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# Drug discovery at the melting point: improving the odds

**Pelago Bioscience, founded in 2013, aims to improve human health by helping its partners to discover and develop better therapeutics for difficult-to-drug targets.**

Only around one in ten drug candidates reach the market, and before that more than half of the candidates fail because of a lack of clinical efficacy. The high failure rate of potential therapeutics increases the cost of developing drugs and also means slow access to suitable treatments for patients with unmet needs. Pelago Bioscience's patented CEllular Thermal Shift Assay (CETSA) method allows researchers to avoid these failures by understanding the mode of action and validating their projects earlier in the drug discovery process.

"Traditional drug discovery is often about producing the recombinant protein target, building an in vitro assay, screening for hits, testing, and then starting all over again if the hits aren't effective in cell or tissue models," said Stina Lundgren, head of commercial operations at Pelago Bioscience.

Companies have been finding novel drugs and targets for a long time using traditional methods and the industry can be quite resistant to change.

"Our answer to this was to move off the beaten track and prove that CETSA makes a difference," said Michael Dabrowski, CEO and co-founder. "We are reducing the risk and improving the odds in drug discovery by focusing on the physiologically relevant readout."

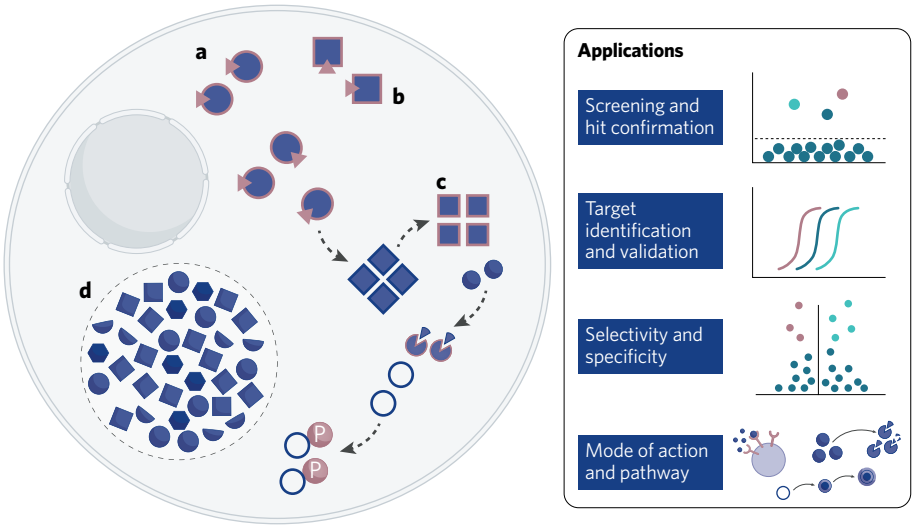


**Fig. 1 | How drugs perturb the biology of the living cell.** The compound (▲) binds to the primary target (**a**) and off-target proteins (**b**) affecting their thermal stability. Compound binding also affects the functional status and thermal stability of associated and downstream proteins (**c**) in the pathway, but most proteins are unaffected (**d**). Four different applications of CETSA relevant for progressing the discovery of novel therapeutics (right).

## The CETSA technology

CETSA, invented by Pär Nordlund at the Karolinska Institutet in Stockholm, Sweden, is the first broadly applicable method to study interactions with proteins in living cells. The technology, further developed by Nordlund's former student, Daniel Martinez Molina (now Pelago's CSO), is based on the observation that proteins melt at different temperatures depending on whether a ligand is bound to the protein.

"Nordlund, Molina and I created Pelago to further develop and commercialize CETSA. Nordlund and Molina are the brilliant inventor and the skilled scientist; I bring the client need and business perspective, focusing on how Pelago generates value in our partnerships. We were profitable right from the beginning," said Dabrowski.

"While CETSA can be used to find 'me too' and 'me better' drugs, its sweet spot is working with the targets where there are fewer options—the so-called 'undruggable' or 'difficult-to-drug' targets," Dabrowski added. "These difficult-to-drug targets include protein–protein interactions and more flexible proteins like transcription factors. Because CETSA is label- and tag-free there is no modification to the cell machinery and therefore our data are physiologically and therapeutically relevant."

CETSA has four different formats; CETSA Navigate and CETSA Navigate MS can be used to probe one to ten proteins with many compounds for early feasibility studies, hit confirmation, lead optimization, and translational work (Fig. 1). CETSA Navigate HT is a high-throughput process for library screening, hit confirmation, and lead optimization that can produce up to 100,000 data points per week.

CETSA Explore is a proteome-wide mass spectrometry-based detection method that can look at the systemic effect of a compound on 6,000 to 8,000 proteins in a single experiment.

"When a drug binds to a protein, we can use CETSA Explore to map the pathway and look at the changes in the functional status of the proteins downstream. This allows drug hunters not only to see the binding to the protein of choice, but also how it impacts other proteins in the pathway," said Dabrowski. "We have carried out internal projects to validate our pathway mapping, looking at inflamed peripheral blood mononuclear cells (PBMCs) and comparing their responses to various anti-inflammatory drugs. This allowed us to find a number of new therapeutic nodes and develop screening assays for these targets."

## Pelago's partnership aims

Clients come to Pelago with a variety of questions, for example asking whether the drug, prodrug or probe hits the target, and does it hit the target more effectively than another drug or cause fewer off-target effects.

"During drug discovery, a lot of time is spent on target validation and compound optimisation, but still a lot of projects fail because the compound binding doesn't have the desired effect in physiologically relevant systems. Using CETSA as a selection tool in the lead generation phase builds confidence in both the compounds and the target," said Lundgren.

Many of the failures in phase 2 clinical development are because of a lack of efficacy.

"Because target engagement is a predictor of efficacy, bringing in CETSA from the beginning will mean that rather than axing projects already in development, companies can focus on those candidates that have a better likelihood of making it to the market. In this way, CETSA brings immense value," said Dabrowski. "We want to work hand-in-hand with pharma and biotech. They are the experts on the biology, and we are the experts in validating the target and the hypothesis."

Pelago's aim is to partner with clients earlier in the discovery process, at the hit generation stage, to reduce the failure rate and improve efficacy from the get-go.

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