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Patient-centered drug discovery as the means to improved R&D productivity

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The pharmaceutical industry is struggling in relation to drug discovery research innovation and productivity improvement. The drug discovery process currently used does not predict clinical efficacy and its sustainability is questionable in view of high costs and attrition rates. In this article we propose an alternative approach that starts with patients and aims at identifying biologic pathways involved in human diseases as a turning point in the discovery of novel therapeutics. This approach utilizes emerging biomedical and technological advances and builds further on the industry's existing knowhow in chemistry and biology. The model calls for changes in the rather linear R&D activity chain currently in practice.

Challenges for today's drug discovery

The pharmaceutical industry faces a major challenge to improve R&D innovation and productivity. Although the industry has already enhanced the effectiveness of drug development operations and embraced external partnerships and collaborations to fuel its portfolio, the question of how best to advance discovery research remains. Innovative discovery research is the engine of productivity. Yet, today, the applied approach is largely a game of chance, operationally industrialized to a series of predefined activities that yield new molecular entities (NMEs) of unpredictable clinical potential. Whether it is phenotypic or target-centric, the discovery process typically involves combinatorial chemical library screening against a defined target or a biological hypothesis in the attempt to identify leads that can be optimized through medicinal chemistry and further preclinical testing to compounds with drug-like properties. The desired molecules are advanced into clinical studies in healthy volunteers and subsequently patients in selected disease areas. This linear path, from target selection to clinical development, has many flaws. From the outset, it limits the discovery space to known molecular targets and perceived modes of action thus engendering undue caution toward unexploited biological mechanisms [1]. Target selection, however critical, is too often based on data of questionable validity [2]. Perceived success in target modulation is heavily driven by the ability to optimize lead molecules chemically and, to a lesser extent, by establishing the relevance of biology. If no chemical starting points are identified from screening activities, targets are often abandoned and labeled undruggable with little effort being made to identify or switch to other interception modalities (e.g. biologics, vaccines, etc.). Throughout the preclinical discovery phase, molecules are identified and characterized in test systems and animal models that have low clinical relevance and that poorly translate target functions and disease conditions. These attributes collectively front load discovery efforts in time, knowledge and expense, yet rarely mitigate or predict the challenges encountered in the clinic.

Although many innovative drugs have been discovered recently, the sustainability of the discovery process as applied today is questionable in view of costs, high attrition rates and unrelenting demand for more-innovative therapies. Consequently, alternative strategies and economic models to improve R&D productivity have been proposed [3,4]. These have identified factors contributing to low productivity and have proposed changes to the R&D value chain, cycle time, cost and the overall approach to clinical development without, however, addressing how to alter industry's approach to drug discovery fundamentally via an essential rethink focused on increased success rates.

Patient-centered drug discovery research

Drugs no longer fail in the clinic as a result of undesirable physicochemical properties or pharmacokinetic profiles [5,6]. Industry's investment in medicinal chemistry knowhow and ADME testing has paid off. Recent analysis of clinical attrition rates attributes failure primarily to insufficient efficacy (>50%) and safety concerns (≈20%) [6]. This is unsurprising because the clinical relevance and characterization of most targets pursued in discovery are not well established. Accordingly, any departure from previous ways of discovering new treatments should center on patients directly. Here we

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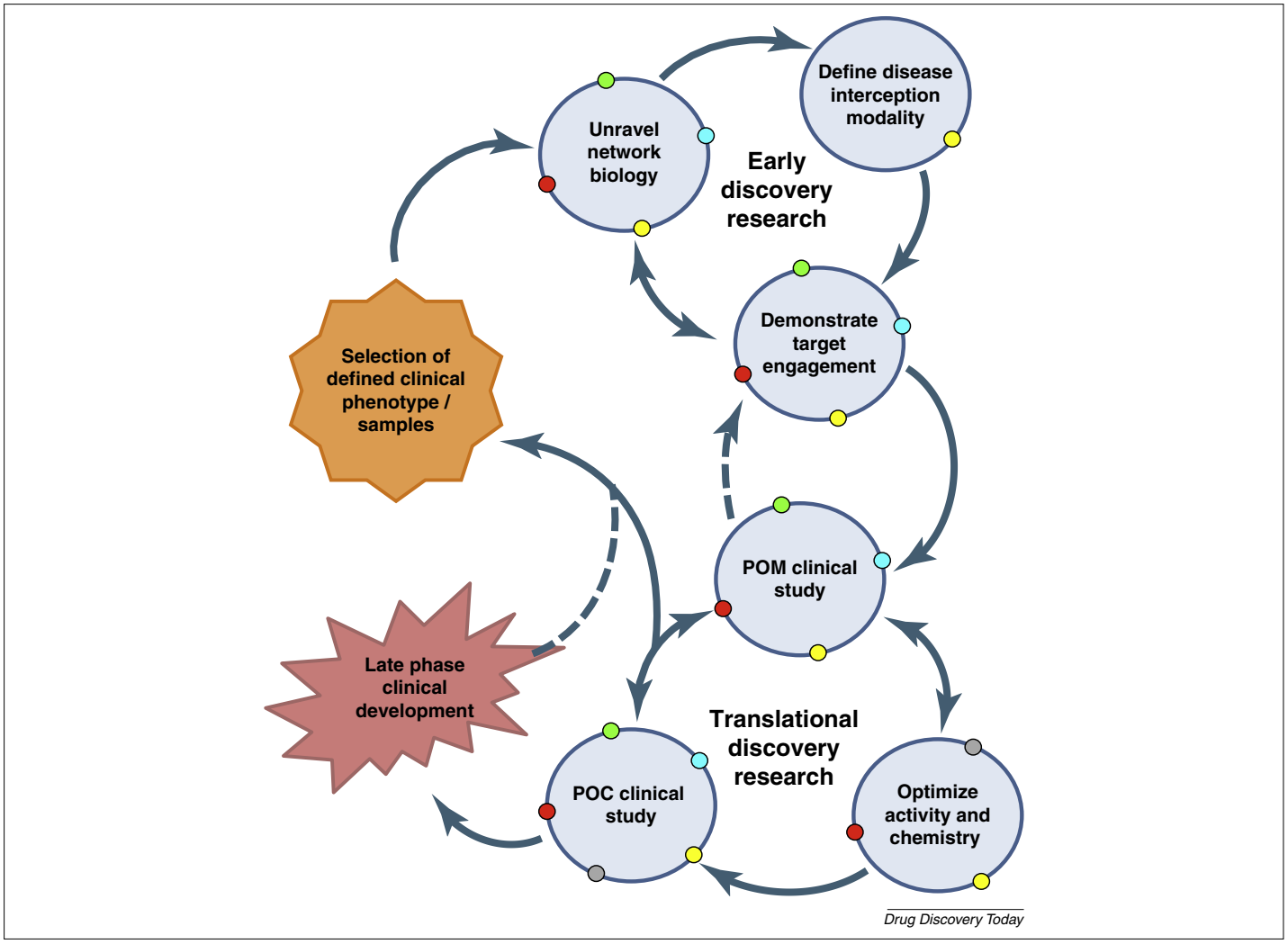

FIGURE 1

Schematic overview of the outlined model for patient-centered drug discovery. Methods most relevant for each activity are color-coded: red for biospecimens; green for single-cell assessment; blue for multiparameter readout technologies; yellow for predictive biosimulation and modeling; gray for conventional tools used in drug discovery and development. *Abbreviations*: POM, proof-of-mechanism study; POC, proof-of-concept study.

outline an alternative strategy that is largely built on biomedical research principles throughout the entire discovery phase and that focuses primarily on unraveling biological pathways and their clinical relevance before major commitments are made in optimizing and advancing potential therapies to the clinic (Fig. 1). This strategy adopts newly evolving technologies, emphasizing those that utilize patient-derived materials. Our focus aims at improved understanding of underlying disease biology as well as the predicted dynamics of the intervening pharmacology. The model highlights two distinct research phases, early discovery and translational discovery with clear go–no-go steps in between based on the demonstration of target engagement. The activities in each cycle are interconnected, emphasizing the complexity and importance of establishing target engagement and clinical proof-of-mechanism (POM).

In the proposed model, discovery projects start with selection of a target patient population. Whereas a disease phenotype based on clinical observation and routine laboratory analyses is the obvious starting point, further in-depth characterization of the patient population at the molecular level by means of omics biomarker analyses defines and identifies more-homogeneous patient subgroups for targeting in experimental drug discovery settings. Biological networks underlying the selected clinical phenotype of interest can be unraveled using the latest technologies that make use of samples or cells derived directly from healthy volunteers or patients (primary or induced pluripotent stem cells). By virtue of their origin, these systems are more reliable for (re)stating crucial aspects of disease pathogenesis and generating patient-specific cellular disease models [7,8]. Thereafter, discovery research could embrace many new technologies and scientific disciplines and embed them earlier in the experimental phase of discovery programs. New developments in multiparameter readout technologies, single cell assessments and methods for predictive biosimulation and modeling are of particular interest in this context. These can be applied directly to patients or patient-derived biospecimens in models with different levels of complexity, thereby enabling truly translational research between bed and bench (Fig. 2).

Multiparameter readout technologies at the gene (DNAseq, RNAseq, ChIPseq, epigenetics) and protein (multiplex protein assays, etc.) levels generate broad and in-depth molecular information from patient-derived samples, which can be invaluable in understanding disease mechanisms and responses to therapy [9,10]. In addition, modern high-resolution histology, immunohistochemistry, RNA in situ hybridization and imaging technologies permit 3D tissue reconstruction which can be applied to assess

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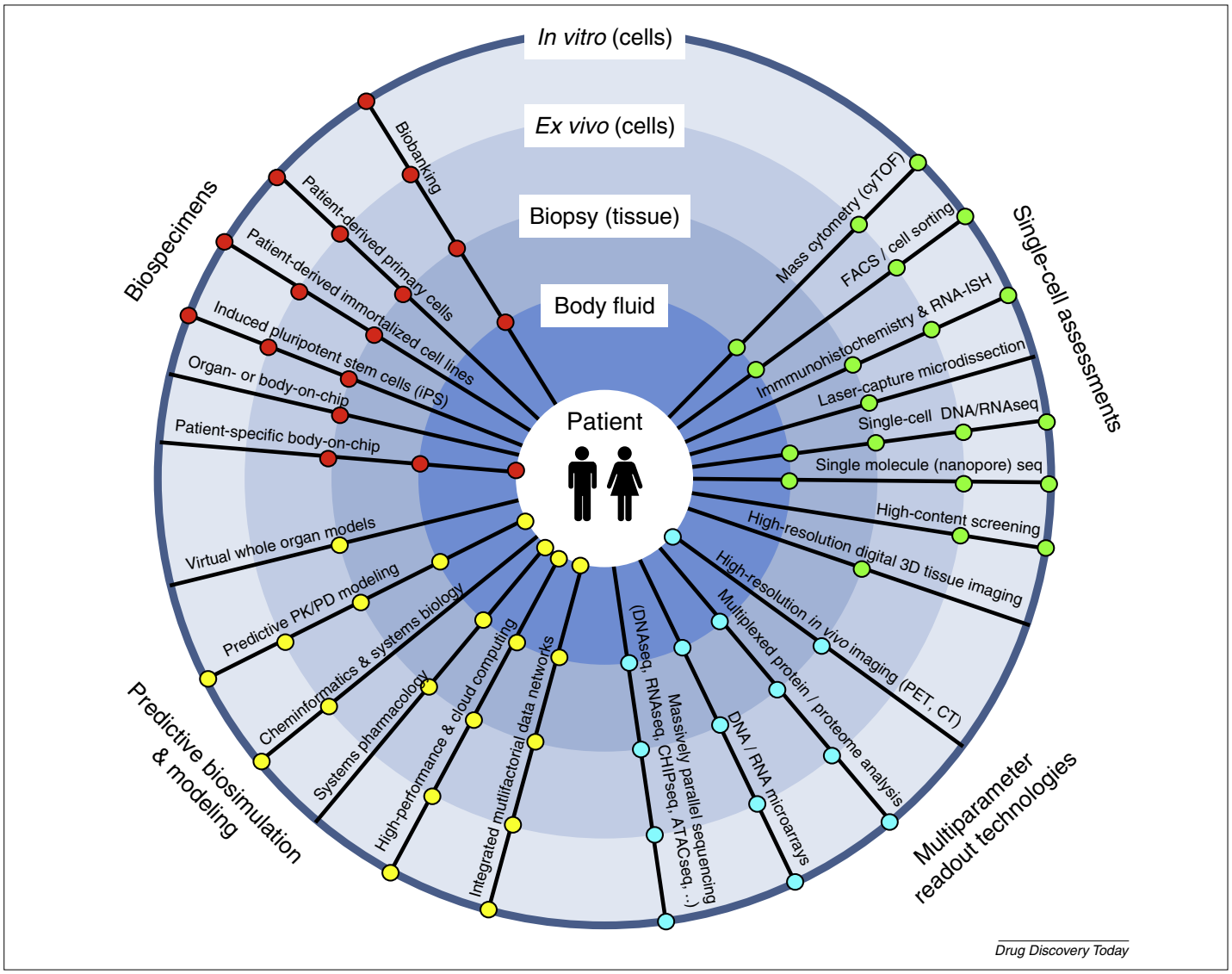

FIGURE 2

Diagram representing important components of patient-centered discovery research. The listed methods and technologies are meant to be representative (rather than comprehensive) for established and new developments in the respective areas and do not indicate prioritization. The colored dots indicate for each tool the different types of patient-derived source materials that are in scope.

structural and biological changes in normal and diseased tissues [11]. Other imaging techniques [such as positron emission tomography (PET), optical imaging, X-ray, computerized tomography (CT) and magnetic resonance imaging (MRI)] enable further molecular and functional characterization of organs and tissues in preclinical and clinical settings at the level of enzymatic activity, receptor, neurotransmitter and metabolic mechanisms, as well as various other biological processes [12,13].

The above mentioned technologies examine samples in ultimate detail. Their evolution also enables application at the individual cell level. Depending on the source material (body fluid or tissue), individual or groups of similar cells can be isolated using cell sorting or laser-captured micro-dissection methods, and examined minutely to assess intracellular dynamics and functional signaling. Interestingly, many of these analyses can also be applied directly to patient-derived samples that have been treated *ex vivo* with known or novel compounds of interest. If correlated with or predicted for a desired outcome or an unwanted side-effect, such analyses could, in a later stage of development, facilitate personalized medicine.

A comprehensive understanding of the disease biology network can point toward effective interceptions for prevention, control or cure. The insights thus gained in the disease biology at the molecular level could indicate whether a traditional single target approach or, alternatively, a more complex strategy (e.g. simultaneously pursuing multiple targets or selecting targets or molecules active in specific cell types only) is warranted. Conventional structural biology tools, combined with cheminformatics and computational chemogenomic analyses, can guide the choice of intervening methodology (small molecule, antibody, vaccine, etc.) and assist in identifying ligands for pathway perturbation experiments. Combinatorial high-throughput screening is often critiqued for poor yield, whereas its aim, in the new model, is to be selective. The required screening activities should ideally be performed on patient cells or systems that are closely linked to the clinic and provide evidence of desired network engagement. At this crucial point, an array of emerging experimental and virtual platforms such as organ- and body-on-a-chip [14,15], *in silico* predictive biosimulation [16–18] and virtual whole organ models [19] can enable additional

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assessment of pathway modulation and potential liabilities before initiating costly clinical trials. Although these technologies are not unchallenged, they are already beginning to revolutionize drug discovery and development testing strategies. In light of this, the need to optimize initial lead compounds or ligands preclinically to improve typical drug-like properties early in the process is diminishing. Hence our proposed strategy advocates advance demonstration of POM as a cornerstone of the process. Such POM study should demonstrate desired pharmacological effects that can be monitored by means of specific biomarkers (e.g. omics, imaging, etc.) and/or cellular multiparametric readouts as determined earlier in the process.

Only when POM studies demonstrate that the proposed intervention in the biology network is mechanistically valid should further optimization of lead molecules be pursued through medicinal chemistry for small molecules, or the counterpart toolbox for biological molecules. The final optimized molecule can be assessed, if required, in the experimental setting used in the initial phases of discovery, complemented with additional experiments for regulatory purposes. Successful POM studies can be followed by a proof-of-concept (POC) study with patient selection and study design being guided by the application of analysis tools used earlier in discovery. This can generate valuable information to explain, for instance, inter-individual variation in efficacy or safety during clinical studies. The above approach continuously tests the working paradigm in patient-linked settings, thereby facilitating adjustment when a tested hypothesis fails to meet expectations. Unraveling the relevant network biology should afford a solid basis for multiple discovery projects because it allows application to multiple clinical disorders sharing similar biological mechanisms.

Evolving translational paradigm in drug discovery

Unlike traditional research-based drug discovery which applies basic cellular mechanisms in the design of new therapies, our approach targets clinically relevant disease mechanisms and guides the identification of relevant interception modalities that directly address patient needs. Although the value of this approach has often been asserted, no roadmap for its implementation in drug discovery has, so far, been set out comprehensively. Many translational tools (transcriptomics, biosimulation, biomarkers, cellular readouts, etc.) have been individually emphasized and showcased to enrich certain components of drug discovery [20–22]. This, however, has occurred mainly within the existing drug discovery framework (i.e. from target identification to NME declaration), whereas we propose a holistic approach aimed at transformational change. The term translational has frequently been misapplied to describe enhanced animal models and in vitro systems, improved predictability of therapeutic outcome, among other factors, as a means of closing the gap between bed and bench [23–25]. Without a direct link to patient characteristics, however, it could be questioned if the foregoing can be regarded as being truly translational. The benefits of understanding patient needs to improve discovery productivity have been acknowledged, yet there has been little patient-oriented experimental research in early drug discovery. Only recently has a patient-oriented screening approach been advocated using cancer and nonmalignant human cells from the same tissue to improve the screening reliability of potential anticancer compounds [26].

Earlier attempts at implementing translational philosophy in the field of HIV drug discovery have proven successful thanks, in particular, to the establishment of close functional links between drug discovery research and the clinic, making use of then state-of-the-art technologies [27]. Similarly, recent drug discovery in oncology takes diversity in patients and their molecular cancer subtypes into account early on, and drives the subsequent selection of the molecularly targeted patient population. Modern translational research can benefit from ease of sourcing of many patient-derived materials and real clinical data, as well as novel technological developments (Fig. 2). These tools enable a shift in paradigm away from traditional drug discovery that is largely based on observational analogies between preclinical models and clinical phenotypes. The cyclical nature of translational research from bench to bedside and back again has been outlined previously in the context of drug discovery [28,29]. The patient-centered model we propose builds further on this, most notably by laying major emphasis on the patient at all stages, adopting and integrating novel technologies and methodologies, while continuously assimilating newly generated information with the aim of revealing novel insights into the disease and appropriate interception modalities to pursue.

Implications and challenges

Understanding disease biology and its underlying mechanisms is paramount in defining successful treatments for many diseases. Those where blood is the target (hematology, immunology, infectious diseases) are obvious candidates to pursue discovery research using our approach. In such diseases multiparametric and/or single-cell technology readouts enable simultaneous assessment of protein surface markers and intracellular proteins in cell subpopulations of interest [30]. For example, single cell analyses of clinical samples uncovered a system-wide view of the immune signaling in healthy human hematopoiesis [31] and B lymphopoiesis [32], which enabled comparison against cancer and revealed biologically relevant starting points for pharmacologic intervention and mechanistic studies. Similarly, in seeking more-effective therapeutic strategies for infectious diseases such as HIV-1 or influenza, where host–pathogen interactions have an important role, an integrated systems biology view at single-cell level based on high-dimensional omics analyses in infected patients could identify host cell factors as novel avenues for drug discovery [33,34].

Our model stresses establishing disease-relevant therapeutic pathways, using patient-derived materials, before selecting individual targets to pursue. It embraces as essential pillars advances in multiparametric readouts, single-cell assessment, biospecimen and predictive biosimulation and modeling. Implementation of this approach is not without its challenges and will require the industry to embrace scientific disciplines that hitherto have been viewed as overly academic or exploratory noncritical. Also, rather than stressing a chemistry-focused approach, our model will necessitate a more integrated application of multidisciplinary scientific fields (e.g. clinical research, biomarkers, omics, bioinformatics, systems pharmacology, etc.) and the building of integrated partnerships and collaborations to address adequately the complexity of disease biology.

Access to high-quality and diverse patient and healthy control clinical samples is essential in this model and might therefore be considered a potential limitation. Fortunately, there are today numerous well-annotated biobanks providing a wide range of tissues, cells and other patient biomaterial, accompanied by relevant laboratory and informatics data [35,36]. In addition, recent advances in isolating and reprogramming somatic cells from frozen tissue samples (up to 11 years) enhance access to a larger source of tissues and, more importantly, enable researchers to reconstitute the onset and progression of disease at a cellular level [8]. Although a one-size-fits-all approach or toolbox might never cover all needs, drug discovery is

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gradually evolving toward a less industrialized and more personalized process shaped by disruptive technology advances. This calls for changes not only in current R&D practices but also in regulations around therapy testing and advances into the clinic. With increased availability of large public datasets and the ability to analyze and integrate multifaceted data forms (chemistry, biology, omics, biomarkers), it is possible to predict biological activity of untested compounds reliably and de-risk potential liabilities [16,17]. Sirota *et al.* demonstrated that systematic computational approaches, building further on gene expression measurements from 100 diseases and on 164 drug compounds, yielded predicted therapeutic potential for these drugs, several of which were already validated preclinically [37]. Such approaches enable one to reposition established or novel compounds to treat a wide range of human diseases. With the arrival of high-throughput sequencing, large-scale data generation projects and web-based cloud computing, the field of computational sciences is evolving rapidly and has become a fundamental component of modern drug discovery [38]. The emergence of more humanized in vitro test systems together with a variety of translational biomarkers and imaging technologies facilitates a better characterization of molecular mechanisms and variations in patient populations. There have been numerous calls to reshape the clinical research landscape and bridge more-effectively the translational gap between discovery and development [39,40]. The approach we advocate would enable further evolution of the clinical research field and, in time, minimize the need for rigorous animal testing and alter fundamentally the approach of industry toward first-in-human and POC studies. The recent arrival of translational amenable test systems and technologies, as described, will particularly optimize biomarker emergence and usage at an early stage. Currently, biomarkers are suboptimally exploited in drug discovery, are used primarily for downstream applications during clinical development and often poorly or only partially reflect clinical reality.

Concluding remarks

It could be argued that applying biomedical research principles in drug discovery prolongs cycle time to deliver NMEs, makes the process and supporting organization unduly complex and risks nonassertion of commercial value in advance of initiating a discovery program. However, knowing disease mechanisms and focusing efforts directly on patients seems the only effective way to increase R&D productivity and reduce clinical attrition and perhaps the cost of drug development. Building such knowledge will take time but, ultimately, it will help researchers to consider disease interception modalities, beyond single target interaction, and facilitate investment in preemptive interception strategies that, in our view, represent the future of healthcare.

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