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Modelling Off-target Interactions (I): Cardiotoxicity

Khaled Barakat

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

Nearly every biological process relies on specific interactions of small molecules with proteins or other cellular components. Off-target (unexpected) interactions of small molecules are usually associated with dysfunctional cellular mechanisms and subsequent severe complications [1]. Computer simulations are currently well suited to address these problems [2-17] as recognized with the 2013 Nobel Prize in Chemistry [18]. Characterizing these interactions at the atomic level will not only help understand the mode of action of many severe side effects, but will also aid in rationally designing safe drugs. Take cardiotoxicity as an example. In this case, a toxic small molecule interacts with a critical class of proteins that control the normal heart rhythm. These proteins mainly involve a wide range of voltage-gated cardiac ion channels. The harmony of the ion flows through these channels creates the characteristic cardiac action potential [19,20]. Blocking these ion channels by small molecules is a critical event that can often lead to acquired cardiac long QT syndrome (LQTS) and fatal cardiac arrhythmias [21]. Despite the long failed history of accurately predicting cardiac ion channel blockade (e.g. CAST [22] and SWORD [23]), the accumulated wealth of experimental data available now [24] makes them an ideal model to build and refine a computational algorithm to better predict off-target interactions. In the absence of experimental crystal structures of these channels, reliable qualitative and quantitative computational models of high sensitivity and specificity are still lacking [12,13]. Most of the pioneering efforts have focused mainly on ligand-based models [25-29]. These models are based only on the physiochemical properties of the blocking ligands and have no relation with the target proteins. Unfortunately, these ion channels interact with a wide array of chemically unrelated molecules rendering ligand-based models very limited in practice [30-33]. Therefore, reliable structural models that can directly predict small molecule binding to cardiac ion channels are warranted [34,35]. Although many structural models have been developed throughout the last three decades to address this problem, the specificity and accuracy of these models are still lagging. Recently and in collaboration with the Li Ka Shing Applied Virology Institute in Alberta, Canada, our team managed to build the most sophisticated model to predict human Ether-à-go-go-Related Gene (hERG) ion channel blockage [2]. This model overcomes many of the pitfalls existed in previous models. The models relied mainly on using a single conformation or only very few conformations of the channel [36,37], used docking scoring functions to estimate binding energies, and had no further processing of the docked structures to investigate the effects of solvent or ions on their stabilities. Our model incorporated all of the missing elements described above and revealed high accuracy and specificity. Applying the same concept to other cardiac ion channels will pave the way towards observing and characterizing small molecule off-target cardiotoxic effects at the atomic level.

Although LQTS has been often attributed to hERG channel blockage, recent studies show that multiple ion channel interactions are in fact required to predict changes QT intervals [38,39]. A multiple channel approach should explain many of the discrepancies that have been observed by only using a hERG blocking-based workflow. For example, a simultaneous blockade of a repolarizing current and a depolarizing current at the same level would have a very limited effect on the overall cellular action potential. That said, a drug that can interact with multiple channels could have a limited effect on the overall cardiac tissue as each individual interaction can balance the other. Several cardiac electrophysiology mathematical models have been developed to address this multi-channel effect. These models predict the overall cellular transmembrane action potential by incorporating all ionic currents components through highly sophisticated relations. A reliable structural model for each cardiac channel combined with a multi-channel mathematical model would constitute the ultimate answer to two important questions; how a drug can affect the cardiac activity, and how to mitigate these interactions? These types of sophisticated models can have a substantial impact on a wide range of basic research and applied/commercial sectors. It can also help identify problematic drugs and help save the lives of many patients currently treated or will be treated with such drugs (work in progress).

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***Corresponding author:** Khaled Barakat, Research Assistant Professor, University of Alberta, University of Alberta, Faculty of Pharmacy and Pharmaceutical Sciences, 02-20G Katz Centre, Edmonton, AB, T6G 2E1, Canada, Tel: 1-780-492- 5783; E-mail: kbarakat@ualberta.ca

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