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From 2D Drug Screening to Predictive Pharmacology: Redefining Preclinical Models in Oncology

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Abstract

Cancer drug development still relies heavily on preclinical models that often fail to predict clinical efficacy. Although two-dimensional (2D) cell cultures and animal models have contributed significantly to cancer research, they do not adequately capture the complexity, heterogeneity, and microenvironmental conditions of human tumors. As a result, pharmacological findings generated with these systems frequently show limited clinical translation. This review discusses the conceptual distinction between drug activity and predictive pharmacology, arguing that successful target modulation in simplified experimental systems does not necessarily predict therapeutic benefit in patients. The limitations of conventional preclinical approaches, including homogeneous drug exposure in 2D cultures and species-specific differences in animal models, are briefly examined. This review further highlights the potential of human-relevant models, such as patient-derived organoids and microphysiological systems, to improve the predictive value of preclinical testing. These platforms allow more realistic evaluation of drug response, resistance mechanisms, and functional biomarkers under conditions that better resemble human tumor biology. Altogether, the integration of functionally informative models into drug development pipelines may support more accurate and clinically relevant pharmacological decision-making.

Keywords: pharmacology; organoids; oncology; translational; prediction

1. Introduction

Despite decades of progress in molecular oncology and drug discovery, the predictive power of preclinical models, like two-dimensional cell cultures and animal models, remains limited. A significant proportion of anticancer agents, that demonstrates promising activity in early-stage research, ultimately fails in clinical trials, often due to lack of efficacy in patients [1]. This gap between preclinical success and clinical outcome raises fundamental questions, regarding the sufficiency of the current experimental systems to support pharmacological decision-making. Traditional drug development relies heavily on two-dimensional (2D) cell cultures and animal models. However, systems like these do not capture the complexity and heterogeneity of human tumors [2,3], even though they have contributed significantly to our understanding of cancer biology, so far. As a result, pharmacological data generated after their use does not translate into clinical benefit.

In this review, we examine current preclinical cancer models and emphasize on the distinction between drug activity and predictive pharmacology [4]. We propose that a shift toward human-relevant, functionally informative systems, such as patient-derived organoids and microphysiological platforms, is necessary to transform preclinical testing from descriptive screening into truly predictive pharmacology.

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2. 2D Cell Cultures

Two-dimensional cell culture systems have long served as the backbone of anticancer drug discovery. These methods offer several advantages, including cost-effectiveness, reproducibility, and suitability for high-throughput screening. These features have enabled the rapid evaluation of thousands of compounds and have contributed to the identification of key molecular targets. However, the pharmacological insights derived from 2D systems are inherently constrained. Cells grown on plastic surfaces in uniform conditions lack the spatial organization, cell–cell interactions, and microenvironmental gradients that characterize tumors *in vivo* [5–7]. Drug exposure in these systems is typically homogeneous, failing to reflect the diffusion limitations and concentration gradients present in solid tumors [8–10]. In addition, cells cultured under 2D conditions frequently undergo metabolic and transcriptional adaptations that differ substantially from tumor behavior *in vivo* [11]. Altered proliferation rates, oxygen exposure, and nutrient availability may influence DNA damage responses, oxidative stress pathways, and drug transporter expression, ultimately affecting pharmacological sensitivity [12–14]. Consequently, compounds targeting replication stress, metabolism, or hypoxia-associated pathways may display response profiles that depend strongly on the experimental architecture itself rather than intrinsic tumor vulnerability.

From a pharmacological standpoint, this leads to systematic distortions. Measures such as IC_{50} values are often interpreted as indicators of drug potency, yet they are highly dependent on experimental conditions that bear little resemblance to physiological reality [15,16]. Consequently, compounds that appear highly effective in 2D screening may perform poorly in clinical settings, while others with modest *in vitro* activity may be overlooked [3,15]. This suggests that 2D systems are not simplified representations of tumors. Instead, they are qualitatively different environments that shape drug response in ways that are not predictive of human biology.

3. Animal Models

Animal models introduce additional layers of biological complexity and have been widely used to validate findings from *in vitro* studies [17]. Xenograft models, in particular, allow human tumor cells to be studied in a living organism, providing insights into tumor growth, angiogenesis, and systemic drug exposure [2,18–21]. Despite these advantages, the predictive value of animal models remains limited. Species-specific differences in drug metabolism, immune function, and DNA damage response pathways can significantly alter therapeutic outcomes [22,23]. In many cases, these differences may appear subtle, yet they are enough to contribute to mismathches between preclinical findings and clinical outcomes. In xenograft systems, stromal composition, cytokine signaling, and immune interactions are often species-mismatched [24,25], potentially altering treatment responses in ways that are difficult to interpret pharmacologically [26]. This limitation becomes particularly relevant for therapies that depend on tumor–immune interactions, replication stress signaling, or microenvironment-mediated resistance mechanisms [14]. Moreover, the use of immunocompromised animals in xenograft studies removes an essential component of tumor biology, which is the interaction with the immune system [27,28]. For therapies that rely on stress responses, such as those targeting replication stress pathways, these interactions may be particularly relevant [29–32].

From a pharmacological perspective, animal models often provide confirmation of activity under specific conditions rather than robust prediction across diverse patient populations. Their scalability and cost further limit their utility for systematic exploration of drug response variability.

4. From Drug Activity to Predictive Pharmacology

One of the main limitations of current preclinical models lies in the widespread assumption that drug activity automatically translates into clinical efficacy prediction. However, drug activity and efficacy prediction represent fundamentally different objectives. Drug activity refers to the ability of a compound to modulate a biological target or pathway under defined conditions. Predictive

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pharmacology, by contrast, requires the capacity to anticipate how a drug will perform across heterogeneous human tumors, taking into account variability in genetic background, microenvironment, and adaptive responses [3,28]. This becomes particularly important for therapies targeting dynamic processes such as replication stress and DNA damage response pathways, where treatment sensitivity may depend strongly on cellular context and adaptive signaling mechanisms. Systems optimized for high-throughput detection of activity are not necessarily suited for capturing the complexity required for prediction [33]. As a result, drug development pipelines may be biased toward compounds that perform well in simplified systems rather than those that are most likely to benefit patients [3].

A shift toward predictive pharmacology therefore requires not only new technologies, but also a redefinition of what constitutes meaningful preclinical evidence. Functional relevance, context-dependence, and reproducibility across biologically diverse systems should be prioritized over isolated measures of potency [1].

5. Human-Relevant Models

In recent years, patient-derived organoids have emerged as a promising platform for modeling human tumors *in vitro*. These three-dimensional structures are obtained and generated directly from patient tissues and retain key features of the original tumor, including cellular heterogeneity, genetic alterations, and aspects of tissue architecture [34]. Unlike 2D cultures, organoids create microenvironments in which gradients of nutrients, oxygen, and drug exposure naturally arise. This allows for more realistic assessment of pharmacological responses, including differential sensitivity across cell populations within the same tumor [35]. Importantly, organoids can be established from multiple patients, enabling the study of inter-individual variability in drug response [36]. From a pharmacological perspective, organoids support the evaluation of dose–response relationships under conditions that better approximate *in vivo* reality. They also facilitate the identification of resistance mechanisms and adaptive responses that may not be apparent in simpler systems [37].

Importantly, organoid systems may allow the simultaneous evaluation of cytotoxicity, adaptive resistance [38–40], and intratumoral heterogeneity [41,42] within the same experimental framework. This is particularly relevant for targeted therapies , where small resistant subpopulations may survive treatment and ultimately drive disease progression [39]. Such phenomena are difficult to capture in conventional homogeneous culture systems.

Beyond organoids, microphysiological systems, often referred to as organ-on-chip technologies, offer additional opportunities to model tissue–tissue interactions, fluid dynamics, and immune components [43]. Microphysiological systems are engineered micro-scale platforms designed to reproduce key structural and functional features of human tissues and organs *in vitro*. These systems can integrate perfusion, vascular barriers, and multicellular tissue architectures, enabling more physiologically relevant modeling of drug distribution, cellular interactions, and treatment response. While still evolving, these platforms have the potential to further enhance the predictive capacity of preclinical testing [44,45].

6. Functional Readouts and the Emergence of Predictive Pharmacology

One of the most significant advantages of human-relevant models is their ability to generate functional readouts of drug response. While genomic and transcriptomic analyses provide valuable insights into potential vulnerabilities, they do not always translate into effective therapeutic strategies [4]. Functional assays, by contrast, directly measure the response of living systems to pharmacological intervention. This enables the identification of biomarkers that reflect the integrated behavior of multiple pathways rather than isolated molecular features [46]. Such biomarkers may be particularly important for therapies targeting complex processes such as replication stress or cell cycle regulation [47]. The integration of molecular profiling with functional testing represents a powerful approach to predictive pharmacology. The correlation of the drug response with the

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underlying biological features helps to define composite biomarkers that stratify patients more accurately and guide treatment decisions [48].

7. Implications for Drug Development

The transition from descriptive screening to predictive pharmacology has important implications for the design of drug development pipelines. Rather than relying on sequential filtering through increasingly complex models, an alternative approach may involve parallel evaluation across multiple human-relevant systems [3]. Such a strategy would prioritize early identification of variability in drug response and enable the selection of candidates with robust performance across diverse contexts. It would also support the development of companion diagnostics and biomarker-driven clinical trials [23].

Importantly, this shift does not imply the abandonment of traditional models, but rather their repositioning within a broader framework. 2D systems and animal models may continue to play valuable roles in mechanistic studies and safety assessment, but their limitations in predicting clinical efficacy should be explicitly acknowledged [23].

8. Discussion

The limited success of many anticancer agents in clinical trials reflects a fundamental challenge in translational pharmacology, which is the inability of current preclinical models to accurately predict human response. This perspective argues that the issue is not merely one of biological complexity, but of conceptual alignment between experimental systems and pharmacological objectives. By distinguishing between drug activity and predictive pharmacology, it becomes clear that new approaches are needed to bridge the gap between preclinical testing and clinical outcome. Human-relevant models, including patient-derived organoids and microphysiological systems, offer a promising path forward. The integration of these platforms into drug development pipelines has the potential to redefine how therapeutic efficacy is evaluated, and shift the focus from isolated measures of potency to context-dependent, patient-relevant responses. In doing so, it may enable a transition toward more accurate, efficient, and ultimately personalized strategies in cancer pharmacology.

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