KDDF
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Asset #6

Ramot At Tel Aviv University

SK4 K+ Channel Blockers: A New Treatment for Cardiac Arrhythmias

Therapeutic Area	Cardiovascular Disease	**Indications**	Cardiac Arrhythmias
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

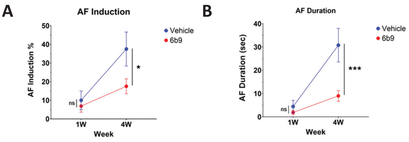
- Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with significant mortality, due to embolic stroke and prevalence within ageing population. In the last decade, pulmonary vein ablation therapy was shown to have favorable anti-AF effects only in selected cases. Nevertheless, this approach is invasive, requires anticoagulants and is limited by cost, complexity, potential life threatening complications and incomplete efficacy because of recurrent AF attacks. Consequently, safe and effective pharmacological treatment options will remain the mainstay therapy for the estimated 30 million North Americans and Europeans that are expected to suffer from AF by 2050.
- SK4 K+ channels are important for the late repolarization of the action potential in the atrium and the pacemaker tissue (SAN, AV nodes). As such SK4 channel block will provide an increase in the atrial refractory period with a slowing of AV conduction.

Technology Advantages

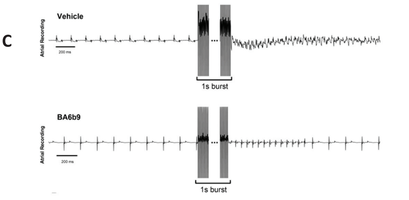
- Current available therapy for AF like catheter ablation raises questionable effectiveness, especially for patients with diabetes, obesity, hypertension, heart failure and for patients who cannot receive anticoagulant therapy. Several companies try to develop drugs against cardiac arrhythmias by targeting known ion channel targets (Nav, Kv, RyR, GAP junctions) but the pipeline body of new drugs is very thin and does not fill the gap of unmet need. Currently, the project is the sole to propose this new cardiac target: SK4 potassium channel blockers as a new therapy for Atrial Fibrillation. Thanks to their restricted expression, SK4 channels represent an ideal target for therapy.
- A novel allosteric SK4 K + channel blocker called BA6b9 act at the channel-calmodulin-PIP2 interface, a previously untargeted region of the channel.
- BA6b9 prolongs atrial and atrioventricular refractory periods and reduce AF induced by carbachol in isolated rat hearts ex vivo.

Key Data

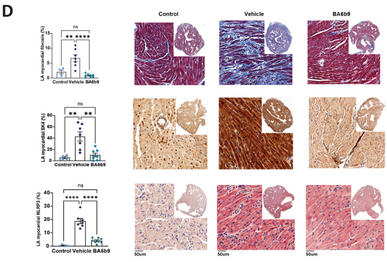
Chronic treatment with BA6b9 reduce AF substrate and structural remodeling in rats with heart failure post MI.



(A-B) AF induction and AF duration in rats post-MI that were implanted with an electrophysiological device that can evaluate AF susceptibility.



(C) Examples of pacing-induced atrial arrhythmias in vehicle and BA6b9 (10mg/Kg/d) treated rats.



(D) Histological results indicating the marked inhibition of left atrial fibrosis, SK4 channel expression and NLRP3 following BA6b9 treatment.

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-IL2023-050048 (2023.01.17)

Patent Family
PCT

Publication(s)

- Burg S. et al. (2022) Allosteric inhibitors targeting the calmodulin-PIP2 interface of SK4 K + channels for atrial fibrillation treatment. Proc Natl Acad Sci U S A. 119(34):e2202926119
- Haron-Khun S. et al. SK 4 K + channels are therapeutic targets for the treatment of cardiac arrhythmias. Embo Molecular Medicine (2017)
- Weisbrod D. et al. Mechanisms underlying the cardiac pacemaker: the role of SK4 calcium-activated potassium channels. Acta Pharmacologica Sinica (2016)
- Weisbrod D. et al. (2013) SK4 Ca2+ activated K+ channel is a critical player in cardiac pacemaker derived from human embryonic stem cells. Proc Natl Acad Sci U S A. 110(18):E1685-94.