SGK1 Inhibition and Attenuation of the Action Potential Duration in Re-Engineered Heart Cell Models of Drug-Induced QT Prolongation

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Dr. Ackerman is a consultant for Abbott, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Invitae, Medtronic, Tenaya Therapeutics, and Thryv Therapeutics. Dr. Ackerman and Mayo Clinic are involved in an equity/IP/royalty relationship with AliveCor, Anumana, ARMGO Pharma, Pfizer, and UpToDate. Dr. Das is a scientific founder and has received equity for Thryv Therapeutics, Inc and Switch Therapeutics and has a consulting relationship with Thryv Therapeutics and Renovacor. Dr. Sager is a scientific founder of and employee for Thryv Therapeutics and has received equity.

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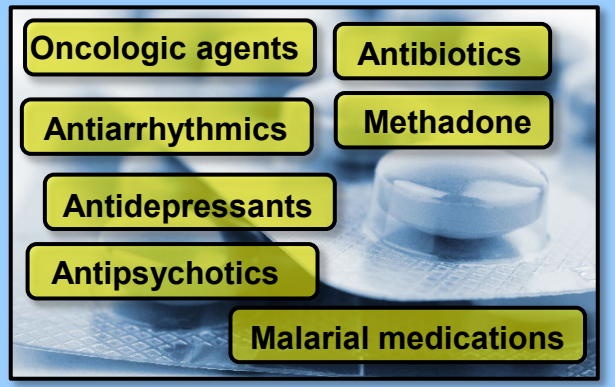
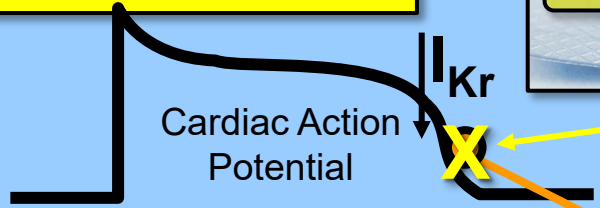
Drug-Induced LQTS (DI-LQTS)

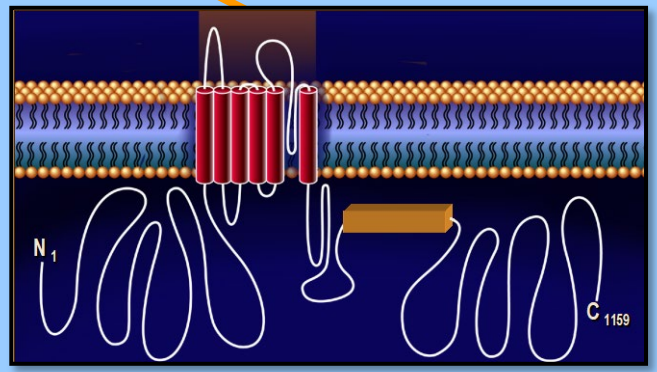
Clinical entity in which administration of a HERG/Ikr blocker such as dofetilide prolongs the cardiac action potential duration (APD) at the cellular level and the QT interval on an ECG that increases the risk for a potentially lethal ventricular arrhythmia.

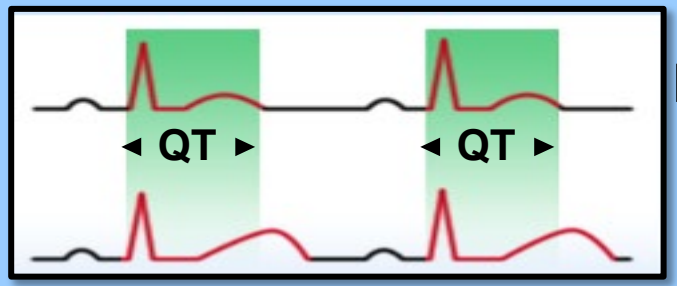




Off-target Effects

KCNH2/HERG (LQT2)

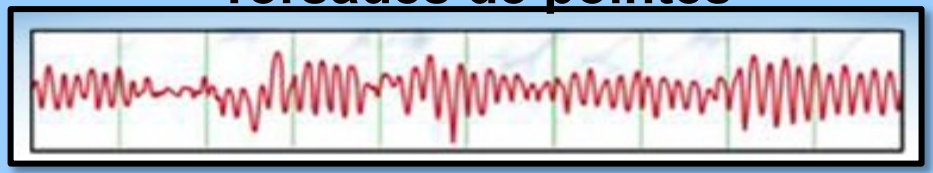




Normal QT interval

Prolonged QT

Torsades de pointes



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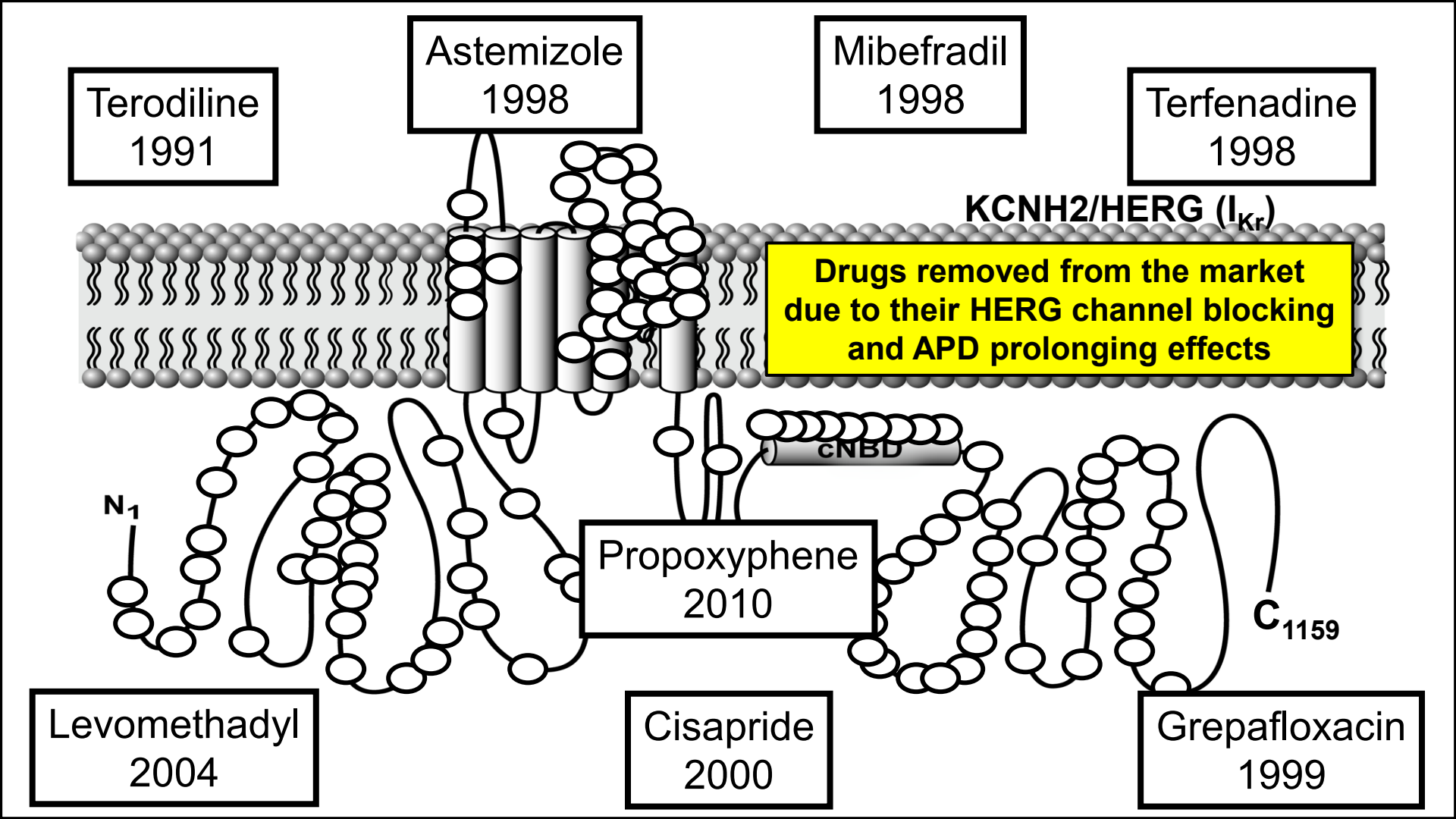

Terodiline
1991
Astemizole
1998
Mibefradil
1998
Terfenadine
1998
KCNH2/HERG (I_{Kr})
Drugs removed from the market due to their HERG channel blocking and APD prolonging effects
cNBD
N_1
Propoxyphene
2010
C_{1159}
Levomethadyl
2004
Cisapride
2000
Grepafloxacin
1999

Serum and glucocorticoid regulated kinase-1 (SGK1) is an important regulator of (SCN5A) Nav1.5-mediated I_{Na} in the heart.

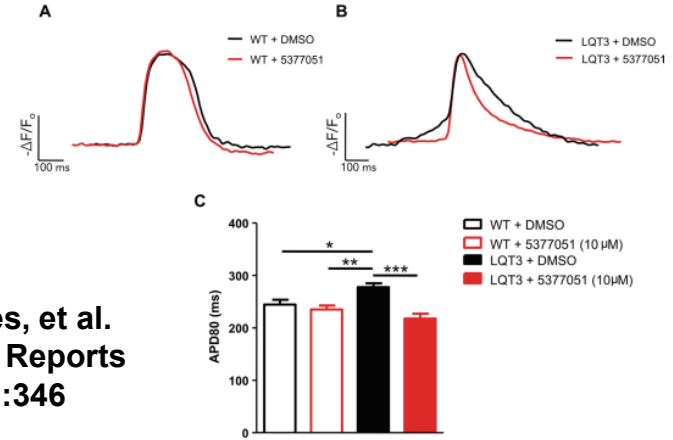
- Small molecule inhibitors of SGK1 may be anti-arrhythmic in cardiac diseases through attenuation of the abnormally increased late I_{Na}.
- There may be a role for inhibition of late I_{Na} to counter drug-induced LQTS (DI-LQTS).
- Recently, we have shown that inhibition of SGK1 reduces the APD90 in iPSC-CM's derived from a patient with LQT3 and attenuates the increase in late I_{Na}.

Objective: To test the efficacy of a novel SGK1 inhibitor (SGK-I) in re-engineered cardiomyocyte models of dofetilide-induced APD prolongation

SCIENTIFIC REPORTS

OPEN

Inhibition of serum and glucocorticoid regulated kinase-1 as novel therapy for cardiac arrhythmia disorders



Bezzerides, et al. Scientific Reports 2017; 7(1):346

Study Design

- Induced pluripotent stem cell derived cardiomyocytes (iPSC-CMs) were generated from a patient with a pathogenic variant in *SCN5A* (c.3965C>T, p.P1332L).
- A CRISPR/Cas9 P1332L variant-corrected isogenic control (IC) was created and served as the normal iPSC-CM line for this study.
- Normal iPSC-CMs were treated with dofetilide [5 nM] to produce a drug induced QT-prolongation (DI-QTP) iPSC-CM model.
- The SGK1-I's therapeutic efficacy for shortening the dofetilide-induced APD90 prolongation was compared to mexiletine.
- The APD90 values were recorded 4 hours after treatment using the voltage-sensing dye, FluoVolt.

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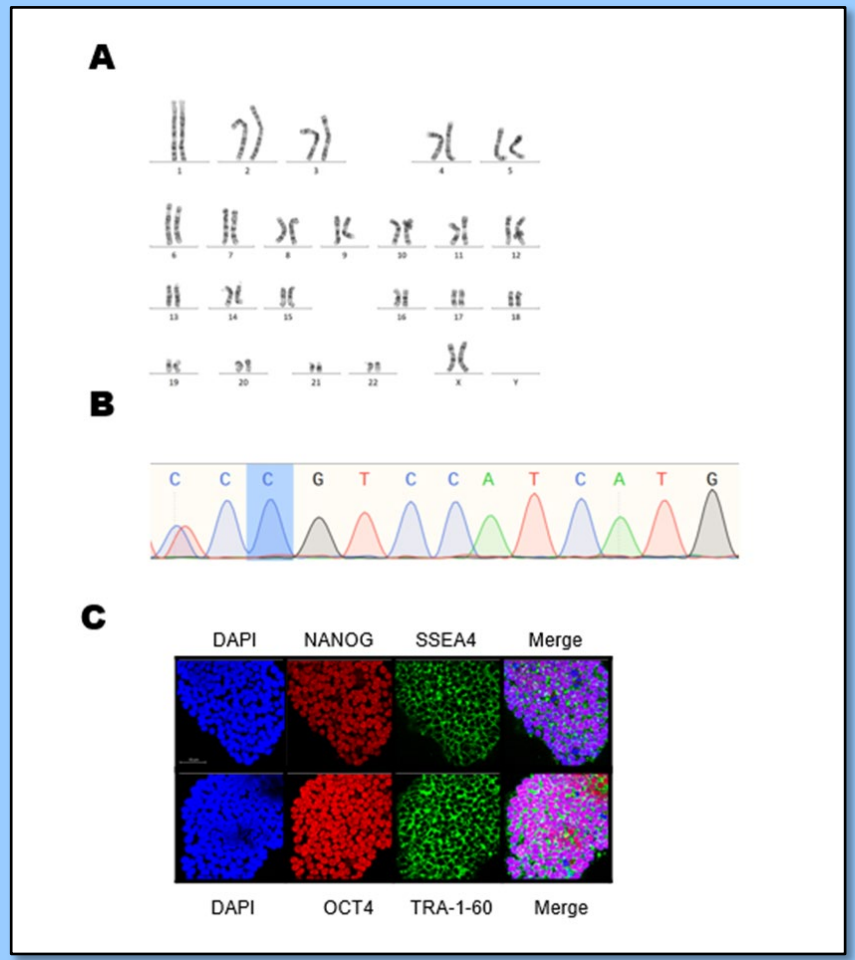
Generation and confirmation of normal iPSC line.



- Normal iPSCs showed a normal female karyotype.
- Sanger sequencing chromatograms showing the wild-type sequence CCG(P) by gene corrected via CRISPR/Cas9 technology from the heterozygous SCN5A-P1332L variant, CCG (P) and CTG(L), in patient iPSCs.
- Representative confocal images of induced pluripotent stem cells (iPSCs) reprogrammed from the normal IPS cell line. The iPSCs demonstrated pluripotent markers (NANOG, SSEA4, OCT4, and TRA-1-60). Scale bar, 20 μm.

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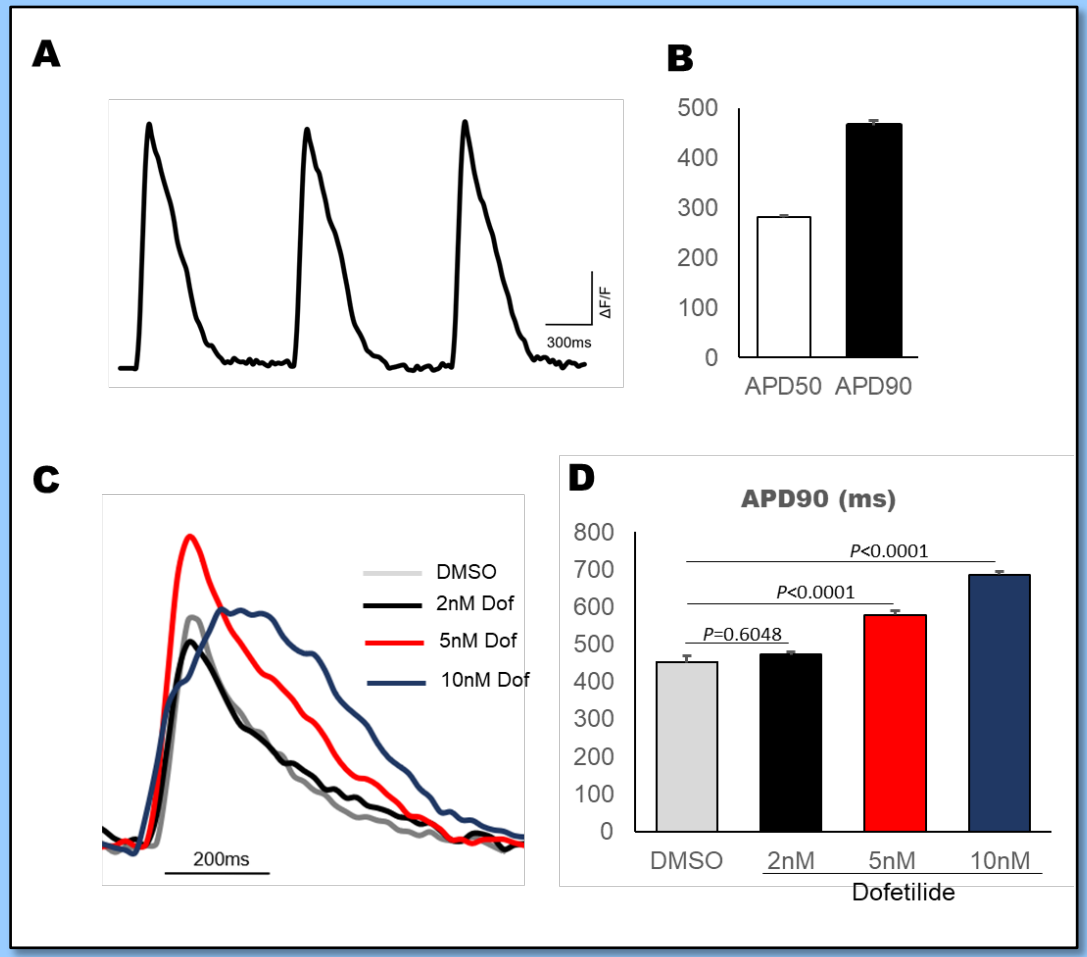
Dofetilide prolonged the action potential duration in normal iPSC-CMs



- At baseline, the re-engineered as normal iPSC-CMs showed a normal APD at 50% repolarization (APD50, 281 ± 4 ms, n=16) and at 90% repolarization (APD90, 466 ± 9 ms, n=16) when paced at a frequency of 1 Hz.

- Two hours after the treatment with dofetilide, the iPSC-CMs demonstrated prolonged APD90 in a dosage dependent manner with a response to 5 nM (APD90, 578 ± 12 ms, n=19, p<0.0001) and 10 nM (APD90, 686 ± 9 ms, n=19, p<0.0001) concentrations of dofetilide.

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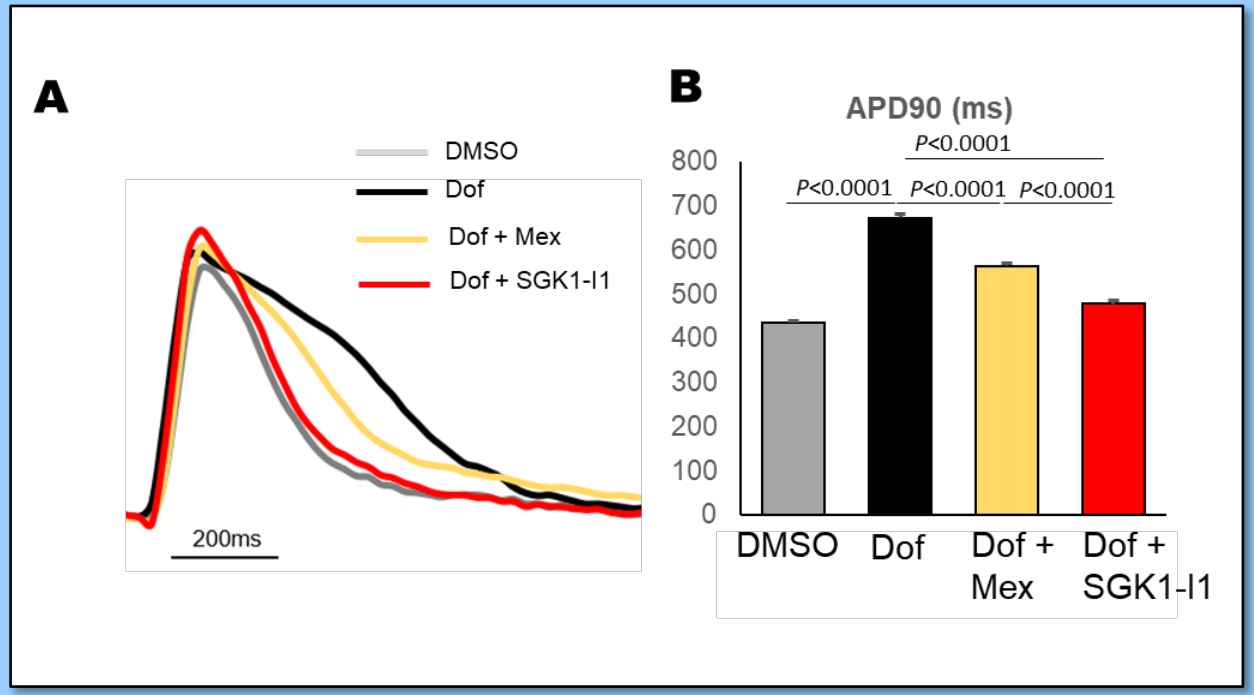
APD shortening effects of a novel SGK1 inhibitor compound in dofetilide treated iPSC-CMs



- The APD90 was significantly prolonged in normal iPSC-CMs treated with 5 nM dofetilide (673 ± 8 ms, n=93, p<0.0001) compared to DMSO (436 ± 4 ms, n=74).
- While 10 μM mexiletine shortened the average APD90 of dofetilide-treated normal iPSC-CMs from 673 ± 4 ms to 563 ± 8 ms (n=96, 46% attenuation, p<0.0001), 30 nM of SGK1-I1 shortened the APD90 from 673 ± 4 ms to 502 ± 7 ms (n=74, 72% attenuation, p<0.0001).

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Conclusions

- Therapeutically inhibiting serum and glucocorticoid regulated kinase-1 (SGK1) effectively shortens the cardiomyocyte APD in a human heart cell model of drug-induced QT prolongation.

- The novel SGK1 inhibitor attenuated the pathological APD prolongation substantially (> 70%) in the iPSC-CM model treated with dofetilide.

- This pre-clinical data supports further development of this therapeutic strategy to counter and neutralize drug-induced QT prolongation and its potential threat of drug-induced sudden cardiac death thereby increasing the safety profile for patients receiving drugs with torsadogenic potential.

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Dr. Charles W. Mayo

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