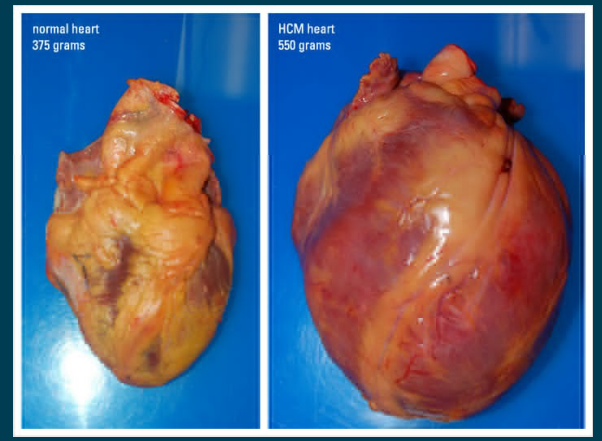
A Humanized Hypertrophic Cardiomyopathy Model to Elucidate the Molecular Mechanism in Disease Pathology

Hypertrophic Cardiomyopathy (HCM)

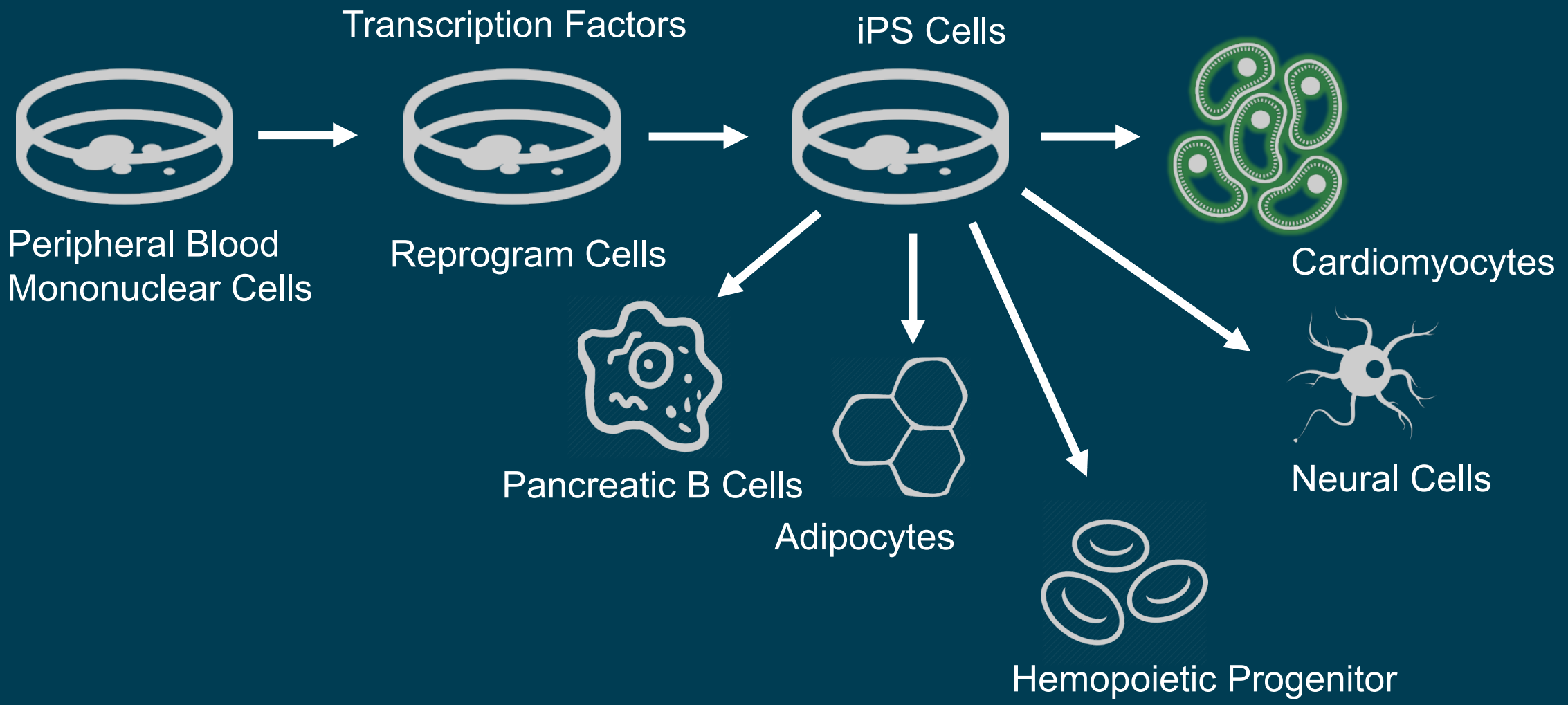
- Most prevalent genetic heart condition
- Enlarged cardiomyocytes = Enlarged heart
- Thickened left ventricular wall
- Arrhythmia induced Sudden Cardiac Death (SCD)



Hypertrophic Cardiomyopathy (HCM)

- Heterogenous genetic mutations
- Human Cardiac biopsies – Difficult, Invasive & Short-Shelf life

Our Approach



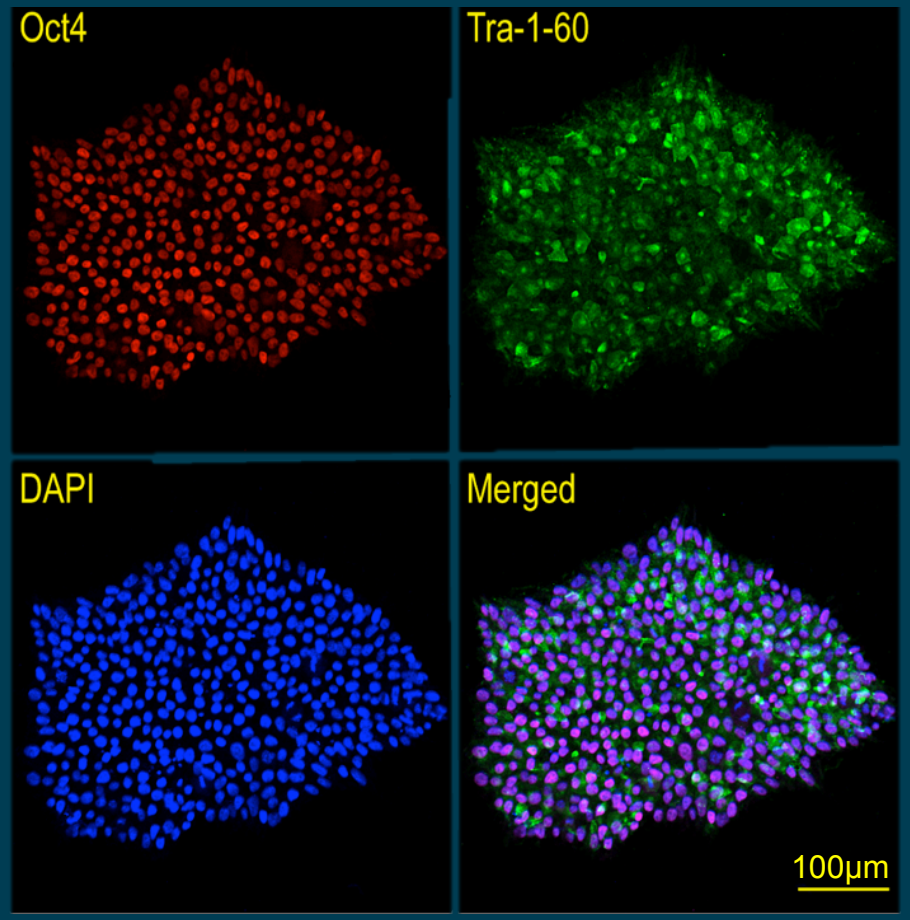
Our Approach

- Induced Pluripotent Stem Cells (iPSCs)
  - Ethical
  - Non-Invasive
  - Immortal cell line

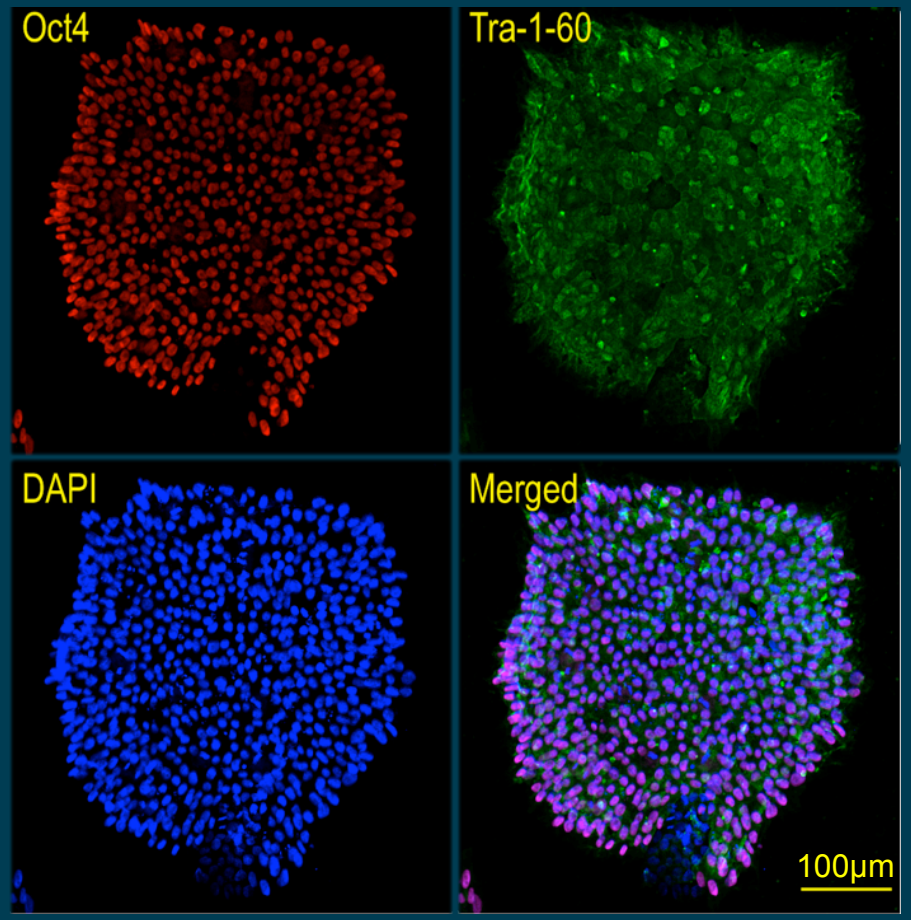
- Multiple Cell lines
  - Heterogeneity of disease causing mutations

Staining for Pluripotency

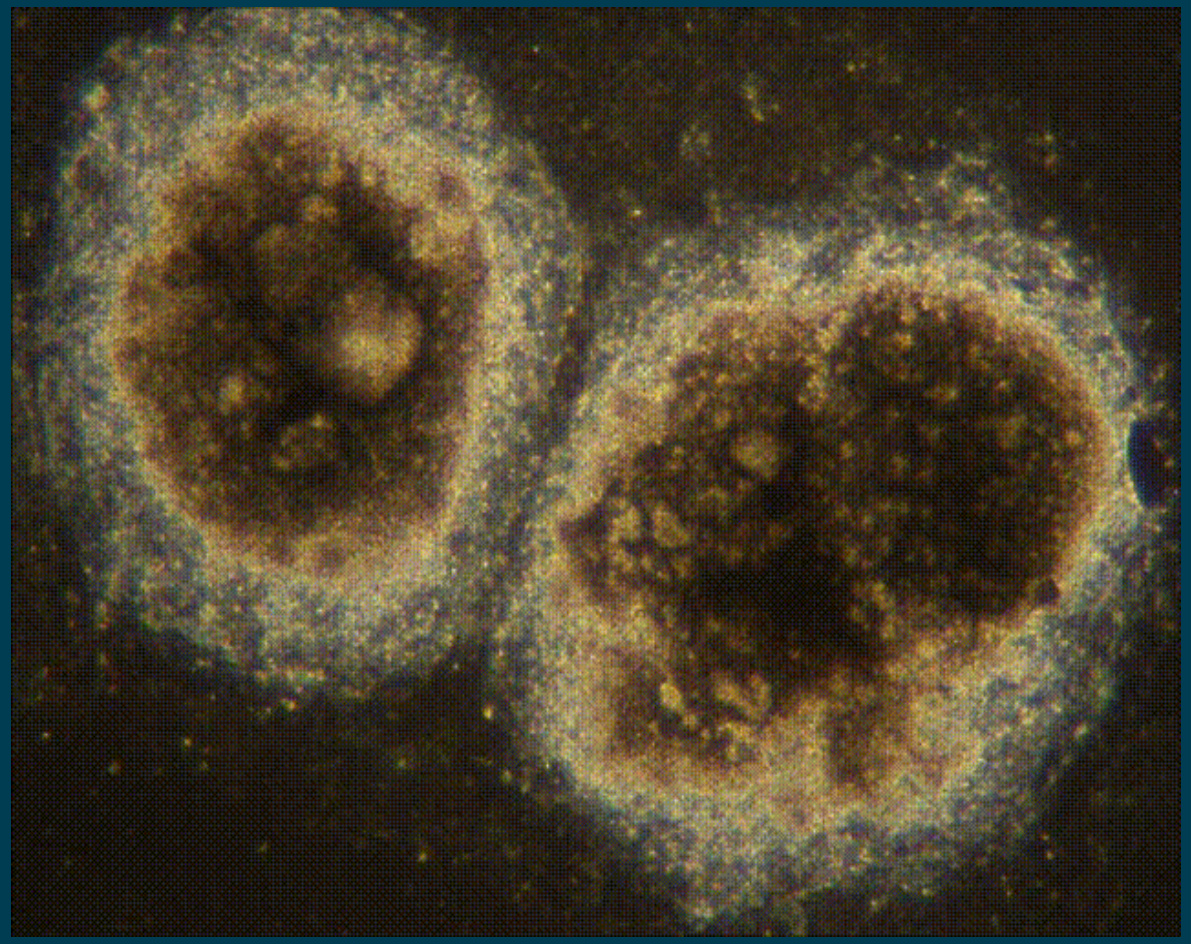
Control-iPSCs

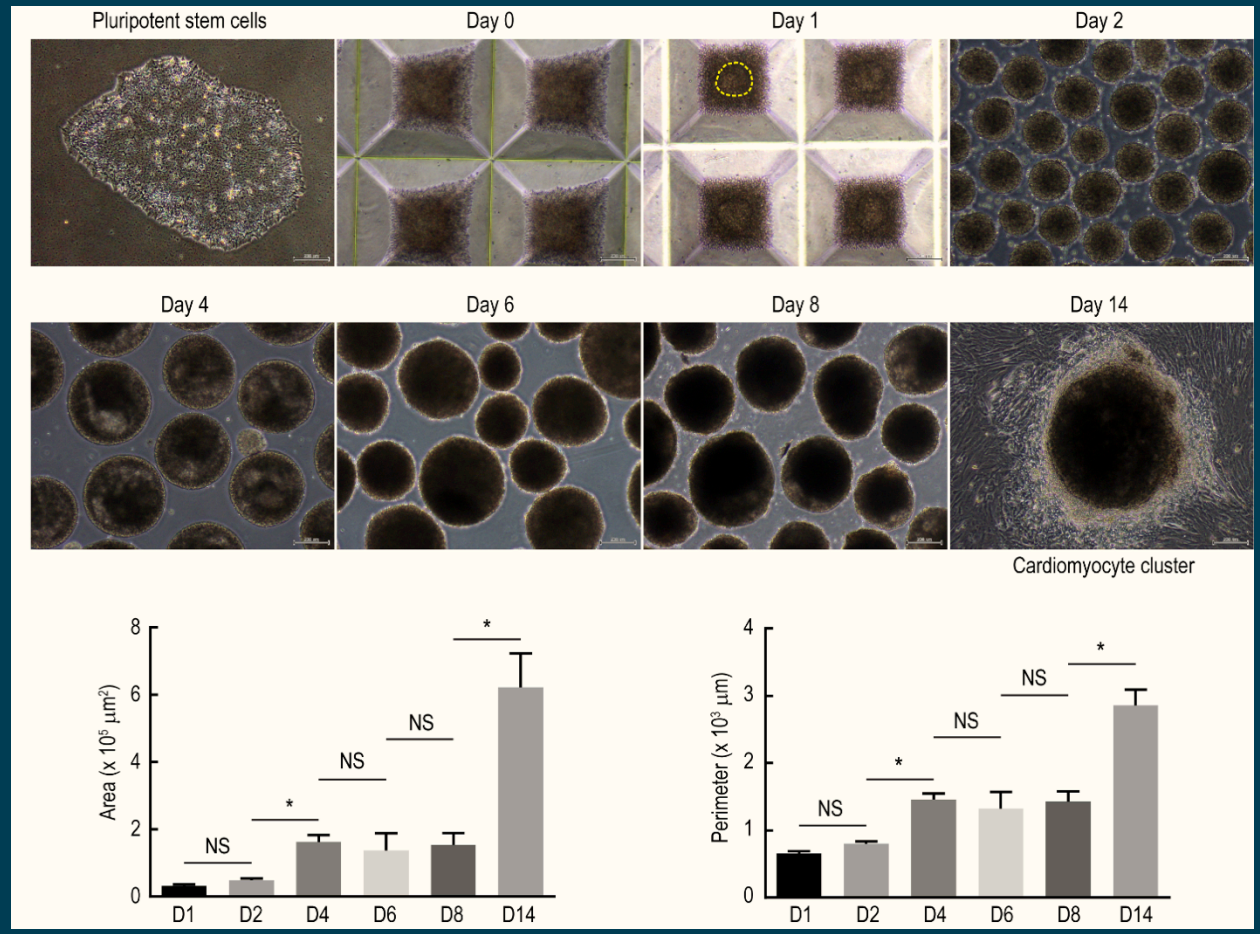


HCM-iPSCs

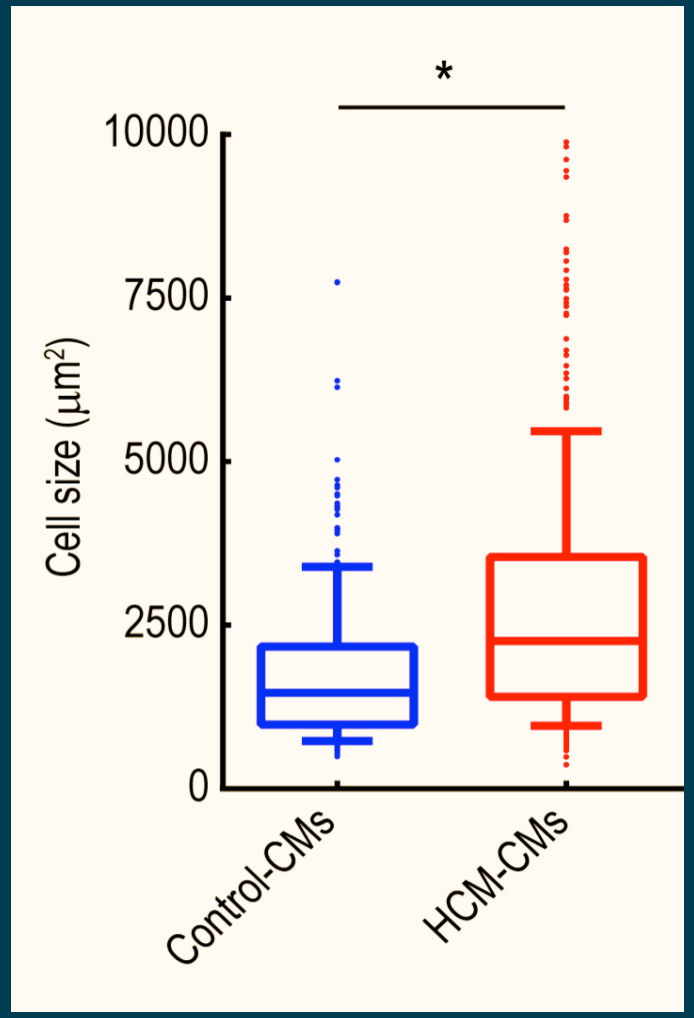


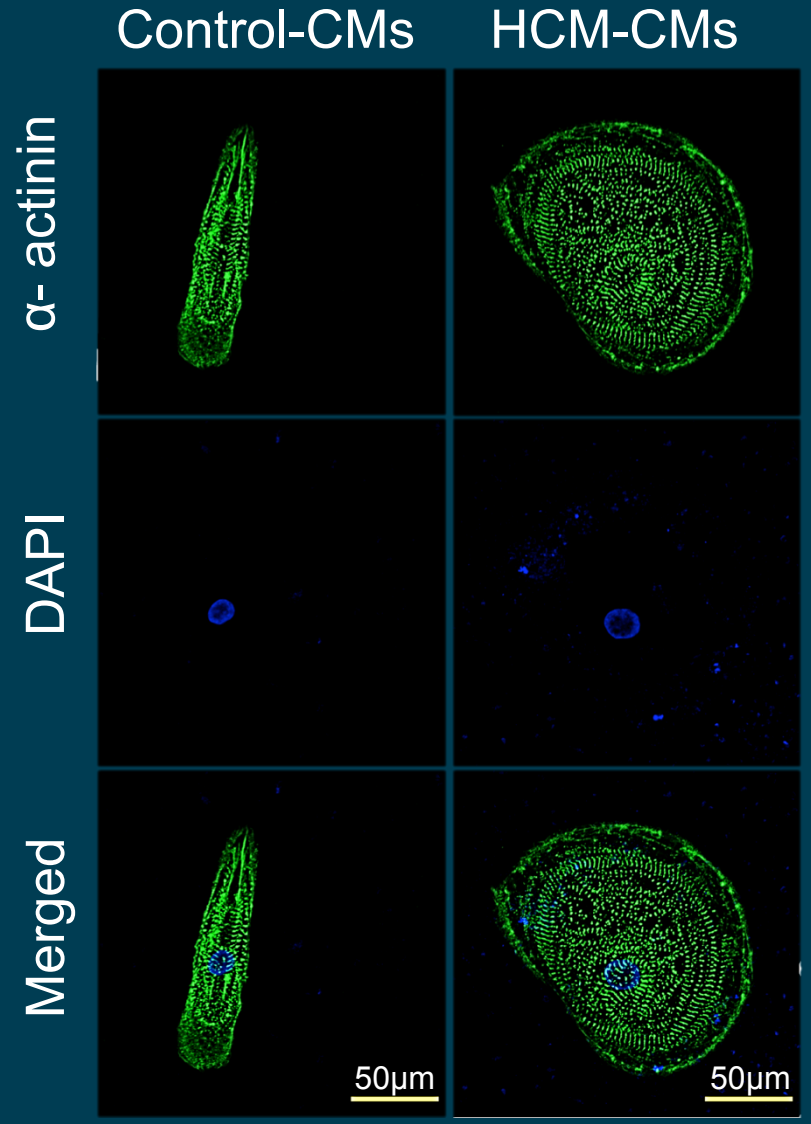
Cardiac Differentiation



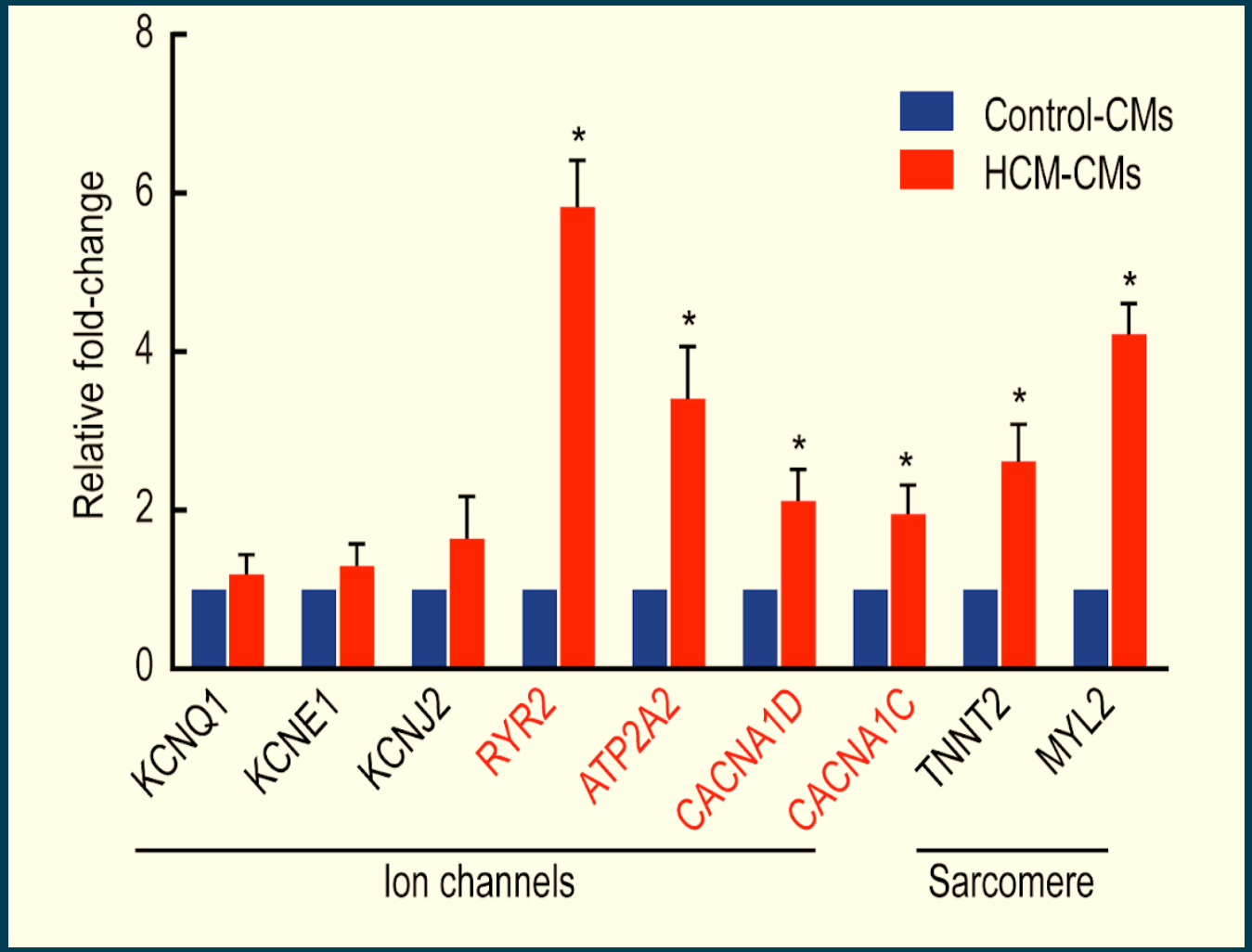


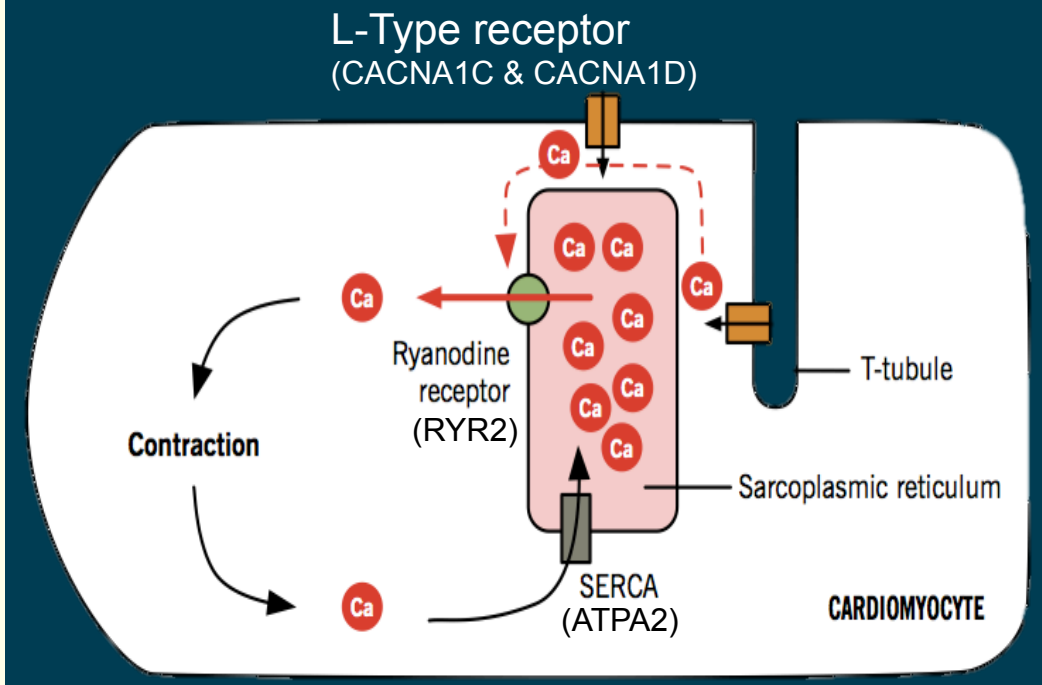
HCM-CMs Display Clinical Phenotypes



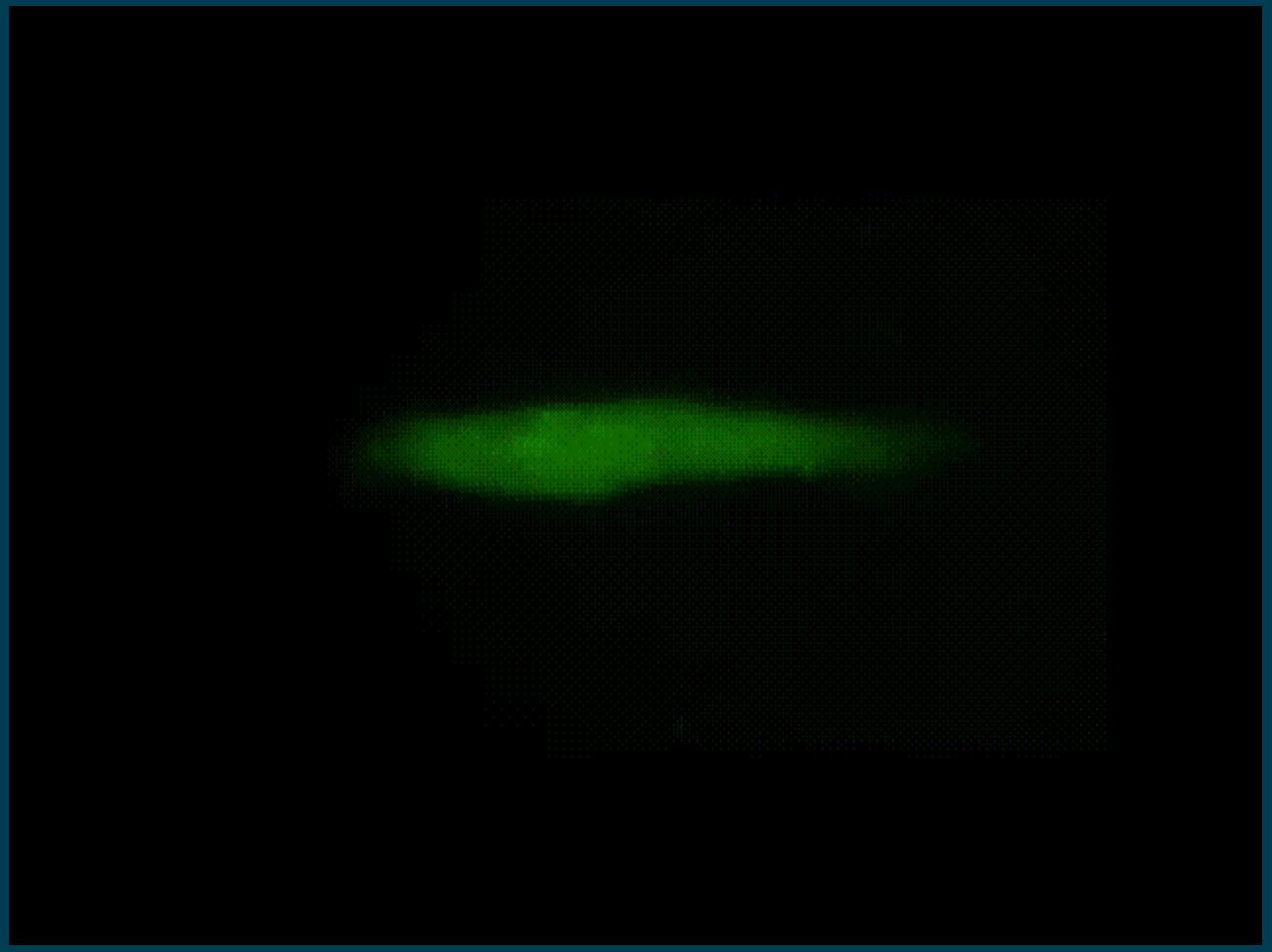


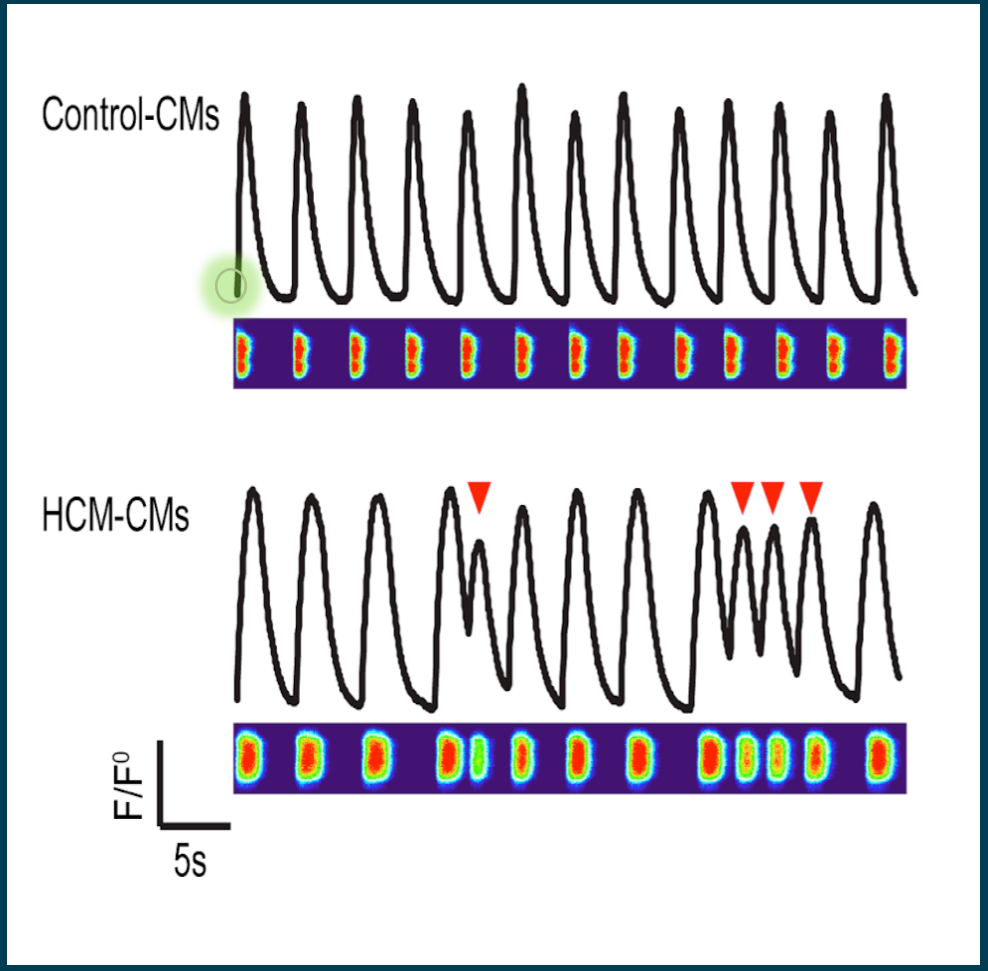
Gene Expression of Ion Channels



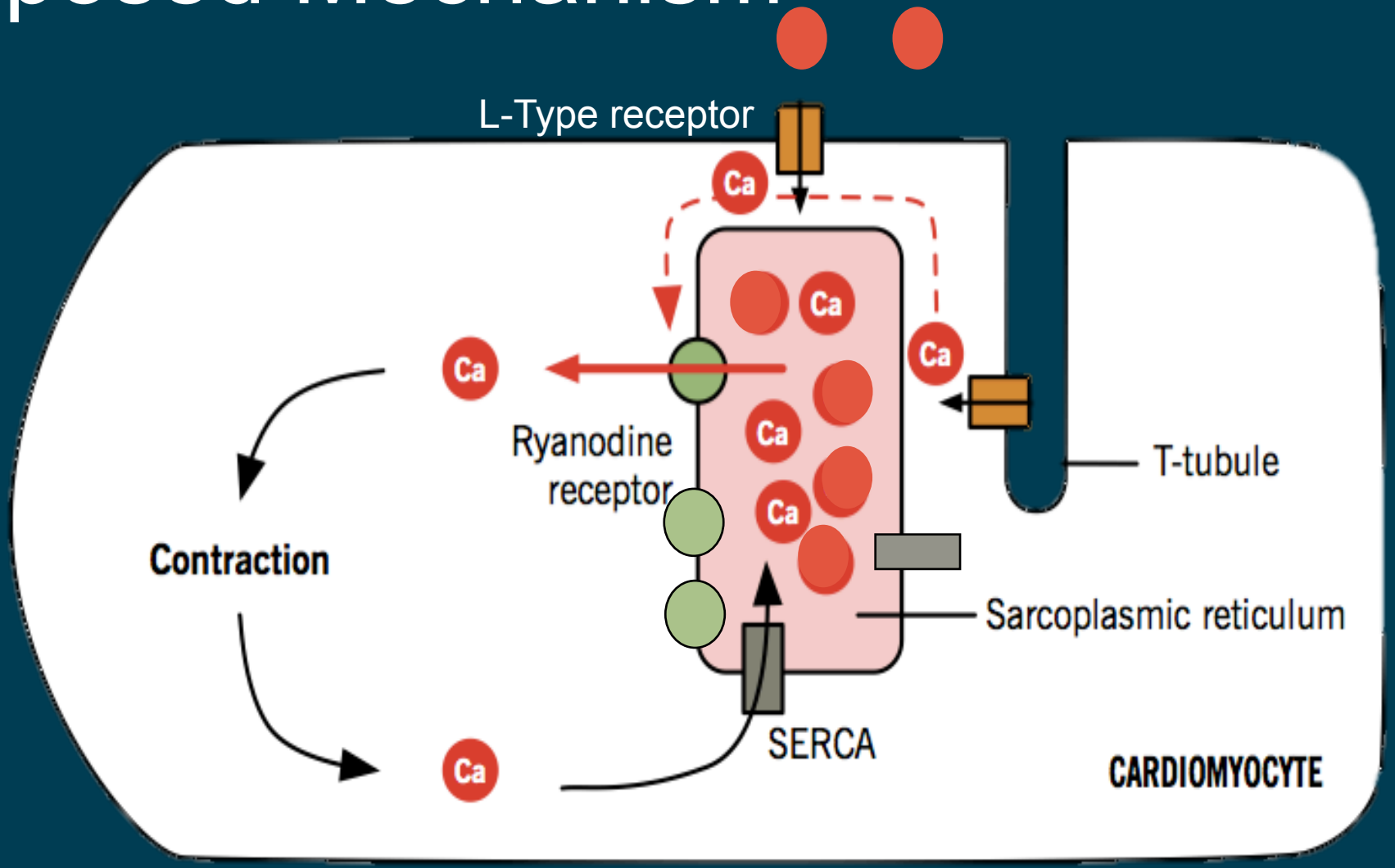


Calcium Imaging



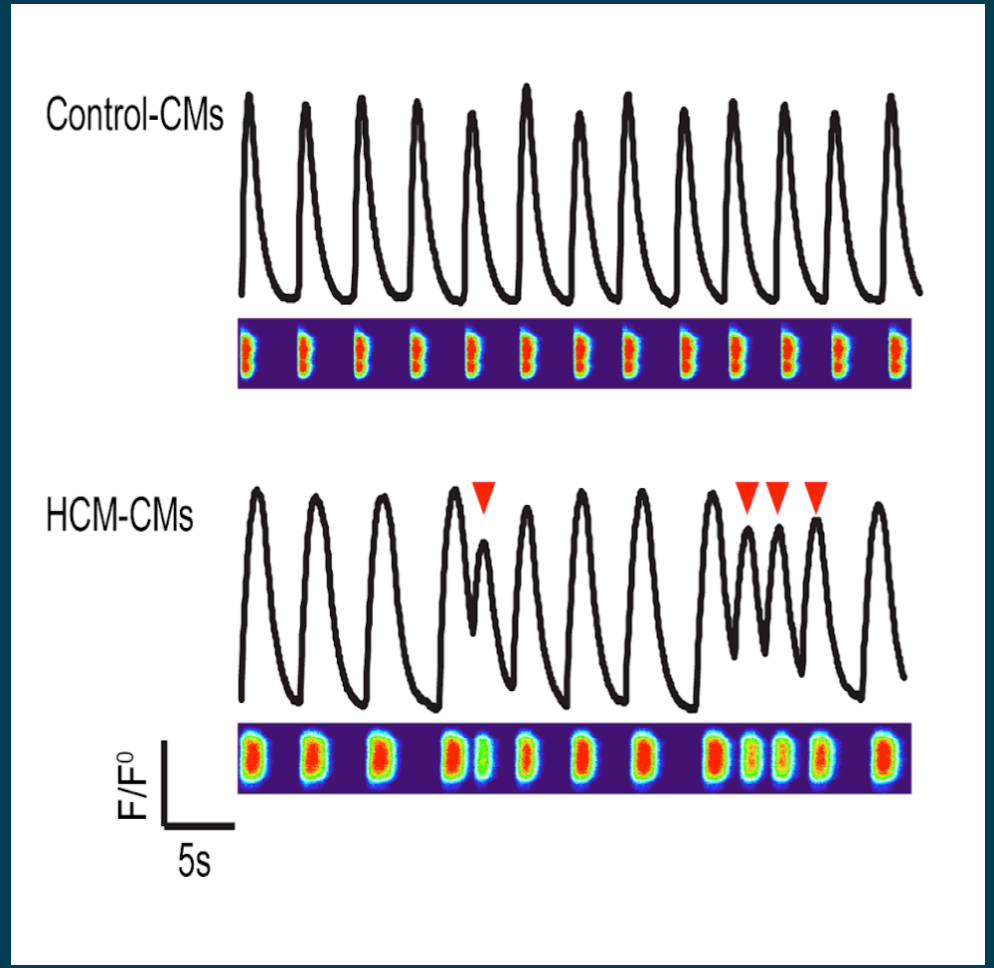


Proposed Mechanism



Proposed Mechanism

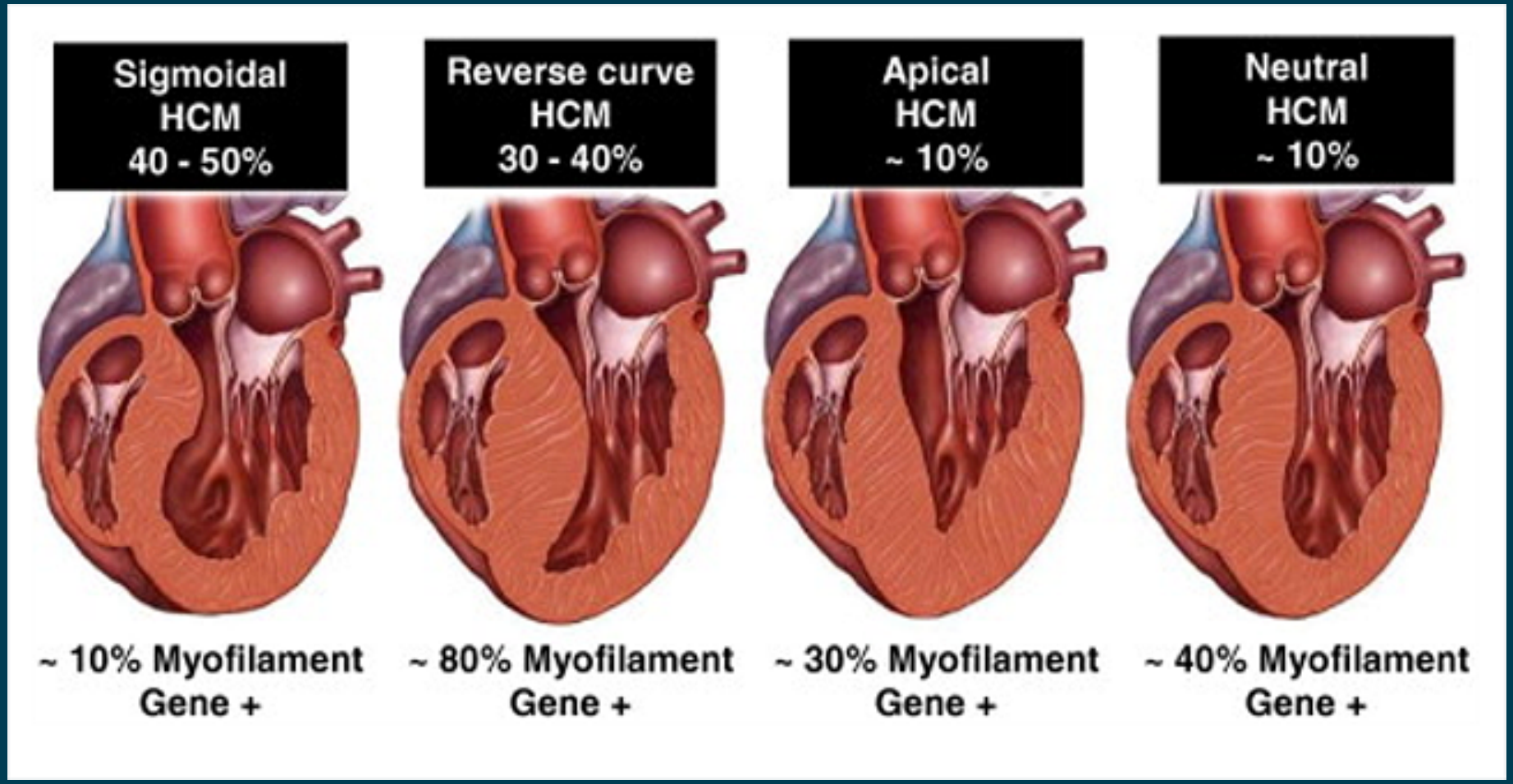
- Abnormal ratio of Ryanodine Receptors to SERCA
- Ryanodine Antagonists – Dantrolene
- Gene Knockdown/Knock-in
- Creation of a Multiscale Cardiac Model



Significance

- Generation of humanized HCM models
- Ethical, non-invasive, efficient (high throughput, long shelf-life)
- Potential for Personalized Medicine
- Findings provide foundation and direction for future research

Types of Hypertrophic Cardiomyopathy



Cardiac Differentiation

- iPSCs dispersed into small clumps via dispase
- Cells were aggregated in aggrewells (5000 cells/well), centrifuged and incubated overnight
- Cells were seeded on low attachment dishes on day 2
- Medium changed on day 4 and day 6
- Embryoid bodies plated on gelatin-coated dishes on day 8
- Beating areas observed between day 11-14
- Specific growth factors used: BMP4, FGF2 (Day 1-4), VEGF, IWP4 (day 4-8)