

SMALL MOLECULES TARGETING KCNQ IN VENTRICULAR ARRHYTHMIA

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Disease indication – Long QT Syndrome (resulting in ventricular arrhythmia, epilepsy, deafness)

Drug format – Small molecule

Drug class – Lead compounds are repurposed drugs

Research stage and preliminary data – Based on *in silico* screening of KCNQ, the researchers selected 26 compounds for *in vitro* testing. Studies in *Xenopus* oocytes further narrowed the focus to three known compounds: Acid Orange 3; Alizarin Blue Black Bg; and 2-[4-(3,4-Dimethylphenoxy)phenyl]-1,3-dioxoisindoline-5-carboxylic acid. Further studies are focused on optimizing these compounds and testing them *in vivo*.

Target – KCNQ family of potassium ion channels

Background – Long QT Syndrome can arise congenitally or as a result of medications that prolong the QT interval. This syndrome occurs when potassium channels involved in the ventricular action potential are slower at repolarizing. A drug promoting more rapid repolarization would lessen the QT interval.

Mode of action – As KCNQ ion channels control repolarization of action potentials, mutations can lead to changes in action potential duration. The small molecules enhance the function of mutated KCNQ to restore normal action potentials. The drugs target site E160 on KCNQ, a known binding site for PIP₂ and ATP.

Competitive edge – Long QT Syndrome (LQTS) is currently treated with beta blockers to reduce the risk of cardiac events. By targeting KCNQ directly, this strategy focuses on the underlying mutation rather than just preventing adverse events. Additionally, this strategy could be used to supplement existing therapies that cause QT prolongation.

Publications

- Lin Y, Grinter SZ, Lu Z, Xu X, ... Cui J. (2021). [Modulating the voltage sensor of a cardiac potassium channel shows antiarrhythmic effects](#). *PNAS*, 118(20): e2024215118.
- [Compound may prevent arrhythmia caused by medicines](#). (2021). *Stony Brook University News*.

Patents – [US 9,345,688](#) & [US 10,064,842](#)

Web Links – Cui [Profile](#) & [Lab](#)