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Drug Intelligence Science (DIS®): Pioneering a high-resolution translational platform to enhance the probability of success for drug discovery and development

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Translational research has a crucial role in bridging the gap between basic biology discoveries and their clinical applications. Deep scientific understanding and advanced technology platforms are both crucial for translational research. Here, I describe a novel integrated Drug Intelligence Science (DIS®) translational platform that combines single cell technology with artificial intelligence (AI) and machine learning (ML) to gain insights into high-resolution cell biology, thus enabling the discovery of disease-relevant targets, high-quality drug candidates, and predictive biomarkers. The innovative DIS® approach has the potential to provide unprecedented mechanistic understanding of human diseases and enable in-depth pharmacological profiling of drug candidates to increase the probability of success (POS) in drug discovery and development.

Keywords: Drug Intelligence Science (DIS®); translational platform; probability of success (POS); drug discovery and development; single cell science; artificial intelligence (AI)/machine learning (ML)

Introduction

The process of discovering and developing drugs is both complex and time-consuming, with a failure rate of 90%, especially for novel therapies.[1] To increase the probability of turning preclinical discoveries into effective clinical outcomes, translational researchers apply innovative scientific and technological methods to gain deeper insights into complex disease biology and clinical pharmacology.[2,3] Although recent translational studies have led to a reduction in failures, major challenges remain for the pharmaceutical industry facing the "Valley of Death", that is, the gap between basic scientific discovery and clinical proof of concept.[4]

Three major challenges are generally considered to contribute to POS in drug discovery and development (Figure 1). First, it is difficult to select an effective therapeutic target based on basic research. Even though extensive progress has been made using preclinical models, such as disease mouse models and human organ chips to capture human disease biology,[5,6] findings through preclinical models cannot fully reflect the complex biology of the human body. Drug targets with true translational value could originate from patients' disease tissue and their unmistakable relevance in a given disease should be demonstrated. With advances in genomic

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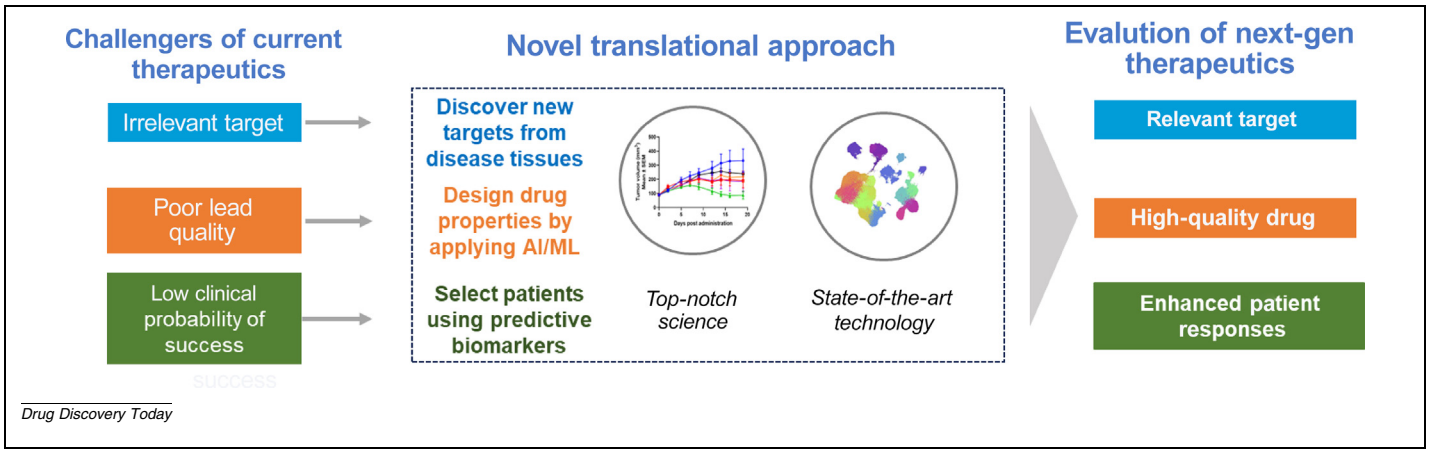

FIGURE 1

Addressing major challenges in research and therapeutics through translational research driven by cutting-edge science and state-of-the-art technology. Effective translational research could discover relevant targets, develop high-quality drugs, and identify better patient responses for the next generation of therapeutics.

and proteomic analysis, genetically marked druggable targets have been directly identified from humans.[7] However, in the absence of mutations or genomic abnormalities that can be linked to disease, target identification is less straight-forward. Therefore, discovered targets often require extensive validation in preclinical biological models as well as in clinical settings where a drug could modulate a target and bring benefit to patients.

Second, highly efficient methods are lacking to discover, optimize, and ultimately select drug candidates for successful clinical outcomes. Despite a higher number of drug candidates entering the clinical development stage in recent years, the actual rate of drug approvals has not improved accordingly.[1] Although the emergence of novel therapeutic modalities, such as cell and gene therapies, has provided additional options for patients, the complexity and the limitations of these options still require tremendous efforts to be impactful for patients. Therefore, it is exciting to see that recent technological developments in AI/ML as well as single cell platforms with application in drug discovery could provide valuable insight into the design and use of effective therapeutics to treat diseases.[8–10] However, these endeavors are still in the early stages and need much improvement and further validation.

Third, despite extensive translational research to understand drug response mechanisms in models that simulate patients, a drug candidate often cannot replicate the preclinical activities in a clinical setting because of the natural heterogeneity among patients.[11,12] Consequently, the pharmaceutical industry has been struggling with low clinical POS even as translational research has made significant progress. To improve clinical outcomes, it is vital to gain greater insight into complex disease biology and drug mechanisms of action in patients to predict the response to a treatment and provide benefit to the most appropriate patient populations. To precisely dissect underlying disease mechanisms and associate them with the pharmacological effects of a particular drug candidate in a heterogeneous patient population, hundreds or thousands of patient samples are needed to perform bulk analyses to achieve statistical significance, given that each sample represents an average readout of diverse cell populations. Processing large numbers of patient samples to gain significant insights from bulk analysis is not only difficult to achieve scientifically, but also time consuming, costly, and logistically challenging.

In sum, the scarcity of promising outcomes in drug discovery and development is driven by the following factors: ineffectiveness in relevant target selection; difficulty in discovering and optimizing high-quality drug candidates; and challenges in translating preclinical data into positive therapeutic outcomes. For the next generation of therapeutics to be truly successful, any improvement that can address these current challenges will be highly impactful. Therefore, it is crucial to develop and implement a novel translational approach combining cutting-edge science with state-of-the-art technologies that can identify translatable targets from human disease, discover and optimize high-quality effective clinical candidates, and ultimately increase patient responses to drug treatments (Figure 1).

In recent years, the drug discovery process has seen significant advancements in AI and ML-driven target identification and *de novo* drug design in a fast and cost-effective manner. These innovations offer hope for a more efficient process and successful outcomes in pharmaceutical research and development.[8–10] In the meantime, single cell technologies have also been increasingly applied to drug discovery efforts to study the biology of single cells at either the protein or genomic level.[10,13] Unlike bulk readouts from mixed cell populations, single-cell analysis could delineate complex diseases and capture patient heterogeneity at a high resolution.[14–17] Therefore, understanding biology at a single cell level in combination with leveraging AI and ML capabilities in drug discovery and development could provide valuable solutions to address the challenges for drug discovery and development.

Drug Intelligence Science (DIS®)

To meet the urgent need to address current gaps in the development of successful therapeutic agents, HiFiBiO Therapeutics established a novel integrated translational platform, termed Drug Intelligence Science (DIS®), which combines single cell technology with AI/ML-supported large-data analytics to generate deep understanding of high-resolution cell biology (Figure 2a). DIS® provides the possibility of studying and manipulating individual cells with unparalleled accuracy, offering profound insight into the fundamental principles of biology with the potential for groundbreaking advancements in drug discovery and development. Furthermore, when cells involved in disease progression are treated with a therapeutic drug, they can be separated into responding and nonresponding states. Applying a single cell technology, the phenotypes and genotypes of heterogenous cell populations can be captured and analyzed using AI and ML to gain unprecedented understanding of disease biology as well as the mechanisms of action of drugs. Learning from drug effects on single cells can be further applied to patient treatment, where single cell analysis can uncover predictive biomarkers for responding and nonresponding patients (Figure 2b). To gain a deeper insight into the connection between cells and patients responding to drug treatments, extensive data collection is necessary to capture information related to cells, drugs, and patients. So far, HiFiBiO Therapeutics has collected and integrated over 15 million single cell transcriptomes covering more than 35 tumor types and 25 autoimmune diseases with drug treatment annotations. These data were collected from two sources: in-house single cell analysis from patient samples using HiFiBiO Therapeutics' own proprietary single cell instrument and algorithms; and publicly available single cell data obtained using an in-house AI/ML-enabled curation tool. Significant efforts have been made to ensure proper annotation, curation, and normalization of the data sets to meet the industry high-quality standards, and the DIS® single cell data sets can be interrogated meaningfully across the rapidly growing database.

Using the DIS® platform, HiFiBiO Therapeutics has generated proof-of-concept results from internal pipeline efforts or external partnerships and demonstrated significant success in novel target discovery from patient samples and deep immune repertoire mining for antibody discovery. Although studies are ongoing for the identification and validation of predictive biomarkers, the initial pilot study has yielded promising results. Therefore, I suggest here that, by combining single cell analysis with AI/ML, one can go beyond the current discovery paradigm and achieve high-resolution translational outcomes relevant to targets, drugs, and patients (Figure 3).

Target identification

Conventional target identification and validation are based on preclinical experiments using cell cultures and animal models. Identifying targets directly from patients is the most relevant approach, but presents formidable challenges. One of the major hurdles is the ability to dissect disease biology accurately using heterogenous patient samples. Using a proprietary microfluidic technology developed by HiFiBiO Therapeutics, patient samples can be analyzed at the single cell level to identify cellular responses associated with disease mechanisms that are not present in healthy individuals. In this way, by specifically targeting aberrant events associated exclusively with disease, we can develop therapeutic drug candidates with fewer or no safety issues because no healthy cells and organs are targeted. More importantly, the mechanisms leading to disease pathogenesis are effectively addressed. The accumulation of single cell data related to different disease states can also be used to link disease scores with the expression of certain targets and provide novel target hypotheses. This approach has achieved proof-of-concept at HiFiBiO Therapeutics using samples from patients with acute myeloid leukemia (AML). Both known targets and novel targets have been identified using this approach, further highlighting the power of the DIS® platform.

Antibody discovery

In recent decades, monoclonal antibodies (mAbs) have emerged as a prominent class of therapeutic agents and are proven to be highly effective in treating various human diseases, particularly cancers, immunological disorders, and infectious diseases.[18] However, the discovery and development of antibody drug candidates need to be improved, particularly in terms of antibody diversity and the speed and quality of lead optimization, for higher success rates in clinical trials. HiFiBiO Therapeutics' proprietary droplet microfluidics technology can screen millions of live B cells in hours with exceptional speed, throughput, and effectiveness, a feature that other antibody discovery platforms lack. This technology provides exceptional deep immune repertoire mining for maximum diversity and optimal quality of clinical candidates, even for difficult multitransmembrane targets.[19,20] Using this approach, HiFiBiO Therapeutics successfully identified several antibody–drug candidates against different types of target, including challenging G-protein-coupled receptors (GPCRs), such as CXCR5 and CCR8. Furthermore, the deep mining of B cell receptor repertoires for desired antibody properties can be achieved in both wet and dry labs through AI/ML algorithms. AI/ML has been applied to provide predictions for antibody affinity maturation, optimal potency, and selectivity, which can then be tested and validated experimentally. The validation of DIS®-driven antibody discovery can be exemplified by the accelerated screening and optimization of neutralizing Coronavirus 2019 (COVID-19) antibodies following the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) outbreak.[21,22] In the short span of 6 months, HiFiBiO Therapeutics utilized the DIS® platform to advance a neutralizing antibody from the initial screening of patients convalescing from COVID-19, to lead optimization and preclinical models to investigational new drug (IND) filing.

Patient stratification

Positioning drug candidates within suitable patient populations is crucial for ensuring clinical success. It is evident that, because of disease heterogeneity, administering a given drug to a group of patients diagnosed with the same disease, for instance lung cancer or lupus, does not guarantee that the drug will help patients equally, rendering the one-size-fits-all approach ineffective. Using the DIS® platform, patient disease samples can be examined to identify gene signatures that define

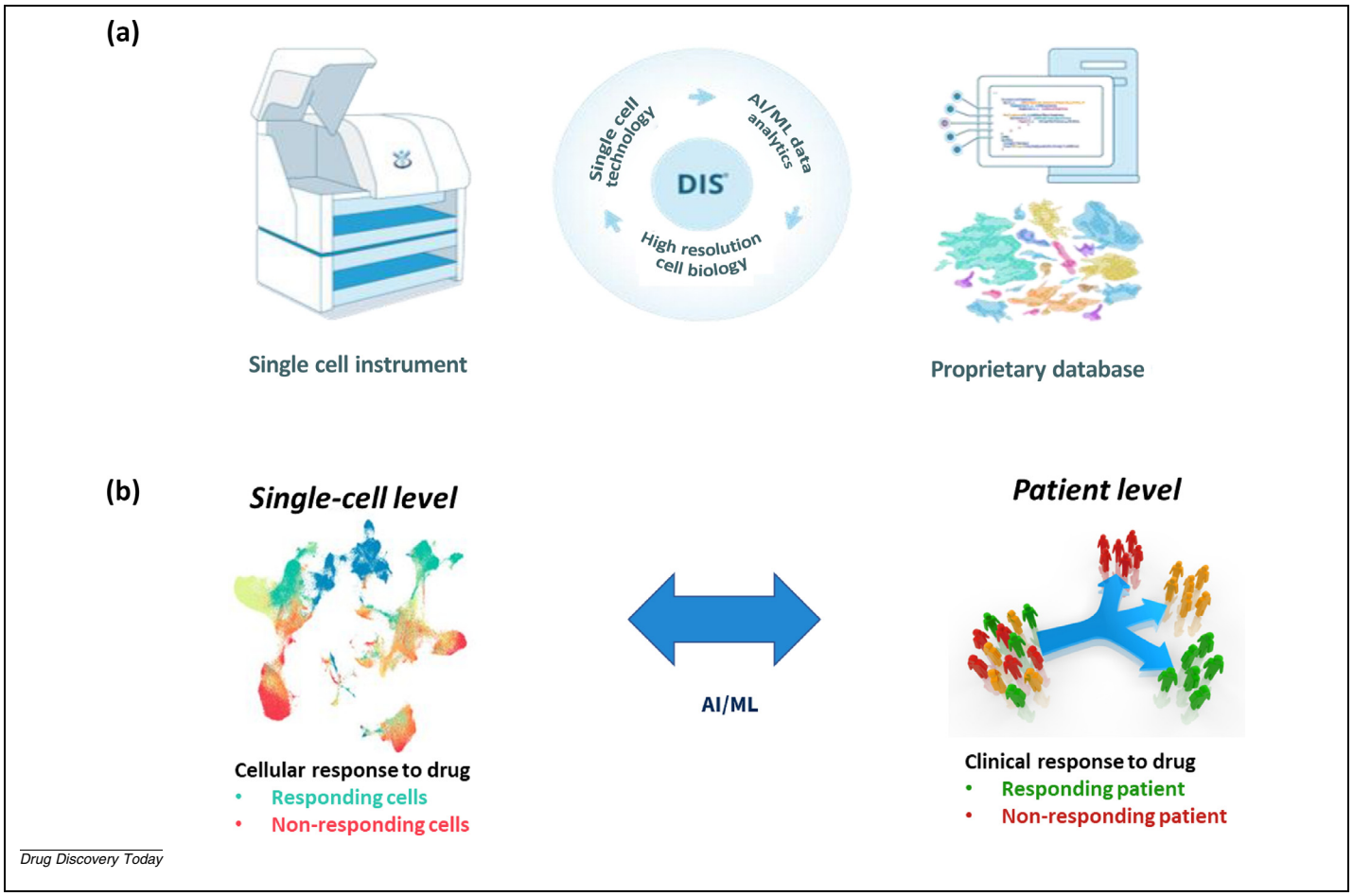

FIGURE 2

Drug Intelligence Science (DIS®) integrates single cell technology with artificial intelligence (AI)/machine learning (ML)-supported large-data analytics to generate a deeper understanding of precision cell biology (a). Drug effects on single cells can be translated into predictive biomarkers for patient responses through AI and ML (b).

unique cell profiles for patients with a higher potential to respond to treatments during clinical trials. Single cell profiling could also be explored *ex vivo* to determine predictive biomarkers associated with drug responses before a clinical trial even starts. In a proof-of-concept study, it was demonstrated that DIS®-derived anti-PD1 signatures could better predict patient responses to treatment with atezolizumab, compared with other reported signatures, resulting in improved hazard ratios across clinical studies in biomarker-positive subpopulations.[23] In clinical settings, instead of obtaining and analyzing thousands of samples from different patients, translational research can leverage single cell analysis to probe the 'individuality' of each patient by analyzing thousands, or even tens of thousands of cells per sample to ensure that the mechanisms of drug response are captured. Given the large data sets generated by single cell analysis at both the genotype and phenotype levels, AI/ML is required to efficiently process the data to generate actionable insights. This approach has so far met with some success.[24–29] Currently, three clinical programs at HiFiBiO Therapeutics are applying DIS® to identify indications for each drug candidate. The selected indications are enriched not only for target expression, but also for immune cells amenable to regulation by corresponding drug candidates based on the understanding of mechanisms of action at the single cell level. In addition, tumor biopsies and peripheral blood mononuclear cell (PBMC) samples are collected before and after drug treatment to validate the predictive biomarkers identified from *ex vivo* studies.

In summary, the DIS® platform connects knowledge obtained at the single cell level with information obtained at the patient level. Specifically, it facilitates decisions about which disease-relevant targets can be selected, it contributes to discovering and optimizing target modulating drug candidates, and it serves to determine which predictive biomarkers can be identified to stratify patient populations. This approach promises to enhance the response rate of patients who are properly treated, thus addressing the industry challenges of achieving high POS in drug discovery and development.

Concluding remarks

As a high-resolution translational platform, DIS® has the potential to transform drug discovery and development by combining AI/ML with single cell science to achieve high-resolution analysis for target discovery, lead optimization, drug candidate identification, and patient selection.

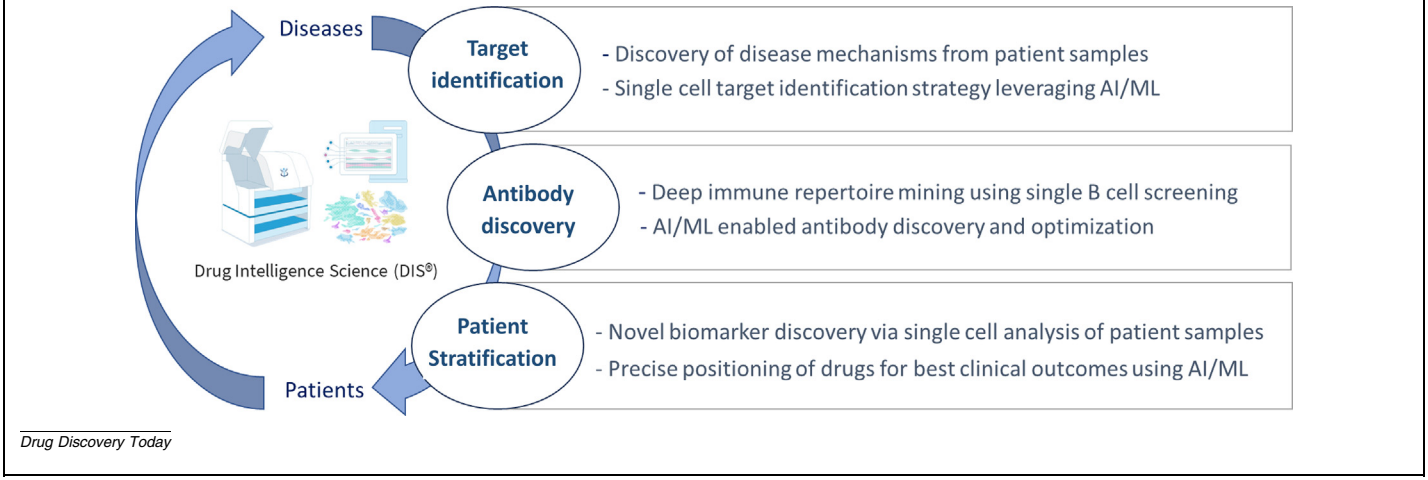

FIGURE 3

Drug Intelligence Science (DIS®) combines single cell analysis with artificial intelligence (AI)/machine learning (ML) to provide a novel high-resolution translational approach. DIS® could transform the paradigm of drug discovery and development by enabling target identification, antibody discovery, and patient stratification at single cell precision to enhance the probability of success (POS) of novel therapeutic drugs.

Although the platform has its own obvious strengths, it clearly also has limitations.

Strengths of DIS®

DIS® delivers a vastly improved understanding of disease biology and pharmacology at a single cell resolution, thereby enhancing POS of drug discovery and development. This approach yields a deeper and more comprehensive understanding of complex scientific principles and a thorough grasp of pharmacological mechanisms through innovative AI/ML analytics. The fact that hundreds or thousands of cells can be analyzed from each patient at the single cell level is highly impactful toward obtaining important disease information. It is superior compared with bulk analysis, because mixed readouts from multiple cell types using bulk analysis lack the resolution needed to dissect disease heterogeneity. Using samples from as few as tens of patients containing thousands of cells each, all major disease mechanisms can be uncovered and dissected clearly at the single cell level. In addition, AI/ML can effectively extract the desired scientific knowledge from these data points. Given that DIS® uses its own proprietary single cell instrument and analytic process, costs are less compared with the classical translational approach, which often requires hundreds or even thousands of patients. Another key strength of DIS® lies in its guided data generation. Rather than relying solely on established data sets using traditional experimental approaches, DIS® uses a strategic and purposeful approach to collect, integrate, analyze, and interpret data. This guided process ensures that the data collected are relevant, reliable, and aligned with the specific objectives of the scientific inquiry. By fusing deep scientific and pharmacological knowledge with an informed data generation strategy at the single cell level aided by AI/ML, DIS® can provide insights that were previously unattainable and achieve a comprehensive understanding of the complex biological mechanisms underlying human diseases. This unique combination empowers researchers, scientists, and pharmaceutical professionals to make informed decisions with greater confidence and precision.

Limitations of DIS®

Although the DIS® platform has been well validated by HiFiBiO Therapeutics over the past few years, having a crucial role in progressing the pipeline through the stages of drug discovery and preclinical development to clinical trials, it has yet to demonstrate the ability to enhance clinical POS. Moreover, some limitations remain on the technical front, because both single cell technology itself and AI/ML applications are capable of being further optimized. In addition, to establish a comprehensive single cell disease atlas with high-quality data integrated from different sources and accurate patient treatment information annotated properly depends on significant financial investments and many years of dedicated work. This effort requires a broader community to join forces, but the outcome could be transformative for the entire pharmaceutical industry.

Taking into account both the strengths and the limitations of DIS®, this distinctive platform could pioneer the advancement of disease biology, revolutionize the drug development process, and shape the future of scientific discoveries in an era when innovative tools and approaches have the potential to significantly transform patient care.

Data availability

No data was used for the research described in the article.

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Declaration of interests

L.S. is employed full time as the founder, chairperson, and CEO of HiFiBiO Therapeutics.

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