FITCHBURG STATE UNIVERSITY

Development Day
May 21st, 2019

Eric Williams

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Biology & Chemistry Department

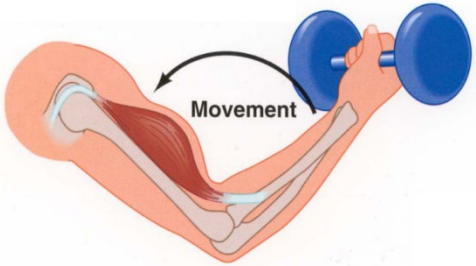
Dysferlinopathy

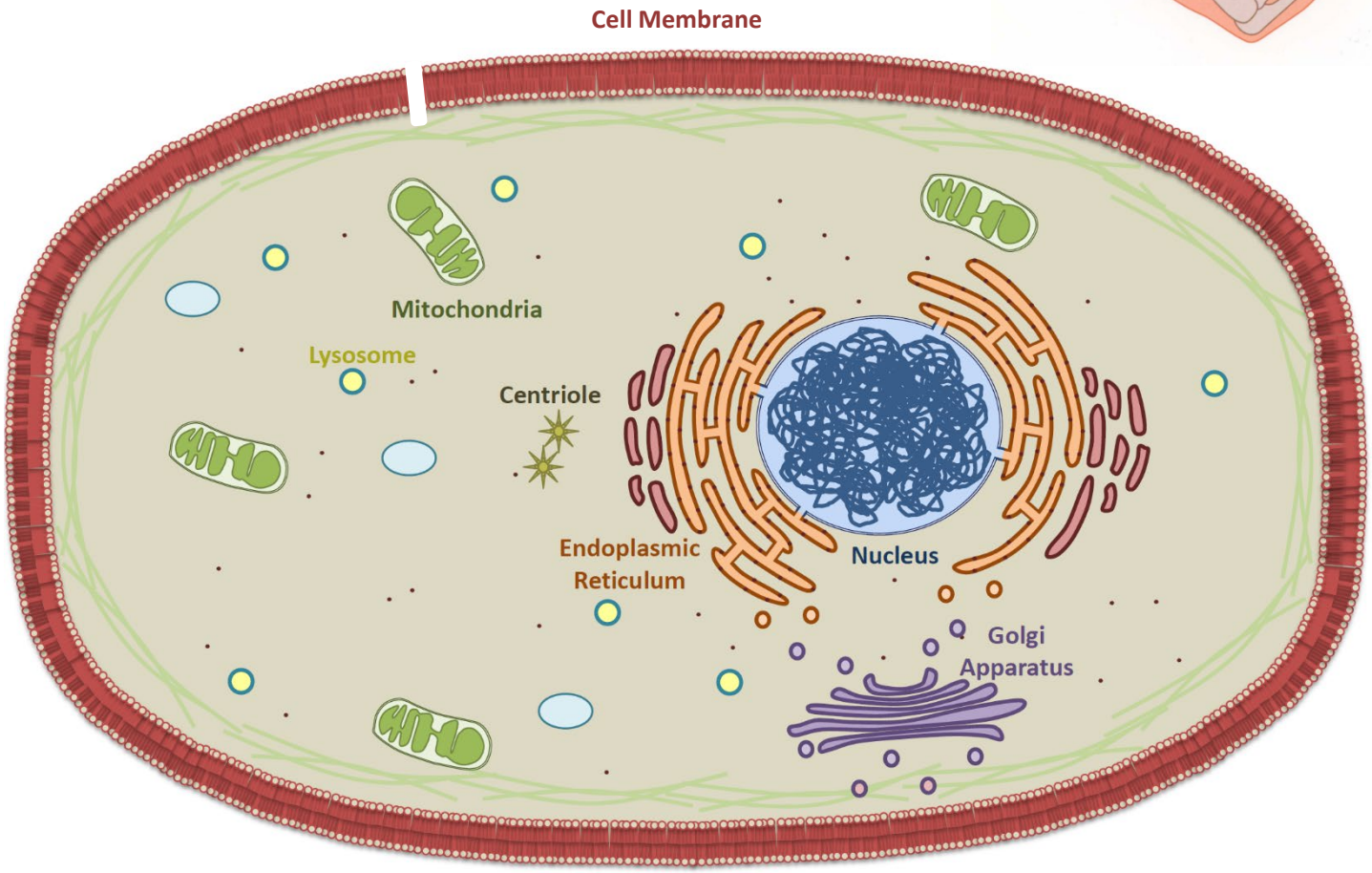
Average age at diagnosis is ~25 years of age

Patients generally require a wheel chair within 5-10 years of diagnosis

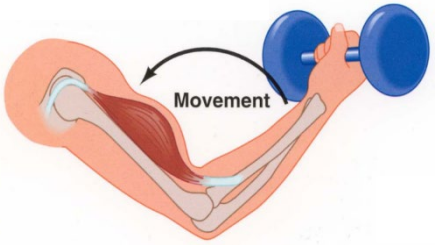
Currently there are no drug treatment options

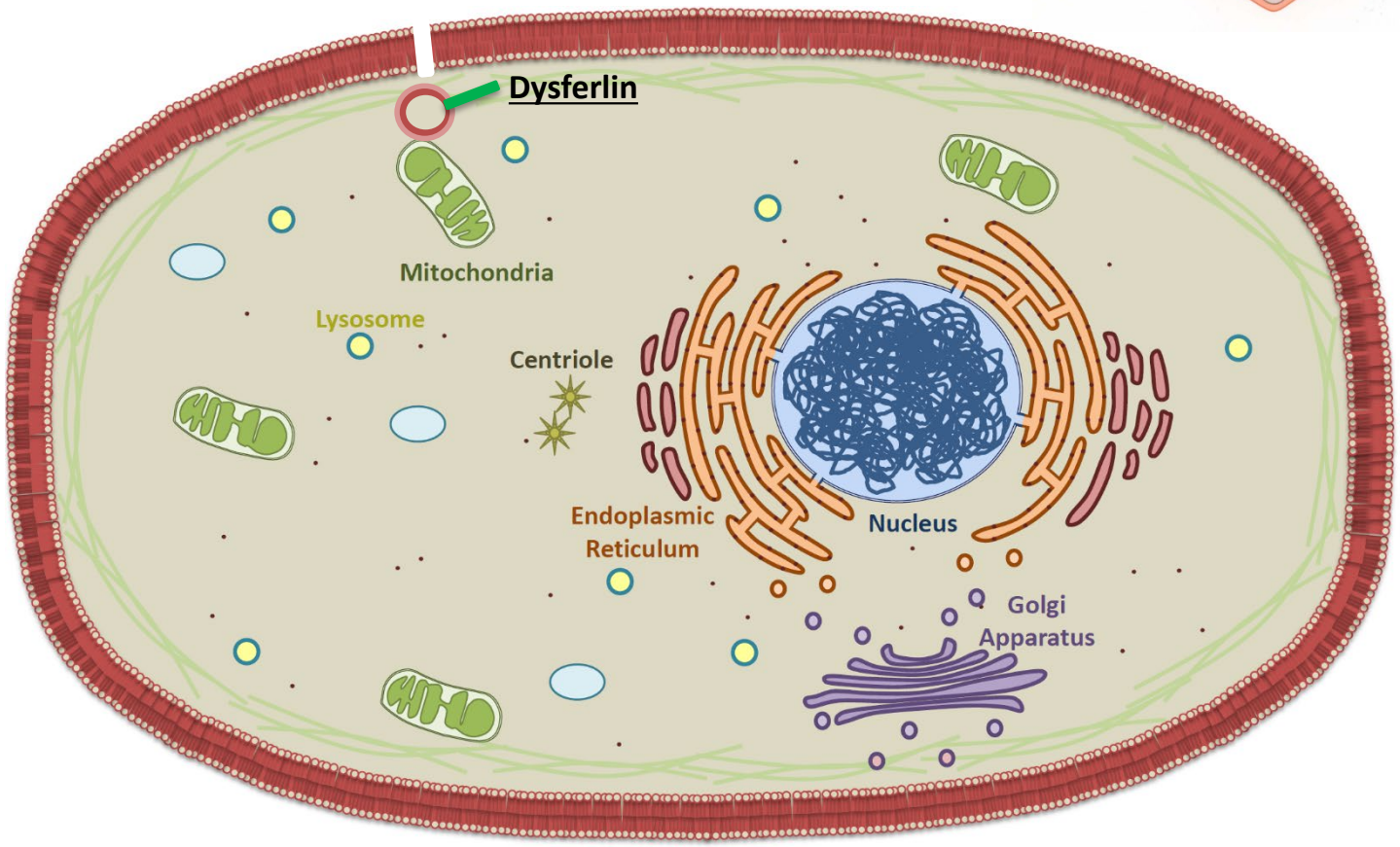
What causes dysferlinopathy?



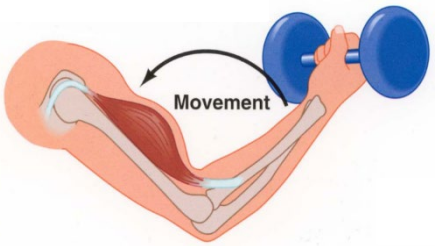


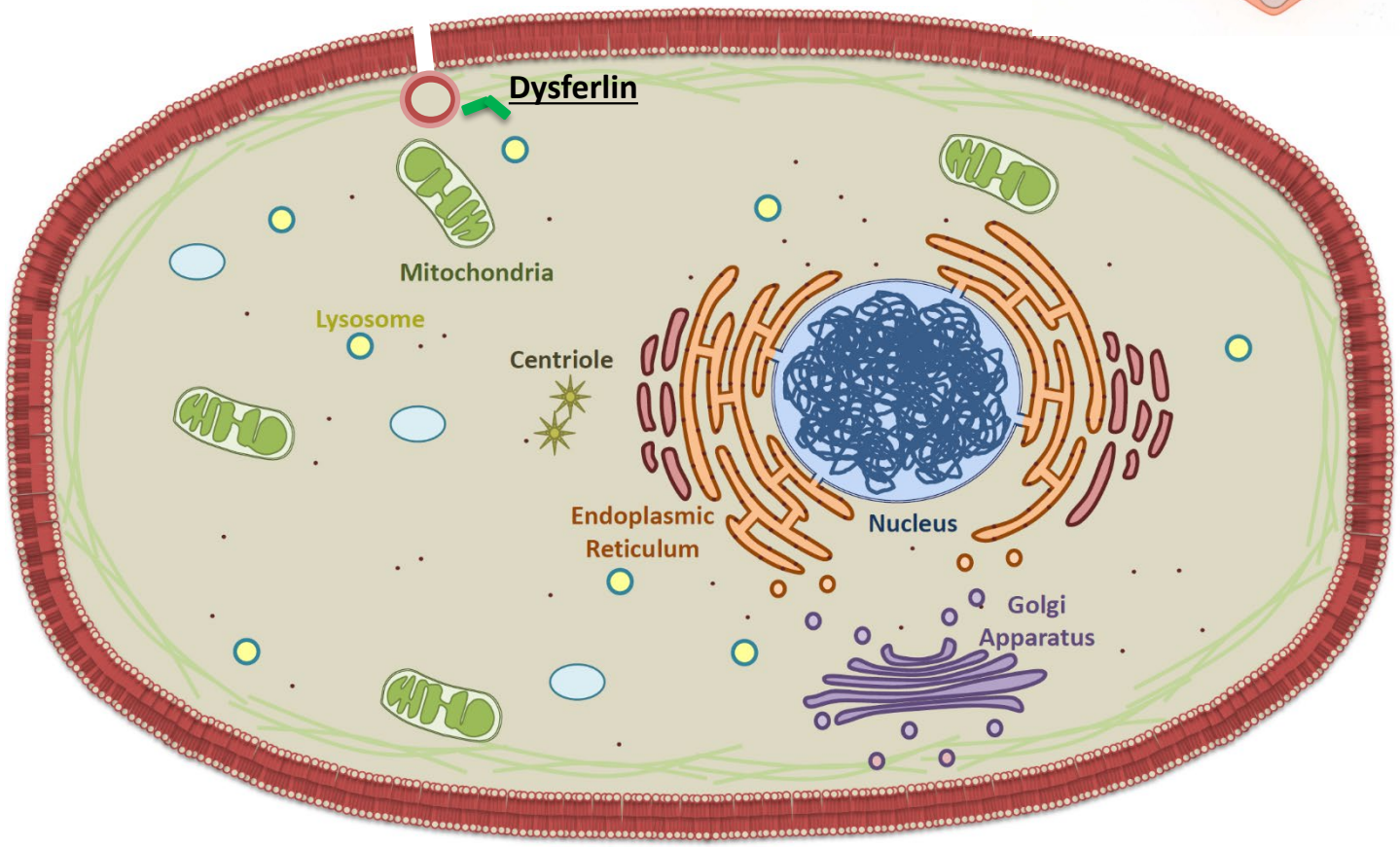
Dysferlin Repairs Membrane Breaks in Human Muscle Cells





People with mutations in Dysferlin can't repair membrane breaks

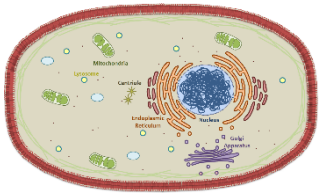


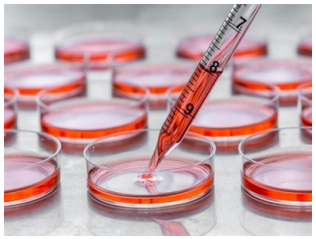


How do we Discover Disease Treatments?

Model Organisms

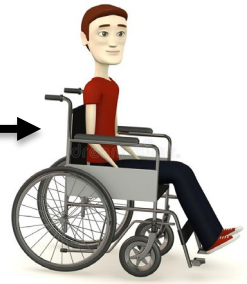
Human Cells





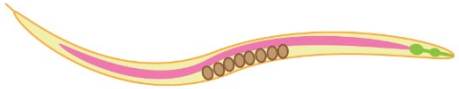
Live Mammals

Clinical Trials



Mutations in Human Dysferlin causes Muscle Loss

Mutations in *C.elegans* Dysferlin causes Infertility

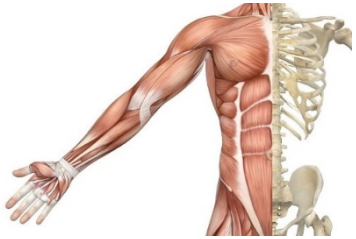


C. elegans Dysferlin

Sperm Development

Mutations

Infertility



Human Dysferlin

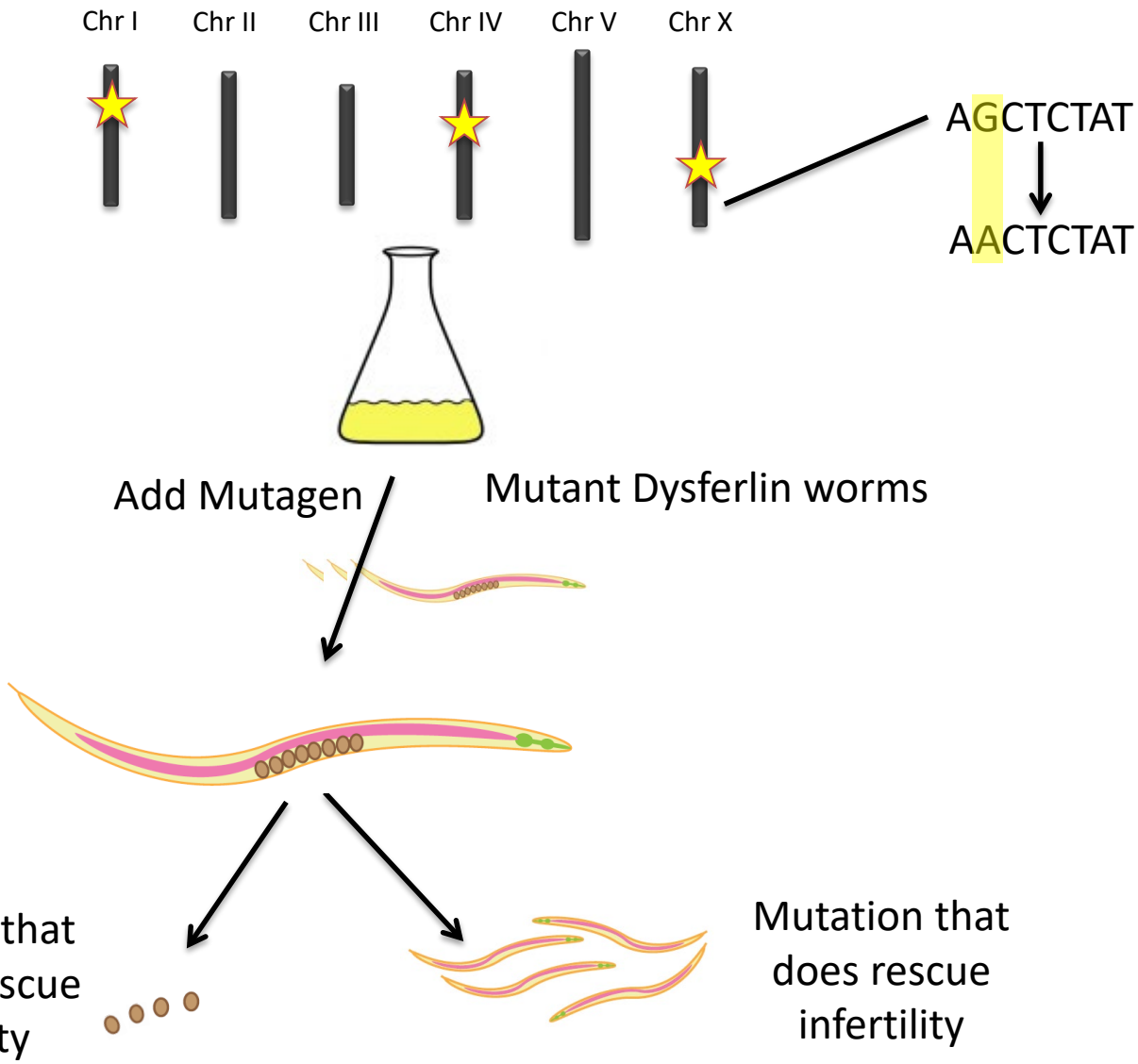
Skeletal Muscle Repair

Mutations

Muscular Dystrophy

If we can find a treatment that rescues infertility in the worm, perhaps the same treatment can rescue muscle loss in human patients

Identifying mutations that rescue *C.elegans* infertility in Dysferlin Mutants

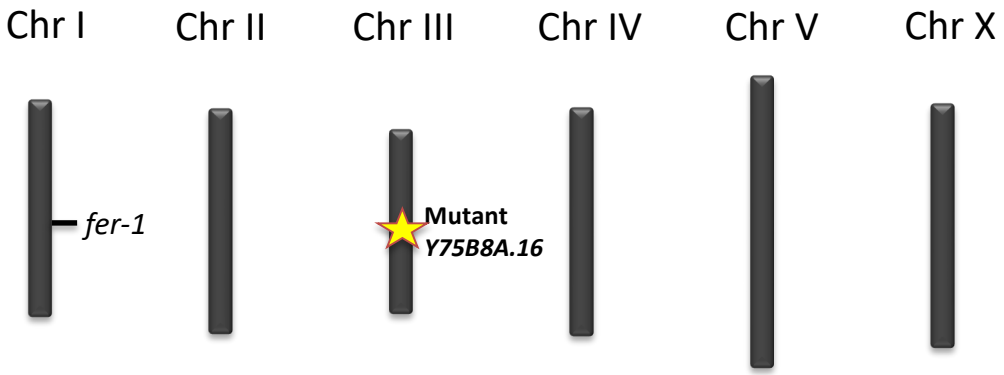


A Mutation in *Y75B8A.16* Restores Fertility of Mutant Dysferlin

Benjamin McGuire

Nicole Zwicker

Khianna Del Valle



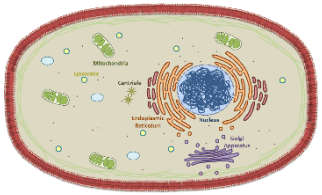
Normal Y75B8A.16 GTC GGA AAA → Infertility

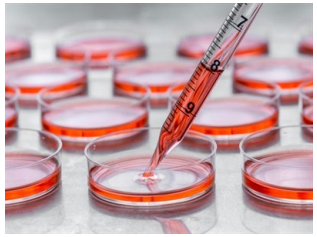
Mutated Y75B8A.16 GTC GAA AAA → Fertility

Results of Model Organism Studies

Model Organisms

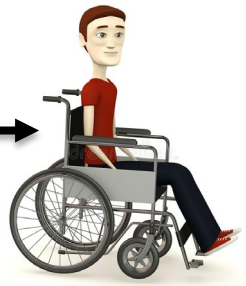
Human Cells





Living Mammals

Clinical Trials



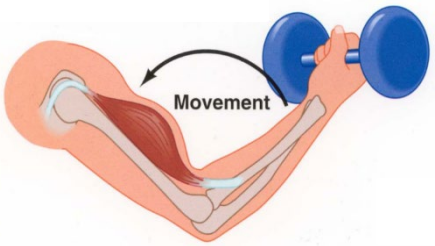
Y75B8A.16 mutation

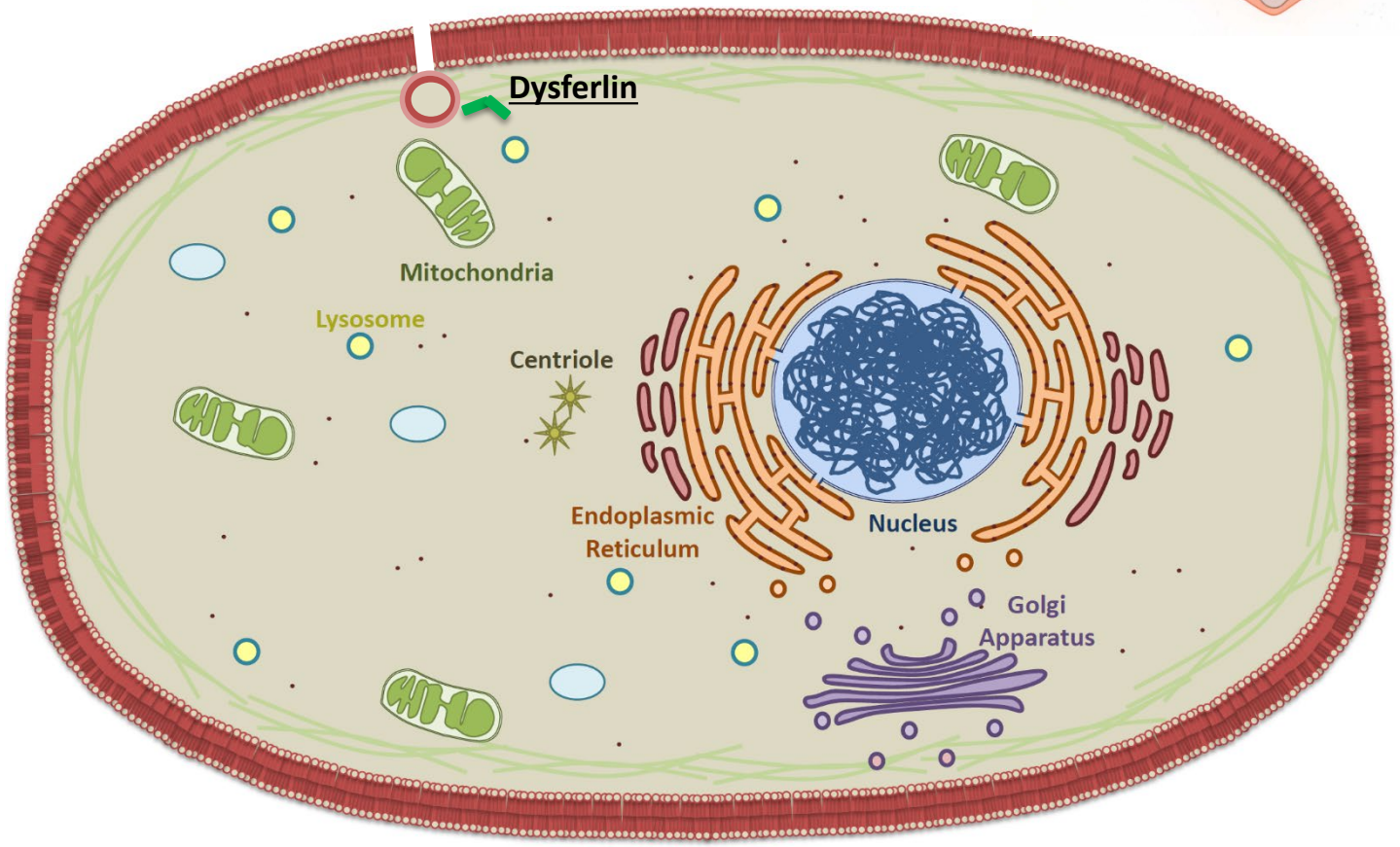
23 unmapped mutations

169 Drugs

?

People with mutations in Dysferlin can't repair membrane breaks



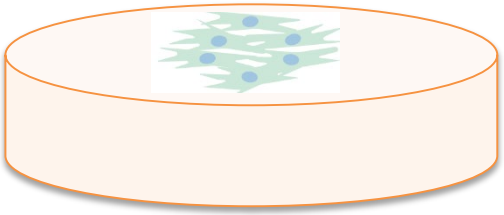


Mutant Dysferlin is Degraded in Human Cells

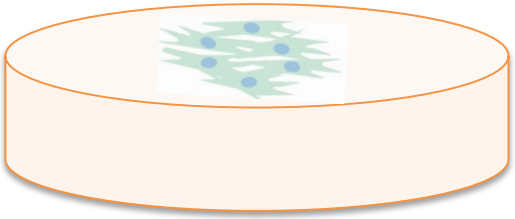
Anthony Manganaro

Sarah Olson

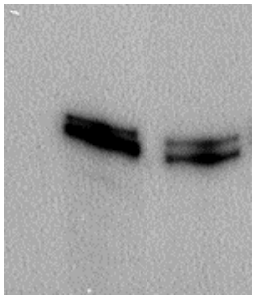
Normal DYSF



Mutant DYSF



DYSF Protein

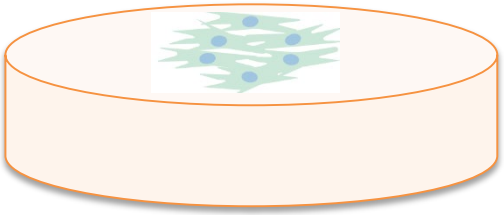


Y75B8A.16 homolog rescues degradation of mutant Dysferlin

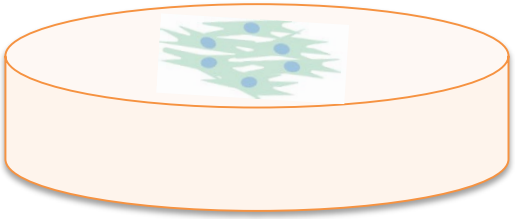
Anthony Manganaro

Sarah Olson

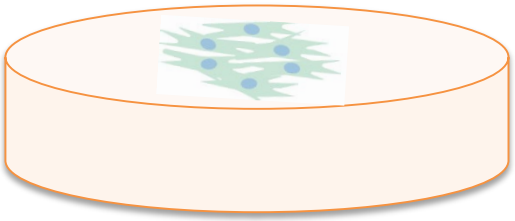
Normal DYSF



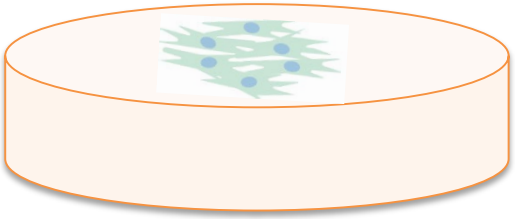
Mutant DYSF



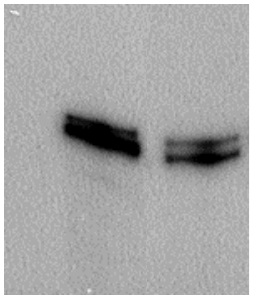
Mutant DYSF + Y75B8A.16 Homolog



Mutant DYSF + mY75B8A.16 Homolog



DYSF Protein



Results of Human Cell Studies

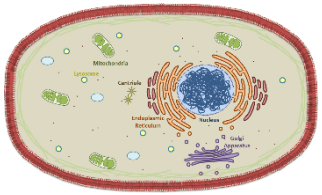
Model Organisms

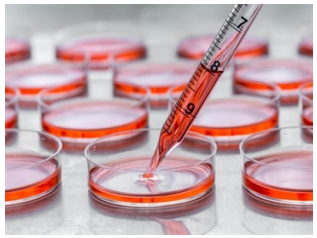
Y75B8A.16 mutation

23 unmapped mutations

169 Drugs

Human Cells





Y75B8A.16 homolog

1 drug

Living Mammals

?

Clinical Trials

?

Acknowledgements

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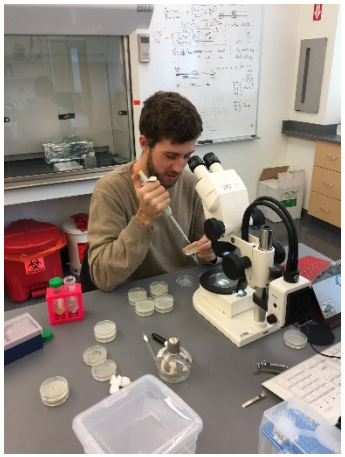

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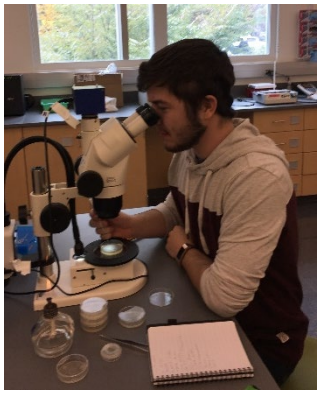
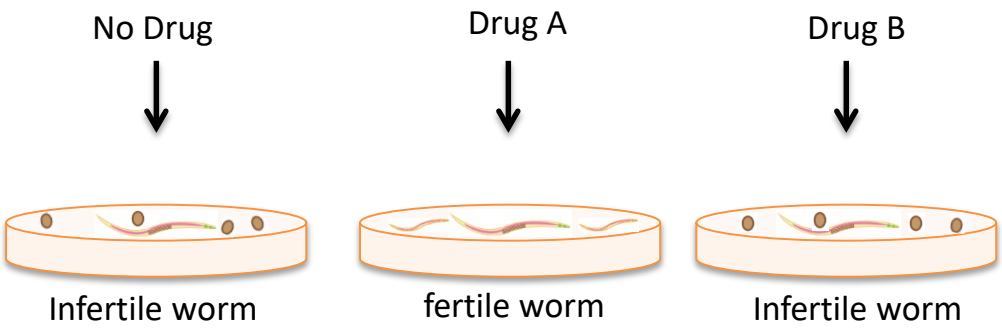


John Sanford

FITCHBURG STATE UNIVERSITY

Special Projects Grant

Experiment 1: Identifying drugs that rescue *C.elegans* infertility in Dysferlin Mutants

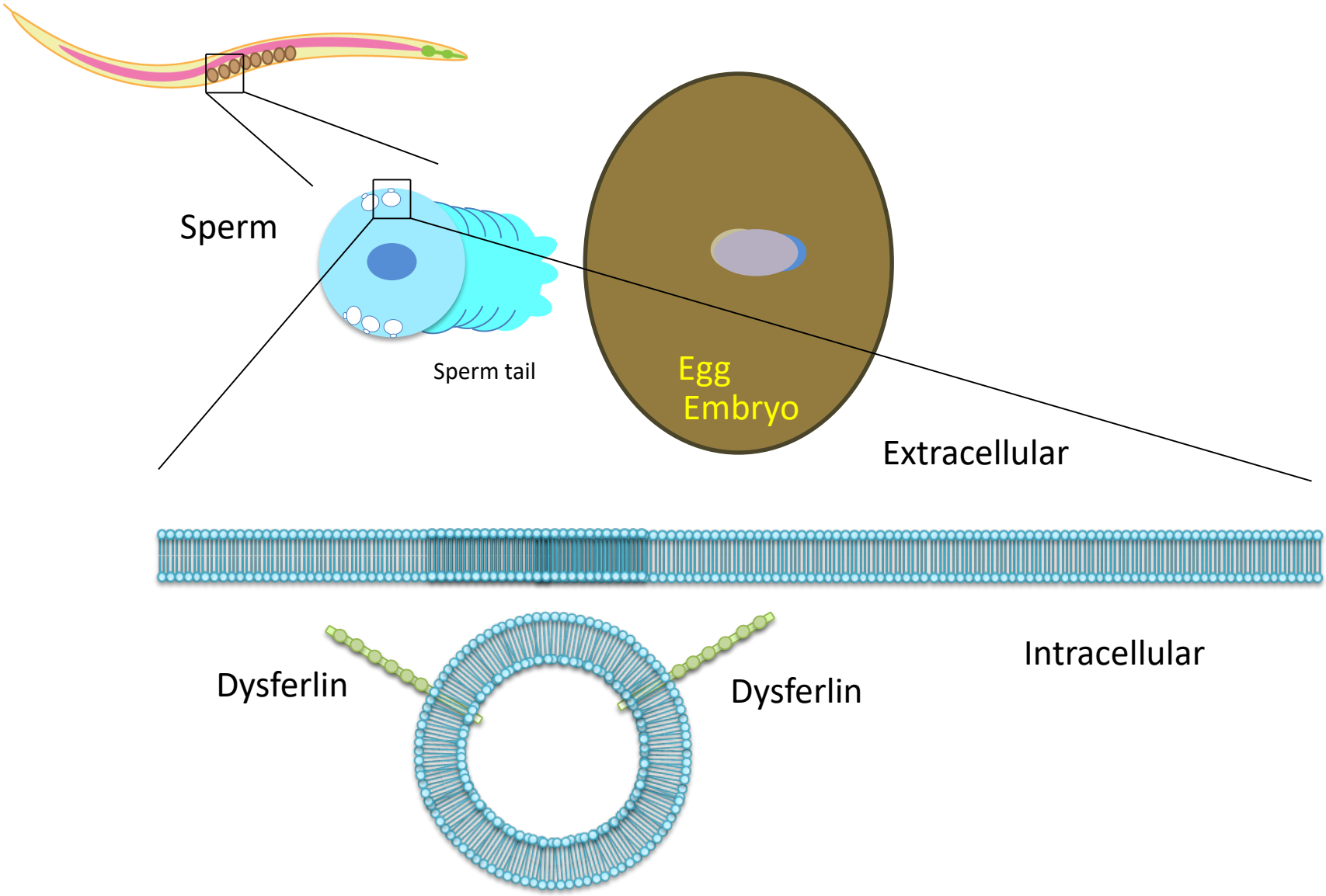


85,000 drugs

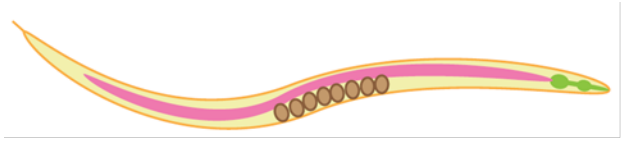
↓

169 drugs restore fertility of mutant worms

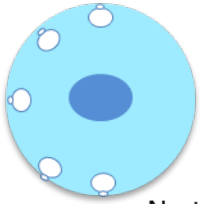
Why do mutations in *C.elegans* dysferlin cause infertility?



Mutations in *C.elegans* Dysferlin cause Infertility

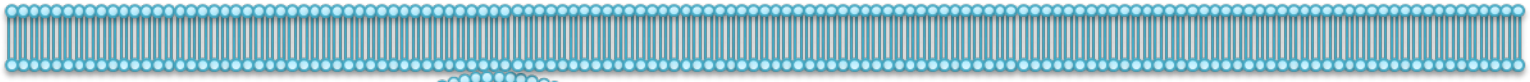


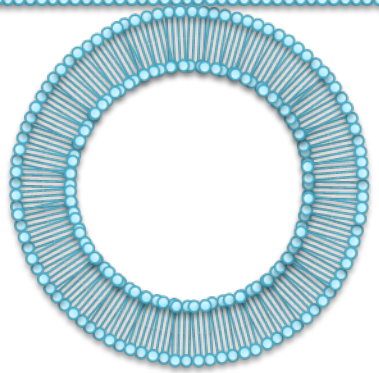
Sperm



No tail

Extracellular





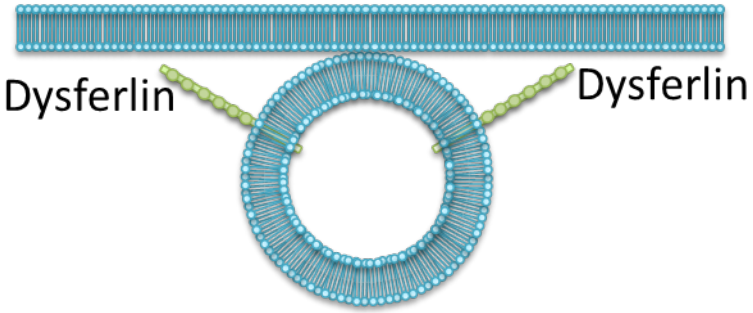
Dysfunctional Dysferlin

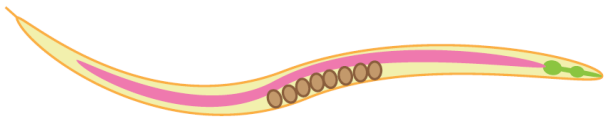
Intracellular

Membranous Organelle

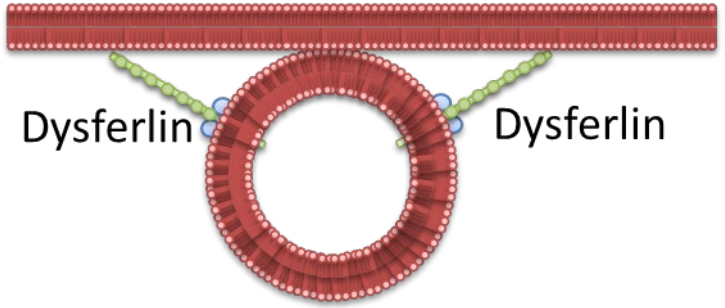
C.elegans Dysferlin and Human Dysferlin have the same Molecular Function: Membrane Fusion

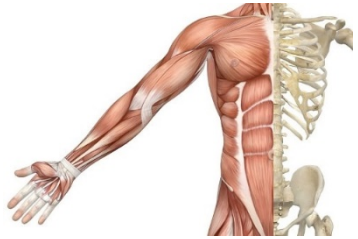
C. elegans Sperm





Human Skeletal Muscle

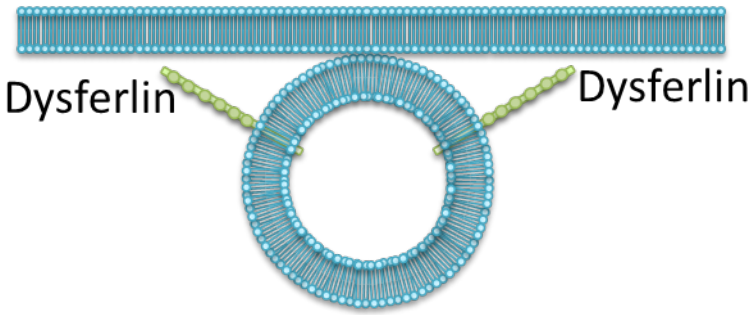


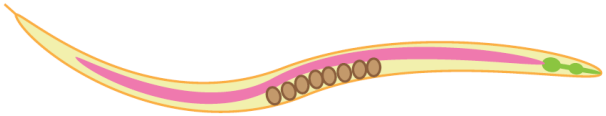


Hypothesis

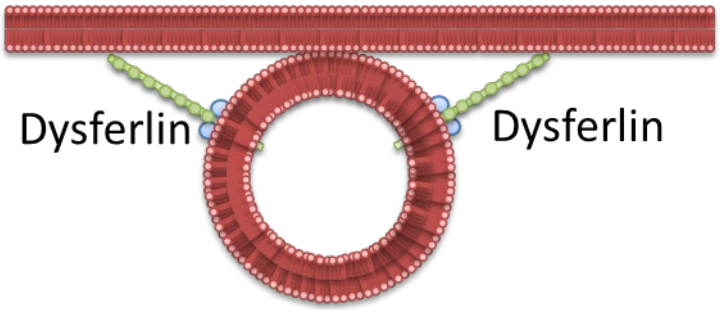
If we can find a treatment that rescues infertility in the worm, perhaps the same treatment can rescue muscle loss in human patients

C. elegans Sperm



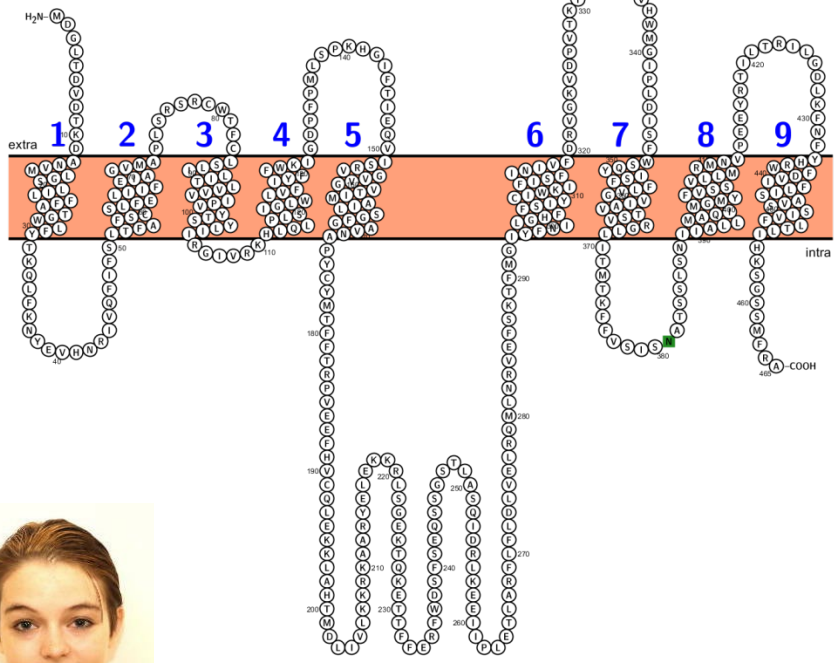


Human Skeletal Muscle

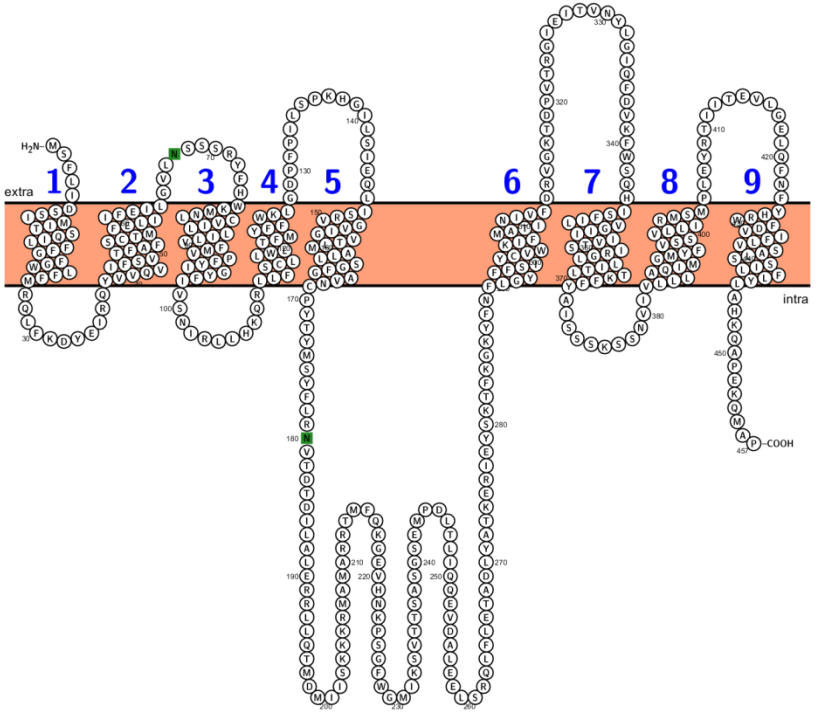


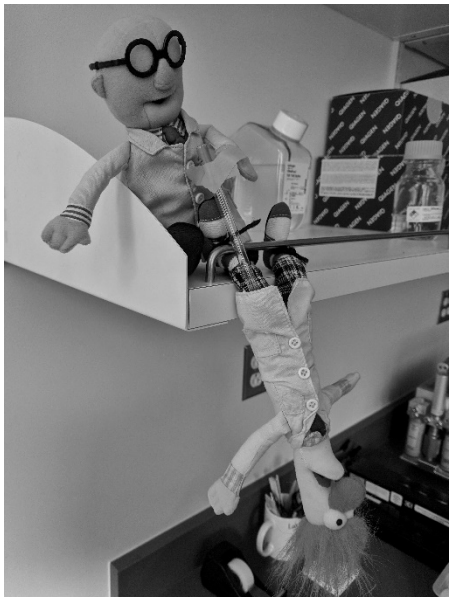
C.elegans Y75B8A.16 and Human GPR89A have Very Similar Protein Structures

C. elegans Y75B9A.16



Human GPR89A






Total eggs laid
275
280
170


Fisher Scientific
Isotemp