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CONTRACTING ORGANIZATION: Children's Hospital Corporation
(DBA Boston Children's Hospital), Boston, MA

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14. ABSTRACT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a inherited arrhythmia syndrome characterized by life-threatening arrhythmias during times of stress or exercise. Dominant mutations in the intracellular calcium (Ca^{2+}) release channel RYR2 are responsible for the majority of clinical cases. Despite maximal medical therapy, patients continue to have breakthrough events or therapy related complications. To response to this unmet clinical need, we have developed a targeted gene therapy to suppress arrhythmias by inhibiting the Ca^{2+} regulated kinase CaMKII. Using adeno-associated virus (AAV) vectors we demonstrated efficacy in cellular and animal models of CPVT by targeted expression of CaMKII peptide inhibitors. This grant proposal is focused on the further refinement and testing of a clinical CaMKII peptide inhibitory vector in preparation for a human clinical trial. During this granting period we have determined the cardiac-specific promoter for optimal transgene expression and laid the foundation for refinement of the peptide inhibitor. We have also expanded our clinical network of CPVT patients and performed analysis of current healthcare costs for CPVT management.

15. SUBJECT TERMS None listed.					
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1. INTRODUCTION:

The purpose of this grant is to refine and optimize a novel cardiac gene therapy for the inherited arrhythmia disorder catecholaminergic polymorphic ventricular tachycardia (CPVT) in preparation for a first in human clinical trial. Mutations in the intracellular calcium (Ca^{2+}) release channel RYR2 are commonly associated with CPVT and lead to life-threatening ventricular arrhythmias during stress or exercise. Without any abnormality at baseline, activation of the Ca^{2+}/calmodulin dependent kinase II (CaMKII) in response to adrenergic stimulation is necessary to unmask the arrhythmogenic potential of RYR2 mutations. We have developed a gene therapy strategy to treat CPVT by targeted cardiac expression of CaMKII peptide-inhibitors using adeno-associated virus (AAV) delivery. Building on previous proof-of-concept research, this project encompasses the necessary steps to construct the optimal clinical vector, define the therapeutic dose, evaluate for possible toxicities, and identify eligible patients for potential treatment. In addition to being the first gene-specific treatment for an inherited cardiovascular syndrome, targeted inhibition of CaMKII may be more universally applicable because CaMKII dysregulation is implicated in several cardiac disorders.

2. KEYWORDS:

Cardiac gene therapy
Catecholaminergic polymorphic ventricular tachycardia (CPVT)
Arrhythmia
Sudden cardiac death
Ventricular arrhythmias
Adeno-associated virus (AAV)

3. ACCOMPLISHMENTS:
What were the major goals of the project?

Specific Aim 1 – To optimize the final product design.	**Timeline**	**Percent Completed**
Major Task 1	Months	
Subtask 1: Submit documents for ACURO approval (mouse studies)	1-4	100%
Milestone # 1 ACURO approval obtained	4	100%

Subtask 2: Optimize inhibitory peptide	1-8	100%
Subtask 3: Optimize promoter	1-8	100%
Subtask 4: Optimize capsid	1-8	75%
Subtask 5: Compare self-complementary AAV to standard AAV	4-8	80%
Subtask 6: Develop an assay to detect transduced cells	4-8	50%
Milestone # 2 Finalized design of the clinical candidate	8	75%
Specific Aim 2 – To evaluate efficacy, dose-response, biodistribution, and safety of the clinical candidate in a murine CPVT model.		
Major Task 2.		
Subtask 1: Research grade vector production (AAV-nGFP then clinical candidate)	6-11	10%
Milestone #3a Delivery of research grade AAV-nGFP	9	10%
Milestone #3b Delivery of research grade clinical candidate	11	10%
Subtask 2: Dose-finding and biodistribution of AAV-nGFP	9-12	Pending
Milestone #4 Define the % cardiomyocyte transduction for a range of viral doses and biodistribution of the AAV-nGFP test vector	12	Pending
Subtask 3: Efficacy and dose-response study	13-18	Pending

Milestone #5 Define the effective dose, efficacy, safety, and biodistribution of the clinical candidate.	18	Pending
Specific Aim 3 – To develop safety data on the final therapy vector in a large animal model		
Major Task 3		
Subtask 1: Submit documents for ACURO approval (swine dose-finding studies at BCH)	6-18	90%
Milestone #6 ACURO approval obtained for swine	18	Pending
Subtask 1: Pre-IND meeting	19-21	Pending
Milestone #7 Finalize design of the large animal safety trial	21	80%
Subtask 2: Production of clinical grade vector (AAV-GFP-P2A-IP1 then AAV-IP1)	13-24	10%
Milestone #8a Delivery of Hyperstack scale AAV-GFP-P2A-IP1	18	Pending
Milestone #8b Delivery of Hyperstack scale clinical candidate (no GFP-P2A)	24	Pending
Subtask 3: Large animal dose-finding and biodistribution using GFP-containing vector and clinically applicable delivery route and equipment. [2 pigs x 5 groups = 10 pigs]	19-24	Pending
Milestone #9 Define target vector dose to match efficacious dose found in mouse model	24	Pending

Subtask 4: Large animal safety and biodistribution study [12 pigs x 2 doses = 24 pigs]	25-34	Pending
Milestone #10 Completion of large animal safety and biodistribution study	34	Pending
Specific Aim 4 – To lay the groundwork for a First-in-Human clinical trial		
Major Task 4		
Subtask 1: Establish a CPVT Network	1-12	100%
Milestone #11 Hold a meeting of CPVT Network participating members	12	66%
Subtask 2: A retrospective chart review	8-24	75%
Milestone #12 Establish natural history and resource utilization of CPVT under the current standard of care.	24	75%
Subtask 3: Collect and test blood from patients with inherited arrhythmia for neutralizing antibodies	1-30	50%
Milestone #13 Determine the frequency of neutralizing antibodies amongst the target population	30	10%
Subtask 4. Finalize Phase I clinical protocol	25-32	Pending
Subtask 5. Prepare IND application	32-36	Pending
Milestone #14 Submission of FDA IND filing for a First-in-Human Phase I study	36	Pending

What was accomplished under these goals?

3.1 Major Activities

During this granting period, we have focused our efforts on finalizing the design of the inhibitory peptide and selection of the final AAV capsid. We have established the platform for production of the clinical AAV vector and submitted the appropriate paperwork for approval of the large animal studies. Our CPVT network has expanded, and we have initiated the studies for determining pre-existing antibodies for our proposed AAVs.

3.2 Specific Objectives

Major Task 1

Selection of the optimal CaMKII inhibitory peptide

To determine the most effective CaMKII inhibitory peptide we proposed the comparison our original proof-of-concept peptide AIP to the more potent CN19o. We also hypothesized that the effectiveness of the inhibitory peptide and subsequent suppression of arrhythmia in CPVT may be affected by fusion to a carrier protein or multimerization. To test these concepts, we created constructs to express either single inhibitory peptides, peptides fused to the RYR2-binding protein FKBP12.6 or as multimers. Our original proposed plan was to use modified RNA(modRNA) to transduce adult cardiomyocytes to test the effectiveness of the inhibitory peptides, but the expression levels were too low. To overcome this limitation, we packaged the peptides into AAV9 particles and injected them into P3-P5 animals harboring the CPVT-associated mutation RYR2-R4650I (Fig. 1A). After two months we performed drug challenges of $RYR2^{R4650I/WT}$ mice with serial injections of isoproterenol, epinephrine, and caffeine while simultaneously monitoring for induction of ventricular arrhythmias (VAs) by ECG. We quantified the total percentage of ventricular ectopy in response to adrenergic stimulation and the presence of ventricular tachycardia (VT) classified as more than three ventricular beats in a row. These data demonstrate that AIPx5 is superior in reducing overall ventricular ectopy (Fig. 1B) and more importantly the fraction of animals with induced VT (Fig. 1C). To ensure that each of the inhibitory peptide constructs were equally expressed within the heart, we created cardiac sections from injected animals and stained for mCherry as an expression marker. Imaging of stained cardiac sections did not reveal significant variation in transduction efficiency (Fig. 1D), strongly suggesting that

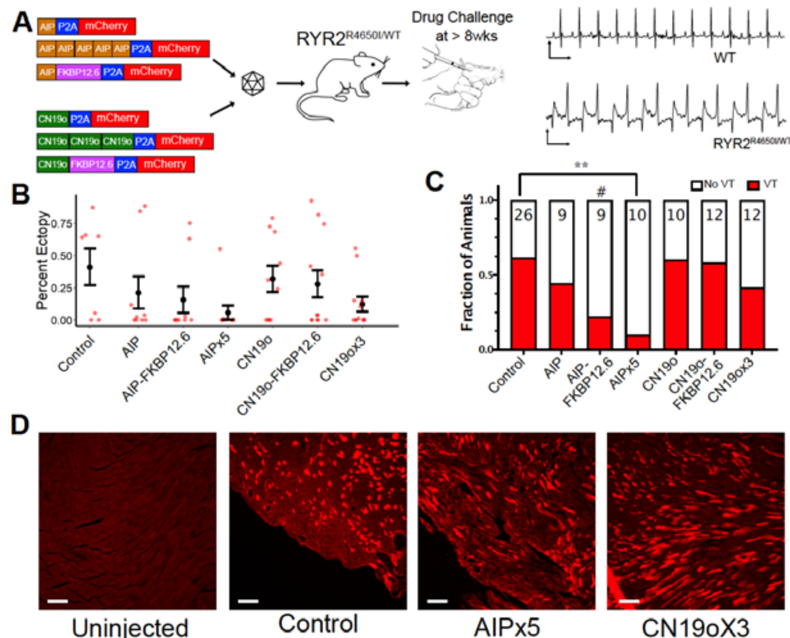

Fig. 1. Optimization of CaMKII peptide inhibitor. A. Schematic of CAMKII inhibitors AIP and CN19o, as multimeters or fused to the RYR2-binding protein FKBP12.6 prior to packaging into AAV9 particles for injection at P3. Animals are administrated isoproterenol, epinephrine and caffeine at 2 months to induce ventricular arrhythmia. **B.** Animals underwent continuous ECG monitoring after adrenergic stimulation and the total number of ectopic ventricular beats were recorded and expressed as a percentage of the total beats. **C.** Quantification of animals with ventricular tachycardia (VT) defined as more than 3 beats. Total N is listed and $^{**}P < 0.01$, $^{\#}P = 0.06$. **D.** Cardiac sections were created from animals uninjected, injected with AAV9 constructs for mCherry (control) or CaMKII peptide inhibitors. Scale bar = 100μm

differences in the effectiveness of arrhythmia suppression are intrinsic to the inhibitory peptides themselves. Subsequent therapeutic vector designs will likely utilize AIPX5 as the primary cargo.

Selection of the AAV capsid

In our original proof-of-concept studies, we used AAV9 as the delivery vector for transduction of the heart for our CaMKII inhibitory gene therapy. While AAV9 has a tropism for the cardiac tissue it also has significant transduction capacity of non-cardiac organs including the brain and liver. Inclusion of a cardiac-specific promoter in our therapeutic construct will aim to restrict expression to the heart, but additional safe-guards for extra-cardiac expression of our CaMKII inhibitory peptides would increase the safety and efficacy of our proposed therapy. To determine the optimal AAV capsid to both enhance specificity of cardiac expression and reduce the effective viral dose, we sought to determine the transduction efficiency of AAV capsids with reported cardiac tropism. We packaged different fluorescent proteins driven by the cardiac troponin-T (cTnT) promoter into selected AAVs including: AAV-6, AAV-2i8, AAV9 and AAV-rh10 (Fig. 2A). These viruses were then subcutaneously injected into P3 animals, each at a dose of $1x10^{11}$ viral genomes per gram (vg/g). After 4 weeks of expression, adult cardiomyocytes (CMs) were isolated by retrograde coronary perfusion of collagenase. We performed fluorescent activated cell sorting (FACs) of isolated CMs after staining with Janelia-fluor 646nm to detect HaloTag protein expression. Using selective gating, we quantified the percentage of CMs expressing each of the fluorescent proteins corresponding to individual AAVs (Fig. 2B). To confirm dominant cardiac transduction by AAV-rh10, we again isolated CMs and performed microscopic imaging which demonstrated significant transduction of cardiomyocytes with HaloTag corresponding to AAV-rh10 (Fig. 1C). Collectively these data strongly suggest that AAV-rh10 has superior cardiac transduction efficiency with the potential to improve target organ specificity and reduce the effective viral dose. To verify this result, we will perform amplicon sequencing of barcoded constructs injected as individual viruses and all within the same animal.

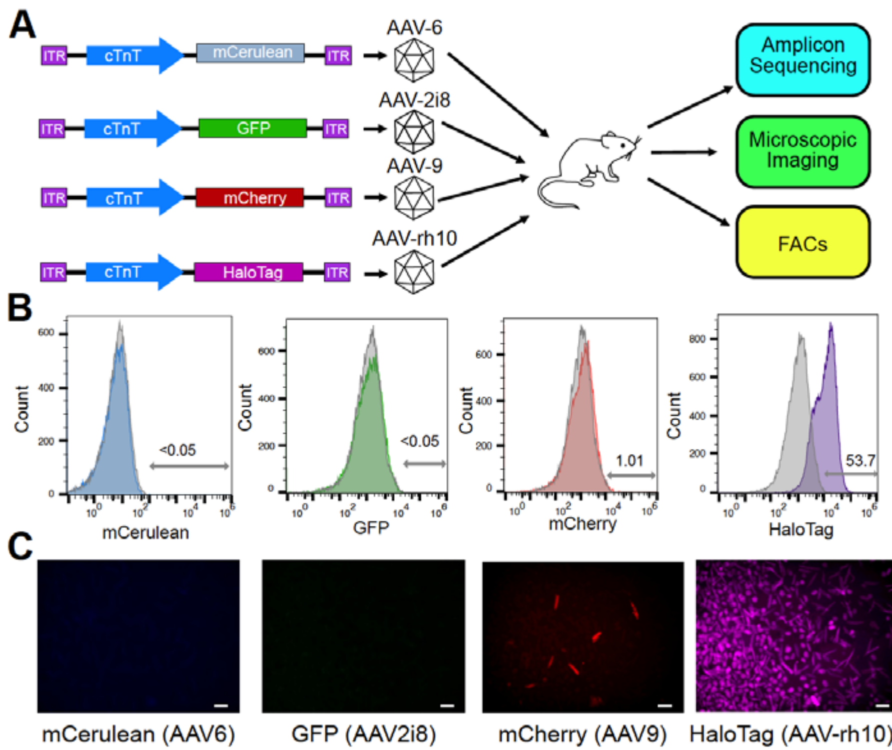

Figure 2. Selection of Cardiac-Specific AAV Capsid. A. Fluorescent proteins were driven by the cardiac T troponin (cTnT) promoter were packaged into individual AAV capsids and injected at a dose of $1x10^{11}$ viral genomes per gram (vg/g) for each virus into P3 animals. After 6 weeks of expression, individual cardiomyocytes (CMs) were isolated for analyses as shown. **B.** Fluorescent activated cell sorting (FACS) was used to quantify the percentage of CMs transduced by each AAV capsid. Cells were stained cell-permanent Janelia-647nm stain to visualize HaloTag expression. **C.** Isolated cells from hearts injected with all four capsids were fixed and imaged. Scale bar = 50µm.

Major Task 2

Research grade vector production (AAV-nGFP then clinical candidate)

To perform both dose-finding efficacy testing in mice and transduction testing in swine, we plan to produce large quantities of our clinical candidate and AAV-nGFP. We have already identified and partnered with a CRO to produce the AAVs in a GLP environment. We are currently in the process of producing the final plasmid clone for AAV production. As outlined in our Changes in Approach, we will replace nGFP with nuclear-localized HaloTag to increase the signal-to-noise ratio for imaging and fluorescent-based assays.

Major Task 3

Submit documents for ACURO approval

To ascertain the probable dose for a clinical trial we have proposed a small pilot study in a large animal model (swine) using our clinical vector. Given the lack of a large animal model for CPVT we will plan to perform a dose finding experiment in pigs to confirm restricted cardiac expression, and a target dose with at least 40% of transduced cardiomyocytes. We have submitted this protocol which has an undergone initial review and is currently pending final approval. Following IACUC approval at Boston Children's Hospital we will submit the necessary documentation to ACURO.

Major Task 4

Establish a CPVT Network

To facilitate the identification of additional CPVT patients eligible for a potential clinical trial thereby increasing the clinical and molecular diversity of patients and better define the natural history of CPVT, we partnered with several institutions as part of the International CPVT network. We have IRB approval for the direct sharing of both samples and clinical data with the British Columbia Children's Hospital and Simon Fraser University. In addition, we have further expanded our network to include Children's Hospital of Atlanta.

We completed Milestone #11 by participating in two CPVT translational research meetings held on November 19th, 2020, and February 10th, 2021, by video conferencing secondary to COVID-19 travel restrictions. These highly productive meetings included researchers and clinicians from Boston Children's Hospital, Simon Fraser University, and University of Calgary and were focused on the clinical management and translational research for CPVT. We are planning on hosting a 3rd such meeting in the last quarter of 2021 or first quarter of 2022, focused on the design of a first-in-human clinical trial with our CPVT network partners.

Collect and test blood from patients with inherited arrhythmia for neutralizing antibodies

The presence of pre-exiting neutralizing antibodies (nAbs) for specific AAV capsids can limit the effective transduction efficiency and can completely prevent transgene delivery. To determine the incidence of pre-existing AAV antibodies we will plan to measure either the presence of nAbs and reactive T-cells (by ELISpot) from our cohort of CPVT patients. The IRB protocol was recently approved, and we have collected samples suitable for ELISpot analysis from 50% of our projected cohort (15 of 30 patients) to estimate the prevalence of pre-existing immunity to our proposed AAV capsid. Additional samples will be collected and analyzed.

What opportunities for training and professional development has the project provided?

Dr. de la Serna Buzon was selected as a research fellow to be part of our T32 training grant based on her work on optimization of gene therapy funded by this project.

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

During the next granting period, we will produce the therapeutic vector for testing in both small and large animal models. We will use our dose-finding experiments in mice to inform the dosing of swine to achieve at least 40% cardiomyocyte transduction. Evaluation of potential toxicity will be performed at a CRO with some initial testing performed at Boston Children's Hospital.

We will host the third CPVT translational research meeting with our CPVT Network collaborators focused on the design of an in-human clinical trial. To inform the design of the clinical trial, we will conclude the analysis of the CPVT clinical study with a specific focus on the determination of treatment success by a combination of exercise stress testing and long-term monitoring. After the completion of patient recruitment, we will perform testing for pre-existing immunity from the selected capsid and establish a registry of potential patients for a clinical trial.

To facilitate the completion of these studies we have recently hired a new post-doc with expertise in cardiac gene therapy (Dr. Nikoleta Pavlaki) with the technical support from a new research assistant. To complete the clinical studies, Dr. Abrams has recruited a senior electrophysiology fellow for a one-year fellowship in cardiovascular genetics.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The discovery that multimerization of CaMKII inhibitory peptides and in particular AIP, enhance their effectiveness at suppressing arrhythmia in a mouse of CPVT, raises intriguing questions about the relationship of CaMKII inhibition and the pathophysiology of CPVT. While the pentameric form of AIP (AIPx5) was found to be most effective, AIP itself was superior to CN19o in suppressing arrhythmia despite the increased potency of CN19o by *in-vitro* kinase assays. We are currently examining the biochemical effects of peptide multimerization on direct CaMKII inhibition and the potential of other targets which may explain AIP's improved effectiveness.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

We have an on-going partnership with a gene therapy company based on our proof-of-concept data for CaMKII inhibition to treat CPVT.

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

5.1 Changes in approach

Our initial gene therapy vectors utilized GFP as a marker for transduction efficiency. While we are currently developing an RNAscope probe to detect the bio-distribution of our proposed cargo AIPx5, we will continue to use fluorescent markers in parallel for transduction efficiency measurements. Because of intrinsic background fluorescence within the heart, GFP has a lower-than-expected signal to noise ratio. To overcome this limitation, we will use the self-labeling protein HaloTag as an expression marker for all future constructs which require a fluorescent protein. This approach also increases flexibility in the selection of other fluorescent transgenes such as biosensors.

Despite improved expression in isolated adult cardiomyocytes with AAV transduction over modified RNA transfection the throughput and reliability of imaging Ca^{2+} release events were insufficient to accurately determine the effectiveness of individual CaMKII inhibitory peptide constructs. Therefore, we elected to perform *in-vivo* testing with our putative gene therapy vectors. This approach did dramatically increase the time necessary to determine the optimal inhibitory peptide but eliminated the potential problem of an uncertain correlation of single-cell Ca^{2+} assays to arrhythmia suppression in a CPVT mouse model. Ultimately our extensive animal studies provide significant confidence in the selection of multimerized CaMKII inhibitory peptides as the most effective method for CPVT gene therapy. These data will facilitate the rapid determination of the optimal dose in our proposed mouse and swine experiments.

Actual or anticipated problems or delays and actions or plans to resolve them

5.2 Actual or anticipated problems or delays

The ongoing global coronavirus pandemic continues to cause delays in obtaining critical regents and recruiting qualified personnel. Furthermore, the limitations on available childcare for staff also limited productivity. To overcome these issues, we instituted regular Zoom meetings so that staff could work remotely if necessary. We also adjusted our experimental approaches in terms of mouse breeding and finding alternatives to back-ordered reagents whenever possible.

Again because of the pandemic and variable local and national injection rates, access to medical care has been more limited at times. Therefore, patient recruitment for clinical studies has been slower than normal. To overcome this limitation, we have expanded our CPVT network and initiated a rapid patient identification and recruitment system starting with an initial virtual visit followed by in-person clinical visits and possible recruitment if indicated.

Changes that had a significant impact on expenditures

The COVID pandemic and lab shutdown/slowdown delayed development work on the therapeutic candidate. Although we have made significant progress, we have not yet settled on the final design. This has impacted expenditures by delaying our outsourcing of the production of the vectors and contracting with CRO for large animal safety studies.

Significant changes in use or care of human subjects

There are no significant changes in the care or use of vertebrate animals, biohazards and/or select agents. The IRB to participate in the international CPVT registry was finalized as was the amendment to obtain samples for testing of pre-existing AAV immunity. The large animal protocol has been submitted and is currently under review. No large-animal experiments will be performed until the appropriate approvals have been obtained.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

We submitted a provisional US patent application on 7/6/2017 for our proposed gene therapy. A formal application was submitted on 1/2/2020 and currently is pending under number 16/628,162. We have partnered with a gene therapy company as part of a sponsored research agreement with an option for license.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	William Pu, MD
Project Role:	PI
Researcher Identifier:	0000-0002-4551-8079
Nearest person month worked:	1
Contribution to Project:	Overall co-direction of the project along with Dr. Bezzerides
Funding Support:	Committed effort fully supported by this award

Name:	Vassilios Bezzerides MD, PhD
Project Role:	Co-investigator
Researcher Identifier:	0000-0003-0825-6580
Nearest person month worked:	1
Contribution to Project:	Overall co-direction of the project along with Dr. Pu
Funding Support:	Committed effort fully supported by this award

Name:	Dominic Abrams MBBS
Project Role:	Institutional Collaborator
Researcher Identifier:	0000-0003-0825-6580
Nearest person month worked:	1
Contribution to Project:	Assistance with establishment of CPVT network
Funding Support:	Departmental

Name:	Sofi de la Serna Buzon
Project Role:	Postdoctoral Fellow
Researcher Identifier:	NA
Nearest person month worked:	4
Contribution to Project:	Dr. de la Serna Buzon completed the promoter optimization and is performing the experiments to select the CaMKII inhibitory peptide. She will continue with the production of additional AAVs for dose-finding.
Funding Support:	Committed effort fully supported by this award

Name:	Suya Wang
Project Role:	Postdoctoral Fellow
Researcher Identifier:	NA
Nearest person month worked:	9
Contribution to Project:	Dr. Wang performed the comparison of self-complementary versus standard AAV. She also assisted with the design of testing the CaMKII peptides
Funding Support:	Committed effort fully supported by this award

Name:	Jasmine Feng
Project Role:	Research assistant
Researcher Identifier:	NA
Nearest person month worked:	12
Contribution to Project:	Ms. Feng assisted with construction of the AAVs for peptide and promoter testing.
Funding Support:	Committed effort fully supported by this award

Name:	Thomas Samenuk
Project Role:	Research assistant
Researcher Identifier:	NA
Nearest person month worked:	1
Contribution to Project:	Mr. Samenuk determined the lack of effect of microRNA targeting sequence for miR124. Currently improving on non-promoter expression specification.
Funding Support:	Committed effort fully supported by this award

Name:	Daisuke Yoshinaga
Project Role:	Postdoctoral Fellow
Researcher Identifier:	NA
Nearest person month worked:	12
Contribution to Project:	Dr. Yoshinaga assisted with imaging of cardiomyocytes along with other research members.
Funding Support:	Committed effort fully supported by this award

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Organization Name: University of British Columbia
Location of Organization: (if foreign location list country) British Columbia, Canada
Partner's contribution to the project:
The University of British Columbia is part of international registry of CPVT patients providing clinical information for analysis.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: