computational toxicology

in silico assessment of the hERG channel inhibition potential for the early drug cardiotoxicity testing

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In vivo toxicity

Drug development

Screen
Pick leads

Assay parent compounds

CYP UGT screening

Assay metabolites

In vivo toxicity

PHASE I CT

PHASE II/III CT

Pick candidate

Pharmacovigilance

Dossier

Pharmaco economics

Synthesis scale-up

Phys-chem properties

ADME

Metabolic stability

Mutagenicity

Long-term toxicity
drug withdrawals

- Cardiotoxicity: 21
- Hepatotoxicity: 4
- Nephrotoxicity: 15
- Other: 7

1990 - 2007
**TdP – Torsades de Pointes**

**mechanism**

- inhibition of rapid delayed rectifier potassium current \(I_{Kr}\)
- inhibition of the channel encoded by the hERG gene

### Diagram Description

- **TdP** waveform
- **LQTS** waveform showing P, Q, R, S, and T waves
- **membrane potential** vs. **time** graph with labeled currents: \(I_{Na}\), \(I_{Ca}\), \(I_{to}\), and \(I_{Ks}\) moving over time
proarrythmic potency assessment
in silico – in vitro – in vivo extrapolation

- rubidium flux
- radioactive ligands binding
- fluorescence assessment
- electrophysiological methods (HEK, CHO, XO cell lines) - patch clamp
toxicity prediction

in vitro prediction

in vivo verification

in vitro population

drug induced arrhythmias

in vivo individual
toxicity prediction

in silico

prediction
verification

in vitro

prediction
verification

in vivo

in vitro

in vivo population

in vivo individual

drug induced arrhythmias
• **INPUT:** *in vitro* experimental settings + phys-chem descriptors

*derived from available literature*

- cell model \{XO / CHO / HEK\}
- temperature \[^\circ\text{C}\]
- K+ bath concentration \[^\text{mM}\]
- t1 pulse \[^\text{s}\]
- t2 pulse \[^\text{s}\]
- holding potential \[^\text{mV}\]
- depolarization level \[^\text{mV}\]
- measurement potential \[^\text{mV}\]
proarrhythmische potency *in silico*
prediction algorithms & methods

**INPUT:** in vitro experimental settings + phys-chem descriptors

calculated in Marvin Beans package

- sdf files either derived from PubChem or drawn in MarvinSketch
- 41 plugins
- 107 numeric inputs natively
- 30 parameters after the sensitivity analysis
proarrythmic potency in silico
prediction algorithms & methods

- **OUTPUT:** concentration – inhibition relation
proarythmic potency in silico
prediction algorithms & methods

• INPUT: in vitro experimental settings + phys-chem descriptors

• OUTPUT: concentration – inhibition relation

• ALGORITHMS: ANN; Random Forests (+ hybrid systems)

• VALIDATION: internal (10-fold CV) & external (dataset – 193 data points)

• FLEXIBILITY: various cell systems and settings
proarrhythmic potency \textit{in silico}

prediction algorithms & methods

- **RESULTS**

<table>
<thead>
<tr>
<th>model</th>
<th>RandomForest 100 trees</th>
<th>ANN 15_7_5 logistic</th>
<th>Expert committee (RF10+RF100+ANN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>validation RMSE</td>
<td>0.21</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>results</td>
<td>![Graph]</td>
<td>![Graph]</td>
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</tbody>
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in vitro
proarrythmic potency in silico
prediction algorithms & methods

- RESULTS – Expert committee

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<th>new structures</th>
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<tbody>
<tr>
<td>within 2-fold</td>
<td>89.41%</td>
<td>76.85%</td>
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results

![Graph showing predicted vs observed values for within 2-fold](image1)

![Graph showing predicted vs observed values for new structures](image2)
• RESULTS – Expert committee

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![Graphs showing predicted vs observed values for Methadone, Sparfloxacin, Atomoxetine, and Doxorubicin]
CONCLUSIONS

- proarythmic potency *in silico* prediction algorithms & methods

- structure mining for succes/failures analysis - ongoing project

- first known system for hERG concentration – inhibition relation prediction

- publicly available database ([www.tox-portal.net](http://www.tox-portal.net))

- all models are available in CompToxOne computer system (distributed as OpenSource under GPL license - [www.tox-comp.net](http://www.tox-comp.net))
acknowledgements

team

Sebastian Polak PhD
Barbara Wiśniowska PhD
Miłosz Polak
Kamil Fijorek
Anna Glinka

project financed by the Polish National Center for Research and Development LIDER project number LIDER/02/187/L-1/09
3rd International Workshop
Computational Pharmacy

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September 2011

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THANK YOU
proarrythmic potency in silico
prediction results

more information can be found at the
www.tox-portal.net