



Prediction of Adverse Drug Reactions Using Systems Biology

Presentation at the



ICCS

International Conference
on Chemical Structures

Cédric Merlot, June 7th 2011

Summary



⊙ PredTox collaboration

⊙ Principles

⊙ Case studies

- Off-target side-effect
- Mapping targets onto pathways
- Application in discovery project

PredTox Collaboration



⊙ Collaboration between Genkyotex and drugdesigntech

- Research project for NCE Early Safety Evaluation
- From hit discovery to PCD candidate
- Genkyotex provides molecules and experimentation
- drugdesigntech develops and applies the software

⊙ Constraints

- Adequate experimental timelines and cost

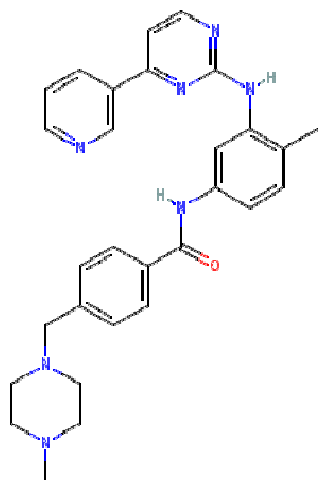
⊙ Outcome

- A single lead optimization program was necessary to deliver a clinical candidate

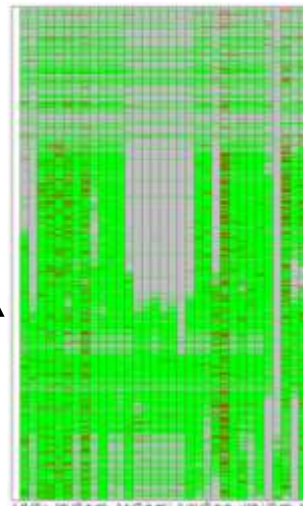
Principles



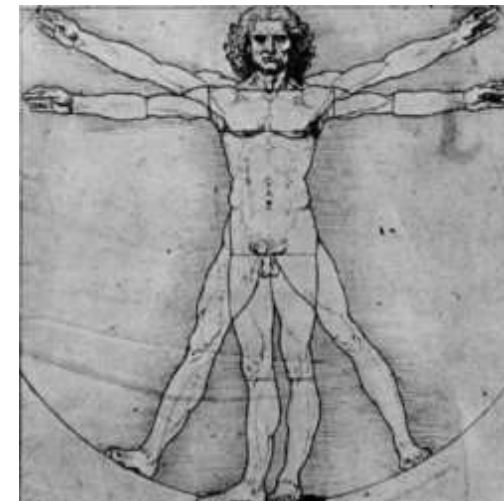
⊙ Predict pharmacological effects from the structure, in a multi-step procedure



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Compounds



Principles



- ⊙ **Proposes a mechanism of action**
 - Which targets, which pathways are involved
 - Identify other modes of actions (eg chemical reactivity)
- ⊙ **Mechanism of action can be translated into biomarkers or short-term assays**
 - A must-have, to provide rapid and experimental confirmation and follow-up
- ⊙ **Supported by more data than simple drug – adverse event associations**
 - More comprehensive than current prediction algorithms

Activity Prediction – Data Sources



⊙ Data collected from multiple sources

- PubChem (<http://pubchem.ncbi.nlm.nih.gov>)
- DrugBank (<http://www.drugbank.ca>)
- ChEMBL (<https://www.ebi.ac.uk/chembl/db>)
- Small datasets from literature and patents

⊙ Traditional cheminformatics data management

- Integrate all the structures in a single repository
- Salt stripping, structure normalization...

Structure and merge available information

Activity Prediction – Organize Biodata



⊙ Requirements

- Combine several data sources to build large data sets
- Keep source information (assay protocol)

⊙ Uses phylogenetic trees to organize targets

- GPCRDB (<http://www.gpcr.org>)
- Enzymes (<http://ca.expasy.org/enzyme>)
- SwissProt (<http://expasy.org/sprot>)

⊙ Associate each assay to a target

- Annotations found in database (eg ChEMBL)
- Manually

Fragment analysis



⊙ Unique method developed for fragment analysis

- Cheminformatics algorithm development
- Combined to medicinal chemists's input

⊙ Suite of tools and protocols

- Fragment enumeration
- Statistical evaluation of fragment-target association
- Structural evaluation (automate medicinal chemist's eye)
- Prediction module
- Result visualization

PSPP: Predicted Safety Pharmacological Profile

Pathways and ADR sources



⊙ Pathways database

- KEGGS (<http://www.genome.jp/kegg>), signaling and metabolism
- Literature searches for additional pathways or biological systems

⊙ Adverse Events Reports

- SIDER (<http://sideeffects.embl.de>), data extracted from public documents
- drugcite.com, directly based on FDA's Adverse Events Reporting System (AERS)

Example 1 – Basics

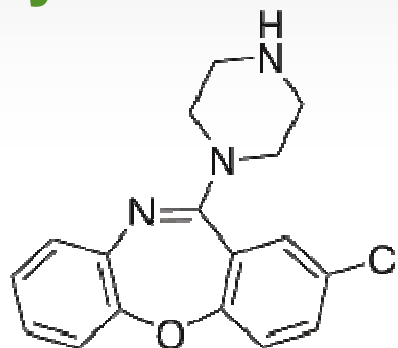


⊙ Amoxapine: “mono-target” ADR

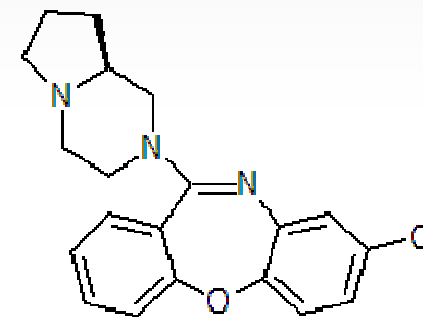
- Strong norepinephrine reuptake inhibitor (PubChem)

⊙ Activities predicted by PSPP

- Prostaglandin
- Dopamine D4



amoxapine



dopamine D4 inhibitor
(PubChem)

⊙ Known secondary activities

- “One of its major metabolites, 7-hydroxyamoxapine, has a dopamine receptor blocking effect, making this drug a common cause of neuroleptic malignant syndrome” (Wikipedia)

Example 2 – Heart Block



- ⊙ **Heart Block: impairment of conduction in heart excitation (Dorland, 27th ed.)**
- ⊙ **Dataset: 61 drugs associated with Heart Block from SIDER**
- ⊙ **Method**
 - Calculate PSPP for all structures
 - Map predictions on pathways and biological systems
- ⊙ **Result: 27 drugs map on two biological systems involving noradrenaline and dopamine neurotransmitters**
 - Adrenergic receptor beta (non selective or beta 1)
 - Histamine receptor H3
 - Muscarinic receptors
 - Dopamine receptor (non-selective)

Example 2 – Predicted Profiles



PCID	Name	Adrenoreceptor Beta (non-selec. or beta 1)	Histamine H3	Dopamine	Muscarinic (M1, M2, M3)	Other predictions	Primary pharmacology
2249	atenolol						Beta 1 receptor blocker
59768	esmolol						Beta 1 receptor blocker
4411	nadolol						Beta 1 receptor blocker
2369	betaxolol						Beta 1 receptor blocker
4171	metoprolol						Beta 1 receptor blocker
3386	fluoxetine					hERG	Selective serotonin reuptake inhibitor
4828	pindolol						Beta blocker
4946	propranolol						Beta blocker
3410	formoterol						Beta 2 agonist
3869	labetalol						mixed alpha/beta adrenergic antagonist
2583	carteolol						Non selective beta blocker
3914	levobunolol						Non selective beta blocker
5478	timolol						Non selective beta blocker
4011	maprotiline						Norepinephrine reuptake inhibitor
60815	remifentanyl					NK2, opioid mu, delta	Opioid mu receptor agonist
60612	dexmedetomidine					alpha 1, FNT, steroid monooxygenase	Agonist of alpha 2 adrenergic receptor
4543	nortriptyline					hERG, FNT	Antagonist histamine, Serotonine-Norepinehrine Dopamine reuptake inhibitor
2756	cimetidine						Histamine H2 receptor antagonist
3148	dolasetron					hERG, 5HT3	Serotonin 5HT3 receptor antagonist
2160	amitriptyline					hERG, FNT	Serotonine-Norepinehrine reuptake inhibitor
2895	cyclobenzaprine						Unclear
4585	olanzapine					hERG, oxytocin	5-HT2 serotonin receptor
4583	ofloxacin					PI3K	Chemotherapeutic antibiotic of the fluoroquinolone drug
119607	valdecoxib					COX2, SAPK2a, BRAF1, TGFR1	COX2 inhibitor
4745	pergolide					hERG, 5HT1, Opioid mu	Non selective beta blocker
2170	amoxapine					hERG, Prostagladin	Norepinehrine reuptake inhibitor
71273	ropivacaine						Local anesthetic

Example 2 – Literature search



- ⊙ **Beta blockers known to cause bradycardia**
- ⊙ **Dopamine receptors positively regulate heart rate**
- ⊙ **Muscarinic M2 receptors negatively regulate heart rate**
- ⊙ **Histamine H3 receptors involved in arrhythmias**
 - **Increased severity of reperfusion arrhythmias in mouse hearts lacking histamine H3-receptors, Motohiro Koyama, Paul M. Heerd, and Roberto Levi, Biochemical and Biophysical Research Communications 306 (2003) 792–796)**

**All the receptors are involved
in the heart rate regulation system**

Example 2 – Conclusions



- ⊙ All predictions well described in the literature, no breakthrough
- ⊙ Validates the approach of mapping isolated target predictions onto pathways to provide a potential MOA
- ⊙ Structure-target associations might be direct (compound is a modulator) or indirect (compound modulates another target in the same pathway)
- ⊙ Easy to go from MOA to biomarker identification

Mapping predictions onto pathways proposes a mode of action, and biomarker

Example 3 – Cirrhosis



◎ Cirrhosis

- liver disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered with fibrous septa surrounding regenerated or regenerating parenchymal nodules.

◎ Dataset

- 25 drugs associated with Cirrhosis from SIDER

◎ Results

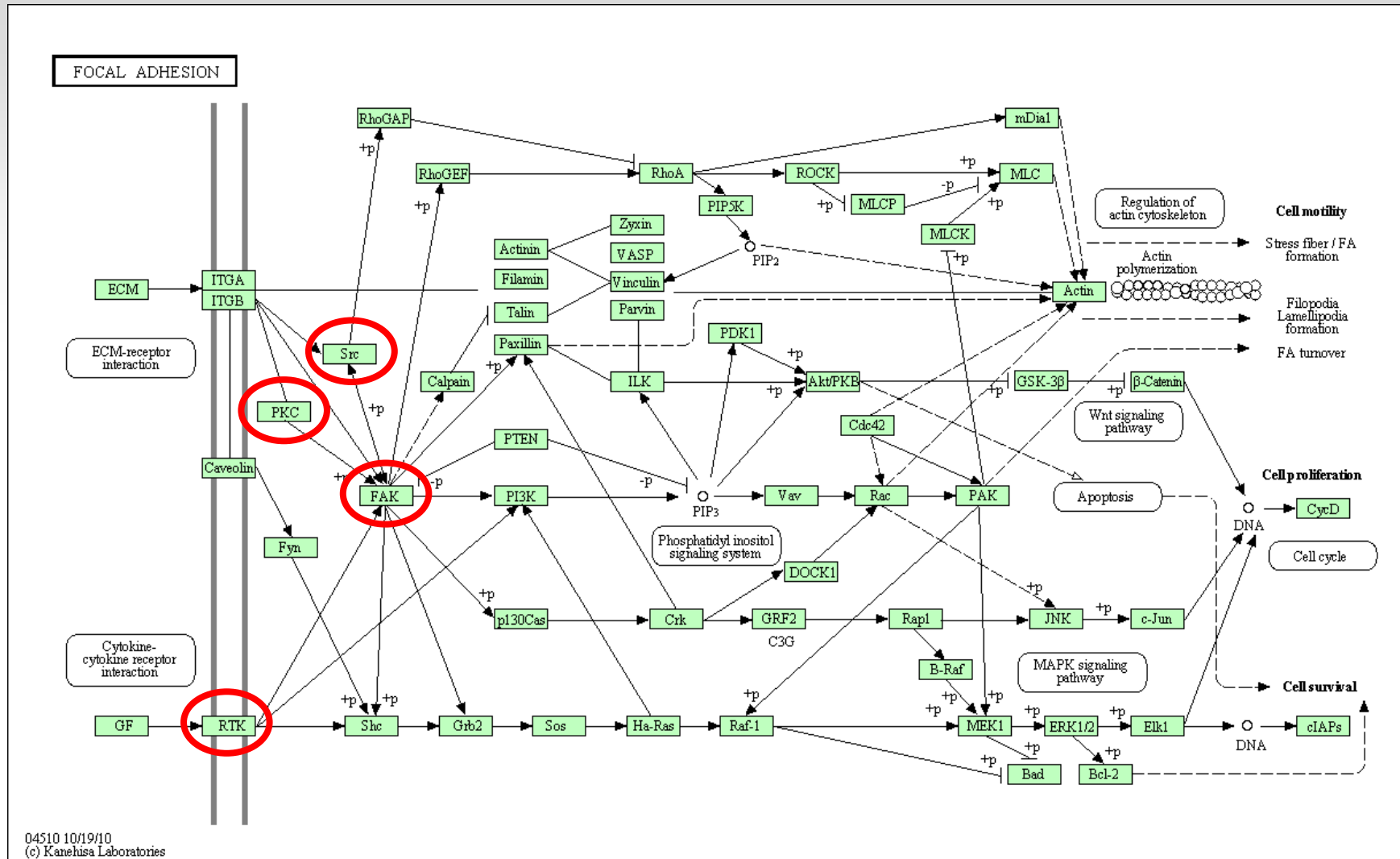
- 8 drugs map on the focal adhesion pathway

Example 3 – Predicted Profiles



PCID	Name	FAK	SRC	PKC	PDGF	Primary pharmacology
3015	Cyproterone					Androgen receptors antagonist
2726	Chlorpromazine					CNS
3032	Diclofenac					COX
4112	Methotrexate					Dihydrofolate reductase inhibitor
104865	Bosentan					Endothelin recetor antagonist
3793	Itraconazole					Ergosterol
71158	Acamprosate					GABA
3121	Valproic acid					Histone deacetylase inhibitor
2676	Cerivastatin					HMG-CoA
3403	Fluvastatin					HMG-CoA
3962	Lovastatin					HMG-CoA
4889	Pravastatin					HMG-CoA
4205	Mirtazapine					Noradrenergic and serotonergic antidepressants
2156	Amiodarone					Potassium channel blocker-like actions
3339	Fenofibrate					PPAR alpha
5353980	Sulfasalazine					Prodrug, releases 5-ASA
5362070	Balsalazide					Prodrug, releases 5-ASA
213039	Darunavir					Protease inhibitor
5029	Rabeprazole					Proton pump inhibitors
5656	Venlafaxine					Serotonin-norepinephrine_reuptake_inhibitor
5487	Tizanidine					α -2 adrenergic agonist.
3081884	Glatiramer acetate					
4075	5-aminosalicylic acid					
41781	Torasemide					
5493381	Deferasirox					

Example 3 – Mapping



Example 3 – Literature search



- ◎ **Many links exist between FAK and hepatic stellate cells proliferation, which play a key role in the development of liver fibrosis, which in turn leads ultimately to cirrhosis**
- **Relationship between focal adhesion kinase and hepatic stellate cell proliferation during rat hepatic fibrogenesis, Hui-Qing Jiang, Xiao-Lan Zhang, Li Liu, Chang-Chun Yang, World Journal of Gastroenterology, 2004**
- **Focal adhesion kinase and phospholipase C gamma involvement in adhesion and migration of human hepatic stellate cells. Carloni V, Romanelli RG, Pinzani M, Laffi G, Gentilini P., Gastroenterology. 1997**

Example 3 – Conclusions



- ◎ **Cirrhosis is a multi-factorial and complex disease**
 - Impossible to explain all observations
- ◎ **Pathway analysis might have highlighted one possible mode of action**
 - Which is also supported by literature search
- ◎ **FAK expression (protein or mRNA) is a potential biomarker associated to the observed liability**
 - Propose experimental tools to confirm and follow-up the predictions

Example 4 – Hit Discovery



⊙ Hit discovery project with Genkyotex

- Rational selection of chemical series
- Select 1 out of 5 available after screening campaign
- PSPP was calculated for all series of positives

⊙ PSPP and follow-up

- One series predicted to hit several targets in one biological system
- Alteration of the biological system was observed *in vivo*
- Associated fragment spun across the scaffold
- This series was discarded

Example 5 – Lead Optimization



- ⊙ **Aim: identifying and following-up potential liabilities in the selected series**

- ⊙ **PSPP was calculated for each compound**
 - Modulation of target X found highly probable for some compounds
 - Literature search on target X's pathways
 - Found one major system, and several biomarkers

- ⊙ **Experimental confirmation**
 - One biomarker evaluated *in vivo*
 - Statistically significant changes were observed *in vivo* in rats and mice

Example 5 – Lead Optimization



⊙ Experimental follow-up

- Safety is one of the parameters to optimize
- Biomarker was evaluated for all compounds tested *in vivo* for the rest of the project

⊙ Side-effect no more observed

- Focus on decorations not associated with Target X

⊙ Biomarker evaluated, but no change observed versus control in GLP preclinical study

Idées reçues



**Predictions do not replace experiments
They help to rationalize them**

**Predictions do not kill valuable leads
They turn them into better candidates**

Outcome and Next Steps



- ◎ **Several successful applications**
 - Retrospective validation
 - Prospective validation
- ◎ **Ask the right questions**
 - Rather than making predictions
- ◎ **Propose experimental follow-up**
 - Must be integrated with wet experiments

drugdesigntech seeks new partners to further develop the approach in real projects

Thank you



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