Targeted Antibody-Oligonucleotide Conjugate Reduces *PRKAG2* mRNA in Mouse and NHP Cardiac Tissue: A Promising Approach for PRKAG2 Syndrome

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Background

- **PRKAG2 Syndrome** is a progressive, autosomal dominant cardiac disorder characterized by hypertrophic cardiomyopathy, arrhythmias, and heart failure, with an elevated risk of sudden cardiac arrest, even in young individuals.
- The disease is caused by mutations in the *PRKAG2* gene that lead to increased AMP-activated protein kinase (AMPK) activity and pathological **glycogen accumulation in the heart**.
- **Antibody oligonucleotide conjugates (AOCs)** represent a novel approach for delivering small interfering RNA (siRNA) therapeutics directly to cardiac cells via intravenous administration.[1,2]
- **AOC 1072** is designed to target and degrade *PRKAG2* mRNA to restore normal AMPK activity and reduce glycogen accumulation, offering a promising therapeutic strategy for PRKAG2 Syndrome.

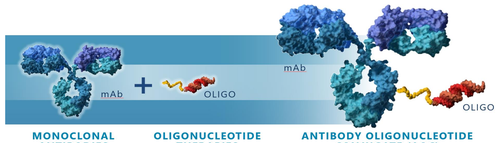

Figure 1. AOC components and model. mAb, monoclonal antibody; oligo, oligonucleotide.

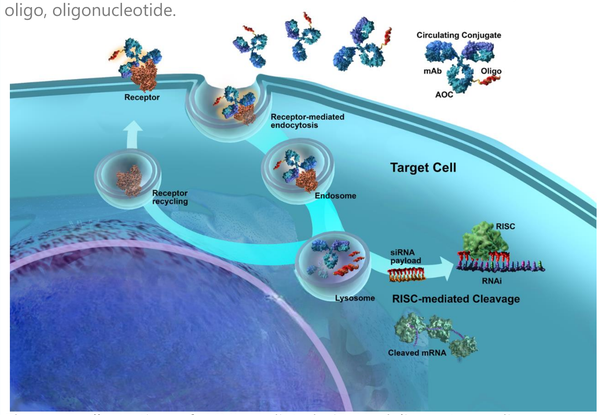

Figure 2. Illustration of AOC-mediated siRNA delivery to cardiomyocytes. mRNA, messenger ribonucleic acid; RISC, ribonucleic acid induced silencing complex; RNAi, ribonucleic acid interference.

Objective and Hypothesis

Objective

To investigate the **tolerability** and **efficacy** of AOC 1072 in mice and non-human primates (NHPs).

Hypothesis

AOC 1072 is a novel therapeutic agent for PRKAG2 Syndrome that **targets the root cause of the disease** by reducing the expression of pathogenic *PRKAG2* variants.

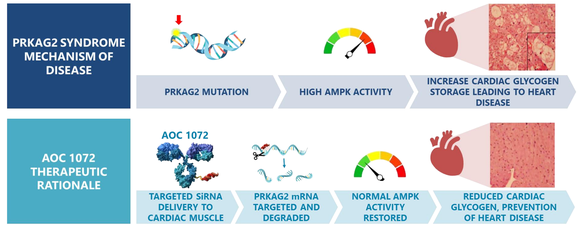

Figure 3. Therapeutic Rationale. AOC 1072 targets the root cause of PRKAG2 Syndrome by delivering siRNA to degrade *PRKAG2* mRNA, restoring normal AMPK activity and reducing cardiac glycogen accumulation.

Results

Durable and dose-dependent *PRKAG2* mRNA reduction in mice treated with AOC 1072 containing a mouse TfR1-targeting antibody (mAOC 1072)

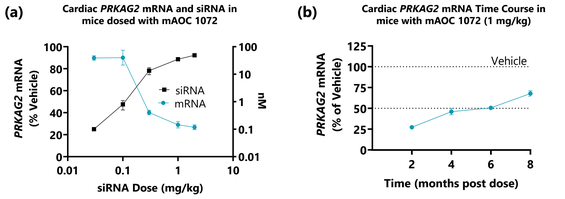

Figure 4. **(a)** Dose-dependent cardiac siRNA delivery and *PRAKG2* mRNA reduction in mice 28 days after a single dose with the mouse surrogate, mAOC 1072. **(b)** Durable *PRKAG2* mRNA reduction after a single dose of mAOC 1072 at 1 mg/kg (siRNA component), n=4.

Results (Continued)

Efficacy in a mouse model of PRKAG2^{R531G} Syndrome

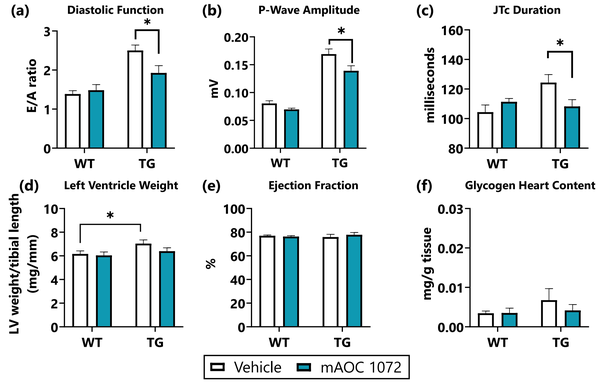

Figure 5. Treatment with mAOC 1072 at 3 mg/kg (siRNA component) Q8W for 24–32 weeks improved **(a)** cardiac diastolic function and electrocardiogram (ECG) parameters related to **(b)** right atrial size (P-wave amplitude) and **(c)** cardiac repolarization (JTc) in transgenic (TG) mice expressing the PRKAG2-R531G disease variant. **(d)** Left ventricular weight was also attenuated after treatment with mAOC 1072 in TG mice but **(e)** ejection fraction was normal and **(f)** no glycogen accumulation was observed in the heart. n=16-20 *$p<0.05$

Dose-dependent reduction of *PRKAG2* mRNA in NHPs with the clinical candidate AOC 1072

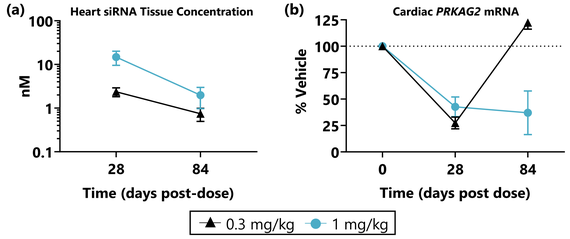

Figure 6. Cardiac levels of **(a)** siRNA and **(b)** *PRKAG2* mRNA in NHPs treated with a single dose of AOC 1072 at 1 or 0.3 mg/kg (siRNA component) for 28 or 84 days, n=3.

Results (Continued)

Tolerability of AOC 1072 in NHPs

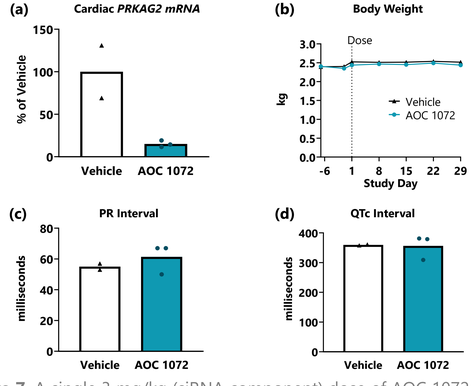

Figure 7. A single 3 mg/kg (siRNA component) dose of AOC 1072 for 28 days **(a)** reduced cardiac *PRKAG2* mRNA levels by 85% versus the phosphate-buffered saline (PBS) control, with no changes in **(b)** body weight, **(c)** PR interval, or **(d)** corrected QT (QTc) interval.

Conclusions

- AOC 1072 represents a promising therapeutic approach for **addressing the underlying genetic cause** of PRKAG2 Syndrome.
- In a PRKAG2 disease model, mouse AOC 1072 achieved **potent and sustained suppression** of *PRKAG2* expression.
- Treatment with mouse AOC 1072 **reduced skeletal muscle glycogen accumulation** and **improved diastolic function**.
- In NHPs, AOC 1072 demonstrated **robust *PRKAG2* mRNA reduction** and was **well tolerated**.
- AOCs have the potential to establish a **new class of precision therapeutics** for genetic cardiomyopathies.

References

1. Malecova, B. et. al. Nucleic Acids Res. 2023;51(12): 5901-5910
2. Cochran, M. et. al. J Med Chem. 2024;67(17):14852-14867

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