SK4 K+ channel blockers: a new treatment for cardiac arrhythmias (Ramot)

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Bernard Attali, T.A.U Tel Aviv University, Medicine-Sackler Faculty, Physiology and Pharmacology

We discovered a previously unidentified target in the heart, namely the SK4 calcium-activated K+ channels, which are functionally expressed in pacemaker cells and atrial cardiomyocytes. They are crucial for proper cardiac rhythm and represent a completely new therapeutic target for the treatment of cardiac arrhythmias. SK4 channel blockers successfully prevented cardiac arrhythmias in in vitro and in vivo models of ventricular arrhythmias.

UNMET NEED

Cardiac arrhythmias, affect more than 4% of the population worldwide. While 80% of cardiac sudden death arise from ventricular arrhythmias, atrial fibrillation (AF) is associated with significant mortality, due to embolic stroke and prevalence within ageing population. Current therapies have major limitations including limited efficacy and risk of pro-arrhythmic side effects.

OUR SOLUTION

Thanks to their impact on the refractory period and the maximum diastolic potential, SK4 channel blockers are valuable for preventing cardiac arrhythmias. As a proof of concept, we used in vitro and in vivo models of cardiac arrhythmias, including human induced-pluripotent stem cells from diseased patients and transgenic mice to show that SK4 channel blockers successfully prevent cardiac arrhythmias.

OUR PRODUCT

The existing SK4 channel blockers acting on the channel pore are not suitable for clinical development because of poor oral availability and selectivity. We designed a new SK4 channel blocker BA6b, which targets a different and more specific channel region, the intracellular calmodulin binding domain. This molecule has beneficial effect on a rat model of atrial fibrillation. We are currently optimizing this blocker molecule to seek for a lead and test the NCE on in vitro and in vivo models of cardiac arrhythmias.

KNOW-HOW FOR GENERATION OF NCEs

We plan to design NCEs to optimize our current template by rationale chemistry, targeting them at the proximal C terminus of the channel, where Ca2+-calmodulin binds. Our deep knowledge of the structural constraints for the channel target and the existence of available 3-D structural models of the interface as well as our ability to perform docking studies will prove very useful to improve the hit efficacy approach.

DIFFERENTIATION

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, our project is the sole to propose this new cardiac target: SK4 potassium channel blockers as a new therapy for cardiac arrhythmias. Thanks to their restricted expression, SK4 channels represent an ideal target for therapy.

PATENTS

A provisional application for patent titled “Treatment of cardiac arrhythmia disorders by blocking SK4 potassium channel” was filed through Ramot (Ramot reference 2016070-01, PCT filed December 2016). It is expected to have a long life span due to the long patent protections years ahead and the possibility of layering additional patent applications covering new data that will be generated.

REFERENCES

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Contact for more information:

Ariela Markel, VP Business Development, Healthcare , 02-6586608

Ramot at Tel Aviv University Ltd. P.O. Box 39296, Tel Aviv 61392 ISRAEL
Phone: +972-3-6406608
Fax: +972-3-6406675