Nov 1, 2023

Dr. Julie Stacey
Editor-in-Chief *eBioMedicine*

Dear Dr. Stacey:

Attached please find our manuscript entitled “The SK4 channel allosteric blocker, BA6b9, reduces atrial fibrillation substrate in rats with reduced ejection fraction following myocardial infarction”, which we would like to submit for publication in *eBioMedicine*.

In this study, we present solid proof-of-concept evidence that long-term inhibition of calcium-activated SK4 K+ channels by a novel allosteric blocker of the channels (BA6b9), represents a promising new therapeutic strategy to target the atrial overexpression of these channels in the setting of heart failure (HF) after myocardial infarction (MI). Moreover, this treatment dramatically inhibits the deleterious atrial remodeling and increased atrial fibrillation (AF) susceptibility that develops in this setting over time.

Atrial fibrillation (AF) and heart failure (HF) are the two dominant cardiovascular diseases of this century. AF is a progressive, age-related disease affecting millions of patients worldwide and is associated with severe complications such as thrombo-embolic events, impaired cognitive function and increased mortality. HF occurs as frequently as AF and the co-existence of these two diseases is very common. Failure rates of AF therapy in HF patients are high mainly since HF induces structural remodeling of the atrial myocardium, which in turn impairs electrical activation of the atria predisposing HF patients to AF.

We previously identified a new druggable target in the heart, namely the calcium-activated SK4 K+ channels, whose existence was overlooked in cardiac tissues ([1](#_ENREF_1)). More recently, we demonstrated that the SK4 channel protein is widely expressed in atria of rat and human hearts and to a lower extent in the ventricles. In addition, we designed a novel allosteric blocker, BA6b9, intended to target the calmodulin-PIP2 binding domain, a previously untargeted region of SK4 channels, leading to potent and specific inhibition of the SK4 K+ channels ([2](#_ENREF_2)). SK4 K+ channels are also expressed in fibroblasts and macrophages, which like atrial cardiomyocytes possess the inflammatory signaling machinery that is activated during atrial remodeling and AF progression. Hence, we assumed that SK4 K+ channels are pro-arrhythmic and pro-inflammatory and blocking them may prevent atrial remodeling and AF progression, especially in the post-MI setting.

In the present study, we examined the ability of BA6b9 to alter AF susceptibility and atrial remodeling in a HF rat model following MI. We found that the atrial levels of SK4 K+ channels are indeed markedly upregulated post-MI, in conjunction with increased expression of NLRP3 inflammasome, lateralization of atrial connexin Cx43 and increased collagen deposition. Treatment with BA6b9 attenuated all the above detrimental changes, and markedly inhibited the susceptibility to AF indicating that blockade of SK4 K+ channels by BA6b9 not only favors rhythm control but can also inhibit structural remodeling, a property that is highly desired, notably in the setting of HF. We believe that our findings should be of high interest for many basic scientists and clinicians.

This manuscript is original, no part of it has been published previously, nor is any part of it under consideration for publication elsewhere. We have no conflict of interest to disclose. All authors approved the written content and figures in the submitted manuscript.

Thank you for your consideration of this manuscript.

Sincerely,

Yoram Etzion

Bernard Attali

**References**

1. Weisbrod D, Peretz A, Ziskind A, Menaker N, Oz S, Barad L, et al. 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. 2013;110(18):E1685-94.

2. Burg S, Shapiro S, Peretz A, Haimov E, Redko B, Yeheskel A, et al. Allosteric inhibitors targeting the calmodulin-PIP2 interface of SK4 K(+) channels for atrial fibrillation treatment. Proc Natl Acad Sci U S A. 2022;119(34):e2202926119.