# AIM 1

**The goal is to find patients that have had “triggered pAF” as their phenotype**

1. I will get patients from the CCTS from UIC and obtain clinical data before diagnosis and after
2. Evaluate time-based markers (weight change, burden of AF, echo parameters)
3. Filter out those with highly co-morbid pAF, leaving those that are somewhat younger/less-comorbid as target population.
4. Of those, will identify patients that have had pAF ablation (retrospectively)
5. Will look at EGM/EAM data on those retrospective patients and evaluate if there are intracardiac patterns (triggered/un-triggered, voltage, scar burden, atrial geometry)
6. Will compare those population-level patients with the subset of EPS patients to see if there is a pattern against a “gold-standard”

**Aim 1: Identify triggered-variants of pAF using clinical and electrical sub-phenotypes.** a. *Hypothesis: Intracardiac and extracardiac electrical features classify pAF into triggered versus re-entrant variants.* a. Our clinical sub-phenotype will be generated using population-level data that incorporates ECG, imaging, burden, and recurrence.  
a. Our electrical sub-phenotype will be generated during EPS for pAF ablation, using intracardiac markers (EGM, voltage, scar) and will be used to validate our findings.

# AIM 2

**The goal is to identify if there is a VTA-pAF phenotype from intracardiac lab data.**

1. Will enroll patients undergoing EPS/PVI for pAF
2. Before enrollment, evaluate if they classify/fall into a phenotype category from aim 1
3. Will interview these patients to get neuropsychological patterns prior to PVI
4. During the case, before PVI, will get baseline EPS. EPS will include SA node properties. HRV/GEH before and after PVI.
5. During the case will also get systemic/IVC levels of NE, EPI, CRP, ESR, hsTn, ANP, nt-BNP.
6. Will get CS-levels of NPY, Gal, S100B before and after ablation. Also get systemic levels at baseline.
7. During case, if feasible, will use epi/iso to evaluate vagal effects and re-measure NPY/Gal.
8. During case, if feasible, will use VNS and re-measure NPY/Gal levels (and NE).
9. After ablation, will measure S100B (GP glial cells)
10. Use these components to classify patients as “autonomic” or not in terms of their AF
11. Compare them to patients in Aim 1 as a “gold standard”

**Aim 2: Investigate the autonomic determinants of triggered-variants of pAF.** a. Levels of serum and coronary sinus neurohormonal biomarkers can be measured during EPS. *Hypothesis: Levels of NPY and Gal will be greater in those with triggered vs. re-entrant pAF.*  
a. Physiological stress can be induced through catecholamine infusion, and can affect arrhythmogenesis. *Hypothesis: The electrical threshold for arrythmogenesis will be decreased in those with triggered pAF as compared to baseline.*  
a. Neuropsychological stress can be measured through clinical interview and using mental stress challenge. *Hypothesis: Levels of NPY and Gal will be higher at baseline in those with increased burden of psychological stress.*

# AIM 3

**The goal is to see if there are high-risk genes that lead to vagal-withdrawal (Emory). If there are, those variants likely increase risk of pAF as well and we can see it (UIC).**

1. Will evaluate patients identify as high-risk of vagal withdrawal to stress (MSI-VTA). This is rest + stress reactivity vagal withdrawal.
2. Evaluate common genetic variants in this population in those that did GWAS.
3. Use WES/next-gen sequencing to look for novel variants
4. Identify these variants and look at them in the AF population at UIC.
5. See if these variants or polymorphisms are related to the VTA-pAF phenotype, AF burden, recurrence after ablation.

**Aim 3: Evaluate the role of ANS receptor polymorphisms with vagally-triggered arrhythmias.** a. We will identify individuals that are classified as having resting and stress-induced vagal withdrawal with their risk of CV mortality. We will obtain next-generation sequencing on those individuals. *Hypothesis: Novel variants exist that may explain the risk of vagally-triggered arrhythmias.*  
a. A candidate gene-approach can be used to identify common variants in cardiovagal outflow receptors (Y2R and Gal1R). *Hypothesis: In triggered pAF, those classified in* ***1c****, will have an increased rate of receptor polymorphisms.*