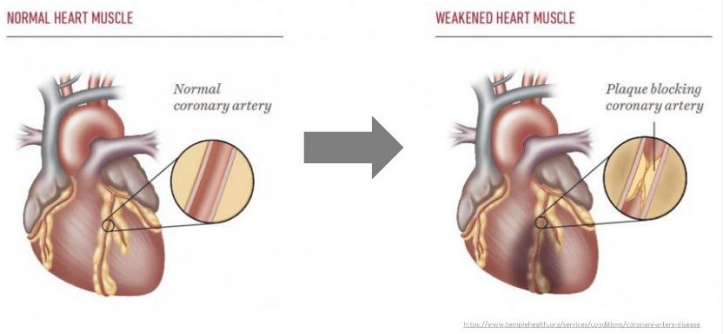
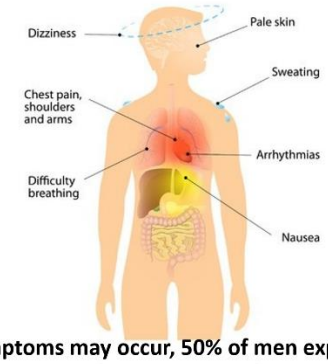
What is Coronary Artery Disease (CAD)?



Coronary Artery Disease occurs due to a buildup of plague in the coronary artery leading to a weakening of the heart muscle.

What are the symptoms of CAD?

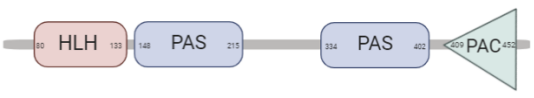


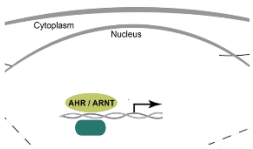
Though these early symptoms may occur, 50% of men experience a heart attack as their first symptom of CAD

While some will experience symptoms such as nausea and sweating when suffering from CAD, half of men experience heart attack as their first symptom.

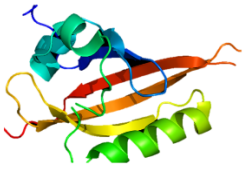
What gene is mutated in CAD?

Human ARNT Gene

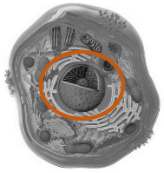




Biological Process

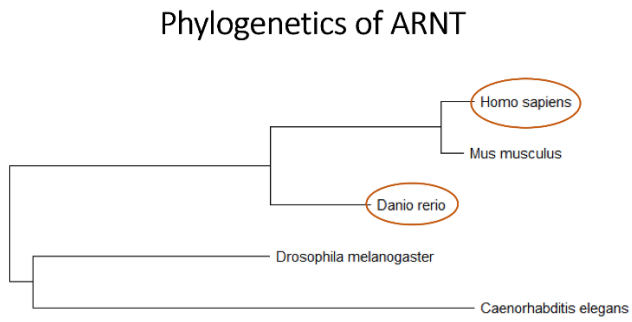


Molecular Function

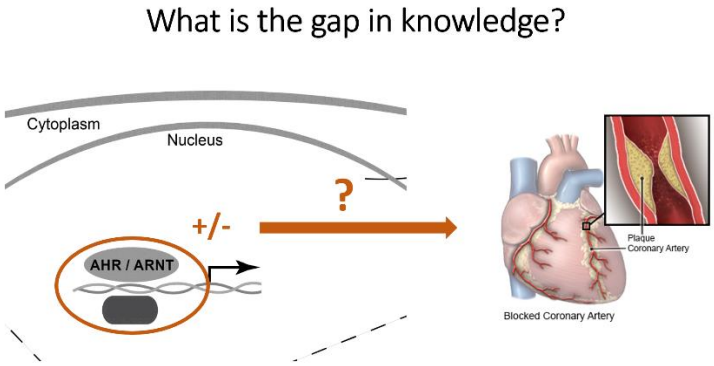


Cellular Component

The human ARNT gene has been found to be mutated in those with CAD. This gene's gene ontology shows that it functions as a transcription factor on the biological level, has domains that allow binding within the protein and with other proteins on the molecular level and, on the cellular level, is found to be localized in the nucleus.

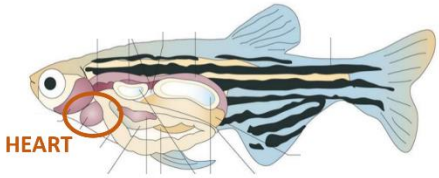


This maximum likelihood tree shows the relationship of ARNT among humans and model organisms, being most closely related to those with cardio vascular systems most like ours.



The gap in knowledge is how this ARNT protein that works as a transcriptional regulator leads to the proliferation of CAD.

What model organism should be used?



For these specific aims we will be using the model organism Danio Rerio due to the visibility of its heart both to the naked eye and the ability to dye the cardiovascular system in order to be able to see the CAD phenotype more clearly.

What is the overall goal?

To understand how mutations in the ARNT gene contribute to endothelial cell proliferation and in turn Coronary Artery Disease.

How?

AIM 1:

We will use Sanger Sequencing to determine all SNPs in ARNT that lead to the CAD phenotype.

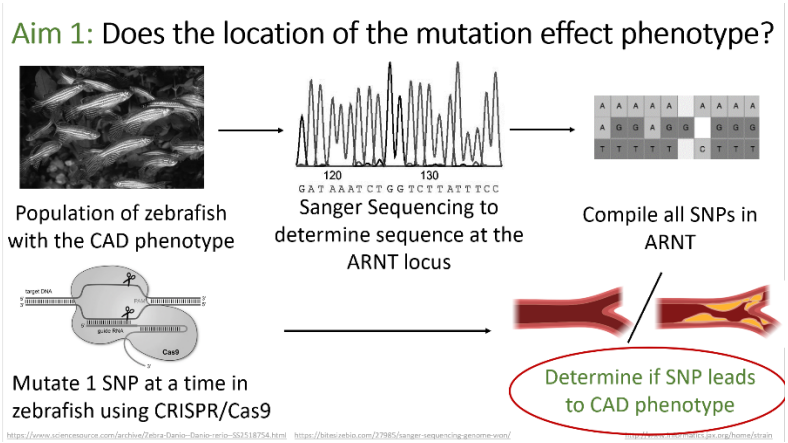
AIM 2:

We will perform RNA-seq on tissue from WT *Danio rerio* and those with CAD to determine differentially expressed genes.

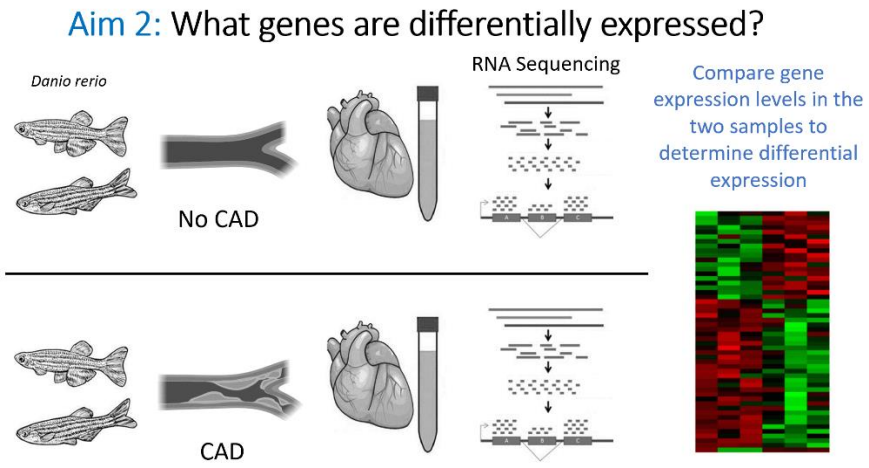
AIM 3:

We will use TAP tagging to identify proteins associated with ARNT and its function.

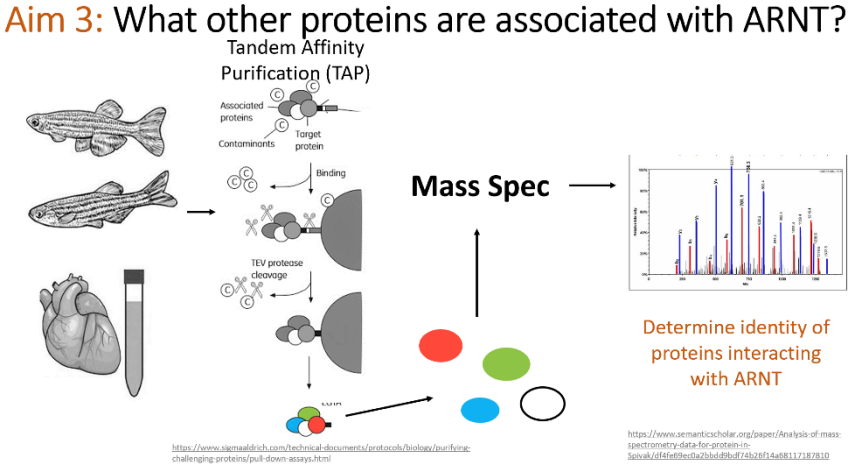
The overall goal is to understand how the ARNT gene is linked to the proliferation of CAD. We will investigate this using these three specific aims.



In order to determine if the location within ARNT of the mutation matters and effects the proliferation of CAD, we will use sanger sequencing on the ARNT locus in the genome of a population of zebrafish known to have CAD. We will then compare the causative SNPs to the severity of the CAD in order to rank them in severity.

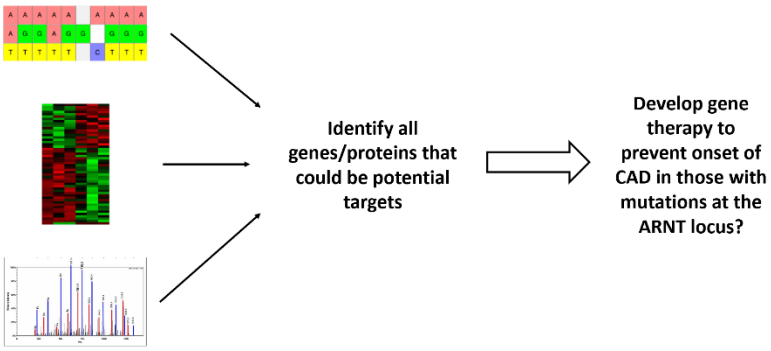


In the second aim we will take samples of heart tissue from populations of zebrafish both with and without CAD then perform RNA sequencing on the samples to identify genes that are up or down regulated in the population with CAD in order to identify potential interactions that we will also investigate in Aim 3.



In Aim 3 we will use TAP tagging to identify protein interactions with ARNT. By identifying these proteins it will also identify other protein targets for potential gene therapy to treat CAD.

Looking to the future: Potential gene therapy?



In the future the findings of these specific aims could be used to develop a potential gene therapy to help prevent those with mutations at the ARNT locus from developing CAD.