

WuXi AppTec HTS 2.0 Platform to Advance Molecular Glues Drug Discovery

Tiantian Jin, Naifu Zhang, Shiyao Sun, Hao Chen, Zuyuan Shen, Xiaoming Miao, Weihui Guo, Wenji Su,
Discovery Biology Platform, WuXi Biology, WuXi AppTec

WuXi Biology

Molecular Glues (MGs) Drug Discovery

Emerging interest and evidence have revealed molecular glues (MGs) as promising drug candidates by the capability to induce protein proximity and enhance existing protein-protein interaction. Therefore molecular glues show extensive market prospect by improving druggability of previously intractable targets, in both degradative and non-degradative scenarios. However the challenge of molecular glues drug discovery remains, mainly because of lacking rational design. In this presentation, we will summarize the WuXi AppTec's hit finding capabilities and demonstrate how this comprehensive platform can significantly accelerate the process of molecular glues drug discovery.

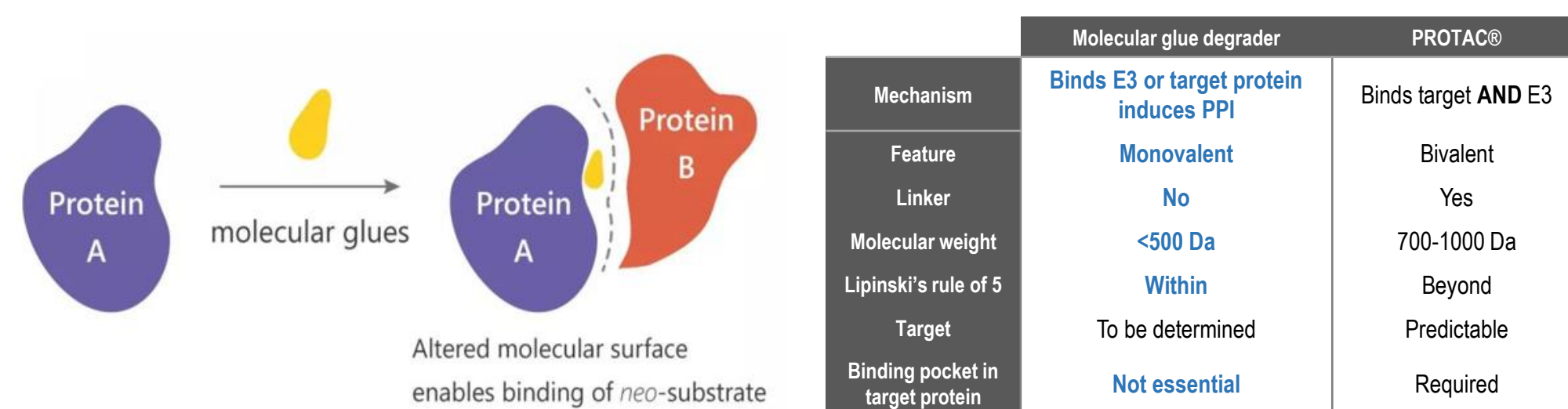


Figure 1. Mechanism and Features of Molecular Glues

Diversity Library and Focused Subset

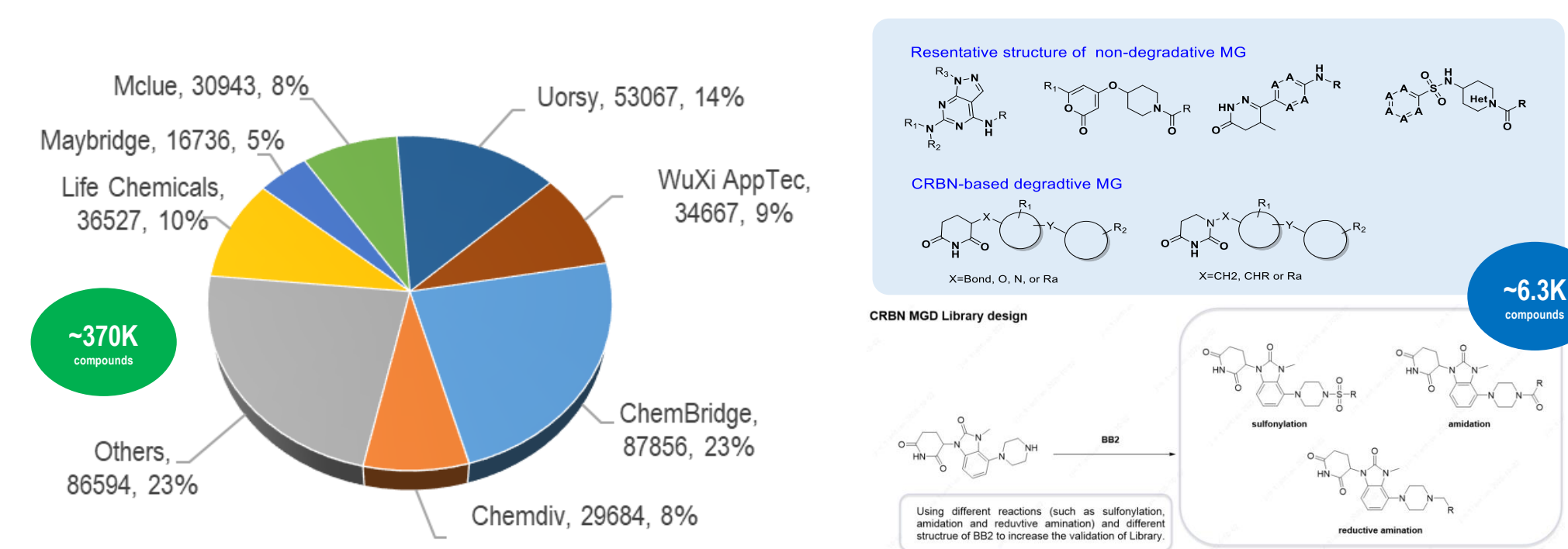


Figure 2. Upgraded 370,000+ Diversity Small Molecule Library and New Molecular Glues Focused Libraries: Left: Most MGs hit finding relies on diversity screen. A carefully curated collection with enhanced chemical diversity and drug-like properties to improve hit identification. Right: Focused MGs library is an alternative screening strategy. We included specifically designed CRBN-targeting molecular glues, focusing on increasing structural diversity to enhance the potential for protein degradation.

One-stop HTS Platform for MGs Hit Finding

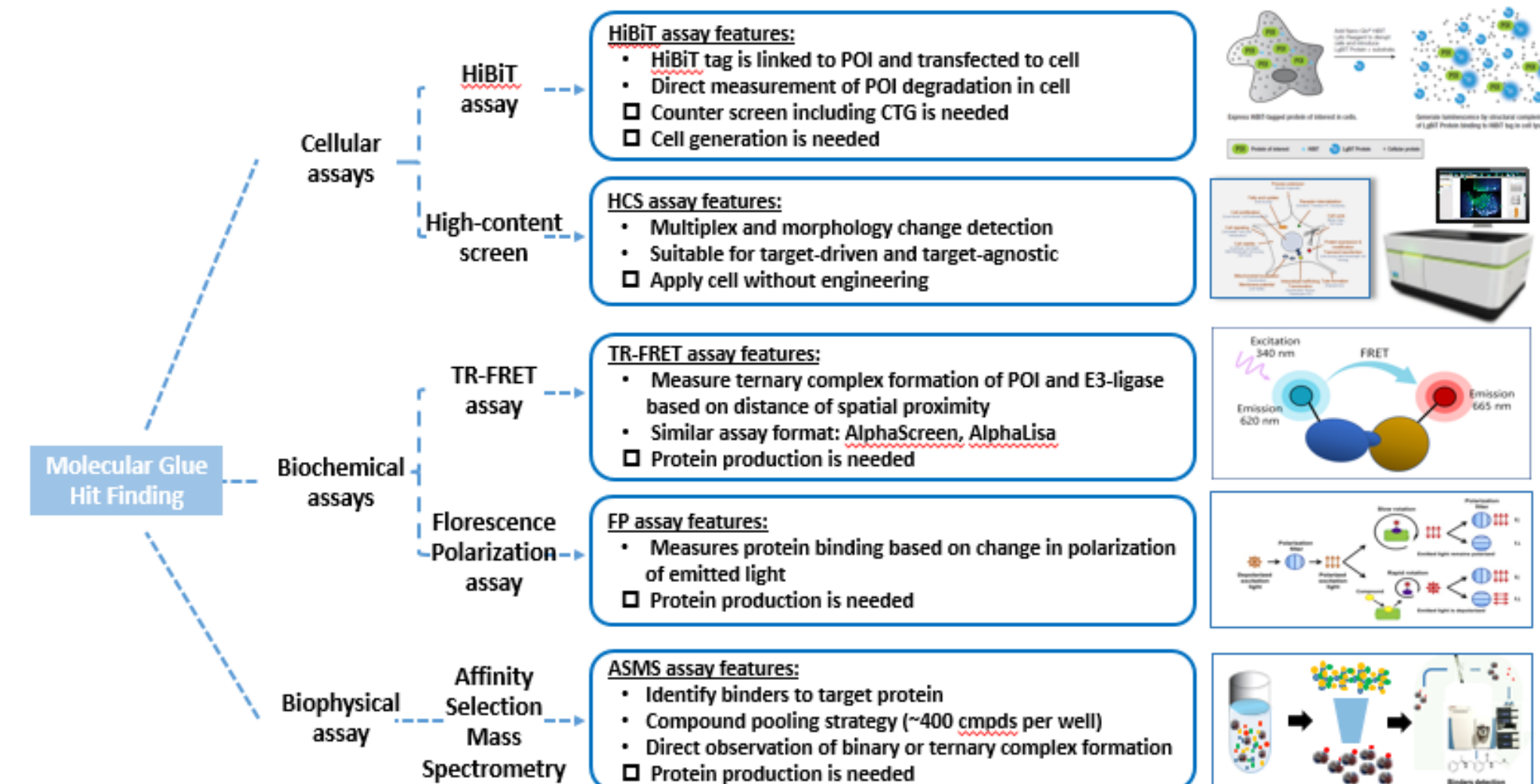


Figure 3. Various HTS Assays for MGs Hit Finding: A comprehensive MGs hit finding assay platform -- covering cellular assays, biochemical assays and biophysical assays -- ensures the identification of tractable MGs starting points from different study rationales.

MGs HTS: From Serendipitous to Rational Screen

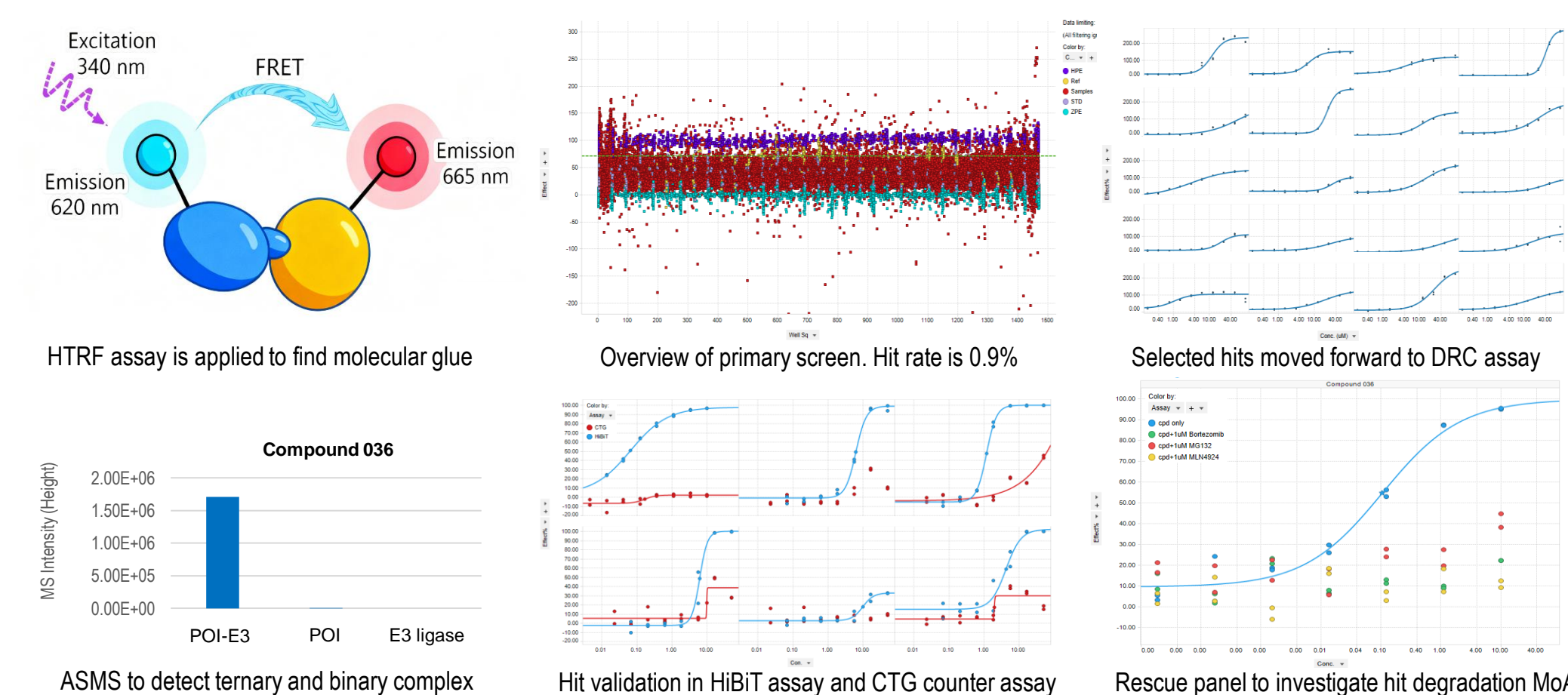


Figure 4. First-in-class POI-E3 Ligase Molecular Glue Hit Finding Campaign: Screening assay was performed using biochemical HTRF technology to detect ternary complex formation. Primary screen was conducted in 1536-w format and hit rate is ~0.9%. Selected hits moved forward to SD hit confirmation and DRC hit confirmation to reach EC50. ASMS as secondary assay to measure binding affinity. Further cell-based HiBiT screen and cell viability counter screen were applied to validate cmpd function activity and filter out false positives. Refined hits were further examined in rescue panel to investigate degradation MoA.

D2B: Solution to MGs Hit to Lead Discovery

'Direct-to-biology' (D2B), a cost and time-effective approach to empower TPD molecule discovery, small molecule and peptide optimization and rapid SAR exploration.

The D2B platform integrates the capabilities of WuXi AppTec's MedChem, HTC, HTS, and CADD teams, offering a comprehensive service and streamlining the iterative design-make-test cycles by directly testing high throughput synthesized compounds biologically, with a typical turnaround cycle of about only 2-3 weeks.

Integrated Direct to Biology (D2B) Platform

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|------------------|--|-------------------|---|
| Scenarios | <ul style="list-style-type: none">TPD Molecule DiscoverySM/Peptide OptimizationSAR Exploration | Highlights | <ul style="list-style-type: none">Rapid Decision-MakingCost-EffectiveTime-Effective |
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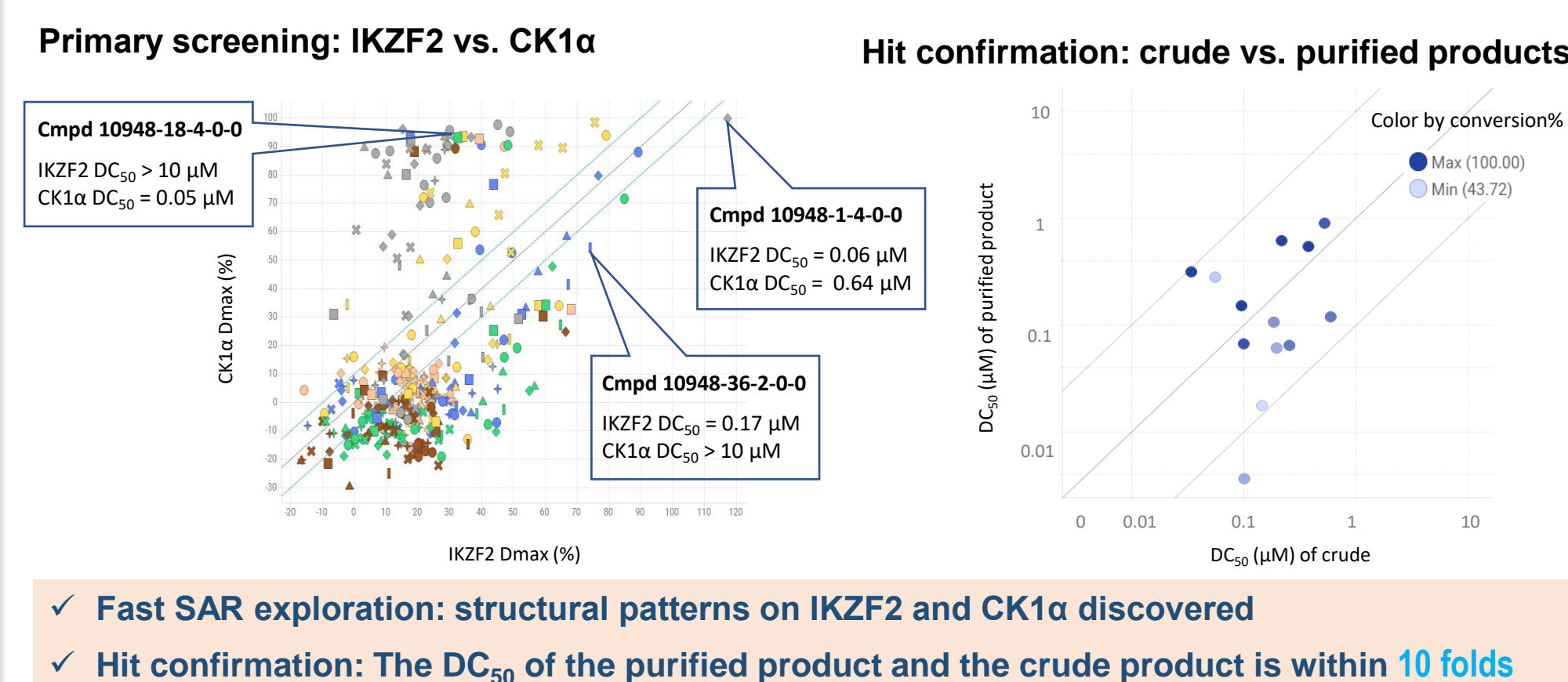
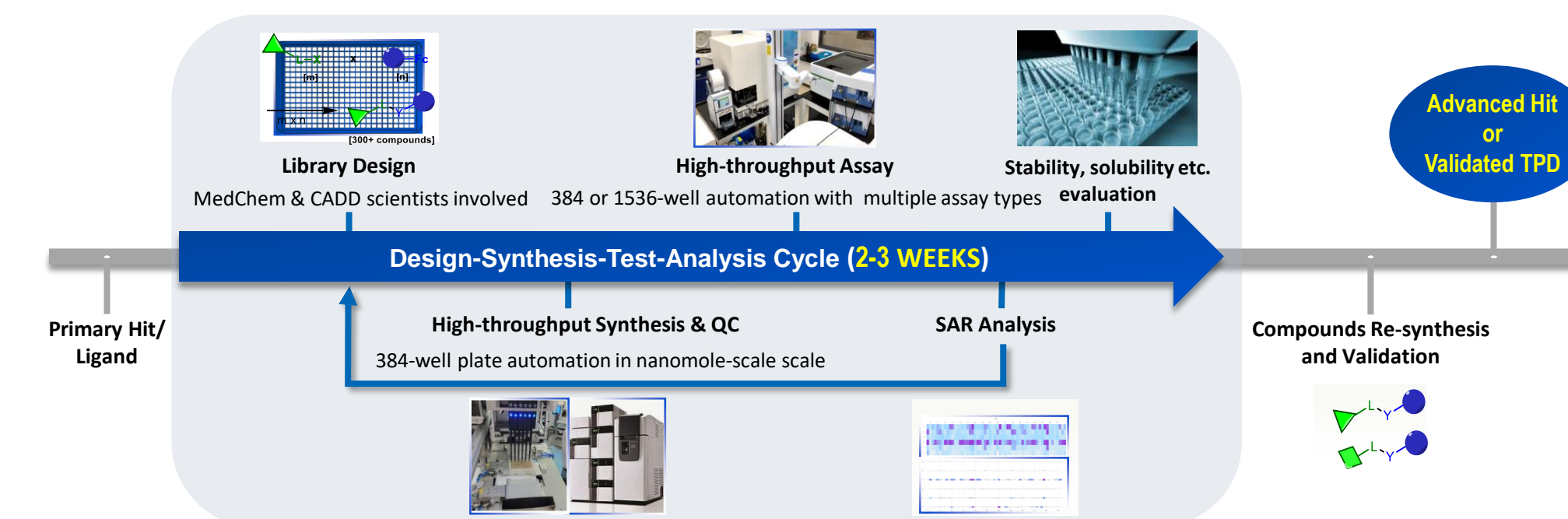


Figure 5. D2B compound Cellular HiBiT Degradation Test

Summary

In WuXi AppTec HTS 2.0 platform, we aim to provide an integrated solution to quickly identify validated molecular glue hits, and then enable a seamless design-make-test cycle using D2B technology to profile the hits and accelerate molecular glue drug discovery.