

CASE STUDY

How Syngene screened inhibitors of protein-protein interaction in HTS mode for accelerated drug discovery



Syngene
Putting Science to Work

The Challenge

A biotech company approached Syngene to develop an HTRF assay for screening inhibitors of protein-protein interaction in high throughput screening (HTS) mode. We were required to screen 50,000 compounds against two different transcription factors in a challenging megadalton-size multiprotein complex. Another requirement was to establish a counter-screen for identifying interfering compounds. Syngene was required to deliver both against tight timelines while ensuring high-quality output.



The Solution

Syngene is equipped with various types of instruments to enable HTS solutions. We have multiple HTS-ready plate readers of different makes (PerkinElmer® EnVision®, Tecan Spark®), which can read in autonomous mode once the plates are stacked on the instruments. Further, we have multiple liquid handlers and dispensers (Tecan Freedom Evo®, Beckman Coulter Echo, Thermo Multidrop Combi, Integra Assist Plus), which can be programmed to dispense volumes ranging from nano to micro-liters.

Syngene scientists developed two biochemical HTRF assays and tailored them to run in a high-throughput mode. One major challenge was working with megadalton (MDa) size protein complexes resulting in a lack of uniformity (drift in signal) in the assay plates. We identified the root cause to be the sticky nature of the proteins. To resolve this issue, we undertook pre-treatment of all plasticware (including pipette tips) with suitable conditioning buffers resulting in plate uniformity of acceptable levels.

As part of the screening, we ran 486 384-well plates for two targets, including counter screening in 12 days (40 plates on average/day). Plate-wise quality control (QC) parameters, Z' values, and signal-fold for both Target 1 and Target 2 are shown in Figure 1.

We obtained consistent Z' values (0.8 ± 0.05) for the entire screening. The signal fold varied slightly across different days but was in the acceptable range per the validation studies.

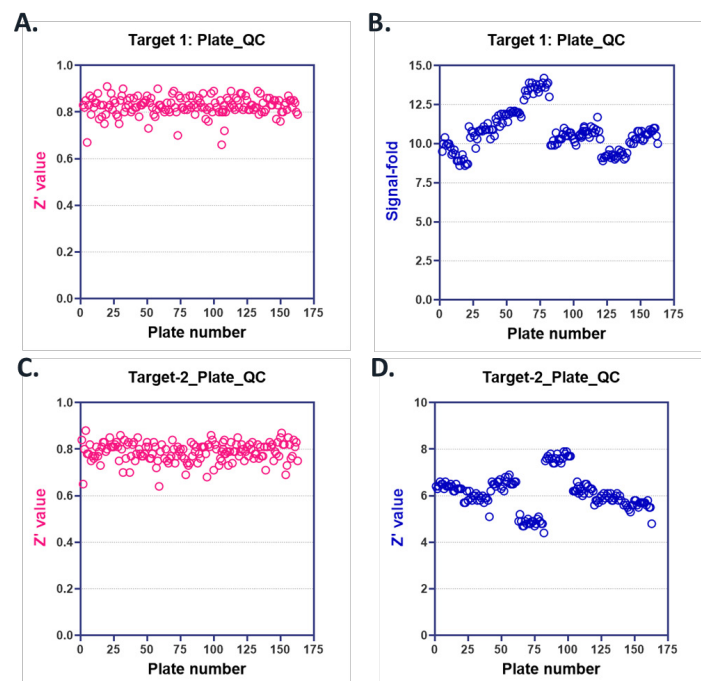
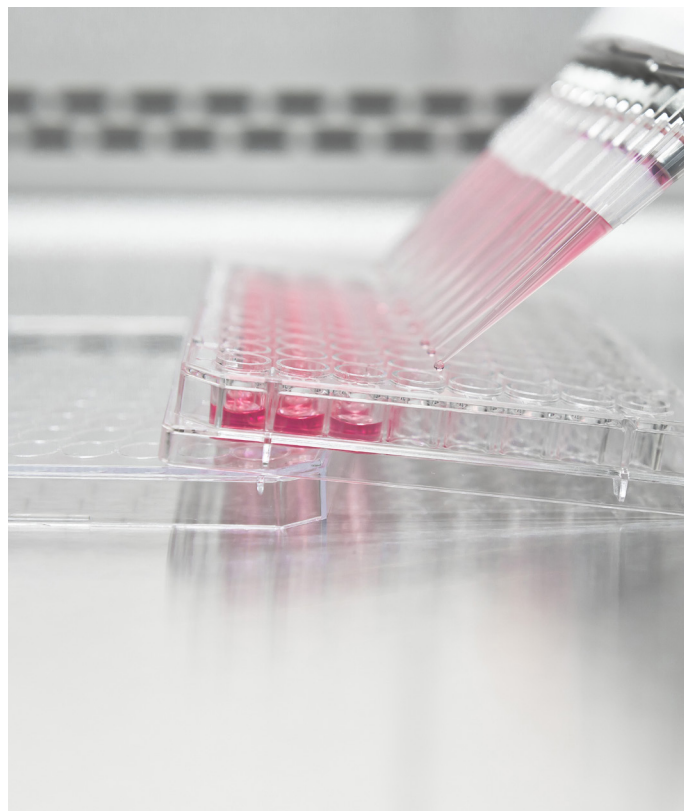


Figure 1: Quality control parameters for two targets. Scatter plots of (A and C) Z' values and (B and D) signal-fold are shown for Target 1 (A and B) and Target B (C and D).



The table below provides a summary of the screenings focusing on critical parameters.

Description	HTS 1
Library size	45,000
Targets	2
Counter screen	1
Total number of 384-plates screened	486 (2 targets + 1 counter screen)
Type of HTS assay	Homogeneous Time Resolved Fluorescence (Biochemical)
HTS assay development	In-house
Automation and plate uniformity	In-house
HTS readiness demonstration	Pilot run with 5,000 compounds
Number of 384-well plates screened/day	40
Number of compounds screened/day	11,200
Total number of days of plate screening	12
Average signal-fold observed	11 ± 1.3 (Target 1; 162 plates) 6 ± 0.8 (Target 2; 162 plates) 12 ± 1.7 (counter screen; 162 plates)
Average Z' for the entire screen	0.8 ± 0.05 (486 plates)

Table 1: Summary of the high throughput screening project

Results Delivered

Syngene leveraged its in-house expertise and automation capabilities to deliver high throughput screenings of high quality within the agreed-upon timelines at optimum costs. The client was very well satisfied with the quality of our output, which enabled them to identify hits and proceed to hit triage at an accelerated pace. Further, even after completing this project, the client continued to work with us for routine screening of compounds as part of the hit-to-lead phase.

To learn more about our drug discovery services, [contact our team](#) 



About Syngene

Syngene International Ltd. (BSE: 539268, NSE: SYNGENE, ISIN: INE398R01022) is an integrated research, development and manufacturing services company serving the global pharmaceutical, biotechnology, nutrition, animal health, consumer goods and specialty chemical sectors. Syngene's more than 5200 scientists offer both skills and the capacity to deliver great science, robust data management and IP security and quality manufacturing at speed to improve time-to-market and lower the cost of innovation. With a combination of dedicated research facilities for Amgen, Baxter and Bristol-Myers Squibb as well as 2 Mn sq. ft of specialist discovery, development and manufacturing facilities, Syngene works with biotech companies pursuing leading-edge science as well as multinationals, including GSK and Merck KGaA.

For more details, visit www.syngeneintl.com or write to us at bdc@syngeneintl.com

