ENHANCING DRUG SAFETY ASSESSMENT WITH AUTOMATED INSTRUMENTATION IN SECONDARY PHARMACOLOGY

Zhiying Nie,Yanan Zhao, Qiang Xia,Mingyang Yuan, Ziye Cui, Meihui Shi,Tiejjun Bing, Fujun Zhang, Xiao Guo, Ben Wei
ICE Bioscience Inc, Beijing, China

ICE Innovative CRO+Explorer ICE Bioscience

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Background

In the development of new drugs, it is crucial to know the safety profile of drug candidates in advance, as this can prevent the drug from being withdrawn from the market due to safety concerns after launch, thus reducing the risk for pharmaceutical companies.

It is estimated that approximately 75% of all adverse drug reactions (ADRs) are dose-dependent type A reactions, which can be predicted according to the pharmacological profiles of drug candidates. The pharmacological profiles are mainly divided into primary effects, which are related to the action of the compound at its intended target, and secondary effects, which arise from interactions with non-primary targets, i.e. off-target effects. Off-target interactions are often the cause of ADRs in animal models or clinical studies, so careful characterization and identification of the secondary pharmacological profiles of drug candidates early in the drug discovery process could help reduce the incidence of type A ADRs.

For this reason, we have established 90+ screening models for the safety assessment of targets covering key areas such as the central nervous system, cardiovascular system, metabolism and immunity. The agonistic or antagonistic effects of compounds on these targets were evaluated by functional activity screening to evaluate the safety of compounds and to provide a reference point for late-stage drug discovery.

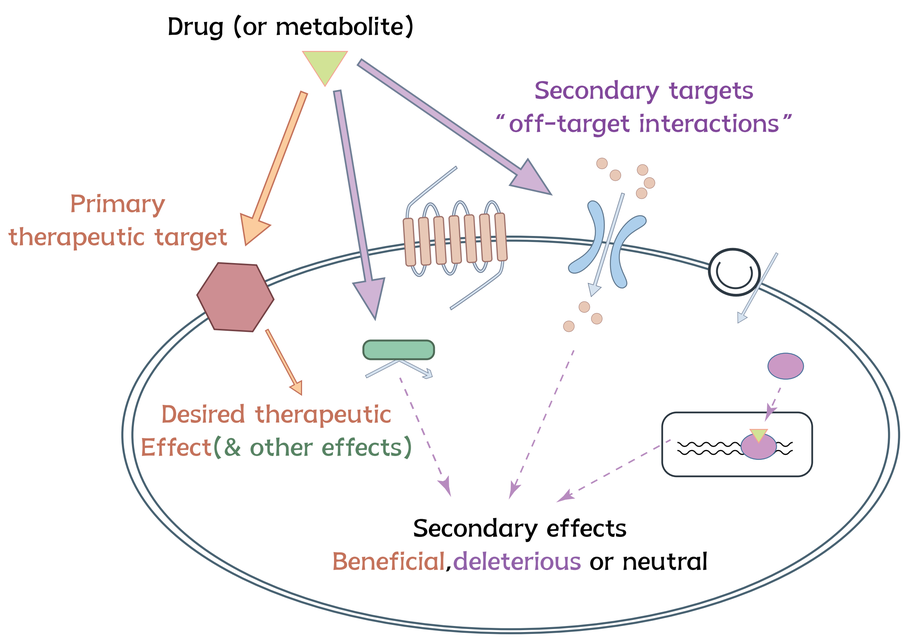


Figure 1: Mechanisms of drug action. To mediate a biological effect, a drug, or its metabolite(s), must bind to the primary therapeutic target or to other molecular targets. Only a small protein ligand interface region facilitates that interaction, thus off-target interactions may occur both at targets closely related to the therapeutic target or/and at structurally distinct targets. Secondary effects mediated by off-targets can be deleterious, beneficial or neutral.

Table: Advantages of ICESTP SAFETYPANEL® 90 Plus Dose Response

Functional assay format	Curve-based screening
Ability to distinguish agonist and antagonist	Robust /reproducible data
Ability to detect allosteric pharmacology	Ability to highlight partial agonists
Closed to the physiological situation. For example, 1 mM ATP used in kinase assays	Potential to highlight solubility issues
Provide 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

In Vitro Off-Target Screening: ICESTP SAFETYPANEL® 90 Plus Dose Response

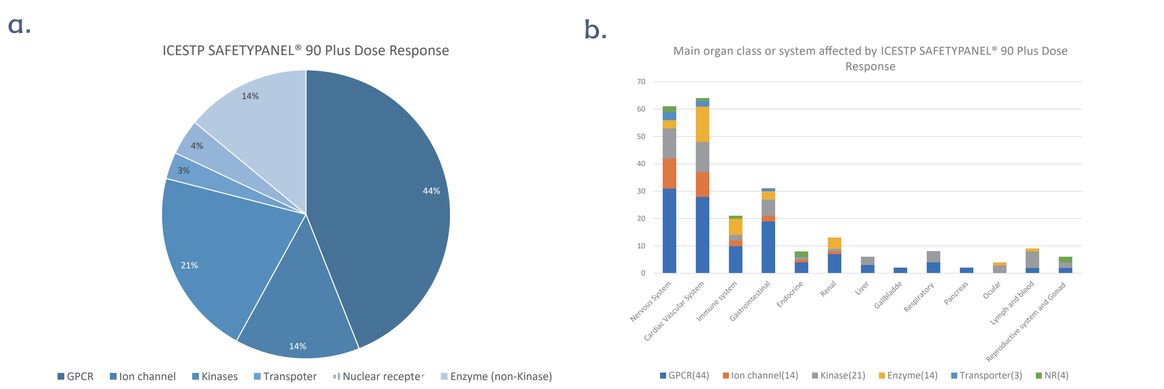


Figure 2. An overall composition of ICESTP SAFETYPANEL® 90 Plus Dose Response
ICESTP SAFETYPANEL® 90 Plus Dose Response provides 100 key molecular targets related to drug safety, which mainly consist of G protein-coupled receptors (GPCRs, 44 proteins) and 21 protein kinases, but it also includes 14 ion channels, 14 enzymes(non-kinase), three transporters and four nuclear receptors (Figure. 2a). ICESTP SAFETYPANEL® 90 Plus Dose Response covering a wide range of target organ systems (Figure. 2b).

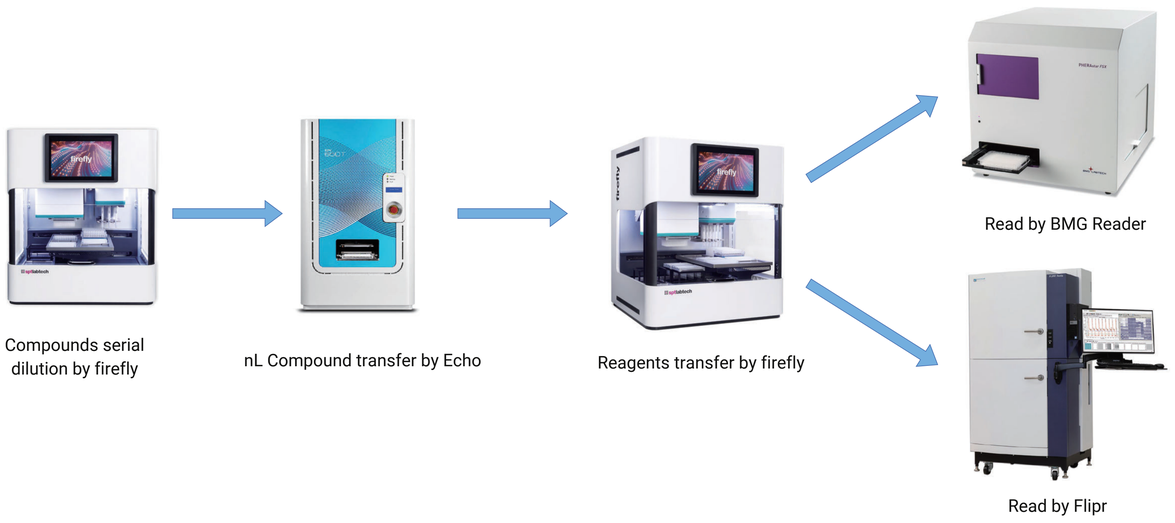
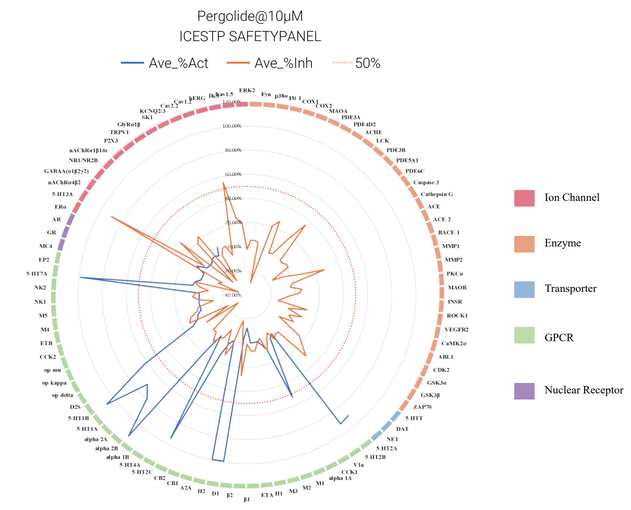


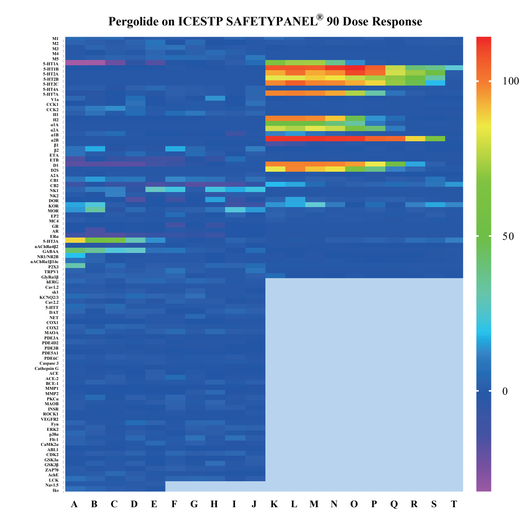
Figure 3. Operation Process of ICESTP SAFETYPANEL® 90 Plus Dose Response
The ICESTP SAFETYPANEL® 90 Plus comprises 156 assays, integrating both single-point and dose-response screening methodologies within a functional assay framework, including techniques such as Automatic patch clamp, FLIPR Calcium Flux, HTRF, ADP-Glo, FP, etc. The utilization of SPT Labtech's firefly® automated liquid handling platform and acoustic liquid handler ECHO665 for high-throughput sample processing, thereby enhancing the efficiency and precision of safety assessments for the ICESTP 90 Plus-targets panel.

Pergolide Tested in ICESTP SAFETYPANEL® 90 Dose Response

a. Pergolide with functional assay format in ICESTP SAFETYPANEL



b. Pergolide activation or inhibition using dose response with function assay format in ICESTP SAFETYPANEL® 90 Dose Response



c. Pergolide EC50 or IC50 with functional assay format ICESTP SAFETYPANEL® 90 Dose Response

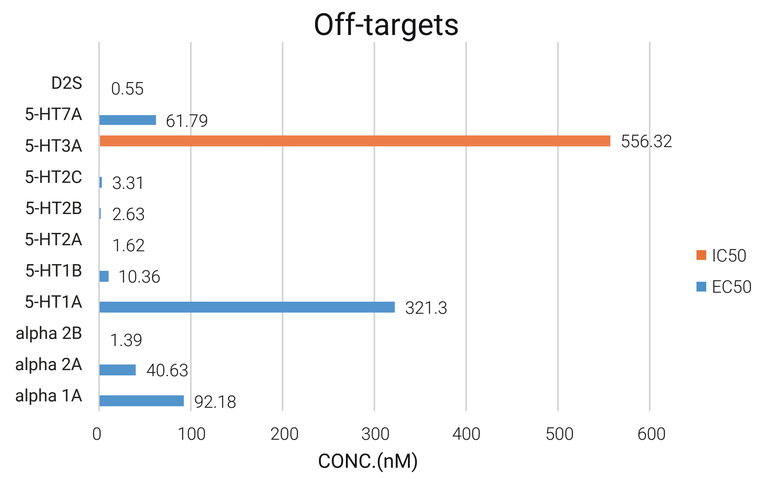


Figure 4. Results of Pergolide tested by ICESTP SAFETYPANEL® 90 Dose Response
Using Pergolide as a case study(showed in Figure. 4a. and Figure. 4b.), we tested its off-target profile in ICESTP SAFETYPANEL® 90 Dose Response (showed in Figure. 4c), and subsequently utilized the off-target representation to elucidate its ADR mechanisms. It provides 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.

- Pergolide is a dopamine receptor agonist commonly utilized in the treatment of Parkinson' s disease and other conditions, has been associated with an increased risk of valvulopathy, leading to its withdrawal from the US and Canadian markets in 2007.
- Based on the test results, we attempt to provide potential explanations for the various adverse reactions caused by off-target reactions of Pergolide:
- **Cardiovascular system:** Orthostatic hypotension (incidence rate of about 9%), palpitations, tachycardia, congestive heart failure, etc.
- **Nervous system:** Dyskinesia (incidence rate of about 62.4%), hallucinations, insomnia (incidence rate of about 7.9%), dizziness, dystonia, etc.
- **Gastrointestinal system:** Nausea (incidence rate of about 24.3%), vomiting, constipation, diarrhea, etc.
- **Other:** Rhinitis, skin itching, edema, etc.

References

◇ Bowes, J. et al. Reducing safety-related drug attrition: the use of in vitro pharmacological profiling. Nat. Rev. Drug Discov. 11, 909–922 (2012).

◇ Lynch JJ 3rd. et al. Potential functional and pathological side effects related to off-target pharmacological activity. J Pharmacol Toxicol Methods.; 87, 108-126(2017).

◇ Richard J. Brennan. et al. The state of the art in secondary pharmacology and its impact on the safety of new medicines. Nat. Rev. Drug Discov. 23, 525-545 (2024).

◇ "Serotonin 5-HT2B receptor agonism and valvular heart disease: implications for the development of psilocybin and related agents " Expert Opinion on Drug Safety, 2023. The article mentions that Pergolide may lead to heart valve pathology as evidenced by thickening of the valves and restriction of movement, which in turn can lead to regurgitation of blood, pulmonary hypertension and heart failure.

◇ "Dopamine D2, but not D4, receptor agonists are emThis literature indicates that dopamine D2 receptor agonists trigger a strong emetic response in ferrets and gives the mechanism of emesis; it can explain the gastrointestinal side effects of Pergolide (such as vomiting, diarrhea).

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