Moving Beyond Selection:

How to Make DEL Screening Generate Progressable Hit Matter

Exploring the quantitative and biological factors that determine whether DEL selection outputs translate into meaningful discovery decisions.

ZOBIO SELECTION.STRUCTURE.SUCCESS.

The Expanding Role of DNA-Encoded Libraries in Drug Discovery

DEL technology came about from the drive to screen ever larger collections of molecules to discover the "ideal" drug starting point. This motivation persists with current libraries theoretically including over 1 trillion compounds. However, at ZoBio, we don't think it's a question of Quantity, rather, it's more about the Quality of the hits a DEL screen delivers. Can you orthogonally confirm a hit? Can you elucidate the 3D structure of the DEL hit bound to the target?

We have developed an integrated strategy that starts with your goals and turns them into progressable, structurally enabled starting points for your most challenging targets.

Gregg Siegal, CEO

In this paper:

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Hit Quality vs Hit Quantity

Many of today's discovery programs focus on targets that do not behave like traditional enzyme systems. Protein–protein interactions, transient complexes, and shallow binding surfaces often lack the well-defined pockets that conventional small molecules prefer.

Fragment-based drug discovery is still one of the best ways to probe these systems. However, fragments typically form only a limited number of interactions with the target, resulting in weak binding that can complicate progression and structural characterization.

DELs complement fragments well because larger molecules can establish broader interaction networks across the target surface. The increased number of interactions increases the likelihood of identifying ligands with meaningful affinity, particularly in difficult systems. Moreover, the entire DEL can be screened in "1 pot", making it fast and efficient. However, expanding library size also introduces greater complexity which can lead to a situation where you are overwhelmed with "hits" but don't have a high level of confidence in them and lack the resources to comprehensively test them.

If you cannot confidently distinguish genuine binders from artifacts, even the largest DEL campaign becomes difficult to progress.

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Where DEL campaigns fall short

DEL workflows often appear straightforward on paper: immobilize the target, perform the selection, sequence enriched compounds, and identify hits. However, consider a scenario in which the immobilized protein partially denatures during preparation. In such a case, the DEL selection may yield hits that preferentially bind to misfolded or inactive protein conformations, rather than the intended functional target. This concrete example illustrates how underlying biology can compromise the meaningfulness of the output and potentially yield false or misleading results.

If your protein loses functionality during immobilization, if the target complex does not fully form, or if only a fraction of the protein remains available for binding, the selection signalt quickly becomes difficult to interpret. This becomes especially important when you want to identify compounds with a specific mechanism of action.
Imagine you want to identify compounds that compete with a known binding partner. You perform selections in the presence and absence of that partner and compare enrichment patterns between conditions.

The logic sounds simple.

But what happens if the partner concentration does not fully saturate the target? Or if the immobilized target only partially retains activity? In that case, the sequence output no longer reflects the biology you intended to study.

1

Competitive binders may appear absent.

2

Artifacts may appear enriched.

3

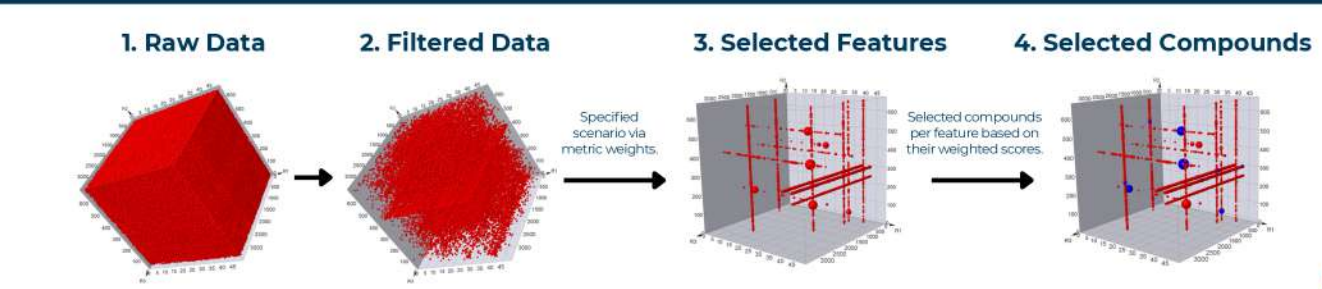
Valuable chemistry may be lost in noisy datasets.

Without a quantitative understanding of occupancy and interaction behavior before screening begins, you risk misinterpreting the entire experiment. Increasing the size of selection outputs does not resolve this issue; improved experimental control is required.

Why quantitative understanding changes outcomes

At ZoBio, DEL screening commences well before library selection by establishing a quantitative understanding of the biological system, an approach supported by best practices outlined in recent literature.

This process utilizes carefully characterized, crystallography-grade protein, together with surface plasmon resonance (SPR) and complementary biophysical techniques. Such rigor enables a precise definition of affinity, occupancy, saturation behavior, and target engagement prior to initiating the DEL experiment, thereby increasing the reliability and interpretability of subsequent screening results. That information dramatically changes the quality of the selection.



Instead of relying on assumptions about target behavior, you can optimize selection conditions around measured interaction data. You can ensure fully saturated complexes during screening while avoiding unnecessary consumption of valuable binding partners. You can probe competitive or allosteric mechanisms with significantly greater confidence because you understand how the biological system behaves before the selection begins.

Most importantly, you can interpret enrichment patterns in thecorrect biological context. This quantitative framework also enhances downstream decision-making. The in-house analysis platform enables interactive interrogation of selection outputs, facilitating collaborative evaluation of hits, adaptation of selection strategies, and refinement of progression decisions throughout the campaign.

So, instead of a ranked list of compounds, this approach provides a clearer understanding. Especially, which hits are significant, the reasons for their relevance, and their alignment with the overall discovery strategy.

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Benefits of integrated DEL workflows

An ideal DEL workflow integrates protein science, quantitative biophysics, DEL selection, orthogonal validation, and structural biology. That continuity matters because every stage of the campaign influences the next. Working with ZoBio means the same small scientific team remains involved throughout the project, allowing detailed knowledge of protein stability, functionality, assay behavior, and binding interactions to be transferred directly from one stage to the next rather than being lost across disconnected workflows.

1. We use the same carefully characterized protein(s) across assay development, DEL selection, and structural studies. That consistency significantly improves the transition from hit identification to structural characterization.

2. After selection, we analyze enrichment patterns using our interactive analysis platform and prioritize compounds for off-DNA synthesis and validation.

3. We then confirm binding using orthogonal biochemical and biophysical assays to remove artifacts and strengthen confidence in the data.

4. Validated hits progress directly into structural studies, including X-ray crystallography, where you can visualize binding modes, evaluate mechanisms of action, and guide optimization strategies.

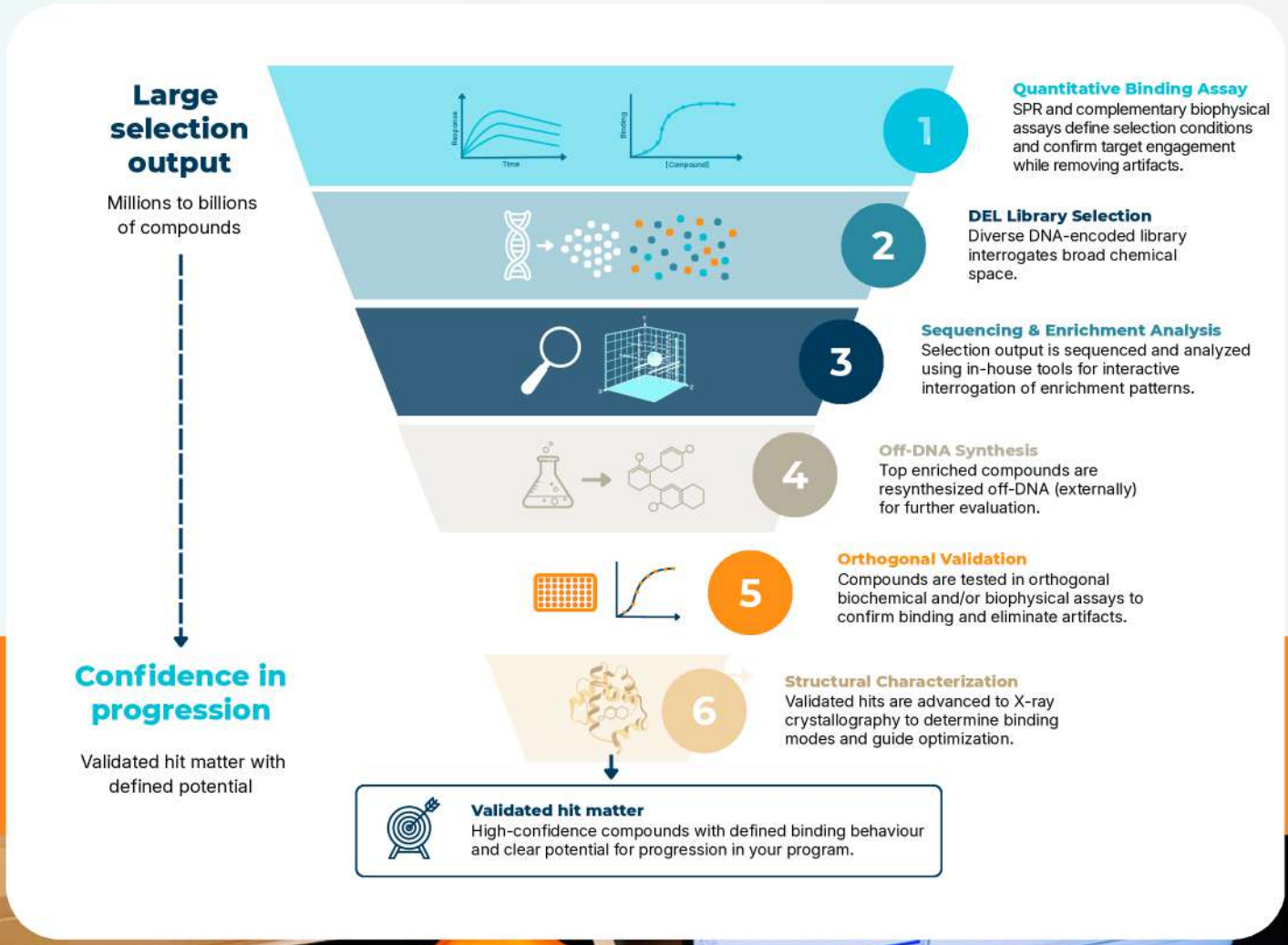
5. Where necessary, we also reassess binding behavior under crystallography conditions to maximize the likelihood of obtaining structurally informative complexes.

By integrating these stages from the start, you reduce disconnects between screening, validation, and structural interpretation. More importantly, you increase the likelihood that the resulting hit matter can actually progress.

From selection output to progressable hit matter

DEL screening continues to gain momentum in modern drug discovery and has already led to compounds entering clinical development. That success reflects the power of DEL technology. But technology alone does not generate progressable hit matter.

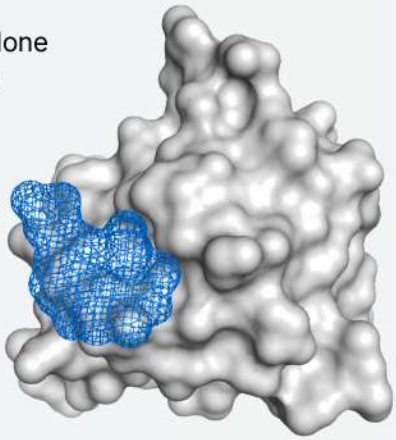
Robust protein science, quantitative understanding, integrated validation, and structural insight remain essential for accurate hit interpretation and confident program advancement. At ZoBio, we built our DEL approach around that reality. Rather than focusing solely on library scale or selection throughput, our approach emphasizes generative hits with defined mechanisms to support meaningful progression decisions.



From selection output to progressable hit matter

DEL screening continues to gain momentum in modern drug discovery and has already led to compounds entering clinical development across target classes, including kinases, methyltransferases, protein–protein interactions, and molecular glues.

That success reflects the power of DEL technology. But technology alone does not generate progressable hit matter. Structural characterization remains essential for understanding how validated DEL hits interact with their target proteins and for supporting progression decisions with greater confidence.



The crystal structure shown here illustrates a validated DEL-derived hit bound to its target protein, providing direct insight into binding mode and mechanism of action.

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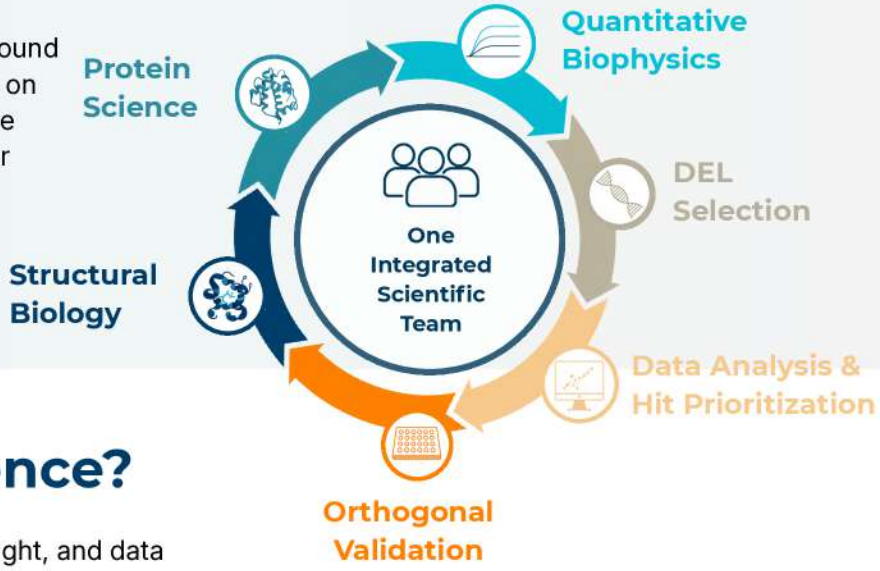

The ZoBio Difference?

Biological knowledge, experimental insight, and data flow seamlessly across the entire workflow.

Discuss your DEL strategy with ZoBio

If you want to explore how DEL screening fits your target, mechanism of action, or broader discovery workflow, our team is happy to discuss the scientific and strategic considerations behind a successful campaign.