Why Promising Compounds Still Fail: Improving Translatability Earlier in Drug Discovery

San Diego, California Sep 10, 2026 (Issuewire.com**)** - Some compounds seem highly promising in early discovery, showing strong activity against the target and performing well in an initial assay. They quickly become the focus of an optimization program.

However, that early promise doesn't always pan out as testing advances. A molecule that performs well in a biochemical or cellular assay may behave very differently once exposure, cell permeability, intracellular localization, target abundance, protein turnover or toxicity come into play. This gap between early activity and performance in more realistic biological systems remains a persistent challenge in drug discovery.

Potency Is Only Part of the Pharmacological Picture

A molecule can be highly active against its target and still have poor solubility, weak pharmacokinetics, metabolic instability, inadequate selectivity or other liabilities. When potency becomes the dominant measure of progress, those issues can receive attention too late.

Discovery teams are therefore looking at a wider set of pharmacological characteristics earlier in the

process. Binding kinetics and the duration of target engagement, for example, can provide information that a potency value alone cannot. A highly potent compound may be less attractive if its interaction with the target is too transient or if engagement is not sustained in a relevant biological context.

Biomarker planning can provide another useful perspective. Thinking about biomarkers during discovery can help teams consider how they may determine whether the intended mechanism is operating in vivo and, later, in patients.

The result is a different approach to optimization. Potency is considered alongside selectivity, drug metabolism and pharmacokinetics (DMPK), absorption, distribution, metabolism and excretion (ADME) properties, exposure, target engagement and safety signals.

Trade-offs are unavoidable. A compound with somewhat lower potency may still be the better choice if it provides stronger exposure, more durable target engagement or a cleaner overall profile. Additional gains in potency may have limited value if important liabilities remain.

Multiparameter optimization gives medicinal chemists a way to evaluate those properties together. It also provides a more realistic basis for deciding which compounds deserve further work.

Better Models Can Reveal Problems That Simple Assays Miss

A biochemical assay can establish whether a molecule interacts with its intended target, but it can't reproduce everything that influences pharmacology inside a cell, tissue or organism.

These differences matter as testing moves into more physiologically relevant systems. Cell permeability may determine whether enough compound reaches an intracellular target. Target abundance and protein turnover can influence the duration of a response. Exposure, tissue environment and toxicity can alter behavior that looked straightforward in an earlier assay.

The challenge can be even greater with newer modalities. Targeted protein degraders depend on more than target binding. Antibody-drug conjugate (ADC) payloads bring additional considerations related to delivery, intracellular behavior and biological context. As discovery chemistry expands beyond conventional small molecules, teams need evidence that a mechanism continues to work as the biological model becomes more realistic.

More sophisticated models provide that evidence, but they also produce more complicated data sets.

A modern discovery program may need to consider biological activity, selectivity, target engagement, ADME-related properties and other measurements at the same time. Generating the data is only part of the job. Teams must also decide which findings are important enough to change the next experiment.

That puts greater value on how quickly information moves between chemistry and biology.

Shortening the Distance Between an Experiment and the Next Decision

Drug discovery is often described as a design-make-test cycle. In practice, design, synthesis and testing can still occur in relatively separate workflows. Chemists make compounds, biology teams test them, and the results return to chemistry for the next round of design.

When that feedback takes too long, the next chemistry cycle may already be underway. An important

result can arrive after the team has made another set of design decisions.

Closer integration makes the data more useful while there is still an opportunity to act. If testing reveals poor permeability, unexpected biological behavior, weak target engagement or an ADME liability, chemists can investigate the finding in the next design cycle rather than several cycles later.

Direct-to-Biology workflows are one way to tighten this connection by linking compound design, synthesis and biological testing more closely. Faster testing is useful, although speed alone isn't the point. The larger benefit comes from allowing new chemical and biological information to influence what scientists make next.

Tao Guo, Ph.D., senior vice president, Research Chemistry Services, Integrated Program Management, at WuXi AppTec, has described medicinal chemistry as becoming more involved from the beginning of discovery programs. Chemists and biologists collaborate on target hypotheses, validation and experimental design. This allows chemical feasibility and biological understanding to develop together, making it easier to recognize when the evidence for a chemical series is weakening.

Know When a Chemical Series Is Telling You Something

Deciding what to stop can be as important as deciding what to advance. The quality of the chemical matter entering a program has a direct effect on those decisions. A larger screening library doesn't necessarily provide better starting points. Diversity, relevance and compound quality help determine what chemists have available once hits move into optimization.

Several chemical series may initially appear promising, and potency can make one stand out early. As ADME, exposure, selectivity and other information accumulate, rankings can change.

Persistent liabilities deserve attention. Repeated problems with solubility, metabolism, exposure or selectivity may indicate that a series has limitations that another round of chemistry is unlikely to resolve.

Rapid triage can help teams identify that pattern earlier. Higher-quality library design, multiparameter optimization and earlier testing provide a broader evidence base for deciding whether continued exploration is justified.

These decisions affect more than efficiency. A compound that advances must also withstand a different set of practical demands as it approaches development.

Better Translatability Starts Before Development

No assay or technology can predict with certainty whether an early discovery compound will become a successful drug. Discovery teams can, however, learn more about the risks before large amounts of time and resources are committed.

A strong potency result needs to be considered in the context of the molecule's wider pharmacological behavior. Mechanisms need to hold up in increasingly relevant biological systems. New findings need to reach the scientists making the next design decision while those findings can still influence the program.

There is also a practical side to translatability. Process feasibility and scalability have traditionally received more attention after candidate selection. Earlier consideration of these factors can reveal compounds that may be difficult to synthesize, purify or manufacture reproducibly.

A molecule can therefore look promising by the standards of an early experiment and still be poorly suited for what comes next.

Improving translatability depends on recognizing those gaps sooner. Better information, interpreted at the right point in the discovery process, gives teams more opportunity to improve a compound, change direction or move resources to a stronger chemical series.

The question is ultimately broader than whether a compound performs well in the experiment in front of us. What matters is whether the evidence continues to support its path toward a viable medicine.

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