CERTARA

Secondary Intelligence[™]

Safety issues account for about a quarter of the attrition in drug projects. If it is a result of the primary pharmacology, you have to either drop the target entirely or manage the risk. However, if this arises from off-target activity, you have the additional option to dial this out and avoid the associated adverse events (AEs). This is the discipline of Secondary Pharmacology, the focus of Certara's new in silico technology.

SECONDARY INTELLIGENCE: PREDICTIVE TECHNOLOGY FOR IMPROVING SAFETY PROFILES

Secondary Intelligence uses off-target screening data to quantitatively predict safety outcomes in vivo and in the clinic?

Secondary Intelligence[™] assembles, curates and visualizes all secondary pharmacology analyses, providing key information on potential AEs, quantitatively rating each compound as to its likelihood of causing off-target safety issues that could impact clinical progress. The first module in Certara's ToxStudio[™] integrated modelling & simulation platform for safety pharmacology, toxicology and patient safety, Secondary Intelligence[™] is the only tool available to address this translational challenge.

- Secondary Intelligence assembles curated, organised information for a compound's secondary pharmacology readouts and analysis in one place.
- It provides up-to-date literature-based information on the expected side effects of a given compound as it engages with a particular off-target receptor in clinical use.
- This data enables virtual in vitro in vivo extrapolation (IVIVE).
- It rates each compound with a 'low', 'intermediate' or 'high' likelihood of causing AEs at the off-target receptor in clinical use, based on quantitative analysis of clinically used drugs that specifically target that receptor, and on its predicted plasma Cmax

Like radar, Secondary Pharmacology provides early alerts and allows you to decide on your next move.

For each receptor, we evaluated That data is what you would We detailed their main all the drugs that target it for expect to happen with your their therapeutic efficacy, and pharmacodynamic effects and compound in clinical use if its for which an interaction at this side effects, summarized in a interaction with this receptor receptor was their primary table for each receptor. was sufficiently high at clinical pharmacological effect. We collated data on the reported To aid visualization and go/ free plasma concentration for Receptor Liability Pathway for no go decision making, the SW eliciting PD effects, collected each of the side effects, using the categorizes your test compounds potency data from in vitro assays structure of Adverse Outcome relative to the reference drugs to and plotted the ratio of the free Pathways to assess how hard we determine likelihood of causing AE plasma concentration divided by have to hit that receptor to see in clinical use. the Ki (or IC50) for each drug. those effects.



s Project Compounds F	Receptors	Compos	ind Assessmen	nt Thresholds						Project: demo1 Com
5 sodium Receptor Summary						😨 😑 Compound A Data ((Na _v 1.5 _{sodium} subset)			
Receptor				Na v 1.5 se	odium (GtP)	RLP Parameter	Value	Unit	Assay Notes	
Alternate Name			Cardiac sodium channel			Cu	0.025	μM	estimated	
Class			Ion channel			IC50_NAV1PT5	5.2	μM	CRO_panel_data	
Modulation			\oplus		\otimes	Qnet_1x	0.0728	uC/uF	rescaled ORd model	
/lain organ/organ system(s) a	ffected				CNS; GIT; CVS	Qnet 2x	0.0727	uC/uF	rescaled ORd model	
Liability of most concern					QRS prolongation	Onet 4x	0.0724	uC/uE	rescaled ORd model	
Commonest associated side effects					Dizziness; GI disturbances	and_44	0.0124	dordi		
pected safety pharmacology	outcomes				QRS prolongation					
Translatable biomarker										
Translatable biomarker hat target this receptor (M,W Ajmaline	r /,D)	Chm	Drb ^	Other compounds that	ƠQRS t target this receptor (R,V)	Compound A Data © Drug comparison	Visualisation for Na _v 1.5 _{se}	diam		
Translatable biomarker hat target this receptor (M,W Ajmaline Aprindine Cibenzoline	r /,D)	Chm Chm Chm	Drb Crb	Other compounds that	ƠQRS target this receptor (R,V)	Compound A Data 1 © Drug comparison	Visualisation for Na $_{\rm v}$ 1.5 $_{\rm kc}$	diam		1
Translatable biomarker hat target this receptor (M.W Ajmaline Aprindine Cibenzoline Disopyramide	r /,D) GtP	Chm Chm Chm Chm	Drb * Drb * Drb *	Other compounds that	∆10RS	Compound A Data Orug comparison	Visualisation for Na $_{\rm V}$ 1.5 $_{\rm kc}$		H-Quindine HPropatenone HProcanamide	
Translatable biomarker hat target this receptor (M.W Ajmaline Aprindine Cibenzoline Disopyramide Encainide	r (,D) GtP	Chm Chm Chm Chm Chm	Drb forb forb forb forb forb forb forb fo	- Other compounds that	ΔtQRS	Compound A Data 1 © Drug comparison	Visualisation for Na $_{\rm v}$ 1.5 $_{\rm ad}$	diam	HQuinkine ProgateDroate HTGLainApp HTGLainApp HTGLainApp HTGLAINAPP HTGL	
Translatable biomarken that target this receptor (M,W Ajmaline Aprindine Cilbenzoline Disopyramide Encoinide Flecainide	r ,(D) GtP GtP	Chm Chm Chm Chm Chm Chm Chm	Drb 1 Drb 2 Drb 2 Drb 2 Drb 2 Drb 2	- Other compounds that	Δ10RS	Compound A Data 1 © Drug comparison	Visualisation for Na , 1.5 , ,	diam	HQuindane HProgatenone Procatenone Procatenone Honoroto Honor	
Translatable biomarken hat target this receptor (M.W Ajmaline Aprindine Cibenzoline Disopyramide Encainide Flecainide	r LD) GtP GtP	Chm Chm Chm Chm Chm Chm	Drb Prb Prb Prb Prb Prb Prb Prb Prb Prb P	- Other compounds that	Δ1QRS	Compound A Data	Visualisation for Na $_{\rm 0.1.5}$ _{ad}	dum 	HQuinishe Propatence HPhenfold HPhenfold Honorable Honorable Honorable Honorable Hencalade	
Translatable biomarken hat target this receptor (U.W Ajmaline Aprindine Cibenzoline Disopyramide Encainide Flacainide und A Risk at Na.y 1.5, soluen	r AD) GtP GtP	Chm Chm Chm Chm Chm Chm	Drb Drb Drb Drb Drb Drb	- Other compounds that	Δ10RS	Compound A Data © Drug comparison Drugs Jarmetico	Visualisation for Na , 1.5 ,	dum HDIso	+Candane +Piocanamide +Aliscande - Miniscrone +Moniscrone + Locater (ignocane) + Exclande + Exclande + Exclande + Exclande + Exclande + Exclande + Exclande	
Translatable biomarker hat target this receptor (M.W Ajmaline Clearzoline Disopyramide Encalinide Ficcalinide	r AD) GtP GtP	Chm Chm Chm Chm Chm Chm	Drb 1 Drb 1 Drb 1 Drb 2 Drb 2	Other compounds that	Δ: QRS	Compound A Data Drug comparison Drugs targeting	Visualisation for Na , 1.5 ,	dium HOisp	HQunidae HPropatence HPrentaria HPrentaria HPrenta Horandee HPrechade HPrechade HPrechade HPrechade HPrechade HPrechade HPrechade HPrechade HPrechade HPrechade HPRECADE	
Translatable biomarker hat target this receptor (IL), W Ajmaline Aprindine Aprindine Disopyramide Encalmide Flecanide Mathematical States and A Risk et Nay, 15 Add a comm	r AD) GtP GtP GtP	Chm Chm Chm Chm Chm Chm	Drb 1 Drb 1 Drb 1 Drb 1 Drb 2	Other compounds that	Δ1QRS	Compound A Data Compound A Data Drugs trageting this recepto	Visualisation for Na $_{\rm V}$ 1.5 $_{\rm vol}$ r	dium HOlisō ⊢+Ajmali	HQuinishe Propatence HPrenton HPrenton Horamiste H	
Translatable biomarkes hast target this receptor (BLW Almaline Ciberostine Disopyramelo Encalnide Flecalnide and A Risk at Vis15_ kuterit Add a comm	r AD) GtP GtP	Chm Chm Chm Chm Chm	Drb Drb Drb Drb Drb Crb Crb Crb Crb Crb Crb Crb C	Other compounds that	Δ1QRS	Compound A Data © Drug comparison Drugs targeting this recepto Compound.	Wenalitation for Na , 1.5 , , , , , , , , , , , , , , , , , , ,	diam ⊨⊡isộ ⊨+Ajmali	H-Canadre H-Protestence H-Protestence H-Protestence H-Canadre H	

Secondary Intelligence software identifies the key safety/tox information about each receptor, allowing you to focus on how a test compound interacts with that receptor. It can address safety performance against multiple receptors. Secondary Intelligence ranks the likelihood of each off-target interaction during clinical use, color-coding in red, amber or green.



Secondary Intelligence prioritises "receptor interactions of concern" in a variety of data representations, and ranks compounds against each other to make quantitatively based decisions as to which compounds to progress.

About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions, and regulatory agencies across 62 countries.

For more information visit www.certara.com or email sales@certara.com.

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