SGK1 Inhibition Attenuated the Action Potential Duration in Patient- and Genotype-Specific Re-Engineered Heart Cells with Congenital Long QT Syndrome

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American Heart Association Scientific Sessions
Chicago, Illinois
November 5-7, 2022

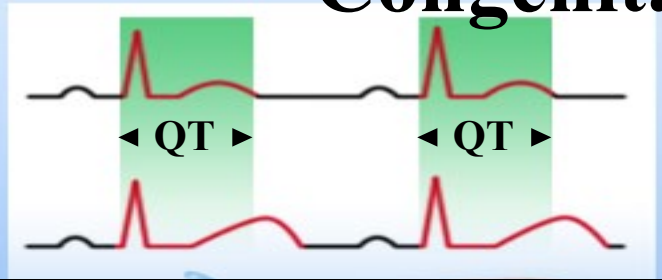
Financial Disclosure

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.

FUNDING SOURCES

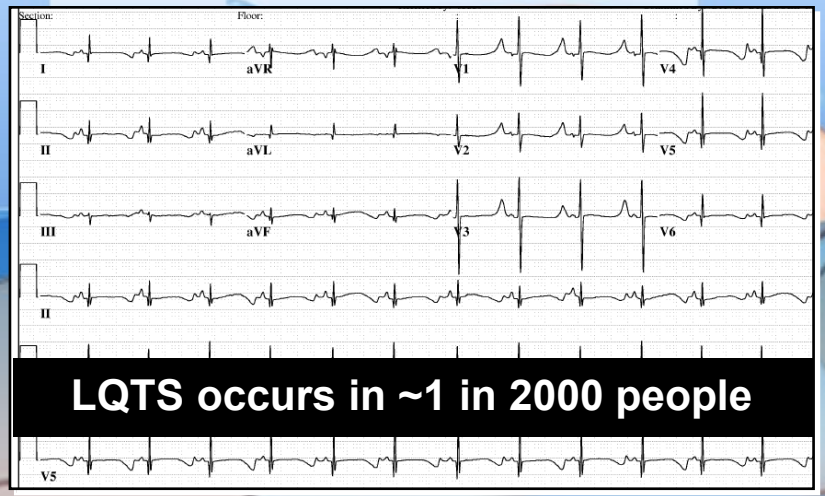
This work was supported by the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program and by an industry-sponsored research agreement with Thryv Therapeutics.

Congenital Long QT Syndrome



Normal QT interval

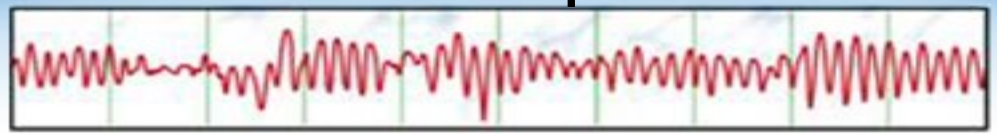
Prolonged QT



LQTS occurs in ~1 in 2000 people

1. Syncope
2. Seizures
3. Sudden death

Torsades de pointes



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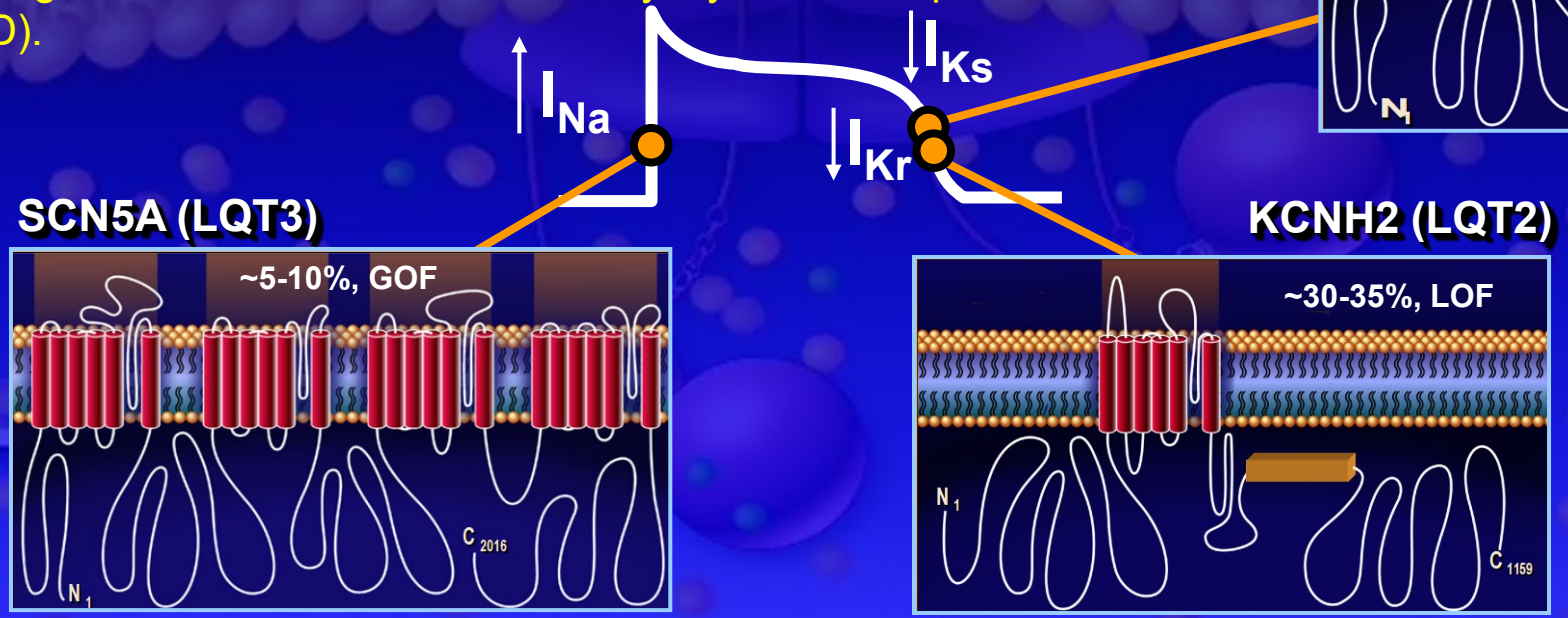
Congenital Long QT Syndrome

- 80% of LQTS stems from either loss-of-function (LOF) or gain-of-function (GOF) pathogenic variants in one of three LQTS-susceptibility genes: *KCNQ1* (LQT1), *KCNH2* (LQT2), or *SCN5A* (LQT3).
- The LOF or GOF of these critical ion channels underlie the pathological prolongation of the ventricular cardiomyocyte's action potential duration (APD).



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}.

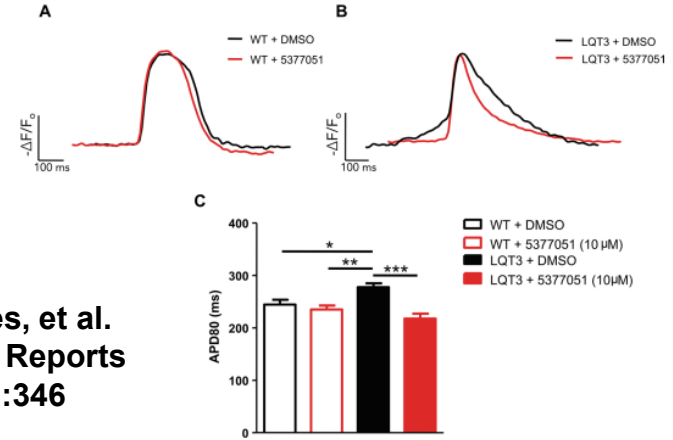
- Recently, a proof-of-concept for a SGK1-inhibitor based therapeutic for LQT3 was reported.

Objective: To test the efficacy of a new potent and selective SGK1 inhibitor (SGK1-I) in human cardiomyocyte models of LQT1, LQT2, and LQT3.

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 patients with either LQT1 (*KCNQ1*), LQT2 (*KCNH2*), or LQT3 (*SCN5A*).
- The mexiletine (MEX)-sensitive SCN5A-P1332L (LQT3) iPSC-CMs were tested initially. A CRISPR/Cas9 P1332L variant-corrected isogenic control (IC) was used as a control.
- The novel SGK1-I's therapeutic efficacy for action potential duration (APD) shortening was compared to MEX.
- The SGK1-I therapeutic efficacy was then tested in SCN5A-R1623Q (LQT3), KCNQ1-V254M (LQT1) and KCNH2-G604S (LQT2) iPSC-CMs.
- The APD90 values were recorded 4 hours after treatment using the voltage-sensing dye, FluoVolt.

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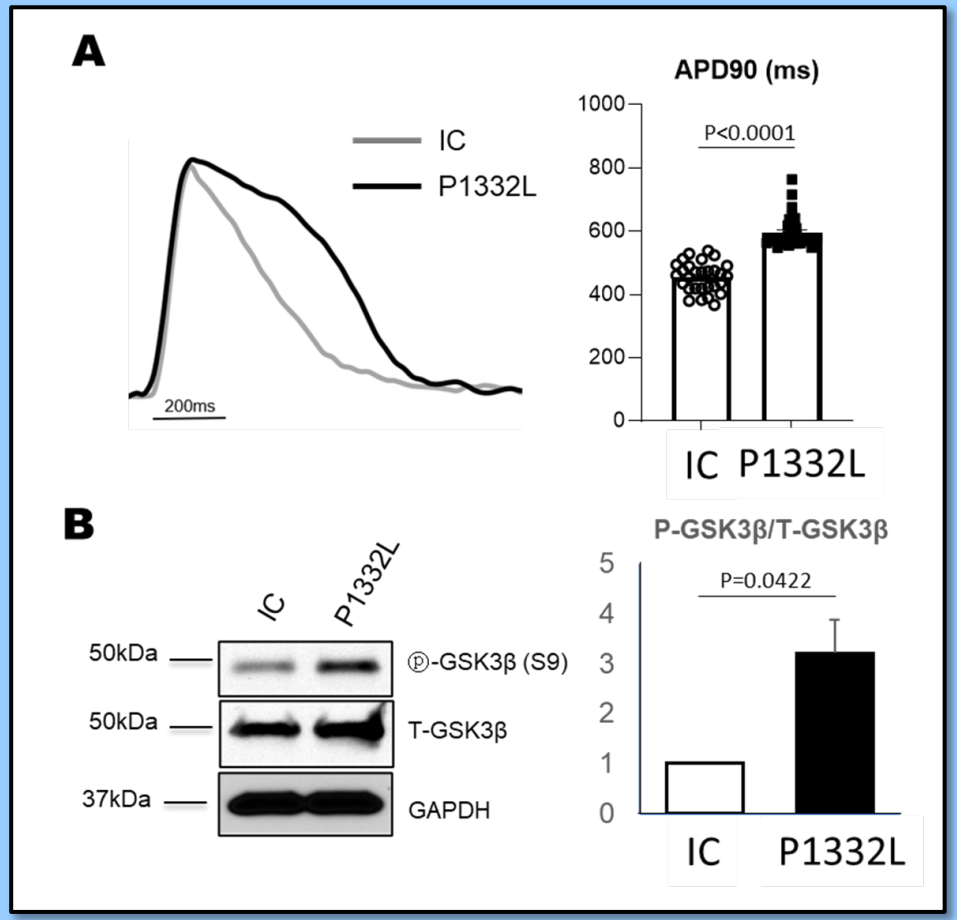
The action potential duration and SGK1 activity are increased in SCN5A-P1332L iPSC-CMs compared to isogenic control iPSC-CMs



- The APD90 was significantly prolonged in SCN5A-P1332L (LQT3) iPSC-CMs compared to its isogenic control (IC, 646 ± 7 ms vs 482 ± 23 ms, p<0.0001).

- Interestingly, the SGK activity in the SCN5A-P1332L (LQT3) iPSC-CMs was up-regulated by about 2-fold compared to the IC iPSC-CMs, determined by immunoblotting with an antibody against phospho (Ser9)-glycogen synthase kinase beta (p-GSK3β), a well-established SGK1 substrate.

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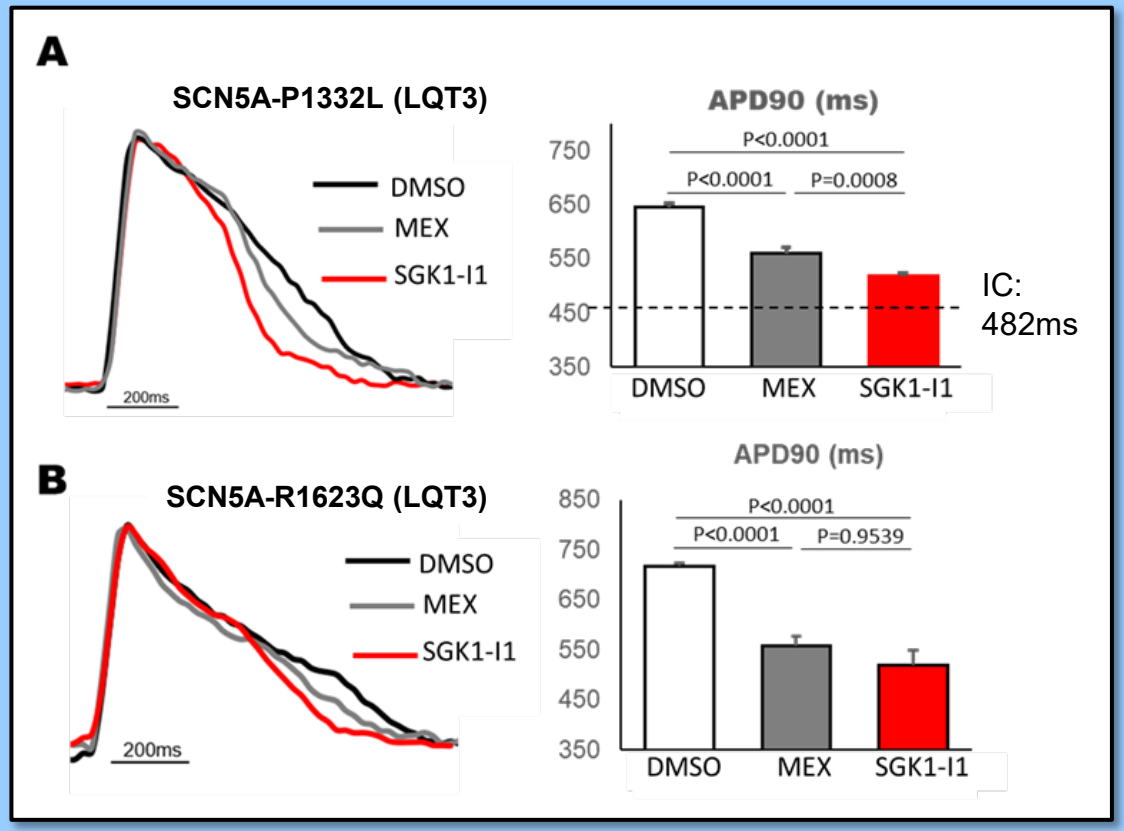
APD shortening effects of a novel SGK1 small molecular inhibitor in LQT3 iPSC-CMs



- MEX shortened the average APD90 from 646 ± 7 ms to 560 ± 7 ms (52% attenuation).
- SGK1-I significantly shortened the APD from 646 ± 7 ms to 518 ± 5 ms (78% attenuation).
- SGK1-I did not further shorten the APD in the IC.
- SGK1-I also shortened the APD90 of the SCN5A-R1623Q (LQT3) iPSC-CMs from 753 ± 8 ms to 475 ± 19 ms compared to 558 ± 19 ms with MEX.

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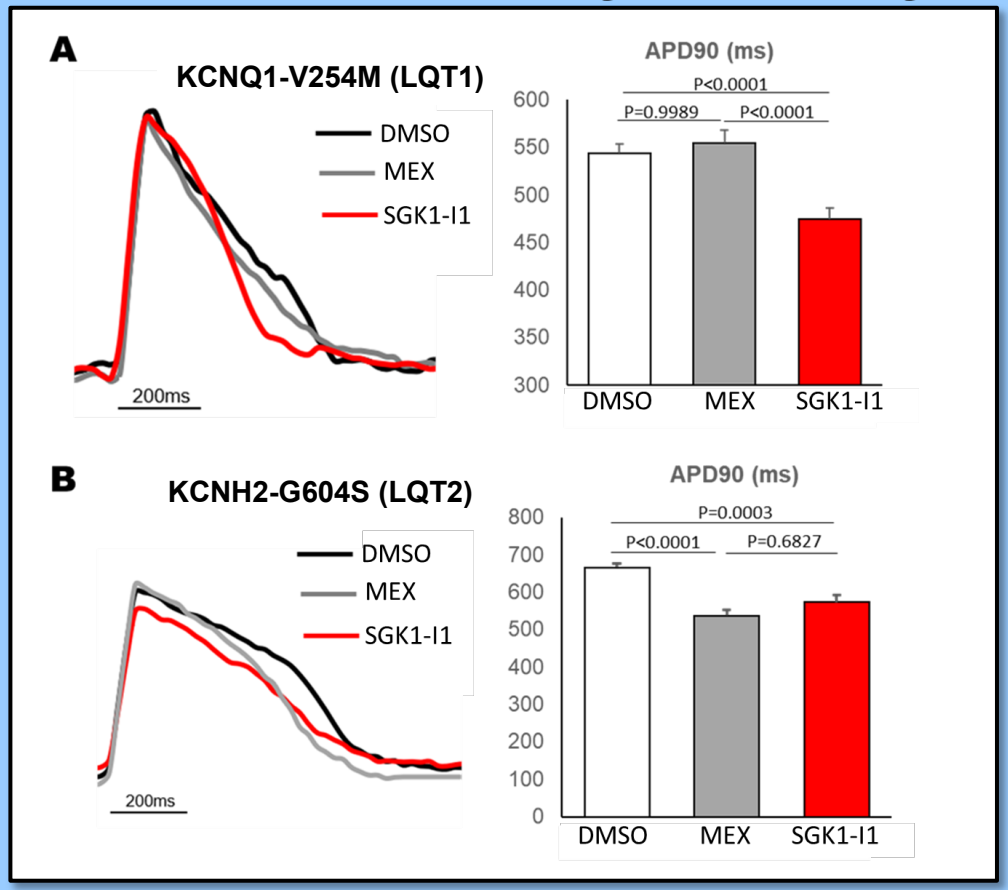
APD shortening effects of a novel SGK1 small molecule inhibitor in LQT1 and LQT2 iPSC-CMs



- Interestingly, while MEX did not reduce the APD90 in the KCNQ1-V254M (LQT1) iPSC-CMs, the novel SGK1-I reduced the APD90 from 544 ± 10 ms to 475 ± 11ms (p=0.0004).

- The SGK1-I shortened the APD90 in KCNH2-G604S (LQT2) (666 ± 10ms to 574 ± 18ms for SGK1-I versus 538 ± 15 ms after MEX).

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Conclusions

- Therapeutically inhibiting serum and glucocorticoid regulated kinase-1 (SGK1) effectively shortens the cardiomyocyte APD in human heart cell models of the 3 major LQTS genotypes.

- The novel SGK1-I attenuated the pathological APD prolongation substantially (> 70%) in the patient-derived SCN5A-P1332L (LQT3) iPSC-CM model.

- These pre-clinical data support further development of SGK1-I as a novel, first-in-class therapy for patients with congenital LQTS.

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