WHITE PAPER

The importance of combination therapy for modern cancer treatments

Introduction

Traditionally, drug discovery has relied on target-based approaches, where specific molecular targets are identified and screened for their interaction with potential drug candidates. However, this approach often overlooks the complex interactions and dynamics within living cells and fails to capture the full complexity of human disease.

Phenotypic cell panel screens on the other hand leverage automation, robotics, and data analysis techniques to enable the screening of thousands of compounds against diverse cellular models that capture the heterogeneity and complexity of human biology, increasing the chances of identifying compounds with broad therapeutic potential. High-throughput, phenotypic cell-based panel screens have emerged as a robust, biologically relevant, and cost- effective tool in the field of drug discovery.

The utilization of high-throughput screens enables rapid evaluation of the efficacy and safety of large compound libraries across diverse cell lines and multiple phenotypic endpoints, allowing for a more comprehensive assessment of the compound's effect on cellular systems. This aids in the identification of potential drug candidates with desired phenotypic characteristics and therapeutic profile.[1] By assessing a wide range of cellular responses, including gene expression patterns, signaling pathways, and physiological changes, these screens uncover the complex underlying biology of diseases and conditions. This comprehensive understanding of cellular behavior allows researchers to identify and prioritize therapeutic candidates that are more likely to succeed in subsequent stages of drug development.

In addition to their biological relevance, these screens offer an economic advantage. The high-throughput nature allows for the efficient screening of large numbers of compounds, reducing the time and resources required to identify and prioritize potential therapeutic candidates. This cost- effective approach accelerates the drug discovery process and increases the likelihood of identifying promising leads for further investigation.

Combination therapy

Combination drug therapy, with the use of two or more drugs with distinct mechanisms of action to target different aspects of the disease, is becoming increasingly important in the field of cancer treatment to improve patient outcomes by maximizing tumor cell killing, overcoming drug resistance, and reducing recurrence. Resistance to anticancer drugs is a major challenge in cancer treatment. Cancer cells can become resistant to single drugs over time, rendering them ineffective. Combining different drugs with different mechanisms of action can help prevent or overcome resistance and improve treatment efficacy.

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Combination therapy can target multiple pathways involved in the development and progression of cancer, leading to a more comprehensive approach to treatment.[2] This approach can also reduce the toxicity and side effects associated with high-dose monotherapy, as lower doses of multiple drugs can be used in combination.[3] Recent advances in understanding the genetic and molecular basis of cancer have allowed for the development of targeted therapies that selectively inhibit specific proteins or pathways involved in cancer development. Combining targeted therapies with traditional chemotherapies or immunotherapies to concurrently attack multiple targets can achieve synergistic effects for enhanced antitumor activity and more sustained tumor regression.[4]

Combination therapy testing using disease relevant cell models has become a critical aspect of the biopharmaceutical industry's efforts to develop more effective cancer treatments.[5] However, identifying the right pair amongst the vast number of possible combinations and determining the appropriate dose of each drug comes with its own set of challenges. Dose optimization can be a difficult but crucial element of an effective combination screen, as certain drugs may exhibit differing efficacy and toxicity profiles when used in combination compared to when they are used as monotherapies. Additionally, the high cost and specialized expertise required for setting up large scale drug combination campaigns along with the complexity of analyzing and interpreting the complex of data generated can be prohibitive for launching combination drug discovery efforts.

Revvity's approach to combination screening

In 2005, CombinatoRx, a biopharmaceutical company, developed a proprietary platform technology to systematically evaluate the combination activity of pairs of approved drugs against a broad range of major diseases.[6] This platform helped to increase the efficiency of combination therapy testing by enabling biopharmaceutical companies to screen thousands of potential drug combinations in a rational hypothesis driven or agnostic manner in relatively short periods of time.

Revvity acquired CombinatoRx's combination cell panel screening technology in 2014, along with its proprietary combination analysis software, Chalice Analyzer[7], enabling Revvity to become a market leader in combination screening services and play an important role in advancing the field of *in vitro* combination drug discovery.

Over the years, Revvity has fine-tuned its combination screening platform, screen designs, and automation and analysis workflows to navigate the vast combinatorial possibilities as well as identify the most optimal concentrations of drug for achieving the desired therapeutic effect. The company's scientific experts work closely with researchers to design and execute comprehensive combination screens tailored to their specific needs whether it be exploring novel interactions for clinical advancement or repurposing existing therapeutics.

Revvity has further developed the Chalice Analyzer software with various combination statistical models to allow for the visualization of dose matrices and analysis of large-scale combination data. Scientists leverage their years of extensive experience and this powerful in-house analysis tool to help clients interpret and prioritize the results from the complex interplay of interactions between the drugs screened.

Revvity has been a key player in the combination drug screening space helping researchers accelerate their drug discovery process by rapidly identifying promising combinations for further evaluation in preclinical and clinical studies. Their combination screening services can be complemented by its broader portfolio of services, including cell line engineering and functional genomics for an integration of technologies and expertise allowing a comprehensive approach to combination screening and enabling a deeper understanding of drug interactions and mechanisms of action.[8]

In summary

Combination drug therapy is a fundamental cornerstone in modern cancer treatment for enhancing treatment efficacy, reducing drug resistance and toxicity as well as addressing disease heterogeneity. However, combination drug development is not without its challenges; determining the most effective drug combinations, managing potential side effects, and maintaining optimal dosages require careful consideration.

The use of high-throughput, phenotypic cell panel screens provide a robust, biologically relevant, and economic means for the identification and prioritization of combination

therapeutic candidates in drug discovery. Revvity's combination screening services leverage the power of large cell line panels and advanced analytical methods to evaluate the effects of different drug combinations on various cellular parameters enabling researchers to make informed decisions in selecting the most promising combination candidate for further development.

As the biopharmaceutical industry continues to focus on personalized medicine, combination therapy and cell panel screening will play increasingly important roles in identifying the most effective treatment strategies for individual patients.

Click to learn more about Revvity's combination screening service

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