FAIL EARLY, MOVE FASTER

A practical guide to making confident drug discovery decisions in complex biology

For project leaders navigating high-stakes early discovery in oncology, every decision carries weight. Every delay costs time, money and momentum. The pressure to move forward is constant. The pressure to be right is even stronger.

This guide is designed to help you make earlier, more confident decisions without increasing risk.

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DROWNING IN DATA, STARVING FOR EVIDENCE

Why more data hasn’t made decisions easier

Drug discovery teams are generating more data than ever, with high-throughput screening, AI models, omics datasets and phenotypic readouts. The volume is unprecedented. But more data has not necessarily led to more confidence. We have reached a point in the industry where we are often drowning in data but starving for evidence.

In modern oncology and immunology, we have never had more information at our fingertips, from high-throughput screening to AI-driven modeling. Yet, drug failure rates remain stubbornly high.

Across programs, teams often face the same tension:

- Strong biochemical activity
- Encouraging cell phenotypes
- Clean assay performance…

… but low confidence in what to do next.

The friction is a lack of decision-enabling evidence. When biology gets complex, such as understanding target engagement within a heterogeneous tumor microenvironment, uncertainty creeps in.

To manage that uncertainty, teams often fall into the trap of “analysis paralysis.” They ask for one more assay or one more model, hoping the truth will eventually emerge.

This guide is designed to help you break that cycle. In the following pages, we will explore why failing early isn’t a setback, but a competitive advantage that reduces avoidable risk and restores momentum to your program.

~95%

Of all oncology drug canditates fail during clinical trials

* J. Med. Chem. 2024, 67, 18, 16035–16055

WHY EARLY FAILURE IS SO HARD

The human side of scientific hesitation

Drug discovery feels deeply human. Scientists fall in love with their challenges; they want their solutions to work. When you have spent years researching a specific protein or pathway, walking away feels like a personal defeat.

For a single-asset biotech, “killing” a program can feel like an existential threat. In larger portfolios, it is often a battle of psychology versus resources. Organizations tend to stretch funding to keep a program alive rather than increasing decision density: the number of high-quality, program-altering decisions made per year.

Delay is not dedication. Failing early is a strategic success rather than a failure of science.

But there is a hidden cost to persistence. Every month spent optimizing a weak oncology candidate is a month lost for a potentially life-saving breakthrough. We need to reframe our thinking.

By identifying weak “darlings” and “killing” them sooner, you preserve the most valuable assets you have: time, budget and your team’s focus. This shift in mindset moves you away from fear and toward the confidence of knowing exactly where to place your bets.

Reframe early failure as:

- Risk reduction
- Capital protection
- Portfolio strategy
- A path to momentum

The best organizations don’t avoid failure, but manage it earlier.

THE EARLY DECISION TEST: A SIMPLE FRAMEWORK TO INCREASE CONFIDENCE

Use this practical checklist to evaluate your program's momentum

Before you greenlight the next round of experiments, put your program through this decision test. If you can't answer these questions with confidence, you might be generating data instead of evidence:

1. Does this data change what we do next?
If the result is positive, we move on. If the answer is "no," it's noise. If you say, "We'll just try a different cell line," the experiment is not a decision-maker. Decision-enabling evidence should guide prioritization, not just generate insight. ☐

2. Have we tested engagement in a biologically relevant system?
Are you looking at a purified protein in a tube, or are you seeing the compound bind the target inside an intact, physiological system? Activity without target engagement creates hidden risk. Understanding whether your compound interacts with the intended protein in relevant biology is critical. ☐

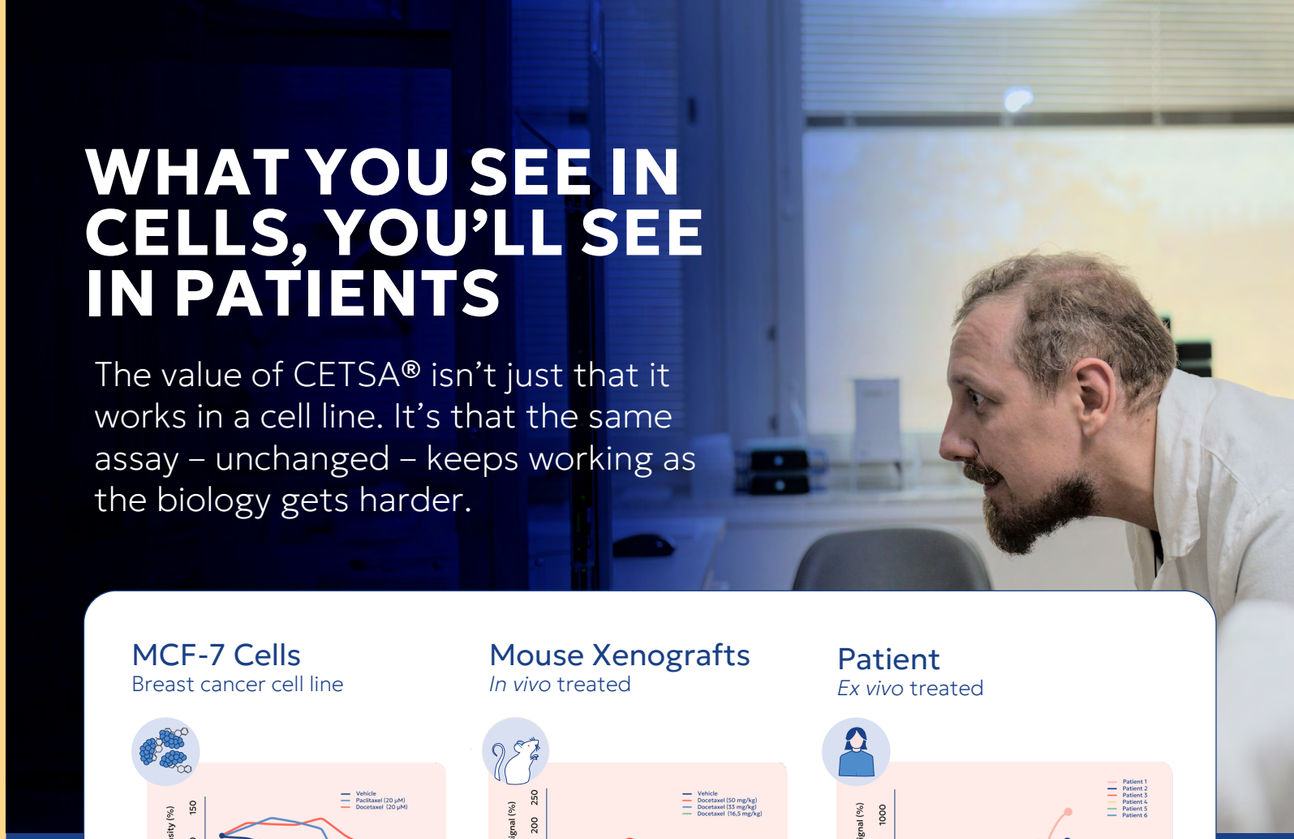
3. What would make us stop?
Have you defined, in advance, exactly what data would make you walk away from this lead? Define failure criteria early. This reduces bias and protects resources. ☐

4. Are we optimizing parameters before validating biology?
Are you spending weeks on potency before you've even confirmed the compound hits the target in the cell? Affinity, permeability and selectivity are important, but they should not replace biological validation. ☐

5. Are we comparing candidates in the same system?
To prioritize, you need a "level playing field" where every candidate is measured by the same yardstick. Comparative evidence is more powerful than isolated datasets. ☐

These questions help shift the focus from experiment density to decision density.

This mindset is especially important in oncology, where complex signaling networks increase the risk of late surprises.



WHAT YOU SEE IN CELLS, YOU'LL SEE IN PATIENTS

The value of CETSA® isn't just that it works in a cell line. It's that the same assay – unchanged – keeps working as the biology gets harder.

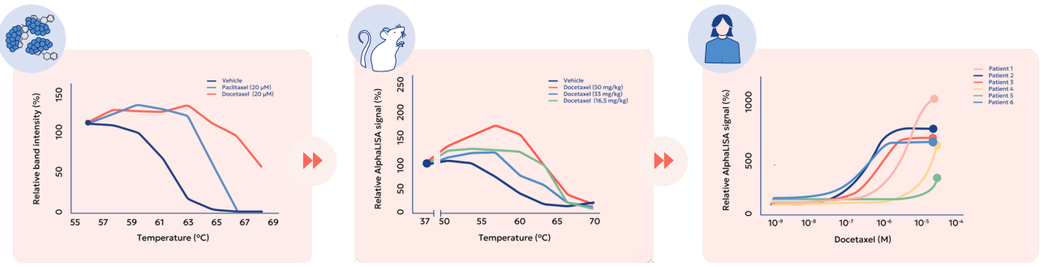


Figure 1. CETSA target-engagement readouts generated using the same assay format in MCF-7 cells, mouse xenografts, and patient tissue. Adapted from Langebäck et al., Scientific Reports (2019) 9:19384.

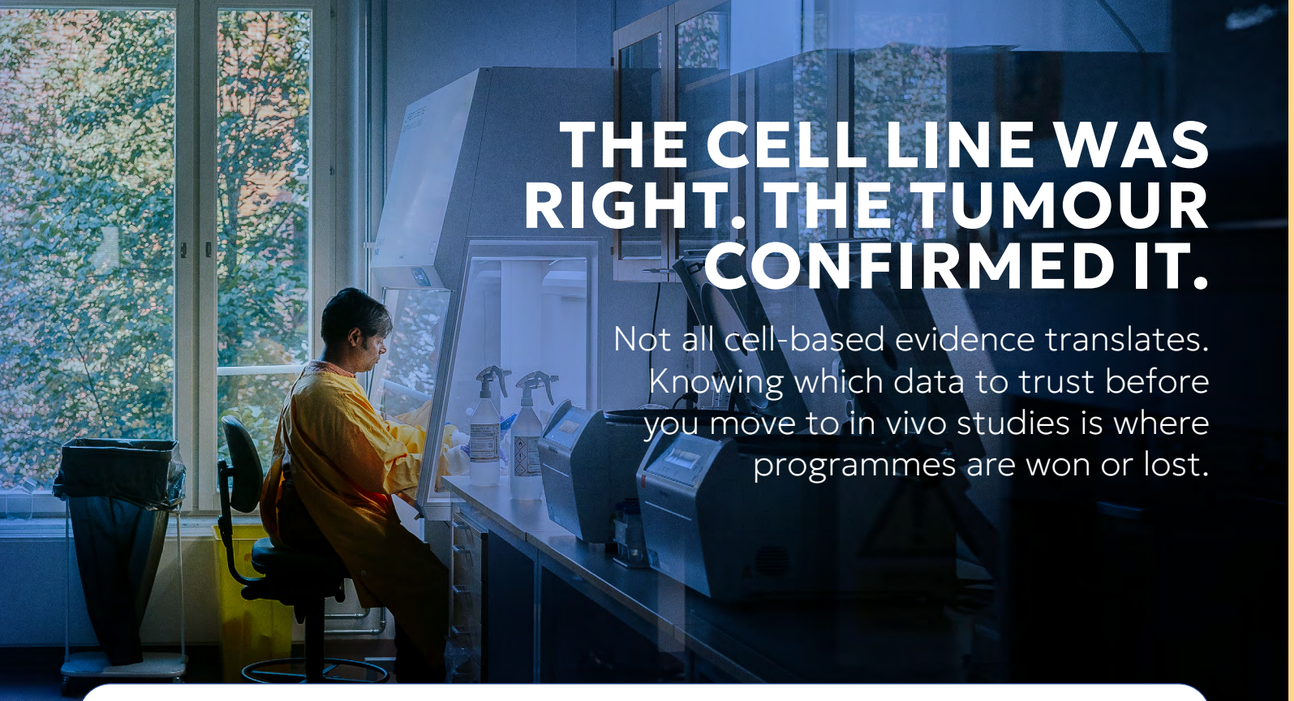
Data that only holds up in a flask isn't data you can make decisions with. The real question is whether your evidence survives contact with increasingly complex biology – and whether you find out early enough to act.

In a breast cancer study published in Scientific Reports (Figure 1), the same CETSA assay was run in a cell line, in mouse tumors, and in tissue taken directly from patients. No modification. No re-validation. The same tool, all the way through.

Because CETSA delivers a readout in minutes rather than days, the samples stayed biologically intact – closer to the original tumour environment than extended culture allows. And the clinical finding was striking: up to a 100-fold difference in drug sensitivity between individual patients, visible at the target engagement level for the first time.

That kind of insight doesn't come from a cell line. It comes from an assay that can actually reach patient tissue.

Learn more about CETSA



THE CELL LINE WAS RIGHT. THE TUMOUR CONFIRMED IT.

Not all cell-based evidence translates. Knowing which data to trust before you move to in vivo studies is where programmes are won or lost.

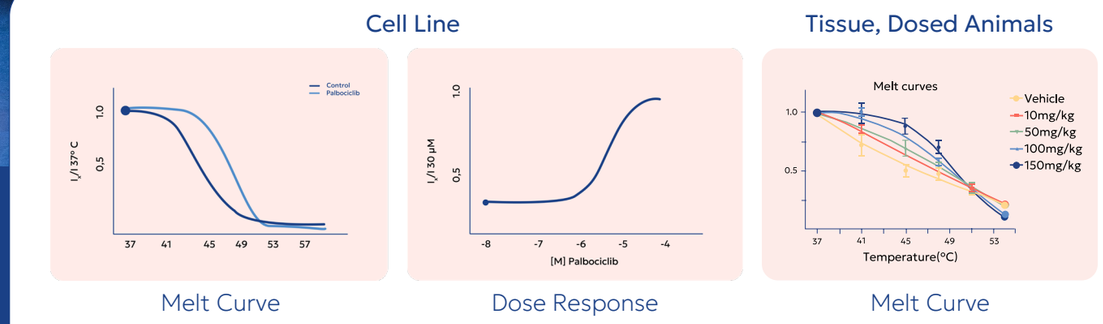


Figure 2. CETSA melt-curve and dose-response data for Palbociclib in intact tumor cells and xenograft tissue from in vivo dosed animals.

In a CDK4 study using the kinase inhibitor Palbociclib – used in a common form of breast cancer – CETSA established clear target engagement in intact tumor cells and then confirmed that signal in xenograft tissue from in vivo dosed animals (Figure 2).

The xenograft data is unambiguous: higher doses, more engagement, all the way up to 150 mg/kg – a clean, concentration-dependent response in real tumour tissue. What the cell line predicted, the tumour confirmed.

The question is never just whether your compound works in a model. It's whether you know before the model stops being enough.

RESPONSIBLE SPEED: THE FAST AND EARLY APPROACH

Why doing the hardest biology first is the fastest way to the clinic.

Speed is often seen as shorthand for compromise. The assumption is that moving faster means cutting corners on detail or depth. But responsible speed is about doing the most relevant experiments as early as possible. In fields like oncology, immunology and neurology, where targets are notoriously difficult, you can't afford to wait for late-stage trials to find out if your biology is right.

Responsible speed means:

- Testing relevant biology earlier
- Reducing reliance on artificial systems
- Validating assumptions before optimization
- Increasing decision confidence

The CETSA advantage
At Pelago Bioscience, we believe the most critical piece of evidence is the moment your compound binds to its target protein.

Our patented CETSA technology allows you to see this binding in:

- Intact systems
- No breaking the cell or stripping away the environment.
- Physiological conditions
- No labels, no tags, no artificial overexpression.
- Translational continuity

The same assay moves with you from cell lines to animal models to primary human tissue, without switching tools or starting again at each stage.

WHAT DOES THIS GIVE YOU?

Eliminating false positives

Identify compounds that look good in simplified systems but fail in live cells.

Actionable windows

Most insights are delivered in a 4–10 week window, with some studies returning results in as little as 10 working days. The level of detail can be scaled to your timeline, fitting perfectly into your decision cycles.

Reduced risk

You are not adding new risk, but uncovering existing risks before they become expensive.

Whether you are working on a novel kinase inhibitor or a complex neuro-target, CETSA provides a versatile tool that bridges the gap between a hypothesis and a clinical candidate.

THE PATH FORWARD

Build on early confidence, not accumulated assumptions.

The goal of drug discovery is not to run experiments; it is to deliver therapies to patients. To do that, we must be willing to face complex biology earlier.

Early clarity preserves optionality
Knowing sooner gives you more strategic choices.

Face complex biology earlier
Avoid false confidence from simplified models.

Decision density matters more than experiment density
Focus on data that drives action.

Reduce avoidable late-stage failure
Every early decision compounds downstream.

The result is not just faster progress. It is stronger alignment, better portfolio prioritization and greater confidence across stakeholders.

At Pelago Bioscience, we provide the evidence you need to lead your program with conviction.

Ready to see the potential in your program?

Talk to our scientific team about applying this framework to your current targets.

Let's find the evidence that moves you forward.

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