CellarisBio

PRODUCT WHITE PAPER

MICRO-TAG® Cellular DNA-Encoded Library (DEL) Discovery Kit

Product Number: Cell-DEL-200

MICRO-TAG® Technology Overview

MICRO-TAG® is a fluorescence-based cellular target engagement platform built on split RNase S enzyme complementation. A short, minimally perturbing peptide tag fused to the target protein enables conditional enzyme reconstitution only when the target remains folded and soluble following thermal challenge. Enzymatic cleavage of an RNA FRET substrate provides amplified, quantitative detection of intracellular target engagement, enabling direct coupling of **Cellular DEL selection** with **real-time cellular engagement readouts**.

Product in Snapshot

MICRO-TAG® Cellular DEL Kit enables:

- Cell-first DNA-Encoded Library discovery under physiologically relevant conditions
- Thermal stress–guided enrichment of intracellular binders
- Real-time monitoring of target engagement during DEL workflows
- Fluorescence-based detection on standard real-time instruments

Designed specifically for:

- Challenging and intrinsically disordered drug targets
- Targets incompatible with purified protein or biochemical DEL formats
- Discovery of binders exhibiting durable cellular engagement

Core value:

- Couples DEL enrichment directly to cellular target engagement
- Enriches for persistent, not transient, binders
- Removes bias introduced by acellular or affinity-only selections

---

Why Cellular DEL + MICRO-TAG

Conventional DEL selections are typically performed against purified proteins or immobilized domains, which often fail to recapitulate native folding, post-translational modification, or multiprotein context. Many high-value targets—such as transcription factors, chromatin regulators, and GPCRs—only exist in their functional form inside cells.

The MICRO-TAG® Cellular DEL workflow enables parallel DEL selections under controlled thermal stress, enriching compounds that maintain intracellular engagement across destabilizing conditions.

Target engagement is continuously monitored using MICRO-TAG® fluorescence readouts, ensuring that DEL hits correspond to true cellular binders rather than biochemical artifacts.

Enzyme Complementation Chemistry and Signal

Detection chemistry:

- Split RNase S enzyme complementation
- 15-aa hydrophilic S-tag fused to the target protein
- Designed to minimize perturbation of native structure

Thermal behavior:

- Folded target → tag accessible → enzyme complements → high fluorescence
- Aggregated target → tag buried → no complementation → low fluorescence

Signal generation:

- Complemented RNase cleaves RNA FRET substrate
- Enzymatic amplification yields high signal-to-noise
- Multiple donor–quencher FRET pairs supported

Cellular DEL Temperature-Guided Workflow

Workflow summary:

- Cells expressing S-tagged target are prepared under non-denaturing conditions
- DNA-Encoded Library is introduced into intact cells or lysates
- Parallel selections are performed under defined thermal stress conditions
- MICRO-TAG® signal confirms target folding and engagement prior to enrichment
- Bound DEL members are isolated, sequenced, and analyzed

Thermal selection logic:

- Controlled temperature ramping destabilizes weak or nonspecific binders
- Persistent binders remain engaged and enriched
- Selection favors compounds with durable intracellular engagement

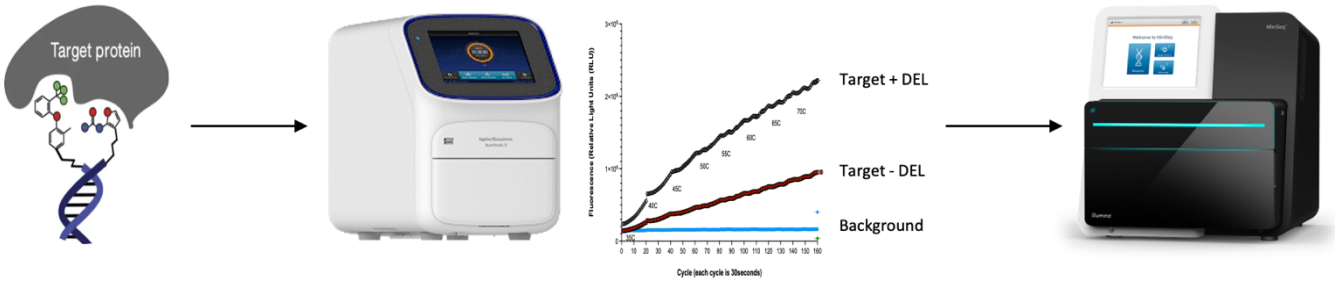

Figure 1. MICRO-TAG–enabled Cellular DEL workflow. Cellular material expressing an S-tagged target are incubated with a DNA-Encoded Library under controlled temperature conditions. Target engagement is verified by MICRO-TAG® fluorescence prior to enrichment, followed by barcode amplification and sequencing of retained library members.

Real-Time Detection and Instrument Compatibility

Compatible platforms:

- Applied Biosystems QuantStudio™ real-time systems
- Other programmable real-time PCR instruments with fluorescence detection

Practical benefits:

- No specialized DEL or biophysical instrumentation required
- Compatible with 96- and 384-well formats
- Scalable, automatable, and HTS-ready

Quantitative Outputs

Supported readouts:

- Real-time fluorescence engagement curves
- Area-under-the-curve (AUC) across thermal conditions
- Per-temperature and aggregate engagement metrics

Why this matters:

- Enables early prioritization of DEL hits by cellular engagement
- Discriminates transient vs persistent binders

- Accelerates triage before medicinal chemistry investment

Therapeutic Modalities Supported

Compatible with most small-molecule modalities, including:

- Reversible inhibitors
- Covalent inhibitors
- Allosteric modulators
- Molecular glues
- Targeted protein degraders (PROTACs and related bifunctionals)
- Stabilizers and neo-interaction inducers
- Fragment-derived and chemically diverse small molecules

Target Classes Supported

The MICRO-TAG® Cellular DEL Kit is specifically tuned for challenging and intrinsically disordered targets, including:

- Transcription factors (e.g., β-catenin, MYC, STAT family)
- Membrane proteins (e.g., GPCRs and other multi-pass receptors)
- Kinases and pseudo-kinases (e.g., KRAS and signaling-associated kinases)
- Structural and scaffolding proteins
- Chromatin-associated and multiprotein complex components
- Other non-traditional or difficult-to-purify protein classes

---

Kit Components

Included:

- DNA-Encoded Library (standard medium-diversity & complexity) (25nmol)
- Real-time–optimized RNA FRET substrate (200µl)
- S-protein enzyme complementation reagent (200µl)
- Positive control target plasmid (10µg)
- Inhibitor for positive control target (10µl, 10mM DMSO stock)
- Assay buffers
- Primers for DEL barcodes

Not included:

- Drug target construct (ordered separate from CellarisBio website)

Variable:

- Custom target constructs - plasmid or stable cell line
- Custom DNA-Encoded Libraries

Expandable:

- Compatible with multiple DEL chemistries
- Custom target constructs and stable cell lines available

DEL Sequencing and Data Analysis

Following cellular DEL enrichment, deep sequencing and downstream data analysis can be performed either independently by the user using in-house or third-party sequencing capabilities, or by CellarisBio as a fee-for-service offering, including library preparation, sequencing, hit calling, and data interpretation.

Applications

- Cellular DEL hit discovery and optimization
- Discovery campaigns for undruggable targets

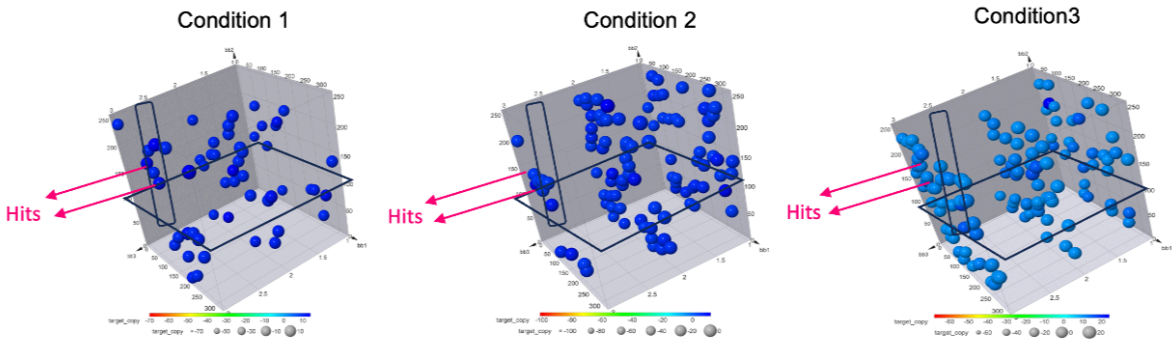

Figure 2. Temperature-guided Cellular DEL enrichment. Thermal challenge enriches library members that maintain intracellular target engagement while depleting weak or nonspecific binders. Enrichment profiles across temperature conditions enable prioritization of compounds with durable cellular engagement.

Summary

The MICRO-TAG® Cellular DEL Kit integrates DNA-Encoded Library discovery directly with real-time cellular target engagement. By enriching compounds under thermal stress and validating engagement in native cellular contexts, the platform enables discovery of durable, mechanism-relevant binders for the most challenging drug targets.

Protocols

www.cellarisbio.com/protocols

References

Babic et al. *Real-Time Cellular Target Engagement Using MICRO-TAG Technology.* SLAS Discovery (2026).