

**3rd Annual Predictive Toxicology**  
half day interactive pre-conference workshop

**Tox IVIVE - inter-individual variability matters!**

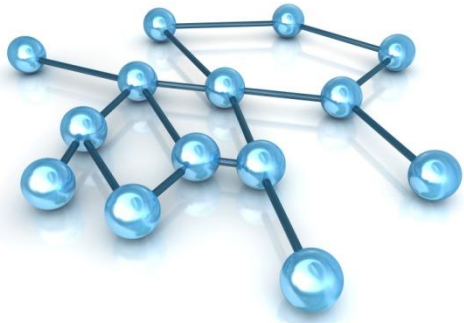
*cardiotoxicity assessment*

Sebastian Polak



Unit of Pharmacoepidemiology and  
Pharmacoeconomics  
Jagiellonian University Medical College





# acknowledgements

## team

Barbara Wiśniowska PhD

Aleksander Mendyk PhD

Miłosz Polak

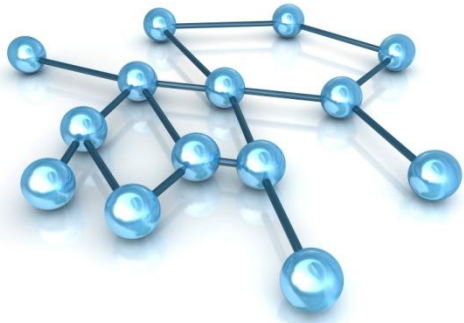
Kamil Fijorek

Anna Glinka

Małgorzata Kozłowska



project financed by the **Polish National Center for Research and Development** LIDER project number LIDER/02/187/L-1/09



# acknowledgements

## contact

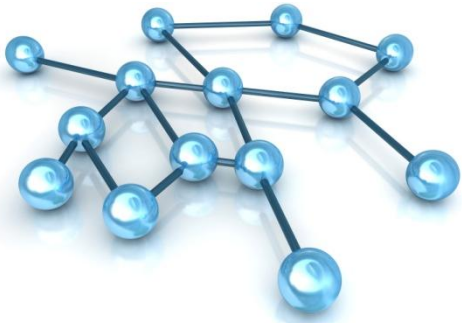
Sebastian Polak PhD

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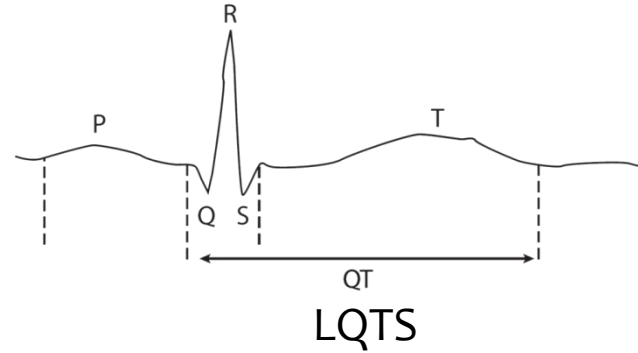
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Development LIDER project number LIDER/02/187/L-1/09**



# TdP – Torsades de Pointes

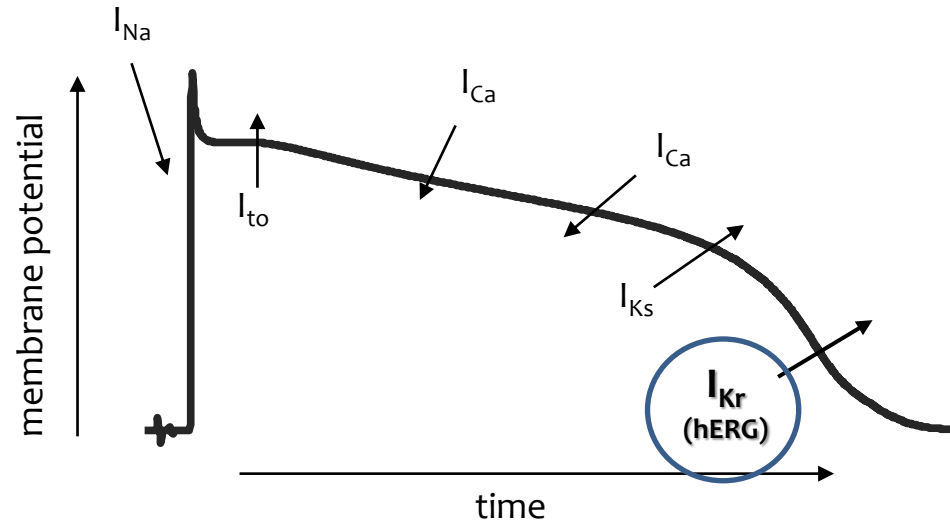


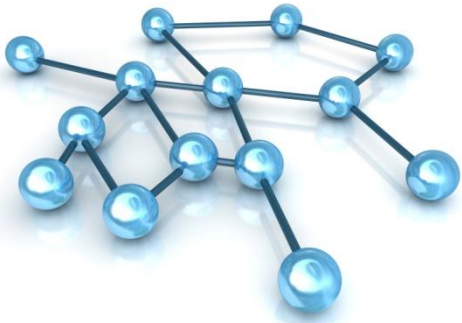
TdP



## mechanism

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





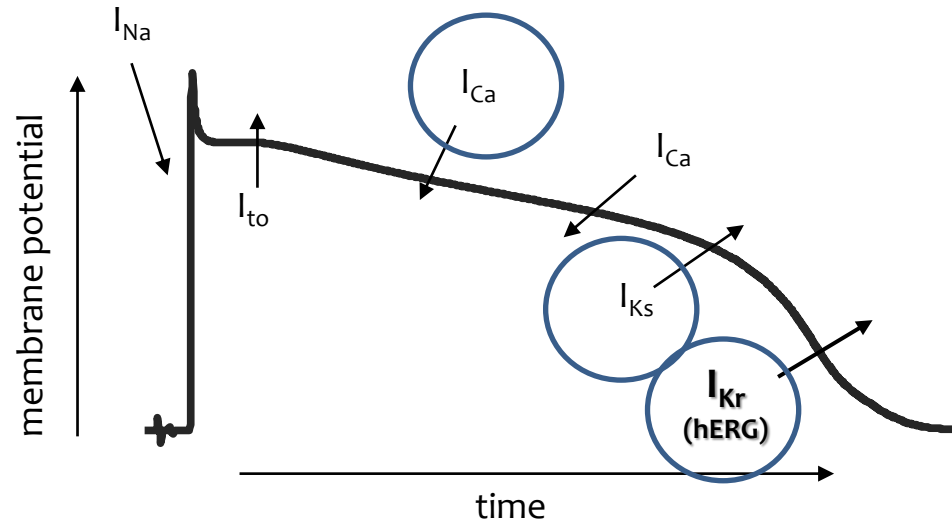
# TdP – Torsades de Pointes

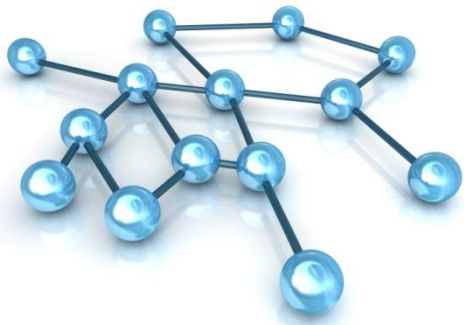
## problems

- drugs inhibiting  $I_{Kr}$  potassium current in vitro – do not express same characteristic in vivo (verapamil)

## potential reasons

- interplay between various ionic channels inhibition





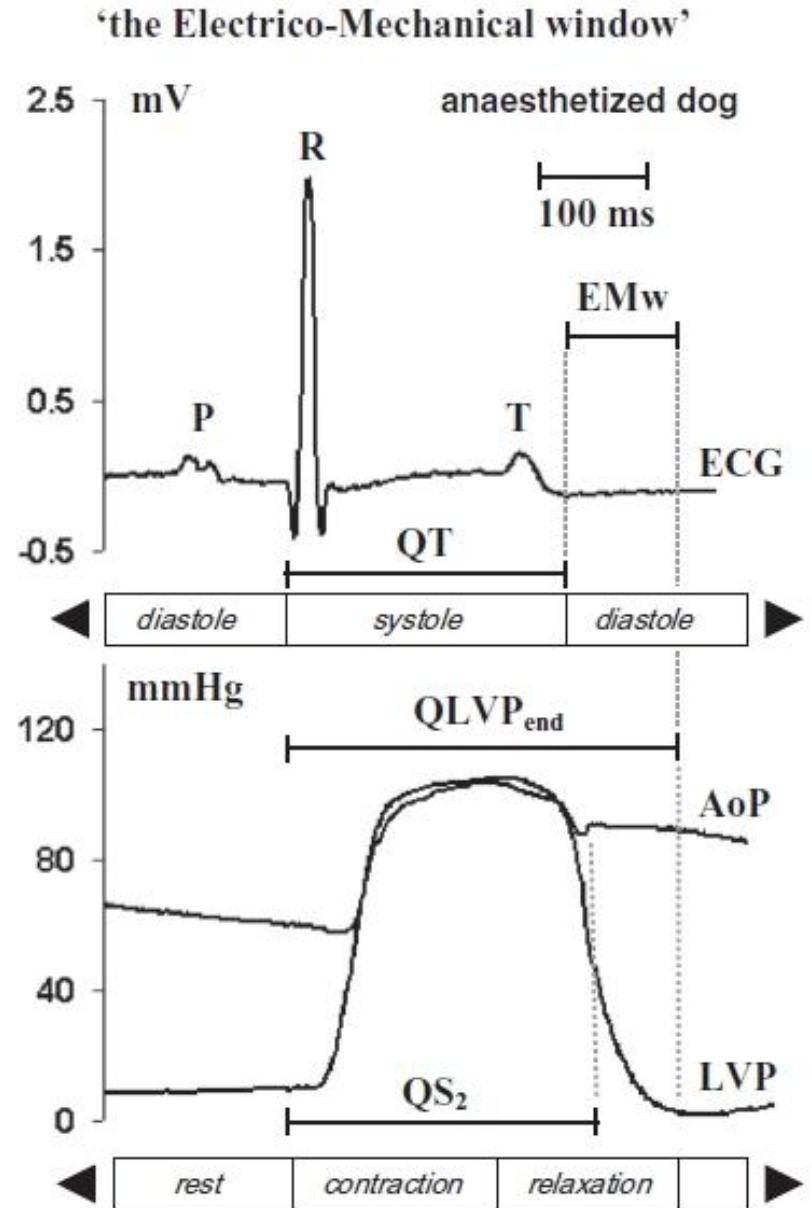
# TdP – Torsades de Pointes

## problems

- interplay between electric and mechanic cardiomyocytes activity

## potential reasons

- parallel investigation of the electric and mechanic activity - the electro-mechanical window

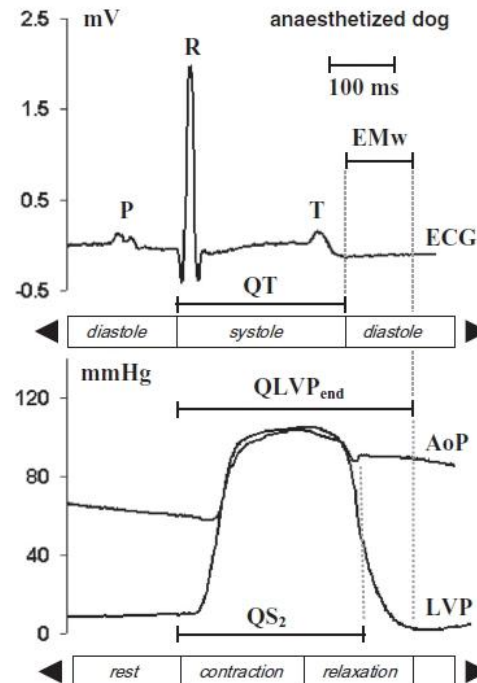


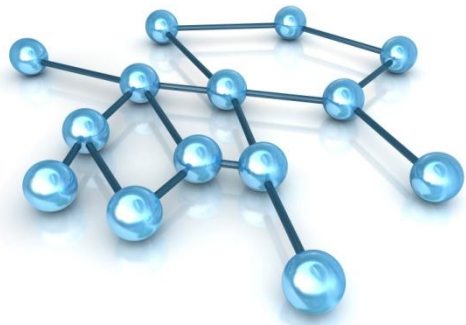


# TdP – Torsades de Pointes

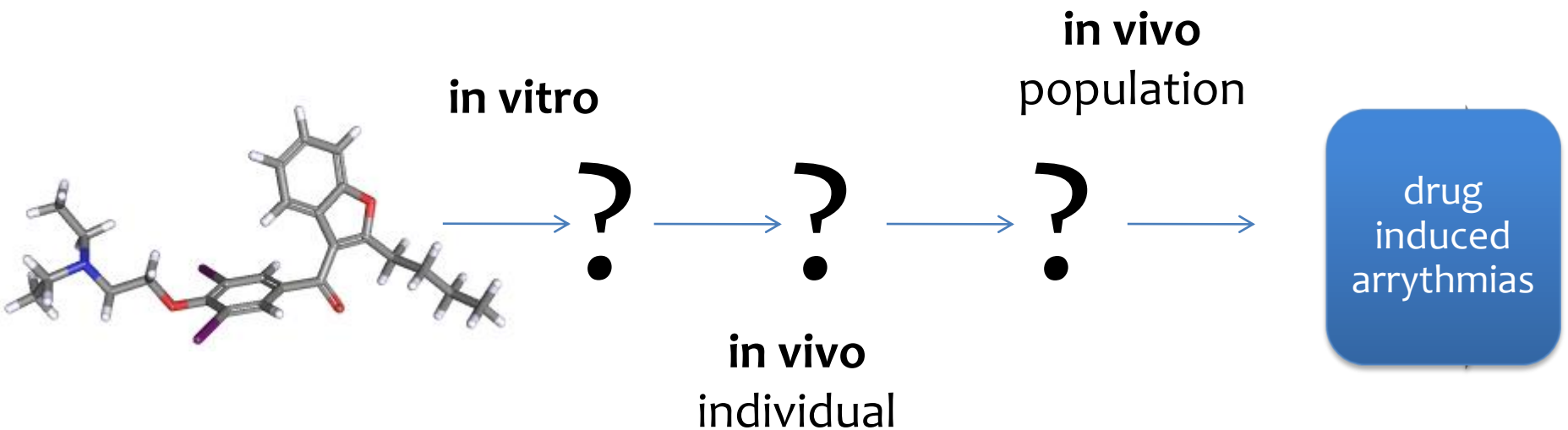
	HR (b.p.m.)	QT (ms)	QTcV (ms)	QLVP <sub>end</sub> (ms)	EMw (ms)	TdP (%)
Baseline	73 ± 3	252 ± 6	265 ± 5	339 ± 8	87 ± 7	0
HMR1556	75 ± 5	319 ± 11†	330 ± 10†	348 ± 10	28 ± 12†	0
Isoprenaline	160 ± 9†	310 ± 8	362 ± 8†	200 ± 6†	-109 ± 6†	100
Saline	153 ± 12	369 ± 13	422 ± 13	223 ± 8	-147 ± 20	100
Mexiletine	152 ± 15	301 ± 29	352 ± 26†	175 ± 5†	-126 ± 27	100
Atenolol	108 ± 12†	316 ± 21	353 ± 16†	293 ± 11†	-23 ± 19†	0
Verapamil	159 ± 26	255 ± 9†	304 ± 4†	240 ± 24	-16 ± 17†	0

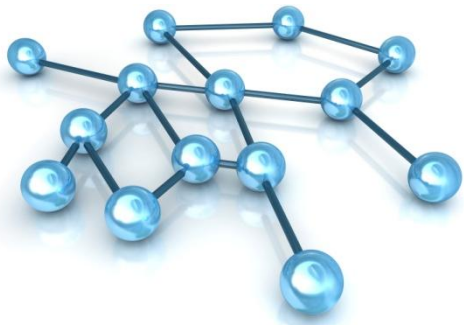
‘the Electrico-Mechanical window’





# toxicity prediction

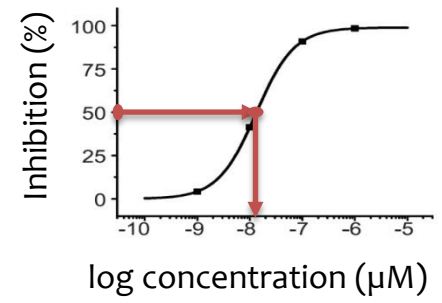
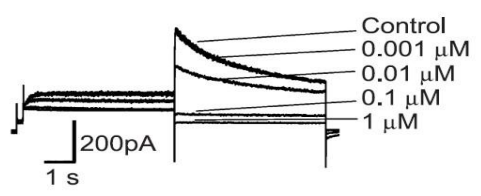
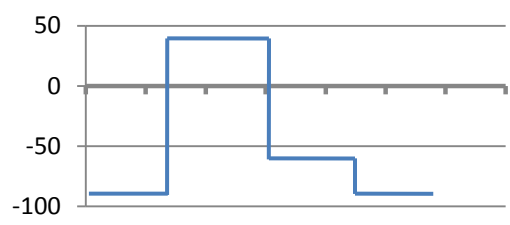
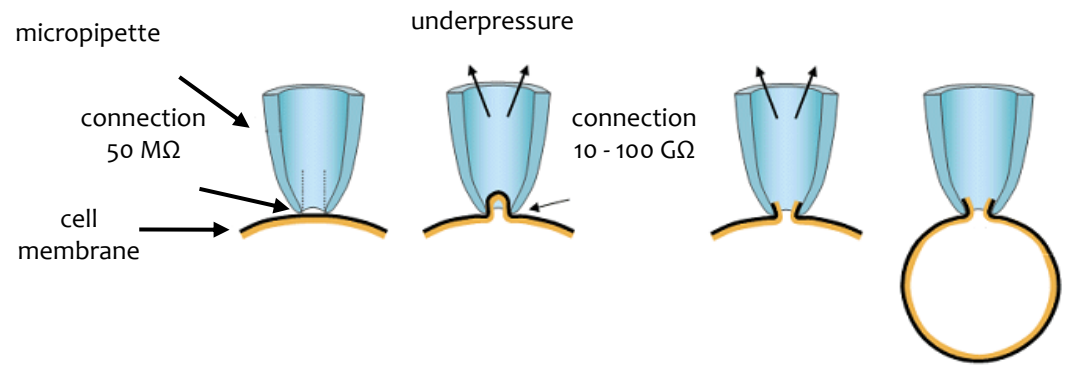


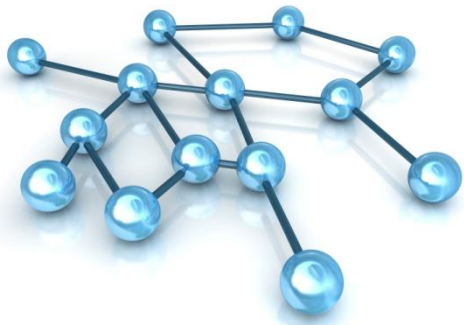


# proarrhythmic potency assessment in vitro

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

in vitro

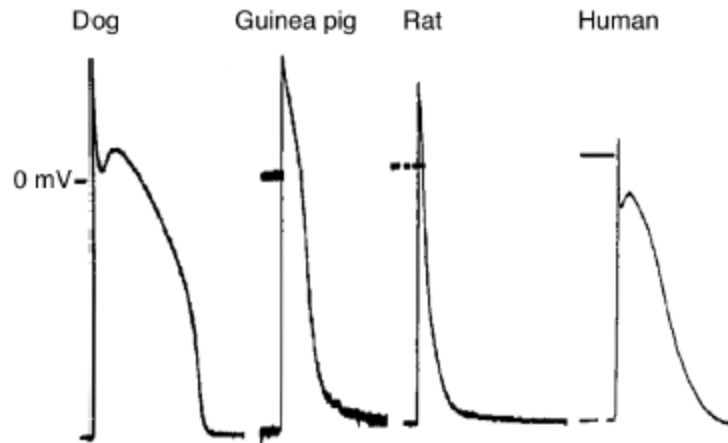




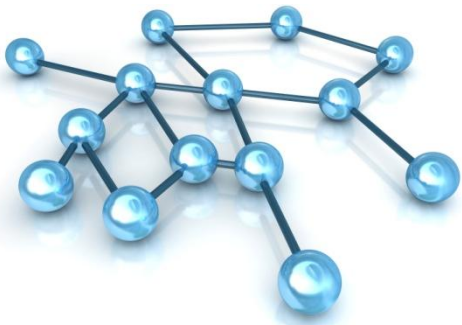
# proarrhythmic potency assessment

## allometric scaling

in vivo



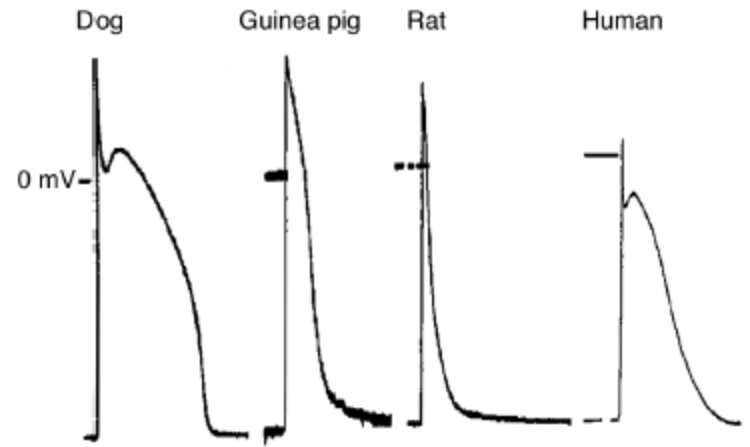
examples of the action potentials recorded from the canine, guinea pig, rat and human atrial myocytes



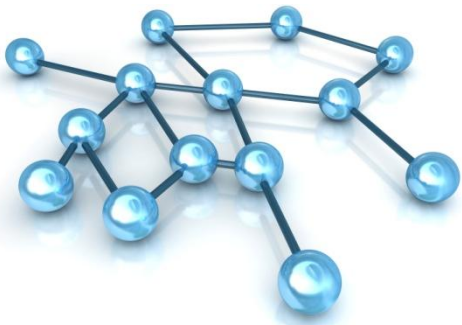
# proarrhythmic potency assessment

## allometric scaling

in vivo

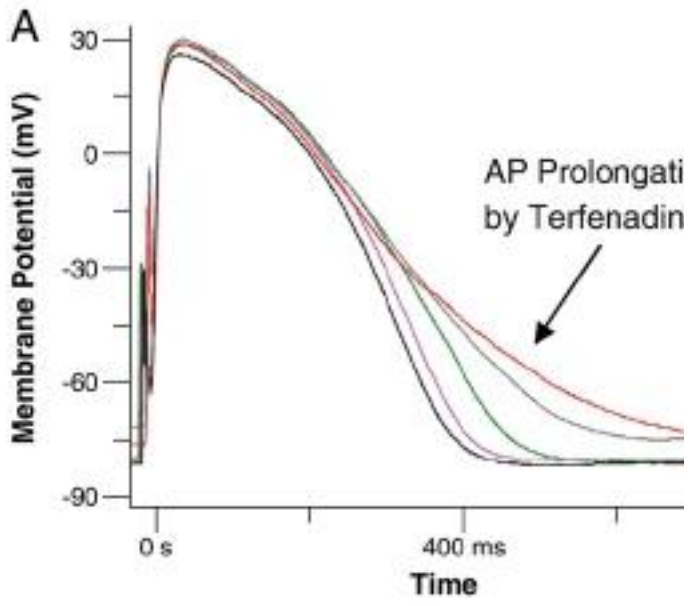


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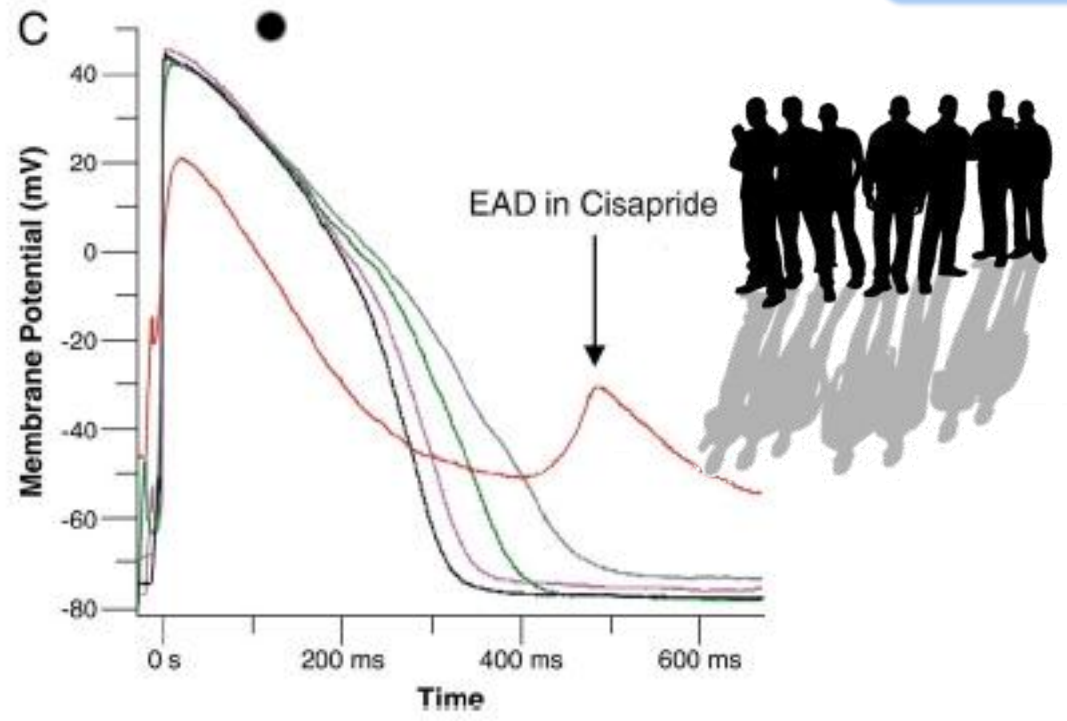


# proarrhythmic potency assessment

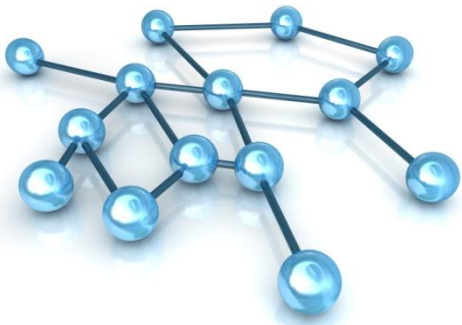
## stem cells derived human cardiac myocytes



in vivo



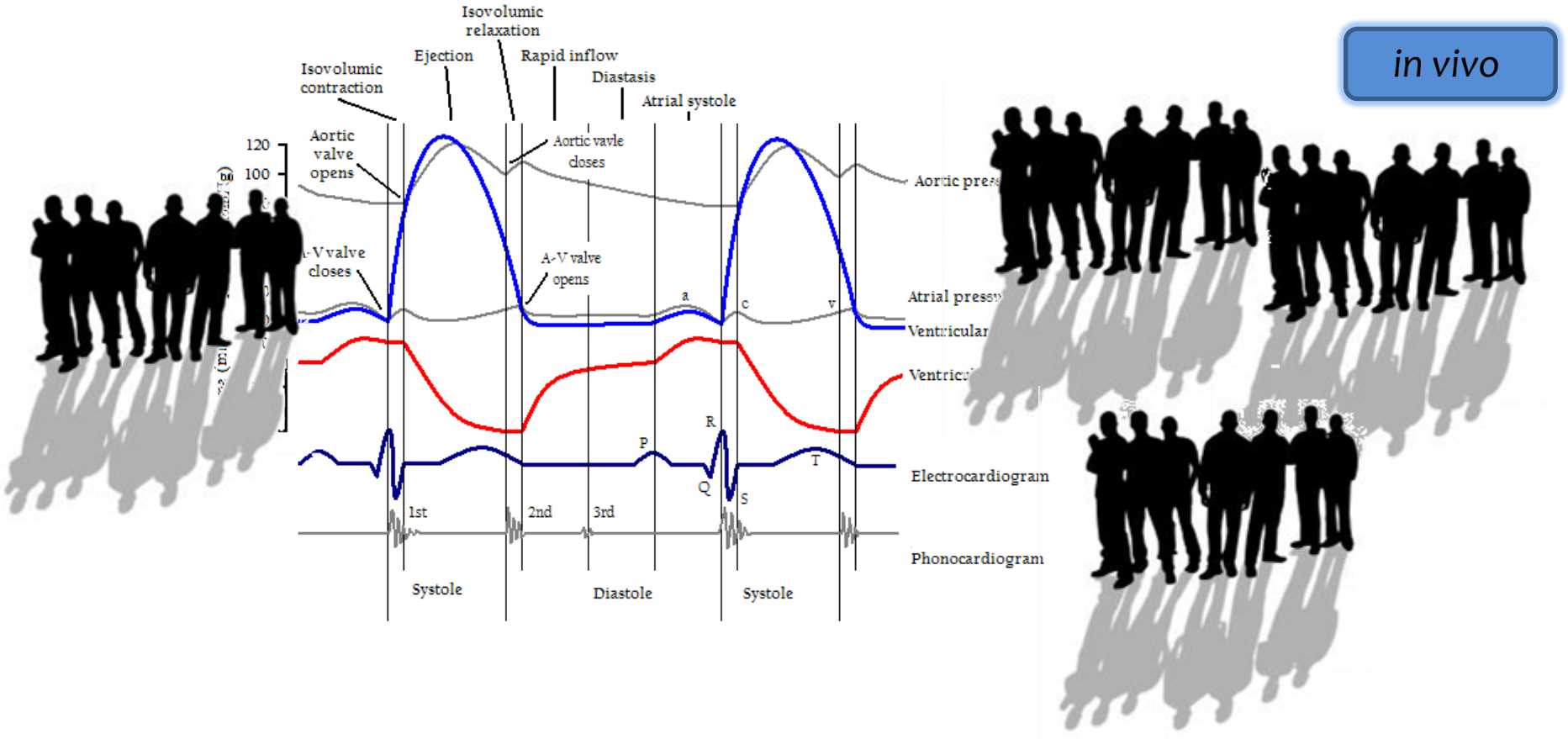
examples of the action potentials recorded from the stem cells derived human cardiac myocytes

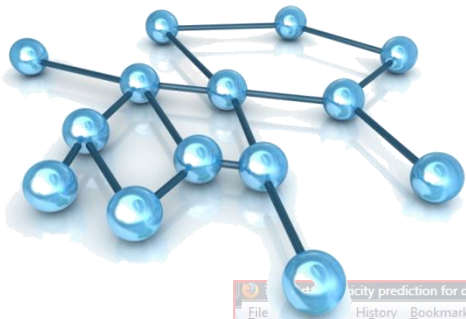


# proarrhythmic potency assessment

## TQTc

in vivo





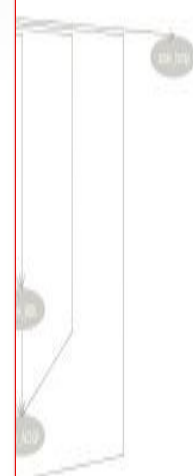
# proarrhythmic potency *in silico*

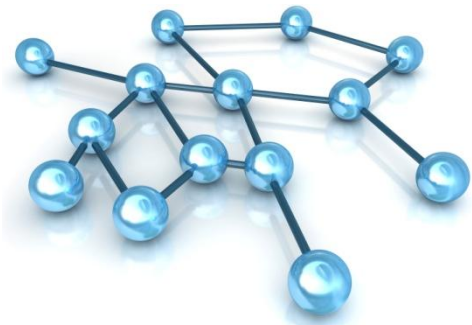
ToxComp.net

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more information can be found at the

## [www.tox-portal.net](http://www.tox-portal.net)





THANK YOU



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Pharmacoeconomics  
Jagiellonian University Medical College

