Identifying a Lead Compound for Mitigation of Drug-Induced QTc-Interval Prolongation

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Introduction
Over 175 approved therapeutic drugs list adverse effects which include QT prolongation. Of these, 24% are oncology drugs. Arrhythmic risk is enhanced by the fact that 14-15% of cancer patients present prolonged QT intervals at screening, putting them at risk of developing Torsades the Pointes if exposed to QT-prolonging drugs.

Torsades de Pointes are generally ventricular arrhythmias, which degenerate if there is a substrate for the sustainment of the Torsades.

QT prolongation is a necessary substrate, brought about by Lø inhibition. A substrate feeds the Torsades after they are triggered. While most Torsades are self-righting, therefore not dangerous, and often undetected - those which are sustained are rapidly lethal.

To address the risk that drugs could contribute to the genesis of a substrate for TdP, we investigated the mitigating effect of a liposome and its components administered intravenously and orally on clinically approved QT-prolonging anticancer drugs (crizotinib and nilotinib), as well as a well-characterized and often used clinical anticancer drug (oxaliplatin: MF) in vitro and in vivo.

Phospholipids (PLs) and Eutectic Blends

**Figure 1. Removal of IKr inhibition by various phospholipids (PLs)**

**Liposomes made with DMPC, DMPG, DMPC/DMPG, LysoPC and LysoPG did not cause any inhibition of the hERG tail current density. Nilotinib alone at 0.1 µM caused 54% of inhibition of the hERG current. Nilotinib co-formulated with DMPC, DMPG, DMPC/LysoPC or LysoPG (Nilo/PLs ratio: 9:1) no longer inhibited the hERG tail current.**

**Figure 2. Fatty acid chain & Nilotinib-induced IKr Inhibition**

100, 120, 140, 160 and 180 LysoPG and 140 EGPG alone did not cause any inhibition of the hERG tail current density. 1 µM Nilotinib caused 70% of inhibition of the hERG current.

Nilotinib when formulated with 100, 120, 140, 160 and 180 LysoPG and 140 EGPG (PLs/Nilo ratio: 9:1) prevented the inhibition of the hERG current. 140 and 160 LysoPG were the most potent PLs against the inhibition of hERG currents by Nilotinib.

In vivo candidate selection

**In vivo candidate selection**

Male Hartley guinea pigs (350 - 400; Charles River) were used in these studies. The animals were anaesthetised with a mixture of 1.0 to 1.5% isoflurane USP in 95% O₂ and 5% CO₂. The jugular vein was cannulated for i.v. infusion of 20 mg/kg oxaliplatin (MF). ECG leads were placed on the animals in a 3-lead configuration.

EU8120, 14:0 LysoPG, 16:0 LysoPG, 14:0 EGP and DMPG (Avanti Polar Lipids, Inc.) were administered as an oral gavage 2 hours prior to the infusion of MF. Three animals were exposed to each PL + MF combination at PLs/MF ratios of 3:1, 1:1 or 0:3:1 (n=3).

**Figure 5. EU8120 prevents IKr inhibition via lipid-receptor interactions**

**EU8120 is constituted of a 1:4:2 ratio of 14:0 LysoPG/myristoyl monoglyceride/myristic fatty acid chain. Changing the constituent ratio to 2:4:2, 3:4:2, 4:4:2 (i.e. increasing the LysoPG content of EU8120) resulted in a loss of QTc mitigation potency. It is hypothesized that Myristoyl monoglyceride and myristic acid are necessary for oral bioavailability.**

Experiments are ongoing to determine the effect of substituting the monoglyceride and fatty acid constituents on QTc mitigation potency.

**Conclusion**

Formulation of 14:0 LPG in a eutectic mixture with a myristoyl monoglyceride and myristic acid (EU8120) given orally to guinea pigs prior to i.v. infusion of nilotinib, crizotinib and Oxaliplatin resulted in significantly reduced QTc prolongation. Four ratios of PLs/MF were tested for mitigation of conduction delays: 3:1, 1:1, 0:3:1, and 0:1:1. Down to 0:3:1 ratio, all the compounds tested mitigated the drug-induced prolongation of QTc intervals. While EGP suppressed the most protection, it caused bradyarrhythmia and was de-prioritized.

Special thanks

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