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CRISPR SCREENING: POWERING TARGETED DRUG DISCOVERY

A conversation with **DR. BENEDICT CROSS**, R&D Manager, Functional Genomic Screening, Horizon Discovery Ltd

Horizon Discovery provides research tools and services to biopharma and diagnostics companies, from small virtual start-ups to multinationals. The company has developed a suite of functional genomic screening technologies, including a CRISPR-Cas9 platform. Horizon's aim is to help its partners to identify, evaluate and validate targets, to understand drug mechanisms of action, and to facilitate studies involving patient stratification. Horizon has optimized more than 50 cell lines for CRISPR screening and carried out more than 300 screens to date.

What is CRISPR and how do you use it to support your customers?
CRISPR-Cas9 is a precision genome editing technology that can knock out, activate or fine-tune the expression of individual genes. We provide access to CRISPR KO (knockout), CRISPRi (interference) and CRISPRa (activation) technologies, which change the phenotype of cells by eliminating, reducing or increasing gene expression.

While CRISPR was initially developed for editing, it is playing an increasingly important role in screening. CRISPR techniques can be scaled up for genome-wide screening using individually cloned sgRNA libraries, allowing rapid, specific and efficient analysis.

CRISPR KO is useful for identifying and prioritizing drug targets, finding the genes that confer drug sensitivity and resistance, guiding patient selection, and identifying targets and pathways for potential combination therapies. CRISPRi comes into its own for modeling druggability and validating hits from a KO screen, and CRISPRa supports the understanding of drug-gene interactions.

Horizon has developed a dual screening approach — what is it?
We are very excited about dual screening. CRISPR KO is a widely used technique, but biology is complex, so loss-of-function studies don't give us the whole picture. Combining our CRISPR screening technologies provides a more detailed overview: running CRISPRa and CRISPRi screening in parallel allows us to identify 'switch' genes that display contrasting effects when they are inhibited compared to when they are activated by a drug of interest. That means we can see where interacting and opposing effects happen within the same signaling pathway.

By using the dual screening approach, drug developers can identify new targets, learn more about their drugs, and reduce the risk of missing an interesting response that may not arise with a single screen.

How can Horizon's CRISPR platform help companies restock their discovery and early-stage pipelines?
In order to maintain a constant flow of drugs through their pipeline, and deal with high levels of attrition, companies need to have a breadth of potential targets and drugs at their fingertips. Using our CRISPR-based screening, we help companies get a wide sweep of candidates, while ensuring that the results returned stay relevant.

When developing a drug, it's important to understand its target and its mechanism of action. This is particularly crucial when repurposing an abandoned asset from another indication. CRISPR technologies help us to understand where a drug acts in the cell, and the pathways it interacts with.

Growing cost pressures mean that clinical trials are increasingly enrolling only the most appropriate patients. How do Horizon's platforms help?
For drug developers, stratified clinical trials can make the process faster and less costly, and for payers and providers, just treating those patients who are likely to respond can both improve outcomes and cut costs.

Our CRISPR KO-based ResponderSCREEN helps researchers find the genes that change patients' responses to a specific drug, by simulating patient and disease genetic diversity. Once the genetics are known, these can be used to predict which patients are more or less likely to respond. Because the screen can be carried out before preclinical and clinical development begins, it has potential to cut development costs and drive early go/no-go decisions.

How do your CRISPR technologies help companies achieve R&D return on investment?
CRISPR screening is a cost-effective, and potentially cost-saving, approach, because it derisks drug development. However, developing a screening platform and recruiting people with the necessary skills is expensive. By outsourcing CRISPR screening to teams like ours, companies avoid these upfront investments.

Developing drugs is highly competitive, and the race to the market needs a rapid turnaround of data. Capacity can be a challenge, even for companies who have CRISPR capabilities in-house, if demand outstrips supply. Outsourcing can provide a more flexible supply of services with better timelines.

What makes Horizon different from the other companies offering CRISPR technologies?
CRISPR has opened up a lot of possibilities, but people can struggle with getting meaningful insights from the data. At Horizon, we recognize that our clients have different requirements, so we provide services at different points in the drug development cycle, from target to product, and work at a number of different levels, from designing screens and selecting cell lines, through providing the raw data, to creating a full bioinformatics analysis of the outcomes.

Our experience and expertise mean that we can collaborate with our clients, building relationships and offering advice. We make sure that we stay at the front of technology, and we are constantly updating our methods and approaches, and adding new tools.

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