Adapting a secondary pharmacology-based tool to flag-up off-target interactions of particular concern in pediatric patients

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Outline of this talk

- In 2021 Certara launched a software tool (Secondary Intelligence™) that enables safety pharmacologists to contextualise their secondary pharmacology readouts in relation to predicted therapeutic plasma concentration in humans
- Earlier this year we released the latest version containing 111 receptors, and also published our first full paper on it
- As part of an ongoing Research Collaboration Agreement with the FDA, Gil asked if we could adapt it for use in predicting off-target safety in pediatric patients
- I will start with a description of Secondary Intelligence, then present the challenges and some initial findings in what is 'work in progress'
- I am not an expert in pediatric pharmacology & therapeutics – this is about the extent of my knowledge:

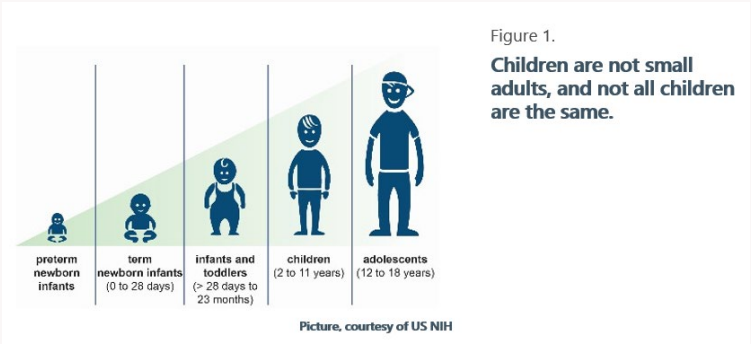

Figure 1.

Children are not small adults, and not all children are the same.

Picture, courtesy of US NIH

- Fortunately, Certara have a long track record of PBPK modelling of pediatric PK, and have world-leading experts in this field…

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Modelling of pediatric PK using physiologically based pharmacokinetics (PBPK)

Received: 10 September 2021 | Revised: 10 January 2022 | Accepted: 13 January 2022
DOI: 10.1002/psp4.12764
ARTICLE
CPT Pharmacometrics Syst Pharmacol. 2022;11:373–383.

Increasing application of pediatric physiologically based pharmacokinetic models across academic and industry organizations

Trevor N. Johnson | **Ben G. Small** | **Karen Rowland Yeo** Certara UK Limited (Simcyp Division), Sheffield, UK

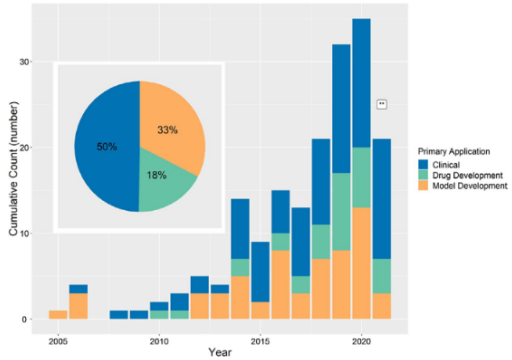
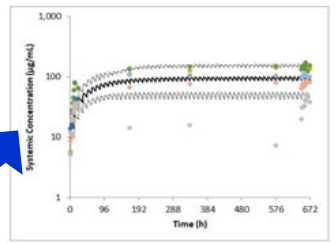


FIGURE 4 Growth in pediatric physiologically based pharmacokinetic by primary application. Stacked bars represent cumulative count (e.g., in 2005 there was one study assigned to model development, and in 2006 there were four studies: one assigned to clinical and three assigned to model development). Inset pie chart shows percentage of the total data set (absolute numbers: clinical 90; drug development, 32; model development, 59) in each primary application. **Partial year recorded

Drugs that achieved marketing approval for use in pediatrics where pediatric PK was modelled using Certara's Simcyp® PBPK Simulator :

Deflazocort	Duchenne muscular dystrophy
Entrectinib	solid tumours
Everolimus	tuberous sclerosis complex-associated seizures
Guanfacine	attention deficit hyperactivity disorder (ADHD)
Quetiapine	schizophrenia and bipolar disorder
Radiprodil	infantile spasm syndrome (West syndrome)
Revumenib	acute leukaemia
Risdiplam	spinal muscular atrophy
Trikafta	cystic fibrosis
Voxelotor	sickle cell disease



Lower haematocrit for SCD in PBPK model led to reduced B:P ratio from **33.16 to 15.5** (consistent with observed data).

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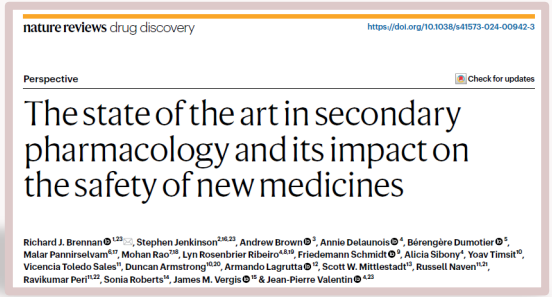
From last year's article by the IQ DruSafe In Vitro Secondary Pharmacology Working Group: the importance of data interpretation and contextualization



nature reviews drug discovery
https://doi.org/10.1038/s41573-024-00942-3
Perspective
Check for updates

The state of the art in secondary pharmacology and its impact on the safety of new medicines

Richard J. Brennan[1,23], Stephen Jenkinson[2,16,23], Andrew Brown[3], Annie Delaunois[4], Bérengère Dumotier[5], Malar Pannirselvam[6,17], Mohan Rao[7,18], Lyn Rosenbrier Ribeiro[4,8,19], Friedemann Schmidt[9], Alicia Sibony[4], Yoav Timsit[10], Vicencia Toledo Sales[11], Duncan Armstrong[10,20], Armando Lagrutta[12], Scott W. Mittlestadt[13], Russell Naven[11,21], Ravikumar Peri[11,22], Sonia Roberts[14], James M. Vergis[15] & Jean-Pierre Valentin[4,23]

Data interpretation and contextualization

When an off-target activity is detected for a compound, this does not necessarily mean it will produce dangerous adverse clinical effects and that its development should be terminated. Secondary pharmacology data require contextualization and interpretation to establish a clear understanding of risk and to avoid discarding what could be promising medicines.

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So, when you get the secondary pharmacology readout, how do you 'interpret and contextualize' it?

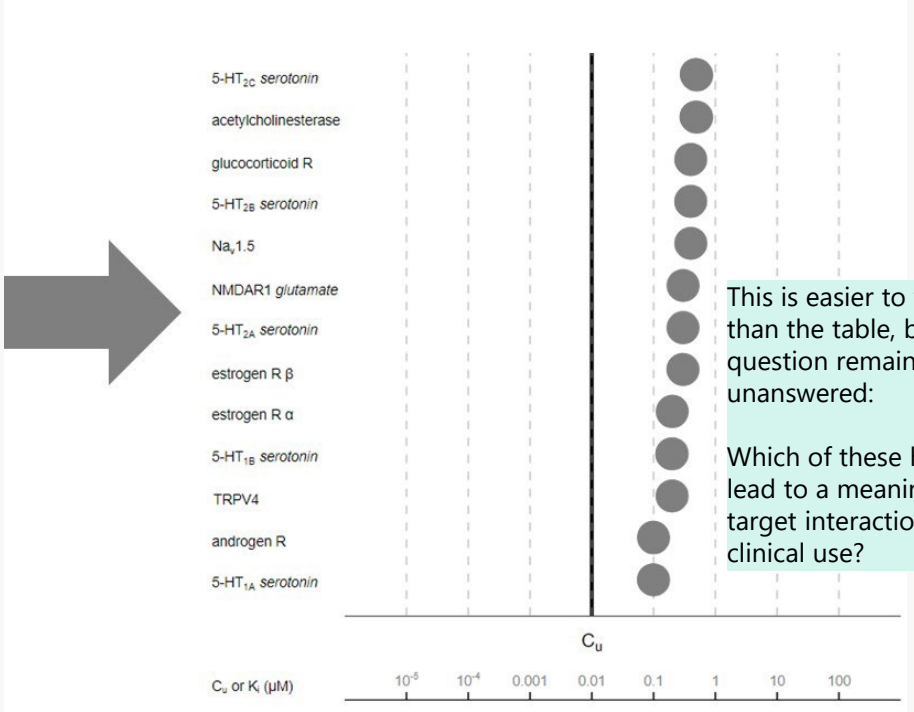
ABOVE PRIMARY TESTS IN RANK ORDER OF POTENCY

CAT. #	PRIMARY ENZYME ASSAY	SPECIES	CONC.	% INH.	IC_{50}*	K_i	n_H
176000	Protein Kinase, ick (p56[dr]) Tyrosine Kinase		10 µM	52	7.87 µM		
156000	Phosphodiesterase PDE5		100 µM	71	17.5 µM		
166000	Protein Kinase, Ca^{2+}/Calmodulin-Dep. PK II		100 µM	57	19.9 µM		
177000	Protein Kinase PKA, Non-Selective		100 µM	50	36.5 µM		
194000	Thromboxane Synthetase		100 µM	66	38.6 µM		
156100	Phosphodiesterase PDE6		100 µM	65	45.9 µM		
106000	Acyl CoA-Cholesterol Acyltransferase, Intestine		100 µM	67	49.3 µM		
132000	Leukotriene C_4 Synthetase		100 µM	52	97.6 µM		

CAT. #	PRIMARY RADIOLIGAND ASSAY	SPECIES	CONC.	% INH.	IC_{50}*	K_i	n_H
219800	Dopamine D_2		10 µM	78	0.814 µM	0.046 µM	0.465
252600	Muscarinic M_1		10 µM	90	2.45 µM	0.59 µM	2.32
203400	Adrenergic α_{1D}		10 µM	92	1.36 µM	0.667 µM	0.981
252900	Muscarinic M_4		10 µM	70	6.31 µM	0.881 µM	1.82
255600	Tachykinin NK_2		10 µM	63	3.62 µM	1.21 µM	0.906

*A standard error of the mean is presented where results are based on multiple, independent determinations.

Which of these hits will lead to a meaningful off-target interaction during clinical use?



This is easier to visualize than the table, but the question remains unanswered:

Which of these hits will lead to a meaningful off-target interaction during clinical use?

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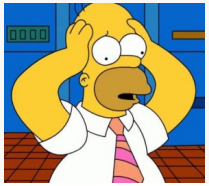
What if you could go from ‘clueless’ to ‘genius’ at the click of a button?



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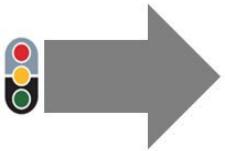

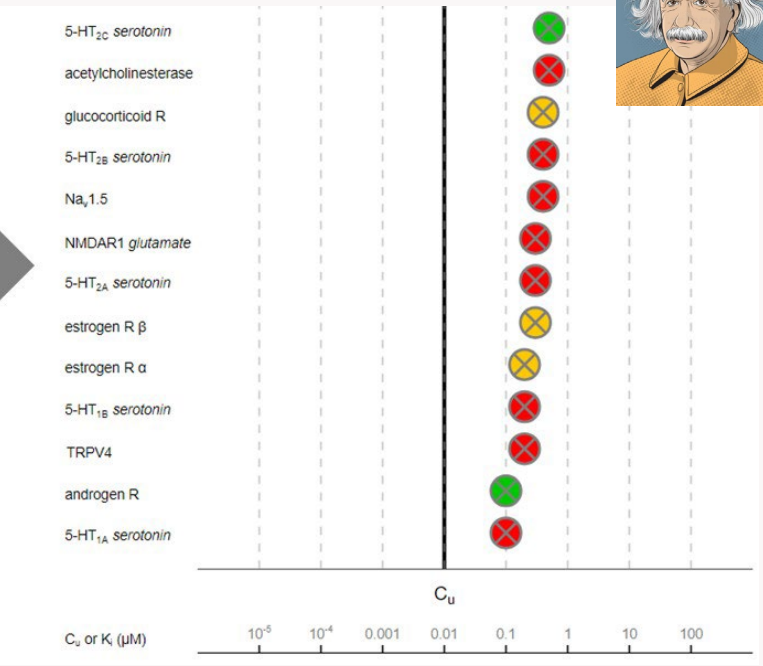

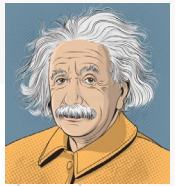

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Comparing K_i/C_u (or C_u/K_i) of a test compound to that of reference drugs is well-established

Previous publications successfully deployed this approach at 5 different off-target receptors:

Receptor	Modulation	Adverse effect	Ratio used	Reference
hERG	Negative	Torsade de pointes	IC_{50}/C_u	Webster et al., 2002
hERG	Negative	Torsade de pointes	IC_{50}/C_u	Redfern et al., 2003
$Na_V1.5$	Negative	QRS prolongation	IC_{50}/C_u	Harmer et al., 2011
ENT_1	Negative	Dyspnoea	IC_{50}/C_u	Rosenbrier Ribeiro & Storer, 2017
5-HT_{2B}	Positive	Cardiac valvulopathy	K_i/C_u	Papoian et al., 2017
$VEGFR_2$	Negative	Blood pressure elevation	C_u/IC_{50}	Collins et al., 2018

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Secondary Intelligence™ software tool

Secondary Intelligence Software

Previous publications have used the same principle: the ratio of K_i or IC_{50} to C_u (or the inverse of this ratio) as a surrogate of in vivo receptor occupancy required to achieve an undesirable PD effect

However, a variety of approaches have been used in terms of data curation criteria and data presentation

We applied a consistent approach across 111 receptors (to date), and put it into a user-friendly software package

For each receptor we expertly curated lists of reference drugs

Reference drugs target that receptor for their therapeutic efficacy; most are marketed drugs but also includes candidate drugs still in clinical development or discontinued

Where available, for each reference drug we sourced and expertly checked data on:

K_i (or IC_{50})
receptor selectivity
lowest effective plasma concentrations in humans
human plasma protein binding data
adverse effects in clinical use

Redfern WS *et al.* (2025) *J Pharmacol Toxicol Methods* **131**: 107570

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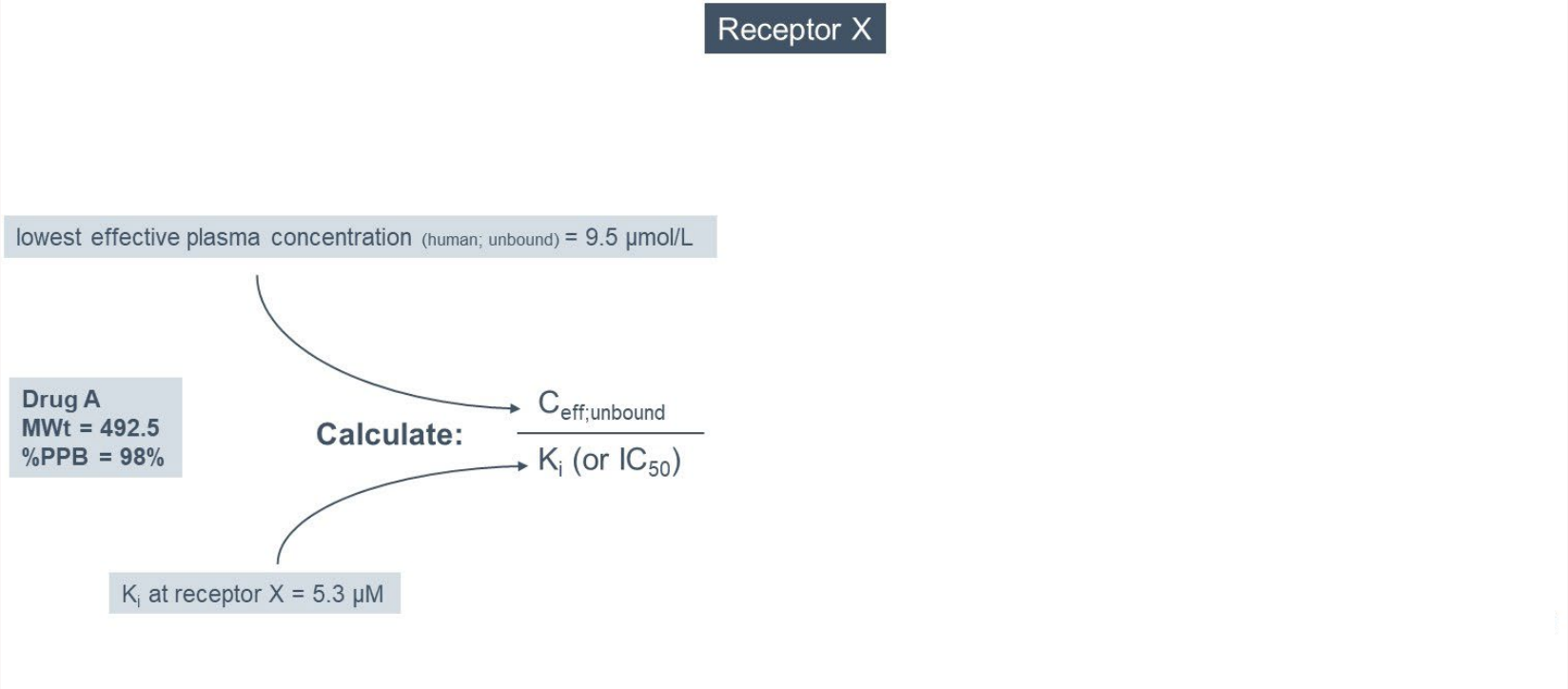
For each reference drug:



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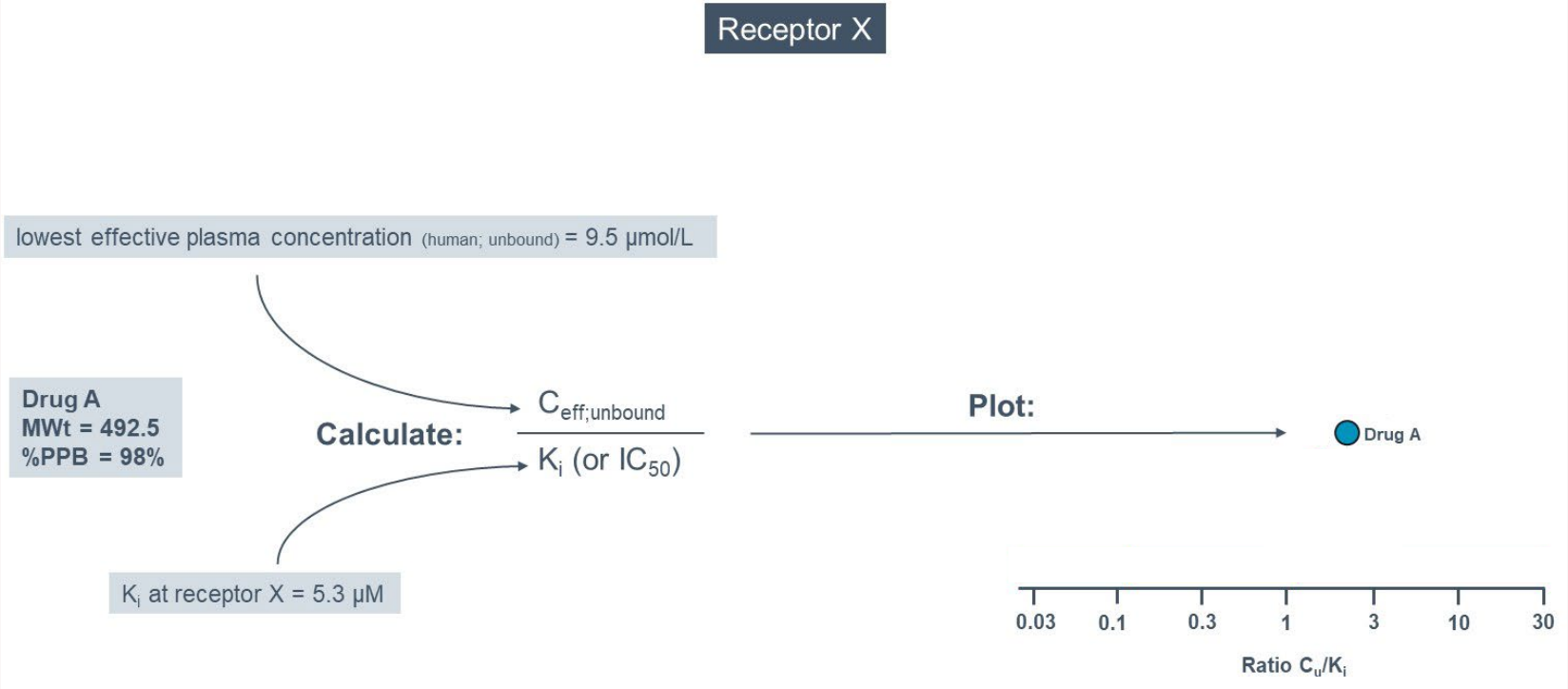

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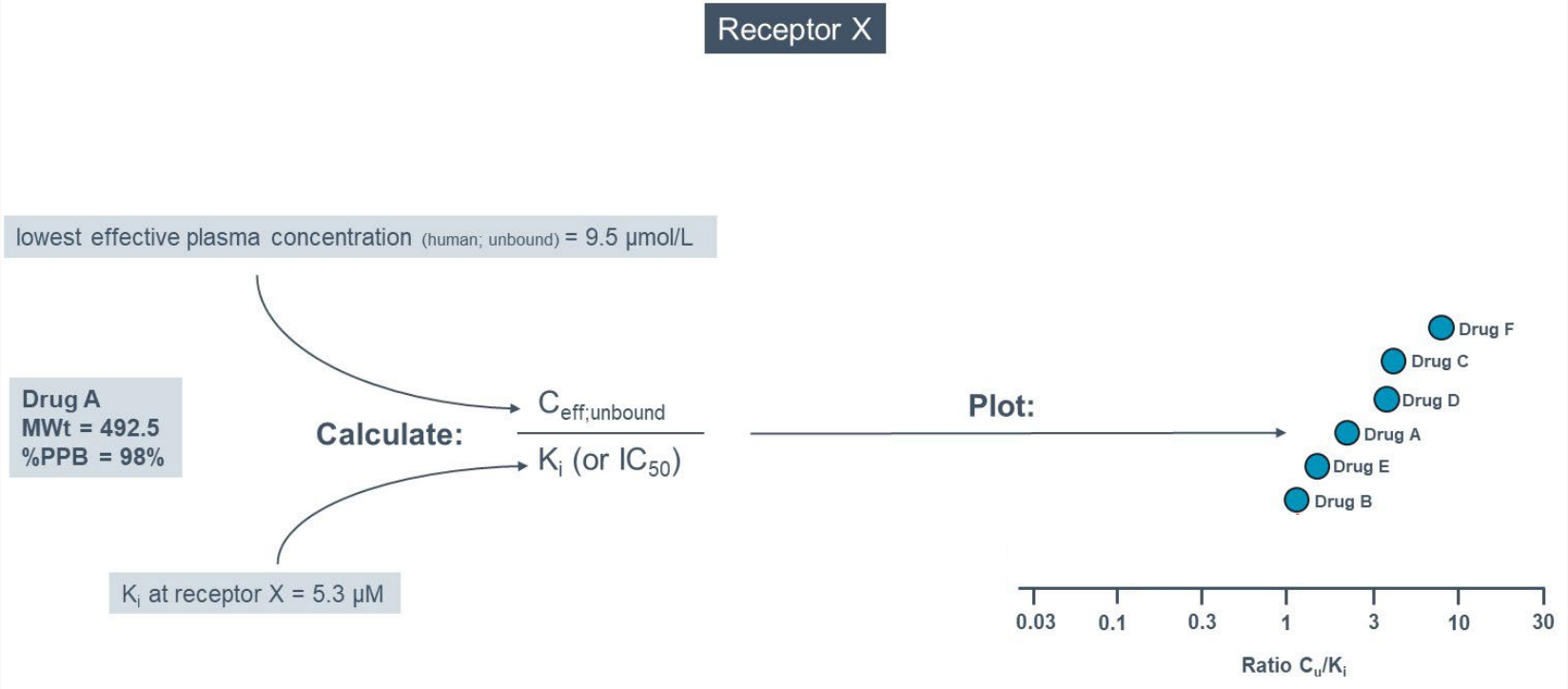

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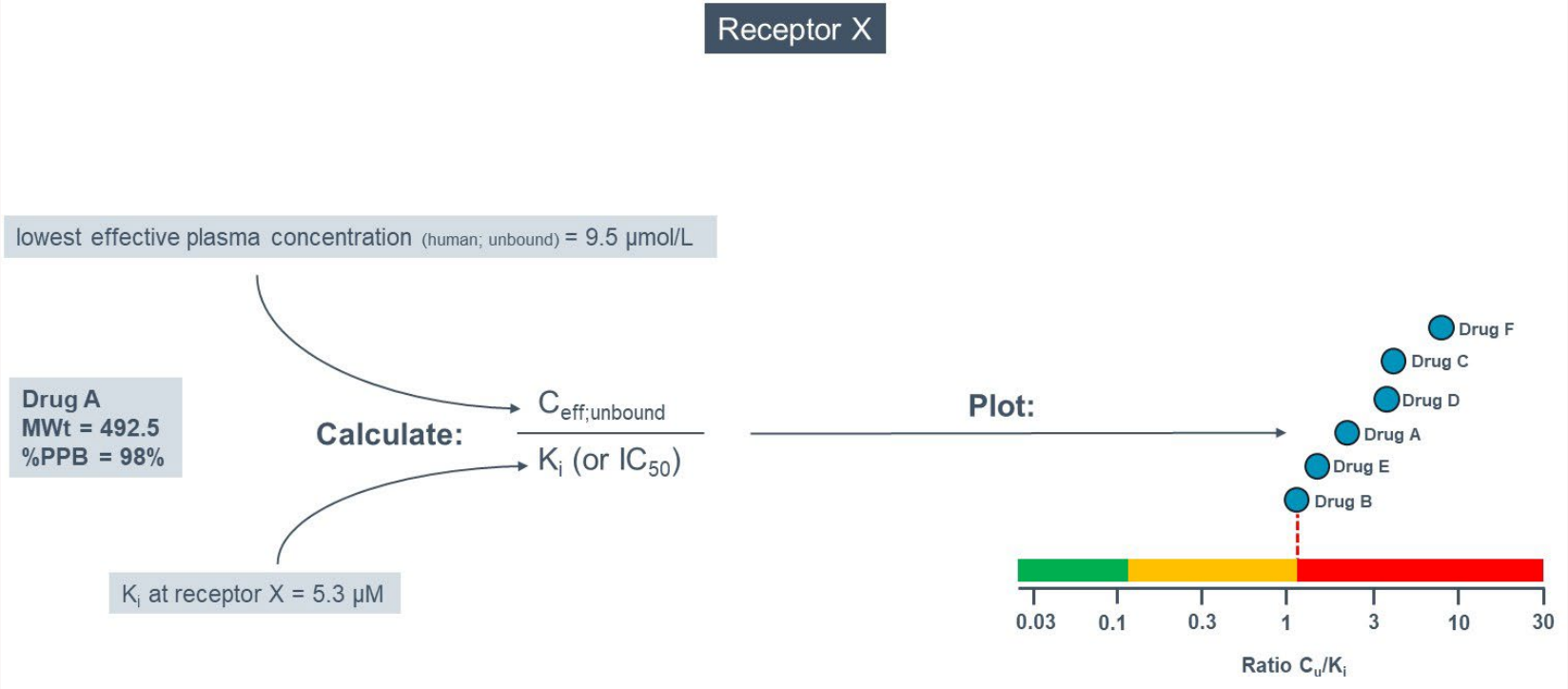
For each reference drug:



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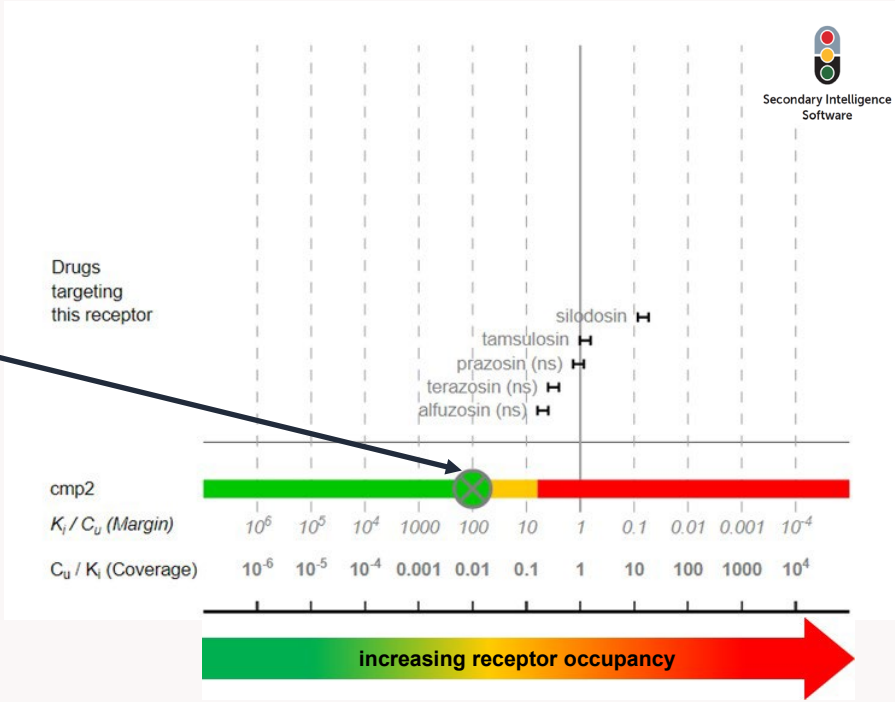
Example of likelihood of a test compound's interaction with one of the receptors during clinical use

Estimated 'occupancy' of this off-target receptor by a test compound at its predicted unbound plasma concentration in clinical use



This compound is deemed to have a low likelihood of causing side effects via this off-target receptor in clinical use, as its receptor occupancy is below the level required to elicit an effect

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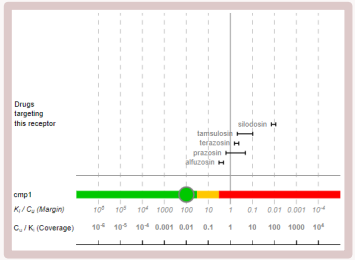
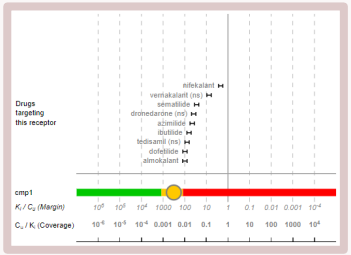
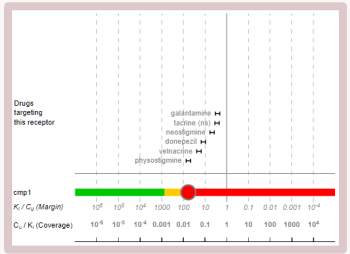
Interpreting the ‘traffic lights’ readout for a test compound

		Likelihood of interaction with this off-target receptor in clinical use	Next steps? (Suggestions)
Receptor ‘X’		**LOW**	**Further investigation probably unnecessary**
Receptor ‘Y’		**MEDIUM**	**Investigate further if predicted free C_{max} increases**
Receptor ‘Z’		**HIGH**	**Consider further investigation of the potential safety issue (in vitro and/or in vivo). Could involve additional endpoints in safety pharmacology and/or toxicology studies, or bespoke studies.**

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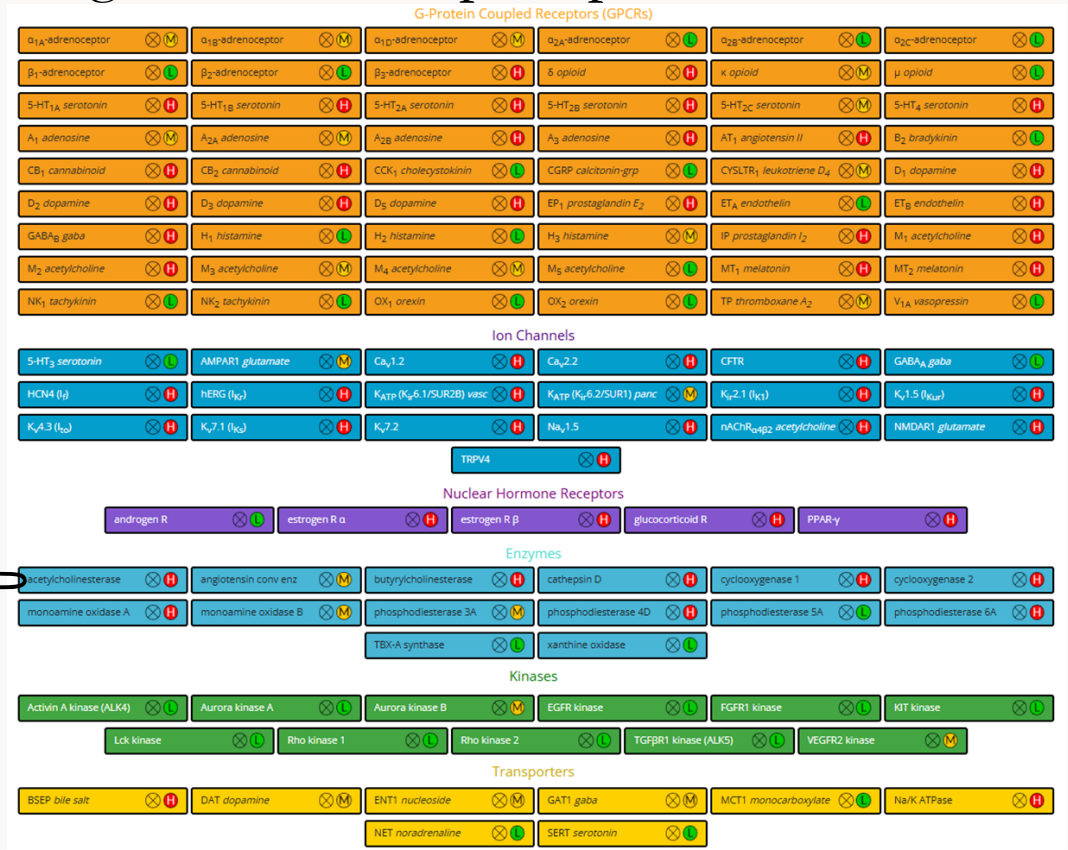
Secondary Intelligence™: Receptor panel

Secondary Intelligence Software



111 receptors arranged by receptor class; includes all 44 receptors in the Bowes panel

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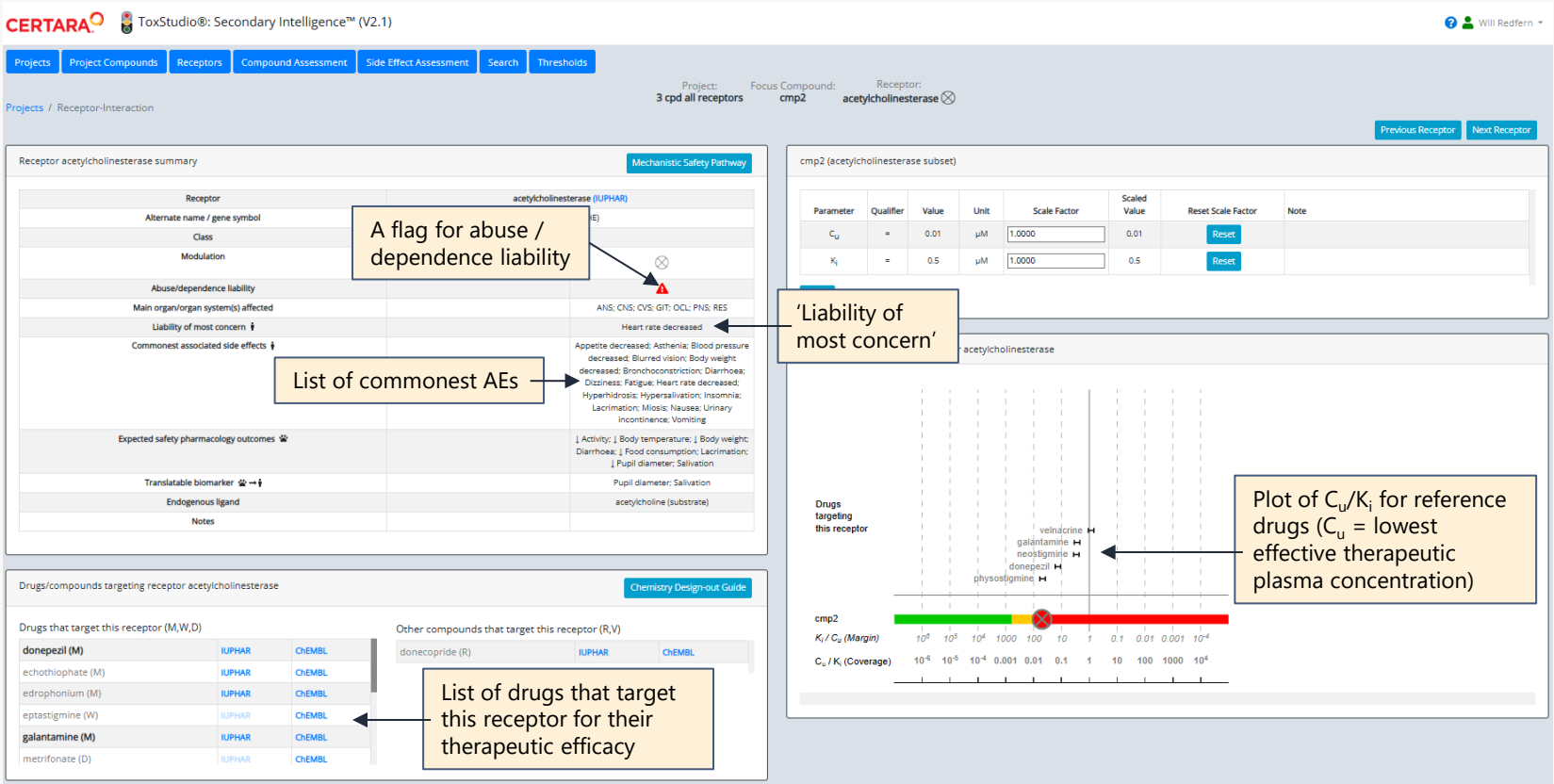
A ‘receptor page’ in Secondary Intelligence



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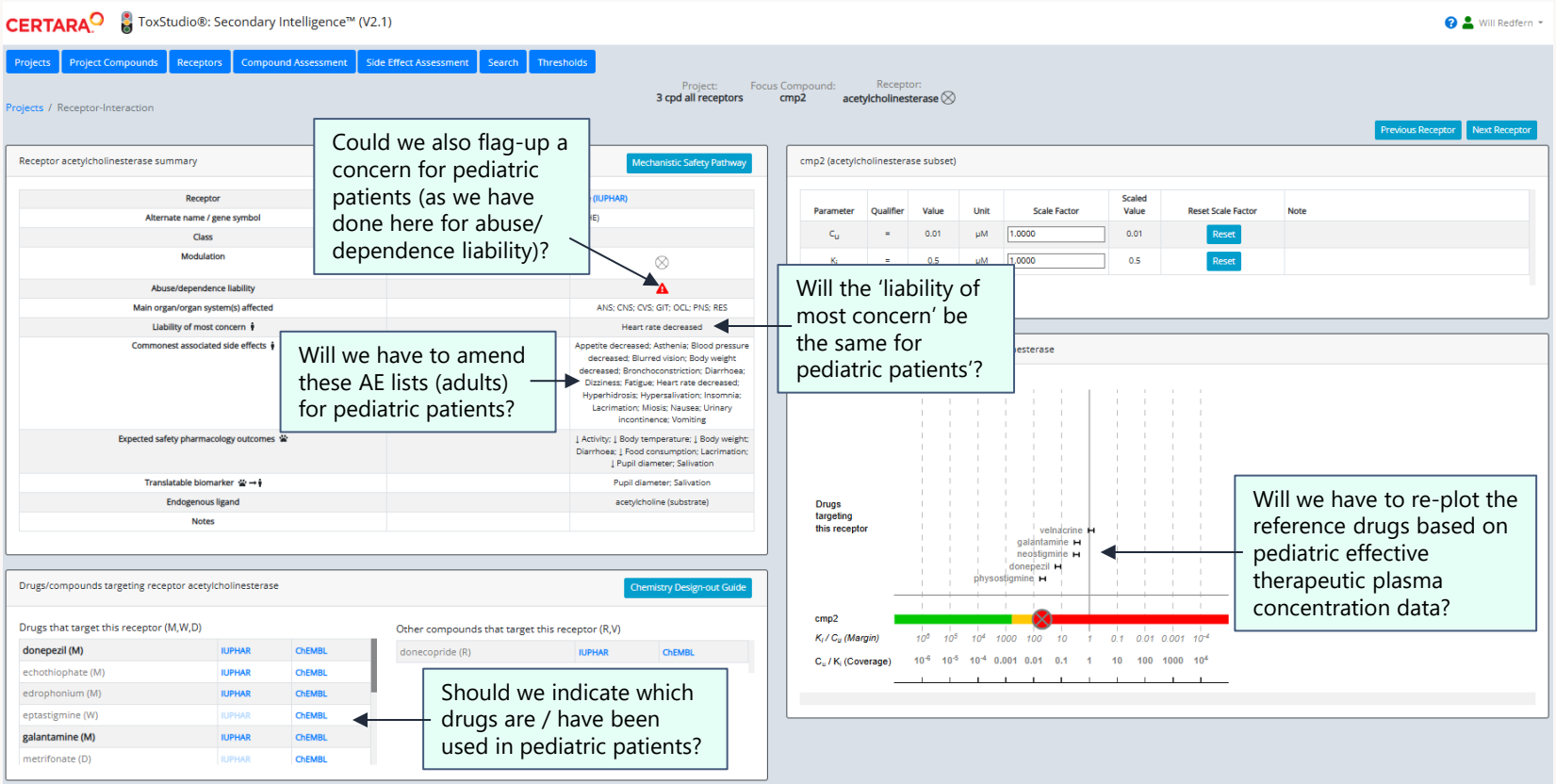
Can we adapt the receptor pages for pediatric patients?



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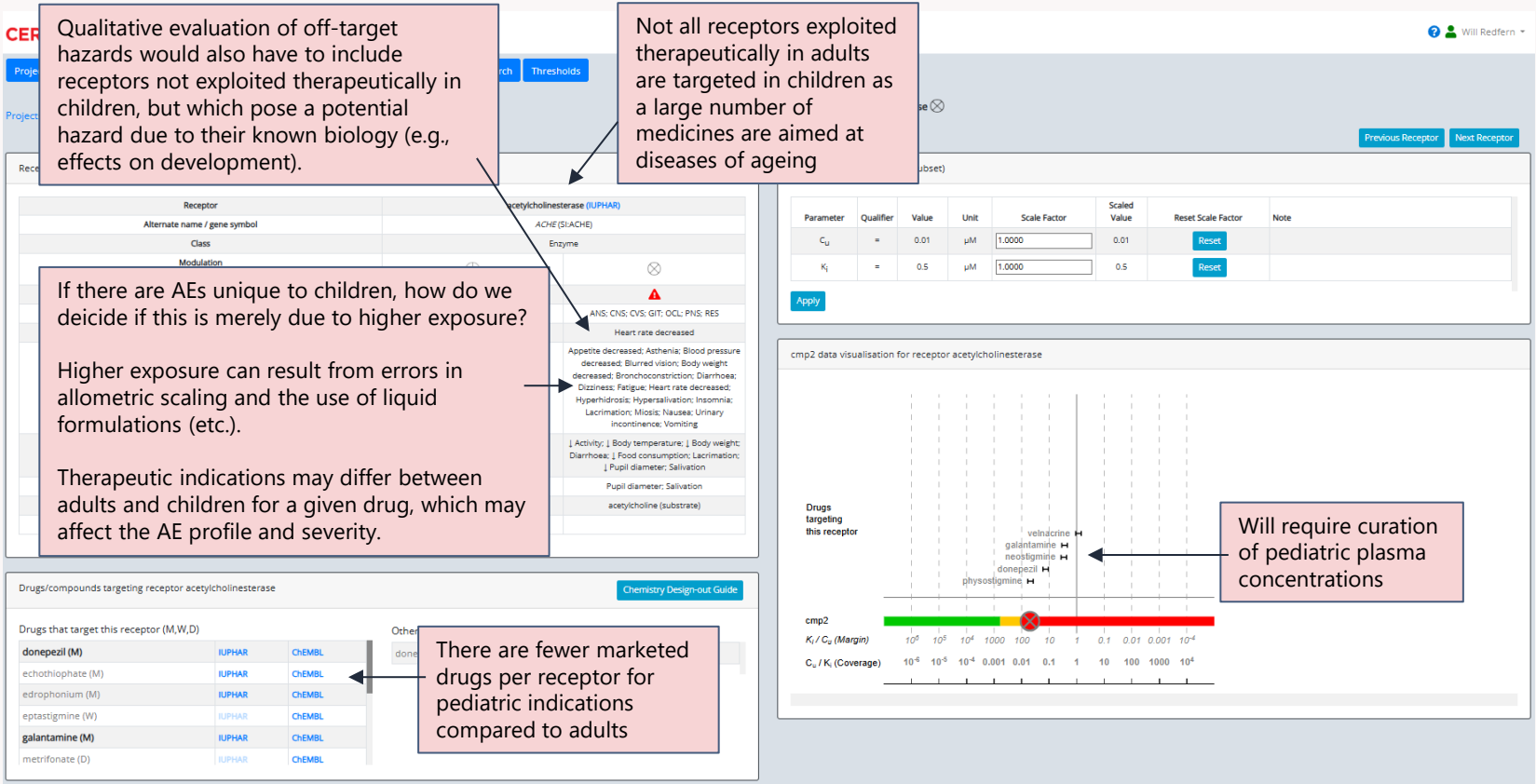
The challenges involve both qualitative information and quantitative data



QUALITATIVE INFORMATION

QUANTITATIVE DATA

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Gap analysis: availability of reference drugs in pediatric patients

Receptor in SI		Therapeutically targeted?	
Abbreviation	Full name	Adults	Pediatrics
5HTR1A	5-HT$_{1A}$ *serotonin*	YES	YES
5HTR1B	5-HT$_{1B}$ *serotonin*	YES	YES
5HTR2A	5-HT$_{2A}$ *serotonin*	YES	YES
5HTR2B	5-HT$_{2B}$ *serotonin*	YES	YES
5HTR2C	5-HT$_{2C}$ *serotonin*	YES	NO
5HTR4	5-HT$_{4}$ *serotonin*	YES	NO
ADORA1	A$_1$ *adenosine*	YES	NO
ADORA2A	A$_{2A}$ *adenosine*	YES	YES
ADORA2B	A$_{2B}$ *adenosine*	YES	NO
ADORA3	A$_3$ *adenosine*	YES	NO
ADRA1A	α_{1A}-adrenoceptor	YES	YES
ADRA1B	α_{1B}-adrenoceptor	YES	NO
ADRA1D	α_{1D}-adrenoceptor	YES	YES
ADRA2A	α_{2A}-adrenoceptor	YES	YES
ADRA2B	α_{2B}-adrenoceptor	YES	YES
ADRA2C	α_{2C}-adrenoceptor	YES	YES
ADRB1	β_1-adrenoceptor	YES	YES
ADRB2	β_2-adrenoceptor	YES	YES
ADRB3	β_3-adrenoceptor	YES	YES
AGTR1	AT$_1$ *angiotensin II*	YES	YES
BKRB2	B$_2$ *bradykinin*	YES	YES
CBR1	CB$_1$ *cannabinoid*	YES	NO
CBR2	CB$_2$ *cannabinoid*	YES	NO
CCKR1	CCK$_1$ *cholecystokinin*	YES	NO
CGRP	CGRP *calcitonin-grp*	YES	YES
CYSLTR1	CYSLTR$_1$ *leukotriene-D$_4$*	YES	YES
DAR1	D$_1$ *dopamine*	YES	YES
DAR2	D$_2$ *dopamine*	YES	YES
DAR3	D$_3$ *dopamine*	YES	NO
DAR5	D$_5$ *dopamine*	YES	YES
DOR	δ *opioid*	YES	NO
ETRA	ET$_A$ *endothelin*	YES	YES
ETRB	ET$_B$ *endothelin*	YES	NO
GABARB	GABA$_B$ *gaba*	YES	YES
HRH1	H$_1$ *histamine*	YES	YES
HRH2	H$_2$ *histamine*	YES	YES
HRH3	H$_3$ *histamine*	YES	NO
KOR	K *opioid*	YES	YES
MACHR1	M$_1$ *acetylcholine*	YES	YES
MACHR2	M$_2$ *acetylcholine*	YES	YES
MACHR3	M$_3$ *acetylcholine*	YES	YES
MACHR4	M$_4$ *acetylcholine*	YES	YES
MACHR5	M$_5$ *acetylcholine*	YES	YES
MOR	μ *opioid*	YES	YES
MTR1	MT$_1$ *melatonin*	YES	YES
MTR2	MT$_2$ *melatonin*	YES	YES
OXR1	OX$_1$ *orexin*	YES	NO
OXR2	OX$_2$ *orexin*	YES	NO
PTGER1	EP$_1$ *prostaglandin E$_2$*	NO	NO
PTGIR	IP *prostaglandin I$_2$*	YES	NO
TACR1	NK$_1$ *tachykinin*	YES	YES
TACR2	NK$_2$ *tachykinin*	YES	NO
TBXA2R	TP *thromboxane A$_2$*	YES	NO
VPRR1A	V$_{1A}$ *vasopressin*	YES	YES

GPCRs

Receptor in SI		Therapeutically targeted?	
Abbreviation	Full name	Adults	Pediatrics
5HTR3	5-HT$_3$ *serotonin*	YES	YES
AMPAR1	AMPAR1 *glutamate*	YES	YES
CAV1PT2	Ca$_v$1.2	YES	YES
CAV2PT2	Ca$_v$2.2	YES	NO
CFTR	CFTR	YES	YES
GABARA	GABA$_A$ *gaba*	YES	YES
HCN4	HCN4 (I_f)	YES	YES
HERG	hERG (I_{Kr})	YES	YES
KATP	K_{ATP} (K_v6.2/SUR1) *panc*	YES	YES
KATPV	K_{ATP} (K_v6.1/SUR2B) *vasc*	YES	NO
KIR2PT1	K_{ir}2.1 (I_{K1})	NO	NO
KV1PT5	K_v1.5 (I_{Kur})	NO	NO
KV4PT3	K_v4.3 (I_{to})	NO	NO
KV7PT1	K_v7.1 (I_{Ks})	YES	YES
KV7PT2	K_v7.2	YES	NO
NACHRA4B2	nAChR$_{\alpha4\beta2}$ *acetylcholine*	YES	NO
NAV1PT5	Na$_v$1.5	YES	YES
NMDAR1	NMDAR1 *glutamate*	YES	YES
TRPV4	TRPV4	NO	NO

Ion channels

Receptor in SI		Therapeutically targeted?	
Abbreviation	Full name	Adults	Pediatrics
ANDR	androgen R	YES	YES
ESTRA	estrogen R α	YES	YES
ESTRB	estrogen R β	YES	NO
GCCR	glucocorticoid R	YES	YES
PPARG	PPAR-γ	YES	NO

Nuclear hormone receptors

Receptor in SI		Therapeutically targeted?	
Abbreviation	Full name	Adults	Pediatrics
ACE	angiotensin conv enz	YES	YES
ACHE	acetylcholinesterase	YES	YES
BCHE	butyrylcholinesterase	YES	NO
COX1	cyclooxygenase 1	YES	YES
COX2	cyclooxygenase 2	YES	YES
CTSD	cathepsin D	YES	NO
MAOA	monoamine oxidase A	YES	NO
MAOB	monoamine oxidase B	YES	NO
PDE3A	phosphodiesterase 3A	YES	YES
PDE4D	phosphodiesterase 4D	YES	YES
PDE5A	phosphodiesterase 5A	YES	YES
PDE6A	phosphodiesterase 6A	YES	NO
TBXAS1	TBX-A synthase	YES	NO
XDH	xanthine oxidase	YES	YES

Enzymes

Receptor in SI		Therapeutically targeted?	
Abbreviation	Full name	Adults	Pediatrics
ALK4	Activin A kinase (ALK4)	YES	NO
ALK5	TGFβR1 kinase (ALK5)	YES	NO
AURKA	Aurora kinase A	YES	NO
AURKB	Aurora kinase B	YES	NO
EGFR	EGFR kinase	YES	NO
FGFR1	FGFR1 kinase	YES	NO
KIT	KIT kinase	YES	NO
LCK	Lck kinase	YES	YES
ROCK1	Rho kinase 1	YES	NO
ROCK2	Rho kinase 2	YES	NO
VEGFR2	VEGFR2 kinase	YES	YES

Kinases

Receptor in SI		Therapeutically targeted?	
Abbreviation	Full name	Adults	Pediatrics
BSEP	BSEP *bile salt*	YES	YES
DAT	DAT *dopamine*	YES	YES
ENT1	ENT1 *nucleoside*	YES	NO
GABAT	GAT1 *gaba*	YES	YES
MCT1	MCT1 *monocarboxylate*	YES	NO
NAKATPASE	Na/K ATPase	YES	NO
NET	NET *noradrenaline*	YES	YES
SERT	SERT *serotonin*	YES	YES

Transporters

Gap analysis of receptors in Secondary Intelligence (currently 111) associated with marketed drugs in pediatric patients compared to adults.

Light blue: 'therapeutically targeted'

Blank: not targeted

60% of the SI receptors targeted therapeutically in adults are targeted therapeutically in pediatric patients (i.e., 40% aren't)

Of the 44-receptor Bowes panel, 5 are not targeted therapeutically in pediatrics.

AEs of therapeutically used drugs provide the most definitive list of AEs associated with interaction with that receptor.

Gaps in receptors targeted in the pediatric population will require curation of potential AEs from AEs in adults and from the known biology of the receptor (particularly where this may be impactful on development).

Interestingly, the class of receptor with the most gaps is the kinases.

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Gap analysis: receptors targeted therapeutically in pediatric patients that are not currently in Secondary Intelligence

Receptor class	Receptor
GPCR	5HTR1D
GPCR	5HTR1E
GPCR	5HTR1F
GPCR	GPBAR1
GPCR	PTGFR
GPCR	TAAR1
Ion channel	NACHRA1
Ion channel	NAV1PT2
Nuclear hormone receptor	PXR
Nuclear hormone receptor	PGR
Kinase	INSR
Kinase	NTRK1
Kinase	FLT1 (VEGFR1)
Kinase	ABL1

Data on these 14 receptors would have to be carefully curated for both adult and pediatric populations.

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Work-in-progress: **qualitative** hazard flagging

- Evaluate drug AEs reported in pediatric patients that either differ from those in adults or are exacerbated compared to adults
- For receptors not targeted therapeutically in pediatric patients, assess potential hazard in pediatric patients from the known biology of the receptor
- Information sources: FDA drug labels; FDA pediatric reports; FAERS; KIDSIDES database; published literature on receptor biology

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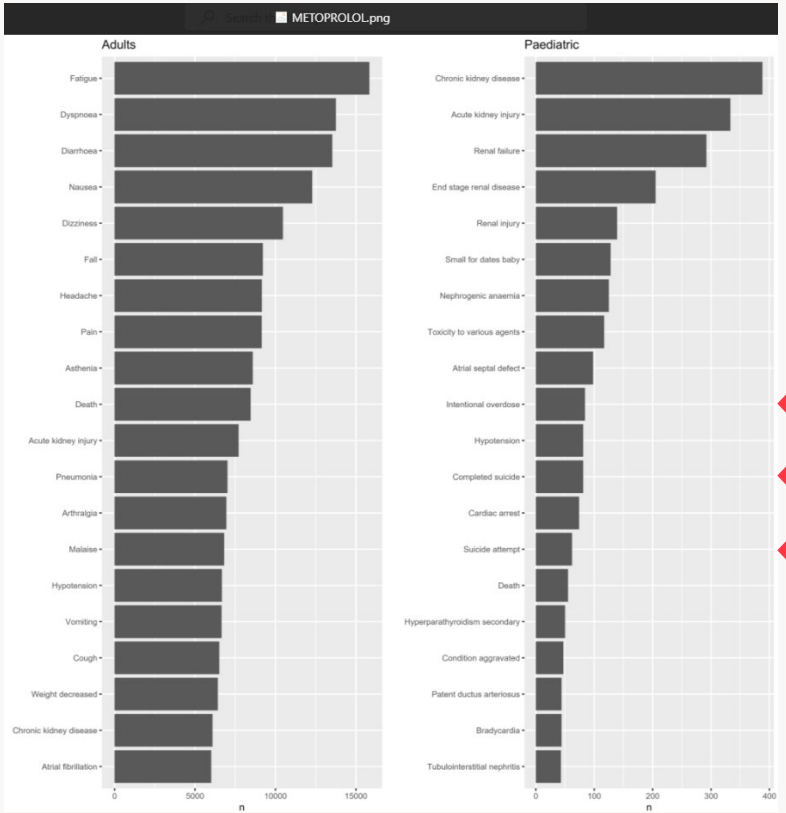
Example of FAERS analysis revealing AEs ‘unique’ to pediatric patients



The following AEs are prominent in the pediatric FAERS list, but absent from the adults list:

intentional overdose
completed suicide
suicide attempt

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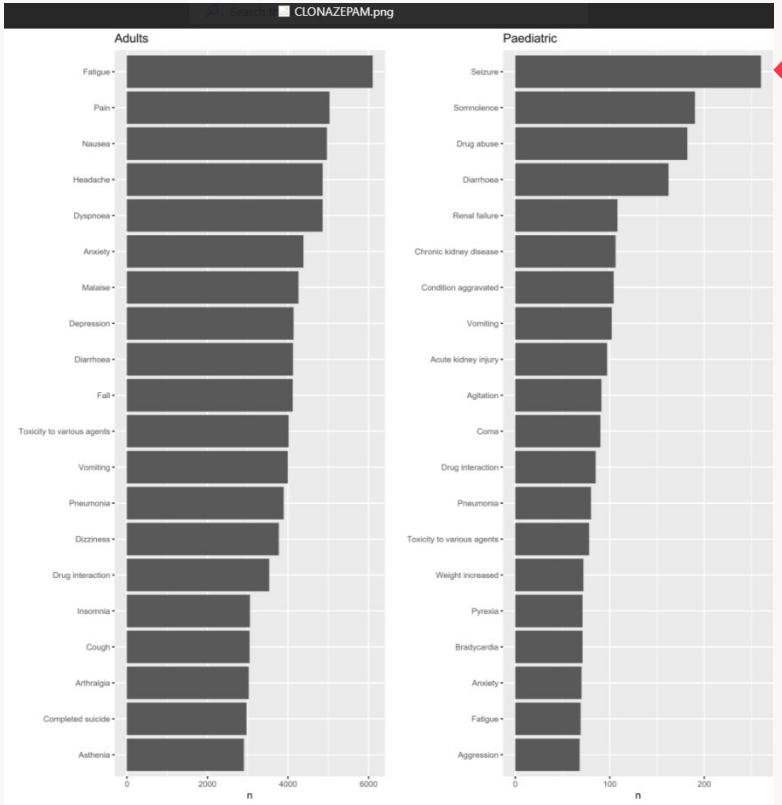
Example of where caution is required when working with FAERS data



On first glance, there appears to be an AE right at the top of the list for pediatric patients (namely, 'seizure') which does not appear in the list of AEs in adults.

However, FAERS will report manifestations of the disease phenotype as well as genuine drug AEs.

In this case, clonazepam Is used to treat epilepsy in children but not adults.

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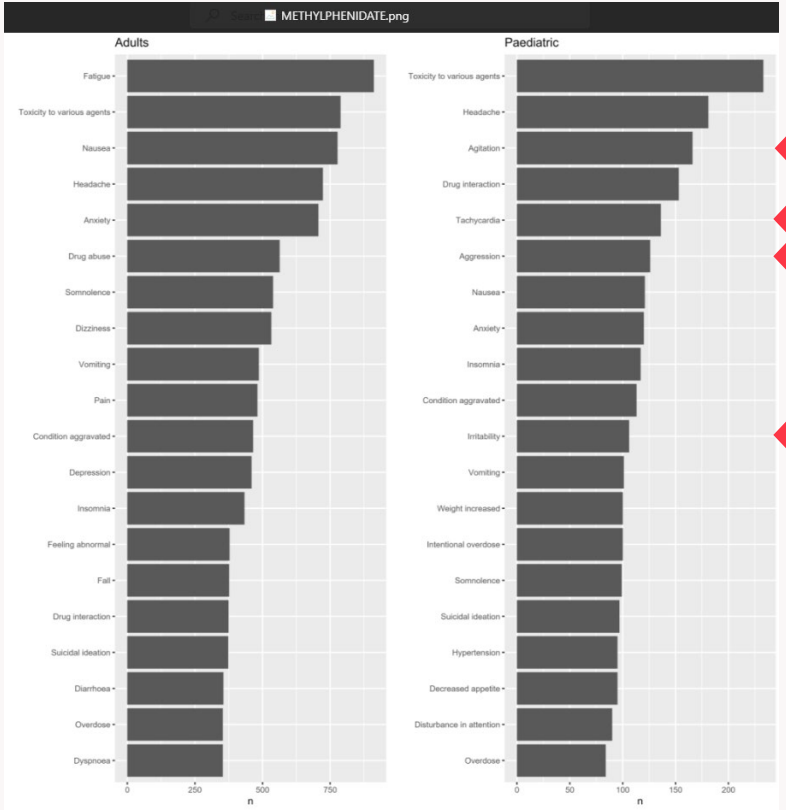
Example of FAERS analysis revealing AEs ‘unique’ to pediatric patients… or is it?



The following AEs are prominent in the pediatric FAERS list, but absent from the adults list:

agitation
tachycardia
aggression
irritability

Tachycardia, aggression and irritability may be genuine AEs; however, agitation may be part of the ADHD phenotype

What we did for the existing build of Secondary Intelligence (using adult AE data) was to take a consensus view of AEs common to most or all of the drugs targeting that receptor.

This involved sourcing AE data from FDA drug labels in addition to FAERS.

This is more challenging in pediatric patients as there are fewer drugs per receptor used in pediatric medicine.

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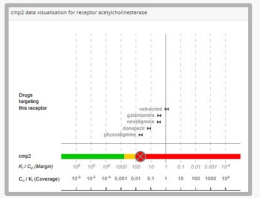
Work-in-progress: **quantitative** risk assessment



- Curate lowest therapeutically effective plasma concentrations for drugs used in pediatric patients
- Plot as per current adult patient C_u/K_i plots in Secondary Intelligence
- Compare to the original plots for adult patients: if they are all close together we can apply a rule-of-thumb across all receptors; if not, we will require separate plots for pediatric patients
- Re-plots of C_u/K_i for reference drugs in Secondary Intelligence for pediatric patients are only necessary if the lowest effective plasma concentrations are lower in pediatric patients (indicating that a lower receptor occupancy is required to elicit a PD effect)
- Information sources: Drug Interaction Database (DIDB® Certara); FDA drug labels; FDA pediatric reports; published literature on pediatric PK

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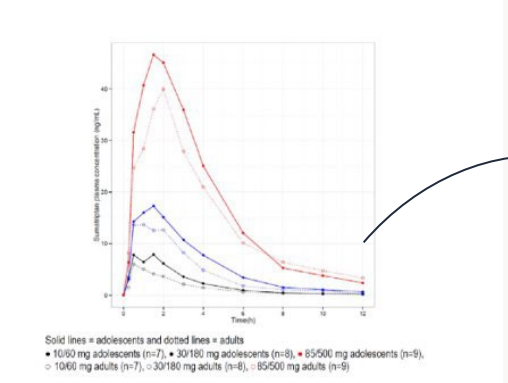
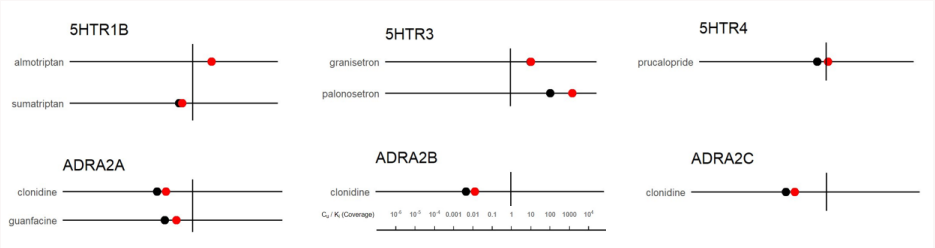
Examples of comparing adult and pediatric therapeutic plasma concentrations



Example with sumatriptan at 3 dose levels in adults and children



(etc.)…for ~80 receptors*

**the total number of receptors associated with marketed pediatric drugs*

Schematic plots of C_u/K_i data for 6 receptors, comparing pediatric (red) to adult (black)

Red symbols on their own are superimposed on the black symbol

- If the above outcome holds firm across all receptors for which we have plasma concentration data (~80 receptors), we won't have to re-plot our C_u/K_i plots for application of Secondary Intelligence to assess off-target risk in pediatric patients.

- There may, however, be exceptions where the lowest therapeutically effective plasma concentration for a given drug is lower in pediatric patients than in adults, which will necessitate a re-plot for that receptor.

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Summary and ongoing work

- There are numerous off-target receptors for which there are no therapeutically used drugs in pediatric patients.
- We are focusing on the receptors where there are drugs used in pediatric patients.
- For drugs evaluated thus far, the plasma C_u in pediatric patients is similar to or higher than in adults. If this holds up with a larger dataset, we can use the same C_u/K_i plots as for adults.
- Analysis of reported AEs in FAERS is revealing the existence of AEs in pediatric patients that are not seen in adults, at least for some drugs.
- Taken together with the evidence pointing to similar plasma exposures, this is quite interesting.
- To address all this within Secondary Intelligence, we may require either a link to ‘pediatric notes’, a separate pediatric analysis, or something in between.

- To be continued…!

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