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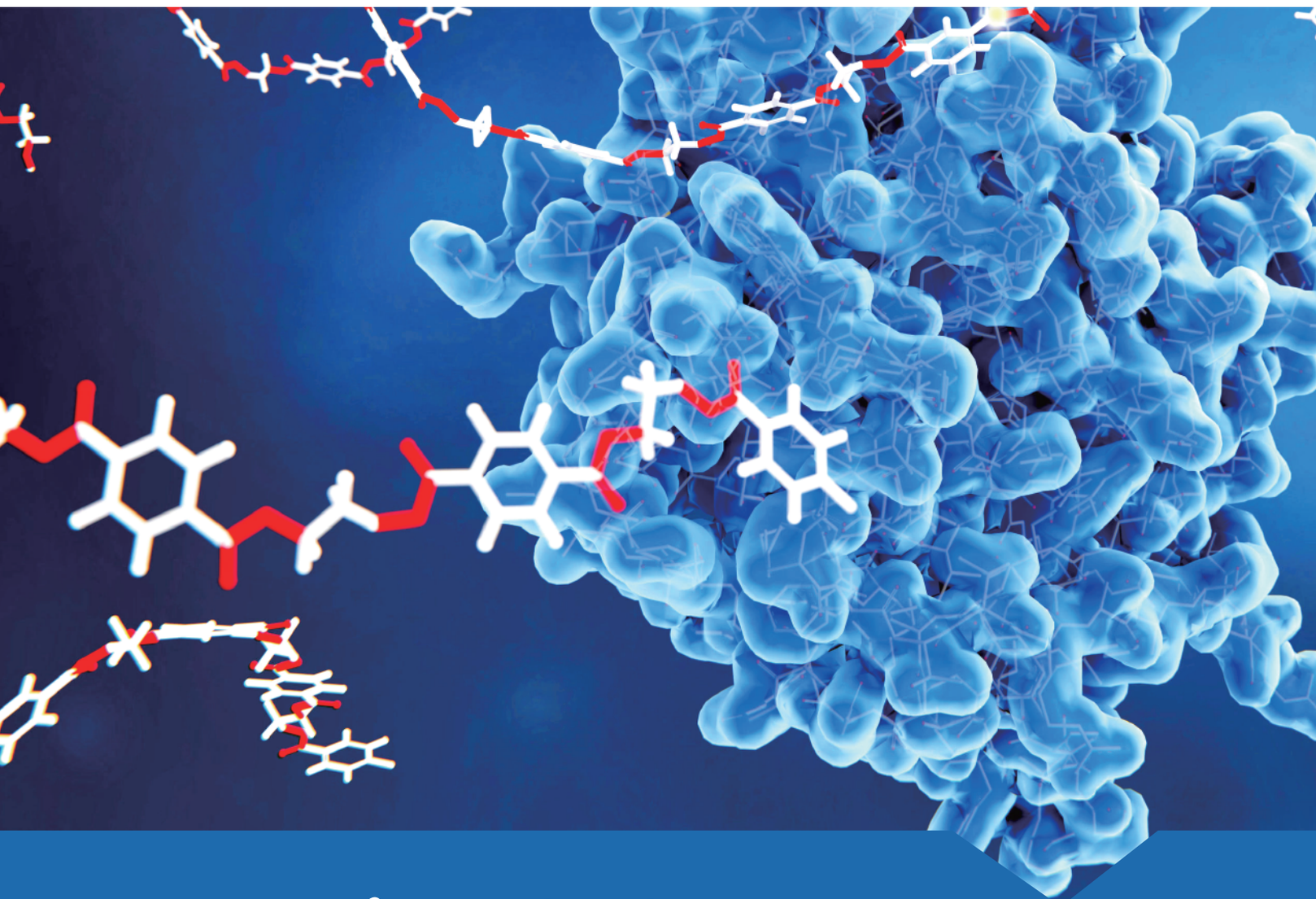
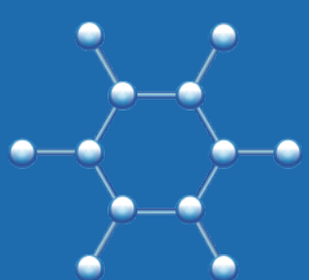
WuXi AppTec

WuXi Biology



In Vitro Safety Pharmacology Profiling

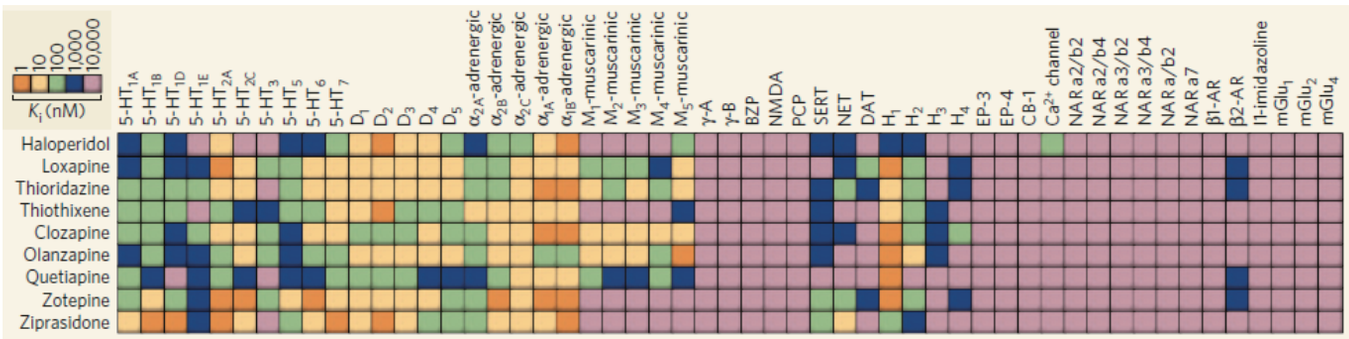


Comprehensive *In Vitro* Off-Target Screening Service

www.wuxibiology.com

Introduction

Safety-related drug failure is a major challenge for the pharmaceutical industry. Around 75% of adverse drug reactions (ADRs) are dose-dependent, related to a pharmacological action of the drug, and predictable. The interactions of drugs with off-target proteins have conventionally been viewed as undesirable 'promiscuity', responsible for unwanted side effects. Secondary pharmacology studies evaluate compound promiscuity, against a broad range of targets that are related to or distinct from the intended therapeutic target. This is a cost-effective approach used by many pharmaceutical companies as a safety screen early in drug discovery process, to predict clinical adverse effects and to reduce safety related attrition.



One drug, many targets. The chart shows the known affinity values of several antipsychotic drugs for a panel of receptors (Hopkins, Nature 2009).

WuXi AppTec *In Vitro* Safety Pharmacology Profiling Panel

WuXi Biology provides *in vitro* safety pharmacology services to identify potential off-target liabilities. three choices can be selected:

- **WuXi AppTec Mini Safety 44 Panel (Mini Safety 44 panel)**

  A primary safety panel, which is designed to identify compounds with the highest risk because it contains targets associated with the most serious ADRs. This panel is recommended for use early in drug discovery stage for early hazard identification.

  The 44 selected targets are recommended by four major pharmaceutical companies ((Bowes J. et al. Nat Rev Drug Discov. 2012), including 24 GPCRs, 8 ion channels, 7 enzymes, 3 monoamine transporters and 2 nuclear hormone receptors.

- **WuXi AppTec Second Safety 54 Panel (Safety Extra 54 panel)**

  A panel of additional 54 targets. This more extensive panel contains such targets that have the combination of either low-hit -rate/high-risk ADRs or high-hit-rate/ lower-risk ADRs. This panel is ideal for broad characterization of a limited number of compounds for lead selection, provides data to drive SAR for lead optimization.

  The 54 selected targets include 26 GPCRs, 5 ion channels, 18 enzymes, 3 nuclear hormone receptors and 2 transmembrane targets.

- **WuXi AppTec Full Safety 98 Panel (Safety 98 panel)**

  The combination of Mini Safety 44 panel and Safety Extra 54 panel.

- **Sources of targets for assays**
  - Human origin of targets overexpressed in stable cell lines
  - Recombinant human enzymes
  - Rat cerebral cortex (6 Channels for binding)

- **Assay format**
  - Function assays: FLIPR (Ca); reporter gene assay
  - Biochemical assay: Enzymatic assay
  - Radio ligand binding assay (Plate filtration or SPA assay)

Testing Format, Timeline, Data Delivery

- **Testing format**
  - 96- or 384-well format
  - Single concentration in duplicate (10 uM in general)
  - 8-10 dose response curves (as follow-up) to confirm positive hits (potency > 50% activation or inhibition omparing to that of control)

- **Assay timeline**
  - 15 working days (Mini Safety 44 panel)
  - 15 working days (Safety Extra 54 panel)
  - 15 working days (Safety 98 panel)

- **Data delivery**
  - Excel or word report
  - Assisting CFDA on-site inspection

Why WuXi Biology

- Both binding and functional assays: more information and fast follow-up
- Faster: turnaround time; easy compound shipping logistics
- Cost effective
- Flexible in target selection; expendable to other assay formats, eg. cAMP, IP1
- Enabling IND filing: documentation and on-site inspection in China

WuXi AppTec Mini Safety 44 Panel (Mini Safety 44 panel)

GPCRs	Receptor (Human)	Main Organ Class or System	Radioligand Binding	Function Assay (Ca^{2+} Assay)
Adenosine receptor	Ad2A	CVS, CNS	√	√
Adrenergic receptors	Alpha1A	CVS, GI, CNS	√	√
	Alpha2A	CVS, CNS	√	√
	Beta1	CVS, GI	√	√
	Beta2	Pulmonary, CVS	√	√
Cannabinoid receptor	CB1	CNS	√	√
	CB2	Immune	√	√
Cholecystokinin receptor	CCKa	GI	√	√
Dopamine receptors	D1	CVS, CNS	√	√
	D2	CVS, CNS, endocrine	√	√
Endothelin receptor	ETa	CVS, development	√	√
Histamine receptor	H1	CVS, immune	√	√
	H2	GI, CVS	√	√
5-Hydroxytryptamine receptor	5HT1A	CNS, endocrine	√	√
	5HT1B	CVS, CNS	√	√
	5HT2A	CVS, CNS	√	√
	5HT2B	CVS, pulmonary, development	√	√
Muscarinic receptor	M1	CNS, GI, CVS	√	√
	M2	CVS	√	√
	M3	GI, pulmonary	√	√
Opioid receptor	Op-delta	CNS, CVS	√	√
	Op-kappa	GI, CNS, CVS	√	√
	Op-mu	CNS, GI, CVS	√	√
Vasopressin receptor	V1a	Renal, CVS	√	√

Channels	Ion Channel (human or rat)	Main Organ Class or System	Radioligand Binding	Function Assay (Manual patch clamp)
Cav1.2 (L-type) Rat Calcium Ion Channel	Dihydropyridine Site	CVS	√	√
K^+ Channel	hERG	CVS	√	√
KV (Non-Selective) Rat Potassium Ion Channel	Kv	CNS	√	√
Sodium Channel Site 1 (Non-Selective) Rat Ion Channel	Sodium Channel Site 1	CNS	√	√
Serotonin	5-HT3a	GI, endocrine	√	√
Nicotinic	nAChR, α7	CNS, CVS, GI, pulmonary	√	√
GABA	GABAA α1β3γ2	CNS	√	√
Glutamate	NMDAR-MK801	CNS	√	na*

Transporter and NR	Transporter NHR (human)	Main Organ Class or System	Radioligand Binding	Function Assay
Transporter	DAT	CNS	√	Dye Uptake
	5HTT	CNS, CVS	√	Dye Uptake
	NET	CNS, CVS	√	Dye Uptake
Steroid Nuclear Receptors	AR	Endocrine	√	Reporter gene assay
	GR	Endocrine, immune	√	Reporter gene assay

Enzymes	Enzyme (human)	Main Organ Class or System	Enzymatic Assay
Protein-Tyrosine Kinase - CTK	LCK	Immune	HTRF
Phosphodiesterase	PDE3A	CVS	Luminescent
	PDE4D2	CNS, immune	Luminescent
Cyclooxygenase	COX1	GI, pulmonary, renal	Fluorescence
	COX2	Immune, CVS	Fluorescence
Monoamine & NRT Synthesis & Metabolism	ACHE	CVS, GI, pulmonary	Optical Density
	MAO-A	CVS, CNS	Luminescent

WuXi AppTec Second Safety 54 Panel (Safety Extra 54 panel)

GPCRs	Receptor (Human)	Main Organ Class or System	Radioligand Binding	Function Assay (Ca^{2+} Assay)
5-Hydroxytryptamine receptor	5HT2C	CNS	√	√
	5HT7	CNS	√	√
Adenosine receptor	ADORA1	CNS	√	√
	ADORA2B	CNS	√	√
	ADORA3	CNS	√	√
Adrenoceptor	Alpha1	CVS, CNS	√	na*
	Alpha1B	CVS, CNS	√	√
	Alpha1D	CVS, CNS	√	√
	Alpha2B	CVS, CNS	√	√
	Alpha2C	Cervix, Endometrium	√	√
Bradykinin receptor	B1	CVS	√	√
	B2	CVS	√	√
Cholecystokinin receptor	CCKB	CNS, Pancreas, Stomach	√	√
Dopamine receptor	D2S	CVS, CNS	√	√
	D3	CVS, CNS	√	na*
	D4	CVS, CNS	√	√
	D5	CVS, CNS	√	√
PGE2 receptor	EP2	Placenta and lung	√	√
	EP4	Bone marrow, Pancreas	√	√
Platelet-Activating Factor	PAF	CVS	√	√
Endothelin receptor	ETB	CVS, development	√	√
Histamine receptor	H3	CVS	√	√
Muscarinic receptor	M4	CNS	√	√
	M5	CNS	√	√
Tachykinin receptor	NK1	Endocervix	√	√
Vasopressin receptor	V2	Adipose tissue	√	√

Channels	Ion Channel (human or rat)	Main Organ Class or System	Radioligand Binding	Function Assay
ATP-sensitive inward rectifier potassium channel	KATP	CNS, CVS	√	na*
Cav1.2 (L-type) Rat Calcium Ion Channel	Phenylalkylamine Site	CNS, CVS	√	na*
GABAA receptor	GABAA α1β2γ2	CNS	√	√
Glutamate (Non-Selective) Rat Ion Channel	AMPA	CNS	√	na*
	NMDA-Ifenprodil	CNS	√	na*

NR	NR (human)	Main Organ Class or System	Radioligand Binding	Function Assay
Estrogen receptor	ER	Cervix, endometrium,	√	Reporter gene assay
Peroxisome proliferator activated receptor gamma	PPARγ	Adipose tissue	√	Reporter gene assay
progesterone receptor	PR	Cervix, endometrium,	√	Reporter gene assay

Transmembrane (Other)	Target Name	Main Organ Class or System	Radioligand Binding	Function Assay
Sigma receptor	Sigma1	CNS	√	na*
	Sigma2	CNS	√	na*

Enzymes	Enzyme (human)	Main Organ Class or System	Enzymatic Assay
Angiotensin converting enzyme	ACE1	RAS	Fluorescence
	ACE2	RAS	Fluorescence
Cholinesterase	BuChE	Liver,Blood plasma	Optical Density
Serine/threonine-protein kinase	PKC alpha	Brain	Luminescent
Serine protease	Cathepsin G	Bone marrow	Optical Density
Monoamine oxidase	MAO-B	CVS, CNS	Luminescent
Histone Deacetylase	HDAC1	Epigenetic gene expression	Fluorescence
	HDAC2	Epigenetic gene expression	Fluorescence
	HDAC8	Epigenetic gene expression	Fluorescence
Serine protease	Thrombin	liver	Fluorescence
	Trypsin	small intestine	Fluorescence
INSR Tyrosine kinase	IRSR	liver, adipose tissue and skeletal muscle	Luminescent
Rho-associated protein kinase	ROCK 1	blood platelets	Luminescent
	ROCK 2	brain	Luminescent
Vascular Endothelial Growth Factor Receptor	VEGFR	placenta, liver, kidney, heart and brain	Luminescent
Phosphodiesterase	PDE1B	CVS, smooth muscle	Luminescent
	PDE2A	CVS, smooth muscle	Luminescent
	PDE5A1	CVS, smooth muscle	Luminescent

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