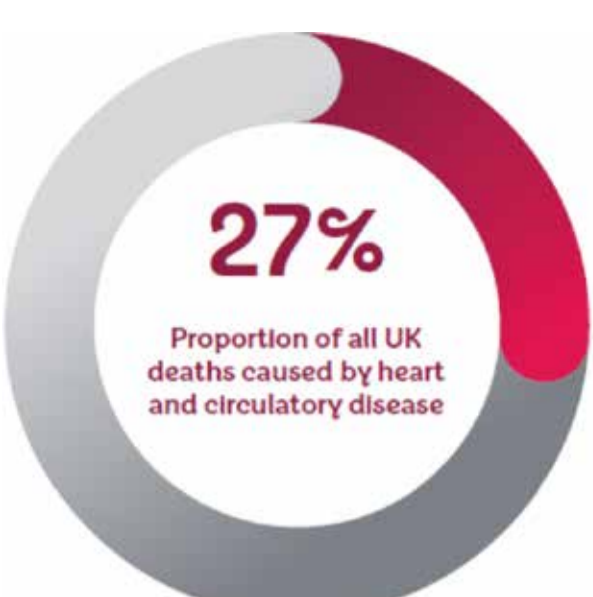


INVESTIGATING THE MOLECULAR AND CELLULAR BASIS OF ZEBRAFISH HEART REGENERATION

Chloe E. Tubman^{1,2,3}, Filipa C. Simões^{1,2,3}, Tatjana Sauka-Spengler^{2,4} and Paul R. Riley^{1,3}

¹Department of Physiology, Anatomy and Genetics, University of Oxford, UK ; ²MRC Weatherall Institute of Molecular Medicine, University of Oxford, UK ;

³Institute of Developmental and Regenerative Medicine, University of Oxford, UK ; ⁴Stowers Institute, Kansas City, USA



Every 5 minutes someone is admitted to a UK hospital due to a heart attack

7 out of 10 Survival rate for heart attacks in the UK today

The total annual healthcare cost of heart and circulatory diseases in the UK is around

£10 BILLION

Approximately 1.4 million people alive in the UK today have survived a heart attack – around 1 M men and 380 K women

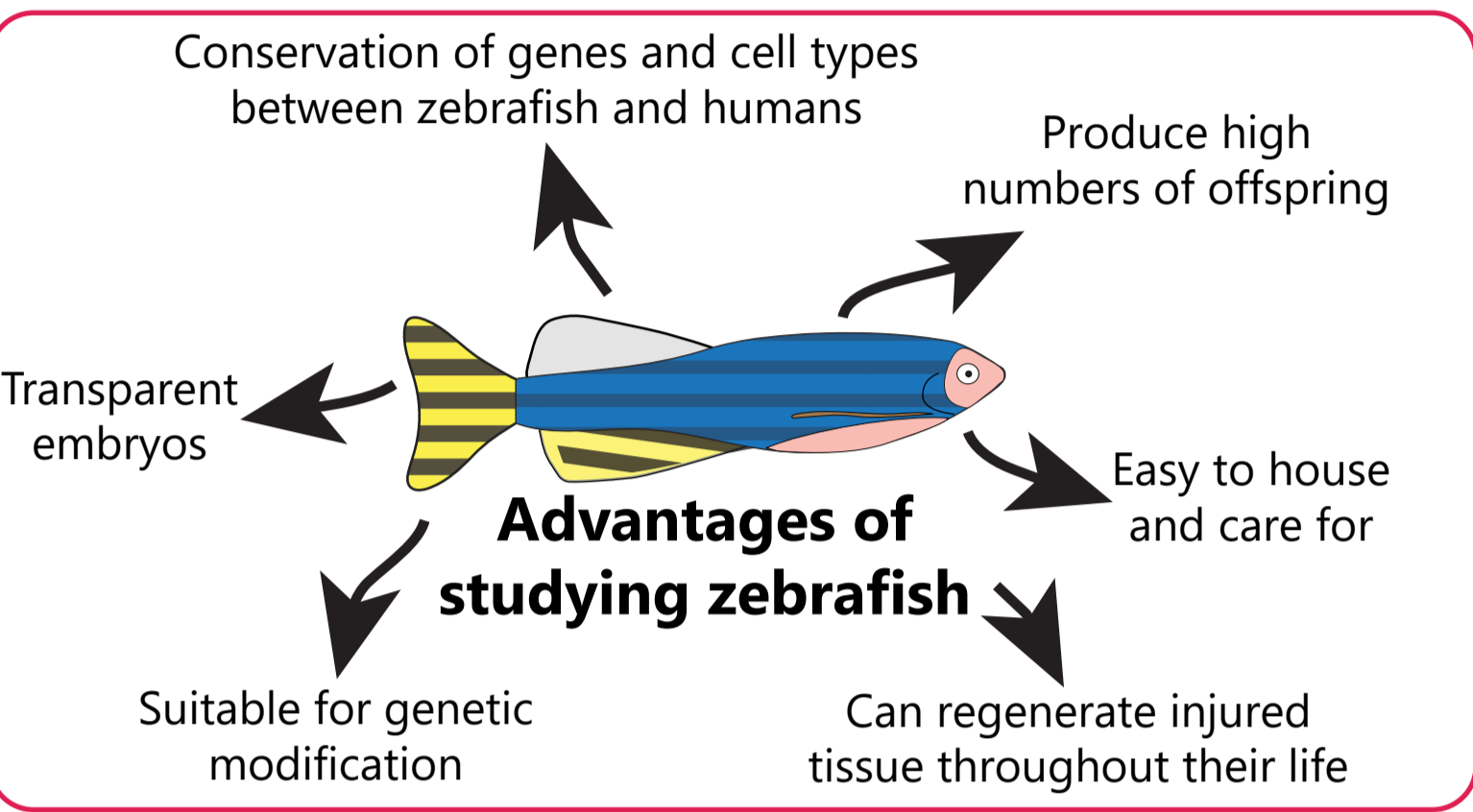
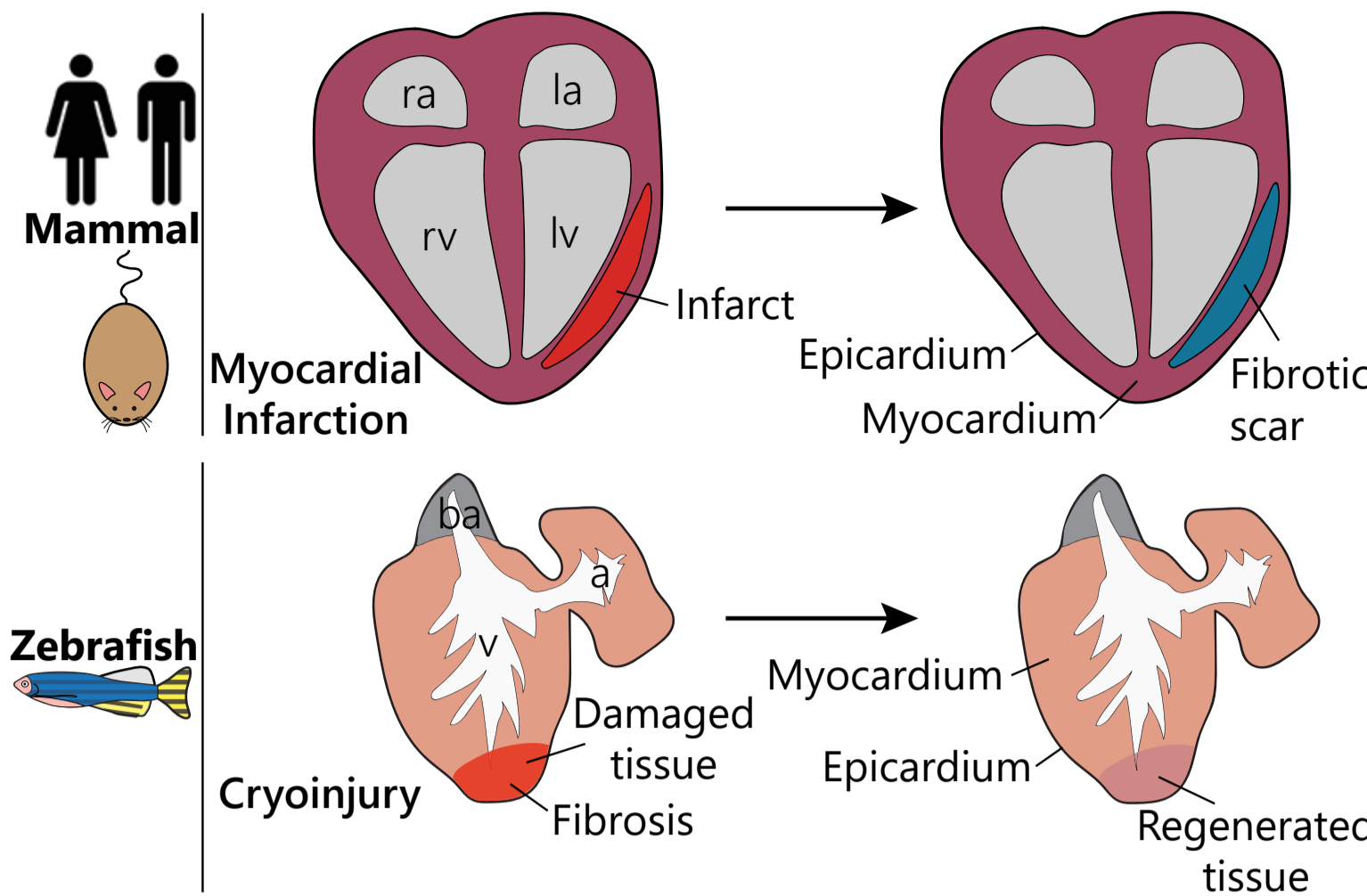
British Heart Foundation 2023

Heart Attack (Myocardial Infarction)

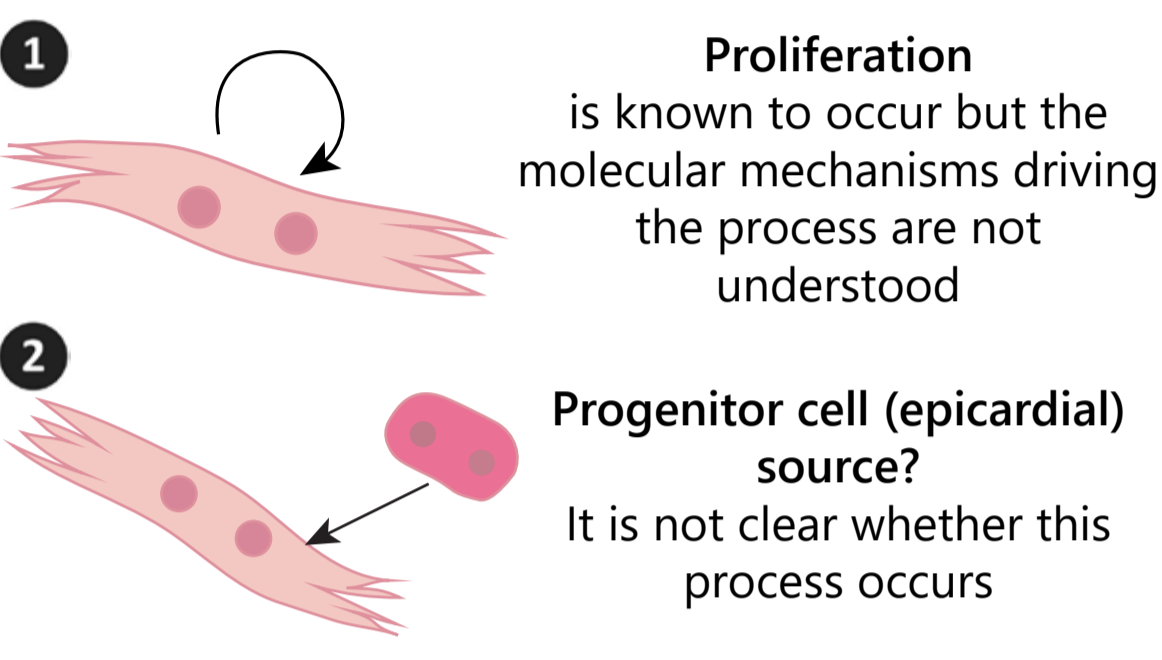
- Blockage of the coronary artery blood flow to heart muscle
- Loss of up to 1/4 of all heart muscle cells (~1 billion)
- Dead cells are irreversibly replaced by a non-functional scar
- Risk of heart failure

- Current treatments for heart failure are not curative
- The only cure is heart transplantation
- Low donor organ availability and toxic immune-suppressive drugs shorten life-expectancy

Can we stimulate endogenous heart muscle repair through regenerative therapy?

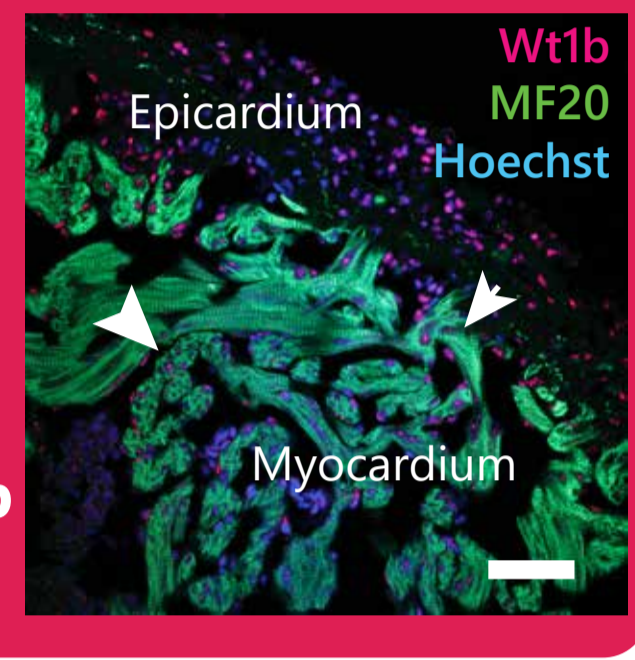


How do zebrafish regenerate heart muscle cells?



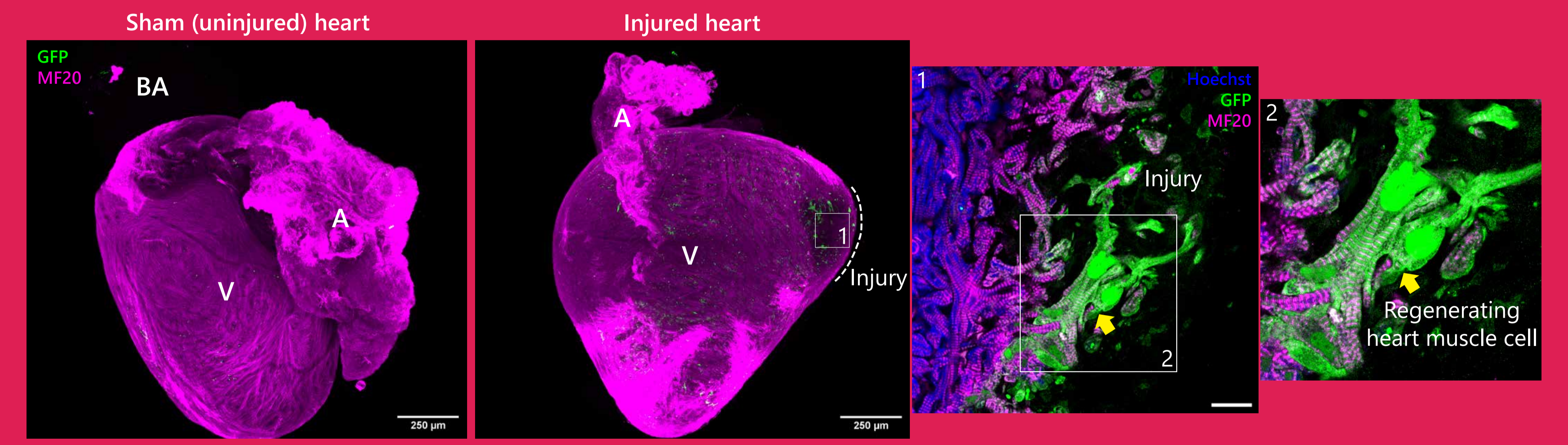
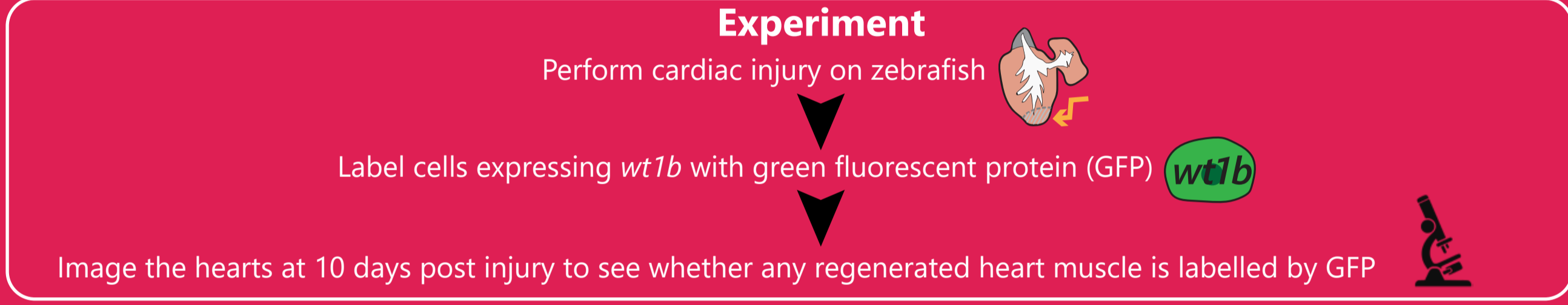
Following the gene *wt1b* to understand heart muscle regeneration

- *Wt1b* is expressed in the epicardium (outer layer of the heart)
- *Wt1b* is not known to function in heart muscle cells
- This image shows *wt1b* expression in the epicardium and regenerating heart muscle in an injured zebrafish heart



What is the function of *Wt1b* in the regenerating heart?

Question 1: Do *wt1b*⁺ cells contribute to heart muscle regeneration?

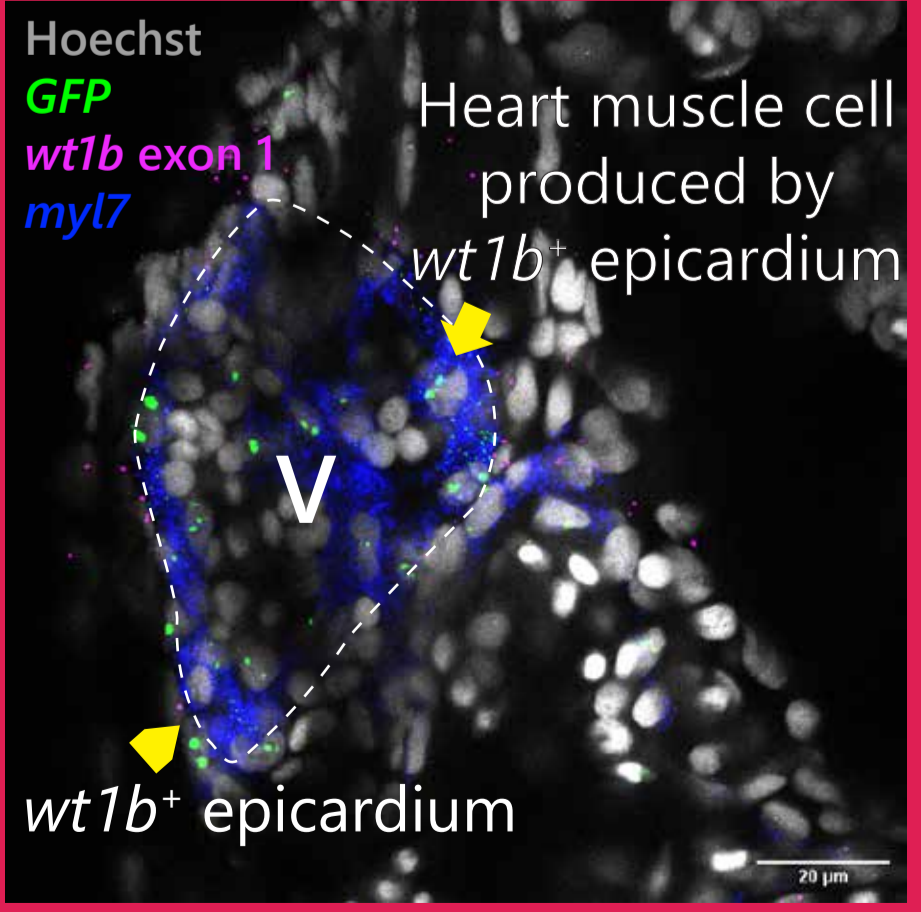
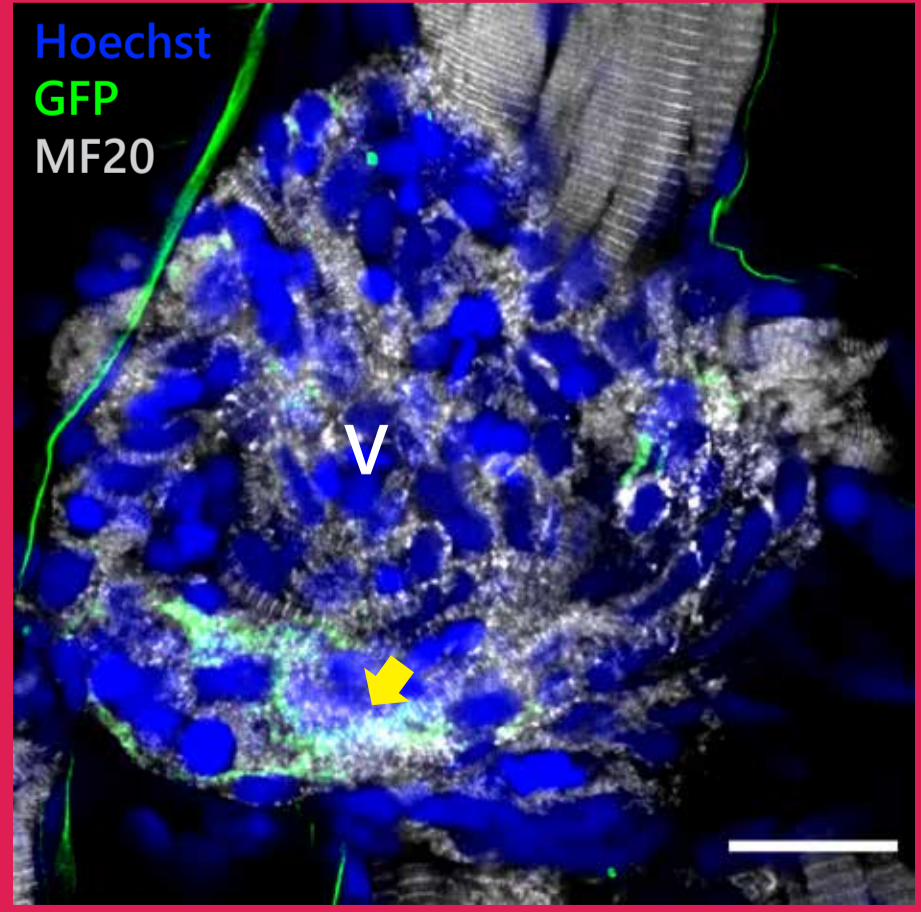
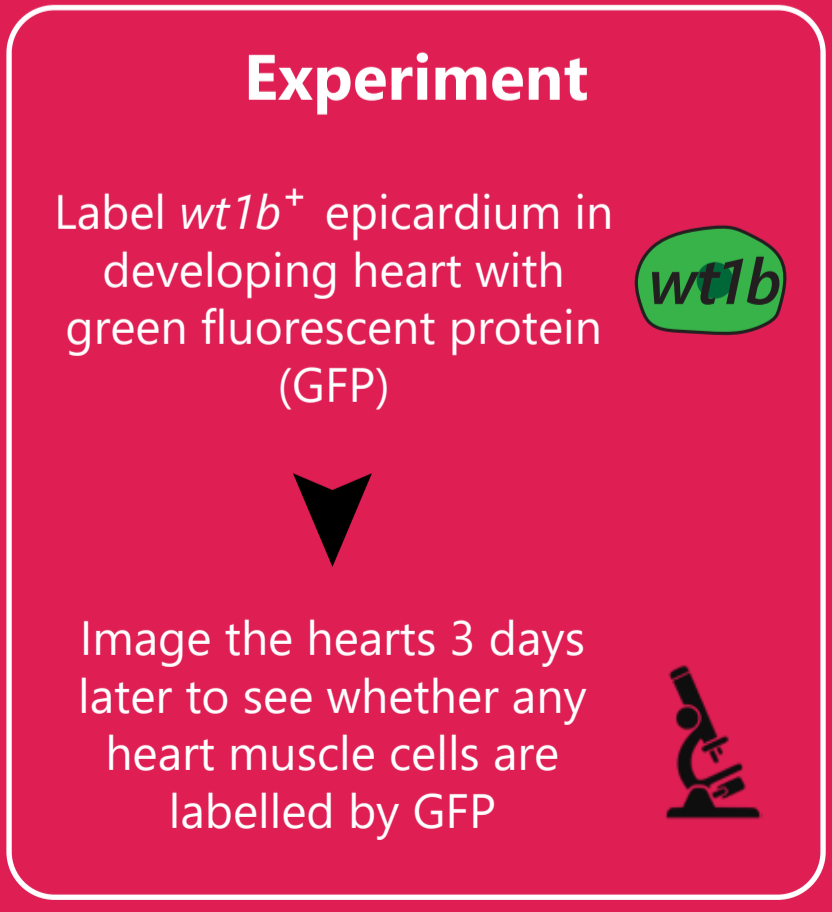


Conclusion: *wt1b*⁺ cells contribute to heart muscle regeneration

Question 2:

Is the *wt1b*⁺ epicardium a progenitor source of heart muscle?
And/Or
Does *Wt1b* play a role in existing heart muscle proliferation?

Developing zebrafish heart



Conclusion: The *wt1b*⁺ epicardium is a progenitor source of heart muscle in development

Conclusions

- First demonstration that the *wt1b*⁺ epicardium is a progenitor source of heart muscle in development
- *wt1b*⁺ cells contribute to heart muscle regeneration

Next step
Determine the molecular mechanism driving the production of new heart muscle from *wt1b*⁺ progenitors in the regenerating heart

Implication
Potential therapeutic target to stimulate heart muscle regeneration in human patients following a heart attack