{ CASE STUDY }

titian

Sygnature Discovery: the creation of a high throughput screening (HTS) facility

Paul Kay, Titian Software Ltd

v1.0. APRIL 2020

visit **titian.co.uk**

1. OVERVIEW

Sygnature Discovery, a contract research organisation (CRO) based in Nottingham and Alderley Park, UK, has utilised Titian's Mosaic sample management in the creation of a high throughput screening (HTS) facility.

Sygnature Discovery provides drug discovery services to customers in many countries. Its contract services range from target validation through to lead optimisation and preclinical services. HTS involves testing a compound screening library against a customer's assay to see if any compound lead candidates can be identified. Previously, Sygnature had outsourced HTS to a third party provider, but in order to improve the scope and quality of its service, Sygnature decided to establish its own HTS capability, combining Mosaic with Genedata's Screener data analysis software and HighRes Biosolutions' lab automation.

> **We decided to build our own HTS capability after feedback from our clients, especially around compound quality in many historical screening libraries. Having the capability housed within our Nottingham labs, where it can be integrated with our other hit-finding functions, will bring an enormous amount of additional value to our clients and their drug discovery projects.**
>
> **Colin Sambrook Smith**
> Director of Computational Sciences & Informatics, Sygnature Discovery

2. CHOOSING SYSTEM COMPONENTS

Sygnature Discovery identified three high-level system requirements, aside from the building and IT logistics, needed to create an appropriate high quality HTS system. These were:

High throughput automated robotic screening

The main benefits this should provide were:

- Testing large numbers of library compounds very quickly and reproducibly
- Operating reliably with minimal operator attendance, or even running unattended for significant periods
- On-line monitoring with remote issue resolution if required

Sample management or LIMS software

The benefits needed here were:

- Interfacing seamlessly with the chosen robotic screening system
- Ability to organise compound libraries and screening campaigns, especially the cherry-picking of hit compounds and associated dose response assays
- Managing screening library source plates within manual stores efficiently

Screening data analysis software

The main benefits sought were:

- Maximising error free data handling pathways through seamless integration with the other system components
- Providing intuitive results processing tools
- Enabling rapid identification of hit compounds by efficient processing of HTS data results

These principle requirements were governed by the following general criteria:

- Using only high quality products from vendors with proven reputations

- The combined system should support Sygnature's envisaged screening business processes including:
  - Acoustic dispensing to allow high precision preparation of assay plates from compound libraries
  - Flexible automation and data analysis that allow execution of a comprehensive array of high-throughput screening assays including both cell and biochemical based assays
- Minimising system implementation lead time by requesting that all sub-systems from each vendor should have established connectivity requiring minimal - or, ideally, no - development work, as this often leads to delivery and testing delays

3. VENDOR SELECTION

Sygnature applied the criteria above to select three vendors to supply the core components of the HTS system.

These were:

HighRes Biosolutions Inc. (HighRes) for the HTS screening automation robotics system

Titian Software Ltd's Mosaic SampleBank for the sample management LIMS software

GeneData AG's Genedata Screener software for analysing and visualising screening data

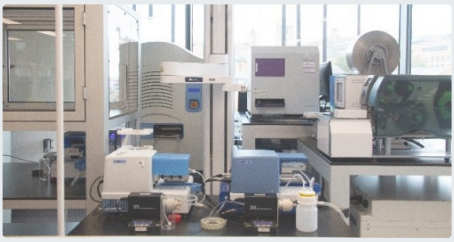
This combined system for Sygnature builds on HighRes, Titian and Genedata's previous experience of integrating components in a single installation. Titian has worked with both Genedata and HighRes on several prior projects. Indeed, this synergistic combination of Cellario, Mosaic and Screener software was proposed at SLAS2018 and noted there by Sygnature's Denise Swift.

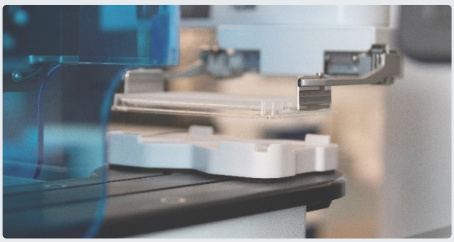
3.1 HIGH THROUGHPUT AUTOMATION ROBOTIC SCREENING SYSTEM

HighRes Biosolutions produces laboratory automation systems, dynamic scheduling software and lab automation instruments with an architecture that allows standard elements to be combined in different ways. The HighRes system chosen is based around the ACell bench-top robotic arm and a Beckman Coulter Echo® (formerly Labcyte) acoustic dispenser, in order to achieve the following benefits:

- Flexibility to adapt to different types of screens, thanks to HighRes' Cellario dynamic scheduling software that controls the automation
- High precision dispensing using acoustic technology, which can carry out operations such as plate replication, cherry picking and preparation of dilution series assay plates
- A modular, expandable system that is capable of running both cell-based and biochemical assays

Sygnature's HTS system also includes its existing proprietary LeadFinder screening compound library plate sets held in environmentally controlled manual stores from BigNeat Ltd. These stores house stackers used on the HighRes robot to ensure minimum human intervention in operations such as plate sorting.





3.2 SAMPLE MANAGEMENT SYSTEM

Titian's Mosaic SampleBank software provides seamless inventory tracking, sample ordering and workflow management in one simple package. Mosaic software is well established as best in class for compound management and is increasingly being used in screening environments for removing error during the development of assays and in project driven testing, especially given the vast range of dilutions with reagents included. It is also able to track and manage any sample type, including small molecules, reagents, DNA, proteins, antibodies, cell lines, blood, serum and tissues.

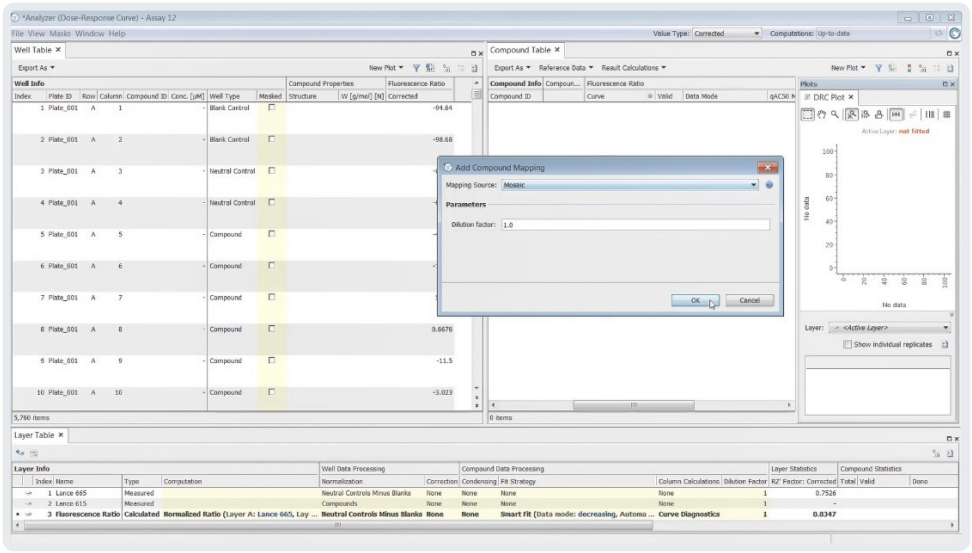
For Sygnature, the following features were of particular importance:

- Ability to manage Sygnature's existing LeadFinder screening compound library plate sets held in environmentally controlled manual stores from BigNeat Ltd
- Comprehensive and off-the-shelf integration with the HighRes automation which provides real time data exchanges between the systems. This means assay plate preparation can be scheduled from compound library sources with dynamic inventory updates
- Mosaic enables Sygnature to accurately monitor the quality of its compound library sources as well as inventory stock levels. This is achieved by reporting the plate survey information carried out on compound source plates by the Echo acoustic dispenser
- Titian brought experience of standard processes, used by other customers with HighRes systems, which fitted the Sygnature workflows
- Mosaic exports compound mapping information directly into Genedata Screener for a smooth data flow, via an existing integration

3.3 SCREENING DATA ANALYSIS SOFTWARE

Genedata Screener® software analyses, visualises, and manages screening data from in-vitro screening assay technologies. Sygnature chose Genedata Screener because it is intuitive and straightforward to use allowing rigorous interrogation of data by plate, batch and whole screen.

Genedata Screener is also fully integrated with the rest of the HTS system and thus able to combine process data from the HighRes robot cell, with substance identity and concentration information from the Mosaic inventory.

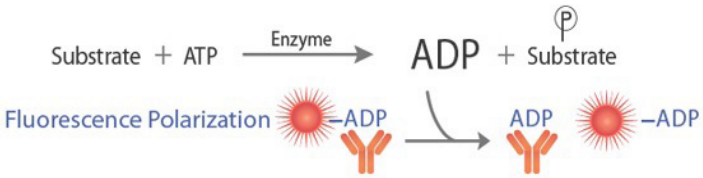


4. SYGNATURE SCREENING EXAMPLE: HPK1

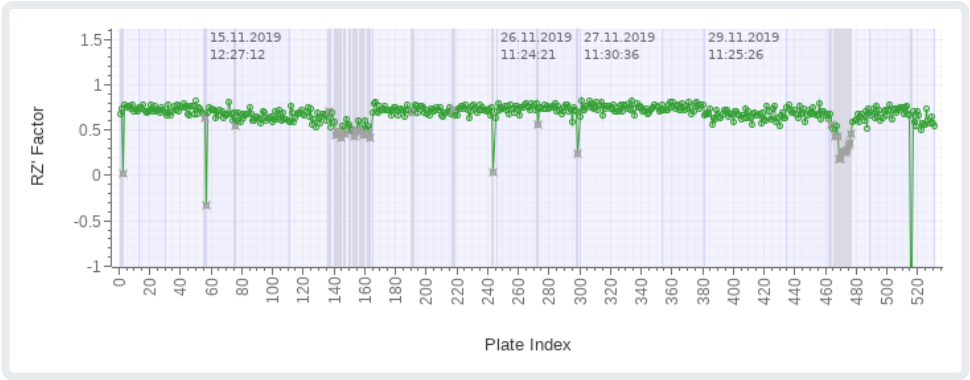
As a screening example for the new integrated HTS system, Sygnature ran a pilot screen for HPK1 (MAP4K1). This pilot screen was an immuno-oncology target involved in negative regulation of T-cell receptor (TCR) signalling.

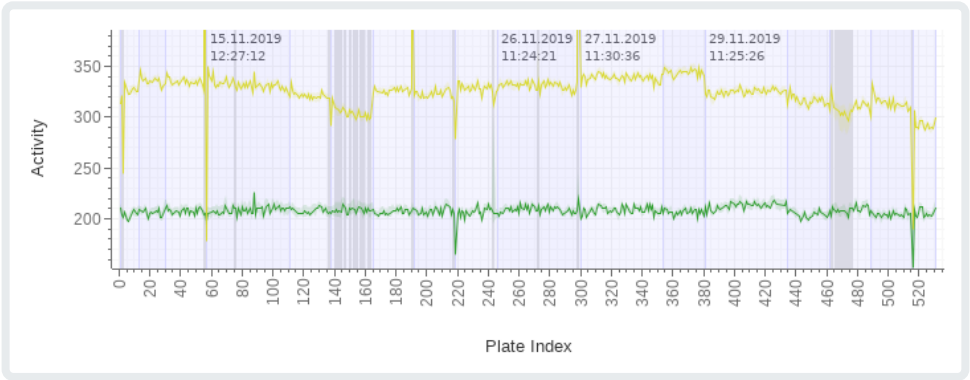
Screening against this target assay hoped to identify novel chemical starting points to develop potent and selective inhibitors of HPK1.

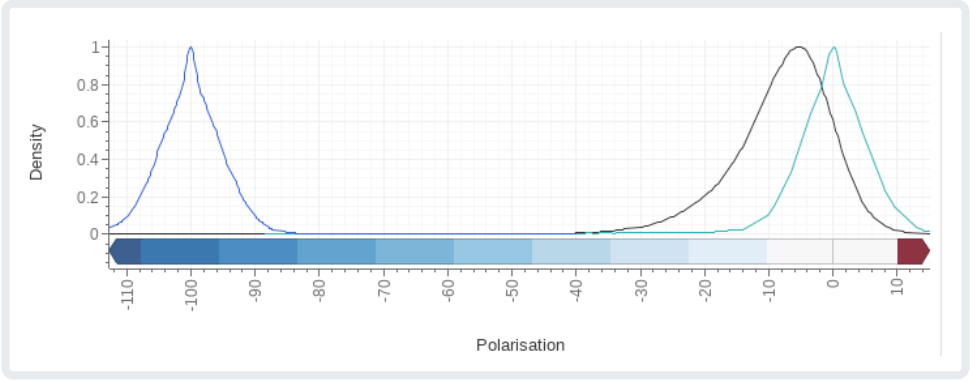
The intrinsic ATPase activity of HPK1 was used to develop the ADP product Fluorescent Polarisation (FP) assay shown below.



Using its new HTS system for the first time, Sygnature screened its 150K small molecule library in less than 4 weeks, with an average Robust Z' >0.7.







The typical daily schedule when running this assay was as follows:

Set up

- Compound orders for the day's assay screening were created in Mosaic software and passed to the HighRes automation to carry out, with Mosaic automatically writing the necessary control scripts.
- Source plates, controls and destination plates were loaded and validated on the HighRes robot.

Compound management

- Creation of screening ready sealed assay plates from compound library source plates.
- Robot runs are typically 5 to 9 hours, and can be run unattended overnight

Screening

- Fresh assay reagents are prepared immediately before the assay is run.
- Assays run on the HighRes automation typically take 4 to 7 hours.

Data analysis

- Mosaic results and HighRes Cellario dispensing logs are checked to see if there are any issues that might affect the results interpretation.
- Data file uploaded to Genedata Screener for quality control (QC) and analysis

As a result of this run, Sygnature observed good reliability from all aspects of its integrated HTS system incorporating Titian Mosaic SampleBank software, HighRes automation and Genedata Screener software. The following general observations were noted:

- Most issues were predominantly caused by the transition from test to production data systems
- There were some liquid dispenser calibration problems causing plate effects that required resolution.
- Extensive testing before starting the screen helped to identify processes that caused issues, i.e. barcoding.

5. BENEFITS FROM USING MOSAIC SOFTWARE

Sygnature's comprehensive integrated screening system derives specific benefits from using Titian's Mosaic software. These are:

- The Mosaic interface makes it easy for scientists to request the compounds they want to test
- Scientists can monitor the progress of their order
- Sample processing is error free, as Mosaic automatically produces the scripts driving the HighRes automation, thus avoiding human programming errors and time-consuming script writing
- Mosaic's integration with the Echo acoustic dispenser means survey data from the Echo can be used to update sample volumes in real time
- Mosaic's linkage with the Screener data analysis software ensures assay endpoint data is paired to the compound plate maps, with no errors
- If an assay fails, Sygnature can use Mosaic's audit trail to trace back to the sample well or robot that created the plates in order to check it is all within QC limits

> **The important thing about Mosaic for us is the fact that it allows us to maintain data integrity. It bypasses the need for human intervention so there should be no errors.**

Denise Swift

Senior Scientist, Sygnature Discovery

6. SUMMARY

Sygnature Discovery summarised its experience in creating the new HTS facility as follows:

- Close collaboration with vendors has helped to get the HTS capability up and running very quickly. Sygnature went from delivery to the initiation of its first HTS screen in less than 6 months.
- The choice of standard equipment and hardware means it was all tried and tested and the vendors could bring experience of previous integrations
- Careful planning and preparation for all stages of the project was required. Significant amounts of IT infrastructure were needed to prepare in addition to lab remodelling.
- Where issues occurred, they were dealt with systematically and rapidly with the help of the vendors
- All of the systems were tested extensively before going live
- Running the HPK1 test case was invaluable in weeding out production issues and shaping operational practices.

In summary, a comprehensive automated HTS system has been successfully established at Sygnature Discovery in Nottingham, UK, in a very short time-frame, in order to complement the company's existing suite of hit finding approaches. This integrated HTS system allows Sygnature to offer a more comprehensive integrated hit discovery platform, enhancing successful early drug discovery for its clients.

Titian's Mosaic software has played an essential role in this success, proving that the benefits it offers of data integrity, robust sample audit trail, and close integrations with multiple vendors bring significant benefits to the drug discovery workflow in screening environments, as well as in compound management.

titian

Thank you for your interest in this document

White papers

Application notes

Product brochures

Video content

Webinar recordings

You can find a collection of further related material in the resources section on Titian's website. Scan the logo QR code with your mobile or tablet to visit.

info@titian.co.uk

www.titian.co.uk

UK Tel:

+44 20 7367 6869

USA Tel:

+1 508 366 2234