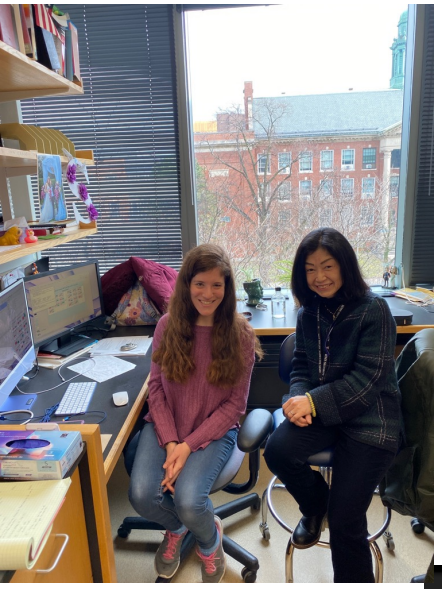
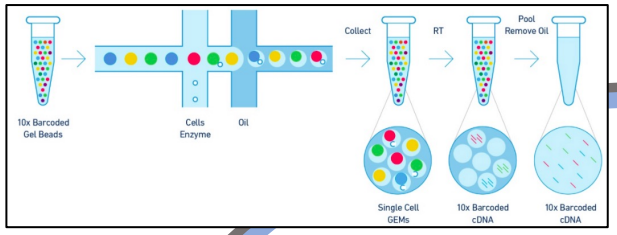
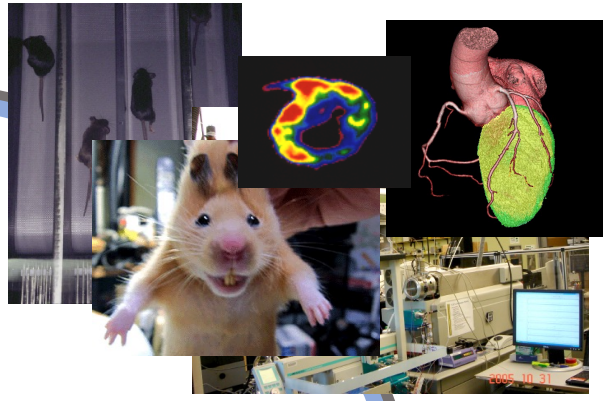
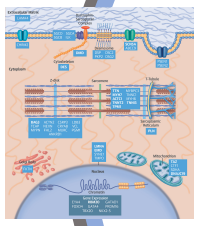


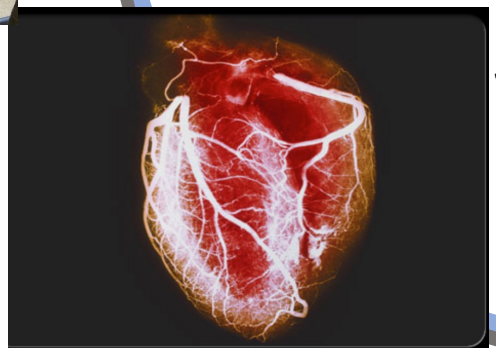


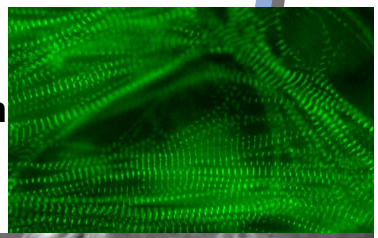


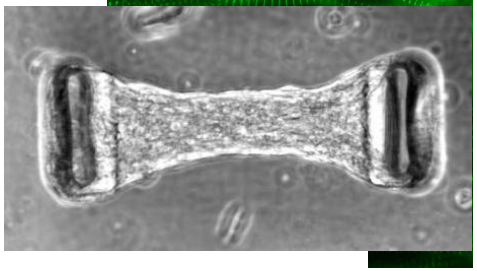
Single Nuclear RNA Sequence



snRNAseq Analyses of Human and Mouse FXN Tissues







Hiroko Wakimoto
Syndi Barish
Mingyue Lun

Jon and Christine Seidman
FAA Leadership Meeting
April 2, 2024

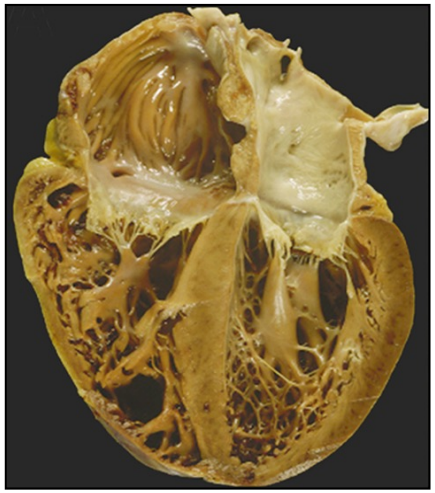
Disclosures: Consultant, Maze Therapeutics, Founder, Myokardia (a Bristol-Myers-Squibb Subsidiary), Board of Directors, Merck* and Burroughs Wellcome Fund* (*CES)

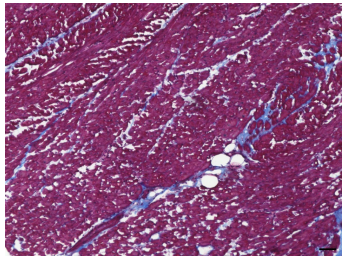
Dilated (DCM) and FXN Cardiomyopathies

Enlarged LV Chamber
Reduced Contractile Performance
Increased Myocardial Fibrosis
Propel Heart Failure
Most Common Cause for Cardiac Tx

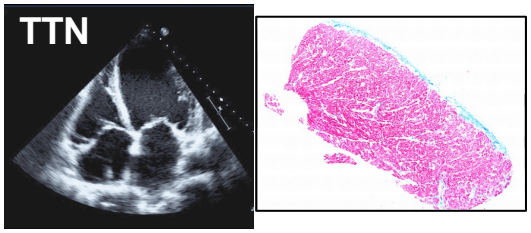
↓

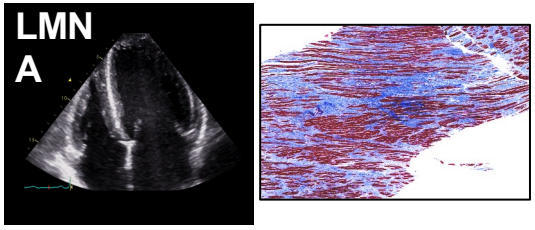
Common Final Pathway

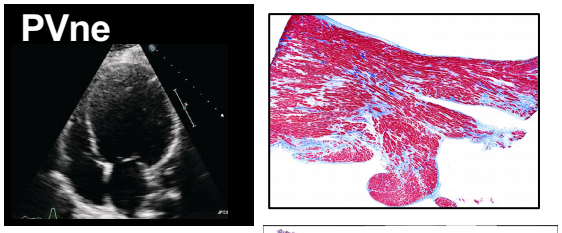


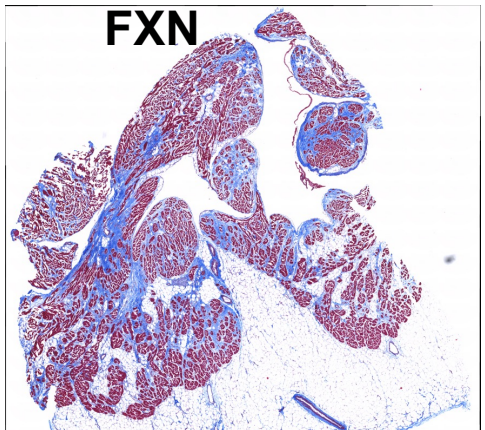


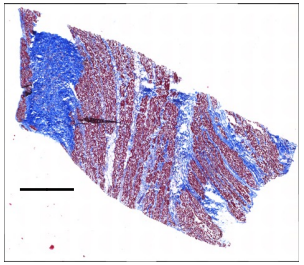
Normal







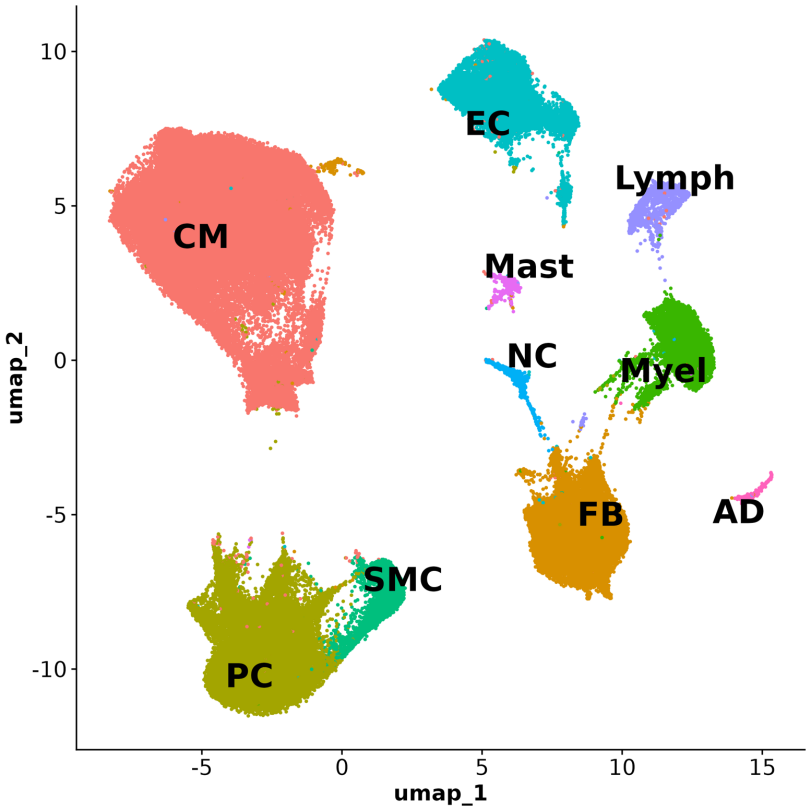


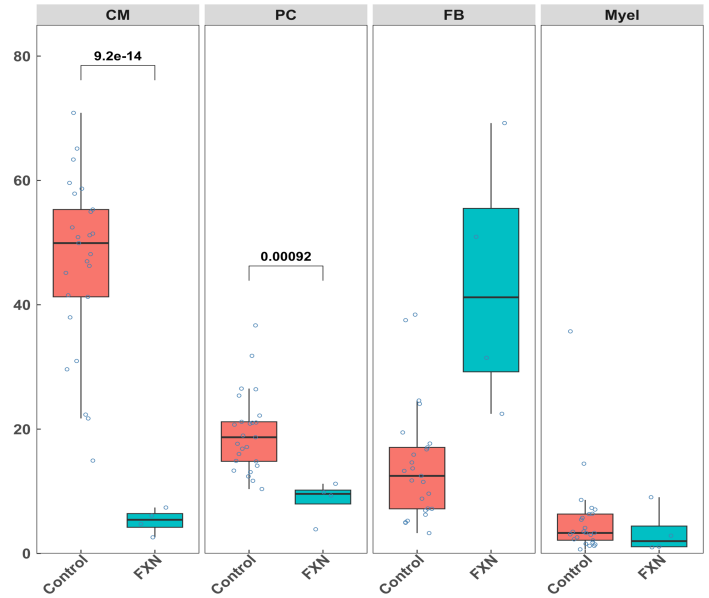


Thank you,
Barbara Tate

1mm

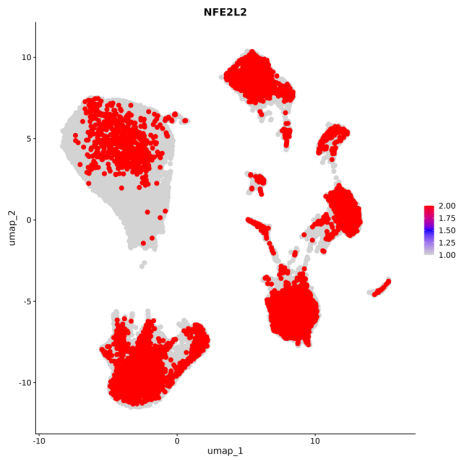
snRNAseq of human FXN deficient and normal cardiac ventricles

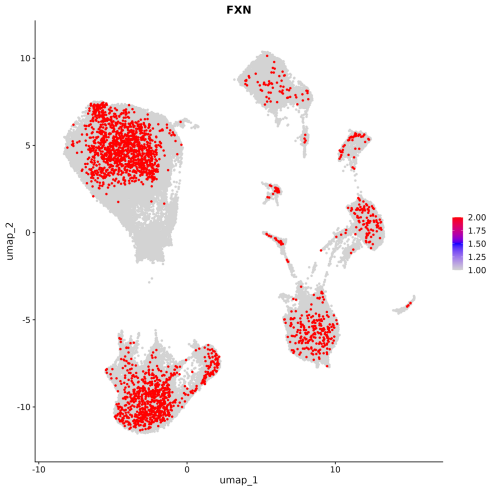


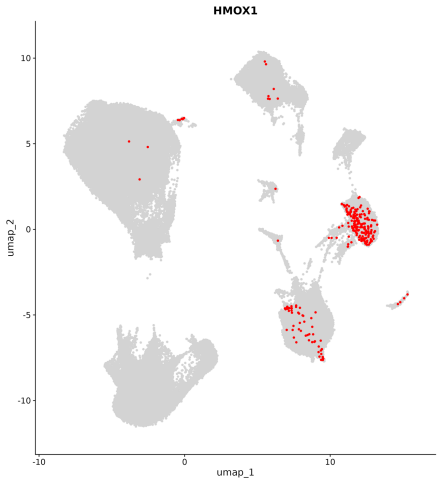


Samples:

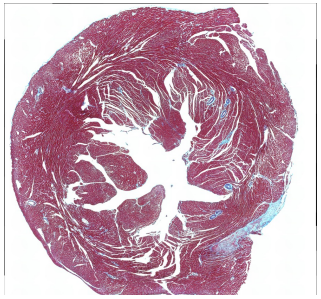
11	RV	Normal
14	LV	Normal
2	RV	FXN
2	LV	FXN

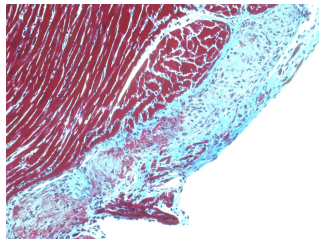


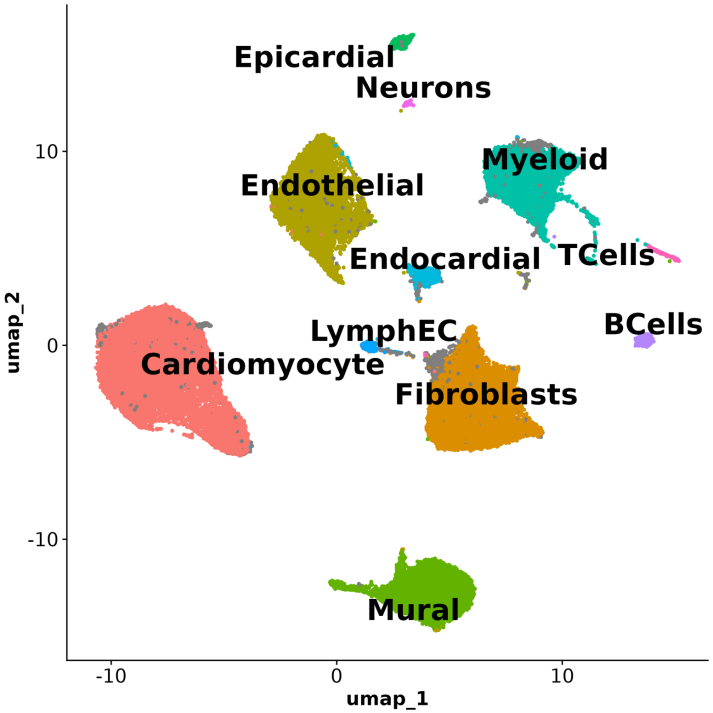




snRNAseq analyses of FXN kd mice

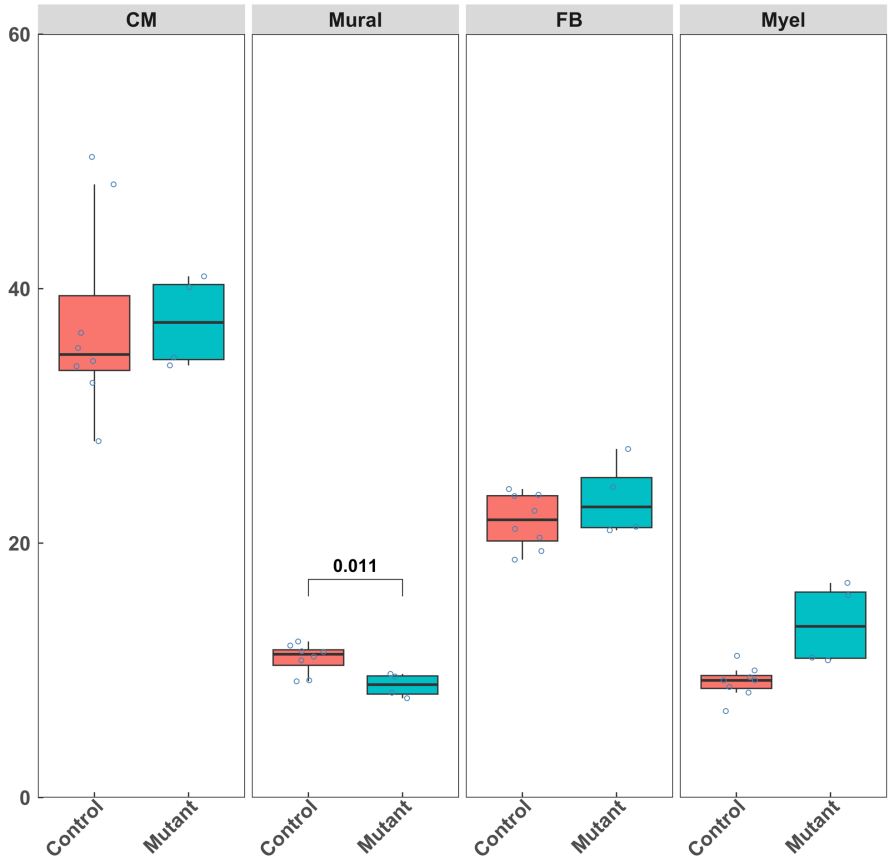




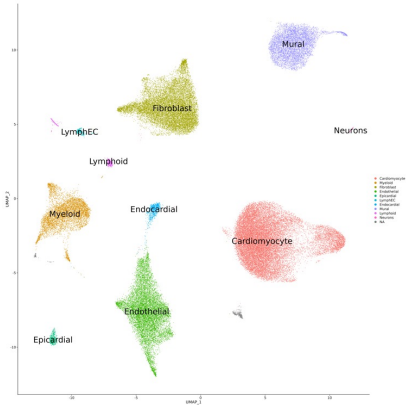


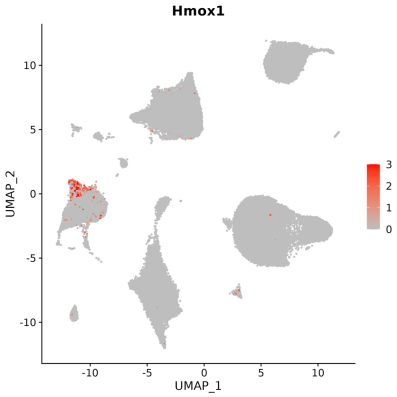
No. mice

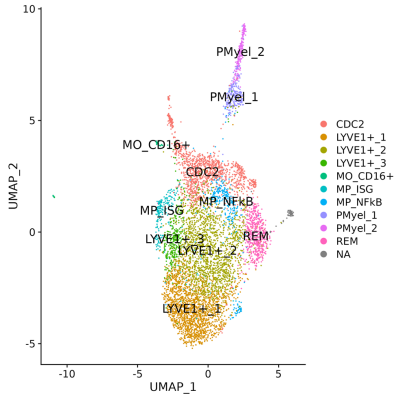
Wildtype	9
FXNkd	4

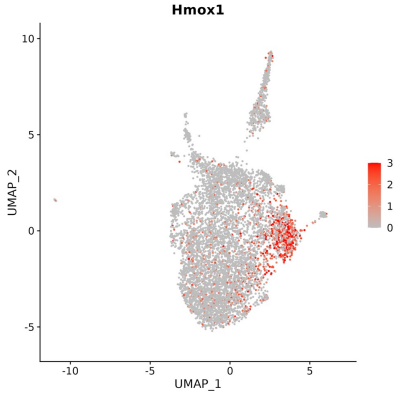


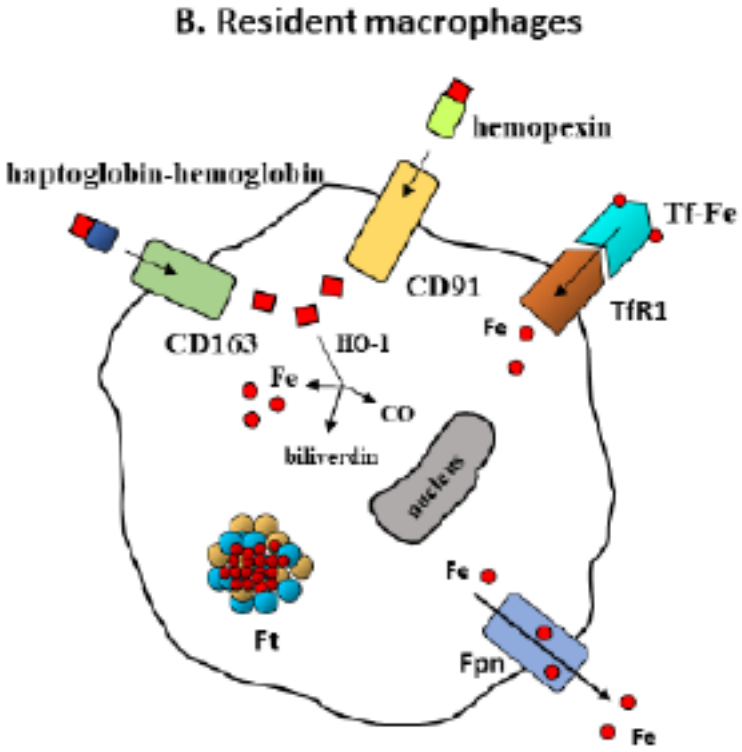
Increased scavenger cells (REM) in FXN deficient tissues



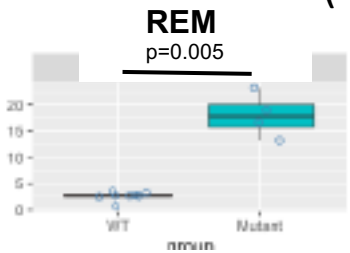




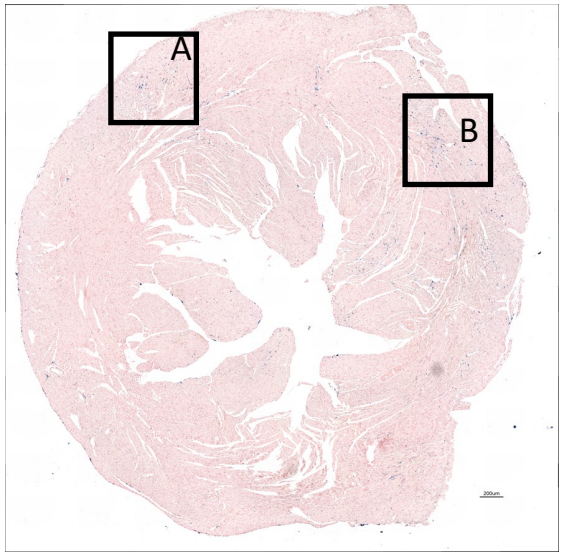


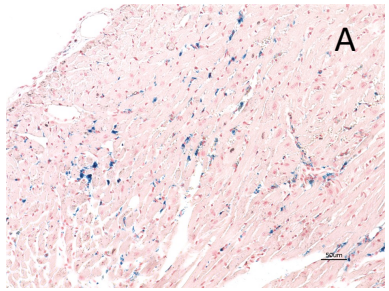


(Recalcati and Cairo, 2021)

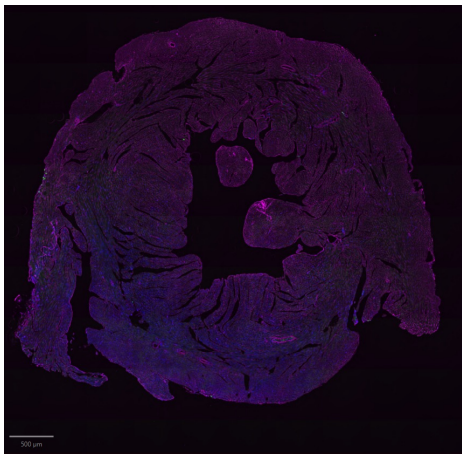


REM cells (HMOX1) and iron deposits (Prussian blue) in patches in *Fxn kd* LVs

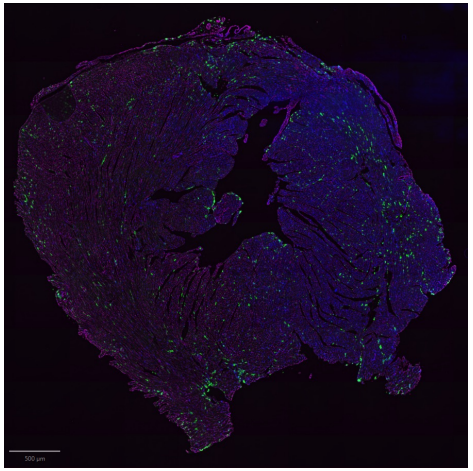


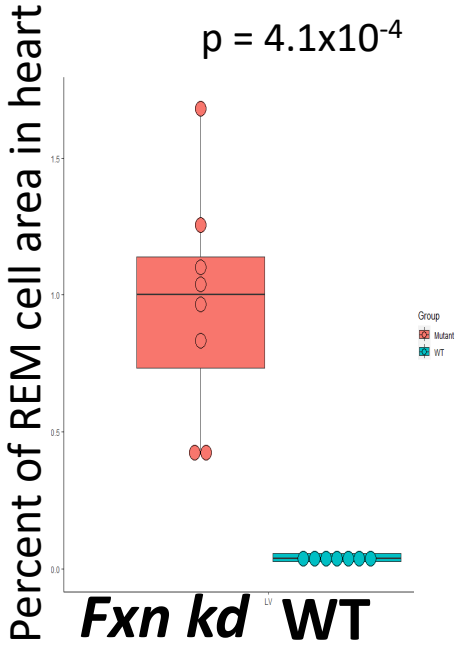


WT LV



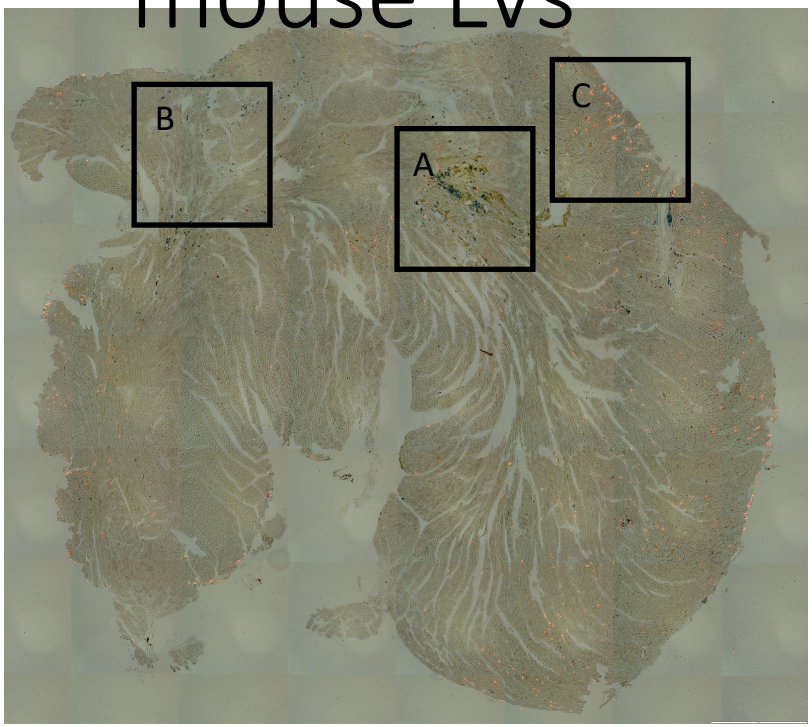
***Fxn kd* LV**

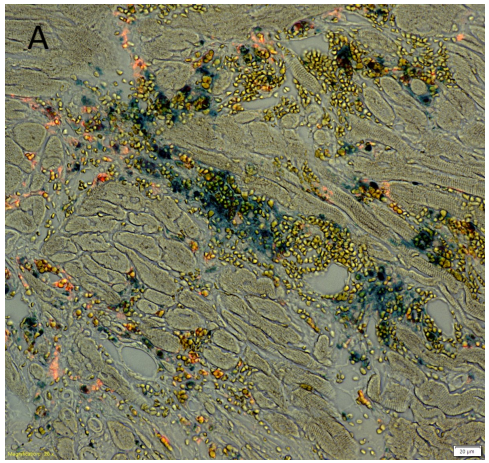


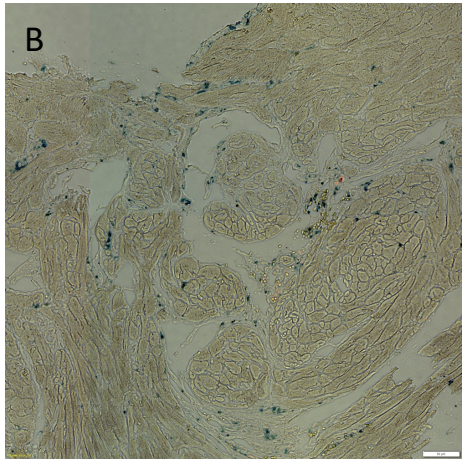


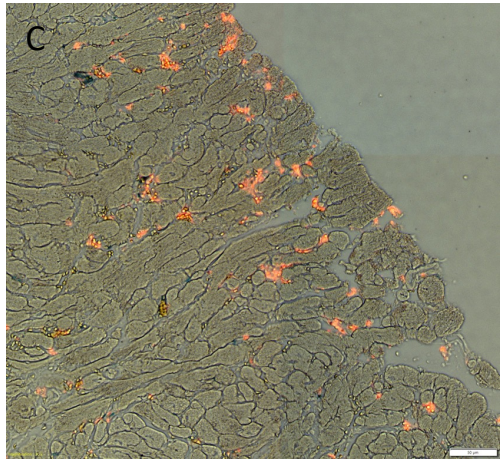
7 WT and 8 *Fxn* null mice
2-3 sections/mouse

Iron staining doesn't always co-localize with REM cells in *Fxn* null mouse LVs









HMOX1
Iron

8 mice
2-3 sections/mouse

Data not shown

- snRNAseq objects (Increased REM cells in all FXN):
  - Mouse quadriceps: 2 WT, 2 FXN kd
  - Mouse diaphragm: 5 WT, 5 FXN kd

  - Human ’back muscle’: 14 FXN deficient
    5 normal
- Bulk RNAseq of nuclear RNA from FXN deficient patients (cardiac) demonstrates impaired FXN splicing (back up slide)

Summary

- snRNAseq of human and mouse heart tissues identifies at least two major cellular consequences of FXN deficiency: a) Pericyte loss; b) REM cell increase
- Fe deposits and REM (HMOX1) cells exist separately and co-localize, but do not co-localize with fibrosis.
- Current hypothesis: 1) REM cells move dying cells/secreted Fe, HMOX1 pathway breaks down secreted Fe and excrete Fe, and REM cells ‘depart’.

2) Pericyte loss contributes to clinical features of FA.

Acknowledgements

GROUP LEADERS:

Hiroko Wakimoto

Syndi Barish

Seidman Lab

Joshua Gorham
Daniel DeLaughter
Mingyue Lun
Viktoria Strohmenger
Steve DePalma
…and the rest of the lab

Mootha Lab

Sarah Calvo
Hong Wang

Toepfer Lab

Flair Cullup

Liu Lab

Zaneta Matuszek

Kennedy Lab

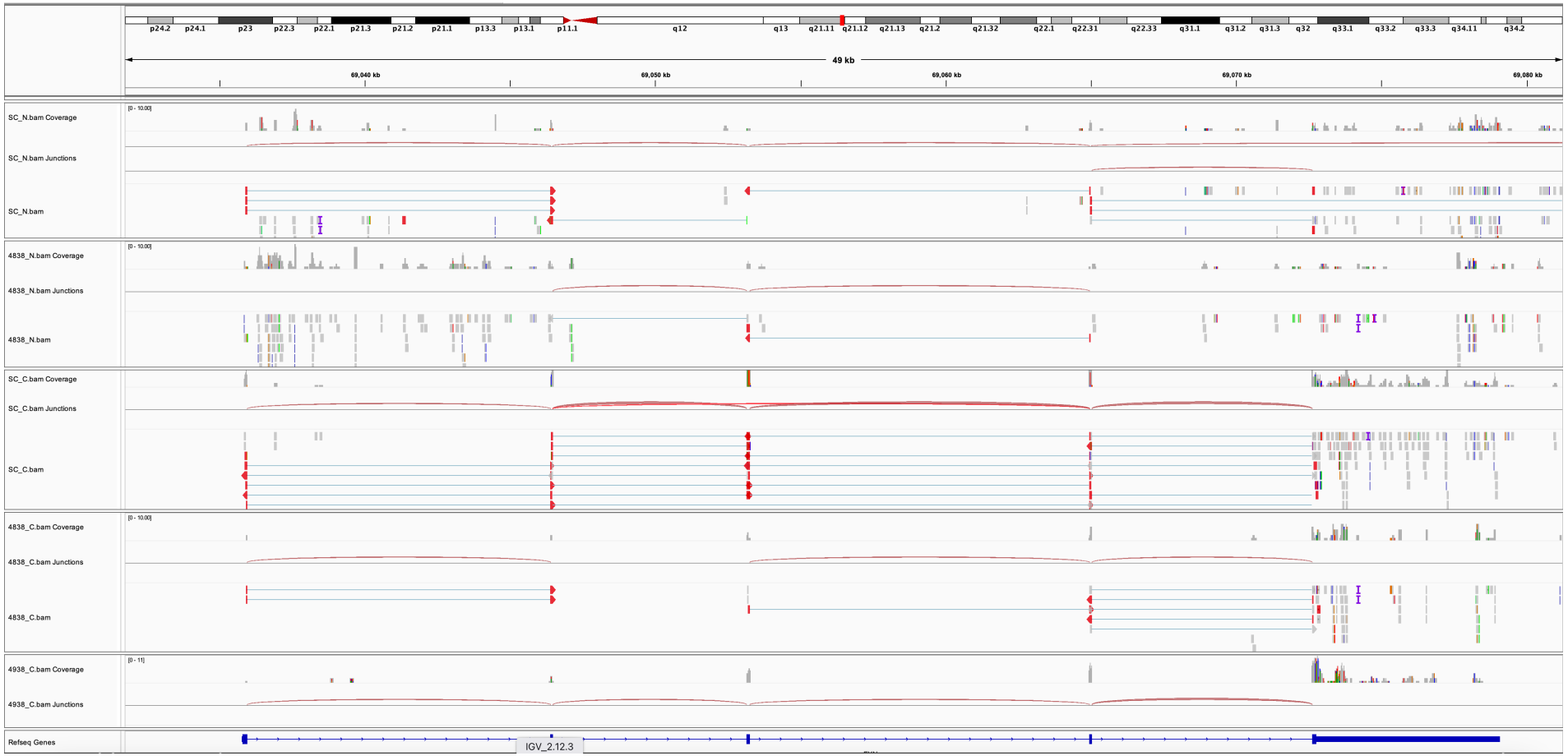
Dong Cao

MicRoN Core

Paula De La Milagrosa
Praju Anekal

FARA

David Lynch
Jen Farmer
Barbara Tate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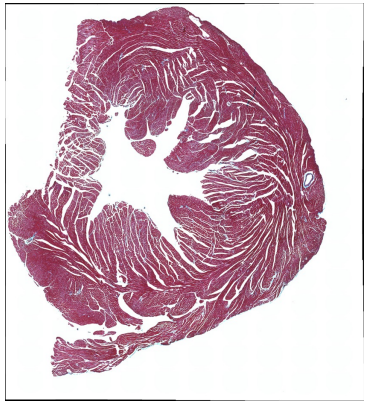
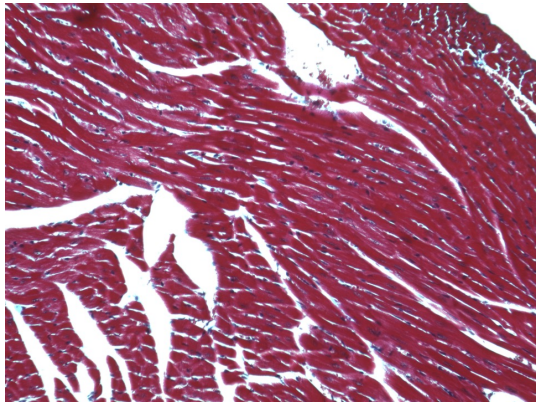
Refseq Genes
IGV_2.12.3

Increased fibrosis in *Fxn* null mouse LVs

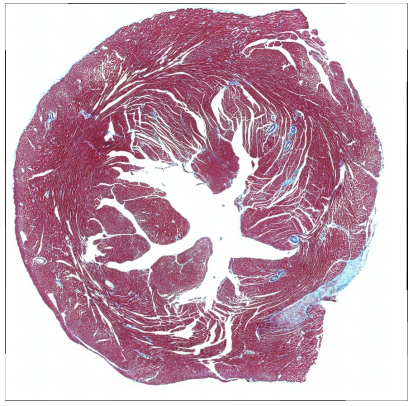
WT: 7 mice
Hypertrophy: 6 mice
Non-Hypertrophy: 2 mice
5-6 sections each

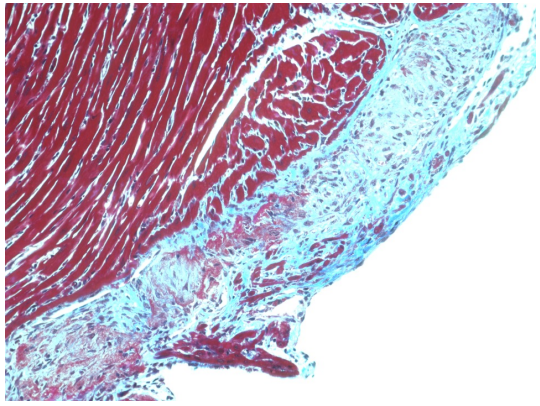
WT

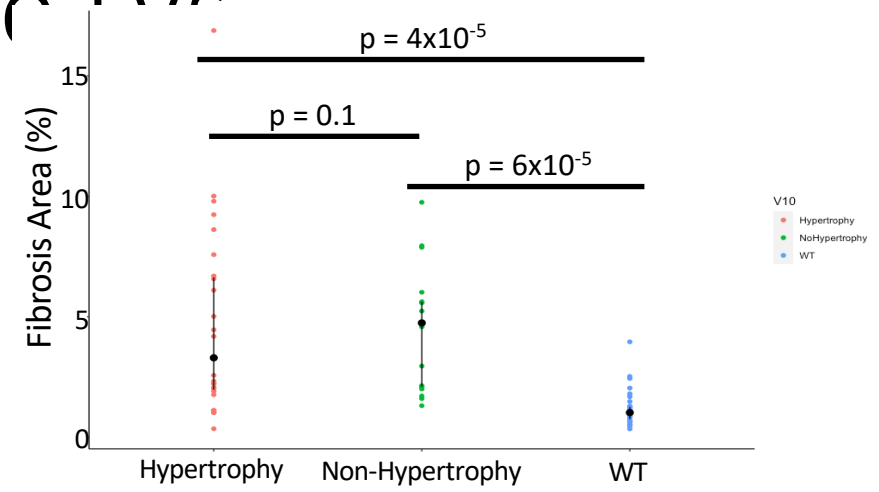


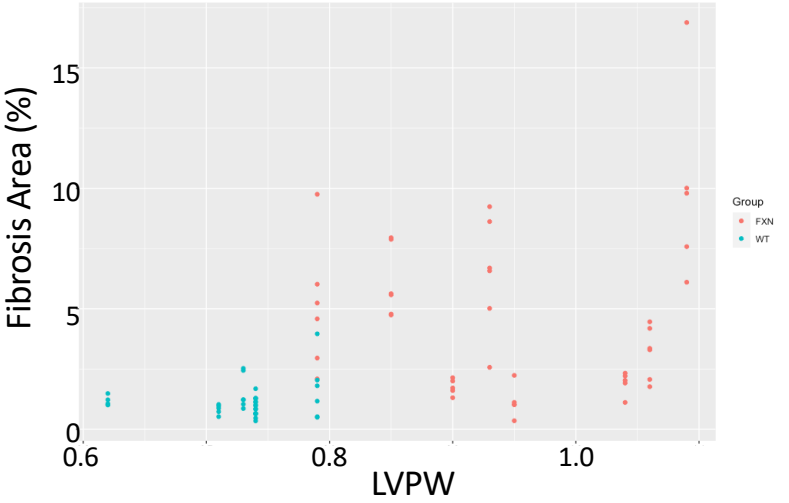


FXN null

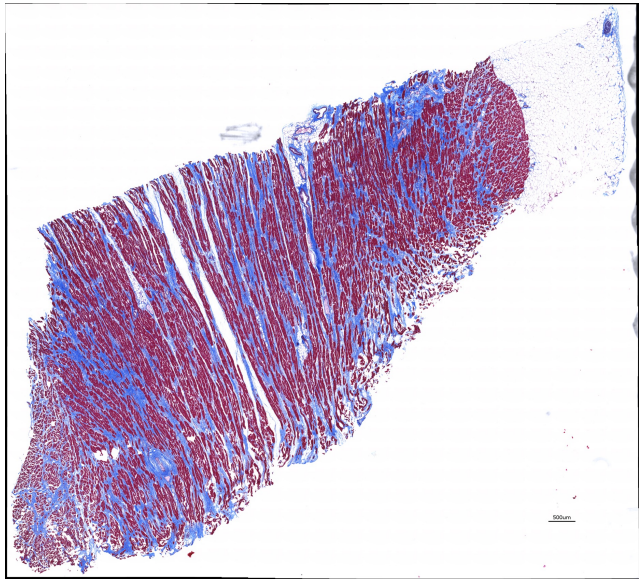


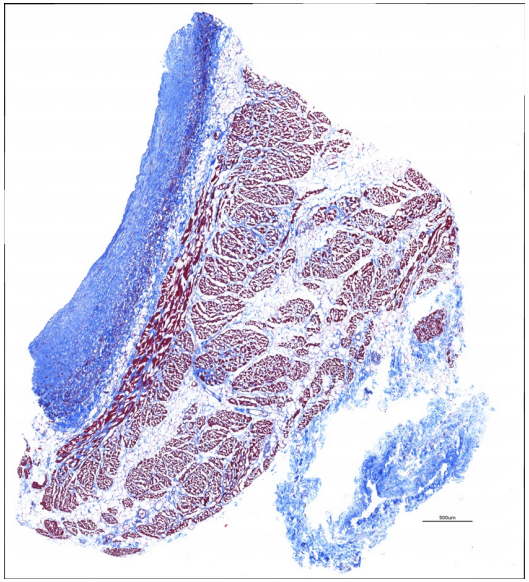


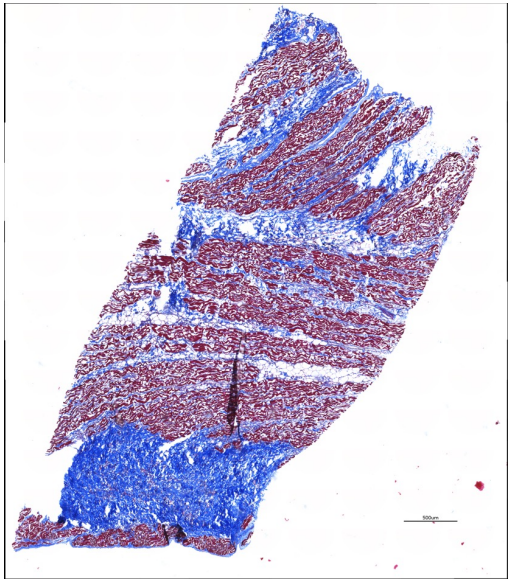




Histology shows a lot of fibrosis







Histology shows a lot of fibrosis