# SK4 K+ channel blockers: a new anti-arrhythmic and anti-fibrotic treatment for atrial fibrillation

## Background

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, affecting 1 % of the population worldwide (**over 50 million cases worldwide**), often associated with heart failure (HF), embolic stroke (x 5 risk), and increased mortality.

AF has a chronic and progressive nature associated with electrical and structural remodeling like **inflammation and interstitial fibrosis** that trigger AF progression.

Current therapies for AF have **partial efficacy with recurrent AF attacks and risk of life-threatening proarrhythmic side effects**. Importantly, the existing therapies do not target atrial inflammation and fibrosis, leaving a substantial unmet need for therapeutic innovation.

## Potential market and target population

persistent AF and persistent/permanent AF with HF (population estimated of at least 20 million people). The pipeline body is rather thin and does not fill the gap as the drugs target only acute sinus rhythm conversion but do not target persistent AF and atrial remodeling (atrial inflammation and fibrosis)

## Our solution and novelty

Our published data indicate that SK4 $K^+$ channels are highly expressed in the heart, predominantly in the atrium of both rodents and humans.

SK4 $K^+$ channels are not only expressed in atrial cardiomyocytes but also in fibroblasts and macrophages, which all possess the **inflammatory signaling machinery, notably the NLRP3 inflammasome** that is activated during atrial remodeling and AF progression in AF animal models and patients with AF.

***We succeeded to design a novel allosteric SK4 $K^+$ channel blocker called BA6b9 that act at the channel-calmodulin-PIP2 interface, a previously untargeted region of the channel***

## Our proof of concept results

*BA6b9 prolongs atrial and atrioventricular refractory periods and reduce AF induced by carbachol in isolated rat hearts ex vivo (Ref 1)*

*BA6b9 inhibits in vivo AF induction and duration in heart failure rat model after myocardial infarction (Fig 1 )*

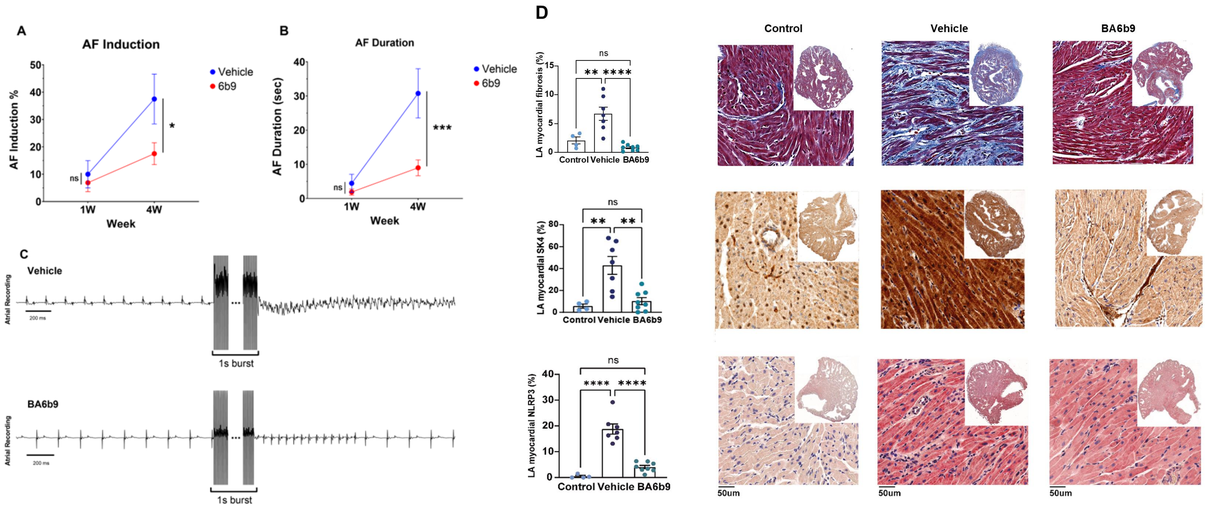


**Figure 1: Chronic treatment with BA6b9 reduce AF substrate and structural remodeling in rats with heart failure post MI. (A-B)**, AF induction and AF duration in rats post-MI that were implanted with an electrophysiological device that can evaluate AF susceptibility. **(C)**, Examples of pacing-induced 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.

## Published results

*1. Allosteric inhibitors targeting the calmodulin-PIP2 interface of SK4 K+ channels for atrial fibrillation treatment. Burg S, Shapiro S, Peretz A, Haimov E, Redko B, Yeheskel A, Simhaev L, Engel H, Raveh A, Ben-Bassat A, Murninkas M, Polak R, Haitin Y, Etzion Y, **Attali B**. Proc Natl Acad Sci U S A. 2022 Aug 23;119(34):e2202926119. doi: 10.1073/pnas.2202926119. Epub 2022*