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Novel Precision Cardiology Treatment for PRKAG2 Cardiomyopathy, a Subset of Patients with Wolff-Parkinson-White Syndrome

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Disclosures

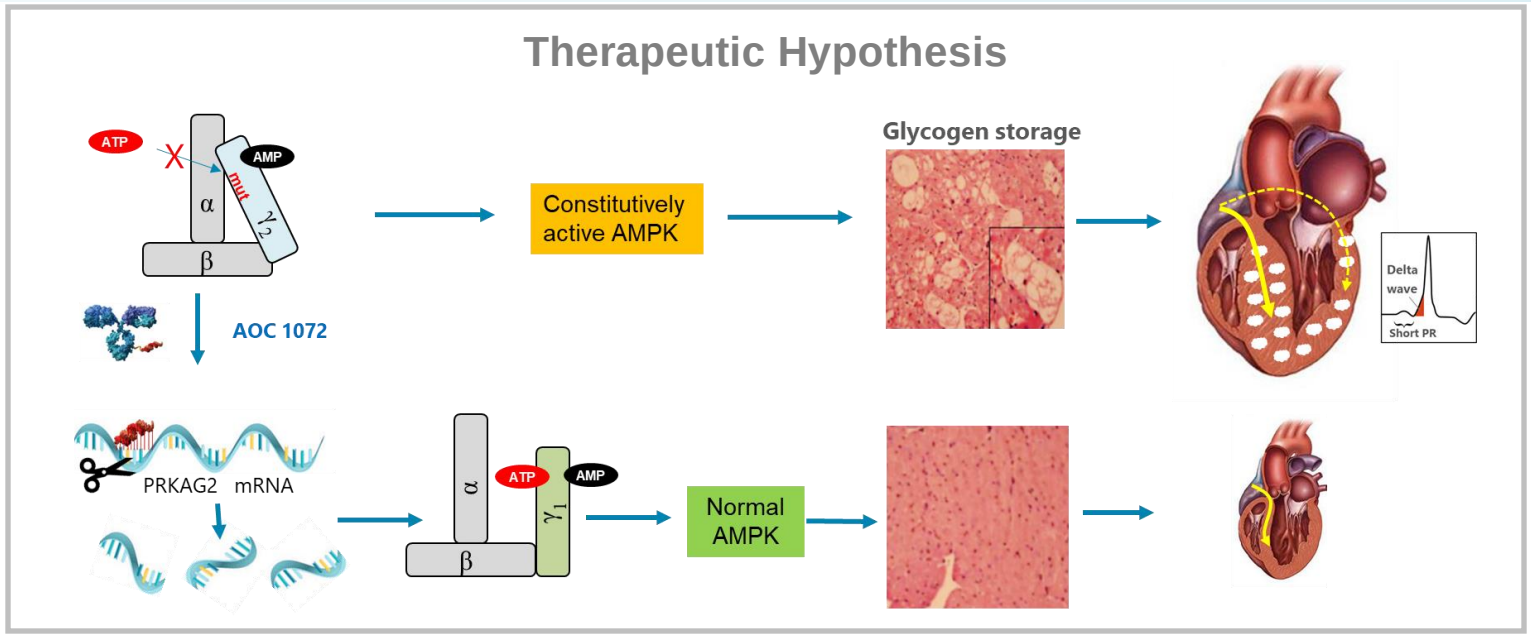
Georgios Karamanlidis and the rest of the authors are employees of Avidity Biosciences, Inc. who receive stock and stock options.

Precision Treatment for the PRKAG2 Syndrome

>5,000
Carriers of a pathogenic PRKAG2 variant (US)

0
DISEASE MODIFYING APPROVED THERAPIES

- Underdiagnosed, progressive cardiac disease associated with increased risk of sudden cardiac death (up to 10%*)
- Caused by mutations in the *PRKAG2* gene that result in increased AMPK activity
- Patients with PRKAG2 syndrome can develop HCM, Wolff-Parkinson White syndrome, conduction disease and arrhythmia



* Circ Arrhythm Electrophysiol . 2016;9(1):e003121. AOC, antibody oligonucleotide conjugate; AMP, adenosine monophosphate; AMPK, 5' adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; HCM, hypertrophic cardiomyopathy; PRKAG2, protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2; WPW, Wolff-Parkinson-White syndrome.

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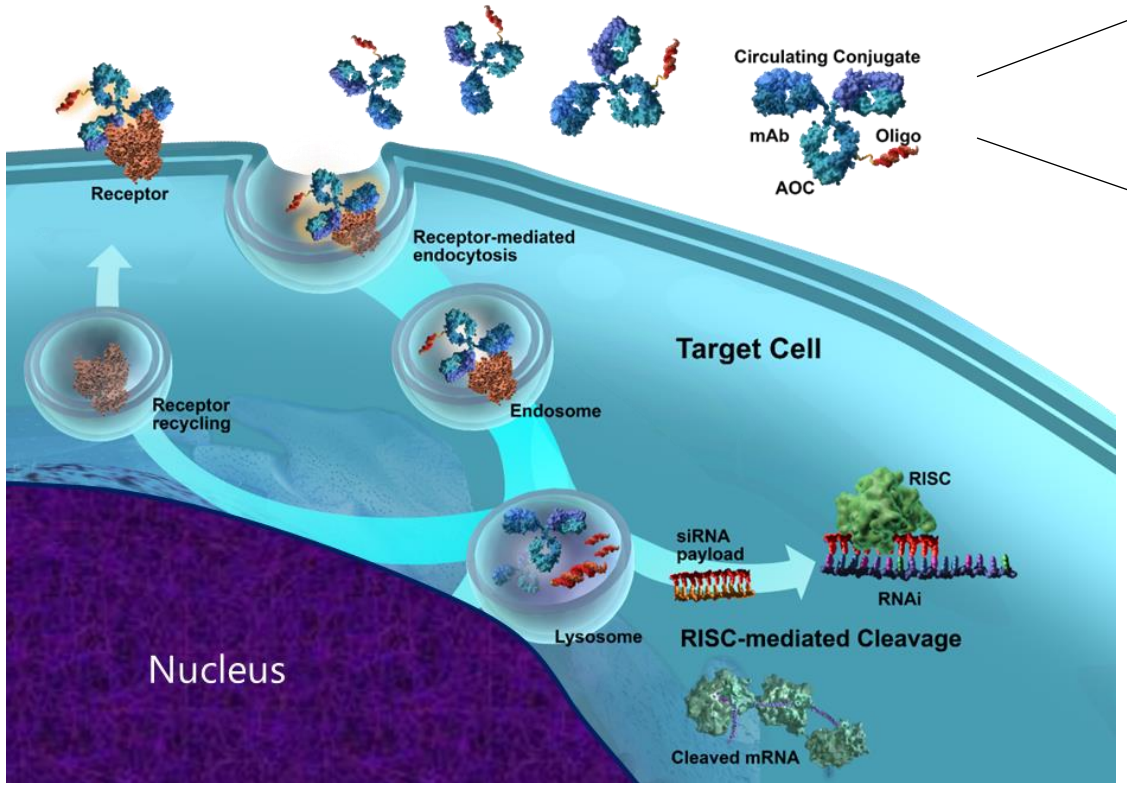
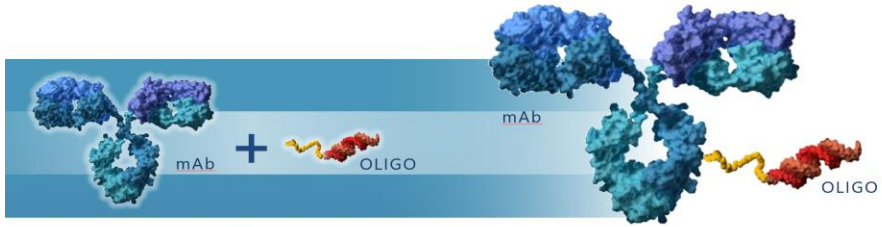
Antibody Oligonucleotide Conjugate (AOC)-Mediated siRNA Delivery for Reduction of Target mRNA



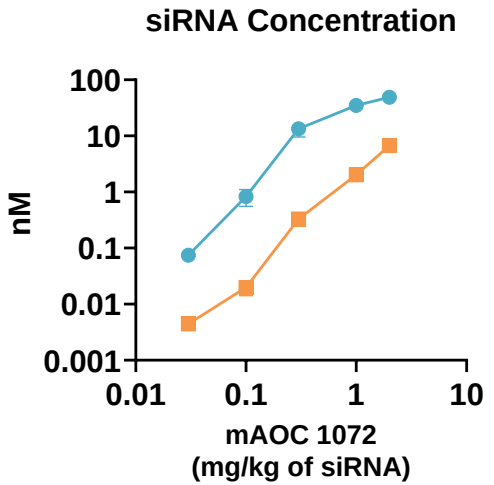


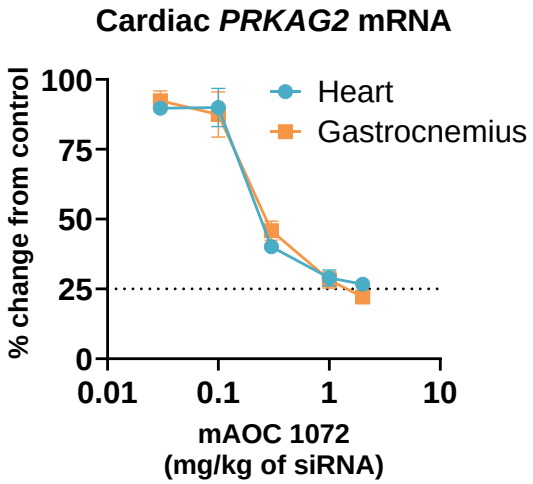
TfR1 antibody + PRKAG2 siRNA = AOC 1072

mAOC 1072 = mouse active AOC PRAKG2, tool compound

AOC 1072 = human/NHP AOC PRKAG2, clinical candidate

Dose-Dependent PRKAG2 mRNA Reduction in Mice Treated with mAOC 1072





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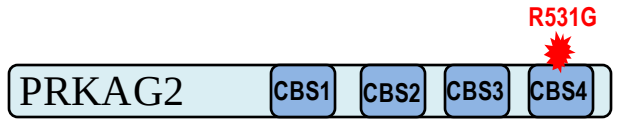
AOC, antibody oligonucleotide conjugate; mAb, monoclonal antibody; mRNA, messenger ribonucleic acid; PRKAG2, protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2; RISC, ribonucleic acid-induced silencing complex; RNAi, ribonucleic acid interference; siRNA, small interfering ribonucleic acid

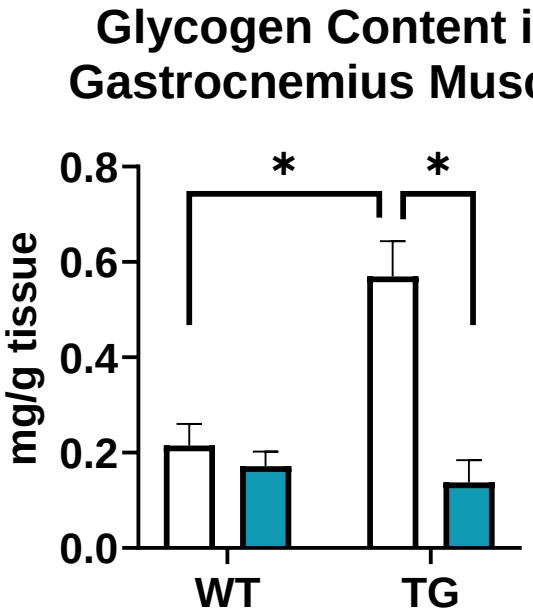
mAOC 1072 Reverses Glycogen Accumulation in Skeletal Muscle in a Mouse Model of PRKAG2 Syndrome

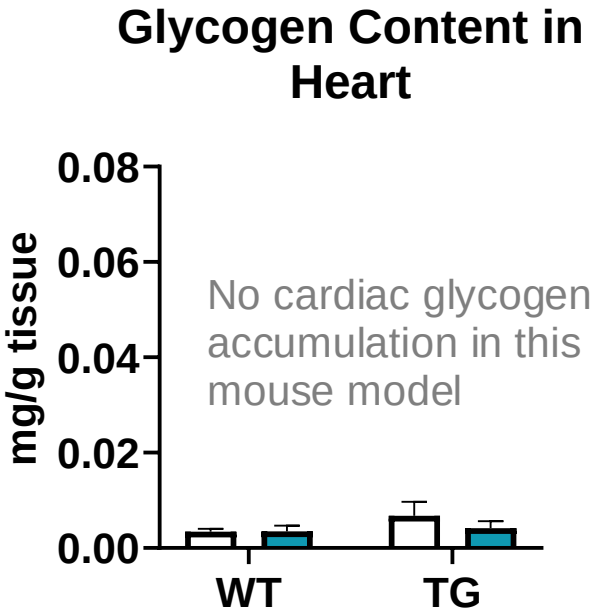


TG mice express the R528G variant (corresponding to R531G human disease variant)

Vehicle

mAOC 1072





No cardiac glycogen accumulation in this mouse model

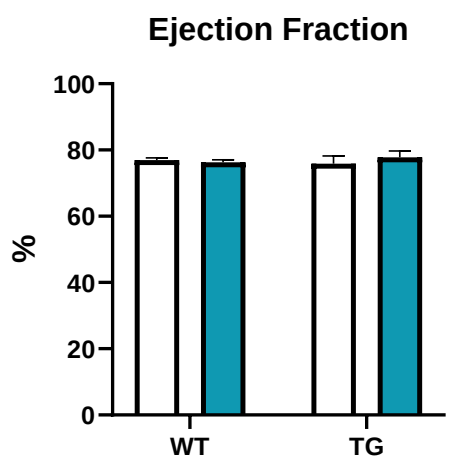
8-12-week-old mice were treated with mAOC 1072 (at 3 mg/kg) of vehicle for 24 weeks (2 doses 12 weeks apart), n=16-20/group, * indicates $p<0.05$

mAOC, mouse active antibody oligonucleotide conjugate; PRKAG2, PRKAG2, protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2; TG, transgenic; WT, wild-type.

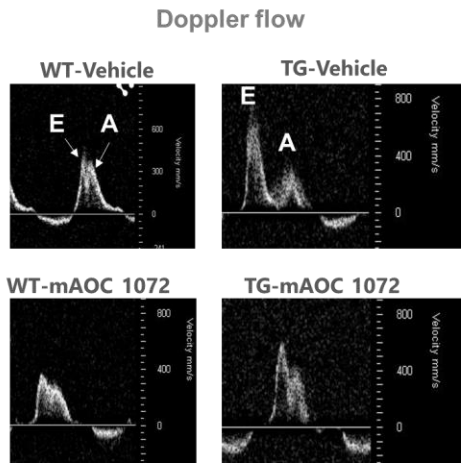
mAOC 1072 Improves Diastolic Dysfunction in a Mouse Model of the PRKAG2 Syndrome

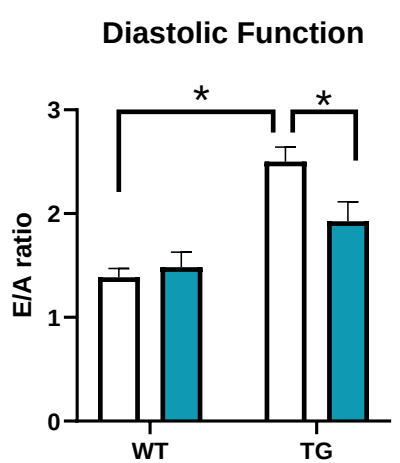
Vehicle
mAOC 1072

Normal Systolic Function

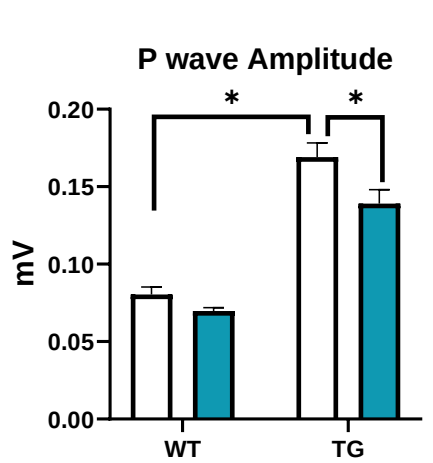


Improvement in Diastolic Function





Reduction of Atrial Enlargement



8-12-week-old mice were treated with AOC (at 3 mg/kg) of vehicle for 32 weeks (3 doses 12 weeks apart)
For diastolic function n=5-7 for WT and for n=9 for TG. For P wave n=16-20/group, * indicates $p<0.05$

mAOC, mouse active antibody oligonucleotide conjugate; PRKAG2, PRKAG2, protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2; TG, transgenic; WT, wild-type.

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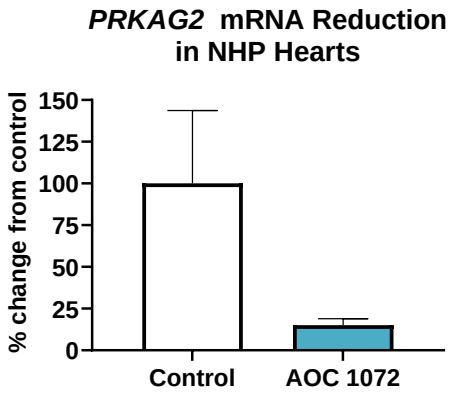
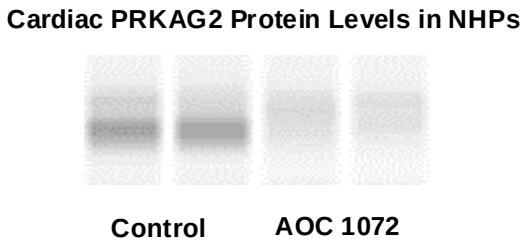
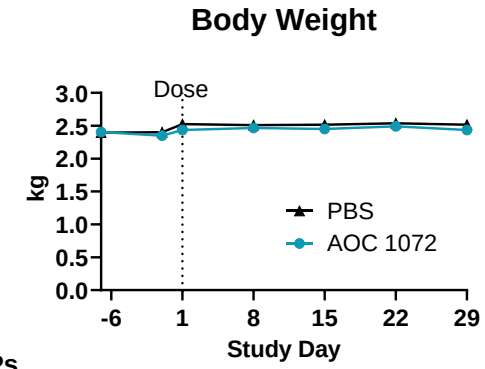
AOC 1072 Resulted in >75% Reduction of *PRKAG2* mRNA in Non-Human Primates

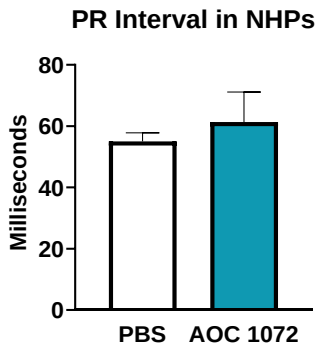
Target mRNA and Protein Reduction

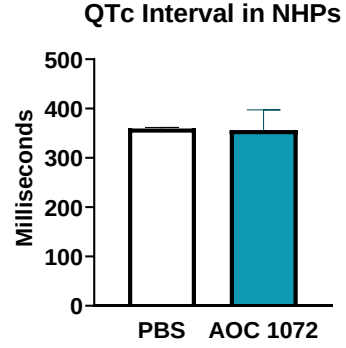




No Changes in Body Weight or on Electrocardiogram







Single dose of AOC 1072 at 3 mg/kg (of siRNA) with evaluation 28 days post-dose. n=2 for the PBS group and n=3 for the AOC 1072 group, Mean +SD

mAOC, mouse active antibody oligonucleotide conjugate; mRNA, messenger ribonucleic acid; NHP, non-human primate; PBS, phosphate-buffered saline; PRKAG2, PRKAG2, protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2.

AOC 1072: The Potential for a New Class of Precision Therapeutics for Patients with PRKAG2 Syndrome

Treatment with AOC 1072:

- Resulted in potent PRKAG2 reduction in mice and NHPs
- Reversed skeletal muscle glycogen accumulation
- Improved diastolic function in a PRKAG2 disease model
- Was well-tolerated in NHPs after a single dose

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AOC, antibody oligonucleotide conjugate; PRKAG2, protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2.