Fully Automated High-Throughput Screening Platform Enables Robust and Scalable Assay Execution Across Diverse Target Classes

WuXi Biology

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Abstract

High-throughput screening (HTS) remains a foundational technology in early drug discovery, responsible for identifying approximately one-third of today's clinical candidates. As therapeutic targets become more complex, the demand for HTS platforms that combine high capacity with scientific flexibility continues to grow. We present a fully automated HTS platform, built within a biosafety level 2 (BSL-2) laboratory, enabling safe and efficient processing of immortalized cell lines, primary cells, and clinical samples. The system integrates robotic liquid handling, plate storage/incubation, and multimodal detection, supporting both endpoint and kinetic assays in 384- and 1536-well formats.

This platform has been deployed across diverse target classes—including kinases, SERPINs, RNA helicases, and GPCRs—using assay types such as ELISA, RT-qPCR, ASMS, fluorescence, luminescence, and absorbance. All assays have been screened using the WuXi 370k small-molecule library in our upgraded HTS 2.0 workflow, representing a 100k increase in compound collection size and a 20% boost in chemical diversity through novel scaffolds. With fully automated orchestration of dispensing, incubation, and detection, we consistently achieve high Z'-factors and low variability, enabling robust and reproducible hit identification. These capabilities position our HTS platform as a scalable, data-driven engine for accelerating early-stage drug discovery.

HTS 2.0: Expanded Small Molecule Library and Fully Automated Screening Platform

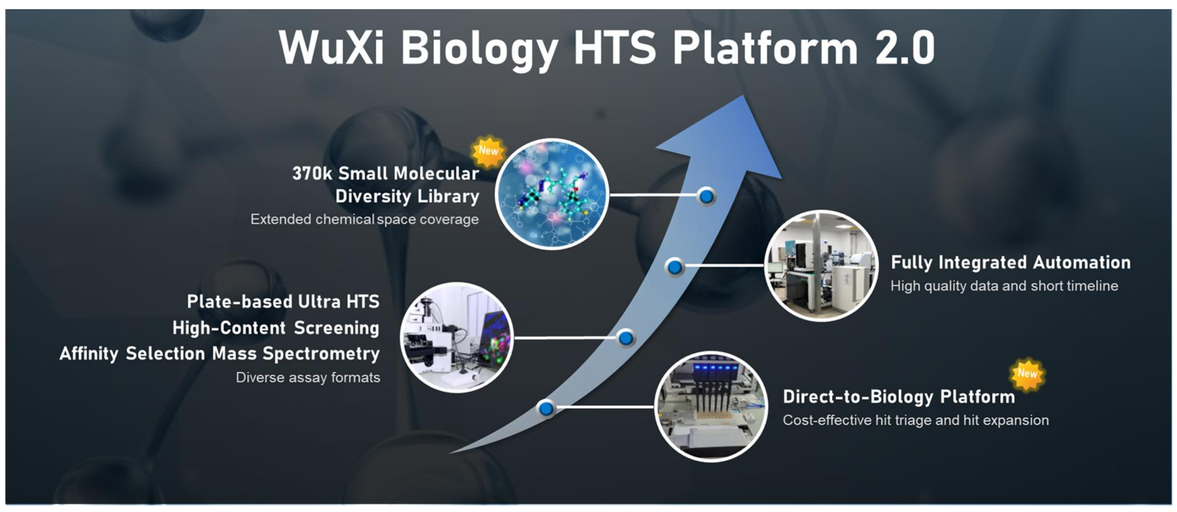


Figure 1. HTS 2.0 Platform Promotion

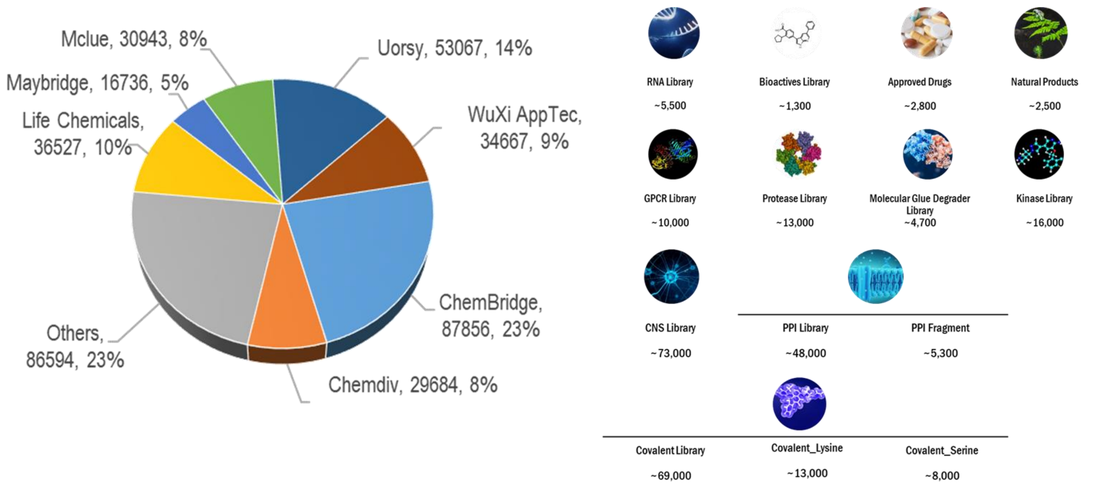


Figure 2. Upgraded 370,000+ Diversity Small Molecule Library and New Focused Libraries: A carefully curated collection with enhanced chemical diversity and drug-like properties to improve hit identification.

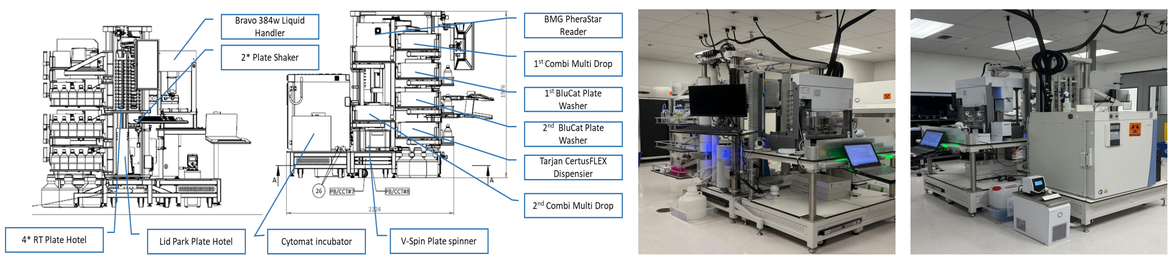


Figure 3. HTS Integrated Fully Automated System: An integrated platform combining robotic liquid handling, plate washing, incubation, and multimodal detection. This automation enables continuous assay processing with improved consistency and approximately 50% higher throughput compared to manual operations.

References

1. Rácz, A., Mihalovits, L.M., Beckers, M. et al. *The changing landscape of medicinal chemistry optimization*. Nat Rev Drug Discov (2025). https://doi.org/10.1038/s41573-025-01225-1

370k ASMS HTS showcase

Target Info

Target X is an RNA helicase that is important for nuclear export of spliced and unspliced mRNA. We have set an ASMS screening for target X inhibitor hit finding.

Work Flow

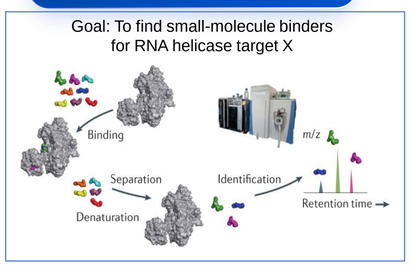
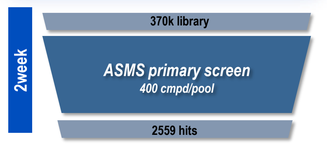


Fig 1. Affinity Selection-Mass Spectrometry (ASMS) Screening Workflow.
ASMS is a binding diagnosis HTS method for hit finding.

Screening Campaign



Primary Screen

The primary screen was carried out successfully with a hit rate of 0.68%. The next step will be hit confirmation with fewer compounds in a pool.

	Mix	Pool number	Library	Hit number	Hit rate
ASMS (370k)	400 cmpd	937	374422	2559	0.68%

Hit Validation

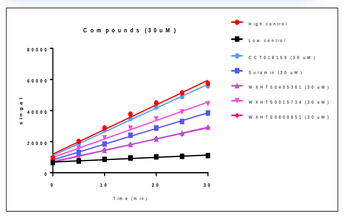
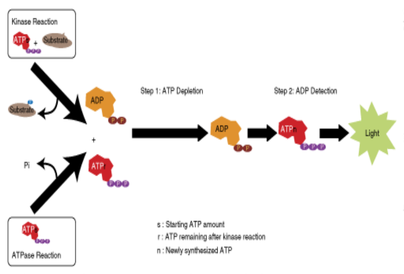


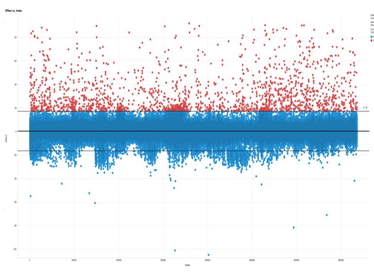
Fig 2. Hit cmpds test at 30uM in helicase assay

Helicase assay is developed as secondary assay to validate hit cmpds function.

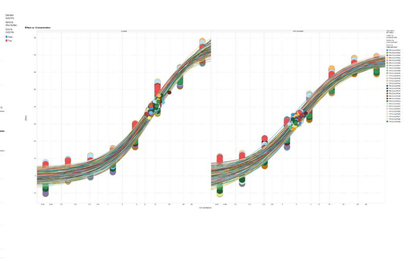
370k Kinase Assay Hit Finding



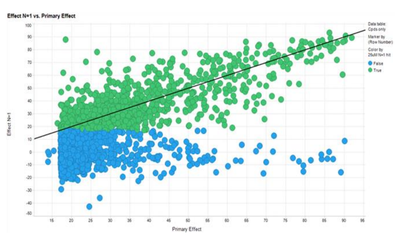
The ADP-Glo™ Kinase assay has a high dynamic range and produces a strong signal at low ATP-to-ADP conversion, making it well suited for screening low-activity kinases such as growth factor receptor tyrosine kinases



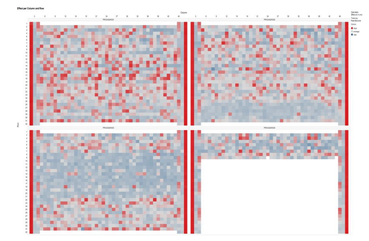
370k primary screen is completed in 3 weeks. Assay window and Z prime is stable for all screening plate. Hit rate is 0.53%.



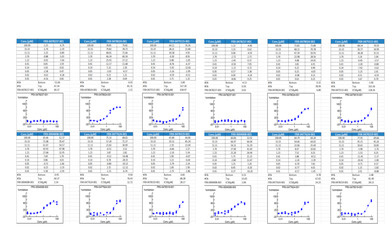
2 Reference compounds are stable across plates



Single dose hit confirmation showed consistent activity of hit cmpd between primary screen and following assays. Hit confirmation rate is ~48%



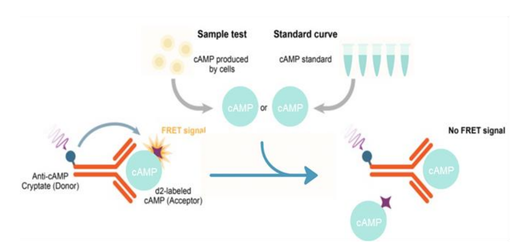
Selected hits moved forward to dose-response confirmation assay in 1536w

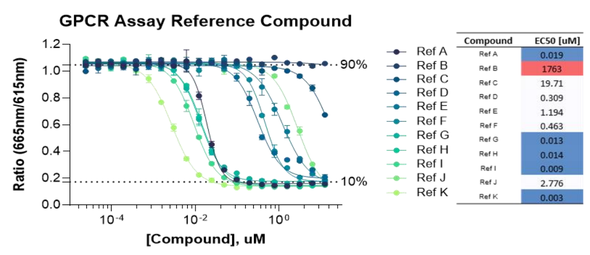


Counter screen (Right) was performed using off-target assay in parallel with hit dose-response confirmation assay (Left)

- Kinase assay was screened against 370k library using ADP-Glo in 1536-w format.
- 370k screen campaign is completed in 3 weeks. Hits have been tested at IC50 and confirmed.

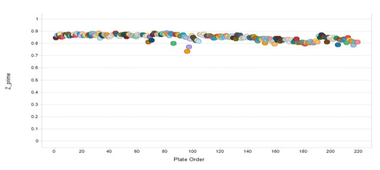
HTS Showcase for GPCR Cell Based Assay



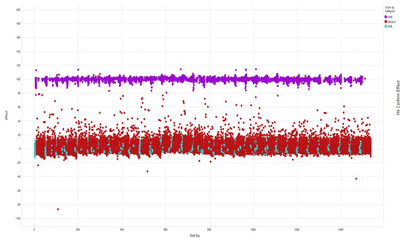


Compound	EC50 [uM]
Ref A	0.019
Ref B	1763
Ref C	19.71
Ref D	0.309
Ref E	1.194
Ref F	0.463
Ref G	0.013
Ref H	0.014
Ref I	0.009
Ref J	2.776
Ref K	0.003

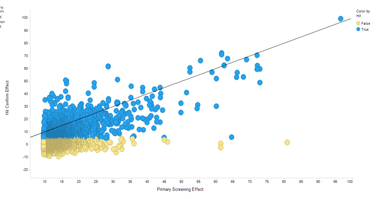
Z' Value



Wuxi Library Screen Compound %Effect Scatter Plot



Hit Confirmation vs. Primary Screen



- A high-throughput 1536-well cell-based assay was developed to screen the WuXi full deck library for modulators of Gs-coupled GPCR signaling via cAMP accumulation.
- The assay showed strong performance with uniform signal distribution (Z' = 0.77) and consistent EC_{50} profiles across 11 GPCR reference agonists.
- In primary, a total of 5,760 active compounds were identified using a >Mean+3SD cutoff, yielding a hit rate of 1.5%, demonstrating the assay's robustness and sensitivity.
- Hit confirmation studies demonstrated consistent activity of hit compounds between the primary screen and follow-up assays, with an overall confirmation rate of about 41%

Summary

- Upgraded 370,000+ Diversity Small Molecule Library: A carefully curated collection with enhanced chemical diversity and drug-like properties to improve hit identification.
- Full Automation: Enabling high-precision, high-efficiency, and fully reproducible screening at scale.
- Consolidated HTS Platforms: Combining HTS, HCS, and ASMS platforms, providing diverse assay formats tailored to your research needs.
- Integrated Screening Cascade: Starting from assay development, move forward to primary screen, followed by hit triage. WuXi HTS aims to provide validated hits as starting point.

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