POWER UP YOUR PIPELINE: MAXIMIZING SINGLE & COMBINATION SCREENING FOR CANCER

A conversation with **DR. DAVID SORRELL**, HTS Platform leader, Horizon Discovery Ltd

Horizon Discovery extended its suite of research tools and services to include high-throughput screening through the acquisition of CombinatoRx's screening platform in 2014. Since the acquisition, Horizon has optimized the platform by including a more extensive panel of cancer-cell lines and an onco-centric compound library. The enhanced screening service called OncoSignature, identifies efficacious cancer drugs or combinations by screening up to 300 cell lines in 3 months, thus aiding patient stratification. Horizon also provides a custom drug-screening service that gives tailored answers to specific research questions, for example: How do my combination drug candidates work in different environments such as hypoxia?

Why is high-throughput combination screening important?
A lot of early cancer treatments were monotherapies, but these weren't always effective and the emergence of drug resistance in tumours is often rapid. Therefore, to improve patient outcomes, physicians increasingly use drug combinations. There are thousands of ongoing combination clinical trials in oncology worldwide. However, this hardly scratches the surface of the potential number of drug combinations that could be achieved using approved and experimental anticancer drugs, which has been estimated to be around 850,000 possible pairwise combinations, and exponential numbers of combinations involving three or more drugs. We have spent over 15 years industrializing our platform for the rapid identification and prioritization of efficacious combinations.

How does Horizon predict which patients will benefit from which single drugs or combinations?
Once clients have found an efficacious drug candidate or combination, they might want to know more about genetic biomarkers that predict patient response to their drug. High levels of non-responding patients can increase the size and costs of clinical trials. Knowing the breadth of drug activity across additional cancer types helps to stratify patients for clinical trials. Using OncoSignature, we can screen drugs alone or in combination- against 300 diverse and well-characterized cancer cell lines, or narrower tissue-specific subsets. Full genomic information is available for 95% of OncoSignature cell lines through the CCLE (Cancer Cell Line Encyclopaedia), maximising results by exploring which mutations drive cell resistance/sensitivity.

How can you help researchers pick the best combinations of drugs?
For clients looking to identify the best combination partner for their pipeline candidate, Horizon's custom option can screen leads in combination with some or all of the 350 molecules in our compound library, which includes current standard-of-care drugs, emerging experimental drugs, and novel chemical probes that target a diverse range of cellular mechanisms. For these screens, cell lines can be selected from our well characterized collections of over 800 cancer cell lines and from our off the shelf catalogue of over 4,000 gene edited standard and haploid cell lines that were engineered to contain important patient relevant gene mutations. Importantly, these gene edited cell lines have a genetically matched isogenic wild type control line, enabling researches to precisely validate the link between drug response and genotype. The use of combinations of three or more drugs in cancer therapy is becoming increasingly common. The screening and analysis of higher order combinations is complex and standardized approaches are lacking. We have extended our bioinformatics tools to support this trend.

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What makes Horizon Discovery different from others providing screening services?
For our custom screening, we work consultatively with our clients to obtain relevant data by offering further assay development and pilot screens, tailoring solutions to answer specific questions. We have tested many of our onco-centric library compounds across hundreds of our cell lines. Consequently, we have a large database of information essential for streamlining the selection of concentrations for a client's combination screen, without need for additional experiments. High-throughput screening produces masses of data, making the analytical step complex. All our high-throughput services are supported by our proprietary Chalice™ software, which was designed to analyse combination high-throughput screening results. The software allows researchers to visualize the data, understand metrics and trends, and gain insights.

What's next for Horizon's high-throughput screening?
Most high-throughput screening studies use two-dimensional cell-based assays. Three-dimensional assays using multicellular spheroids and organoids can generate more physiologically relevant data, but the throughput is lower due to their complexity. To address this bottleneck, we are developing an OncoSignature 3D spheroid offering. As 3D technology develops, we will continue to optimize our clients discovery pipelines with more clinically relevant disease models, in a fast, high throughput way.

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