

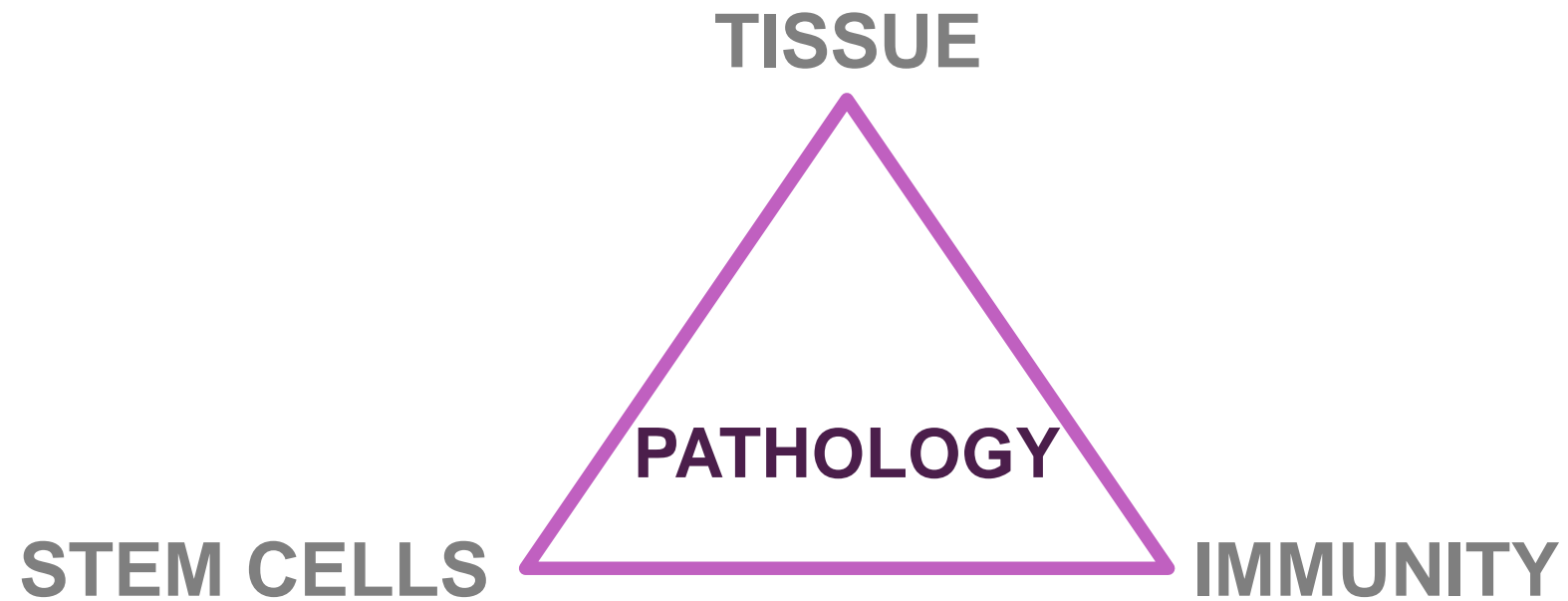
# Developing multi-target drugs for DMD using a common therapeutic modality

Keith Foster

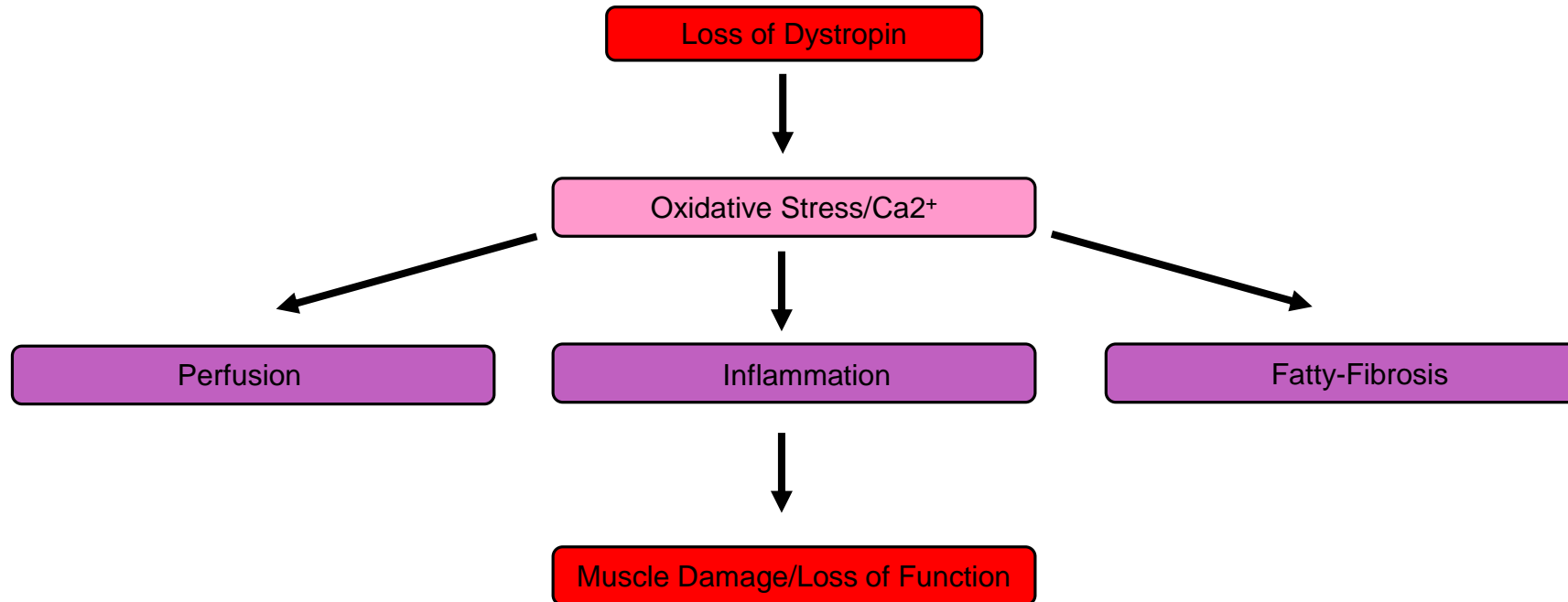
Associate Professor in Translational Medicine

University of Reading

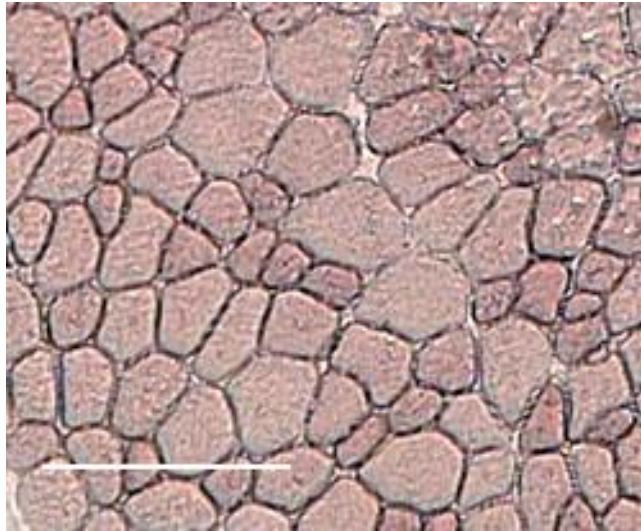
[k.foster@reading.ac.uk](mailto:k.foster@reading.ac.uk)



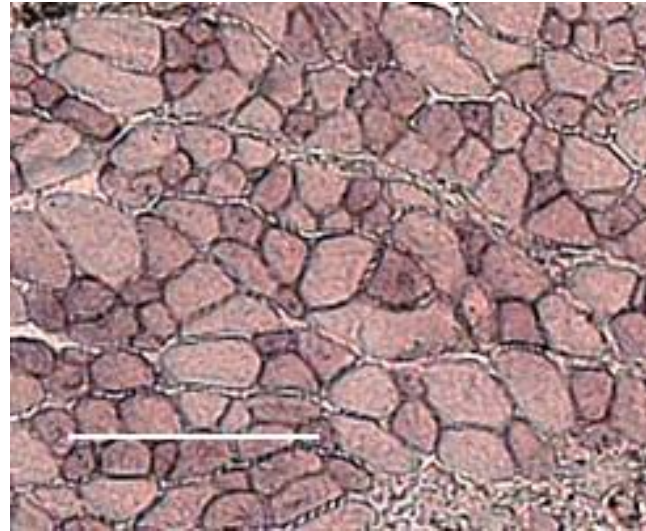
# Impact of Loss of Dystrophin



# ERR $\gamma$ : Oxidative Stress

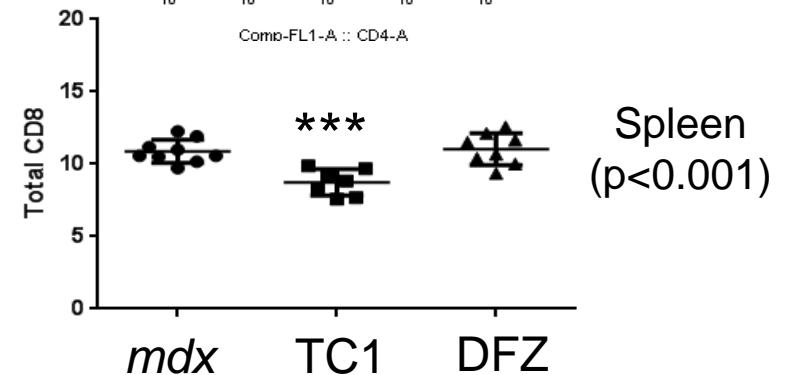
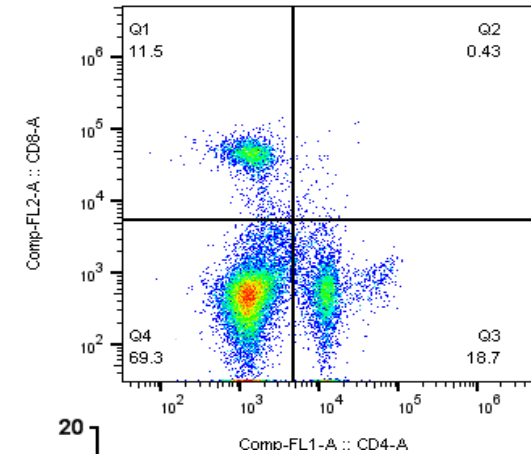
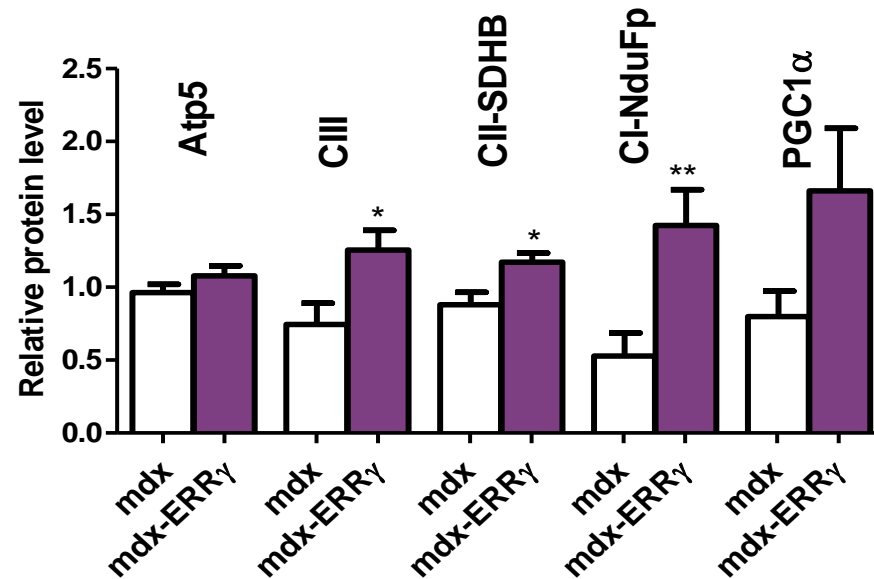
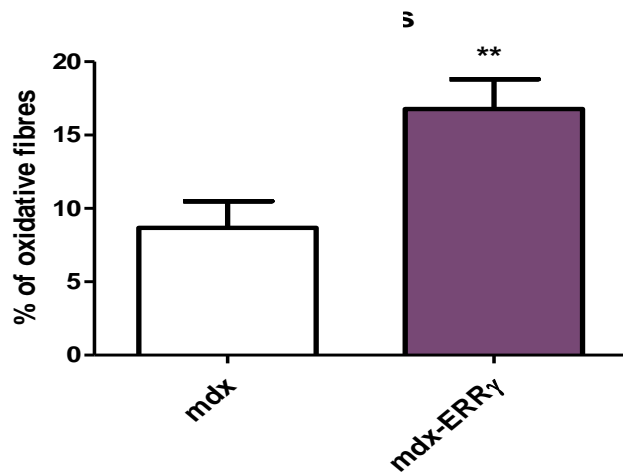


*mdx*

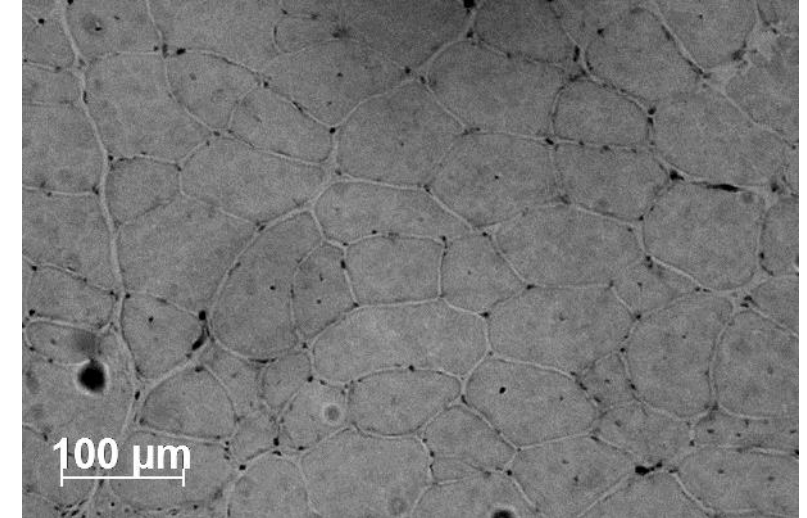
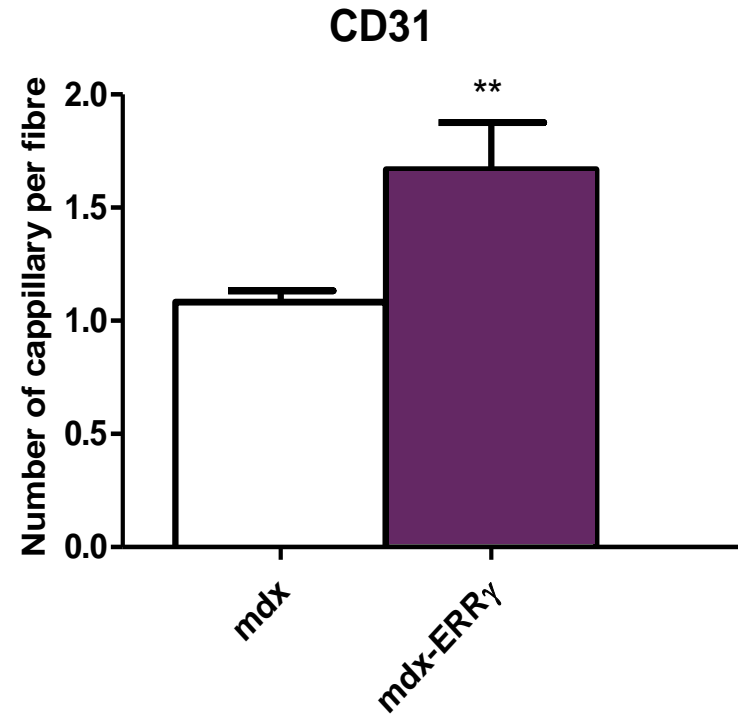
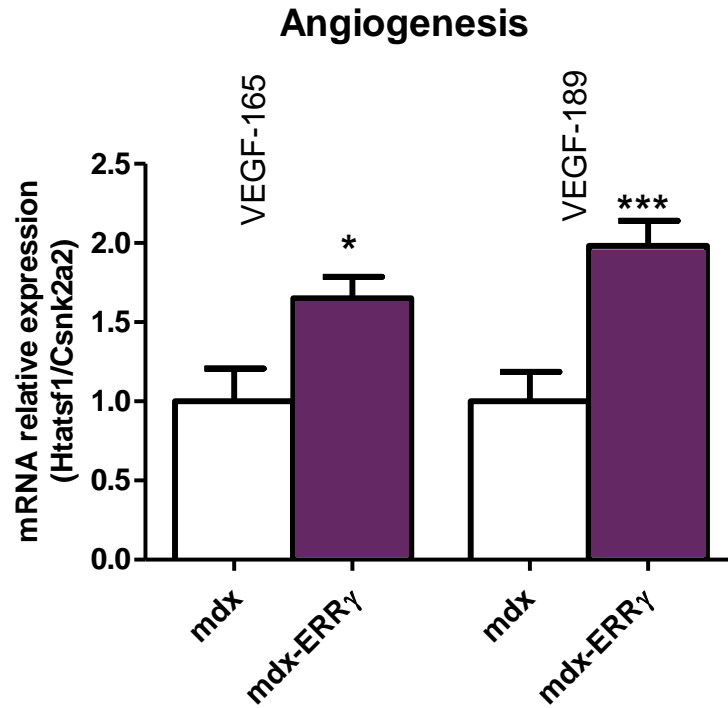


*mdx-ERR $\gamma$*

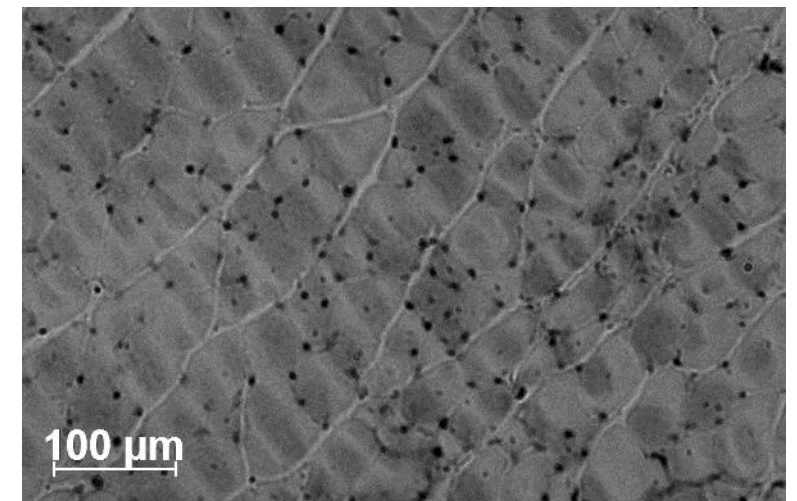
- 100% Increase oxidative potential
- Increased mitochondrial activity
- 20% Reduced inflammation



# ERR $\gamma$ : Oxidative Stress



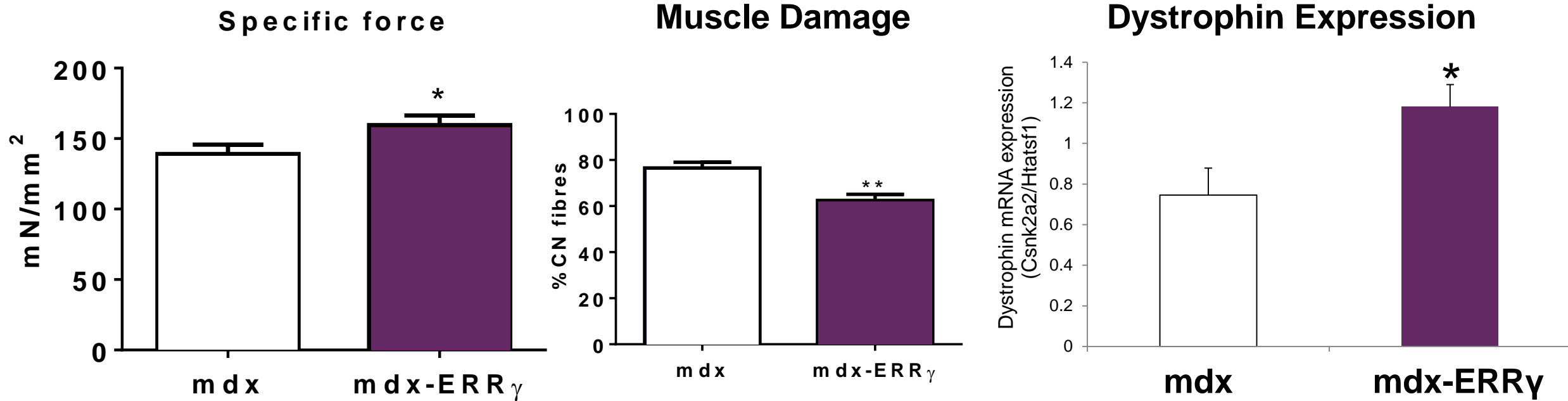
*mdx*



*mdx-ERR $\gamma$*

- 60-90% increase vascular factors potential
- 50% Increase in vascular density

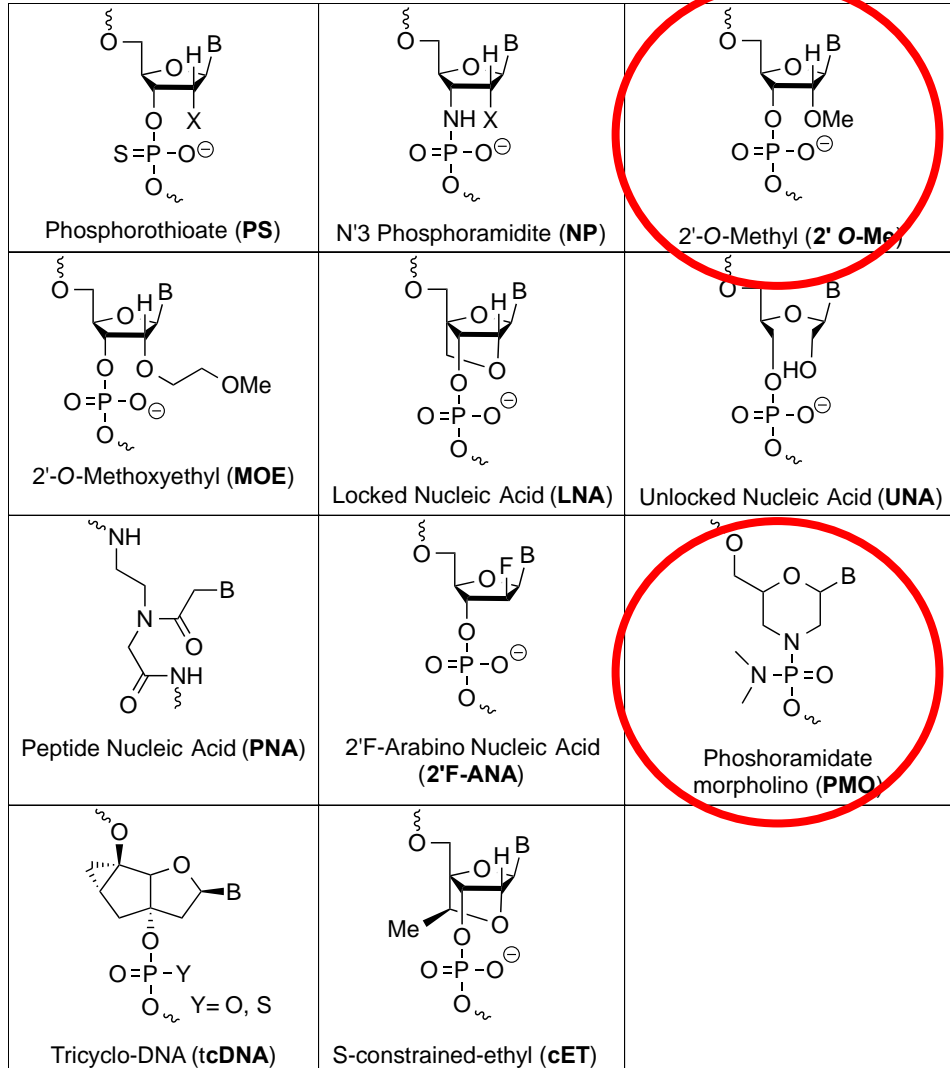
# ERR $\gamma$ : Oxidative Stress



- 14% Increased muscle forces
- 20% Decreases muscle damage
- 60% Increase in dystrophin expression

Standalone therapy and/or improving muscle milieu other drugs

# Translational Bottleneck: Antisense Delivery



	1 Antisense Drug	>1 Antisense Drug
DMD patients	58 %	77 %

Adapted from Aartsma-Rus et al., (2009) Hum Mutat 30: 293-299

- Biomarin: 2'O-Me Antisense Oligonucleotide
  - 1<sup>o</sup> endpoint failed
  - Toxicology limits effective dose
- Wave: 2'O-Me Antisense Oligonucleotide
  - Ongoing clinical trials
  - Toxicology limits at same level as Biomarin
- Sarepta: PMO Antisense Oligonucleotide
  - Approved September 2016
  - Poor PK in heart and brain

Need For Improved Delivery Strategies

Need For Safe Delivery Strategies

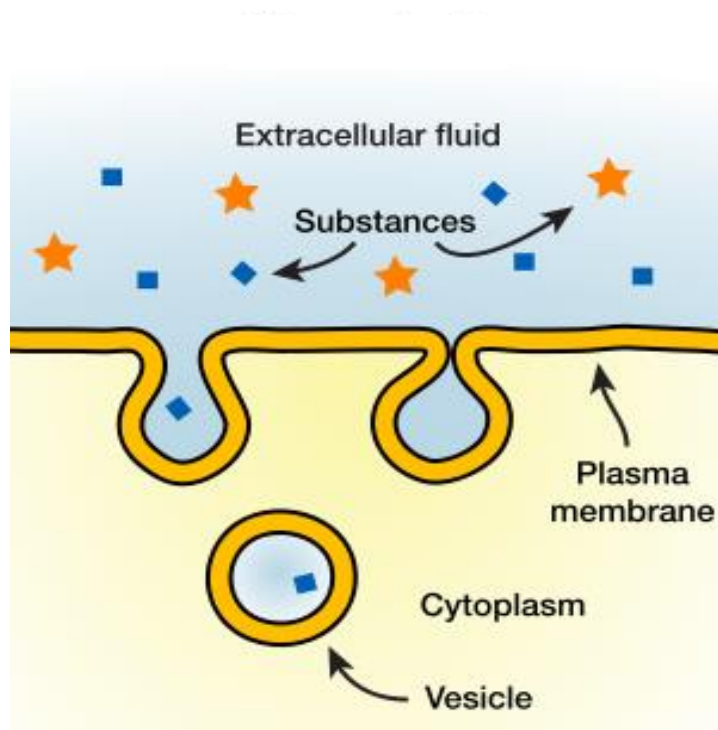




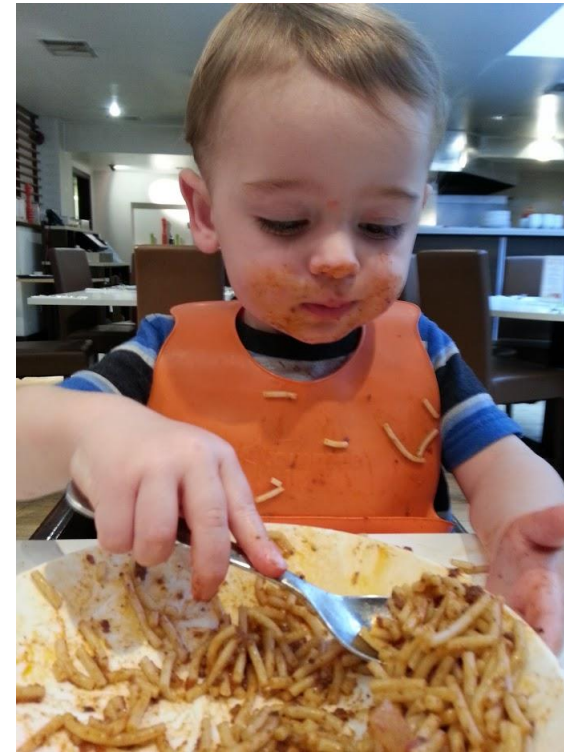
- Keith Foster is founder and CSO at Sutura Therapeutics
- The presentation may contain forward-looking statements. These statements relate to future events or Sutura Therapeutics' future financial performance. Any statements that are not statements of historical fact including without limitation, statements to the effect that the Company or its management "believes", "expects", "anticipates", "plans" (and similar expressions) should be considered forward looking statements. There are a number of important factors that could cause Sutura Therapeutics' actual results to differ materially from those indicated by the forward looking statements. Sutura Therapeutics disclaims any obligation to update any forward looking statement



# Natures Clues: Internalisation of Food



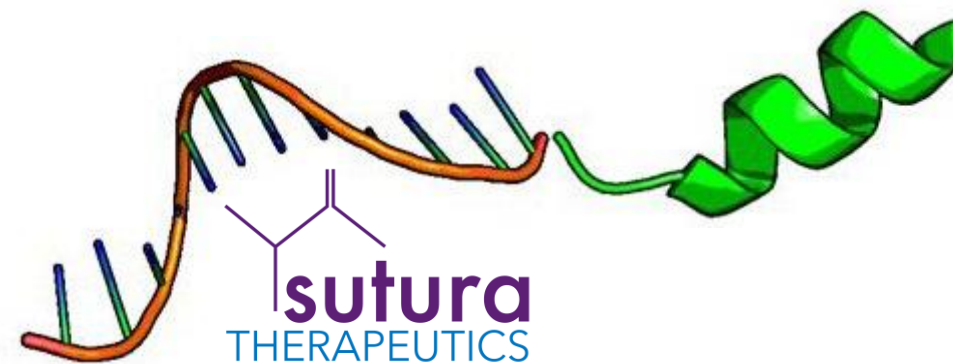
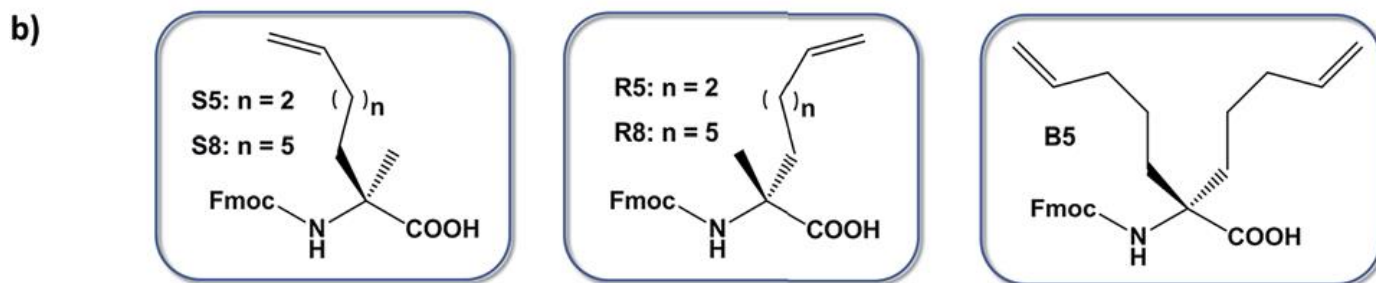
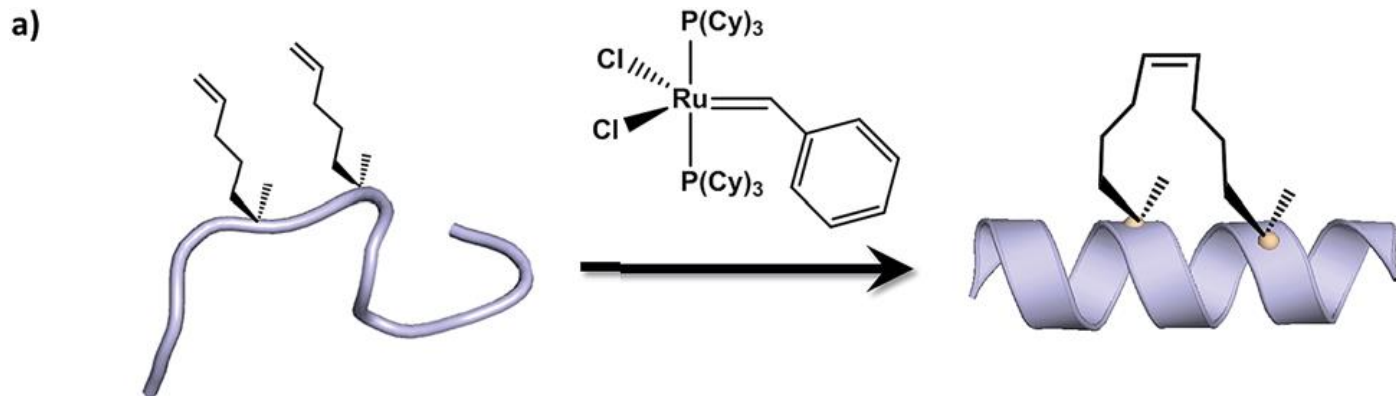
1 Cell



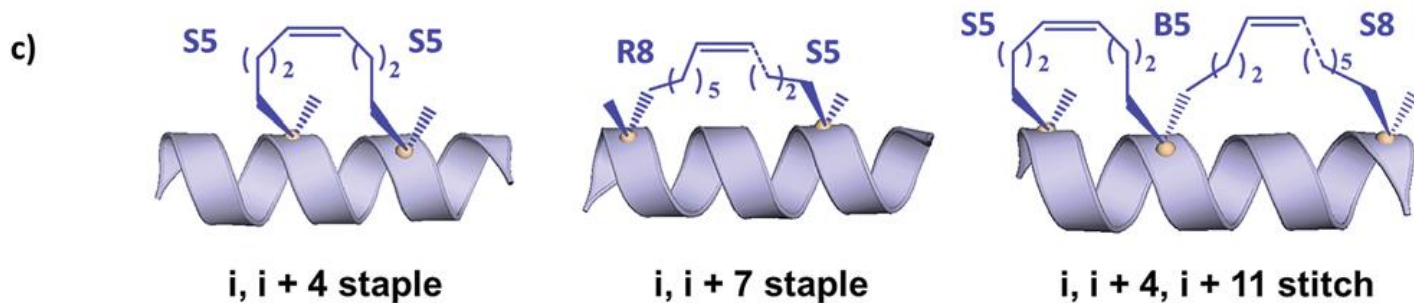
>1 Cell

Energy surveillance is critical for life  
Energy uptake and delivery is critical for life

## Developing 'molecular magnets'



SUT-001

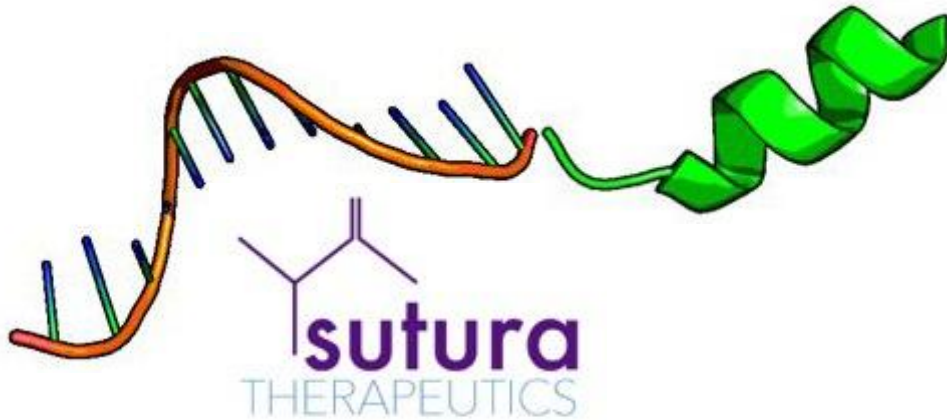


# So What Difference Does the Vehicle Make?



No  
Tissue Delivery

Heart Cell  
Brain Cell

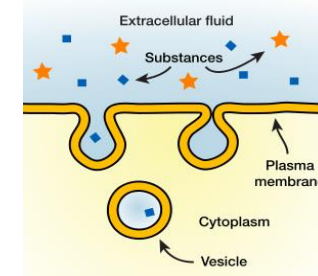
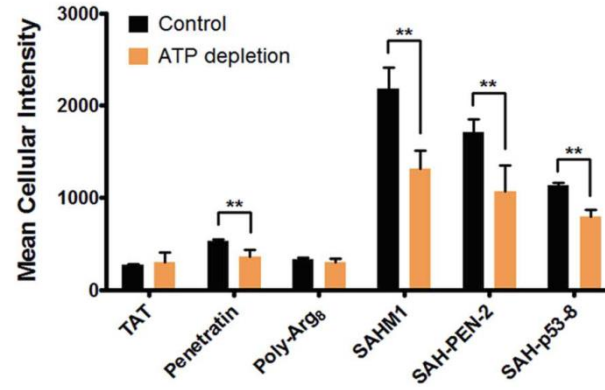
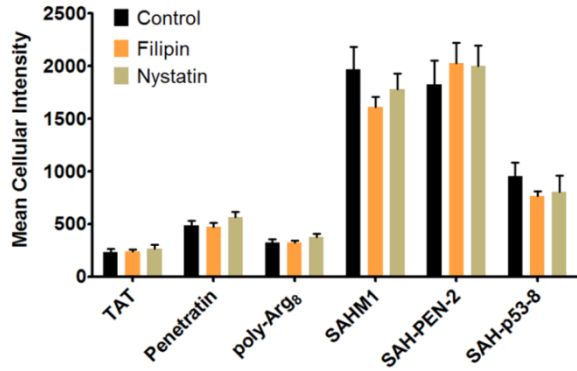


Efficient  
Tissue Delivery

Heart Cell  
Brain Cell

# Cell Entry Mechanisms

## Caveolin Inhibition

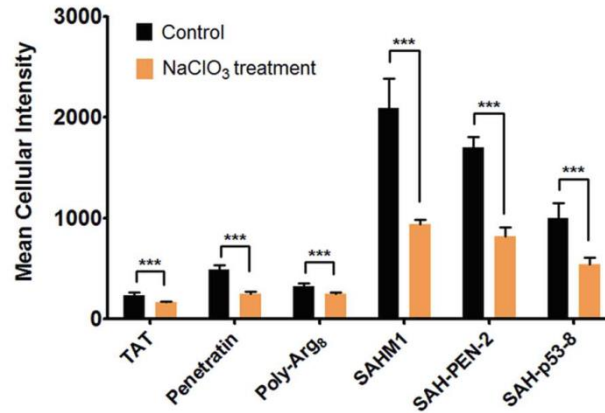
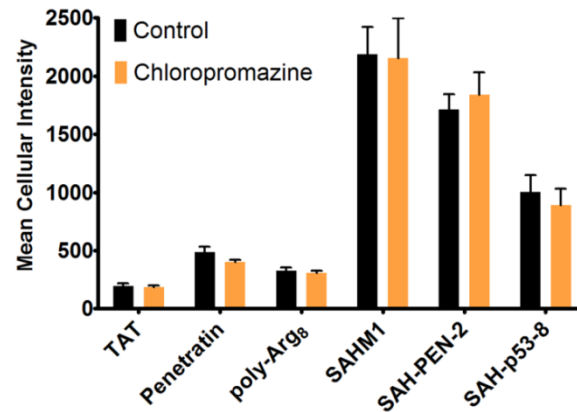


1 Cell



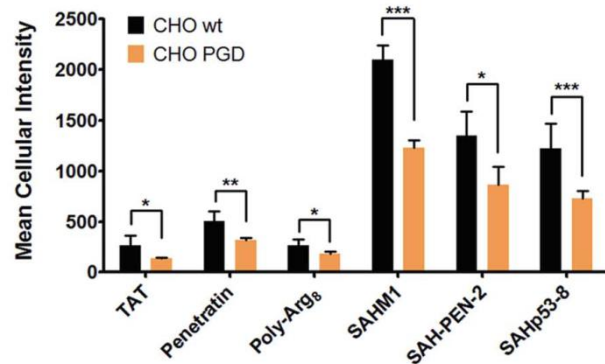
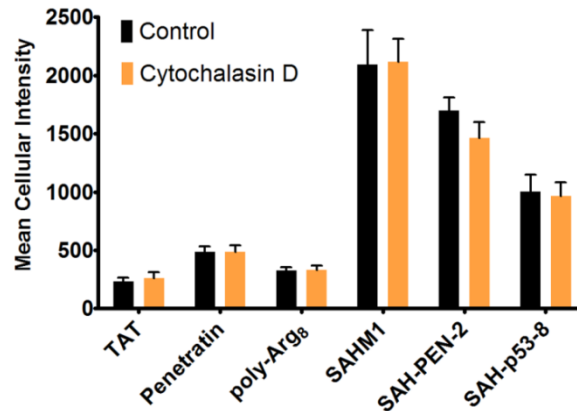
>1 Cell

## Clathrin Inhibition



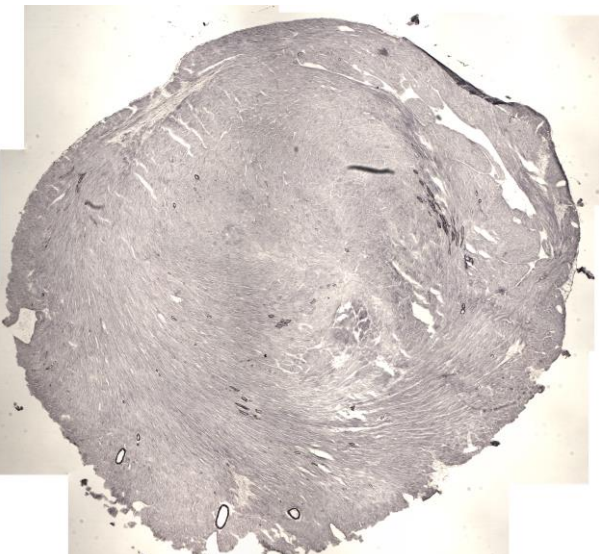
## Macropinocytosis Inhibitor

## Clathrin Inhibition

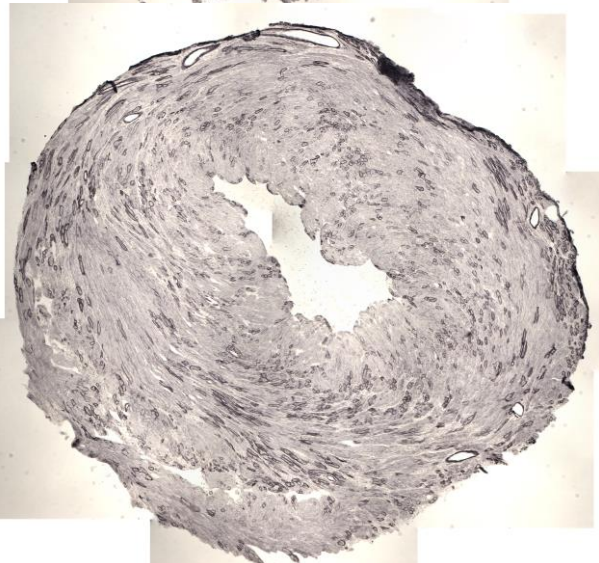


## Macropinocytosis Inhibitor





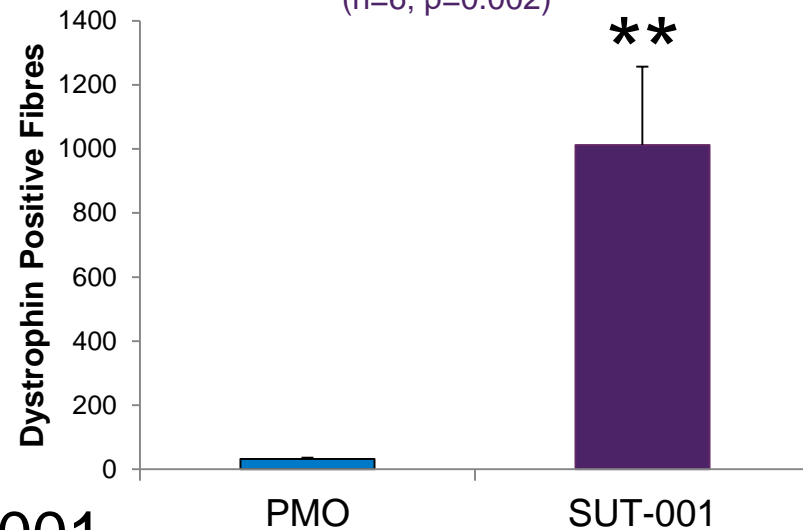
PMO



SUT-001

## Cardiac Muscle

*mdx* 12 week old  
2 week time point  
2 $\mu$ mol/kg injections  
(n=6; p=0.002)

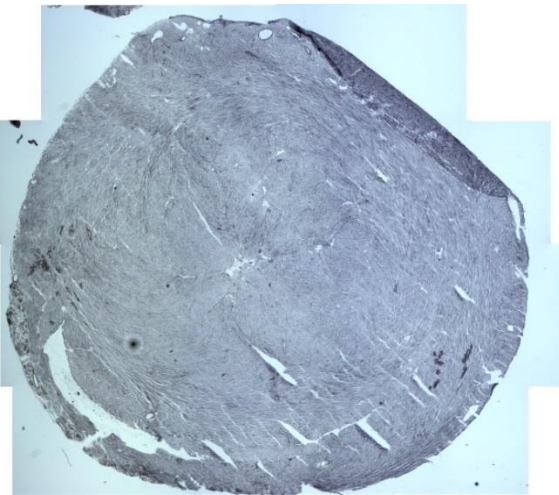


- Naked PMOs are **refractory** to cardiac muscle
- SUT-001 **significantly increases** delivery of PMO to cardiac muscle
- SUT-001 **significantly restores** dystrophin expression in cardiac muscle in DMD mouse model

## Cardiac Muscle

*D2mdx* 12 week old  
2 week time point  
2 $\mu$ mol/kg injections

PMO x1 Dose



30 Positive Fibres

SUT-001 x 1 Dose



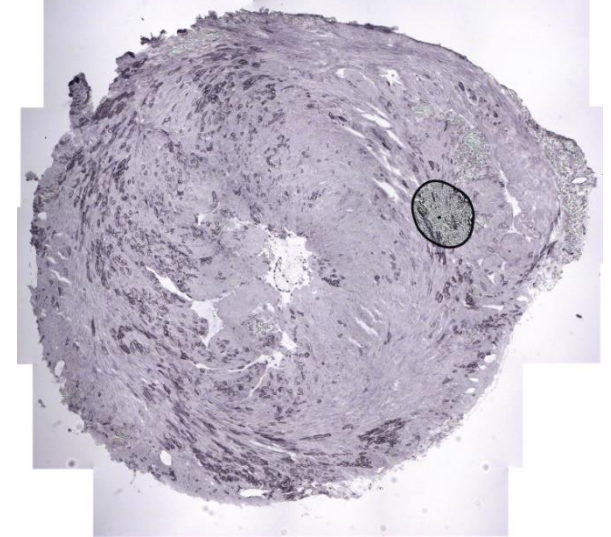
310 Positive Fibres

PMO x 4 Dose



30 Positive Fibres

SUT-001 x 4 Dose

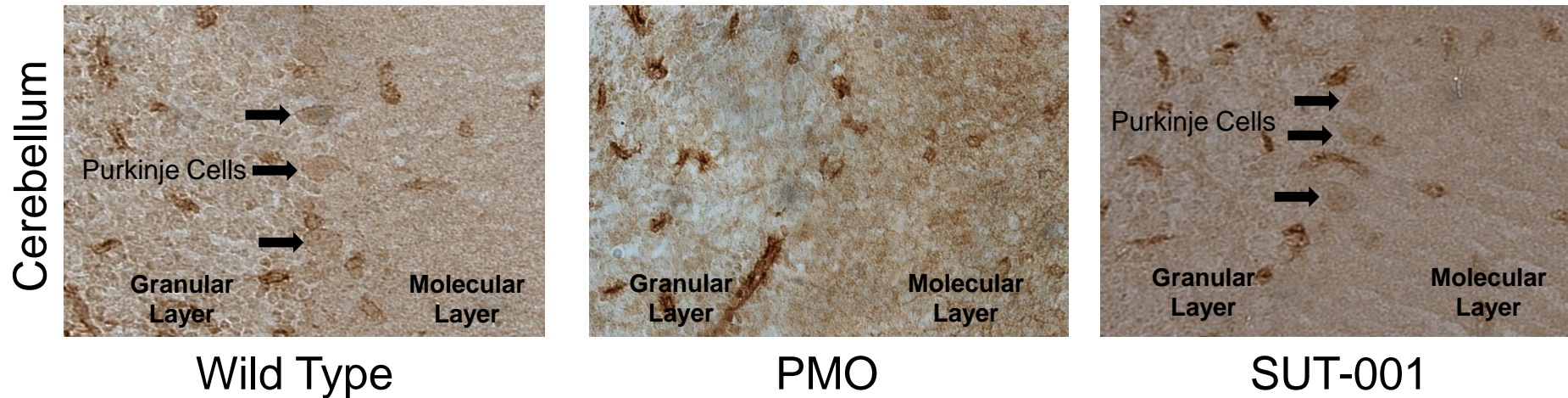


1350 Positive Fibres



## Cerebellum: Purkinje Cells

*mdx* 12 week old (DMD mouse model)  
2 week time point



- Naked PMOs are **refractory** to brain
- SUT-001 **restores** dystrophin expression in cerebellum of DMD mouse model

**Antisense PMO can turn UP or turn DOWN any gene**



## Diaphragm Muscle

*D2mdx* 12 week old  
2 week time point  
2 $\mu$ mol/kg injections

PMO x1 Dose



SUT-001 x 1 Dose



- Dystrophin Fibre = 250 PMO vs 1068 SUT-001 (4 fold)
- PMO BI/10 mdx 10 fold more  $dys^{+ve}$  cf to D2/mdx (gastrocs)

## Improving Cardiac Function

Parameter	Wild Type 18m	SUT-002 KO 18m
<b>E/A ratio</b>	1.15±0.02	1.32±0.04**
<b>IVRT/RR</b>	0.109±0.004	0.094±0.002**
<b>IVCT/RR</b>	0.132±0.008	0.106±0.007**
<b>ET/RR</b>	0.347±0.009	0.335±0.006
<b>E wave</b>	24.76±2.14	21.72±1.54
<b>MPI</b>	0.700±0.28	0.632±0.33
<b>EF%</b>	48.77±1.53	53.50±1.03*
<b>FS%</b>	28.5±1.06	31.91±0.75*
<b>SV µl</b>	42.01±2.70	60.69±3.89***

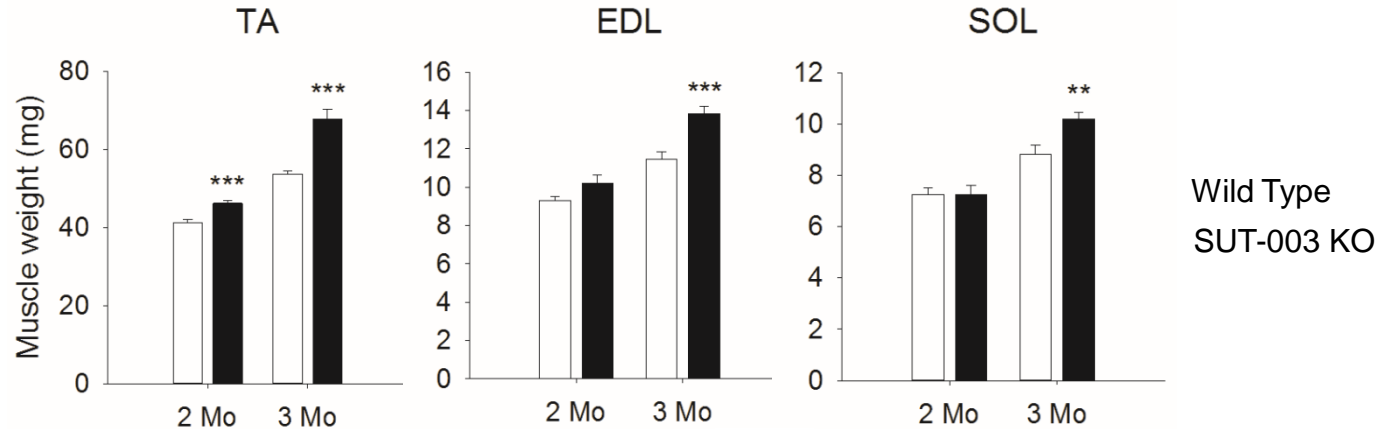
Parameter	Wild Type 18m	SUT-002 KO 18m
<b>Blood Pressure (mmHg)</b>	123.5±2.6	114.5±2.2*

Target gene is amenable to PMO based inhibition

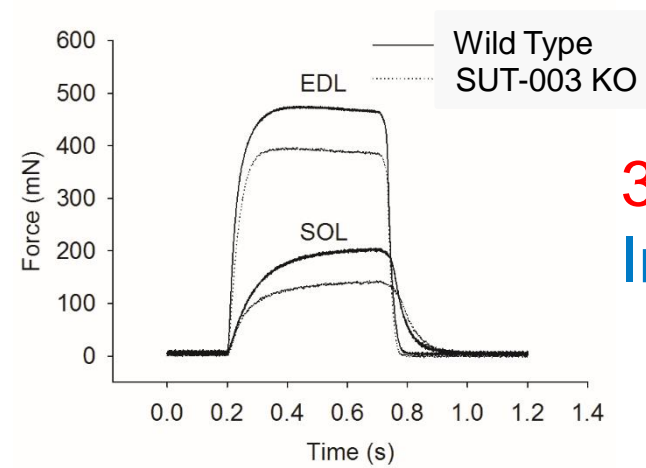
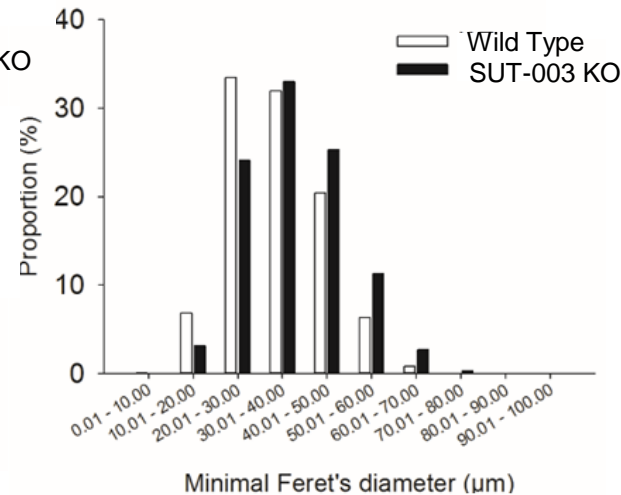
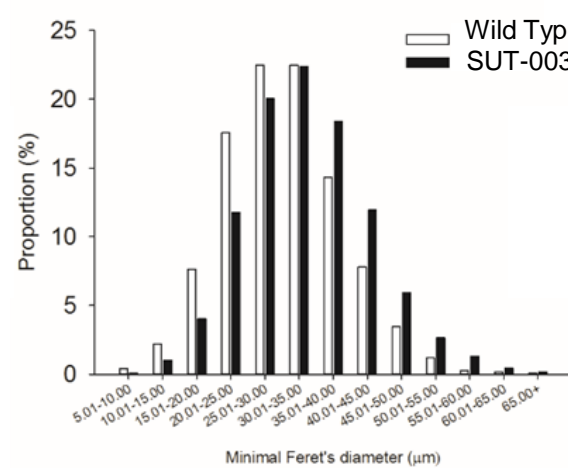
Target gene turned on in LIVER

# Developing Novel Targets: Muscle Function

## Improving Muscle Mass and Function



15% Increased  
In Muscle Mass



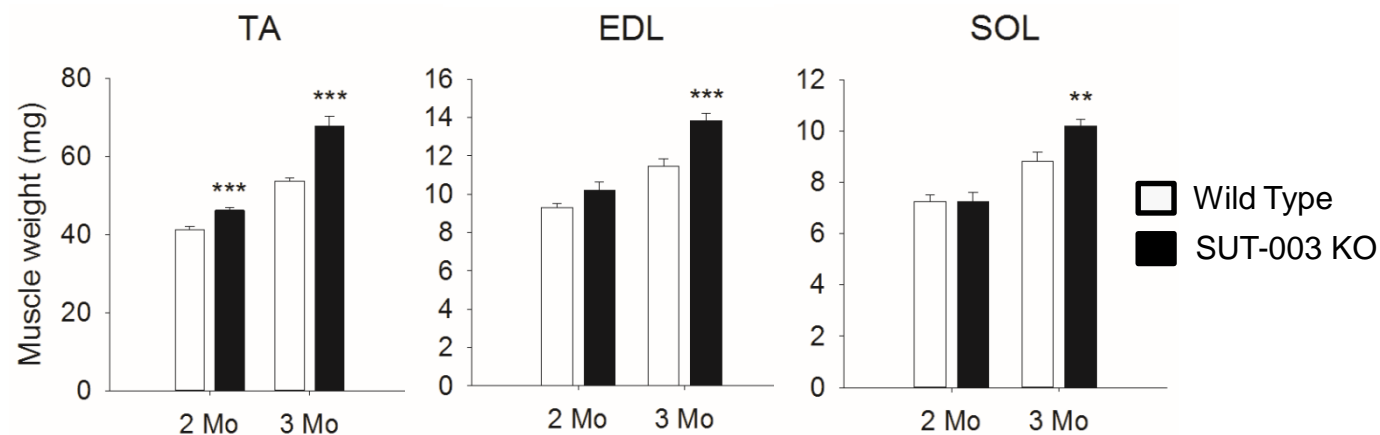
35% Increased  
In Muscle Mass

Target gene is amenable to PMO based inhibition

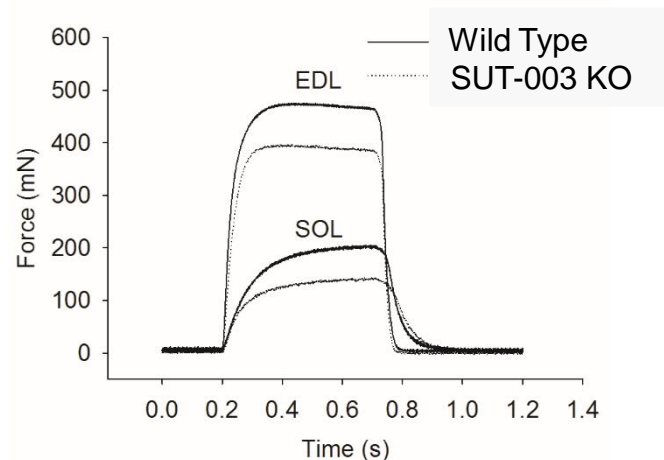
Target gene turned on in LIVER

## Improving Muscle Mass and Function

15% Increase Muscle Mass



35% Increase Muscle Mass

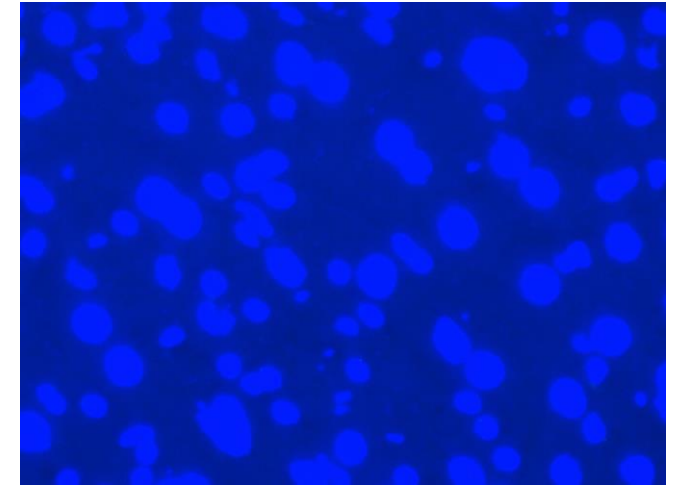
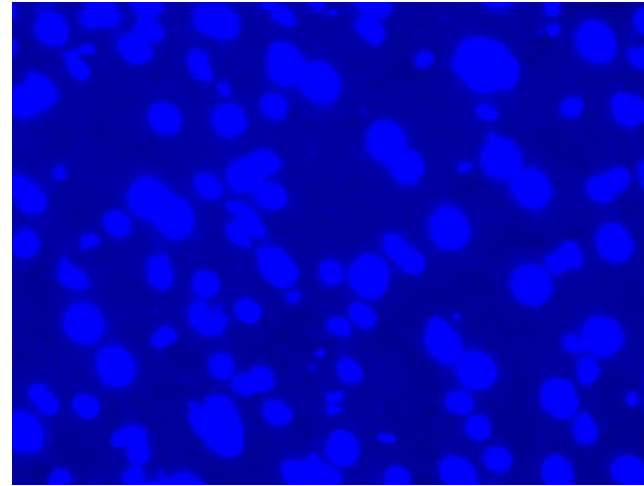
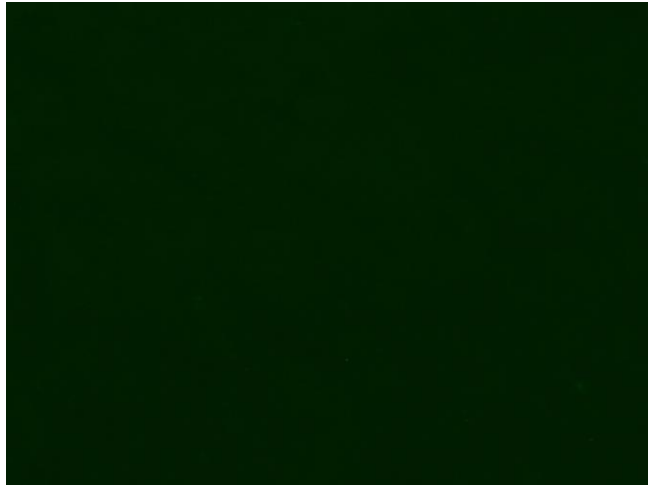


Target gene is amenable to PMO based inhibition

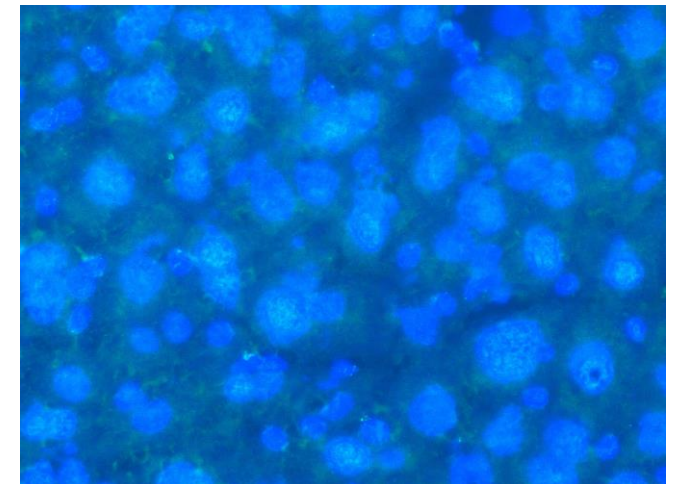
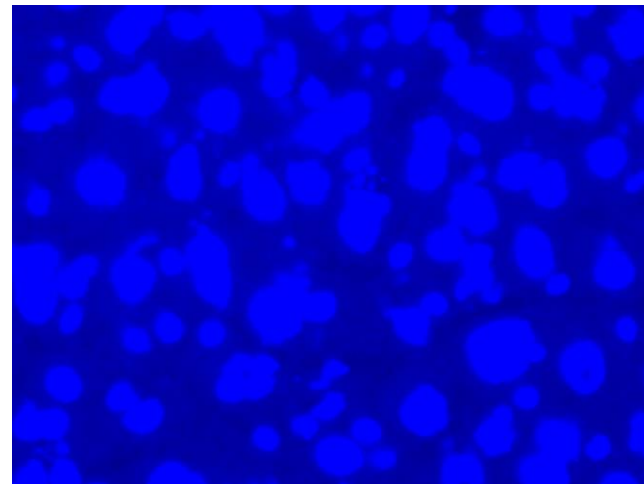
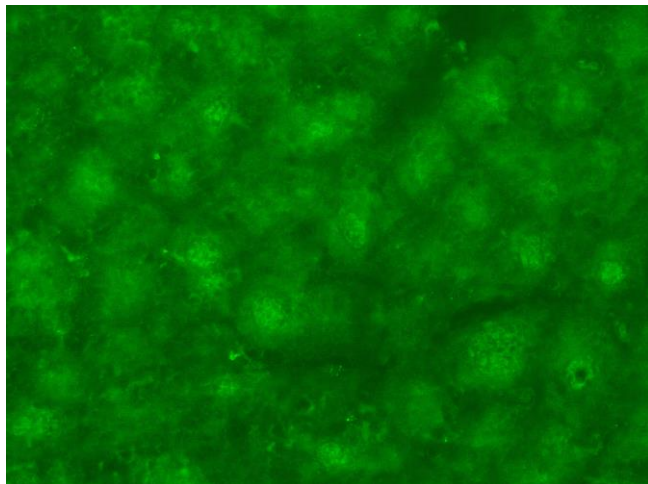
Target gene turned on in LIVER

## Systemic Administration of NG2-PMO

PMO



NG2-PMO

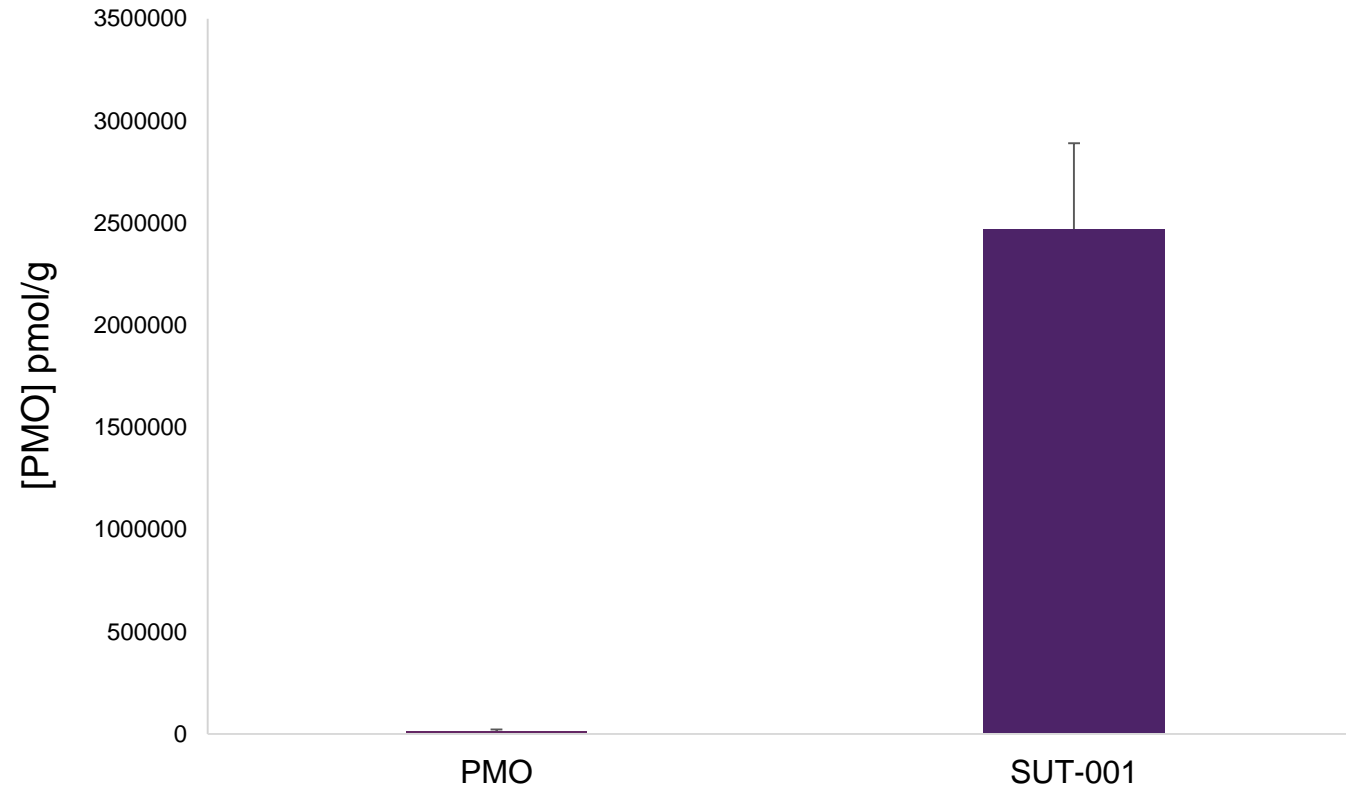


AF488nm (FITC)

DAPI

MERGED

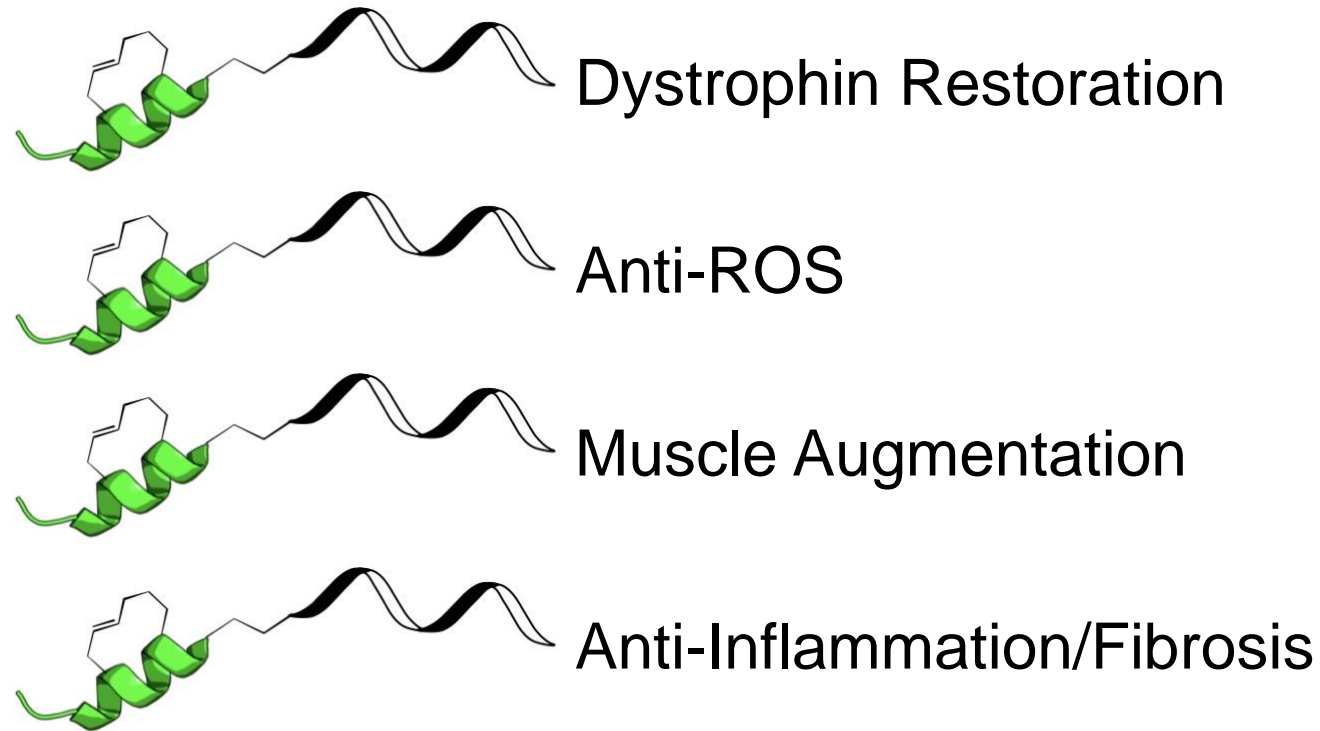
## Systemic Administration of NG2-PMO



- NG2-PMO **significantly increases** PMO delivery to hepatocytes liver (175 fold)



## Delivery Multiple Targets: Common Modality

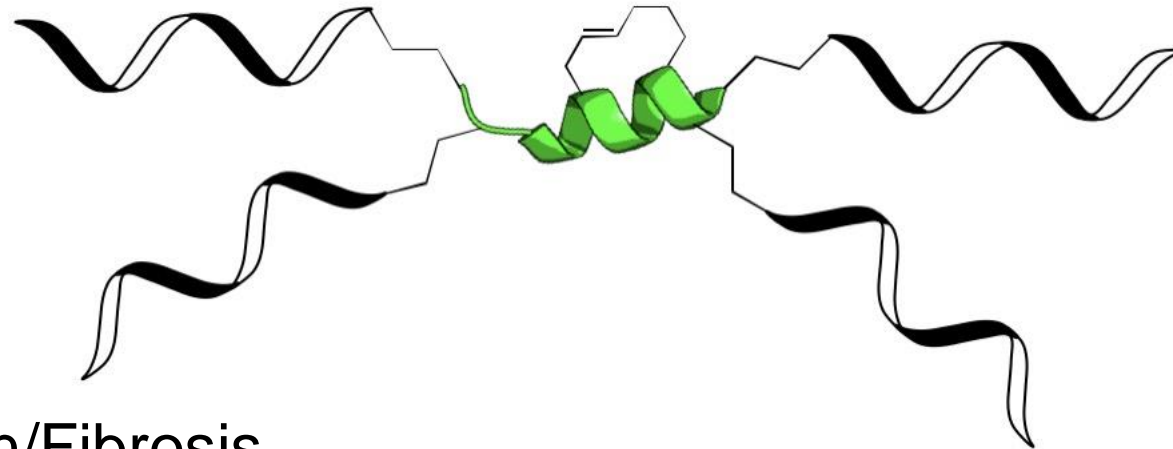


Antisense PMO can turn **UP** or turn **DOWN** any gene  
Holistic Approach to DMD Therapies



## Multi-Drug Delivery System

Dystrophin Restoration



Anti-ROS

Anti-Inflammation/Fibrosis

Muscle Augmentation

**Single Drug!!**

**Holistic Approach to DMD Therapies**

# We All Need Support



# Funding Support

**DUCHENNE  
NOW**



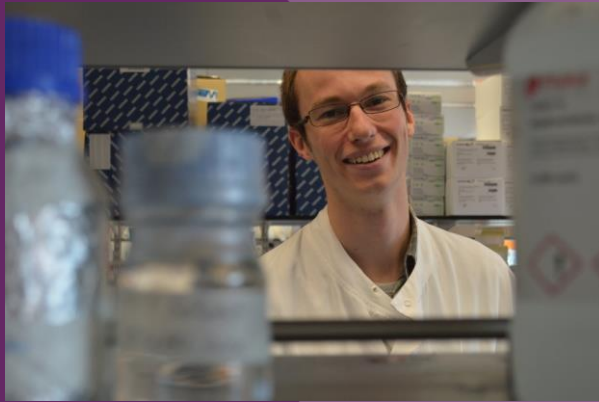
Joining**jack**.

**harrison's  
fund**  
fighting duchenne  
muscular dystrophy

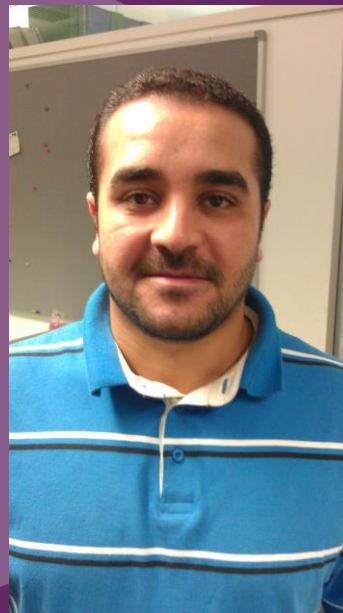


**sutura**  
THERAPEUTICS





Wouter Eilers



Mohamed Elashry



Helen Foster



Adam Gadd



Muzna Al Siyabi



Dammy Pinheiro



Kayvan Hakim-Rad

# My Community

## READING

Ketan Patel  
Andre Cobb

## HULL

Antonios  
Matsakas

## Harvard

Greg Verdine  
Gerry Hilinski  
Qian Chu

## Newcastle

Volker Straub  
Umar Burki

## UCD

Paul Crossey  
Daniel Jones



**Thank You**

# How We View Ourselves

undergraduate

PhD student

postdoc

PI / Professor

technician

seen by  
undergraduate



seen by  
PhD student



seen by  
postdoc



seen by  
PI / Professor



seen by  
technician



created by  
@biomatushiq  
<http://sotak.info/sci.jpg>

@biomatushiq