Test compound selection– Process, methodology, and selected compounds for CIPA efforts

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Purpose of the Compound Selection Effort

- Provide a battery of compounds for training, testing and validating the in silico and stem cell CIPA models
  - Build/calibrate model using compounds with well-characterized torsadogenic risk
  - Test/validate model using subset of compounds in the current set
- Compounds considered as test cases
- Intent of compound set was to provide varied spectrum of multiple electrophysiologic parameters:
  - Degree of torsadogenic clinical risk
  - Actions on ion channels, with attention to multi-channel blockers;
  - Varying levels of block at clinical exposures
  - Inclusion of some compounds with non-hERG TdP risk

Important Considerations

- Selected compounds should not have major proarrhythmic active metabolites
- No insoluble compounds
- Well defined cardiac electrophysiology
- Ranking compounds with regard to clinically demonstrated torsadogenic risk/occurance based partly on published reports, FDA AERS database, other data sources and expert opinion
- Compounds grouped into ‘high’, ‘intermediate’ and ‘very low’ (i.e., none) risk categories
  - Intermediate risk compounds grouped due to difficulty parsing out risk levels within the intermediate bucket
  - ‘Very low’ risk actually indicates no discernable risk
- Culled from much larger list of compounds

Published sources used to pick compounds

- Redfern, et al, 2003:
  - Category 1: Class Ia and Class III anti-arrhythmics, block I_{Kr} and prolong QT
  - Category 2: agents withdrawn due to risk of TdP
  - Category 3: measurable incidence or numerous case reports of TdP in humans
  - Category 4: isolated reports of TdP in humans
  - Category 5: no published reports of TdP in humans when used alone
- Mirams, et al, 2011: Updated assignments to Redfern categories
- Kramer, et al, 2013: torsadogenic (+TdP) or non-torsadogenic (-TdP)
- Credible Meds: categories include Risk of TdP, Possible Risk of TdP
- Pulozzi, et al, 2009: ROR + 95% CI calculated for each drug
- FDA AERS Database: Indicator of risk = EB05
- FDA labeling
  - Black box warnings
  - Warnings and precautions
- Compound-specific references

- Multiple classification schemes, with differing numbers of categories
- Key for our purpose was to identify gradation of risk

High Risk

Compound	Redfern category	Mirams risk	Kramer TdP +	Credible Meds	Pulozzi ROR (adj ROR for non-AA's)	FDA AERS EB05	FDA labeling
azimilide	1					70	
bepridil	3	3	TdP+	Risk of TdP		76	
dofetilide	1	1	TdP+	Risk of TdP	32.3	20	w/p
ibutilide	1		TdP+	Risk of TdP		214	Boxed warning
quinidine	1	1	TdP+	Risk of TdP		33	
vandetanib				Risk of TdP		0.6	Boxed warning
methadone			TdP+	Risk of TdP	48.5	37	w/p
d,l-sotalol	1		TdP+	Risk of TdP			w/p

Intermediate Risk

Compound	Redfern category	Mirams risk	Kramer TdP +	Credible Meds	Pulozzi ROR (adj ROR*)	FDA AERS EB05	FDA labeling
astemizole	2		TdP+	Risk of TdP		18	
chlorpromazine		3	TdP+	Risk of TdP		4	
cisapride	2	2	TdP+	Risk of TdP		30	
clarithromycin	4			Risk of TdP	7.5	6	w/p
clozapine			TdP+	Possible Risk		0.1	w/p
domperidone	4			Risk of TdP		15	
droperidol			TdP+	Risk of TdP		17	Boxed warning
terfenadine	2	2	TdP+	Risk of TdP			
pimozide	3	3	TdP+	Risk of TdP		8	
risperidone	5	5	TdP+	Possible Risk	2.9	1	
ondansetron				Risk of TdP		9	

Very Low Risk

Compound	Redfern category	Mirams risk	Kramer TdP +	Credible Meds	Pulozzi ROR (adj ROR*)	FDA AERS EB05	FDA labeling
diltiazem	5	5	TdP-			2	
loratidine	5		TdP-			6	
metoprolol					5.6	3	
mexiletine		4				2	
nifedipine	4	4	TdP-			0.6	
nitrendipine	5		TdP-			0.6	
ranolazine				Possible Risk		20	
tamoxifen	5			Possible Risk		0.1	
verapamil	5	5	TdP-		5.2	3	

Divergence in CIPA categories vs Redfern and Credible Meds

High risk compounds	Redfern Category	Credible Meds
azimilide	1	
bepridil	3	Risk of TdP
d,l-sotalol	1	Risk of TdP
dofetilide	1	Risk of TdP
ibutilide	1	Risk of TdP
methadone		Risk of TdP
quinidine	1	Risk of TdP
vandetanib		Risk of TdP

Intermediate risk compounds	Redfern Category	Credible Meds
astemizole	2	Risk of TdP
chlorpromazine	3	Risk of TdP
cisapride	2	Risk of TdP
clarithromycin	4	Risk of TdP
clozapine		Possible risk
domperidone	4	Risk of TdP
droperidol	2	Risk of TdP
odansetron		
pimozide	3	Risk of TdP
risperidone	5	Possible risk
terfenadine	2	Risk of TdP

Very low risk compounds	Redfern Category	Credible Meds
diltiazem	5	
loratadine	5	
metoprolol		
mexiletine	4	
nifedipine	4	
nitrendipine	5	
ranolazine		Possible risk
tamoxifen	5	Possible risk
verapamil	5	

Summary

- Initial list of 28 compounds provided for testing and validation of in silico and stem cell CIPA models
- Compounds categorized into 3 risk groups according to published/publically available data and expert clinical opinion

Remaining Questions

- Why did we end up with 3 risk categories?
  - Uncertainties
    - Exposure: critical determinant of potential torsadogenicity
    - Patient status and its influence of arrhythmogenic substrate—e.g., ICU patient vs healthy outpatient
    - Risks conferred by concomitant medications
    - Lack of objective data, denominator for reports of TdP
    - Limited categories for some classification systems (e.g., Credible Meds, Kramer et al)
- What was the thinking behind specific classification assignments?
  - Risperidone: low vs intermediate vs high risk?
  - Quinidine: hERG blockade at concentrations lower than INa blockade; relevant concentrations will need to be used for model testing
- How certain are we about classifications?