



University of Colorado
Anschutz Medical Campus

Leveraging Immune Cells to Heal a Damaged Heart

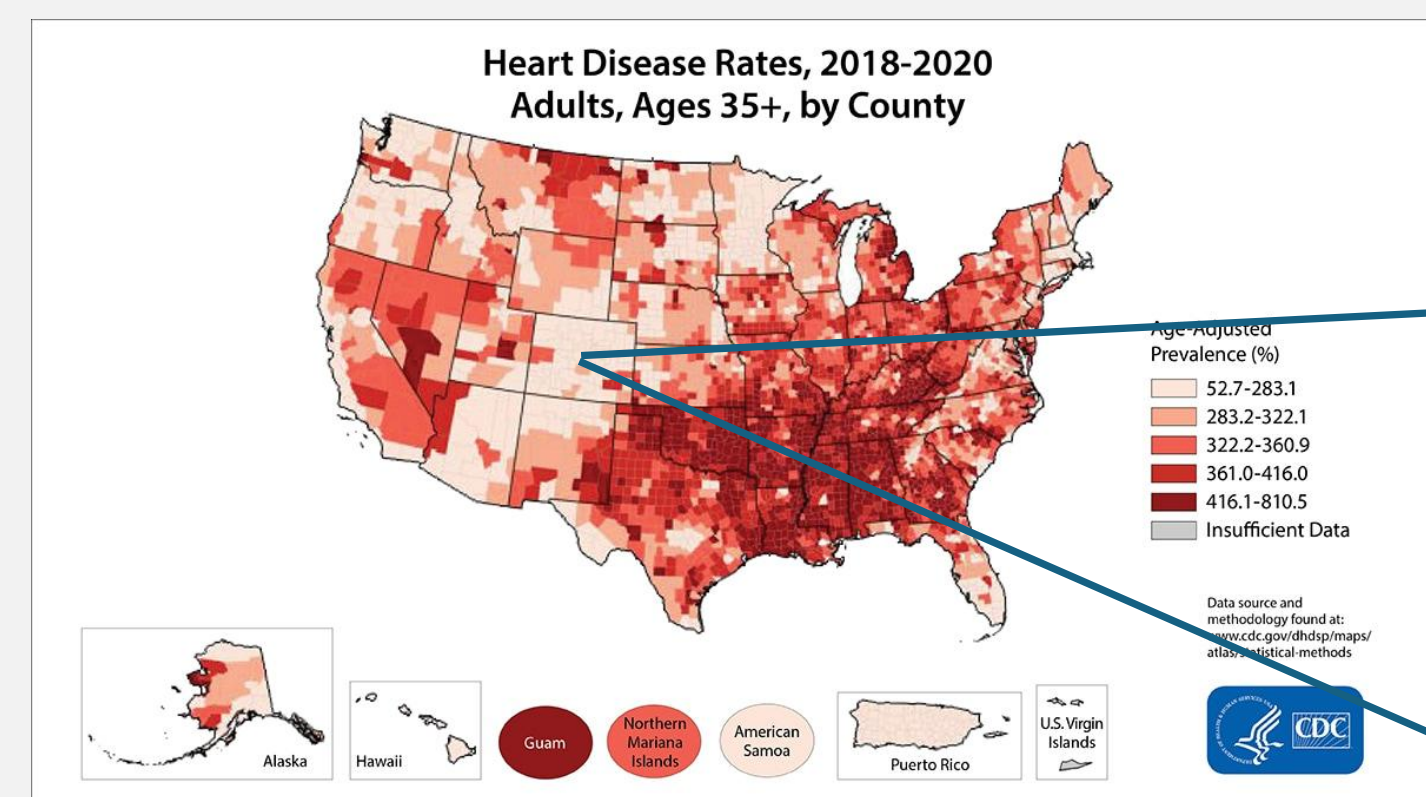
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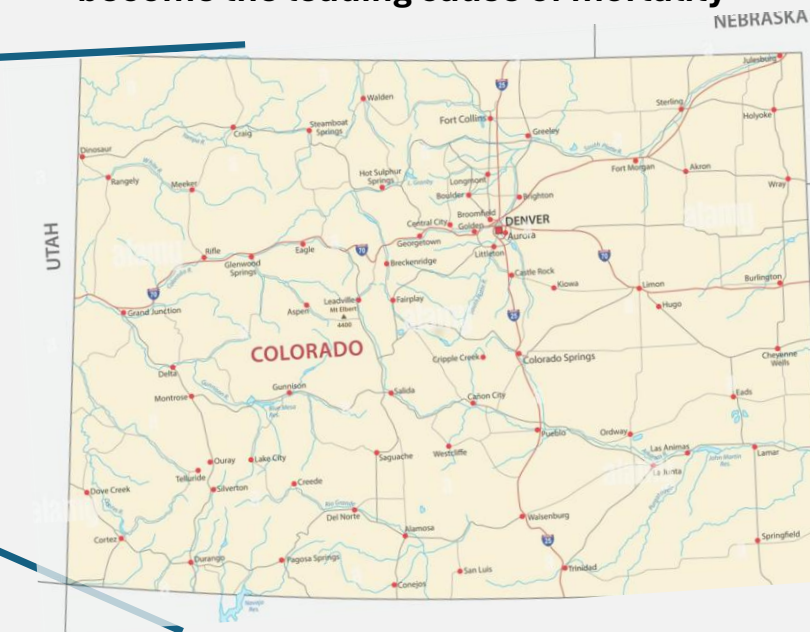
Why YOU Should Care about Cardiovascular Diseases

Heart Disease is the Leading Cause of Death within the USA



Leading Cause of Death in Colorado

- 131 per 100k incidence rate
- The leading cause of death from 1999-2021
- Surpassed Cancer in 2024 again to become the leading cause of mortality



Tissue Resident Macrophages Promote Heart Healing and Decrease Scarring After Heart Attack

HEART ATTACK

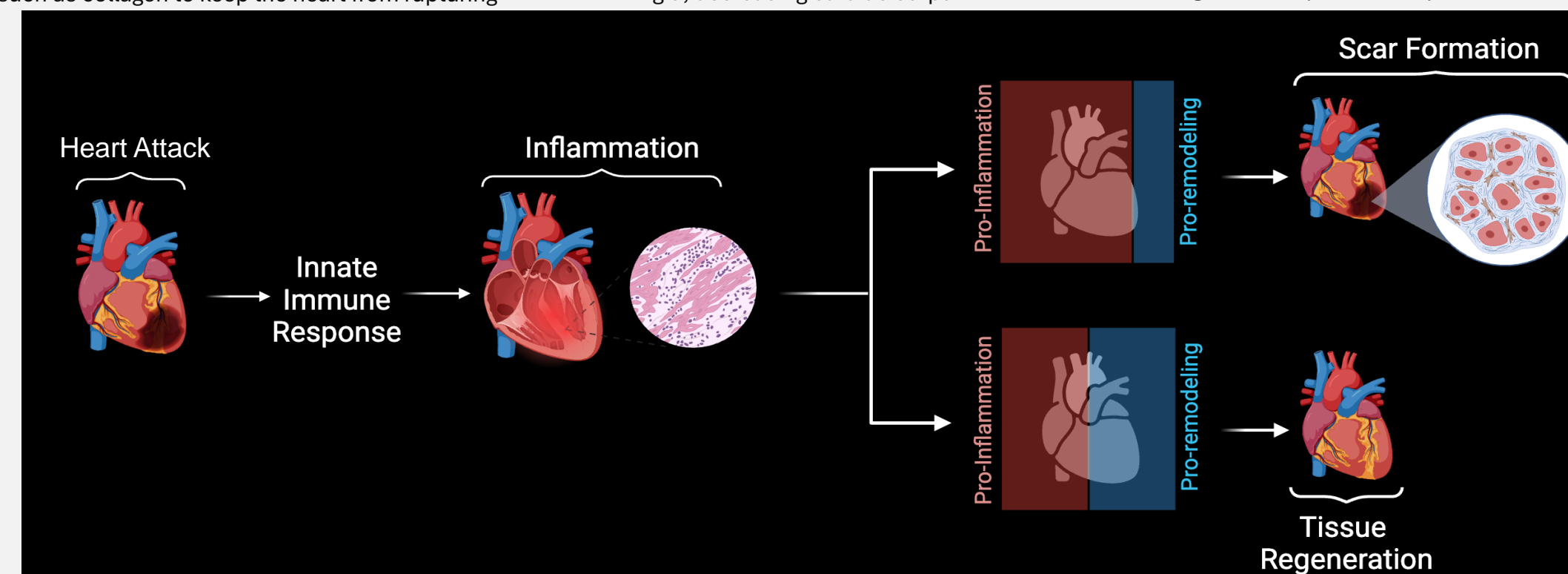
Following a Heart Attack, Immune Cells infiltrate the heart to clear out dead tissue and promote the deposition of proteins such as collagen to keep the heart from rupturing

Healing and Scarring

Too much Collagen deposition can lead to scar formation, making the heart more rigid; decreasing cardiac output

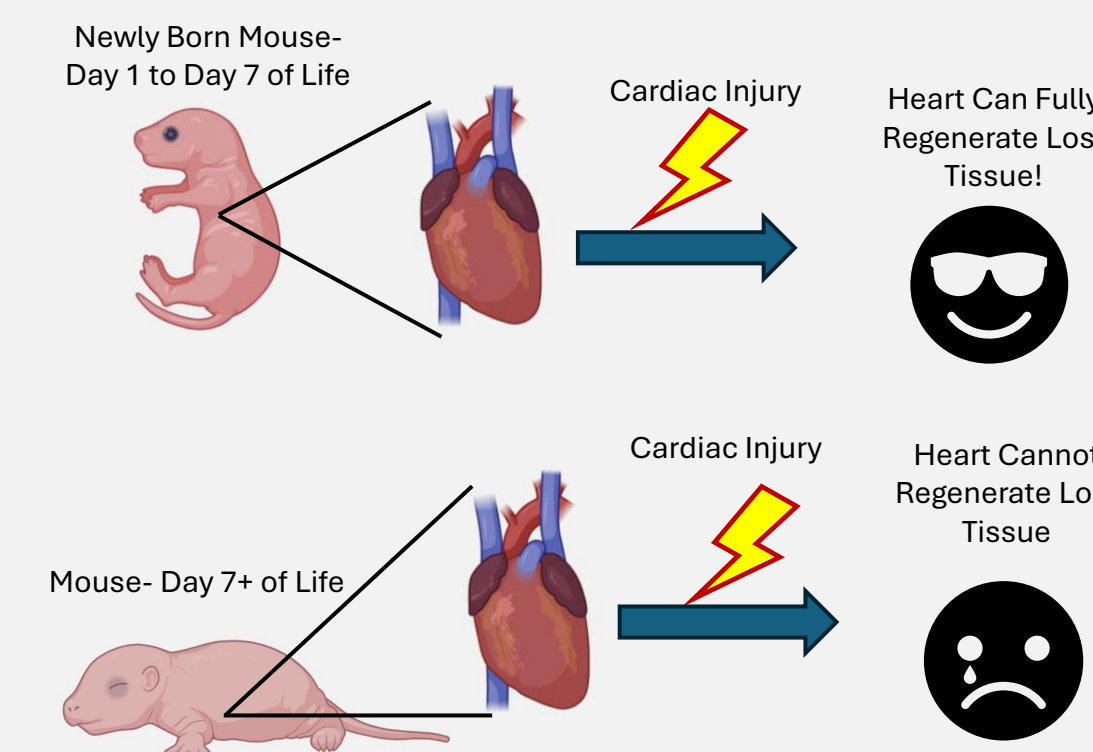
TRMs Can Prevent Harmful Scarring

TRMs promote less inflammation and heart regeneration, meaning these cells can be targeted to improve heart patient outcomes



Why Is My Work Important?

Knowing How TRMs Contribute to Early Heart Maturation May Unlock Therapeutic Targets to Regenerate Heart Tissue in Cardiovascular Disease Patients

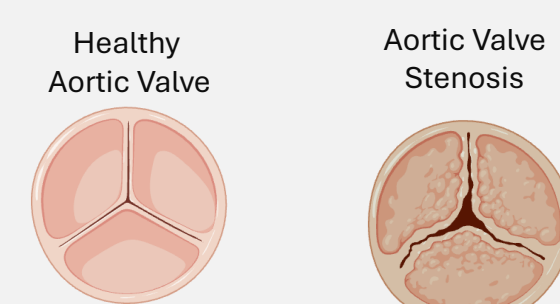


1. Add to previous research showing TRMs may play a role in both the maintenance and loss of this regenerative capacity
2. My work may reveal targets to make heart cells or TRMs more like those early days of life, allowing for heart tissue regeneration in CVD patients.
3. My work could uncover novel targets to reduce the severity of scarring in the hearts of CVD patients

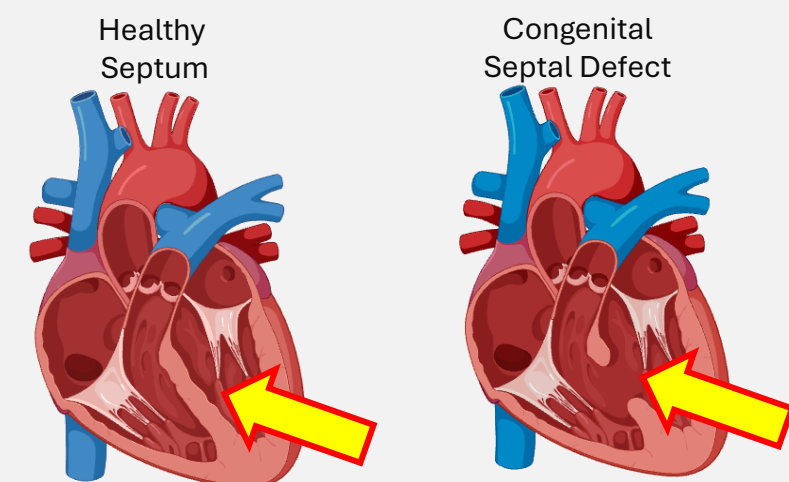
What is Cardiovascular Disease?

Cardiovascular Diseases encompass diseases that effect the heart and blood vessels

Valve Disorders

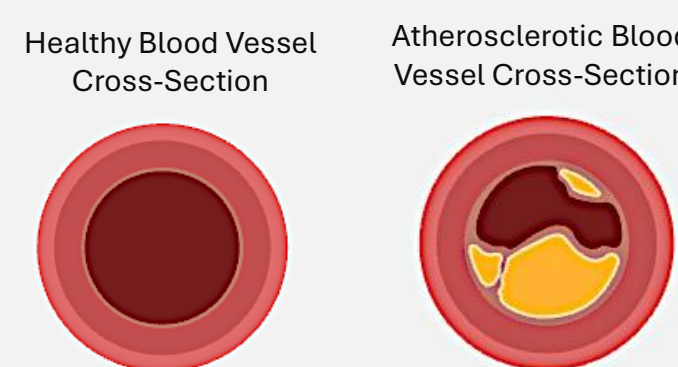


Congenital Disorders



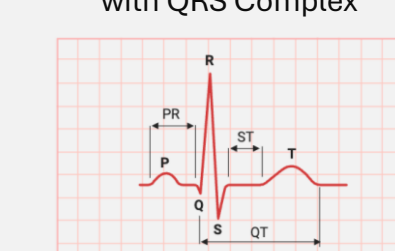
These Diseases Include

Narrowing of the Blood Vessels



Heart Rhythm Disorders

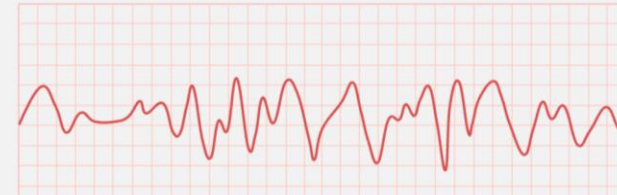
Healthy Heart ECG Reading with QRS Complex



Atrial Fibrillation ECG



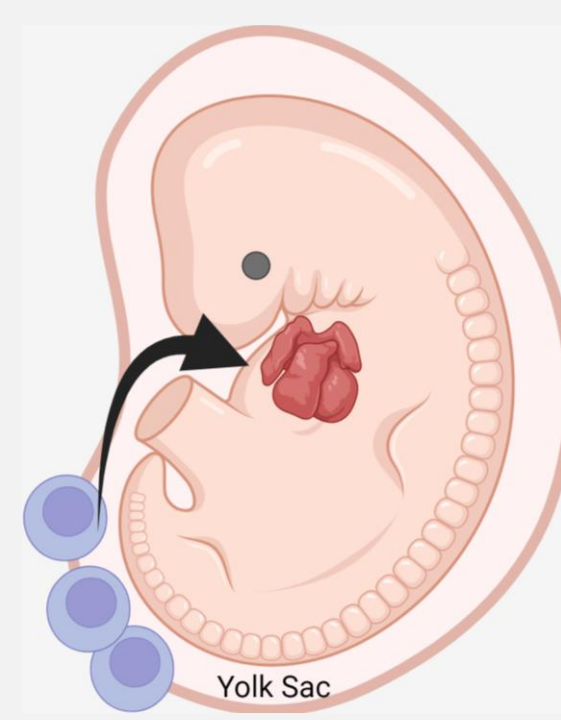
Ventricular Fibrillation ECG



What are Tissue Resident Macrophages (TRMs)?

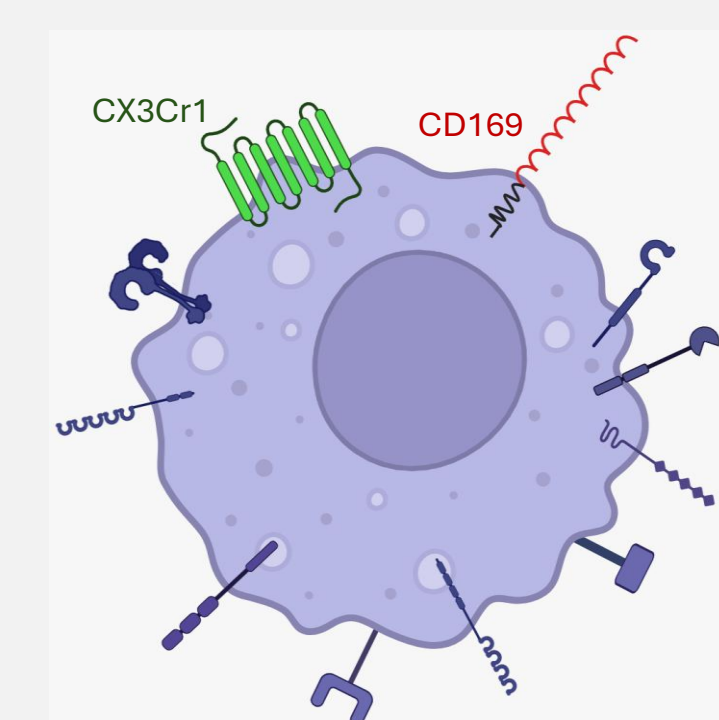
Origin

Unlike most other immune cells, often starting in bone marrow, Tissue Resident Macrophages Originate from the Egg Yolk early in development



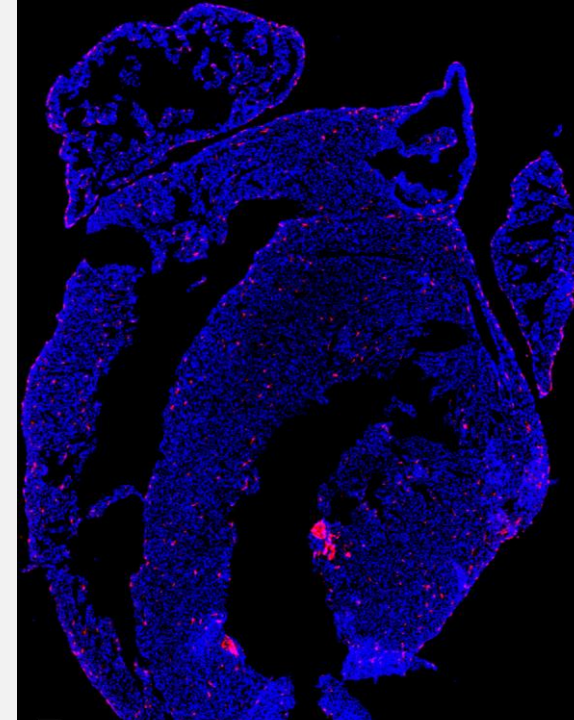
Characteristics

The main way immunologists have defined immune cells is by tying the function of the cell to the proteins it expresses in its cell membrane. Two of these proteins unique to TRMs in the heart are CX3CR1 and CD169



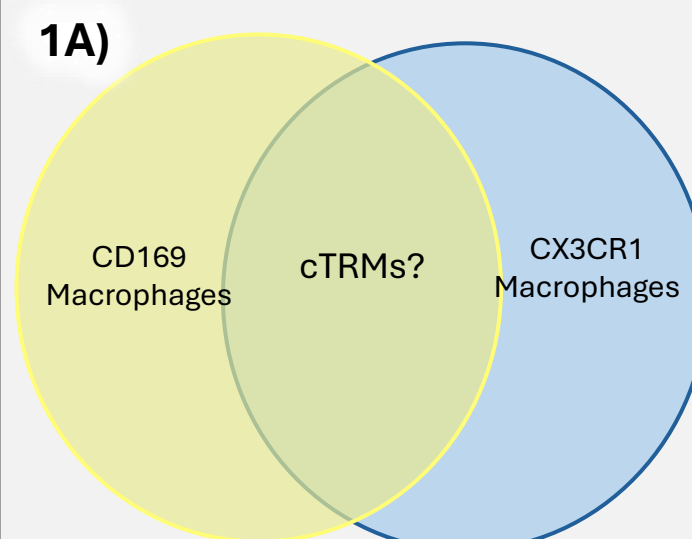
Important for the Heart!

These immune cells are important for the heart's development, maturation, maintenance, and healing after injury. Newborns' hearts can fully regenerate heart tissue after injury, with these immune cells likely contributing to this capacity



My Research Approach

Are Cells That Express My Proteins of Interest Actually Tissue Resident Macrophages?

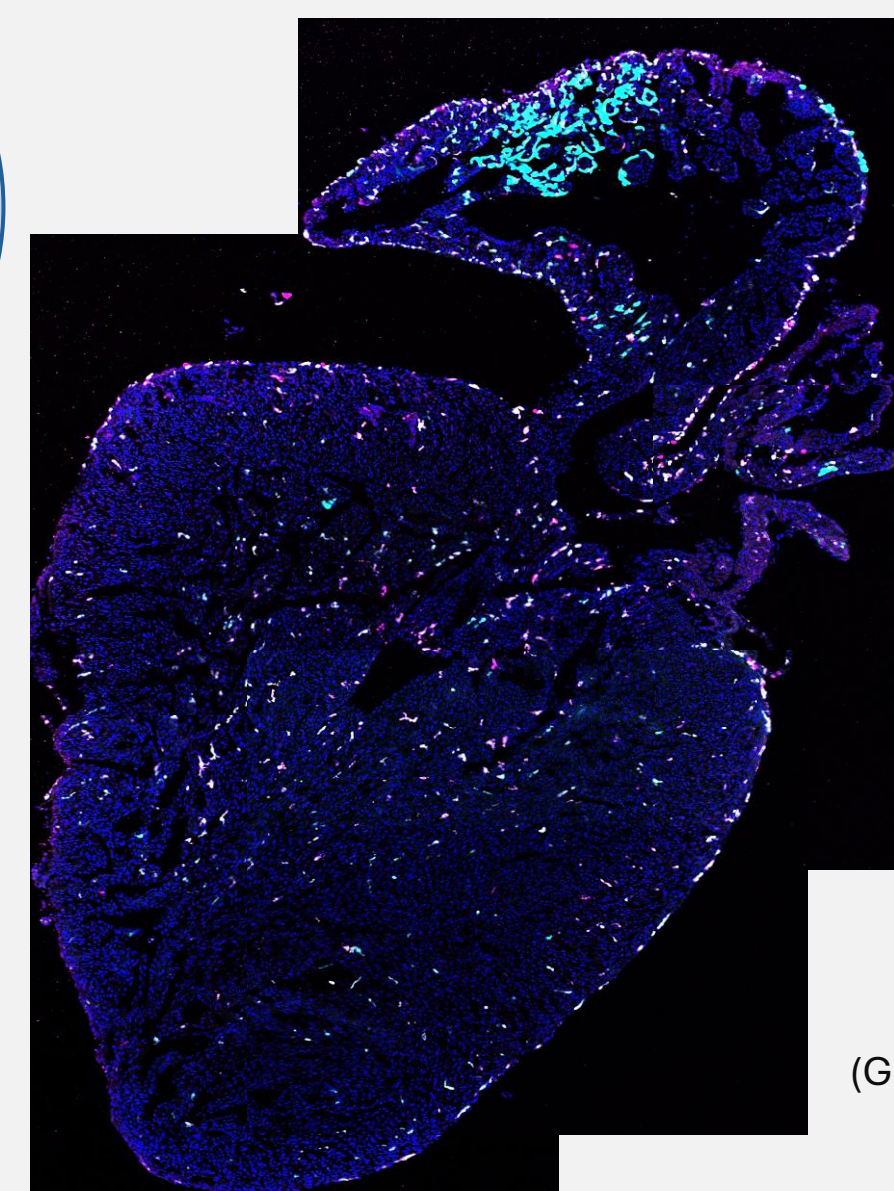


1B) P1 Neonatal Mouse Heart

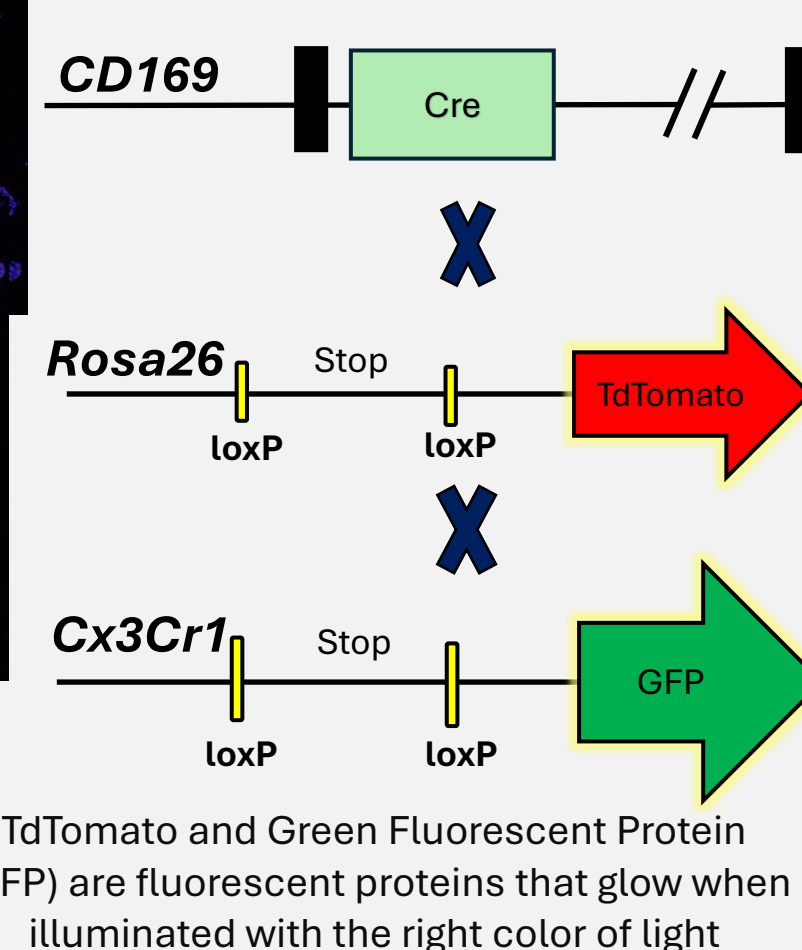
Nucleus of All Cells

CD169 Expressing Cells

CX3CR1 Expressing Cells

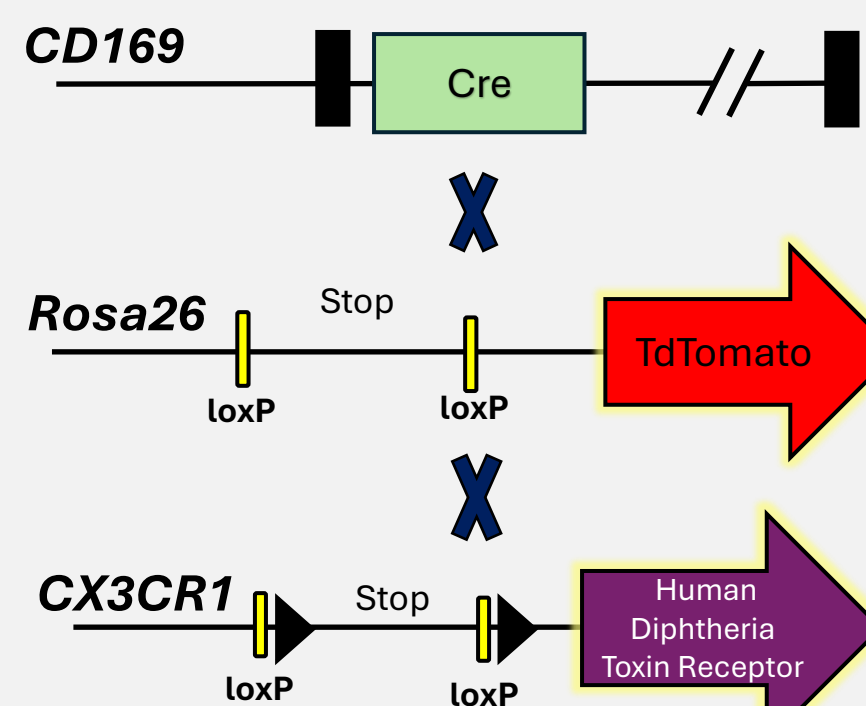


1C) Transgenes Driving Cell Reporters

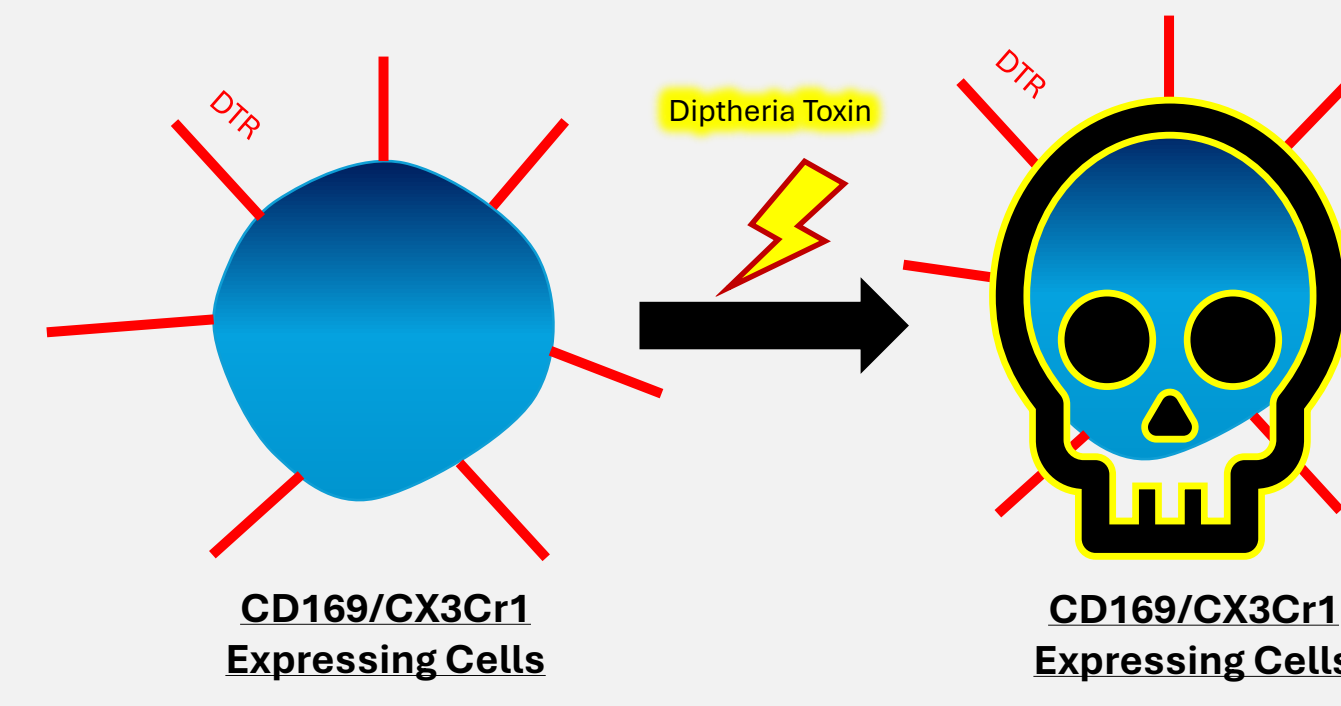


What Role and How Do These Immune Cells Contribute to the Heart's Maturation?

2A) Transgenes Driving Human Diphtheria Toxin Receptor Expression



2B) Injection of Diphtheria Toxin at the right dose should only kill cells that express my proteins of interest



Readouts for Diphtheria Toxin Cell Ablation

After Diphtheria Toxin kills my cells of interest, there should be changes in how the remaining cells in the heart grow and mature during that early newborn window of time where heart regenerative capacity is highest.

Readouts for analysis will include—

- Depletion of TRMs- How many cells remain that show up as red?
- Vascular Density- The ratio of blood vessels to heart cells
- Cardiomyocyte Area- Muscle cell size
- Cardiomyocyte Cell Cycling- Are muscle cells dividing and making more of themselves?
- Fibroblast Dynamics- Are more cells depositing collagen leading to heart stiffness?
- Cell Signaling Alteration- What signals that the cells send each other differ? Are those different signals something we can target therapeutically in disease models?

Key Takeaways

- Cardiovascular Disease (CVD) is the leading cause of mortality in the US and the state of Colorado.
- CVD patients are at higher risks of heart attacks.
- Heart tissue following a heart attack does not regenerate, instead being replaced by depositions of proteins called collagen, leading to fibrosis (aka scarring).
- There is a unique set of immune cells within the heart called tissue resident macrophages that play a pro-reparative role in the heart.
- TRMs may contribute to early regenerative capacity in the heart.
- Studying TRMs in the early maturing heart may lead to therapeutic targets to improve CVD patient outcomes.

Acknowledgements

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