Enhancing drug safety evaluations with automated liquid handling:

Introducing the ICESTP Safety Panel 90 for functional and dose-response screening in secondary pharmacology

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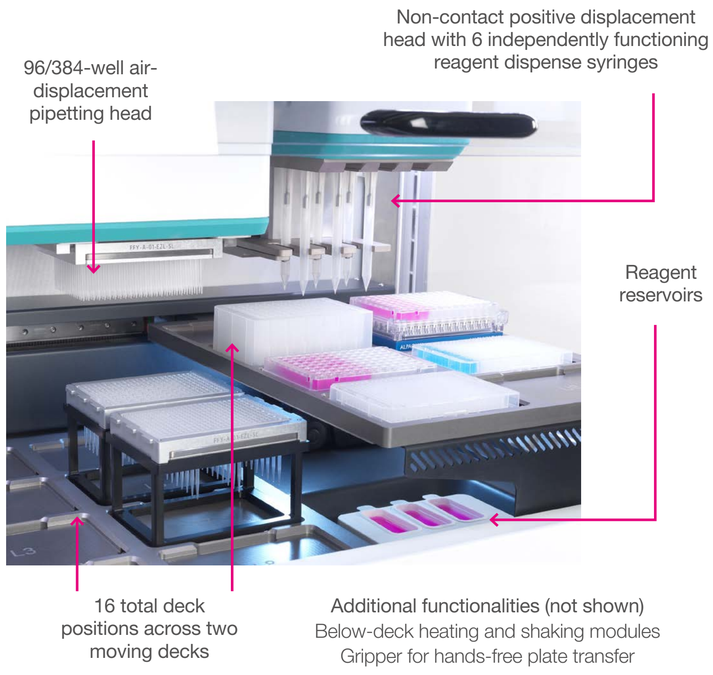
Introduction

The pharmaceutical industry places a high priority on drug safety, recognizing it as a critical aspect of drug development. Advanced safety pharmacology panels are integral to this process, ensuring that potential adverse drug reactions (ADRs) are identified early. ICE Bioscience has developed the *ICESTP Safety Panel 90* to provide a comprehensive secondary safety pharmacology assessment, that is designed to evaluate a drug's interaction with a wide range of targets related to the central nervous system, cardiovascular system, metabolism, and immune system, thereby enhancing the safety assessment of drugs.

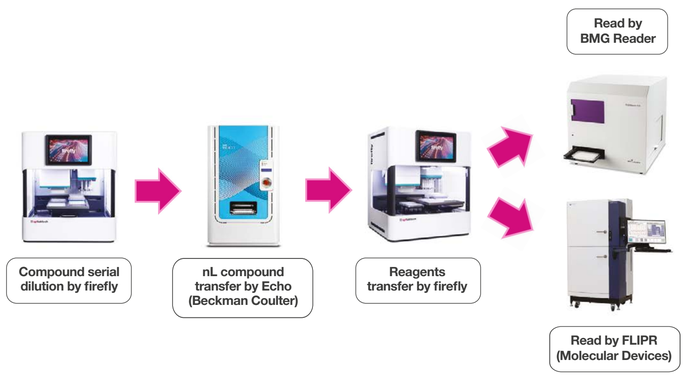
The ICESTP Safety Panel 90 includes 138 assays, incorporating both single-point screening and dose-response screening with a functional assay format, such as Automatic patch clamp, FLIPR calcium flow, and HTRF, for example. In this poster, we demonstrate the use of SPT Labtech's firefly® automated liquid handling platform for high-throughput sample processing to facilitate the safety assessment of a 90-target panel, to improve the efficiency and accuracy of drug safety evaluations.

All-in-one liquid handling with firefly



Methods

Automated systems and workflow supporting the ICESTP Safety Panel 90



Compound serial dilution:

- 20 µL of DMSO diluent is dispensed with the dispense head of firefly
- 10 µL of compound is transferred and mixed with 20 µL DMSO to complete 3-fold of serial dilution using the pipetting head of firefly

Compound transfer:

- 100 nL of diluted compound is transferred to an assay plate by Echo

Reagents transfer:

- In a 384-well plate, 2.5 µL substrate and 2.5 µL enzyme are added with the dispense head of firefly, followed by 1 hour incubation
- 5 µL of detection buffer is added with the dispense head of firefly

Signal detection:

- Results are analyzed on BMG reader or FLIPR

Pergolide tested in ICESTP Safety Panel 90

Pergolide is a dopamine receptor agonist commonly utilized in the treatment of Parkinson's disease and other conditions. It has been associated with an increased risk of cardiac valvulopathy, leading to its withdrawal from the US and Canadian markets in 2007. We tested the off-target profile of Peroglide and subsequently utilized the off-target representation to elucidate its ADR mechanisms, attempting to provide the potential explanations for its drug-target-ADR correlations which provide valuable information for safety-related prediction tasks. This early safety assessment protocol can steer a rational drug development process, facilitating the discovery of safe compounds.

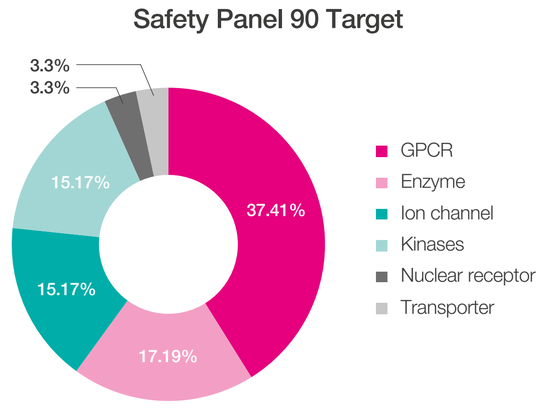


Figure 1. Related class of 90 targets.

Results

Pergolide exhibited low selectivity in the ICESTP Safety Panel 90, with a total of 12 targets showing over 50% activation and 2 targets showing over 50% inhibition at a concentration of 10 µM (Figure 2). The EC50/IC50 dose-response curves, generated using 10 dose levels, are displayed in Figure 3. These off-target effects increase the risk of cardiac valvulopathy.

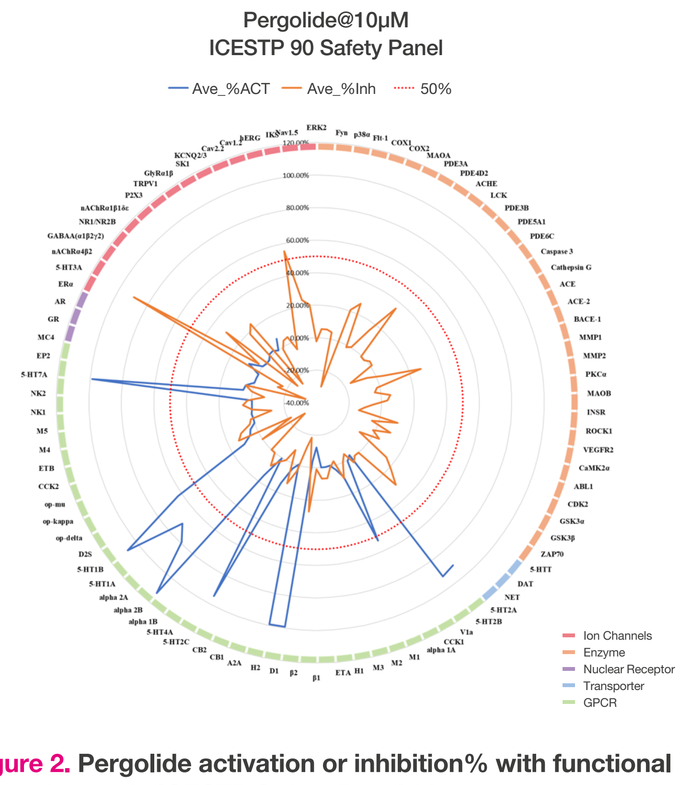


Figure 2. Pergolide activation or inhibition% with functional assay format in ICESTP Safety Panel 90.

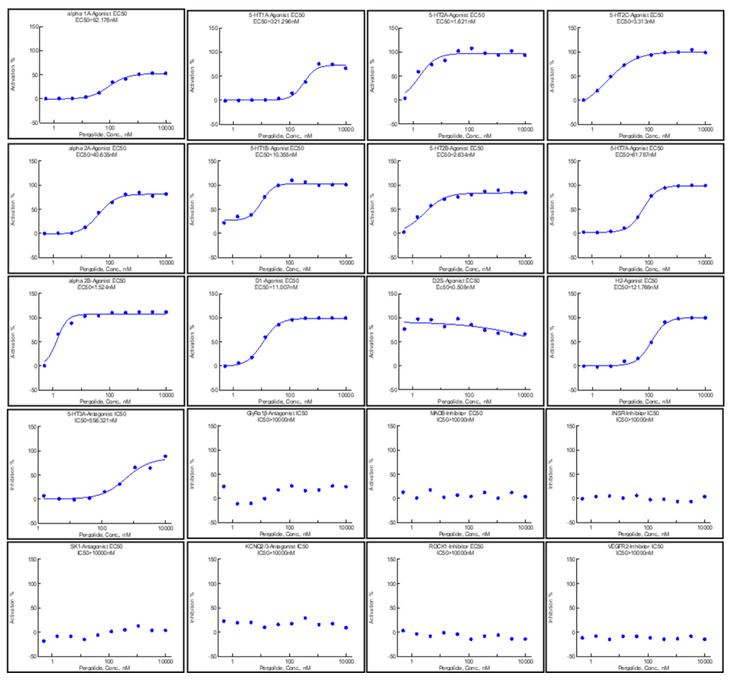


Figure 3. Pergolide activation or inhibition using dose response with function assay format in ICESTP Safety Panel 90 (display of partial data).

Conclusion

In vitro secondary pharmacology profiling can affect the clinical safety of drugs, as indicated by a marked decline in drug off-target promiscuity over the past decade, which has correlated with a reduction in serious adverse events for drugs on the market. ICESTP Safety Panel 90 uses functional assay formats with both single point screening and dose response modes. SPT Labtech's firefly is very well suited to perform both compound serial dilution and precious reagent addition, contributing reliable and high-quality data in the functional assay for ICESTP Safety Panel 90. Thus, firefly is enabling ICE Bioscience to be one of the world's first contract research organizations (CROs) to provide full-functional and curve-fitting for secondary safety pharmacology assessment, covering more than 90 targets.

Advantages of ICESTP Safety Panel 90

Functional assay format	Dose-response screening
Ability to distinguish agonist and antagonist	Robust and reproducible data
Ability to detect allosteric pharmacology	Ability to highlight partial agonists
Close to the physiological situation (e.g. 1 mM ATP used in kinase assays)	Potential to highlight solubility issues
Provides for a more stringent analysis, resulting in fewer follow-up studies	Quickly correlate with *in vivo* exposure values
Efficient and time-saving	Efficient and time-saving

References

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