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Drug discovery through stem cell-based organoid models ☆

Adrian Ranga, Nikolche Gjorevski, Matthias P. Lutolf *

Laboratory of Stem Cell Bioengineering, Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland

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ABSTRACT

The development of new drugs is currently a long and costly process in large part due to the failure of promising drug candidates identified in initial in vitro screens to perform as intended in vivo. New approaches to drug screening are being developed which focus on providing more biomimetic platforms. This review surveys this new generation of drug screening technologies, and provides an overview of recent developments in organoid culture systems which could afford previously unmatched fidelity for testing bioactivity and toxicity. The challenges inherent in such approaches will also be discussed, with a view towards bridging the gap between proof-of-concept studies and a wider implementation within the drug development community.

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1. Introduction

Drug discovery today is at a crossroads: while increasingly large and varied compound libraries are synthesized and tested in primary screens, the promise of the identified lead compounds remains largely unrealized. Indeed, while tremendous investments in automation have enabled the costs and turnaround time for large to medium-scale

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* Corresponding author at: EPFL SV IBI-SV UPLUT, AI 1109 (Bâtiment AI), Station 15, CH-1015 Lausanne.
E-mail addresses: adrian.ranga@epfl.ch (A. Ranga), matthias.lutolf@epfl.ch (M.P. Lutolf).

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primary screening to fall significantly [1], the gap between lead compound validation and success in the clinic is still wide, suggesting that a process still beset by significant limitations in efficiency.

To a significant degree, this inefficiency in taking lead compounds into the clinic may be due to the discrepancy between the simplified in vitro assays currently performed and the complexity of real in vivo pathologies. Indeed, while both drug safety and efficacy intrinsically linked to administration into a complex and heterogeneous three-dimensional (3D) physiological system, most primary drug screening campaigns are still carried out with cell lines grown on two-dimensional (2D) plastic, an entirely reductionist approach where important parts of the drug-biology interaction are lost. The outcome of this primary screening process is the identification of "hits", which satisfy very specific molecular targets or phenotypic requirements. A key problem is that these lead compounds are then validated and optimized in similarly over-simplified culture models. The process of ADMET evaluation (adsorption, distribution, metabolism, excretion, toxicology), while having undergone significant improvements in the last 15 years [2], could still be considered one of the main bottlenecks in the drug development process and could afford the greatest return on technological innovations [3].

As an important additional requirement, regulatory agencies require that identified pro-drugs be tested in two animal models before granting approval to proceed to any human clinical trials. This costly process of validation in animal models often fails due to physiological events linked to fundamental differences between human and animal model physiology. At this increasingly costly step, due to well-known differences in mechanisms of metabolism and toxicology between species, there remains a significant lack of fidelity between current testing procedures and human outcomes, particularly as related to appropriate evaluation of toxicity and drug dose.

These shortcomings have been clearly recognized within the pharmaceutical industry [4], yet few fundamental solutions have currently been implemented. The behavior of cells and their response to drugs continue to be studied in vitro mostly in 2D cell cultures that completely fail to mimic the complexity of the microenvironment. Not surprisingly, drug responsiveness in these settings is therefore often not predictive of the in vivo situation, which dramatically increases the costs of drug discovery.

At the same time, a vast amount of research has been carried out in academia to develop more relevant test-beds for screening and validation efforts (Fig. 1). In particular, there has been a push towards the development of multicellular spheroid models [5], notably in cancer modeling [6], as well as a number of miniaturized approaches culminating in organ-on-chip systems [7]. More recently, there has been a tremendous interest in developing increasingly complex multicellular constructs termed "organoids" [8–10] (Fig. 2). These morphogenetic models, often recapitulating developmental programs from embryology or harnessing adult stem cell-based regenerative processes, have allowed molecular and cell biologists to understand key signaling events required for the initiation and maintenance of multicellular organs. By recapitulating not only the form but also the rudiments of function of their in vivo counterparts, these constructs have the potential to move from laboratory proof-of-concepts to relevant tools in the drug discovery pipeline. Indeed, such organoids could finally provide a key missing link between compound screening and clinical trials, and could serve as models for testing drug efficacy in target organs, for toxicity in liver models or for bioavailability through intestinal system models. In particular, by using primary human cells, especially patient-derived cells with relevant pathologies in conjunction with cellular reprogramming strategies, these techniques could provide an invaluable link to disease-specific human drug screening models.

Ultimately, the wider implementation of these bio-mimicking approaches within the drug development community will require the level of reproducibility and consistency currently achieved with cell lines. Thus, such culture models will require 3D culture conditions which afford the needed flexibility to achieve precise control over the cellular microenvironment as well as a level of scalability. Furthermore, the applicability of such models will be greatly enhanced by adapting to existing infrastructure, notably automatic robotic platforms for experimental setup and assay readouts.

Thus the purpose of this review is first to provide a selected survey of existing state-of-the-art 3D models of in vitro drug evaluation, then to

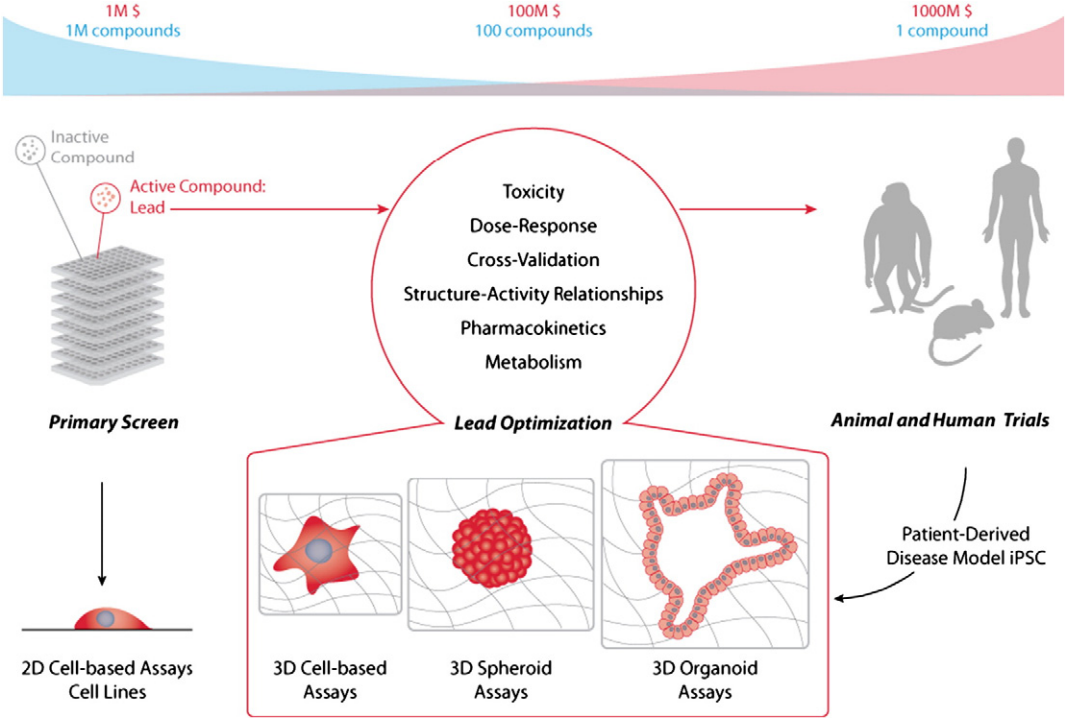

Fig. 1. 3D assays could bridge the gap between primary screening and animal and human trials. Drug discovery pipeline typically proceeds from multiple compounds tested at relatively low cost to few compounds in high-cost high-risk trials. The process of lead optimization and validation can benefit from increasingly representative in vitro technologies.

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