

## ABSTRACT BS-513: Sodium Channel Related Arrhythmias

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### BS-513-01

#### SUPPRESSION-REPLACEMENT GENE THERAPY FOR SCN5A-MEDIATED TYPE 3 LONG QT SYNDROME

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**Background:** Congenital long QT syndrome (LQTS) is an autosomal dominant disorder characterized by delayed repolarization of the myocardium with a prolonged QT interval on electrocardiogram that may manifest as syncope, seizure, or sudden cardiac arrest/death. Long QT syndrome type 3 (LQT3) is caused by gain-of-function mutations in the SCN5A-encoded Na<sub>v</sub>1.5 sodium channel. No current therapies target the molecular cause of LQT3.

**Objective:** To develop an SCN5A suppression-replacement (SupRep) gene therapy to rescue the prolonged cardiac action potential duration (APD) in induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from a patient with LQT3.

**Methods:** Custom designed shRNAs targeting SCN5A were tested for knockdown efficiency using TSA201 cells and RT-qPCR. A dual-component "suppression-and-replacement" (SupRep) SCN5A gene therapy was created by cloning into a single construct a custom-designed SCN5A shRNA that produces ~90% knockdown (suppression) and a "shRNA-immune" (shIMM) SCN5A cDNA (replacement). Patient-specific SCN5A-F1760C iPSC-CMs were generated from a patient with severe LQT3 (QTc > 680ms). FluoVolt voltage dye was used to measure the APD at 90% repolarization (APD<sub>90</sub>).

**Results:** Six unique shRNAs targeting SCN5A were tested, and one candidate shRNA was identified that suppressed the endogenous SCN5A alleles in TSA201 cells with about 92% knockdown efficiency. Compared to control iPSC-CMs, the baseline APD<sub>90</sub> was significantly prolonged in SCN5A-F1760C iPSC-CM cells [680 ± 20 ms (n=30) vs 342 ± 16 ms (n=20), p<0.0001]. Following treatment with SCN5A-SupRep gene therapy, the APD<sub>90</sub> was significantly decreased in F1760C iPSC-CMs compared to untreated cells [F1760C: 680 ± 20 ms (n=30) vs F1760C + SupRep: 470 ± 18 ms (n=39), p<0.0001]. This strategy demonstrated that the SCN5A-SupRep gene-therapy can rescue the pathologically prolonged APD in LQT3 patient-derived iPSC-CMs.

**Conclusion:** We provide the first proof-of-principle gene therapy for correction of LQT3. Akin to our sentinel discovery of SupRep gene therapy for LQT1, SCN5A-SupRep gene therapy successfully corrected/normalized the pathologic APD<sub>90</sub>, thereby eliminating the pathognomonic feature of LQT3.

### BS-513-02

#### GENOME-WIDE ASSOCIATION ANALYSES IDENTIFY NOVEL BRUGADA SYNDROME RISK LOCI AND HIGHLIGHT A NEW MECHANISM OF SODIUM CHANNEL REGULATION IN DISEASE SUSCEPTIBILITY

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**Background:** Brugada syndrome (BrS) is a cardiac arrhythmia disorder associated with sudden death in young adults. With the exception of SCN5A, encoding the cardiac sodium channel NaV1.5, susceptibility genes remain largely unknown.

**Objective:** Evaluate the contribution of the common variants in the genetic architecture of the BrS.

**Methods:** We performed a genome-wide association meta-analysis comprising 2,820 unrelated cases with BrS and 10,001 controls.

**Results:** We identified 21 association signals (18 novel) at 12 loci (10 novel). Seven association signals overlap SCN5A and one overlaps the neighboring SCN10A gene encoding the sodium channel isoform NaV1.8 highlighting the primacy of sodium channel function in BrS susceptibility. Notably, 10 association signals overlapped or are in the vicinity of 8 genes encoding cardiac developmental transcription factors (HEY2, TBX20, ZFPM2, GATA4, WT1, TBX5, IRX3 and IRX5) pointing to transcriptional regulation as a key feature of BrS pathogenesis. One additional association signal overlapped PRKCA, involved in contractility and calcium handling in cardiomyocytes and two other overlapped genes encoding myofiber or microtubule associated proteins, namely MYO18B and MAPRE2. Functional studies of MAPRE2 support a novel mechanism of NaV1.5 modulation. We calculated a polygenic risk score (PRS<sub>BrS</sub>) per individual based on the 21 risk alleles, which was higher in SCN5A negative BrS patients compared to SCN5A positive as well as in cases with a spontaneous type 1 BrS ECG compared to those diagnosed after sodium blockers challenge and particularly in SCN5A negative patients. Based on the PRS<sub>BrS</sub>, we performed a phenome-wide association study in the UK Biobank. PRS<sub>BrS</sub> was associated with greater risk for atrioventricular conduction disorders, a longer ECG activation/conduction times reflected in the P-wave duration, PQ interval duration and QRS duration. In contrast, PRS<sub>BrS</sub> was negatively associated with the QT interval duration and with the occurrence of atrial fibrillation or flutter.

**Conclusion:** Taken together, these findings broaden our understanding of the genetic architecture of Brugada syndrome and provide new insights into its molecular underpinnings.

### BS-513-03

#### SCN5A MUTATIONS AND THE ROLE OF GENETIC BACKGROUND IN THE PATHOPHYSIOLOGY OF BRUGADA SYNDROME

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**Background:** Mutations in SCN5A are identified in approximately 20% to 30% of probands affected by Brugada syndrome (BrS). However, in familial studies, the relationship between SCN5A mutations and BrS remains poorly understood.

**Objective:** The aim of this study was to investigate the association of SCN5A mutations and BrS in a group of large genotyped families.

**Methods:** Families were included if at least 3 family members were carriers of the SCN5A mutation, which was identified in the proband. Families were recruited from 12 tertiary centers in France between 1995 and 2020. Type 1 ST elevation was defined by ≥2 mm J-point elevation with coved ST segment and negative T wave.

**Results:** Forty-nine large families composed of 600 members including 304 mutation carriers (51%) were studied. The