

computational toxicology

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

Sebastian Polak
Aleksander Mendyk

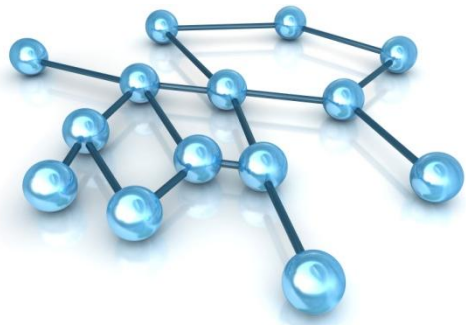
Department of Pharmaceutical Technology and
Biopharmaceutics

Jagiellonian University Medical College

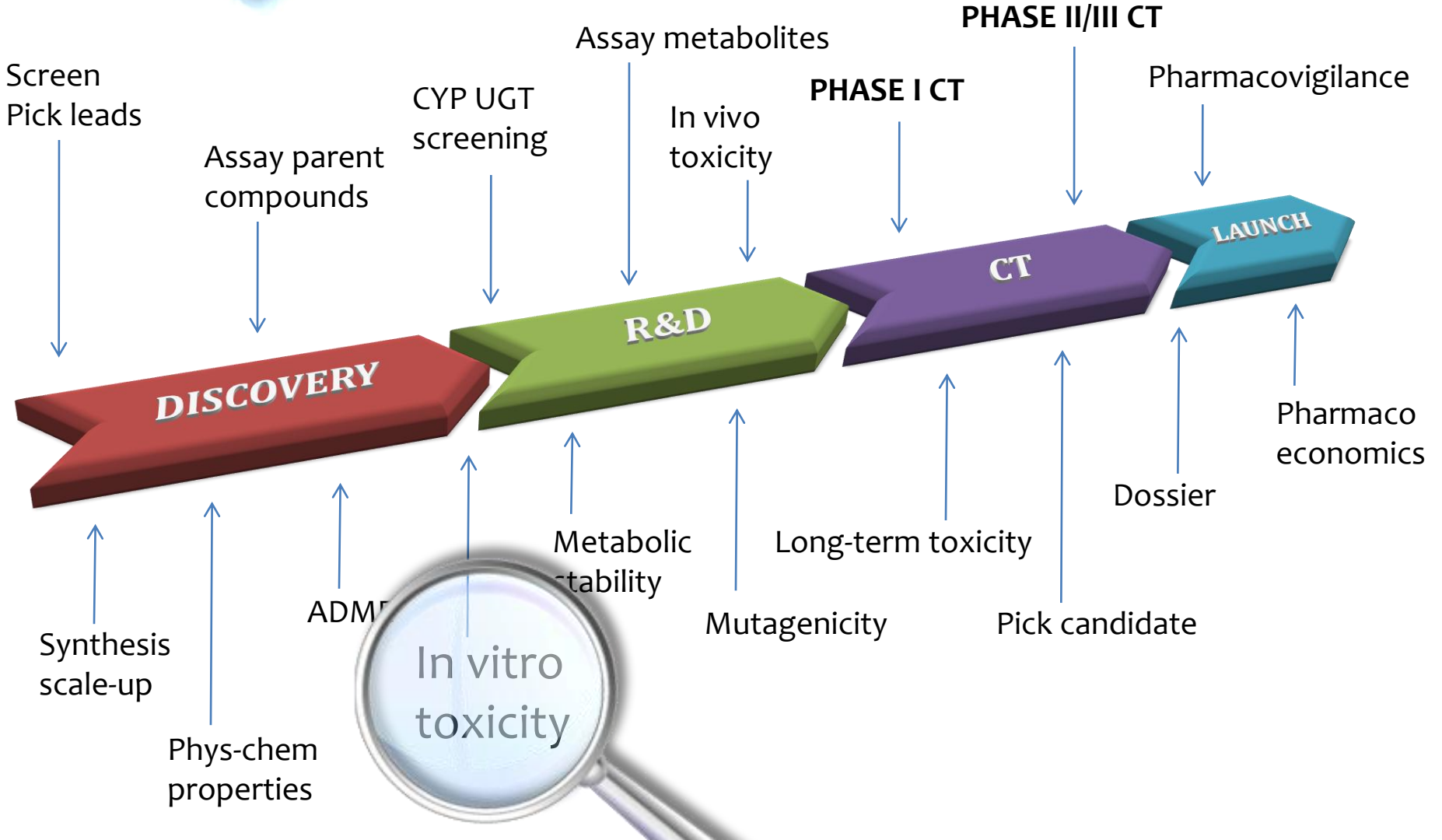
Unit of Pharmacoepidemiology and
Pharmacoeconomics

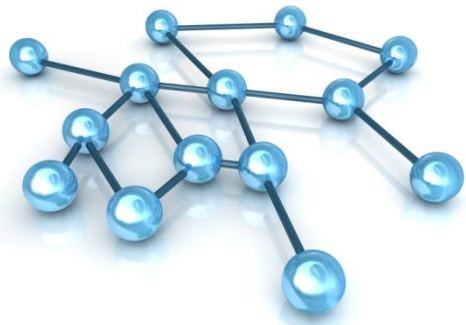
Jagiellonian University Medical College



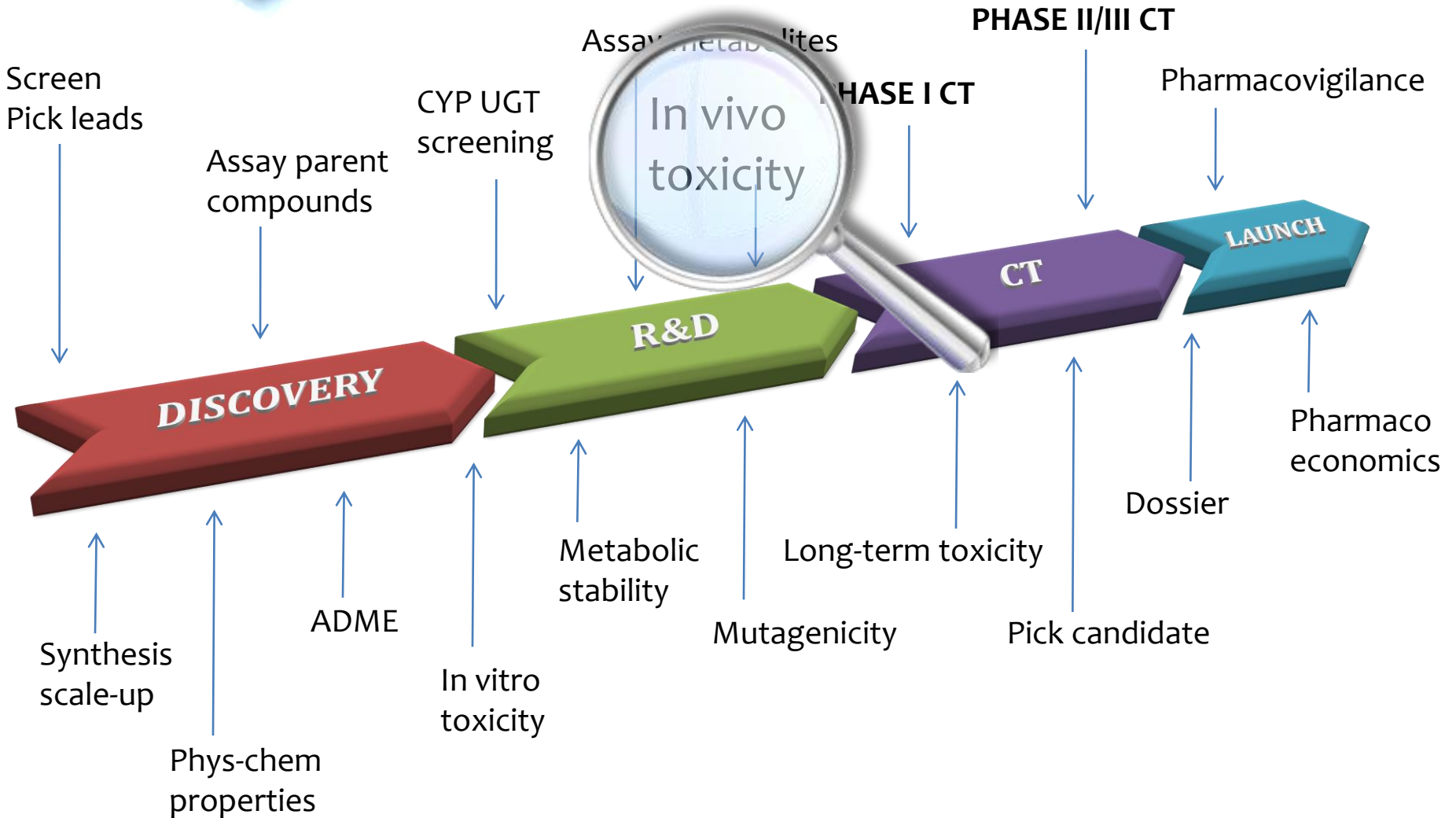


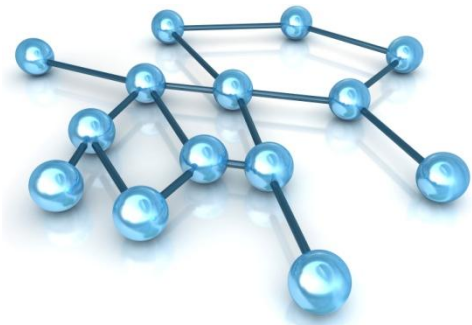
drug development



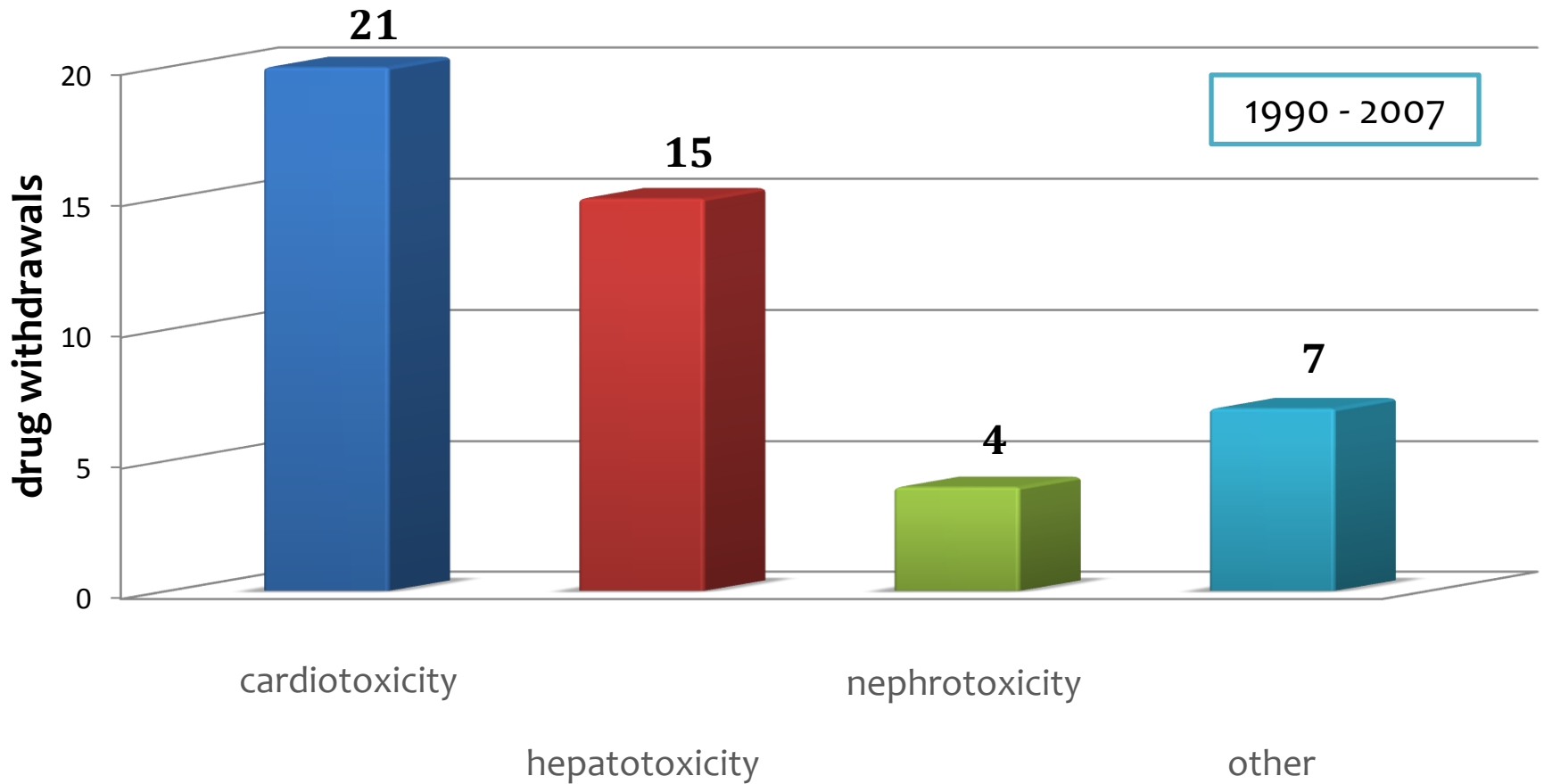


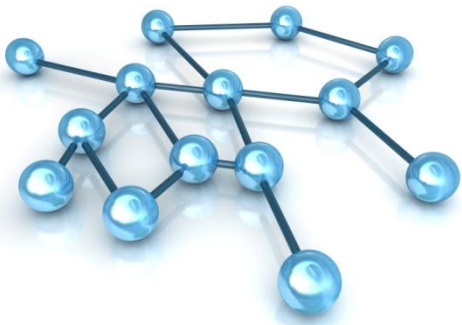
drug development



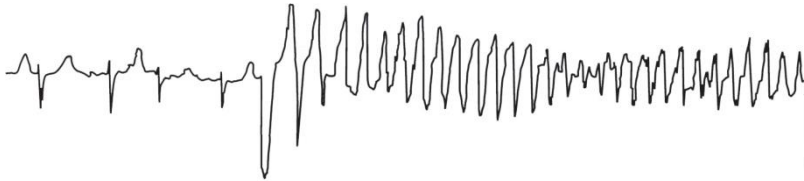


drug withdrawals

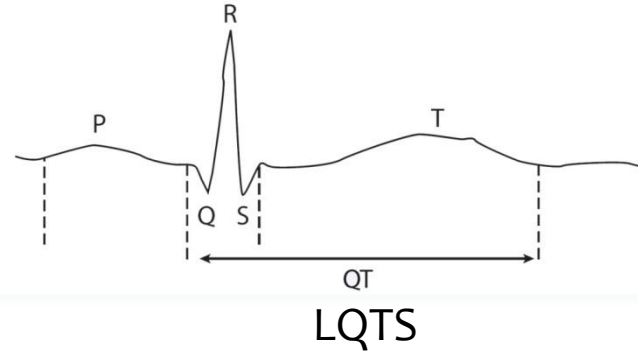




TdP – Torsades de Pointes

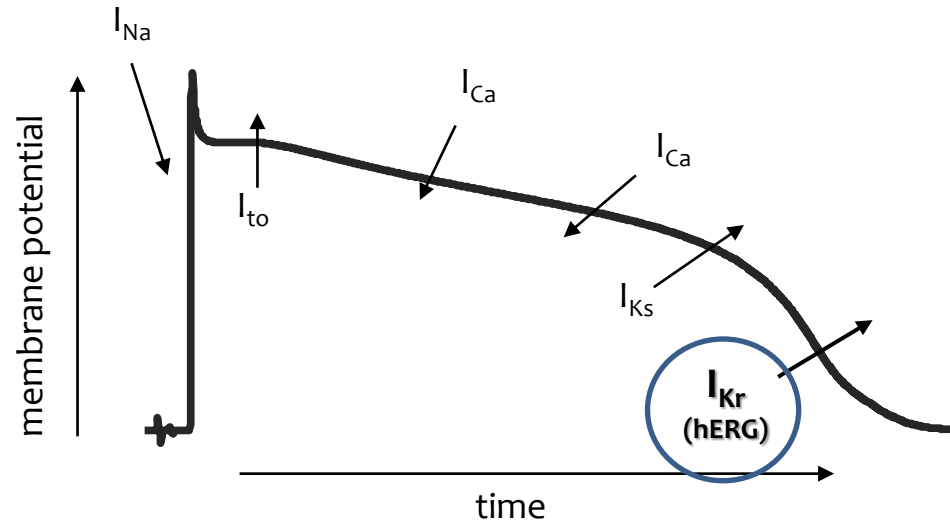


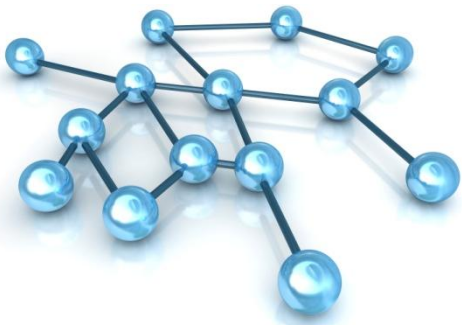
TdP



mechanism

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

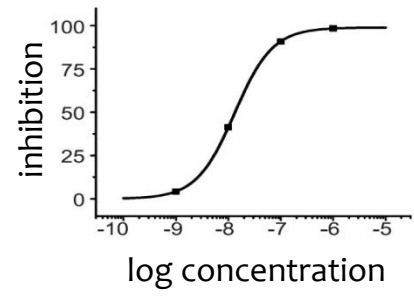
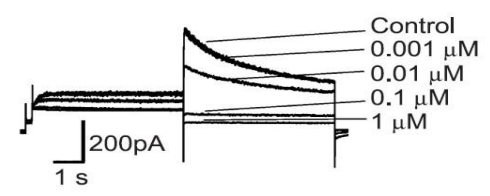
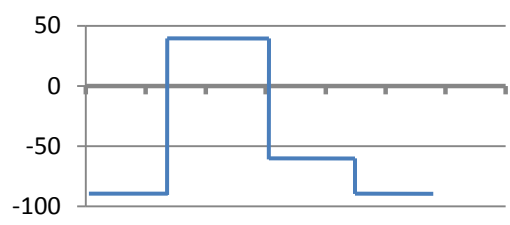
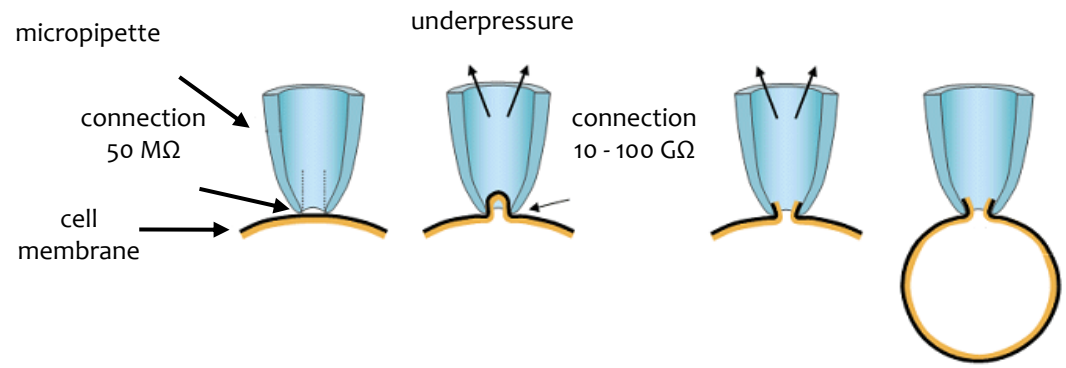


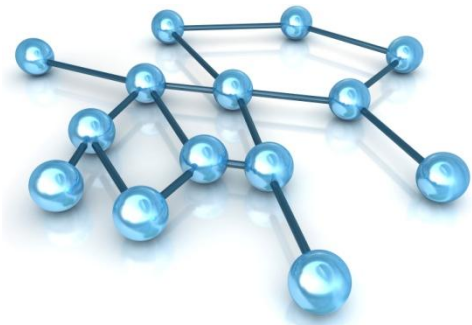


proarrhythmic potency assessment

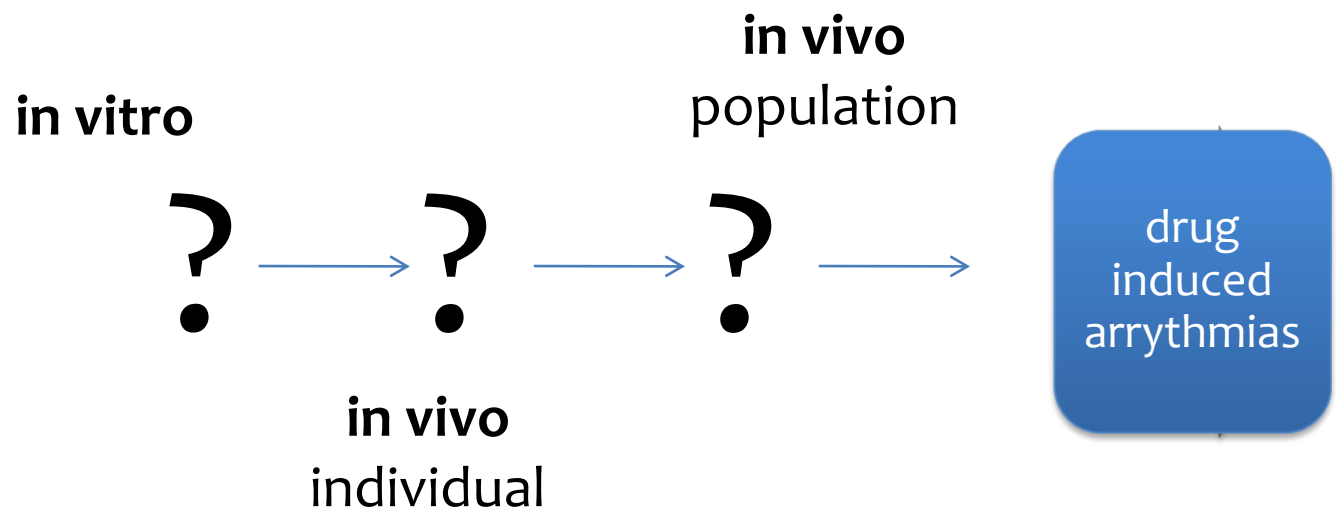
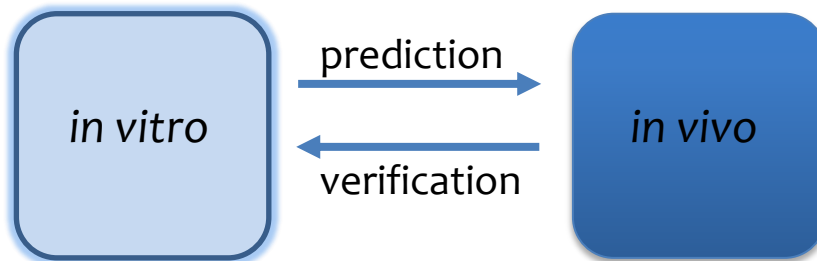
in silico – in vitro – in vivo extrapolation

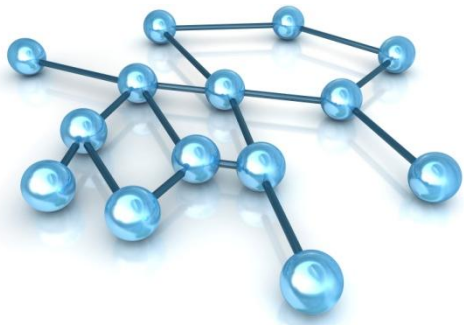
- rubidium flux
- radioactive ligands binding
- fluorescence assessment
- electrophysiological methods (HEK, CHO, XO cell lines) - **patch clamp**



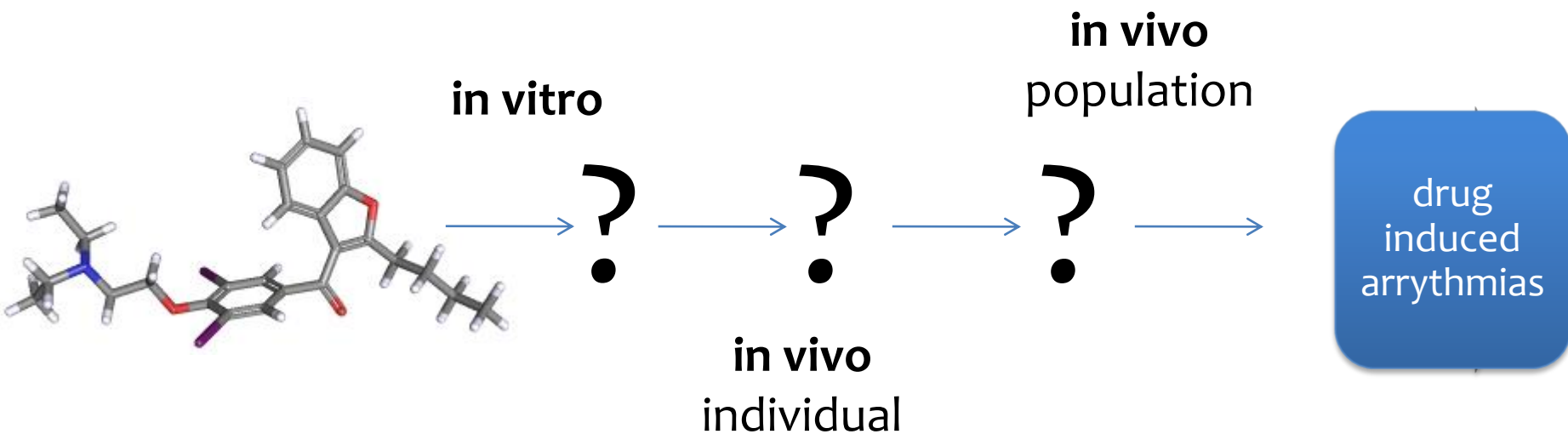


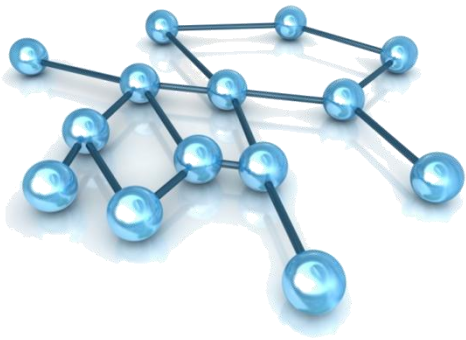
toxicity prediction





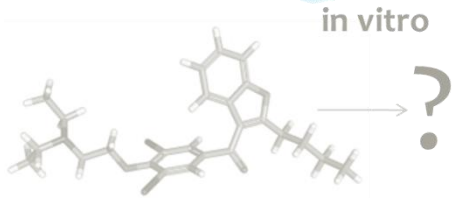
toxicity prediction





proarrhythmic potency *in silico*

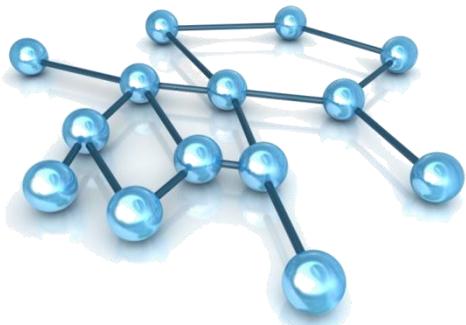
prediction algorithms & methods



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

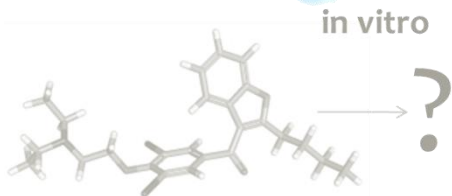
derived from available literature

- cell model {XO / CHO / HEK}
- temperature [oC]
- K⁺ bath concentration [mM]
- t1 pulse [s]
- t2 pulse [s]
- holding potential [mV]
- depolarization level [mV]
- measurement potential [mV]



proarrhythmic potency *in silico*

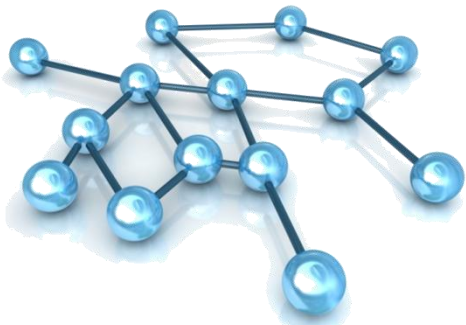
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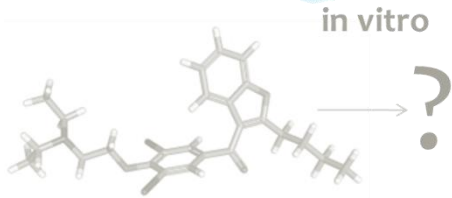
calculated in Marvin Beans package

- sdf files either derived from PubChem or drawn in MarvinSketch
- 41 plugins
- 107 numeric inputs natively
- 30 parameters after the sensitivity analysis

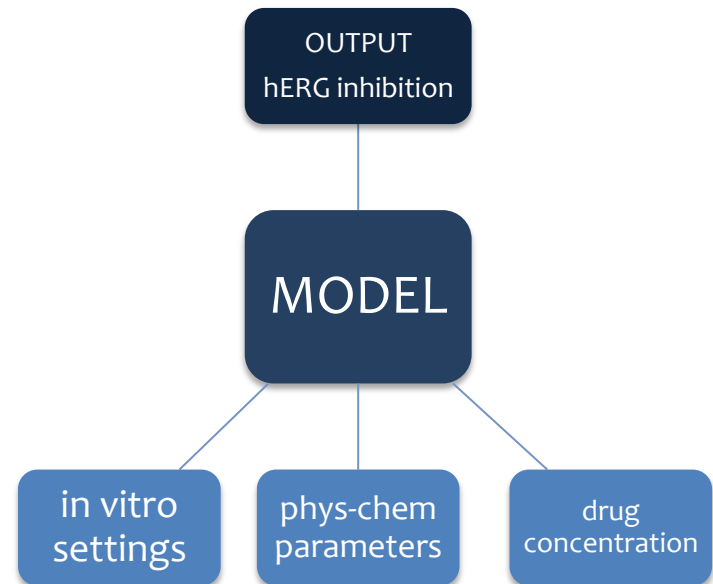
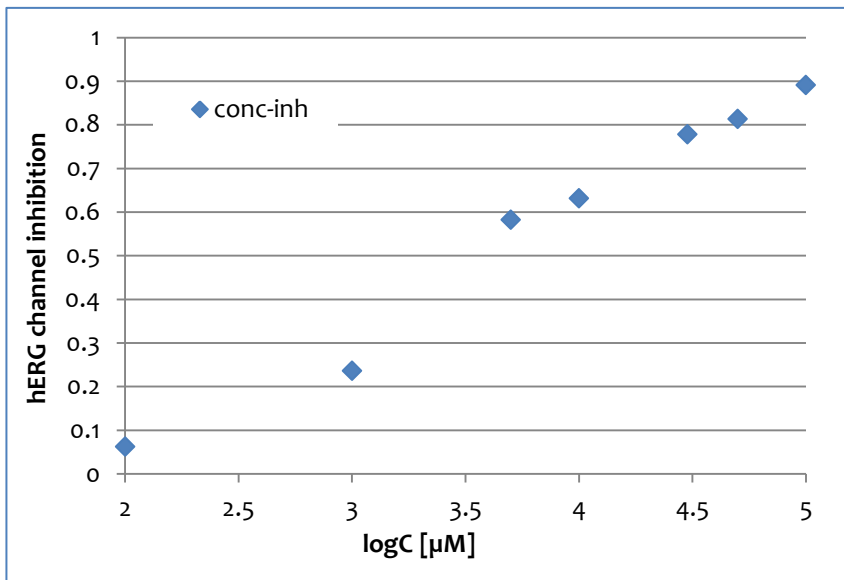


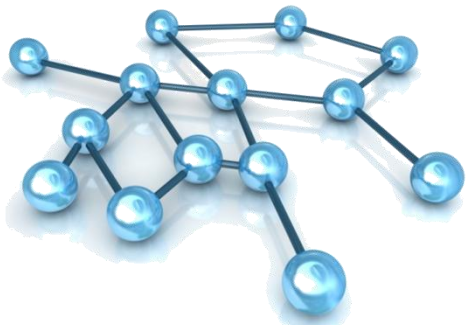
proarrhythmic potency *in silico*

prediction algorithms & methods



- **OUTPUT:** concentration – inhibition relation

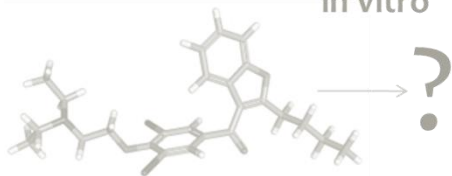




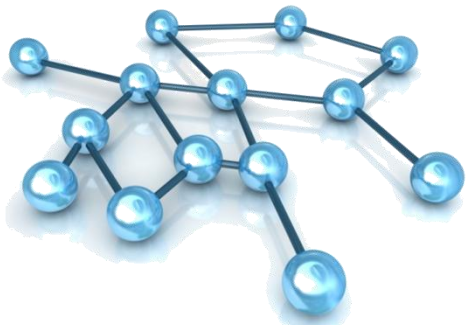
proarrhythmic potency *in silico*

prediction algorithms & methods

in vitro

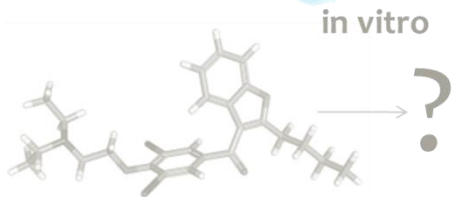


- **INPUT:** in vitro experimental settings + phys-chem descriptors
- **OUTPUT:** concentration – inhibition relation
- **ALGORITHMS:** ANN; Random Forests (+ hybrid systems)
- **VALIDATION:** internal (10-fold CV) & external (dataset – 193 data points)
- **FLEXIBILITY:** various cell systems and settings



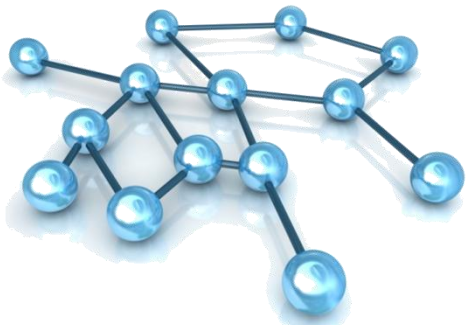
proarrhythmic potency *in silico*

prediction algorithms & methods



- RESULTS**

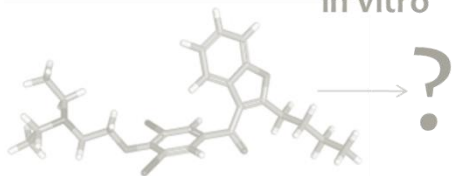
model	RandomForest 100 trees	ANN 15_7_5 logistic	Expert committee (RF10+RF100+ANN)
validation RMSE	0.21	0.20	0.20
results			



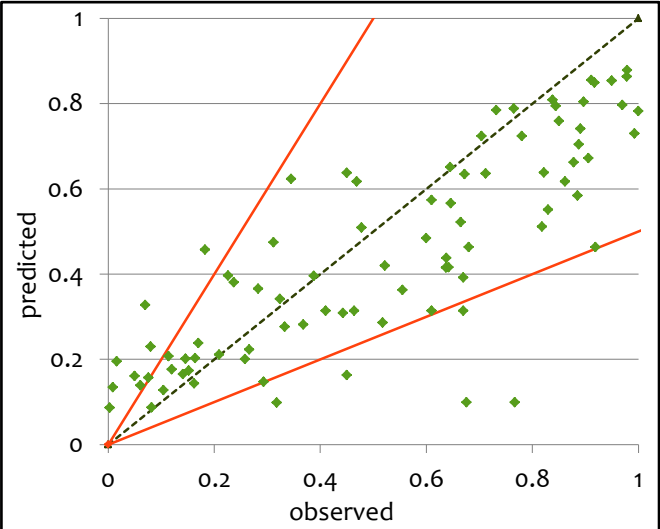
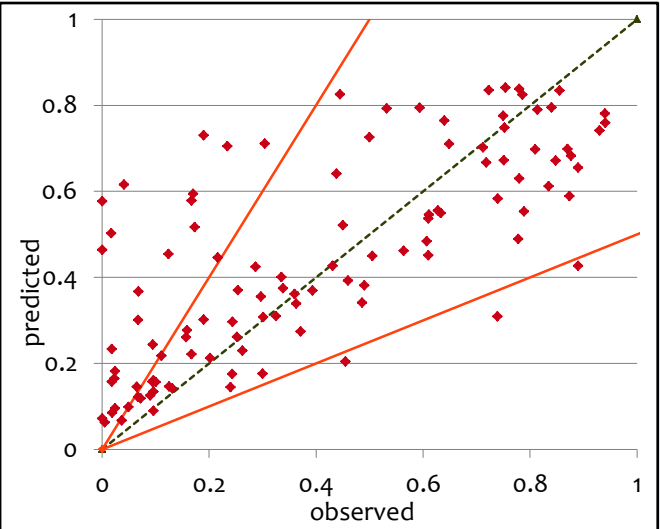
proarrhythmic potency *in silico*

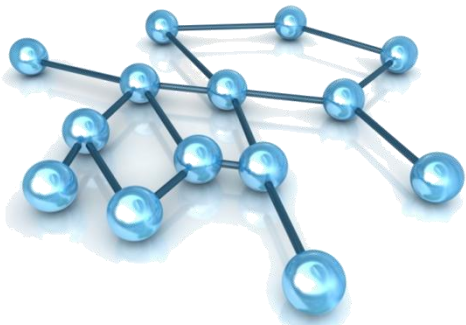
prediction algorithms & methods

in vitro



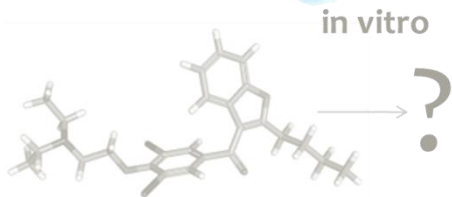
- RESULTS – Expert committee**

model	previously present structures	new structures
within 2-fold	89.41%	76.85%
results		



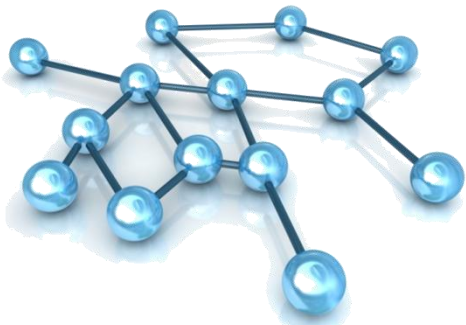
proarrhythmic potency *in silico*

prediction algorithms & methods



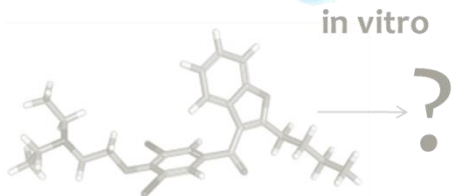
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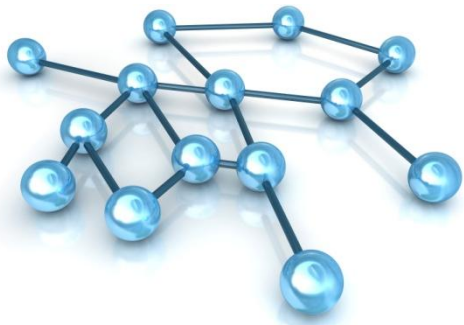
proarrhythmic potency *in silico*

prediction algorithms & methods



- **CONCLUSIONS**

- structure mining for succes/failures analysis - ongoing project
- first known system for hERG concentration – inhibition relation prediction
- publictly available database (www.tox-portal.net)
- all models are available in CompToxOne computer system (distributed as OpenSource under GPL license - www.tox-comp.net)



acknowledgements

team

Sebastian Polak PhD

Barbara Wiśniowska PhD

Miłosz Polak

Kamil Fijorek

Anna Glinka



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THANK YOU



proarrhythmic potency *in silico* prediction results

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- A
- S
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more information can be found at the

www.tox-portal.net

