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# Computational investigations of hERG channel blockers: New insights and current predictive models ☆

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ABSTRACT

Identification of potential human Ether-a-go-go Related-Gene (hERG) potassium channel blockers is an essential part of the drug development and drug safety process in pharmaceutical industries or academic drug discovery centers, as they may lead to drug-induced QT prolongation, arrhythmia and Torsade de Pointes. Recent reports also suggest starting to address such issues at the hit selection stage.
In order to prioritize molecules during the early drug discovery phase and to reduce the risk of drug attrition due to cardiotoxicity during pre-clinical and clinical stages, computational approaches have been developed to predict the potential hERG blockage of new drug candidates.
In this review, we will describe the current *in silico* methods developed and applied to predict and to understand the mechanism of actions of hERG blockers, including ligand-based and structure-based approaches. We then discuss ongoing research on other ion channels and hERG polymorphism susceptible to be involved in LQTS and how systemic approaches can help in the drug safety decision.



**Contents**



## 1. Introduction

Voltage-dependent ion channels give in part rise to the shape and duration of the cellular action potential and this electrical activity of the heart is commonly recorded using electrocardiography (ECG) approaches. These recent years, a particular channel was extensively investigated as it was found to play a major role in both cardiac electrophysiology and drug safety [1]. This protein is encoded by the human ether-a-go-go related gene (hERG), which produces the pore-forming subunit of a delayed rectifier voltage gated $K^+$ channel. The family name "ether-a-go-go" was coined in 1969 [2] and was intended as reference to how the legs of mutant flies shake under ether anesthesia like the go-go dancers of the 1960s [3]. During drug development, there are in fact several types of cardiovascular toxicity that have to be considered, but admittedly, promiscuous block of cardiac hERG

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channels by a variety of structurally different low molecular weight drugs represents a major therapeutic challenge with profound impacts on human health. It is indeed known that genetic disorders and drugs that affect ion channels in the heart can change ECG parameters such as the QT-interval. A special cardiovascular safety concern is commonly referred to as QT interval prolongation (Fig. 1). QT interval (which represents the time from the depolarization to the repolarization of the ventricules) prolongation can cause Torsade de Pointes (TdP), a ventricular tachyarrhythmias. If this episode resolves spontaneously and rapidly, it can trigger syncope and in extreme situations can progress to ventricular fibrillation and sudden death [4,5].

These last years, it was found that many drugs belonging to different chemical and therapeutic groups, such as antiarrhythmics, antihistamines, antifungals, antipsychotics or antitussives, have the potential for QT prolongation and may cause TdP while being relatively potent inhibitors of hERG. For instance terfenadine (*Antihistamine*), astemizole (*Antihistamine*), and cisapride (*Serotonin receptor agonist*) were all approved for human use and were withdrawn from the market as they had safety issues, inducing QT interval prolongations and arrhythmias. Along the same line, vardenafil (*Anti-anginal/vasodilator*) and ziprasidone (*psychiatric drug*) were approved but with cautionary labeling as they can affect the ECG (see sites such as the Internet Drug Index: http://www.rxlist.com or the list of "QTDrugs" at: https://www.crediblemeds.org or at: http://www.sads.org.uk/) [6].

As a result of these observations and because of the unjustified risk of sudden cardiac death, regulatory agencies started to be concerned by the potential risk of Long QT Syndrome (LQTS) caused by drugs and more specifically, given our present understanding of the problem, by hERG (although in theory many other events could cause LQTS and LQTS are not always associated with cardiac toxicity). A first guideline (the regulatory basis for safety pharmacology studies is defined by the international conference on harmonization (ICH) guidelines, e.g., the non clinical guideline S7B) was adopted in 2005 that required from the pharmaceutical companies to identify drugs with QT liability. A second guideline was compiled in parallel (the clinical guideline ICH E14). There, the FDA required for almost all new low molecular weight drugs to be assessed in a "thorough QT" clinical study [7] to determine if the drug prolongs the heart-rate-corrected QT interval (QTc). Additionally, the harmonization for drug labeling was also requested. With these guidelines, it is believed that improving the efficiency and effectiveness of medical product development could be advanced most rapidly by combined analysis of clinical and preclinical data from previous marketing applications. For example, the FDA reviewed >250 thorough QT study reports, of which ~20% have been positive for QT prolongation [8]. Consequently, many drugs had to be withdrawn from the market [9].

As mentioned above and directly related to these guidelines, several studies have shown that the blockage of the delayed rectifier current during the inward rectification (Ikr) was a primary factor in acquired-LQTS. Such deregulation of the voltage dependent $K^+$ ion channel is mediated by the human ether-a-go-go related gene (hERG), a key component of the IKr [4,10]. Seventy-eight Kv channel family have been reported so far [11] and although hERG (defined also as KCNH2 and Kv11.1) is expressed in a wide array of tissues, its physiological function is best characterized in cardiac cells where it plays a critical role in the repolarization of the cardiac action potential [2]. Globally, during the plateau phase, there is reduced $K^+$ permeability whereas the $K^+$ channel remains open during the repolarization phase [12]. Because of the importance of this channel on human health, functional assays measuring drug-induced blockage of hERG current started to be developed and are now routinely used [13,14]. All major pharmaceutical companies have to monitor the potential risk of LQTS induced by new drugs during each stage of the drug discovery process [15]. To assess the hERG channel blockage induced by a drug, electrophysiological experiments (i.e., patch clamp) were the preferred techniques. The drawback is that such studies are expensive and time consuming. Simpler, faster and more "high-throughput", binding assays can also be used but there are concerns about the physiological relevance of such experiments. Of importance is that all these experiments allow to develop databases that should ultimately help to design theoretical models to rapidly flag new molecules as being potential hERG binders [16]. Overall and independently of the assay used, it is in general very difficult to derive guidelines for chemical synthesis from analysis of such experimental data [17]. In the meantime, in order to improve our knowledge over the mechanisms of blockage and possibly facilitate drug development, structural biology investigations and/or mutagenesis studies in

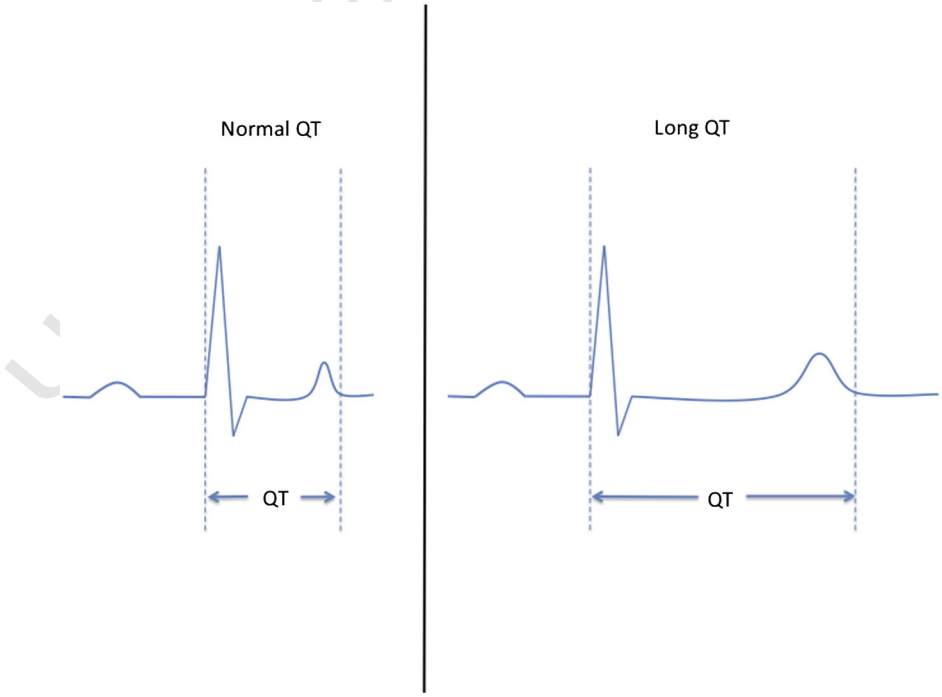


**Fig. 1.** Schema of a normal electrocardiogram (on the left) versus a prolongation of the QT interval (on the right).

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combination with various homology models of the channel were carried out such as to propose likely poses for the drug blockers into the channel and give new ideas for compound optimizations [18]. Ligand-based models were also established such as to suggest key chemical features to avoid during the design of a new drug and where chemical modifications could be introduced in the molecules to reduce binding to the channel [19].

There are however many difficulties with hERG studies and drug development strategies. For instance, the relationship between hERG block and clinical QTc (corrected QT) prolongation is still unclear and some drugs that inhibit hERG (verapamil) do not trigger TdP (and vice versa). While all typical TdP are high-potency hERG blockers, not all hERG blockers cause TdP. For example, both verapamil and ranolazine are hERG blockers and prolong QT, but appear not to be proarrhythmic, because of the effects on calcium (verapamil) or late sodium (ranolazine) currents [20]. Indeed, systemic approach studies suggest the involvement of others proteins and others mechanisms in TdP [21]. Some insights start to be provided about the underlying complexity of such cardiac toxicity problem, stressing the fact that hERG liability does not necessarily translate into TdP risk in humans. Along the same line, estimates are that 40–70% of the new molecular entities developed as potential therapeutic agents test positive when assayed for hERG blocking liability [22]. These molecules are then abandoned while their true torsadogenic potential is unknown. To some extent, these problems could be acceptable if TdP risk could be clearly elicited in clinical trials. However, drug induced TdP from non-antiarrhythmic drugs is a relatively rare event and may not be detected even in clinical trials of several thousands of patients, underlying further the challenges ahead.

Because hERG assays and QT animal studies are expensive and time consuming specially in the early stages of drug discovery, when numerous molecules would need to be assessed, or else because assay results could be misleading, numerous *in silico* models have been developed over the years to assist decision making (see a list of free *in silico* tools and databases at www.vls3d.com, [23]). With this review, we will present the new insights and current predictive *in silico* models developed for hERG and the new investigations based on systemic approaches related to the acquired-LQTS.

## 2. Diagnosis of QT-interval prolongation and harmonization of the data for *in silico* predictions

Numerous issues have been reported on the prediction of drugs that induced LQTS, notably drug-metabolism, drug solubility, the variability of the concentration of inhibition depending upon the experimental methods used and the relation between different clinical observations and QT-interval prolongation [24]. In this review, we will highlight several key points that should be taken into account by drug designers in order to develop novel and more accurate algorithms and protocols.

### 2.1. Detection of QT prolongation at the clinical level

One of the most critical issues in the development of predictive and accurate models is the acquisition of reliable data, not only at the molecular level, but also at the clinical level. Such harmonization is often discussed by the different agencies.

In 2005, based on close to 300,000 case reports of suspected adverse drug reactions for 52 proarrhythmic drugs, De Bruin et al. reported a significant association between the hERG blockage of drugs and ventricular arrhythmias and sudden death. Interestingly, these reports on drug-induced Torsades de Pointes concerned more often women (68%) [25].

Recently, Kesselheim et al. conducted a study comparing prescription information (i.e., drug labels) approved by the FDA and by the European, Canadian and Australian regulatory authorities. They found that significantly fewer adverse drug reactions were listed in the UK label compared with the US label and concluded that the international variations in the presentation of safety data in the drug label could have important implications for patient safety [26]. In addition, substantial differences on safety information exist for several therapeutic classes, notably the cardiovascular system [27].

Warnier et al. did a comparison of the QT interval prolongation labeling for newly approved drugs [28] and concluded that only a moderate agreement in the semantic use of the phrase QT-prolonging properties of a drug in US and EU could be found, although the expected clinical decisions were more consensual. For example, one product (asenapine) had no QT-prolonging properties according to the EU label, whereas this drug possibly prolongs the QT interval according to the semantics in the US label. So, differences in QT labeling language can result in miscommunication of safety information and also in the development of TQT models [29].

### 2.2. Harmonization of the in vitro approaches for in silico prediction

The problem of harmonization is also present at the preclinical level, where different *in vitro* approaches for the determination of hERG binding are applied, such as whole-cell patch clamp electrophysiological assays, fluorescence-based assays, radioligand binding assays or rubidium flux, on different mammalian cell lines i.e., HEK (Human Embryonic Kidney cells), CHO (Chinese Hamster Ovary cells), COS (*Cercopithecus aethiops* cells) and neuroblastoma, or non mammalian cell lines such as XO (*Xenopus laevis* oocytes) [30,31]. For example a measured $IC_{50}$ of 100-fold difference has been determined for loratidine in the function of the cell lines used (100 μM in HEK and lower than 1 μM in XO cells, respectively) [32,33].

Moreno-Galindo studied the impact of the whole-cell patch-clamp configuration on the pharmacological assessment of the hERG channel and estimated that a potential source of error could be related to the conventional whole-cell configuration of the patch-clamp technique (at least on HEK-293 cells). It may have an impact on conclusions regarding the mechanism of inhibition. [34]. However, since the primary goal of pharmaceutical industry is to determine the hERG-blocking potency of drugs ($IC_{50}$), this technique is still recommended for regulatory submissions.

## 3. Ligand-based approaches

As the majority of the *in vitro* experiments to assess drug-induced LQTS are associated to the hERG blockage, understandably *in silico* approaches (and more specifically ligand-based approaches) started to be developed as they are known to be relatively efficient in dealing with this type of data. Interestingly, whereas the first *in silico* model was based on fifteen molecules [35], the most recent one which is also available online is based on more than 4980 diverse molecules collected from several sources [36]. Other groups, essentially in the private sector, have published models with even larger private datasets, as indeed most pharmaceutical companies have their own source of data [37,38]. Recently, experimental data obtained from a primary screen using electrophysiology approaches performed on more than 300,000 structurally diverse compounds were stored in a large database [39]. Although these data can be visualized for a specific query compound, the database is not available to the scientific community for building predictive hERG model. Overall, close to 70 hERG models have been reported in the literature using various molecular descriptors in combination with diverse machine learning methods and showing a large panel of performance (Table 1). Comments about some of these models have been reported previously [40,41].

A majority of the models are classifiers and only a few regression models on a small subset of compounds have been reported [42]. This can be explained by the analysis of the hERG content inside the ChEMBL database, one of the largest repositories of bioactive compounds, on



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**Table 1**
hERG models reported in the literature.

| Authors | Compounds | Methods | Model accuracy |
|---|---|---|---|
| Ekins et al. [35] | 22 | 3D-QSAR | R2 = 0.90 |
| Cavalli et al.[125] | 31 | CoMFA-QSAR | R2 = 0.95 |
| Roche et al. [126] | 472 | Neural network | cc = 0.70 |
| Keserü et al. [62] | 68 | Hologram QSAR | cc = 0.97 |
| Pearlstein et al. [10] | 32 | COMSIA-QSAR | Q2 = 0.571 |
| Aronov et al. [44] | 414 | Pharmacophore/Voting | cc = 0.82 |
| Bains et al. [127] | 124 | Algorithm genetic | ROC = 0.89 |
| Yap et al. [128] | 310 | SVM | acc = 97% |
| Aptula et al. [129] | 19 | QSAR | R2 = 0.87 |
| Tobita et al. [130] | 73 | SVM | acc = 90 - 95% |
| Cianchetta et al. [131] | 882 | GRIND-QSAR | R2 = 0.77 |
| Yoshida et al. [132] | 104 | 2D-QSAR | R2 = 0.70 |
| Seierstad et al. [133] | 439 | 2D-QSAR | R2 = 0.52 |
| Bhavani et al. [134] | 271 | SVM | acc = 93% |
| Coi et al. [135] | 82 | Codessa-QSAR | R2 = 0.82 |
| Dubus et al. [136] | 203 | Recursive partition | acc = 96% |
| Ekins et al. [137] | 99 | Recursive partition/SOM | R2 = 0.83; acc = 95% |
| Sun H. [138] | 1979 | Naives Bayes classifier | acc = 0.87% |
| Gepp et al. [139] | 339 | Decision tree | acc = 76% |
| Song et al. [63] | 90 | Fragment-based-QSAR | R2 = 0.91 |
| Aronov et al. [45] | 194-519 | Pharmacophore/Voting | acc = 78-82% |
| Waring et al. [140] | 7685 | Logistic regression | acc = 70% |
| Leong [141] | 26 | Pharmacophore/SVM | R2 = 0.97 |
| Gavaghan et al. [37] | 8832 | Onion D-optimal design-QSAR | acc = 67-93% |
| Obrezanova et al. [142] | 137 | Gaussian processes | R2 = 0.81 |
| Filz et al. [56] | 163 | PASS program | acc = 87% |
| Li et al. [46] | 491 | SVM | acc = 94% |
| Inanobe et al. [143] | 32 | 3D-QSAR | R2 = 0.90 |
| Jia et al. [144] | 1043 | SVM | acc = 94% |
| Chekmarev et al. [145] | 83 | KNN-SVM-SOM | acc = 67-74% |
| Thai et al. [146] | 313 | Binary QSAR | acc = 82-88% |
| Thai et al. [147] | 285 | Counter propagation NN | acc = 0.93 |
| Nisius et al. [148] | 275 | Similarity-based classifier | acc = 87% |
| Nisius et al. [148] | 232 | SVM-cluster analysis | acc = 0.85 |
| Hansen et al. [149] | 676 | Bias regression-QSAR | RMSE = 0.60 |
| Ermondi et al. [150] | 31 | Almond-QSAR | R2 = 0.93 |
| Doddareddy et al. [48] | 2644 | LDA-SVM | acc = 0.89-0.94 |
| Su et al. [151] | 250 | 4D fingerprint-QSAR | acc = 0.91 |
| Hidaka et al. [152] | 37 | SOM | NA |
| Garg et al. [153] | 68 | 2D-QSAR | R2 = 0.83 |
| Borosy et al. [154] | 25 | Hologram QSAR | R2 = 0.94 |
| O'Brien SE et al. [38] | 58963 | NN | Se = 0.86; Sp = 0.83 |
| Gunturi SB et al. [155] | 166 | kNN-LLR | Q2 = 0.81 |
| Kramer C et al. [156] | 113 | PLS, SVR | R2 = 0.84 |
| Fenu LA et al. [157] | 3916 | NB | acc = 0.53 |
| Obiol-Pardo et al. [96] | 400 | PLS | R2 = 0.52 |
| Robinson R. et al. [158] | 368 | SVM, RF | MCC = 0.10-0.83 |
| Sinha N. et al. [159] | 157 | NN | R2 = 0.73 |
| Du-Cuny L. et al. [160] | 529 | kNN | R2 = 0.59 |
| Kim JH. et al. [161] | 293 | NB, RF | Acc = 0.82-0.96 |
| Su BH. et al. [162] | 2214 | SVM | Acc = 0.73-0.90 |
| Broccatelli F. et al. [24] | 803 | GA-kNN, PLSDA | Acc = 0.76-0.97 |
| Kar S. et al. [163] | 242 | LDA, PLS | R2pred = 0.53-0.60 |
| Tan Y. et al. [164] | 113 | Heuristic | R2 = 0.91 |
| [Wang S. et al. [165] | 806 | NB, RP | Acc = 0.85-0.89 |
| [Wang Z. et al. [166] | 1686 | NB, KNB, PWM | SE = 0.55-0.66 |
| Pourbasheer et al. [167] | 45 | MLR, SVM | Q2 = 0.56- 0.89 |
| Czodrowski P. [43] | 3721 | RF | AUC = 0.66 |
| Czodrowski P. [43] | 694 | RF | AUC = 0.56-0.66 |
| Coi A. et al. [85] | 59 | GA-MLR | Q2 = 0.87 |
| Moorthy N. et al. [168] | 25 | MLR | Q2 = 0.71-0.87 |
| Polak S. et al. [29] | 98 | Various | RMSE = 0.86-1.17 |
| Ruggiu F. et al. [169] | 1889 | Stochastic QSAR sampler | Balanced Acc = 0.66 |
| Mirams GR. et al. [170] | 34 | NB | Acc = 0.62 |
| Liu LL. et al. [171] | 2644 | NB | Acc = 0.58-0.91 |
| Shen MY. Et al. [172] | 1668 | SVM | Acc = 0.87 |
| Braga RC. et al. [36] | 4980 | SVM, RF, GBM, TreeBag | Acc = 0.83-0.93 |
| Kireeva N. et al. [173] | 242 | SVM-GTM | Acc = 0.68 = 0.80 |
| Yu P. et al. [174] | 806 | CPAR, CMAR, CBA | F-score = 0.60-0.78 |
| Kratz K.M. et al. [175] | 86 | Pharmacophore model | AUC = 0.91 |
| Kratz K.M. et al. [175] | 37 | Pharmacophore model | AUC = 0.89 |

which the measurements show a large deviation between the different assays [43]. Such deviation can be reasonably covered with the transformation of the measurement into class.

Based on these models, several structure activity relationships were revealed such as the presence of key features including two hydrophobic features and one hydrogen bond acceptor (preferably a charged

nitrogen) [44,45]. It has been shown that removing carbons and/or changing the electronic environment around the basic nitrogen can result in a reduction in hERG inhibition [46,47]. In addition, transformations that add a hydroxyl group reduce hERG inhibition [36]. Some bioisosteric replacements have resulted in dramatic changes in activity. Replacement of a furane ring by a tetrazole ring resulted in a substantial alteration in hERG binding, changing the compound from a blocker to non-blocker. Modification of chlorine to the hydroxyl group or the nitrile group in an aromatic ring changes an hERG blocker to a non-blocker compound [36]. Using the maximum common substructure search to learn about the structural features specific to hERG blockers, Doddareddy et al. found that the three major factors contributing to the hERG blockage are a positively charged nitrogen atom, high lipophilicity and the absence of negatively charged oxygen atom [48]. It was also confirmed later on by Sherhod et al. based on an emerging pattern mining method. In addition to the known pharmacophores for hERG channel inhibition, other features were characterized like compounds with a quinolinol group that were found to be hERG blockers [49]. It should also be mentioned here that some authors suggest that for the prediction of primary targets, the benefit of using 3D over 2D similarity search appears small while for the prediction of off-targets, like in the case of hERG, the added benefit of using 3D similarity seems to be large [50,51].

Many hERG models have been developed by software companies but are not always easy to evaluate and to compare. On the other hand, some tools (essentially from academic groups) are freely available to predict the hERG activity. We can mention Pred-HERG (http://labmol.farmacia.ufg.br/predherg), Tox-Comp.Net (http://www.tox-comp.net/), and ACD-/I-Lab (https://ilab.acdlabs.com/iLab2/index.php). Not specifically associated to hERG, but with the possibility to provide also interesting output on hERG inhibition, are the use of large chemogenomics databases such as ChEMBL [52], PubChem [53] and ChemProt [54] where it is possible to carry out some search by chemical similarity. Target prediction web services such as the SEA search tool [55], PASS [56], Swiss Target Prediction [57], HitPick [58], SuperPred [59], and admetSAR [60] can also be considered for hERG prediction.

Overall, with these tools it is now possible to estimate the risk for a compound to be an hERG inhibitor and which features contribute to that. For example, we performed a search on three known drugs acting on hERG (terfenadine, astemizole and cisapride) and 2 molecules (vardenafil, ziprasidone) with a warning for QT prolongation on their prescription label. Looking for instance in ChemProt, all of them have been reported with an activity on hERG i.e., terfenadine ($pIC_{50exp}$ = 6.67 [61]), astemizole ($pIC_{50exp}$ = 8.04 [62]), cisapride ($pIC_{50exp}$ = 7.57 [63]), vardenafil ($pIC_{50exp}$ = 4.89 [64]), and ziprasidone (($pIC_{50exp}$ = 6.92 [65]). We then analyzed each compound with the Stardrop package (Optibrium). The Stardrop model for hERG prediction is built on a dataset of about 200 molecules with patch-clamp $IC_{50}$ values for inhibition of hERG $K^+$ channels expressed in mammalian cells. The model returns $pIC_{50}$ values and some additional information such as the distance of the predicted compound from the chemical space of the training set such as to partially assess the reliability of the results. An interesting feature of this package is the "glowing molecule" mode that displays the results of a computational model rendered as a heat map to highlight the regions of the molecule that are responsible for the activity in the model with red indicating structural features that have a positive effect and the cooler blue color a negative effect on the model. In our easy test case (as some of the molecules were certainly present in the training of the statistical model), red areas are zones that are predicted to increase hERG activity and could be important to modify in order to produce optimized compounds. The $pIC_{50}$ values obtained for our 5 test compounds were 6.7 for terfenadine, 8.2 for astemizole, 5.8 for cisapride, 5.8 for vardenafil and 6.6 for ziprasidone. Because hERG activity is only one endpoint, we also computed with the FAF-Drugs2 server [66] some other properties like the Lipinski rule of 5 [67] and the Pfizer's 3/75 rule [68] (the rule is agnostic with regard to the details of the mechanism of toxicity and states that there is a six fold reduction in toxicity *in vivo* (24-fold for bases) when the compound's log $P \leq 3$ and PSA $\geq 75$ Å$^2$) to look at the molecules from another angle. Terfenadine has one violation to the R05 (due a predicted log *P* higher than 5) and falls it the read area (risky zone) of the 3/75 rule. Astemizole passes the R05 but not the 3/75, cisapride passes the R05 and is close to the 3/75 threshold, vardenafil passes the RO5 and the 3/75 rule, while ziprasidone passes the RO5 and is really border line with regard to the 3/75 rule (Fig. 2).

Finally we should notice that natural products start to be screened on hERG and some of them show potential risk for inducing LQTS [69–71]. Integration of such information into hERG models should help to develop new and more accurate *in silico* prediction packages.

## 4. Structure-based approaches

Four identical α-subunits form the hERG $K^+$ channel and each unit accommodates six α-helical transmembrane segments defined as S1–S6. The voltage sensor domain (VSD) is embedded by segments S1–S4. The movement of the gating is governed by the positively charged Lys and Arg in the S4 helix and enables the pore domain to open and to close in response to changes in membrane potential. Segments S5–S6 form the pore domain allowing the $K^+$ ions to cross the membrane. A lengthy S5-P linker that contains an amphipathic helix (the turret helix) and a selectivity filter loop are also present in these segments. Finally, the N-terminal domain, consisting of the Per-Arnt-Sim (PAS) domain, and the C-terminal domain, which is composed of a cyclic nucleotide-binding domain, are located on the intracellular side of the membrane [72] (Fig. 3).

All structure-based studies are performed on homology models as hERG has not yet been crystallized. The structural models are essentially based on bacterial $K^+$ channels KscA (close form) [73], KvaP [74], MthK [75], Kir2.2 [76] and mammalian channel Kv1.2 [77], although the sequence identity is relatively low. A variety of homology models of the open, partially open or closed forms of hERG in combination to docking (rigid and flexible), and molecular dynamics described primarily conformational change differences in the S6 helices. For example, an atomistic hERG model generated by long supercomputer molecular dynamics simulations has developed and used to predict drug cardiotoxicity [78]. In the closed state the S6 helices are smooth, creating a point of constriction below the central cavity [17]. The residue G648 is conserved all over the potassium channel members and seems to act as a hinge point in the bending of the S6 helix. The conformational change produced in S6 allows the $K^+$ ions to get access to the central cavity and could act as a selectivity filter [72,78]. Beside this amino acid, three other residues (Y652, F656 and V659), facing inward towards the pore domain, play an important role in drug binding [79,80]. Additional residues such as T623, S624 and V625, located at the base of the selectivity and W563, F559 and F551 facing outward towards the voltage sensor, contribute to the differences in activation and inactivation properties of hERG [81,82]. Models of the hERG potassium channel and of the drug-binding cavity (surrounding by the S6 segments) are depicted in Fig. 4.

The movement of S4 in hERG has also been studied to explain the gating properties. Elliott et al. [82] suggested that the extent of S4 movement in hERG is large and similar to other Kv channels. This movement is coupled to the opening of channel gates located at the intracellular aspect of the channel via the S4–S5 linker, leading to $K^+$ efflux [83].

Since most hERG-blocking drugs access the pore cavity from the intracellular side of the membrane when the channel opens in response to membrane depolarization, open state pore models are likely to best represent the arrangements of key amino side chains that are productive for drug binding. More specifically, the open state MthK structure was recently suggested to be the best template to model binding of many drugs [84].



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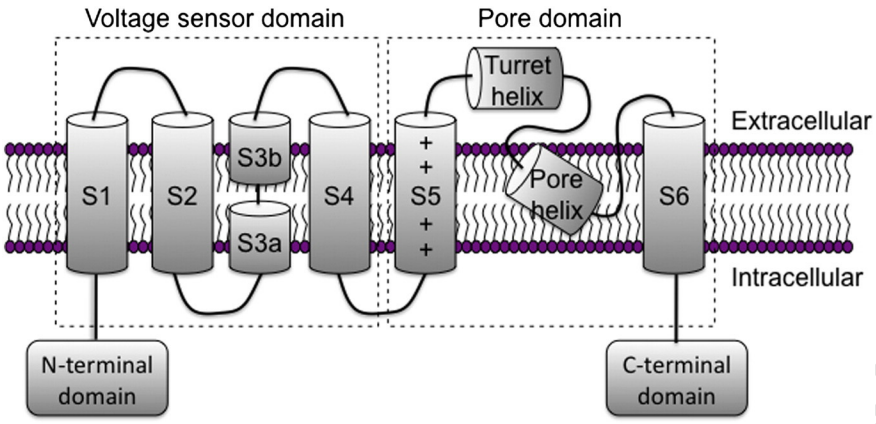


**Fig. 2.** On the left, structural features, which are responsible for the hERG activity based on the Stardrop model, are represented. The red areas indicate features that have a positive effect and the color blue a negative effect on the model. On the right, the Lipinski and Pfizer's 3/75 rules were computed with FAF-Drugs2 and represented in a 2D map. When the studied compound (the blue dot) is on the red area, it means that one of the rules is violated. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

Combinations of structure- and ligand- based approaches to study the different binding modes were also investigated. Coi et al. built four 3D models representing different conformational states of hERG $K^+$ channel and carried out molecular docking-based molecular descriptors to develop QSAR models [85]. However, molecules can block hERG in other sites and thus docking studies need to be performed cautiously. For example fluvoxamine and doxepin blocked the channel independently of mutations around Y652 and F656. Similarly, peptides block in the entrance of $K^+$ channels [61]. An interesting perspective of structure-based approaches is to combine them with hERG polymorphism and drug response variation data. Some clinical studies have reported a higher risk of LQTS induced by drugs in patients having genetic variations in hERG and we could imagine that structure-based approach could provide new structural basis for the development of safer drugs [86–94]. For example, Du et al. estimated the activity of the ranolazine drug (an antianginal) on hERG and concluded the N588K mutation is unlikely to be effective in patients with short QT syndrome. Using docking simulations, the study indicated that the large size of ranozaline favors interactions with the hERG pore [18].

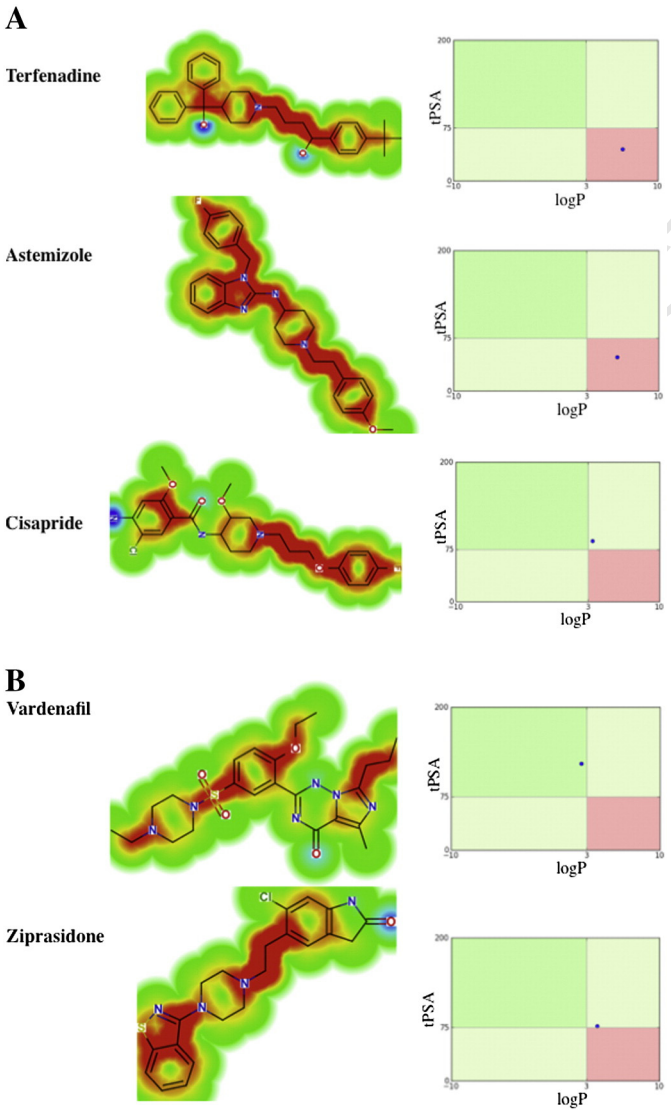


**Fig. 3.** Schema of the hERG potassium channel.

Interestingly, allosteric modulation of the hERG $K^+$ channel started to be studied as an alternative way of interaction. For example, compound A-935142 has recently been stated to possess a binding site responsible for hERG current enhancement, which is different from the pore binding site of the traditional hERG blockers [95,96]. Similarly Yu et al. [97] demonstrated that LUF6200 is an allosteric inhibitor. The binding sites of several peptide blockers like saxitoxin and BeKm-1 are located in the extracellular parts of the hERG $K^+$ channel [98,99]. Multiple binding sites for these diverse compounds on the hERG $K^+$ channel imply a plausible allosteric modulation among them. They might allosterically increase (allosteric inhibitors/negative allosteric modulators) or decrease (allosteric enhancers/positive allosteric modulators) the dissociation rates of typical hERG blockers and thus mediate a greater (or poorer) safety profile for some drugs. Dynamic simulation studies could be performed and help in deciphering the allosteric modulation of some of these compounds.

## 5. Systemic approaches

### *5.1. Multiple ion channels*

The role of hERG in the ventricular repolarization is of critical importance, however, it is widely accepted that the complexity of the events involved in TdP makes the cardiac safety assessment, based only on hERG, a high risk of producing either false positive or negative results. In fact, drug effects on multiple ionic currents may modulate or mask the effects of hERG blockade [100,101]. For example, two drugs displaying low hERG safety margins yet not demonstrating convincing QTc prolongation are eltrombopag (used to treat low blood platelet counts) and lamotrigine (anticonvulsant). Based solely on hERG potency

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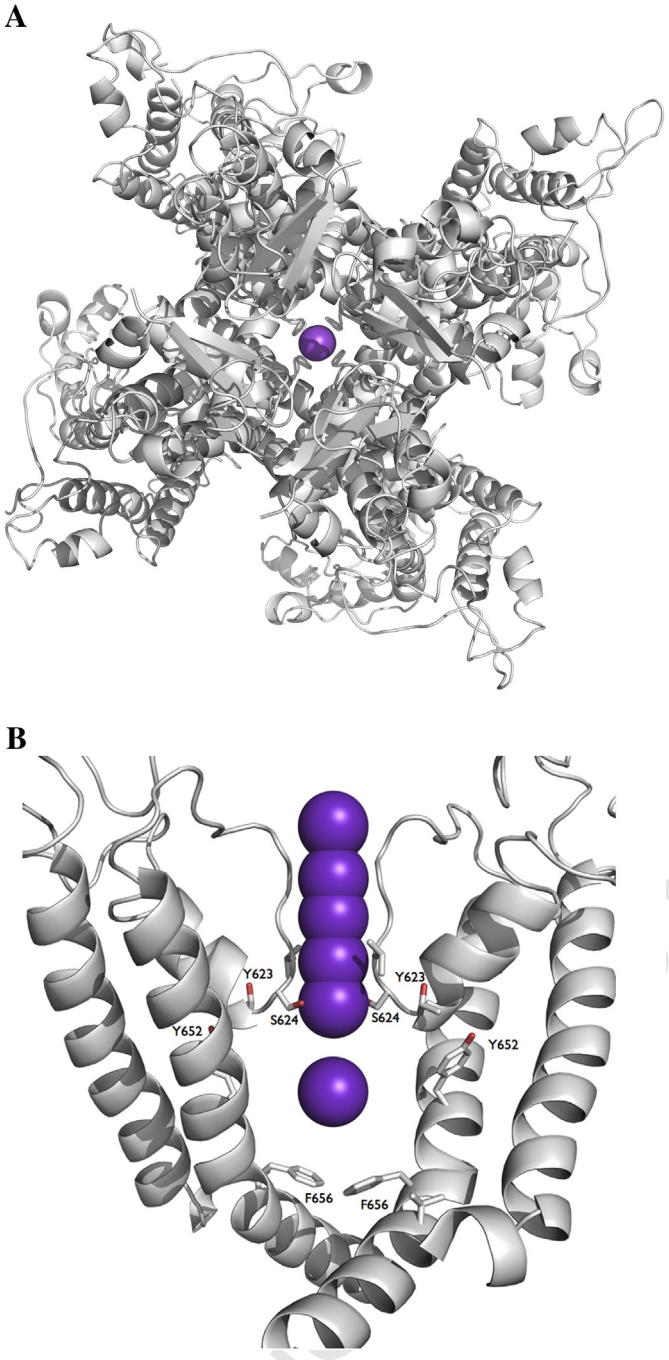


**Fig. 4.** 3D models of the hERG potassium channel. A) 3D representation of the tetrameric hERG potassium channel based on the full-length Shaker potassium channel Kv1.2. B) Dimeric representation of segments S5–S6. Residues involved in most of the drug interactions are depicted in sticks. Each magenta sphere represents a potassium ion. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

and therapeutic plasma exposures, both drugs would likely have been categorized as having high risks for QTc prolongation and subject to unwarranted attrition [21].

A hypothesis is that by blocking the inward current, through calcium or sodium channel, the torsadogenic effect of outward current, by hERG potassium channel, is also blocked. This is the case for example of fluoxetine (antidepressants) and verapamil (treatment of hypertension, cardiac arrhythmia) that have been shown to block opposing currents (repolarizing (outward) hERG current vs. depolarizing (inward) calcium current) [102,103]. However, it seems that the calcium or sodium channel block needs to occur at the same concentration or at a lower concentration than the hERG potassium channel block. For example, bepridil, a calcium channel blocker, was removed from the market in the United States because of TdP. It was shown that bepridil blocks hERG potassium channels at a concentration lower than the one required to block calcium channels, which could explain the acquired-LQTS [8]. Similarly, alfuzosin, which is used for benign prostatic hyperplasia, was shown to mildly prolong the QT interval although it does not block hERG. The drug seems to increase the late sodium current during the cardiac action potential (hNav1.5) and thus extend the QT interval [8].

Based on these observations, recent studies suggest that considering multiple ion channels provides better cardiotoxicity predictions [104]. Obio-Pardo et al. developed a combination of docking simulations on two potassium channels, hERG and KCNQ1, and 3D-QSAR for predicting how the tested compound will block the potassium currents IKr and IKs. As methods based solely on hERG provide a limited picture of the drug effects on the ventricular repolarization, such combination approaches outperform the classic hERG-based models [105]. Multiple QSAR models have also been implemented in a cardiac safety simulator, enabling the *in vitro–in vivo* extrapolation of the drug's proarrhythmic effect and ECG simulation [106]. Therefore, other ions channels that are modulated by drugs and involved in acquired LQTS and TdP are now investigated in combination with hERG [7].

The recent introduction of the IonWorks plate-based device has rendered the multiple ion channel electrophysiological assays popular [107]. To better interpret the integrated drug effect on various ion channels, computational models to predict drug-induced changes in the action of potential (AP) have been developed [108,109]. In these approaches, potency data are directly integrated within the model by reducing conductance in accordance with measured concentration–effect (C–E) curves. So, the modulation of other ion channels is considered in this approach and leads to a better estimation of the cardiac risk assessments. For example Davies et al. have developed a comprehensive model that predicts AP modulation of ventricular midmiocardial cells based on a panel of five ion channels and corresponding C–E curve data [110]. Similarly, Kramer et al. measured the concentration-responses of hERG, Nav1.5 and Cav1.2 currents for 32 torsadogenic and 23 non-torsadogenic drugs from several therapeutic classes in an automated gigaseal patch clamp instrument and developed a logistic regression model that predicted more accurately the torsadogenic potential than models based on hERG effects alone [111].

Overall, the multiple ion channel effects (MICE) approach is believed to be more robust than IKr assay alone at evaluating the proarrhythmic risk of new drugs, with fewer false-positive results.

### 5.2. hERG trafficking inhibition

Recent findings indicated that chronic treatment with various drugs not only inhibits hERG channels but also decreases hERG channel expression in the plasma membrane of cardiomyocytes, which has become another concern in safety pharmacology [112,113].

Understanding of drug-induced hERG trafficking inhibition may provide new strategies for predicting drug-induced QT prolongation and lethal cardiac arrhythmia in pharmaceutical drug development. For example Ficker et al. [114] demonstrated that arsenic trioxide ("antineoplastic" or "cytotoxic" molecule) did not show any direct inhibitory effect on hERG channel activity but disrupted the hERG trafficking by reducing the formation of the hERG-chaperone (Hsp90 and Hsp70). Similarly the antibiotic geldanamycin inhibits the formation of the hERG–Hsp90 complex that accelerates hERG channel degradation [115]. Pentamadine, an antiprotozoal agent does not directly inhibit hERG current but binds to hERG protein in a folding intermediate conformation leading to arrest of channel maturation and disrupted transport from the ER [113,116]. Interestingly, its inhibitory effect is reversed in the presence of pharmacological chaperones, astemizole and



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dofetilide, suggesting that pentamidine and pharmacological chaperones compete for the same binding site within the hERG channel, although the precise mechanism of action of pentamidine has not been elucidated. Probucol, a cholesterol-lowering drug, accelerates the degradation of mature hERG channels from the cell membrane through accelerated caveolin-1 turnover [117]. Wible et al. estimated that around 40% of hERG blockers carry the additional risk of inhibiting hERG trafficking [118].

### 5.3. Transcriptional profiles

Drugs may share similar and undesirable side effects despite being unrelated chemical structures or having different primary mechanisms-of-action (MOA). Exploring similarities in drug-induced transcriptional effects and combining with additional publicly available annotations for LQT side effect enable to identify clusters of drugs with similar expression profiles annotated for channel inhibitors. Babcock et al. [119] performed such analysis combining the drug-induced transcriptional effects from the Connectivity Map (cMap), a collection of Affymetrix™ microarray profiles generated by treating three independent lineages of cancer cell lines with small molecule drugs [120], and the hERG inhibitors annotated using a database of experimental measurements (hERGcentral) and clinical indications [39]. This analysis showed that structurally diverse hERG inhibitors mediate similar physiological effects revealed by transcriptional response profiles. Furthermore, evaluation of enriched gene ontology (GO) annotations among genes up and down regulated indicated positive effects on cholesterol biosynthesis (GO:0006695), isoprenoid biosynthesis (GO:0008299), and the unfolded protein response (GO:0030968), and negative effects on cell cycle checkpoint (GO:0000075), S phase of mitotic cell cycle (GO:0000084), and DNA replication (GO:0006260) although the physiological correlation between hERG block and these processes remains to be investigated.

## 6. Conclusion

Assessing the ability of all new drugs to cause TdP before reaching the market is required from the regulatory agencies and the current approaches focus exclusively on QT prolongation and hERG inhibition. An impressive number of *in silico* studies have been performed to understand the mechanism of drug-hERG blockage and to predict in advance the torsadegenic risk of new potential drugs. However, although these models provided structural key features in the interaction with hERG, safe compounds can be predicted as hERG blockers or even worse the algorithms can fail to detect toxic compounds [121]. Furthermore with such models, some hERG blockers, like fluoxetine or verapamil would probably not be accepted on the market based solely on hERG study. Indeed, it is widely accepted that hERG represents only one of the multiple ionic currents involved in the mechanism of ventricular repolarization and the modulation of these channels by drugs may mask the effect of hERG blockage. These observations have created recent interests in testing entire panels of cardiac ion channels rather than just hERG. Drugs start to be screened on multiple ion channel assays and some *in silico* models start to investigate the combination of the outcome from these assays.

hERG polymorphisms are believed to have a large contribution in the acquisition of LQTS and numerous studies showed the impact of several mutations in the variation of hERG blockage by drugs. However, these results come essentially from *in vitro* studies and only few clinical studies and on a small cohort of people have been reported. Clearly, pharmacogenomic studies on hERG potassium channel in association with computational structure-based approaches can provide new insights on TdP and would be of interest for the development of personalized medicines.

Finally, chronic effects of drugs are not detected in conventional cardiac safety screening. As some therapies are based on a long-term exposure to drugs, such analysis is of large interest. Recently, the use of induced pluripotent stem cell (iPSC)-derived human cardiomyocytes has been proposed to functionally assess chronic drug effects on the action potential duration and cell excitability in cardiac tissue [122,123]. This technology is believed to create new opportunities for cardiovascular research by providing platforms to study the mechanisms of disease pathogenesis that could lead to new therapies or reveal drug sensitivities and has been recommended for adoption in the revised ICH guidelines in the near future [124].

Overall, the field of LQTS is tremendously active and the development of future *in silico* methods more sensitive and more accurate to predict TdP is ongoing. With the application of new and higher throughput assays, new data will be available and exploitable for a broader understanding of the molecular pharmacology of acquired LQTS.

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