Assisting hit-to-lead research

Pelago Bioscience is a specialised CRO, focusing on its patented Cellular Thermal Shift Assay (CETSA), which can assess therapeutically relevant target engagement in cells or tissue of unmodified compounds against the native, full-length proteins of interest. Stina Lundgren, Principal Project Advisor, shared the company's hit-to-lead expertise with Lu Rahman.

CETSA by Pelago can be adapted for different applications to support any stage of the drug discovery process – from low-throughput confirmation and high-throughput discovery to proteome-wide exploration – these methods rely on the same principle: measurements of the 'thermal shift' that occurs when a compound interacts with a protein.

LR: What can help ensure a successful hit-to-lead process?

SL: To ensure an efficient design-make-test-analyse cycle, all compounds designed should be able to generate data that answers a specific question driving the project forward. Further, it is important to ensure access to robust and biologically relevant assays generating actionable data, either directly as the primary screening assay or further down in the screening cascade, enabling hypothesis-driven compound design.

LR: What are the challenges that drug discoverers face?

SL: As the industry focuses on challenging and so called "undruggable" targets, the traditional screening technologies, based on either indirect reporter assays or recombinant proteins in buffer, are often not applicable. Therefore, novel and more biologically relevant screening approaches will need to be used to identify relevant chemical starting points.

LR: What hit-to-lead advances enable drug discovery companies to work more efficiently?

SL: As the drug discovery industry has realised the importance of target engagement assays, and that confirmation of target engagement is essential for discovery and development of safe and efficient drugs, these assays are being included in the screening cascade early in the drug discovery pipeline. Traditionally, target engagement has mainly been assessed on purified proteins in buffer rather than in a physiologically relevant, cellular environment. This could give misleading data and result in late-stage failure. Researchers have access to biologically relevant tools, such as cellular target engagement assays that can be employed in early lead generation phase to guide the project prioritisation and generate data that can strengthen the target and compound validation. A strong correlation between functional readout and cellular target engagement of the compounds against a target protein strengthens both the target hypothesis as well as the confidence in the prioritised compound series. For phenotypic-based drug discovery, the access to efficient target identification tools using unmodified compounds has enabled identification of the biology-driving target protein before initiating the lead optimisation phase.

LR: How can researchers reduce false positives in lead generation?

SL: Apart from using, for example, property filters and removing compounds with known structural liabilities from the compound screening deck before initiating the screening campaign, it is important to have access to counter-screen assays and orthogonal assays for further triaging and confirmation of the hit compounds. Moreover, it is beneficial to utilise screening methods with a low inherent liability towards false positives and focus on technologies that are able to identify high-quality compound hits.

LR: Can they speed up timelines?

SL: Developing and implementing cellular target engagement assays early in the drug discovery process provide valuable guidance to the research teams and ensure the right prioritisation of resources, both within a given drug discovery project and across a wider project portfolio. Hence, target engagement assays in relevant cellular systems could have a large impact on the project timelines, and confirmation of target engagement should preferably be included as a criterion in the lead target profile.

LR: Are there any recent initiatives that you can share?

SL: For hit-to-lead, CETSA is a useful tool for compound screening and hit confirmation and can potentially unlock novel chemical space. The high-throughput CETSA format, known as CETSA Navigate HT, is based on dual-antibody proximity detection systems suitable for miniaturisation in 384 and 1536 microtiter plates. Using this format, we have executed in-house screens on CDK4 and STING using a stratified library of 11,000 drug-like compounds. We are currently triaging hits from both screens and profiling the further in efficacy assays. So far, the data suggests that the format has low liability towards false positives and has yielded a relatively low hit rate but with confirmation on target engagement of the compounds in physiological conditions. The assay has allowed us to identify high and low affinity binders and has yielded new chemical starting points of high biological relevance.

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