

Functional Effect of Failure of Adaptive Responses in Skeletal Muscle During Aging

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**THE UNIVERSITY
of LIVERPOOL**

Skeletal Muscle of Younger Individuals Adapts Rapidly Following Exercise

- **Structural remodelling**
- **Changes in gene expression**

- **Biochemical changes :**

Increases in antioxidant enzymes

and HSPs

TRANSCRIPTION FACTORS

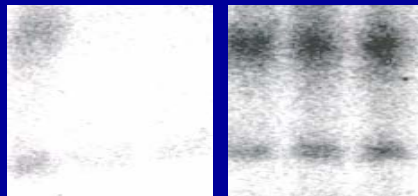
The HSP expression is regulated by **HSF** (HSF1 or HSF2)

NF- κ B and **AP-1** are important mediators of redox-responsive gene expression in skeletal muscle and both NF- κ B and AP-1 are actively involved in the upregulation of antioxidant defence enzymes such as SOD and catalase.

CHARACTERISATION OF ADAPTIVE RESPONSES IN MUSCLES OF ADULT MICE FOLLOWING A NON-DAMAGING CONTRACTION PROTOCOL

Transcription Factor DNA Binding Activity

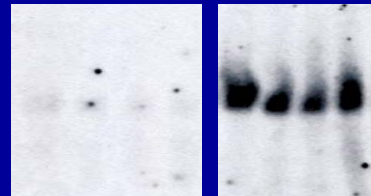
HSF



Pre-
exercise

Post-
exercise

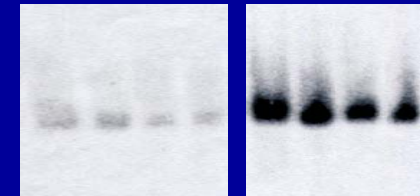
AP-1



Pre-
exercise

Post-
exercise

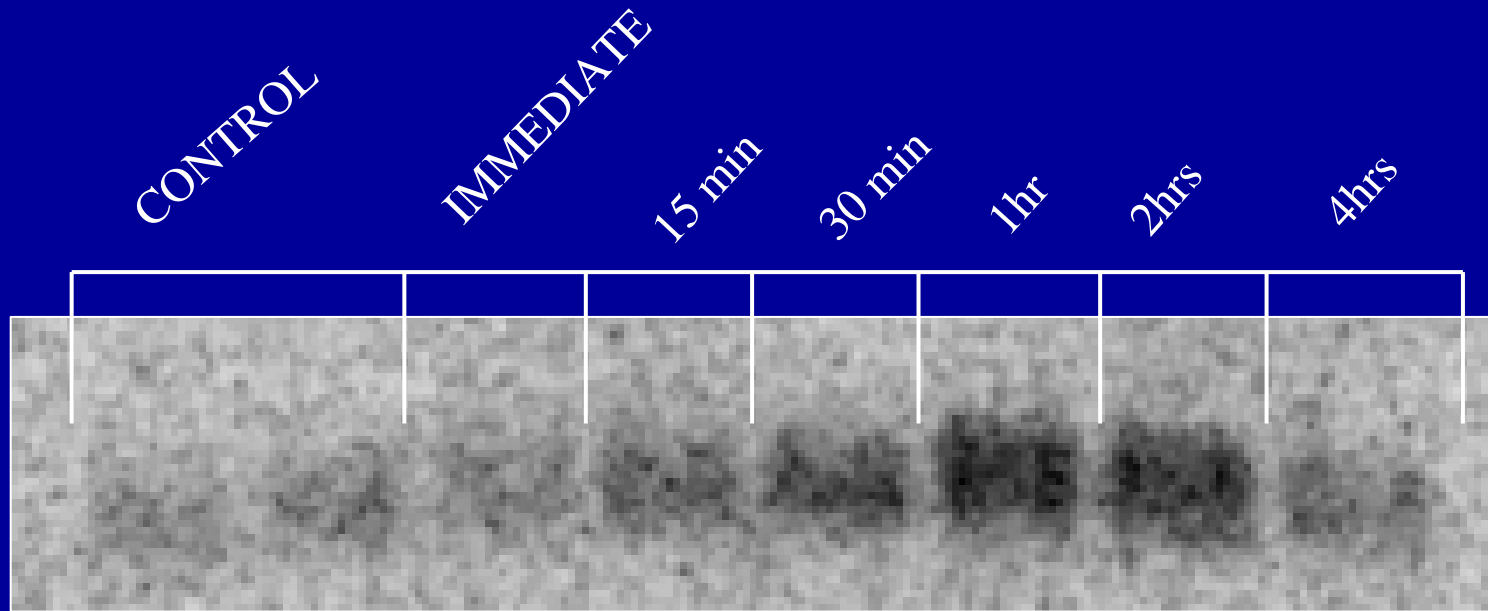
NF κ B



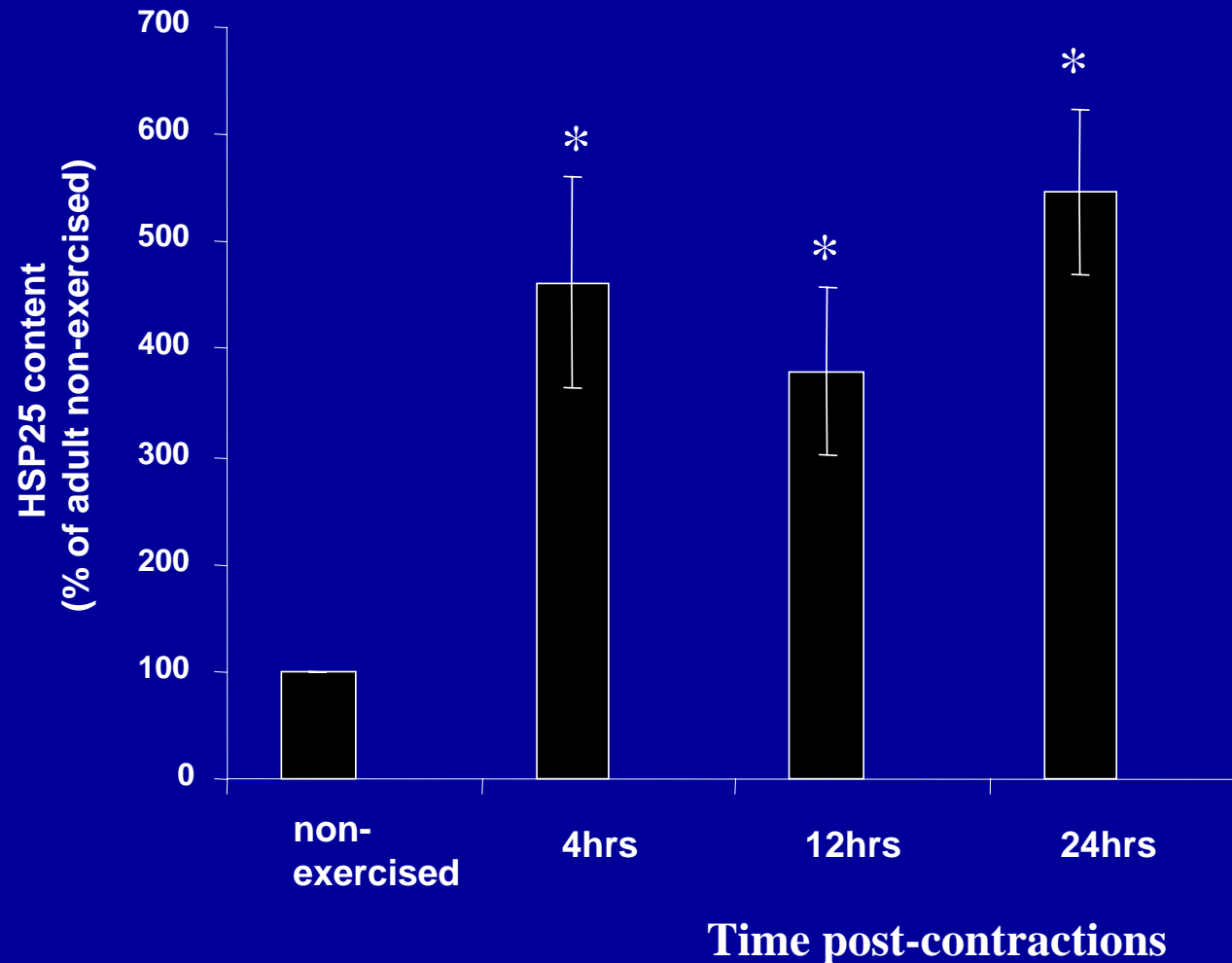
Pre-
exercise

Post-
exercise

HSP25 mRNA Content of Muscles Following a Period of Non-Damaging Isometric Contractions

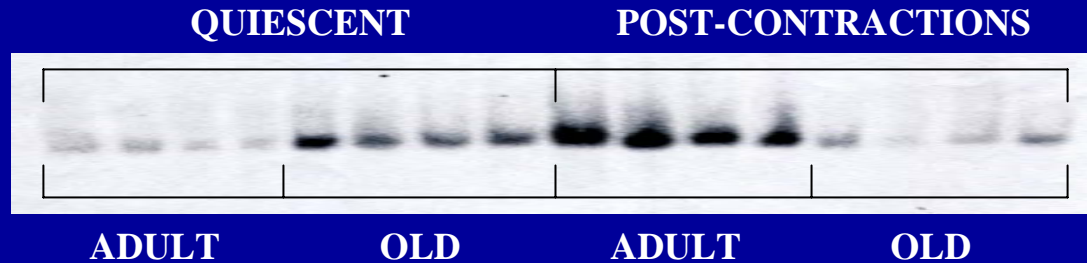


HSP25 Protein Content of Muscles Following a Period of Non-Damaging Contractions

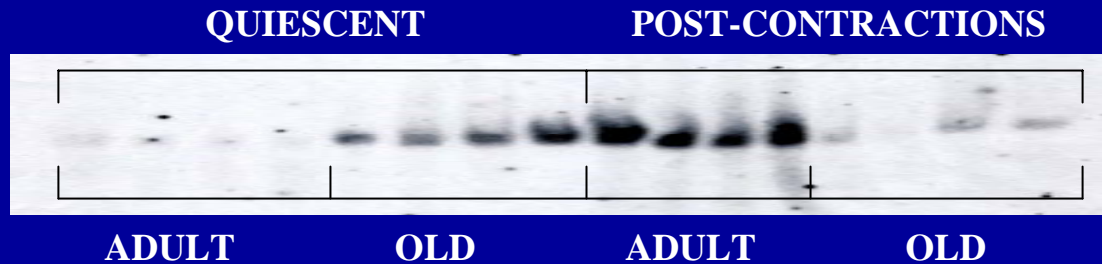


**THE ABILITY OF MUSCLES OF OLD
MICE TO RESPOND TO STRESS IS
ATTENUATED**

NF- κ B DNA Binding Activity

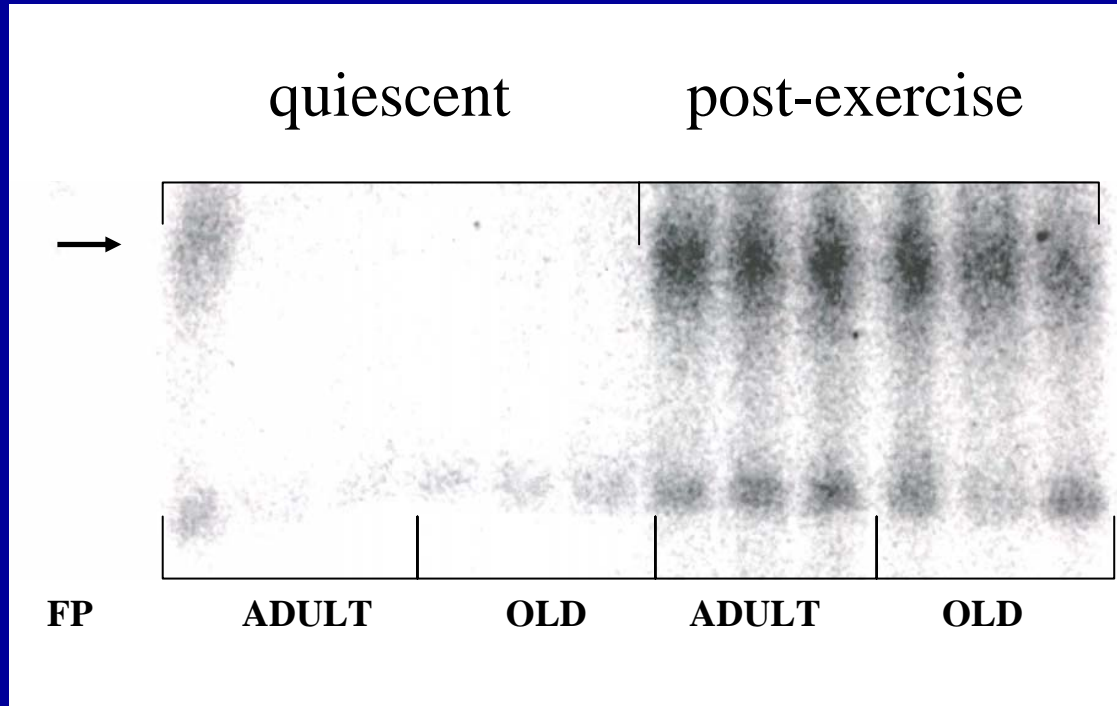


AP-1 DNA Binding Activity



NF- κ B and AP-1 DNA binding activity of whole cell extracts from AT muscle of quiescent adult and old male mice and AT muscles immediately following a period of isometric contractions.

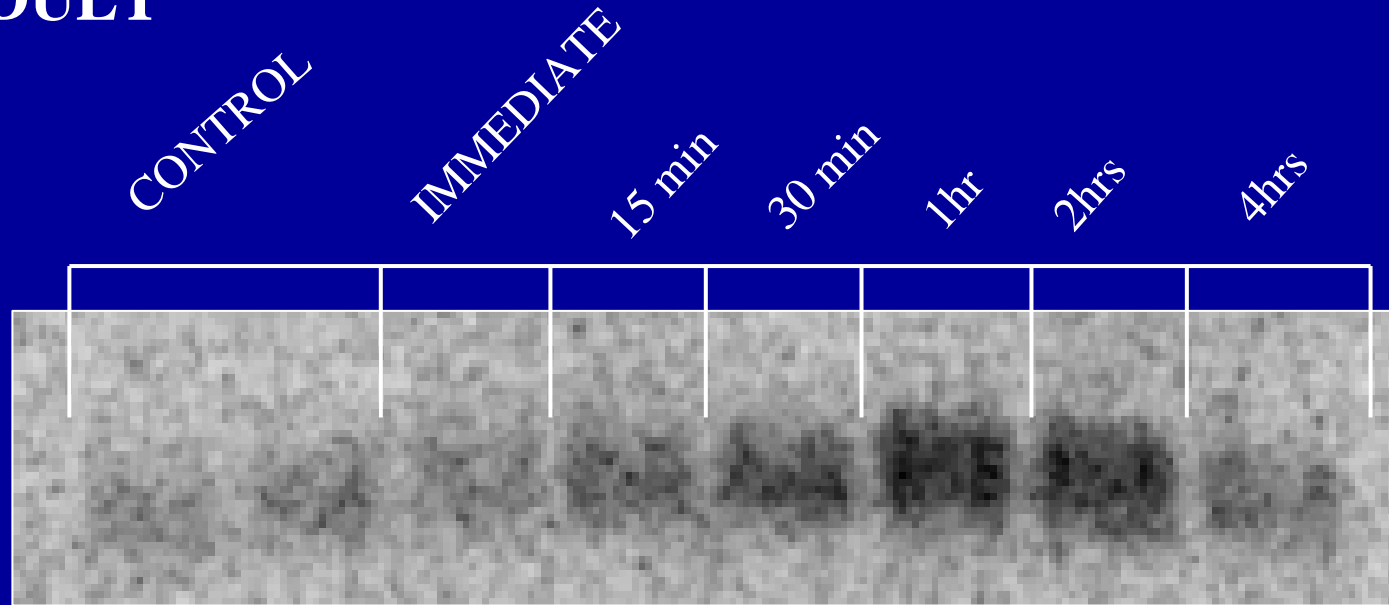
HSF DNA Binding Activity



HSF DNA binding activity of whole cell extracts from AT muscle of quiescent adult and old male mice and AT muscles immediately following a period of isometric contractions.

HSP25 mRNA Content of Muscles Following a Period of Non-Damaging Contractions

ADULT

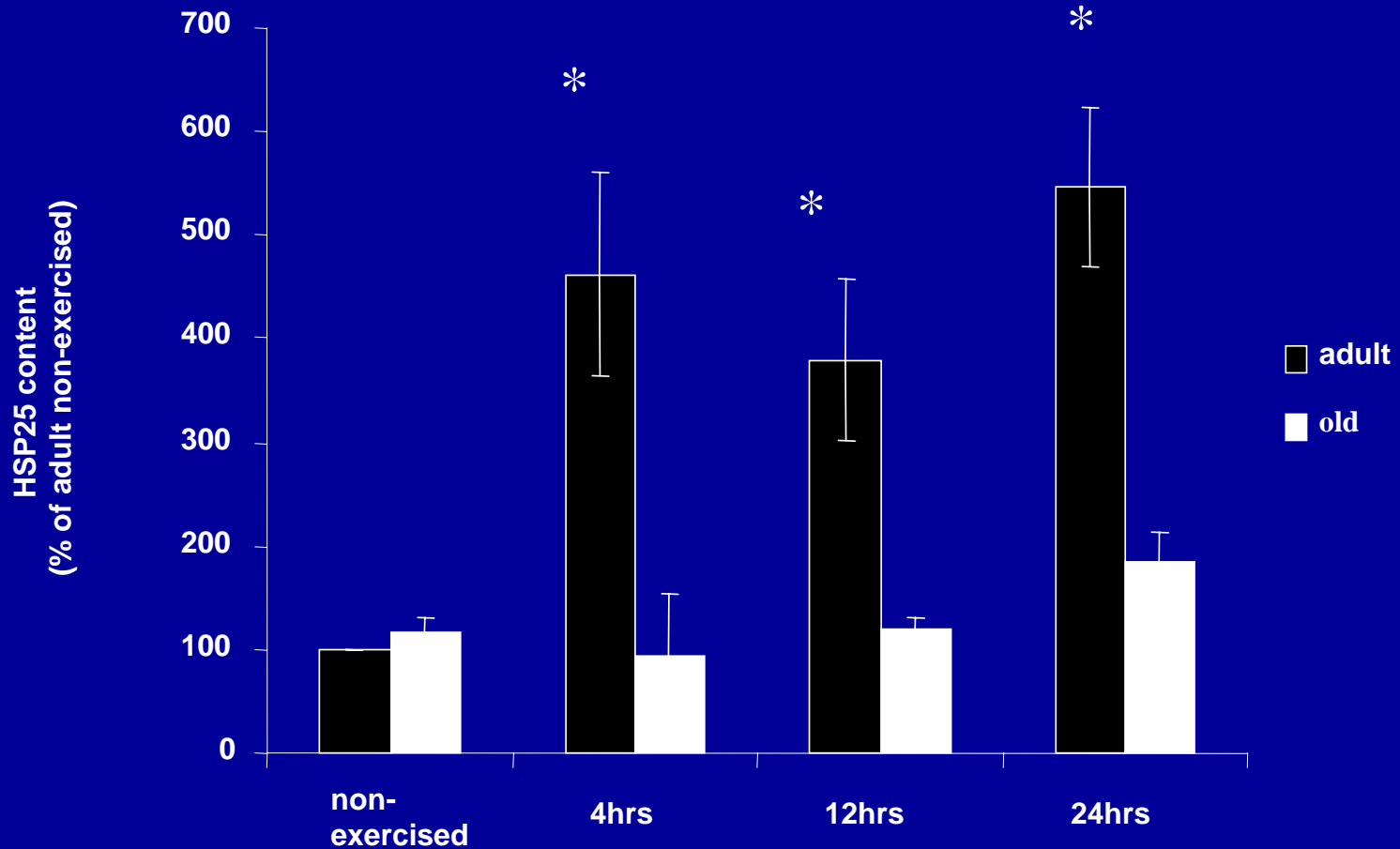


Control 1 hr

OLD



Old Muscles Do Not Produce HSPs in Response to Exercise



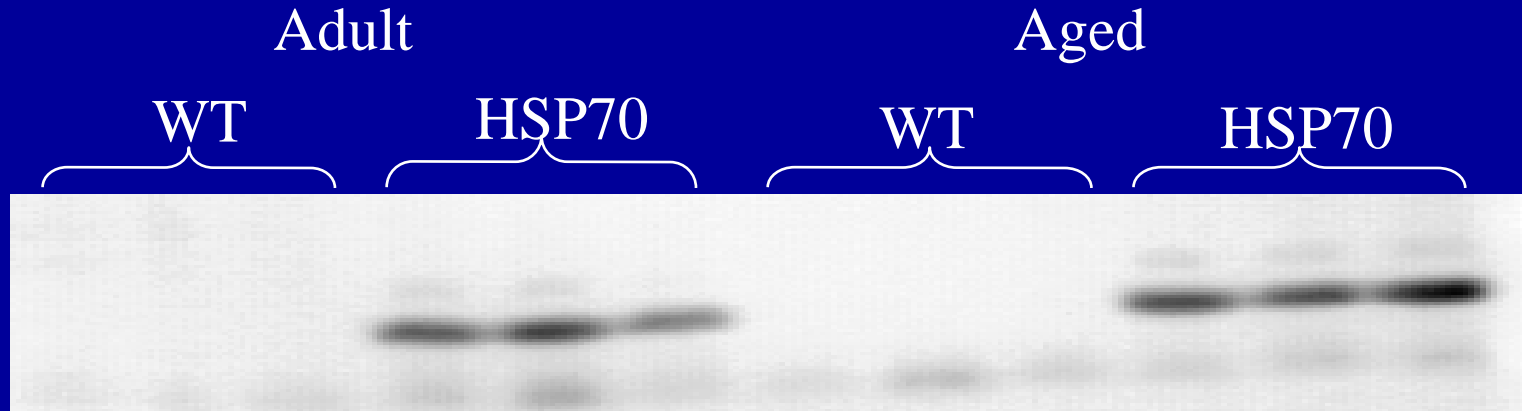
**WHAT IS THE FUNCTIONAL
EFFECT OF THE DECREASED
ABILITY OF OLD MUSCLES TO
PRODUCE HSPs?**

TRANSGENIC APPROACH TO OVEREXPRESS HSP70 IN SKELETAL MUSCLE OF AN ANIMAL MODEL

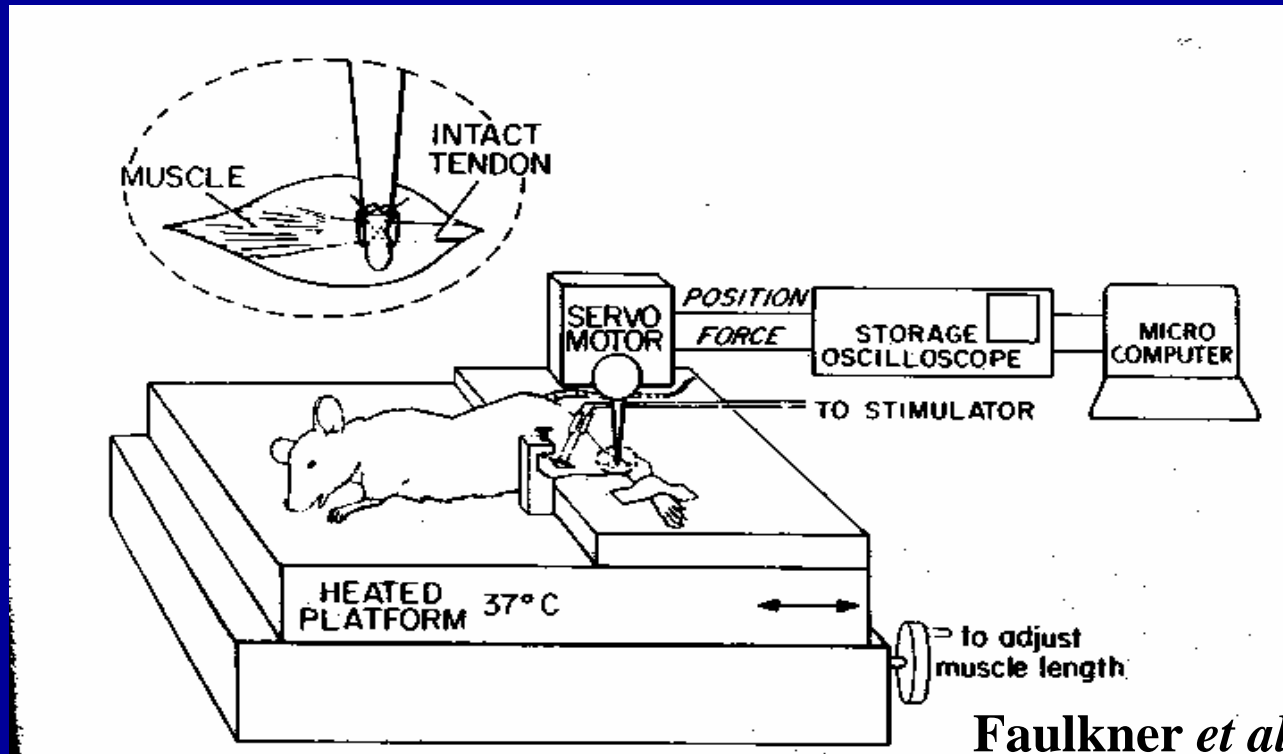
Professors Dillmann and Mestril.
University of California, San Diego.



Mice originally developed to
examine effect of HSP70 overexpression
in the heart: resistant to ischaemic injury
(Marber *et al*, JCI 1995; 95:1446-56)



LENGTHENING CONTRACTION PROTOCOL

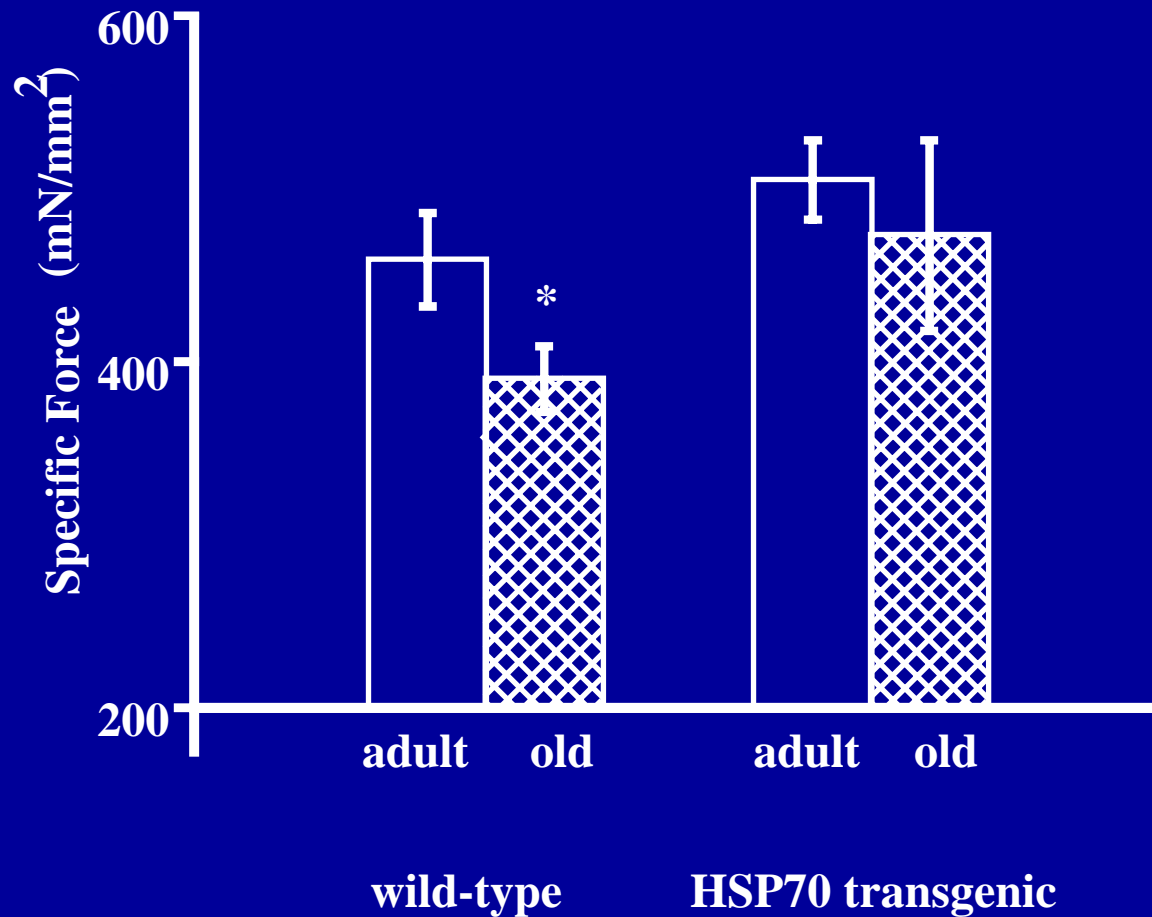


PLAN OF STUDY:

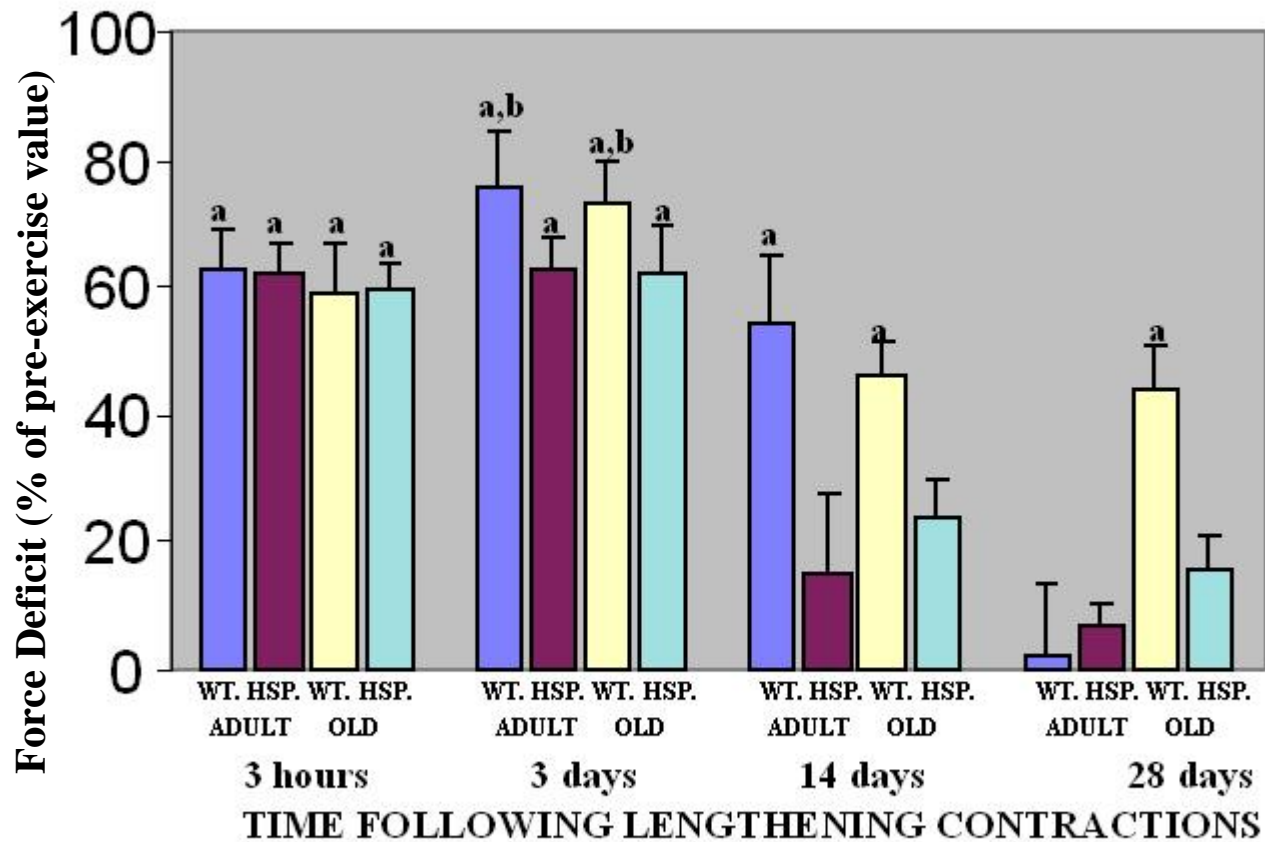
Examine:

- Susceptibility to exercise – induced damage
- Recovery from damage
- Specific force

EFFECT OF OVEREXPRESSION OF HSP70 ON THE SPECIFIC FORCE OF EXTENSOR DIGITORUM LONGUS MUSCLES



FORCE DEFICIT OF MUSCLES OF ADULT AND OLD HSP70 OVEREXPRESSOR AND WT MICE FOLLOWING A PERIOD OF DAMAGING EXERCISE



Other HSP modulated mice:

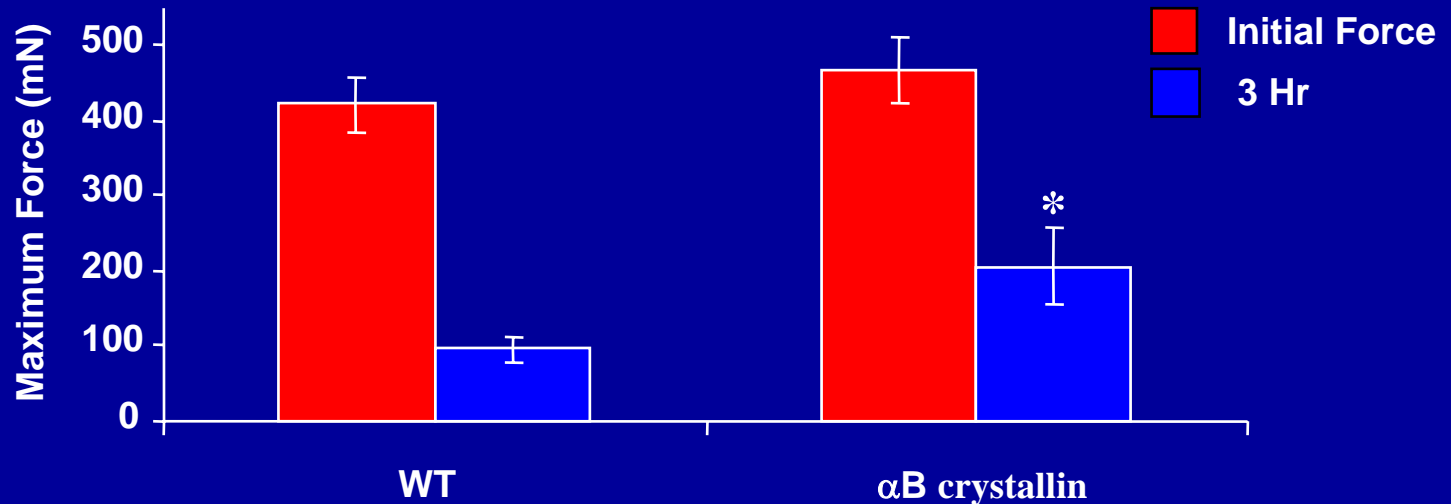
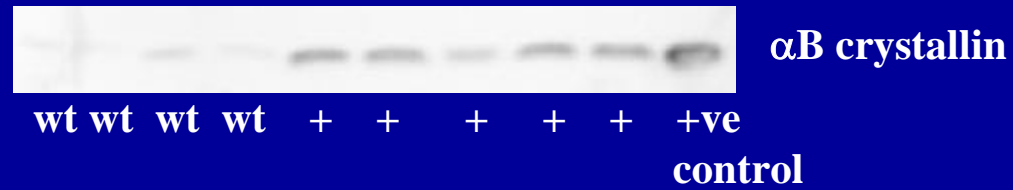
HSP27 and mHSP27 (Dr Dillmann)

HSP10 (Dr Dillmann)

α B crystallin (Dr Dillmann)

HSF1 knockout mice (Dr Benjamin)

Maximum force generated after 3 hours following a period of damaging lengthening contractions in adult WT and α B crystallin overexpressors

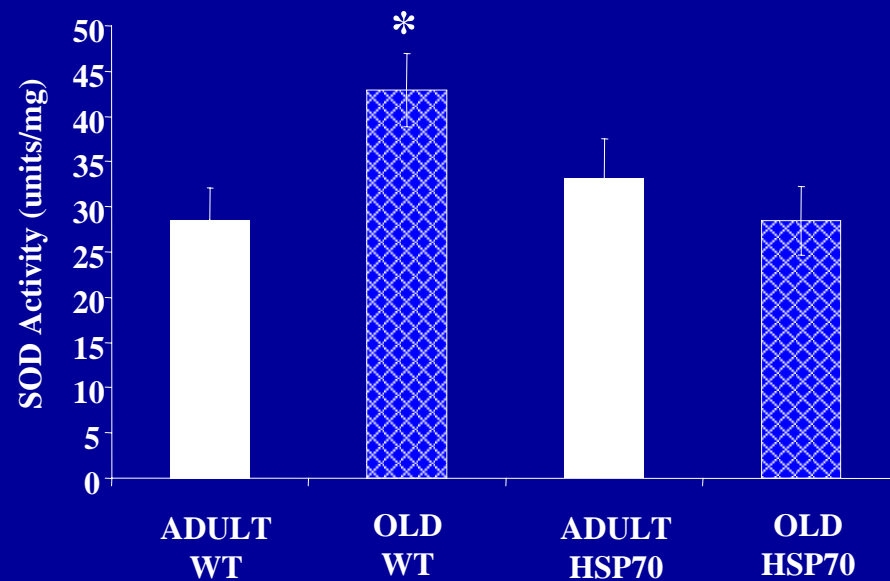
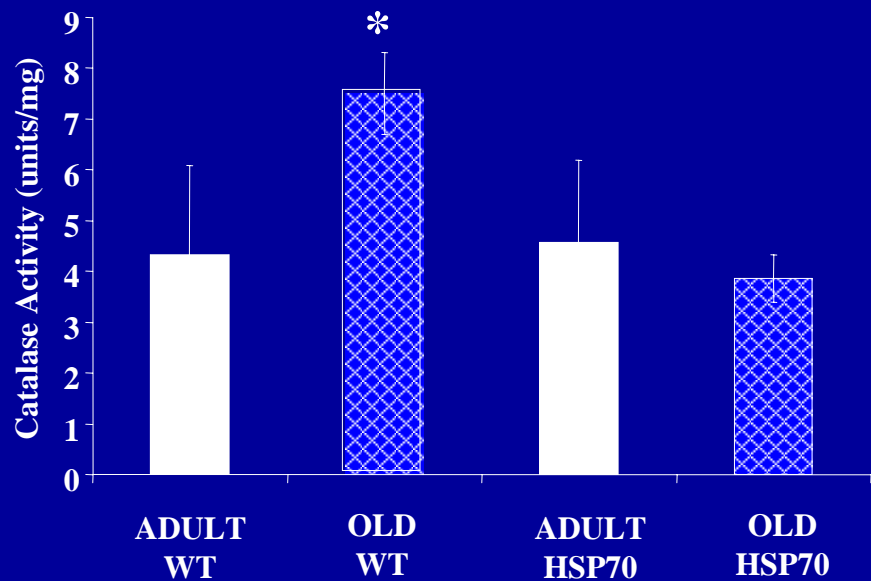


*, $p < 0.05$ cf. WT, 3hr time point

**WHAT IS THE MECHANISM BY
WHICH HSP70 PROVIDES
PROTECTION?**

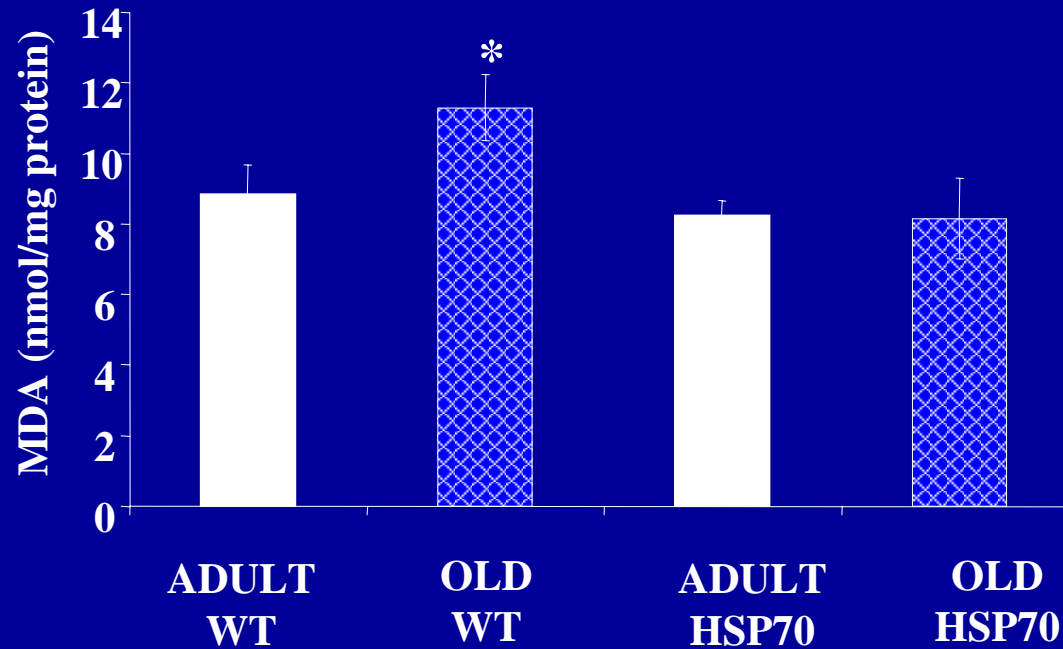
Free radical theory of ageing

Catalase and SOD Activity of Quiescent Muscles from WT and HSP70 Overexpressor Mice

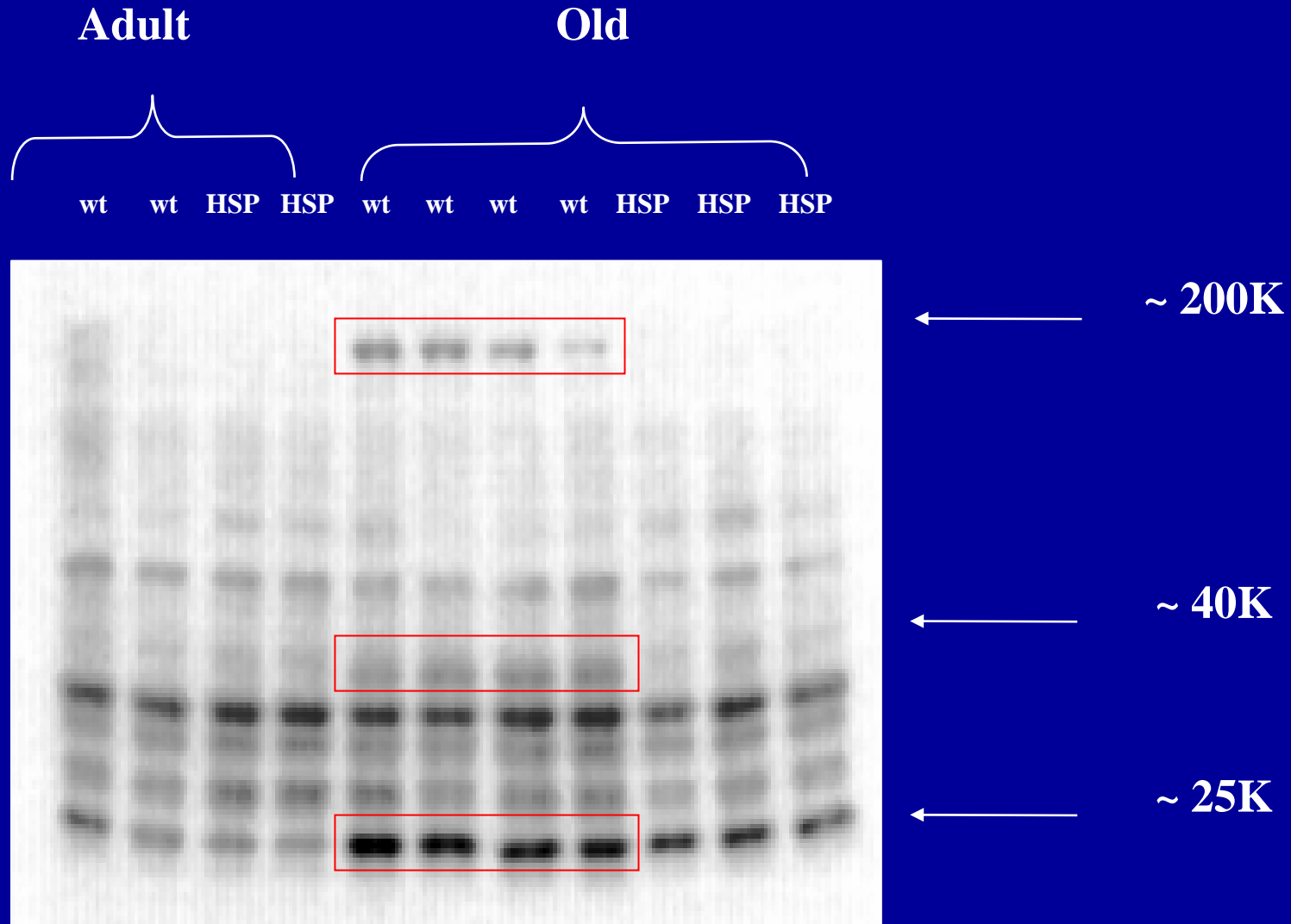


Protein content:
MnSOD – no age effect
CuZnSOD – 57% increase

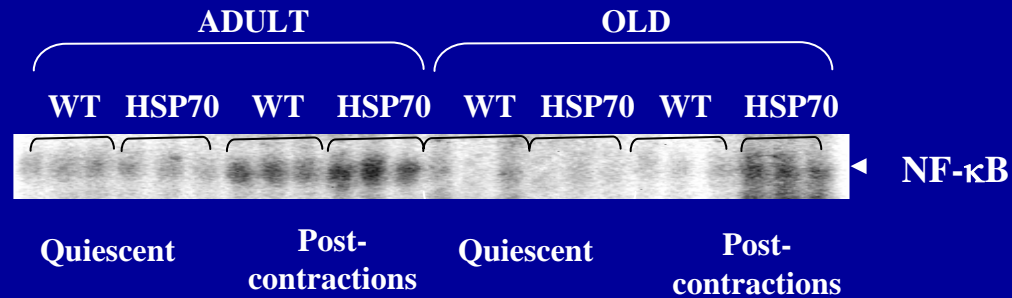
MDA Content of Quiescent Muscles From WT and HSP70 Overexpressor Mice



HSP70 may represent an important mechanism of protection against oxidative damage to proteins



NF κ B DNA Binding Activity in Muscles of Adult and Old WT and HSP70 Mice Following Isometric Contractions



Manipulations that reduce oxidative damage in muscles of old mice restore adaptive responses to isometric contractions and the ability to regenerate fully following damage



Adaptive Responses in Muscles of Mice with Modified Antioxidant Systems

NIA Program-Project

John Faulkner (Ann Arbor)

Malcolm Jackson (Liverpool)

Arlan Richardson (San Antonio)

Holly Van Remmen (San Antonio)

Marie Csete (Atlanta)

- **Adult and old male and female WT mice**
- **Adult and old *MnSOD*^{+/-}; *CuZn SOD*^{+/-}; *CuZn SOD*^{-/-}.**
- ***GPx1*^{-/-}; *GPx4*^{+/-}.**

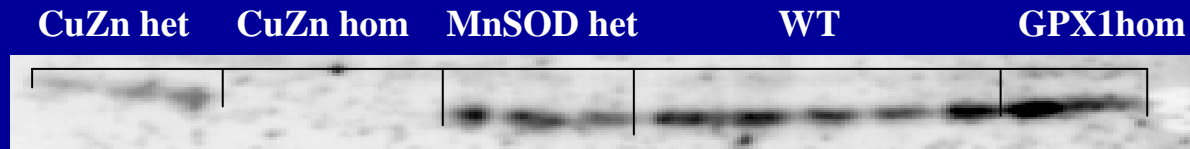
Muller *et al*, FRBM, 2006.

***CuZnSOD*^{-/-} mice (*Sod1*^{-/-} mice).**

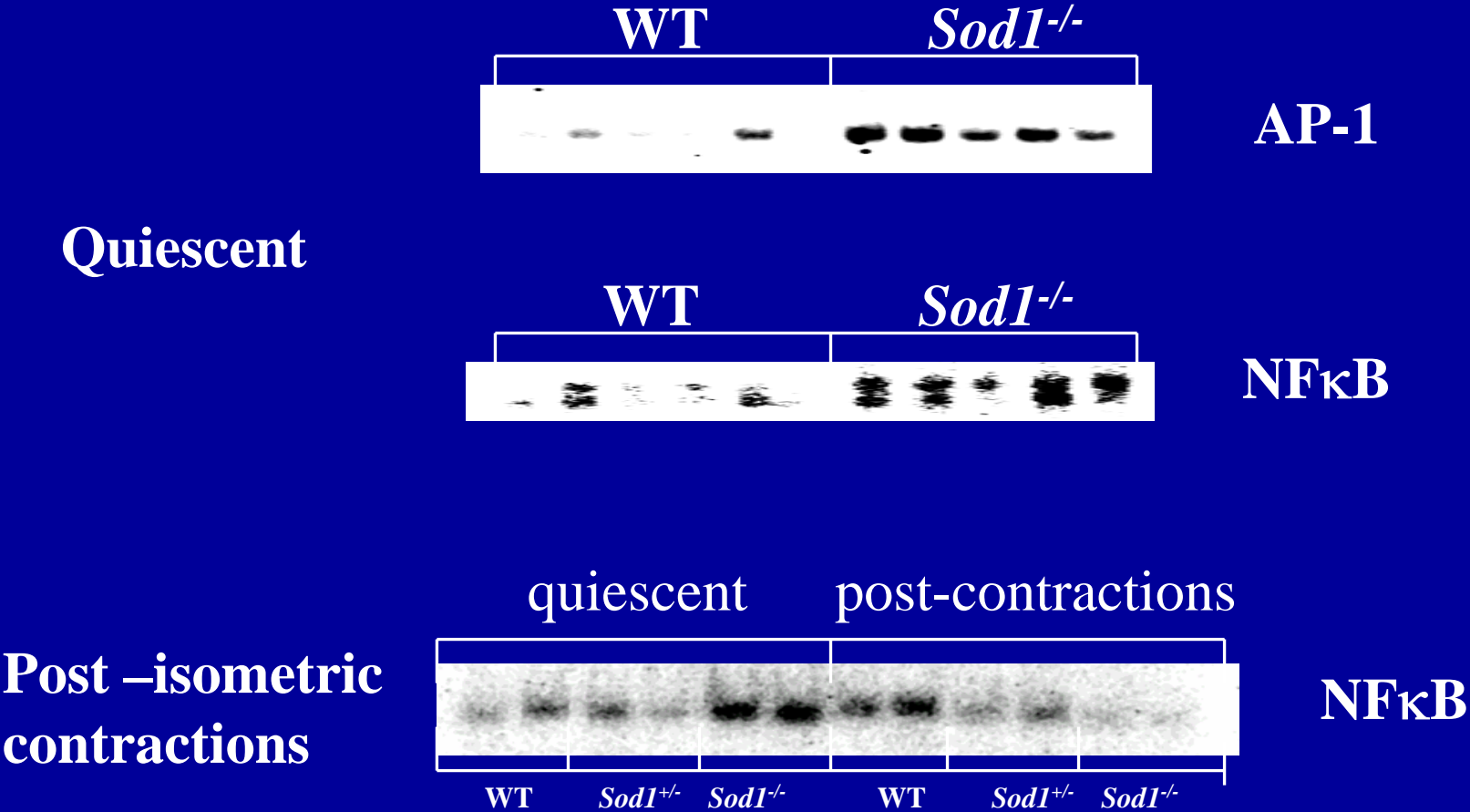
Acceleration of age-related loss of skeletal muscle mass and function.

Characterisation of MnSOD and CuZnSOD Protein levels in Muscles of Knockout Mice

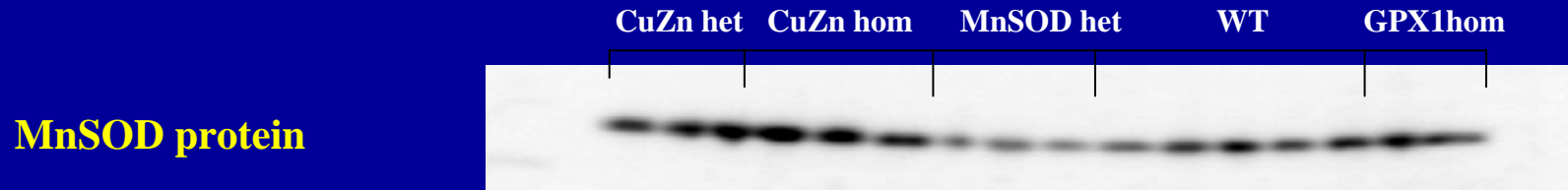
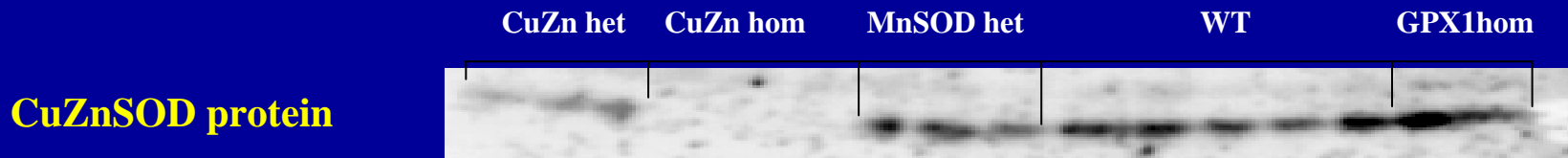
**CuZn SOD
protein levels**



EMSA analysis of muscles of adult WT and *Sod1*^{-/-} mice



Characterisation of MnSOD and CuZnSOD Protein levels in muscles of knockout mice



Summary from *Sod1*^{-/-} mice

- **Knocking out CuZnSOD causes:**
 - **Decreased extracellular hydrogen peroxide content at rest, no increase with contraction protocol**
 - **Increased HSF1, NFκB and AP-1 binding activity in muscles of quiescent mice**
 - **Increased MnSOD content**

CONCLUSIONS

1. Increase in antioxidant enzyme activity and HSP content in muscles of adult mice following isometric contractions.
2. In quiescent muscle of old mice data showed an increase in antioxidant enzyme activity and a marked attenuation in the stress response in comparison with adult mice.
3. Adult *Sod1*^{-/-} mice appear to show some characteristics of the biochemical changes seen in WT muscle during the ageing process.

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Research into Ageing



Help the Aged



NIA Program-Project

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