Published in final edited form as:

Trends Pharmacol Sci. 2012 April ; 33(4): 173–180. doi:10.1016/j.tips.2012.02.001.

The Valley of Death in anticancer drug development: a re-assessment

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Abstract

The past decade has seen an explosion in our understanding of cancer biology and with it many new potential disease targets. Yet our ability to translate these advances into therapies is poor, with a failure rate approaching 90%. Much discussion has been devoted to this so-called ‘Valley of Death’ in anticancer drug development, but the problem persists. Could we have overlooked some straight-forward explanations to this highly complex problem? Important aspects of tumor physiology, drug pharmacokinetics, preclinical models, drug delivery, and clinical translation are not often emphasized and could be critical. This perspective summarizes current views on the problem and suggests feasible alternatives.

The Valley of Death

Failure to translate our rapidly expanding knowledge of cell biology into effective therapeutics has been a topic of lively and ongoing debate in the scientific community [1–9] as well as popular press [10–13]; the latter being particularly critical. The issue is urgent for anticancer drug development where the late-stage attrition rate for oncology drugs is as high as 70% in Phase II and 59% in Phase III trials[14]. Commentators have delineated numerous underlying factors for this conundrum, often referred to as the ‘Valley of Death’. Clearly, financial and other economic and nontechnical factors play a major role (summarized in Table 1). However, there are scientific issues that, although well known in their respective fields, are not prominent in the debate and could be as important to bridging the divide (summarized in Table 2). These issues fall under five main categories: (i) tumor physiology, (ii) drug pharmacokinetics, (iii) preclinical models, (iv) drug delivery, and (iv) clinical translation. This perspective highlights underappreciated aspects of anticancer drug development that could help reduce attrition rates and improve R&D productivity.

The tumor microenvironment

The rise of molecular biology and emergence of the genomics era have led to major progress in understanding of cancer cell biology. But this focus has also overshadowed knowledge of cancer at the tissue level. A prime example is the prevalence of hypoxic and acidic microenvironments in human solid tumors. Although hypoxia is recognized as an important target for cancer therapy[15], the concept is not routinely incorporated into preclinical

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models. A central issue is the definition of “normoxia”. Normoxia is often equated with the ambient air found in tissue culture incubators. However, no tissue in the body exists in 20–21% oxygen. Tissue levels can range from zero in bone marrow to 14% in well perfused organs (lung, liver, kidney, heart) with circulating levels of 10–12%. [16, 17] Human solid tumors are typically hypoxic at 0–5% O₂ [18]. Low oxygen levels can induce stabilization of the transcription factor hypoxia-inducible factor 1 alpha (HIF-1 α), which upregulates over sixty genes, including those for the glycolytic phenotype that produce lactate-mediated extracellular acidification [19, 20]. Thus, gene expression profiles are much different under hypoxia than the standard hyperoxic conditions of traditional *in vitro* models. The impact on drug development is illustrated by the camptothecins. The canonical mechanism of action for camptothecins is DNA damage-induced apoptosis associated with inhibition of nuclear topoisomerase I during replication; results generated under standard hyperoxic culture conditions. However, topotecan and the active metabolites of irinotecan and rubitecan are also known to act via topoisomerase I-mediated inhibition of HIF-1 α transcription [21–23]. In addition, the marked interaction of irinotecan and rapamycin is only observed under hypoxic conditions that induce HIF-1 α [24]. Conversely, reports that camptothecins have a mechanism employing reactive oxygen species [25–28] are likely not clinically relevant in hypoxic solid tumors.

Hypoxia is also important for hematologic malignancies, given increasing evidence that leukemic stem cells are the root cause of disease, and, like hematopoietic stem cells (HSCs), leukemic stem cells prefer a hypoxic environment. This led Eliasson and Jonsson to conclude that “if important steps in early hematopoietic differentiation, including the regulation of primitive HSCs and progenitors, take place at hypoxia, then many of these experiments have to be redone at appropriate O₂ concentrations (1–3%)” [29]. Clearly, this conclusion could apply to much of what we know about cancer biology from traditional cell culture models. Moreover, much of what we *do* know about tumor hypoxia comes from the field of radiation oncology that lacks a strong drug development culture. The approach that currently characterizes this field - repurposing of drugs developed for other applications (e.g., bioreductive prodrugs of DNA-reactive cytotoxins) – suffers from lack of selectivity. Moreover, the identification of truly selective molecular targets that are needed to develop small molecule inhibitors in hypoxic cells is in its infancy. Both approaches must overcome the challenge of drug penetration through poorly perfused tissue. Accordingly, experts in the field have recently called tumor hypoxia “the best validated target that has yet to be exploited in oncology” [15].

The acidic extracellular environment associated with tumor hypoxia also deserves consideration. Acidic extracellular pHe coupled with maintenance of a physiological intracellular pHi creates a pH gradient unique to tumors that can have a profound impact on the uptake, retention and activity of anticancer drugs [30–37]. Doxorubicin, one of the most important and most utilized chemotherapy drugs in the armamentarium, is a weak base and therefore will be excluded from acidic tumors [32, 34]. The pKa and associated charge dynamics of small molecule drugs at acidic versus physiological pH should therefore be a critical parameter in anticancer drug design [38], yet this concept is not generally appreciated [39, 40]. Simply screening compounds that possess ionizable groups in tumor cells adapted to growth at pH 6.8 versus standard pH 7.4 conditions can yield a completely different order of activity and hence selection of drug candidates [30].

The impact of exposure time

Typically, the initial stage in drug discovery and development is target-to-hit in which a large number of compounds from combinatorial/parallel chemistry are subjected to high-throughput screening against an isolated molecular target in a cell-free assay. The endpoint

is potency measured as concentration that produces half-maximal response (IC₅₀, ED₅₀). Potency remains the primary endpoint when screening advances to cell-based assays, despite the various biological barriers between drug and molecular target that could affect the interaction kinetic. Compounds are ranked by effective concentration without regard to exposure time. For example, the NCI-60 screen exposes tumor cell lines to compounds for a fixed 48 h exposure time, regardless of individual tumor growth or drug action kinetics. Endpoints include concentrations that produce increasing levels of effect (growth inhibition: GI₅₀; cytostasis: TGI; cytotoxicity: LC₅₀). However, exposure time is critical. For example, in the TF-1a erythroleukemia model, the IC₅₀ concentration of cytarabine is 373-fold lower at 72 versus 48 h exposure. In contrast, the IC₅₀ for daunorubicin is only 5-fold lower. The drugs exhibit similar potency at 72 h, but daunorubicin is over 80 times more active at 48 h (D. Adams, unpublished observation). Drug response heat maps comparing such agents with others against multiple cell lines will clearly look very different at different exposure times.

As early as 1908, investigators studying antimicrobials determined that drug response for a specified effect was not simply concentration-dependent, but a complex function of both concentration and exposure time, modeled as $C^n \times T$, where n is the concentration coefficient[41]. Hence, drugs can be compared by equal effect level and exposure time (i.e., IC₅₀ at 48 h) only if their concentration coefficients are similar. A surprising number of diverse anticancer agents follow this simple, hyperbolic pharmacodynamic model and exhibit a range of n values, e.g., from <1 (5-FU) to >4 (etoposide) in breast[42] and bladder[43] cancer cell lines. Creation of a pharmacodynamic endpoint that accounts for variation in concentration coefficient improves correlation to animal[44] and clinical[45] activities. In addition, recognition of the impact of exposure time in preclinical models can alter subsequent clinical trial design. After the experimental drug crisnatol was administered by infusion rather than short-term bolus dosing, long-term responses were observed in a phase I glioma trial[46]. Therefore, drug development algorithms would benefit from early evaluation of the impact of exposure time on response. Although kinetic experiments are not easily amenable to high-throughput processes, the increase in data quality versus quantity is a tradeoff worth considering.

Choice of preclinical model

Three-dimensional primary tumor models have been demonstrated to provide more clinically relevant results than the typical monolayer cell line models[47]. Because these models are necessarily low-throughput, they have been overshadowed by high-throughput technologies that can rapidly generate large databases of information for biostatistical analyses that yield the now familiar pathway or heat maps of drug response. Whether this will be a superior approach given its inherent limitations remains to be seen. In a similar vein, the use of cancer stem cell versus traditional bulk tumor models in drug development might improve our ability to hit the root cause of disease. For example, several agents that target the hedgehog pathway, which regulates cancer stem cell survival and the tumor microenvironment, are now in clinical trials with promising early results [48]. Likewise, a novel monoclonal antibody that targets the Wnt signaling pathway has advanced to Phase I testing [49]. Models or screening based on cancer stem cells is not facile due to their small population and the difficulty of maintaining and expanding these cells in culture without losing their pluripotent nature. However, the quality of information they yield may be more valuable than the quantity. The same may be said for *in vivo* models, in which the ability of murine xenografts to predict clinical toxicity or activity remains controversial even with the advent of genetic engineering [50–53]. A new approach is the “co-clinical trial” concept of Pandolfi and coworkers in which preclinical trials in genetically engineered mice are conducted in parallel with human phase I/II clinical trials [54]. This approach has proved successful in acute promyelocytic leukemia (APL), where APL mouse models recapitulated

not only the biological and pathological features of human disease but also the drug response profile.

Drug delivery to tumors

The emergence of biomarker-driven drug development is an important step toward the goal of personalized medicine. However, correlation of molecular biomarker data to tumor response (with parallel measurement of active drug in tumor target tissue) is rare and is required for accurate interpretation. Comparatively little effort has been devoted to tumor pharmacokinetics as we continue to use plasma pharmacokinetics as a surrogate (the property of kinetic homogeneity), despite considerable evidence from the field of tumor angiogenesis that tumors develop their own unique, often compromised vasculature [55]. The few studies that have been done are instructive. For example, Wolf and colleagues assessed tumor uptake and retention of 5-fluorouracil by ^{19}F -MRS in sixty patients with a spectrum of tumor types. Responses were observed in 60% of patients who retained drug, but in none of the patients who did not[56].

The field of molecular imaging has expanded in response to the rapidly increasing number of molecular biomarkers. To date, imaging drug delivery has been largely restricted to radioisotope labeling of the agent itself, which is costly, can require complex radiochemistry and can alter pharmacokinetics[57]. However, emergence of the new field of theranostics, a term first coined in 2002, presents some exciting possibilities. A theranostic combines a signal emitter (MRI, CT, PET/SPECT, US, FMT, PAT, optical) and carrier (e.g., liposomes, micelles, viruses, antibodies, dendrimers, polymers, nanocomposites with magnetic iron and silica cores) with a therapeutic payload coupled to a targeting ligand to simultaneously treat and image a tumor (reviewed in [58]). As yet theranostics have not reached clinical evaluation. Barriers include difficulty in matching the dose required for therapy with that for imaging, limited nanoparticle tissue penetration, complex manufacturing processes, storage and shelf-life issues, biocompatibility and toxicity concerns [59]. In addition, most theranostic uptake studies *in vitro* are done under traditional culture conditions; some studies fail to report this experimental detail altogether. Nevertheless, rapid advances are being made to overcome limitations. For example, optical imaging with near infra-red labels applied to drug carriers is a promising alternative, but suffers from poor deep tissue penetration of external light sources. One approach to enhancing optical imaging is development of miniature optical biosensors implanted at the tumor site. The technology for such implantable biosensors is becoming available, driven by application to glucose monitoring in diabetes [60, 61]. Such sensors can be multichannel, permitting real-time quantitation of tumor PK/PD. The impact could be substantial as illustrated by recent market entry of an implantable radiation dosimeter (DVS®, Sixel Technologies) that has revealed systematic variance in radiation dose administered to patients with breast and prostate cancers[62].

Changing clinical practice

The previous categories all reflect missed connections on the “bench” side of the bridge across the Valley of Death. There are similar issues on the “bedside” of the bridge. For example, consider the concept of pharmacokinetically-guided dosing. Although there is consensus that such individualized dosing of cancer chemotherapeutics is of value, particularly for reducing toxicity, methotrexate is the only oncology drug in which therapeutic drug monitoring (TDM) for dose adjustment is standard practice[63]. TDM is normally associated with older cytotoxic drugs, but several newer targeted agents (e.g., imatinib) meet traditional criteria for TDM, spurring calls for its application[64]. Slow

acceptance of TDM into clinical practice has prompted some authors to question its very future[65] even though it clearly addresses the current goal of personalized medicine.

Just as effective concentration is stressed over exposure time in preclinical development, dose, particularly the maximum tolerated dose (MTD) is the focus of clinical development. Exposure time is secondary. This practice derives from the concept of dose intensity formulated in 1984, which is based on the assumption that dose scheduling or infusion time does not directly determine effectiveness in killing tumor cells[66]. However, in 1986, Collins argued that drugs should be developed based on exposure – as – AUC rather than maximum tolerated dose, because there was a better correlation between mouse and human data. The idea was modified and supported by the European Organization for Research and Treatment of Cancer (EORTC)[67]. Carboplatin is one drug where AUC is much better than mg/m² dosing as a predictor of toxicity. There is also evidence that AUC is prognostic for toxicity and/or tumor response for busulfan, methotrexate, 5-fluorouracil, etoposide, irinotecan and docetaxel [68]. Although pharmacokinetic guidance has been used successfully, it is not easy to implement and not standard practice in clinical trial design.

Another challenge in translational research is the design of combination chemotherapy regimens. This area is of increased importance in the era of targeted agents, prompting the USA Food and Drug Administration (FDA) to recently issue guidance on evaluation of drug combinations up front, rather than requiring prior approval of one or both drugs as single agents. Preclinical evaluation of drug combinations has a long history. One of the most utilized methods, the combination index of Chou and Talalay, dates to 1984[69]. An important endpoint for clinical translation of this method is the dose reduction index – the amounts that each agent can be reduced in a synergistic combination yet maintain the efficacy of the drugs when used alone. Sequence of administration and drug ratio are additional critical determinants. Despite extensive preclinical studies, combination clinical trials are still primarily based on MTD dosing with near simultaneous administration. Drug ratio is not considered, because until recently[70] it could not be controlled *in vivo*. The potential of ratiometric rather than MTD dosing is illustrated by CPX-351, a liposomal drug formulation that delivers cytarabine and daunorubicin in a synergistic 5:1 molar ratio with demonstrated activity in relapsed or refractory AML[71]. Failure to appreciate the determinants of drug interaction presents the very real possibility that patients could be exposed to antagonistic drug combinations that produce toxicity without efficacy. Moreover, once this result is observed clinically, the combination will likely never be tried again, even though it could be quite active under the proper exposure conditions.

Determination of patient sensitivity and resistance to chemotherapy to guide treatment is a hot topic in clinical drug development, driven by the advent of genomic signatures of drug response. Prior to the genomics era, this important aspect of personalized medicine was the domain of *in vitro* chemosensitivity testing, which included the human tumor cloning (HTC), histoculture drug response (HDRA), extreme drug resistance (EDRA), and differential staining cytotoxicity (DiSC) assays. Again, a significant amount of preclinical work was devoted to this task and the results were impressive. The HTCA assay, for example, was 69% accurate in predicting drug sensitivity and a remarkable 91% accurate in predicting drug resistance in the clinic. The HTCA assay out-performed clinician choice in head-to-head trials, but was never incorporated into clinical practice [72]. Likewise, the EDRA assay (Oncotech) was not widely used even though it was FDA-approved and reimbursed by Medicare. In operation since the 1980s, Oncotech went out of business in June of last year. Perhaps companies that utilize genomic signatures will replace this service to cancer patients. Certainly, such signatures can help determine whether a patient tumor expresses the oncogenic pathway targeted by the respective therapeutic(s). To date, two genomic signatures for cancer have been validated: the 21 gene Oncotype DX and 70 gene

MammaPrint tests to predict prognosis and benefit from chemotherapy for women with breast cancer. In addition, recent work indicates that much smaller signatures may be equally effective [73]. These results are promising, but challenges remain. Whether gene signatures can predict drug pharmacokinetics or improve upon direct exposure of primary specimens to drugs that have multiple and often unanticipated mechanisms of action remains an open question.

Some paths forward

The Valley of Death in anticancer drug development is a highly complex problem with numerous driving forces. The need for solutions is urgent as illustrated by recent financial reports. Of the twelve pharmaceutical companies that spent the most on R&D, return on investment fell 3.4 percentage points in 2010, a 29% decline, while the cost of bringing a new molecular entity (NME) to market rose from \$830 million to \$1.05 billion [74].

The pharmacological audit trail (PhAT) of Workman and colleagues, first proposed in 2003 [75] and updated in 2010 [76], represents a current path forward based on the molecular profile of a patient's tumor with associated PK and PD endpoints. This approach emphasizes the application of molecular biomarkers of clinical response early in the development process. The risk of failure can be assessed at each of nine sequential stages in a hierarchy as development proceeds. First, a patient population is identified whose tumors express a cancer-selective mutation or pathway. Next, a targeted agent that exploits this biology is identified. Genetic tests for the specific mutations are validated and drug pharmacokinetics defined. Pharmacodynamic assays are then validated and induction of tumor apoptosis confirmed. Biomarkers of clinical response are established. Upon disease progression, molecular mechanisms of drug resistance are identified such that appropriate alternative targeted therapies can be initiated. Successful applications of this approach include the BRAF inhibitor vemurafenib, the ALK inhibitor crizotinib, and the poly(ADP) ribose polymerase (PARP) inhibitor olaparib. For the latter agent, clinical responses were observed to monotherapy in proof-of-concept Phase II trials in advanced breast and recurrent ovarian cancers that expressed BRCA1 and 2 mutations [77, 78]. However, a subsequent Phase II trial in women with ovarian and triple negative breast cancer indicated response to olaparib was not entirely BRCA1/2-dependent [79]. Such results suggest that reliance on molecular biomarkers alone may not be sufficient to predict the population of patients who would benefit from therapy [80].

As summarized in Table 2, there are other paths that should be considered. A key principle is that tumor physiology is as important as molecular biology. Principles of tumor physiology should be applied to preclinical development in which drug response as a function of both concentration and exposure time is measured under clinically relevant conditions: pH 7.4 and 10% oxygen for blood-borne tumors and acidic pH and 1–5% oxygen for solid tumors. Studies done under non-physiological conditions should be reported as such. Preclinical models should focus on primary or low passage human tumors preferably maintained in 3-dimensional culture. Alternatively, studies should be conducted in the appropriate cancer stem cell model if one is available. Gupta *et al.* recently reported a high-throughput screen that revealed selective inhibitors of breast cancer stem cells [81]. A notable hit was salinomycin, an agricultural antibiotic in use for over thirty years. Salinomycin has now been shown to inhibit Wnt signaling and induce apoptosis in stem cells from leukemia, osteosarcoma and colon, lung, gastric, prostate and pancreatic carcinomas [82–88].

In addition to assessing molecular targets and associated pathways, a clinical workup should include imaging of tumor pH (e.g., by dynamic nuclear polarization enhanced magnetic

resonance [89]), hypoxia [by positron emission tomography (PET) and magnetic resonance imaging (MRI) [90]), and tumor perfusion (by contrast-enhanced, microbubble ultrasound [91]). This information can help guide treatment selection including use of hypoxia-activated prodrugs or agents with acidic pK_as that can exploit the tumor pH gradient. For tumors such as pancreatic cancer in which tissue perfusion is impaired by desmoplastic tumor stroma, combination of chemotherapy with hedgehog pathway inhibitors could be considered to improve drug delivery [92]. Ideally, imaging of drug delivery to tumor tissue will be possible and permit real-time therapeutic drug monitoring. This would allow dosing to tumor tissue saturation rather than toxicity. As stated previously, rapid advances in the field of nanotechnology-driven theranostics coupled with external fiber optic or implantable biosensors could make this a reality and should be a priority. Progress is being made as exemplified by the work of Kim *et al.* with deformable, tumor homing chitosan-based nanoparticles loaded with paclitaxel and labeled with the near infrared dye Cy5.5 [93]. Moreover, targeting tumor physiology (specifically pH regulation) is emerging as a therapeutic strategy [94]. Phase I/II trials of a monoclonal antibody that targets carbonic anhydrase IX (Girentuximab; Willex AG) combined with interferon- α in metastatic clear-cell renal carcinoma indicated the therapy was well tolerated and led to both disease stabilization and a significant increase in 2-year survival [95]. A phase III trial (ARISER) will report results later this year. Of note, carbonic anhydrase IX has both diagnostic and prognostic value in this disease [96].

Changes in clinical practice are also needed. Clinical evaluation should move from a focus on MTD dosing to exposure (AUC) that produces changes in response biomarkers. In addition to traditional outcome biomarkers (e.g., myelosuppression), these predictive biomarkers can now be assessed in circulating tumor cells rather than traditional biopsies. In the case of drug combinations, the current MTD model should be replaced with a synergy model applying optimized drug concentrations, ratio and sequence of exposure.

Rethinking clinical trial design should be another focus. Incorporation of Phase 0 clinical trials into clinical development is an important first step and one that is increasingly embraced; there are currently more than 4,500 registered Phase 0 clinical cancer trials listed on clinicaltrials.gov. The primary goal of Phase 0 trials is to obtain preliminary PK/PD and proof-of-mechanism data at non-therapeutic drug exposures with minimal toxicity. Such trials can compress drug development timelines as illustrated by the PARP inhibitor ABT888 [97, 98]. Follow-on Phase I trials of ABT888 have demonstrated drug response biomarker utility in both peripheral blood mononuclear and circulating tumor cells [99]. The value of genetically-informed Phase II/III trials is illustrated by crizotinib (Xalkori; Pfizer), which was approved just four years after discovery of the EML4-ALK gene fusion in lung cancer patients [100]. Adaptive trial designs that allow rapid dose escalation, expansion cohorts in Phase I for hypothesis testing, and introduction of randomized Phase II/III trials with early-stopping rules represent new approaches to increase efficiency and reduce cost [76]. Lessons learned from our experience in pediatric cancer should also be considered. A key point is that most of the progress – a 30% improvement in overall cure rate since 1971 – has come from clinical research that was made possible because over 90% of pediatric cancer patients are enrolled on treatment protocols versus only 3% of adults [101]. Barriers to participation in clinical research, particularly the insurance health care payment system, must be reduced and better regulatory guidance provided if certain study designs are required for specific agent approvals.

Concluding remarks

In summary, given the continuing and likely increasing restrictions on resources to support bringing new therapies to cancer patients, it is worth taking stock of our current processes

and re-thinking our assumptions. The current emphasis on genetic molecular approaches has certainly paid dividends. However, advances in understanding and modeling tumor physiology and in drug delivery and monitoring also have important roles to play. Multidisciplinary approaches to both translational and clinical research must evolve along with the respective reward systems. Both the public and private sectors that support the enterprise and the cancer patients who bear the enormous burden of this disease would benefit.

Acknowledgments

This work was supported in part by Small Business Innovation Research Grant CA125871 from the National Cancer Institute. The author acknowledges the invaluable scientific contributions and mentorship in anticancer drug development of Drs. O. Michael Colvin, David Rizzieri, and Mark Dewhirst from Duke University, Durham, NC; Drs. Mansukh Wani and Govindarajan Manikumar from Research Triangle Institute International, Research Triangle Park, NC and Dr. Lee Roy Morgan from DEKK-TEC, Inc., New Orleans, LA. This paper is dedicated to the memory of Drs. Robert Silber and Monroe Wall whose commitment to bringing new therapies to cancer patients inspired this author and many others.

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Table 1

Reported factors that contribute to the Valley of Death in anticancer drug development

Factor	Cause(s)	Reference
Lack of efficacy and safety	Lack of predictive animal models and strong evidence for MOA-based efficacy; failure to eliminate compounds with MOA-based toxicity; increasing safety hurdles; poor pharmacokinetics	[3, 4, 14, 40]
Lack of financial resources	Risk-averse mentality at NIH, pharma, venture capital; majority of NIH support funds basic research, less than 5% for translational research	[4–6]
Lack of human resources	Consolidation in pharmaceutical industry; >35,000 jobs lost in 2010 alone	[5, 102, 103]
Lack of required research structure	Individual investigator model versus multidisciplinary team	[6]
Lack of support expertise	Different support and management structures for basic versus translational and clinical research	[5]
Communication	Poor communication between clinical and basic scientists and between scientists and the business community	[6]
Design of clinical trials	Lack of medically and statistically meaningful endpoints; lack of and failure to incorporate validated biomarkers; lack of appropriate patient selection; lack of pharmacokinetic guidance	[7, 14, 104, 105]
Healthcare culture	Failure to adopt results from clinical studies into clinical practice	[106]
Lack of incentives in academia	Reward/promotion structure in academia; difficulty in assessing outcomes of translational research to reward effort	[5]
Profit structure in industry	Large pharma seeks blockbuster drugs in large markets versus orphan drugs; pressure from Wall Street for short-term profits	[9, 107]
Focus on high risk diseases	Trade-off high potential profits for high attrition rate; compounds with novel MOAs have higher attrition rates	[1, 14, 108]
Focus on technology	Human genome project has generated unlimited potential targets, but few have been validated	[102]
Choice of drug type	Focus is on small molecules while biologicals have higher rates of success	[14]
Lack of predictive discovery models	Current target-centric approach; many targeted agents affect essential cellular functions and behave like cytotoxics	[104, 109]
Lack of predictive development models	Failure to capture tumor heterogeneity and cellular complexity; inadequate understanding of pathway connectivity in tumor versus normal cells; limited support for clinically relevant model development	[2, 108]
Adverse regulatory environment	Initial clinical experience is in patients with advanced, refractory disease; inadequate funding of regulatory agencies like FDA; lack of global regulatory harmonization	[2, 9, 110]
Intellectual property issues	Limited patent lifetime relative to the extended development time; overarching patents that restrict research in key fields	[111]
Aggressive pricing may create barriers to reimbursement	High attrition rates amplify costs of drug development that are passed on to patients	[2, 107]
Lack of innovation	Pipelines all focus on a limited number of mechanisms and targets; lack of compelling new biology, enabling technologies, genomics-derived tumor-specific targets, and therapeutic concepts	[3, 110]
Feasibility and cost of manufacture and development	Complex drug molecules or drug carriers; overall cost to bring NME to market now estimated at \$1 billion	[3, 7]
Commercial issues	Alignment of corporate R&D with marketing goals; awareness of competitor programs; over-management of R&D by those lacking scientific-medical expertise; resources focused on marketing	[14, 107]

Table 2

Approaches to improve anticancer drug development

Traditional approach	Proposed approach	Reference
Employ preclinical cell culture models at pH 7.4 and ambient oxygen (21%)	Employ preclinical cell culture models at physiological tumor pH (6.5–7.0) and oxygen (0–5%)	[24]
Rank compounds by effective concentration (IC ₅₀ , ED ₅₀)	Rank compounds by effective exposure (C ⁿ xT)	[42, 43]
Screen for antitumor activity against bulk tumor	Screen for antitumor activity against tumor stem cells	[81]
Screen for antitumor activity against primary tumors in murine subcutaneous xenografts	Screen for antitumor activity against metastatic disease in orthotopic models or genetically-engineered mice with cancer-specific mutations	[54]
Optimize drug candidates by standard ADMET parameters	Optimize drug candidates according to charge dynamics that exploit the tumor pH gradient	[38–40]
Rely on rodent models to predict clinical activity	Utilize 3-dimensional culture of primary human tumors and biomarker-driven Phase 0 trials to predict pharmacokinetics and activity	[47, 112]
Focus on oncogenic molecular pathways as biomarkers for drug response	Incorporate tumor drug uptake and retention as a primary marker for drug response	[56]
Design drug carriers to improve formulation	Design drug carriers for tumor-specific delivery and for imaging drug delivery: theranostics	[58, 113, 114]
Use plasma pharmacokinetics to model drug delivery to solid tumors	Measure tumor pharmacokinetics directly for drug or drug carrier; apply miniaturized, implantable imaging technology	[56]
Dose to normal tissue toxicity	Dose to tumor drug saturation; minimize toxicity	
Treat all patients with the same dose and schedule	Treat patients based on their unique tumor physiology (e.g., level of hypoxia) and pharmacogenomics; utilize therapeutic drug monitoring for pharmacokinetically-guided dose adjustment	[115]
Create drug combinations based on discreet MOA and non-overlapping toxicities; use standard MTD dosing	Create drug combinations based on synergy in preclinical models; use ratiometric dosing with optimal sequence of administration	[116, 117]
Traditional Phase I/II trial designs to establish the MTD according to Response Evaluation Criteria in Solid Tumors (RECIST)	Biomarker-driven adaptive or continual reassessment designs; randomized Phase II/III trials	[76]