WHITE PAPER

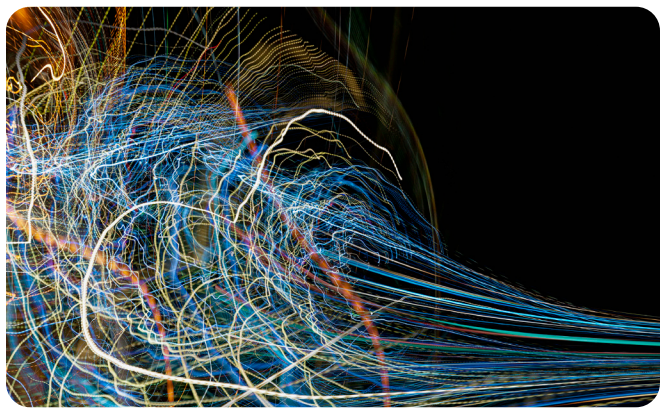
Relevance of multiparametric screening to drug discovery efforts

What is multiparametric screening?

Multiparametric screening is a generalized term for investigating multiple parameters at once. The idea is to gather a more accurate and comprehensive understanding of a given subject than can be obtained by focussing on just one factor alone. When broken down, the defined individual components to be investigated are entirely dependent on the context in which you are to use them.

In the context of modern medicine, multiparametric techniques have transformed patient experience. For example, the introduction of Multiparametric Magnetic Resonance Imaging (mpMRI) as an advanced imaging technique has revolutionized the diagnostic process for cancer patients. It combines multiple parameters, each sensitive to different tissue properties. This paints a more comprehensive and detailed picture of potentially malignant areas of tissue that could not have been obtained with one single metric alone.[1]

This same logic can be applied to drug development. Multiparametric screening is particularly useful for navigating the mazes of genetically complex diseases by delivering information on a variety of parameters at once. As such, it is often employed to evaluate the effect of modulating select genes on a particular metric of interest.[2-4]



Why is this important to drug discovery?

The universally shared goal of drug discovery is to uncover new therapeutics that will revolutionize the way we treat certain diseases for the better or to uncover potential therapies for morbidities where treatment is currently beyond our reach. One substantial hindrance to this goal has always been wasted time and resources due to attrition.[5] A detailed understanding as to the way new therapeutic candidates function, and their efficacy in appropriate models of disease, allows researchers to gauge the likelihood of future success early in the development process.[2,5] This is where high-throughput multiparametric screening techniques prove to be pivotal, especially in the context of functional genomic screening.

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The utilization of gene modulation techniques, such as high-throughput siRNA or CRISPR-based screens, plays a crucial role in modern drug discovery efforts. By comprehensively assessing the effects of gene modulation on cellular phenotype, this approach offers valuable insights into disease mechanisms and the mode of action of the therapeutics being developed to mitigate them.[6]

One of the key advantages of gene modulation technologies is the ability to unravel the complexities of disease biology in a systematic way. In an arrayed format, methodically perturbing genes of interest using siRNA or CRISPR, researchers can examine resulting phenotypic changes from a multitude of different parameters to decipher the role of specific genes in disease processes. Alternatively, in a pooled format, researchers can identify previously unknown key genetic players in sensitivity or resistance to a new therapeutic. These comprehensive approaches enable the researcher to amass a deeper understanding of disease mechanisms and pathways, which is essential for the development of effective therapeutic strategies.[2,7–9]

By evaluating various cellular parameters such as cell viability, proliferation, apoptosis, and gene expression, researchers can gather a comprehensive picture to understand the impact of target modulation, enhance confidence in target selection, and increase the chances of success in subsequent drug discovery efforts.

Additionally, gene modulation in an arrayed format may contribute to the identification of novel therapeutic approaches. Investigating the knockdown or editing of certain genes may uncover synergistic interactions between previously known therapeutics, revealing effective new therapeutic combinations. Furthermore, the systematic approach supplied with multiparametric arrayed format genetic perturbations can unveil genetic vulnerabilities or synthetically lethal interactions that can be selectively exploited to target disease.

As we are now firmly placed in an era of drug discovery led by computational techniques such as AI, another area in which this format of screening is beneficial for the field of drug discovery is the role it can play in target validation and lead optimization. Researchers can confirm the relevance and effectiveness of their identified targets by computational means. This approach helps prioritize and select the most promising targets for further development and allows for further refinement and improvement of drug candidates before they enter clinical trials. This potentially improves their chance of success as they reach the next stage of development.[10]

Multiparametric screening with high-content imaging

As an endpoint readout, high-content imaging has emerged as a critical tool in drug discovery due to its ability to provide high-quality quantitative information about cellular and sub-cellular processes. By combining automated microscopy, advanced imaging techniques, and data-analysis algorithms, high-content imaging enables researchers to extract valuable data on cellular phenotypes, drug effects, and target engagement.[11]

One key advantage of high-content imaging is its ability to capture rich data sets from multiparametric assay set-ups, from individual cells or cell populations. Traditional imaging techniques often provide limited information, focussing on a single aspect of cellular behavior. In contrast, high-content imaging allows for the simultaneous measurements of multiple cellular parameters, such as morphology, protein expression, organelle localization, and cellular dynamics. This provides researchers with a more nuanced understanding of complex biological processes, including information on potential off-target effects or compound-induced changes in cellular physiology. Not only can this be achieved by analyzing multiple facets of an assay, such as multiple targets via as many fluorescent markers, but also by multiplexed staining of cellular compartments using technologies such as Cell Painting.[12,13]

What can Revvity offer for drug development efforts?

Revvity offers a variety of functional genomic screening services to aid in the rapid validation of drug development processes. Our functional genomic screens are available for hundreds or thousands of genes in a single experiment, extending up to whole genome perturbation libraries. With integrated solutions for RNA modulation and CRISPR-based perturbations including CRISPRi and CRISPRa, our screening portfolio provides the option to access a complete

functional genomics platform. Using either cell lines or primary cell cultures, Revvity's screening platform can perform pooled, arrayed, and even single-cell screens with our easily customizable library technologies and formats. Revvity also offers a variety of endpoint readouts and models of disease for the assay itself. With the option to select more than one readout for the same assay set-up - it's not just the input of the assay that can be multiparametric in nature.

In addition to functional genomic screening, Revvity also offers a wide range of resources for high-content cellular imaging and analysis solutions for both *in vitro* and *in vivo* contexts, including services, systems, reagents, microplates, software, and automation.

Concluding remarks

In conclusion, multiparametric gene modulation screening, in various technical flavors, is of the utmost importance to the field of drug discovery. It provides a comprehensive understanding of disease mechanisms, identifies potential therapeutic targets, and enables the development of novel therapeutic approaches and patient stratifications. As our knowledge of genetics and disease biology continues to expand as a scientific community, multiparametric gene modulation screens will remain an indispensable tool in the quest for effective and personalized therapeutics.

Interested in learning more?

Check out these resources:

- Functional genomic screening
- CRISPR and RNAi in primary cells
- Cellular and In Vivo Imaging Solutions
- On-demand webinar – Leveraging multiplatform cell-based screening for target ID
- How do functional genomic and cell panel screening combine to identify novel targets

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