design strategies to access the intrinsic therapeutic potential of molecular targets and expedite the realization of clinical value will improve the productivity by which transformative medicines are delivered to patients. Contemporary examples indicate that the rapid identification of risk-balanced clinical candidates, differentiation strategies informed by clinical experience with lead molecules, and investments to increase the 'druggable' proteome are promising tactics to this end.

Declaration of Interests

C.M.N.A., D.H., T.S.M., and P.V. are employed by Pfizer Inc., M.E. was previously employed by Pfizer Inc., and some or all may hold Pfizer shares.

Acknowledgments

The authors would like to sincerely thank the many Pfizer colleagues who have contributed to the perspectives shared in this paper and who have reviewed the manuscript, in particular Kathy Fernando, Jennifer Lafontaine, Jennifer Liras, Mark Noe, Gianluca Nucci, Don Palazini, Andrew Prigodich, and Dennis Scott.

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