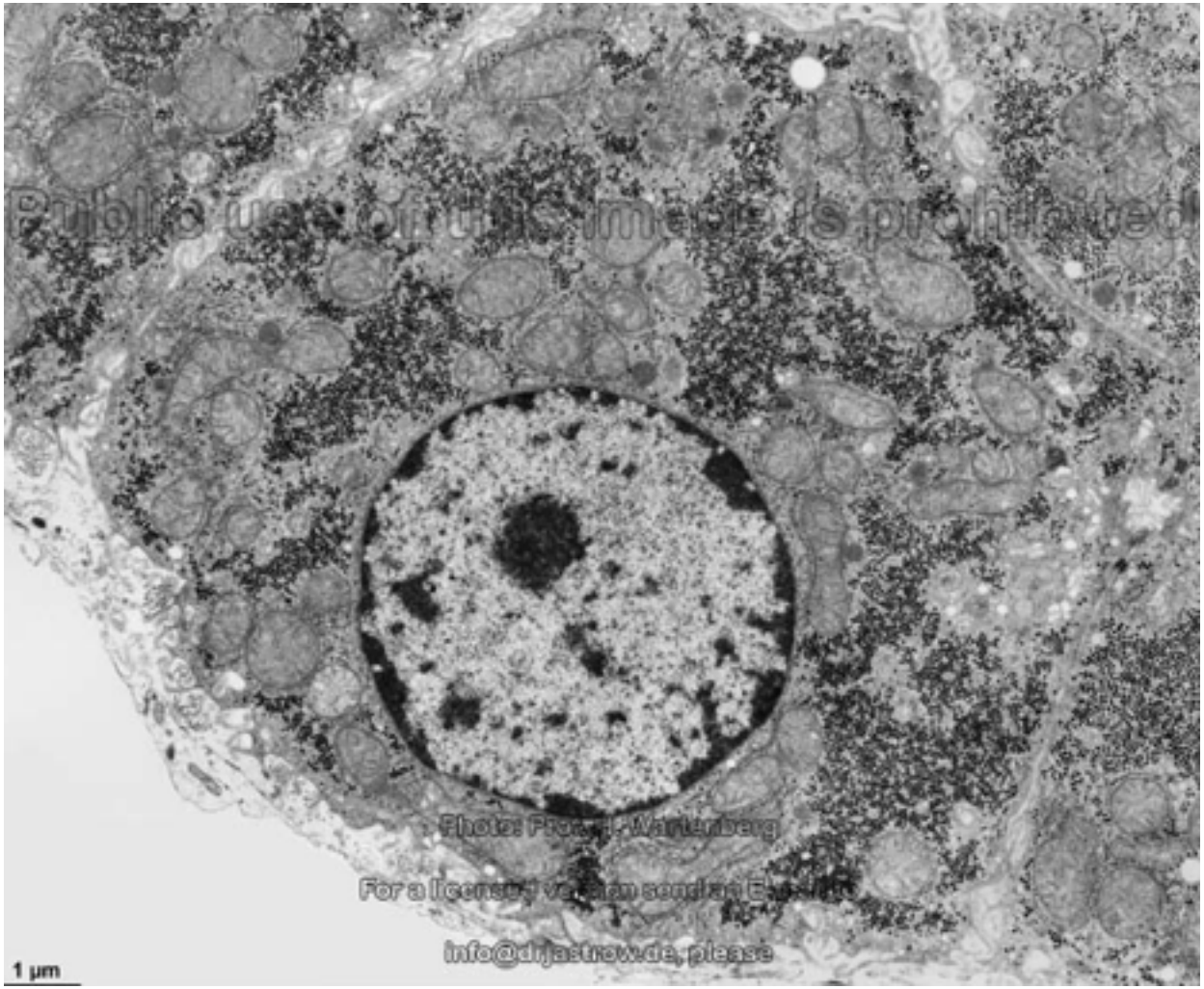
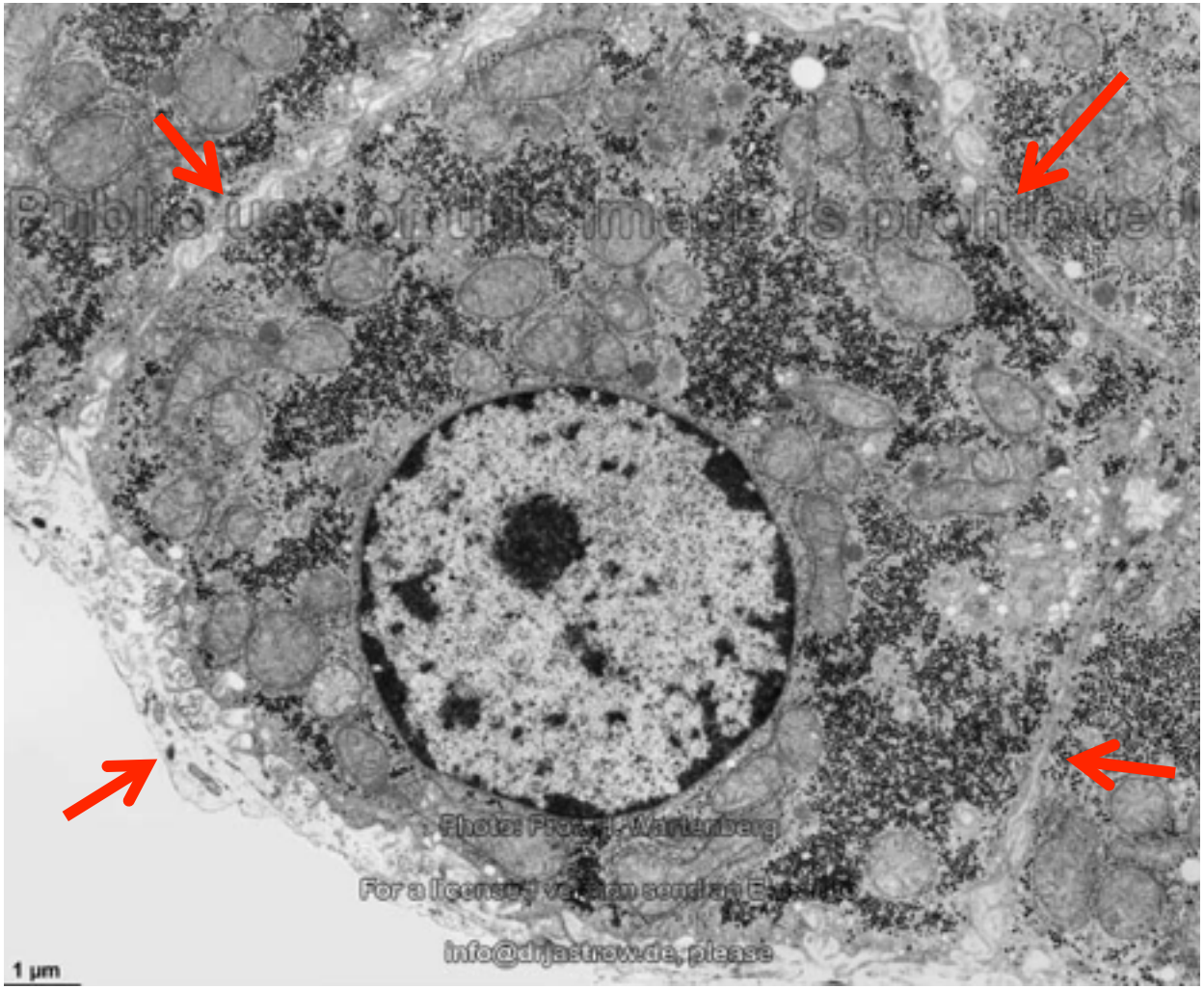
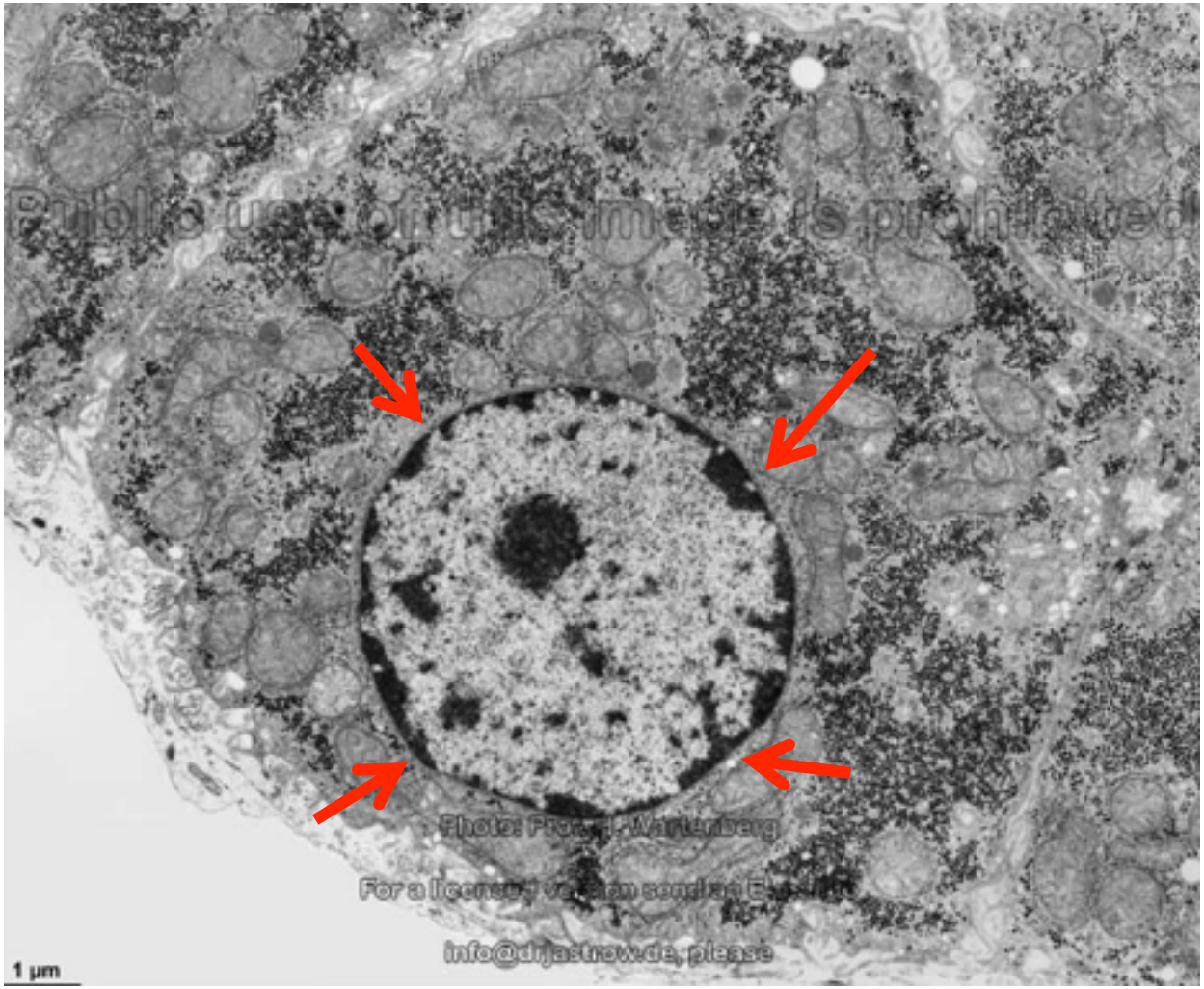
A Consensus Model for FSHD Identifies Opportunities for Therapy

Stephen J. Tapscott, MD, PhD
Fred Hutchinson Cancer Research Center
Seattle, WA

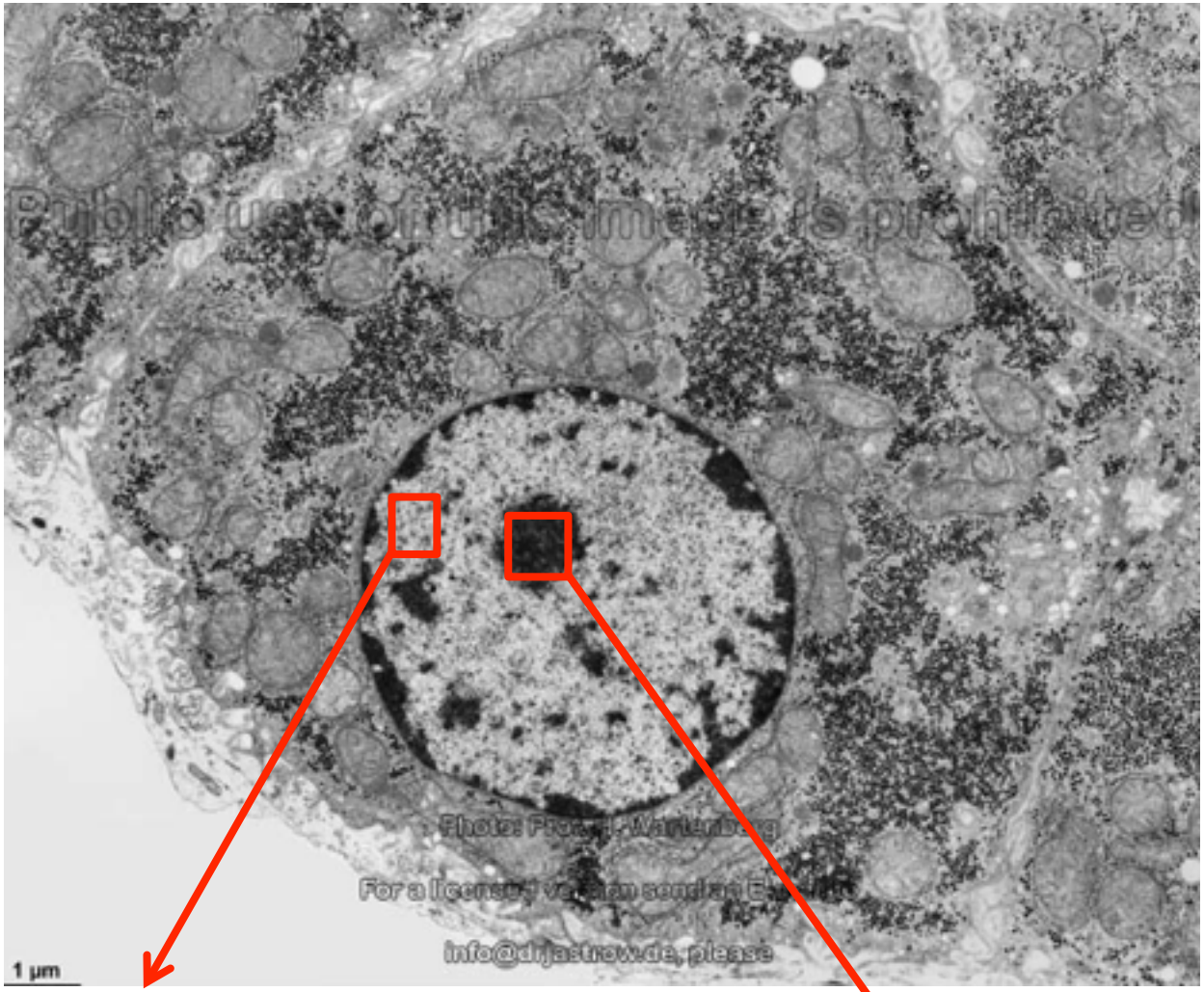

1 µm



Cell



Cell Nucleus

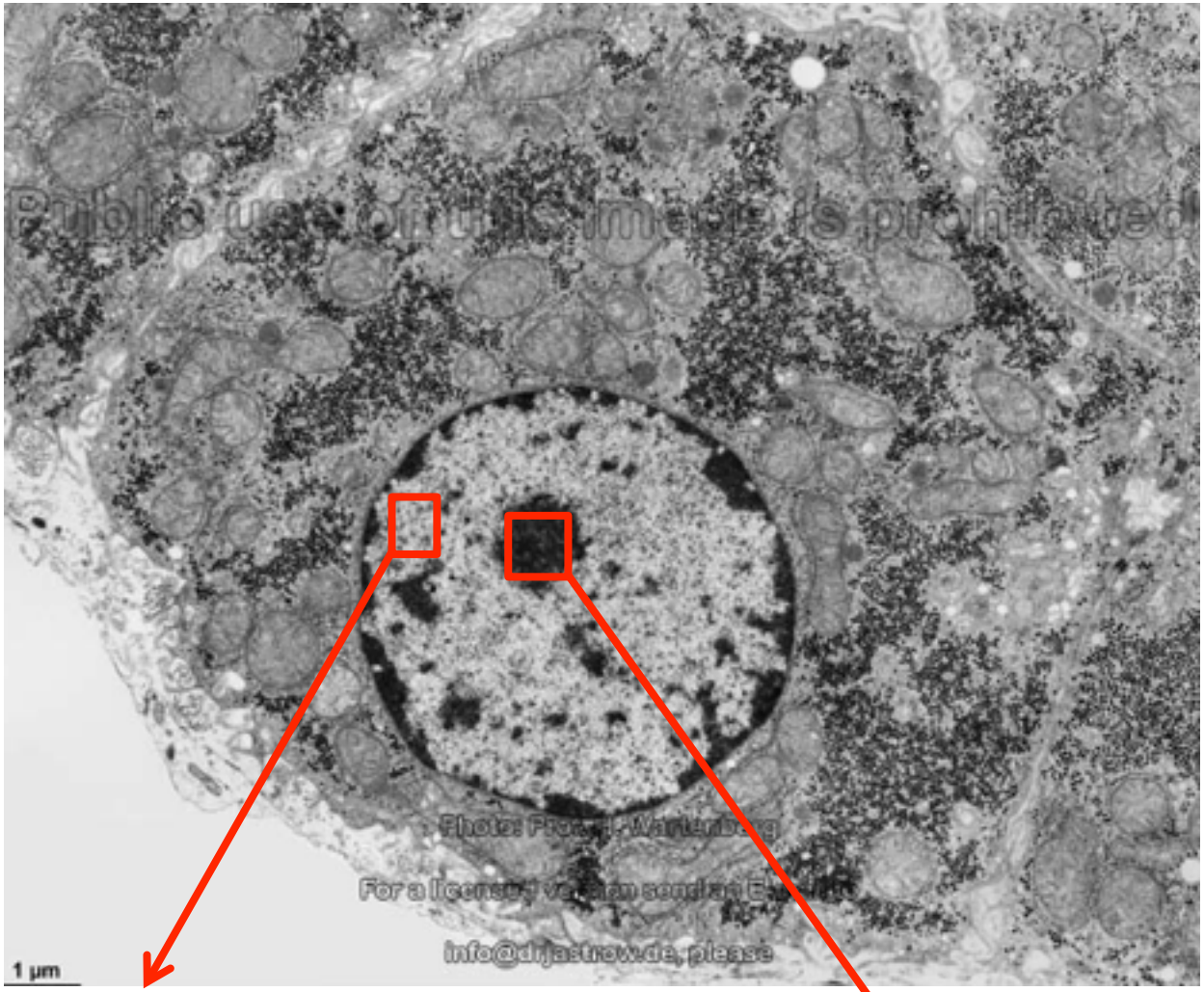


Light = Genes On

Euchromatin

Dark = Genes Off

Heterochromatin



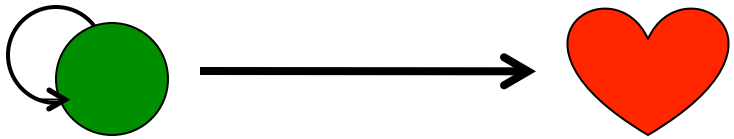
Light = Genes On

Out in the living room

Dark = Genes Off

Stored in the attic

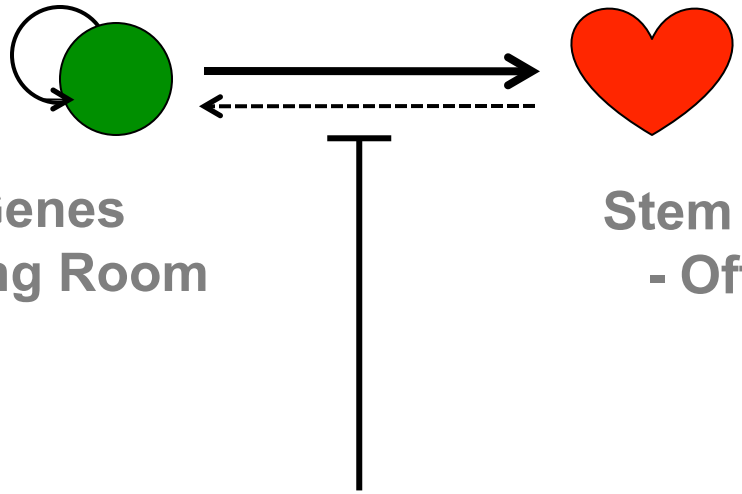
Stem Cell **Differentiated Cell**



Stem Cell Genes
- On, Living Room

Stem Cell Genes
- Off, Attic

Stem Cell **Differentiated Cell**



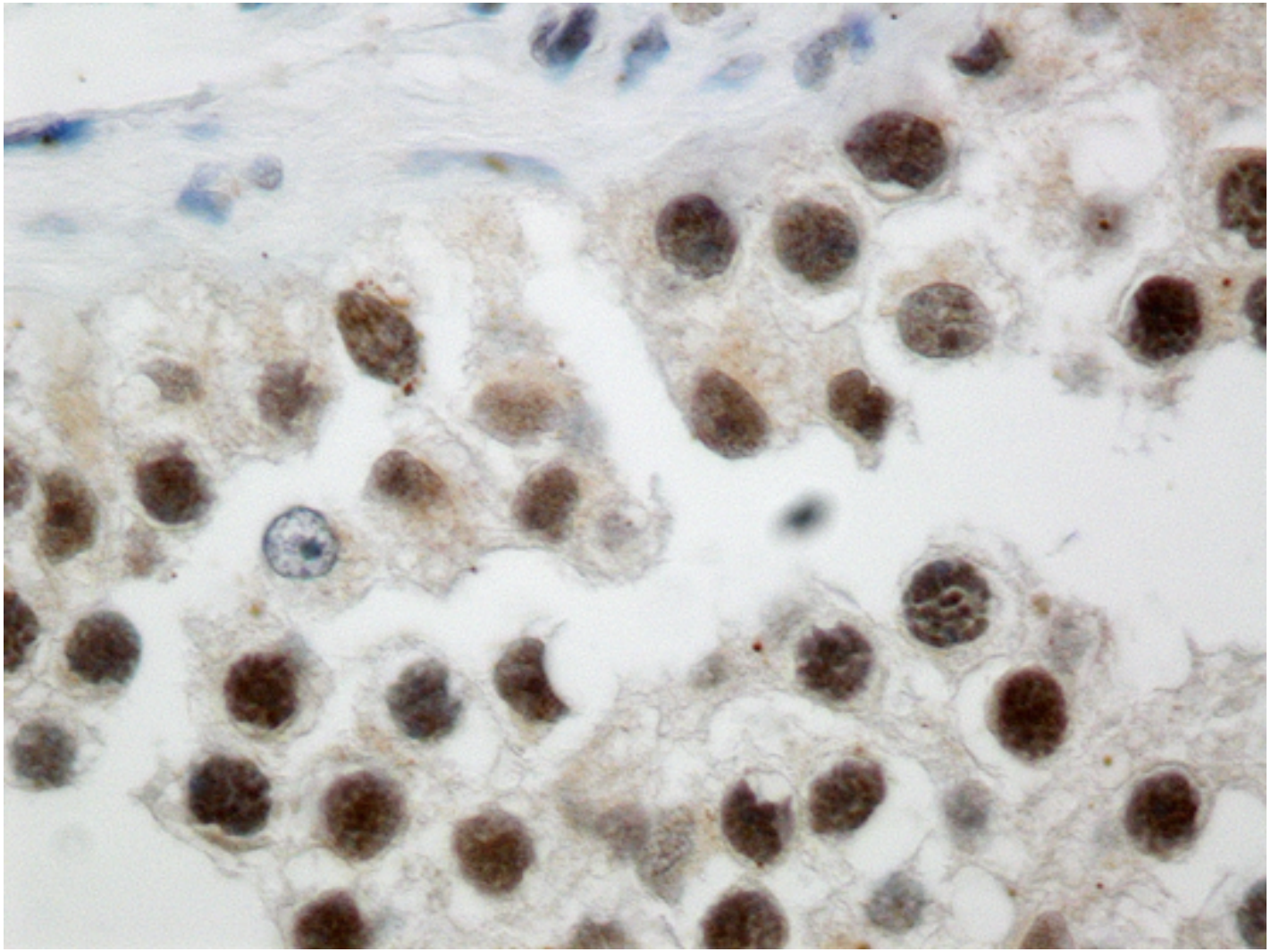
Stem Cell Genes
- On, Living Room

Stem Cell Genes
- Off, Attic

DNA Methylation &
Heterochromatin
Lock the Attic Door

DUX4 is abundantly expressed in healthy human testis

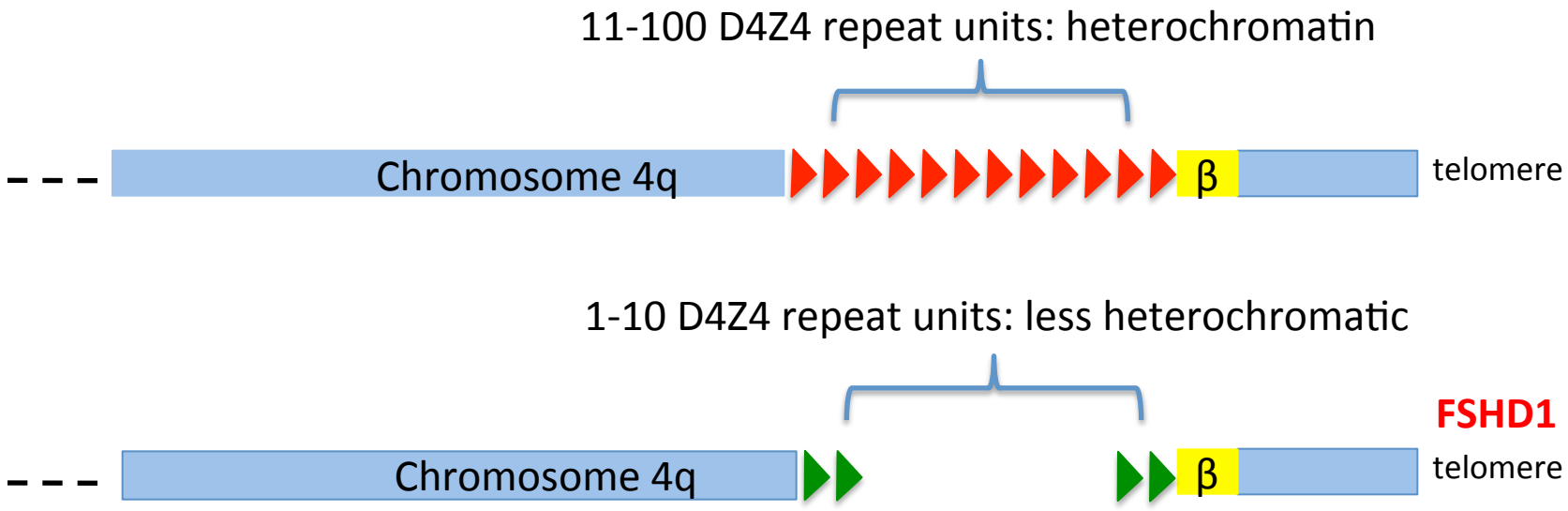
DUX4 IHC of testis



Brown = DUX4 immunodection

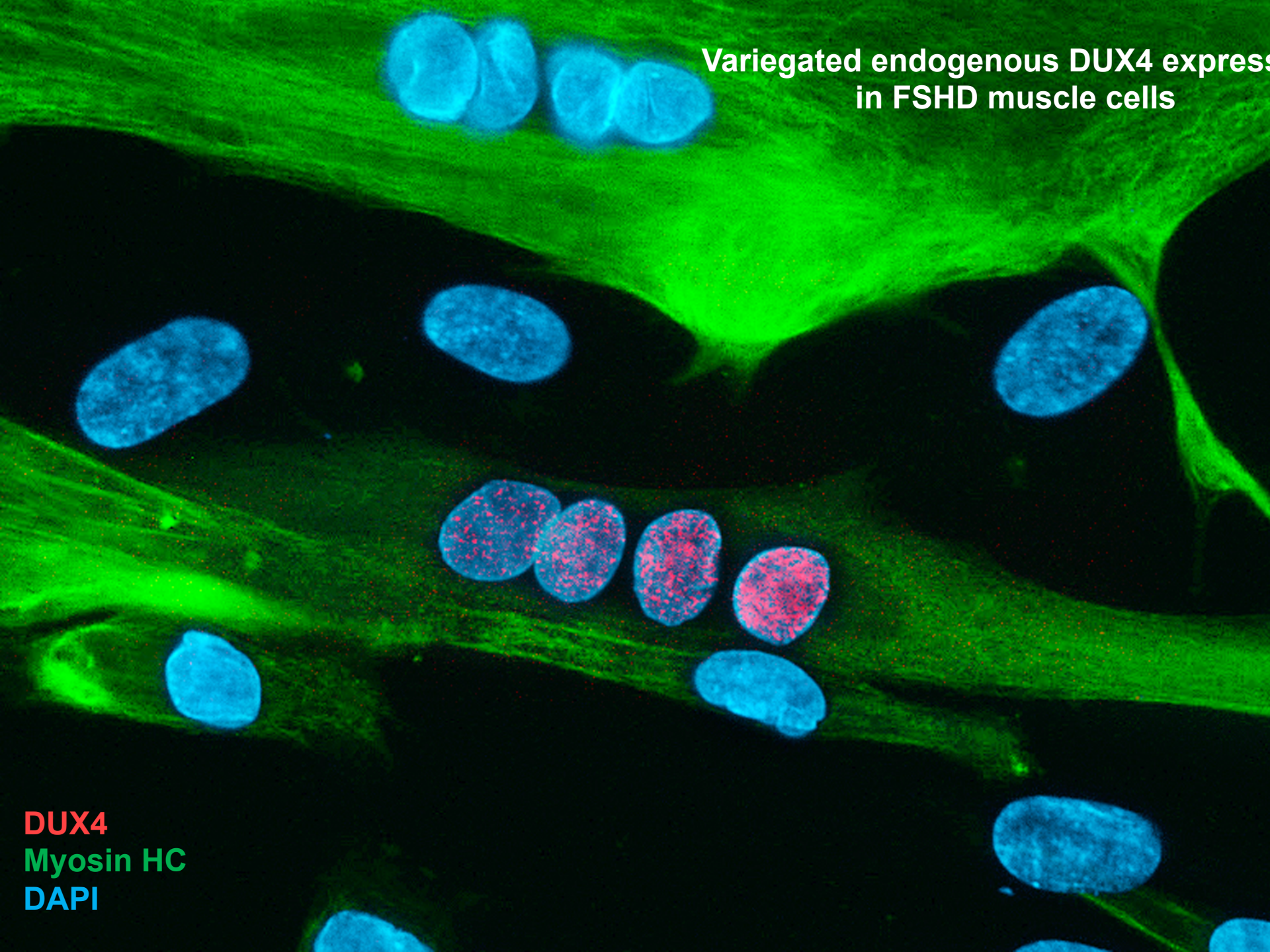
Snider, Geng et al. *PLoS Genet,* 2010

Fewer D4Z4 repeats have less repressive heterochromatin



= heterochromatin (H3K9me3, H3K27me3, meCpG)

= less heterochromatic (H3K4me3, less meCpG)


Variegated endogenous DUX4 expres
in FSHD muscle cells
DUX4
Myosin HC
DAPI

A Developmental Model of FSHD

- DUX4 is expressed in the testis germ-line
  - Possible role in stem cell biology
- DUX4 is repressed (moved to the attic) in muscle
  - Repeat-mediated silencing
- Inefficient repression causes FSHD
  - Fewer repeats = less efficient repression
  - Faulty lock (e.g., SMCHD1 in FSHD2)
- Results in occasional bursts of DUX4 in muscle

DUX4 is a transcription factor

- DUX4 can “turn-on” other genes
  - When DUX4 comes out of the attic it brings a lot of genes with it!
- Turns on germline genes in skeletal muscle
  - Tells the muscle to become a germline cell

Candidate Mechanisms for FSHD

- **Activation of a germline program muscle cells**
  - Confusion causes death and dysfunction
- **Immune response to germline proteins**
  - FSHD cells express Cancer Testis Antigens

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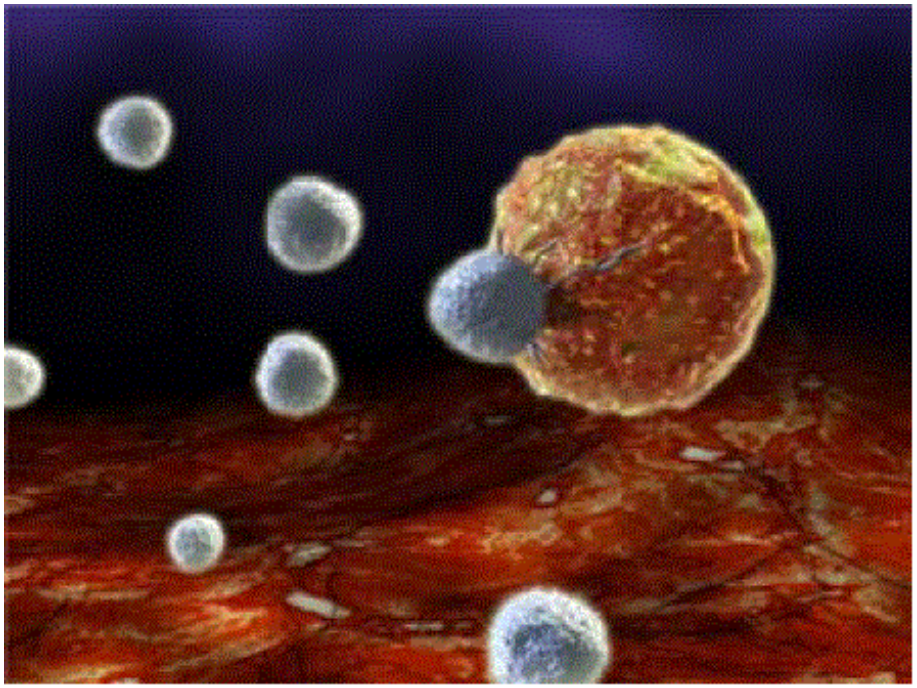

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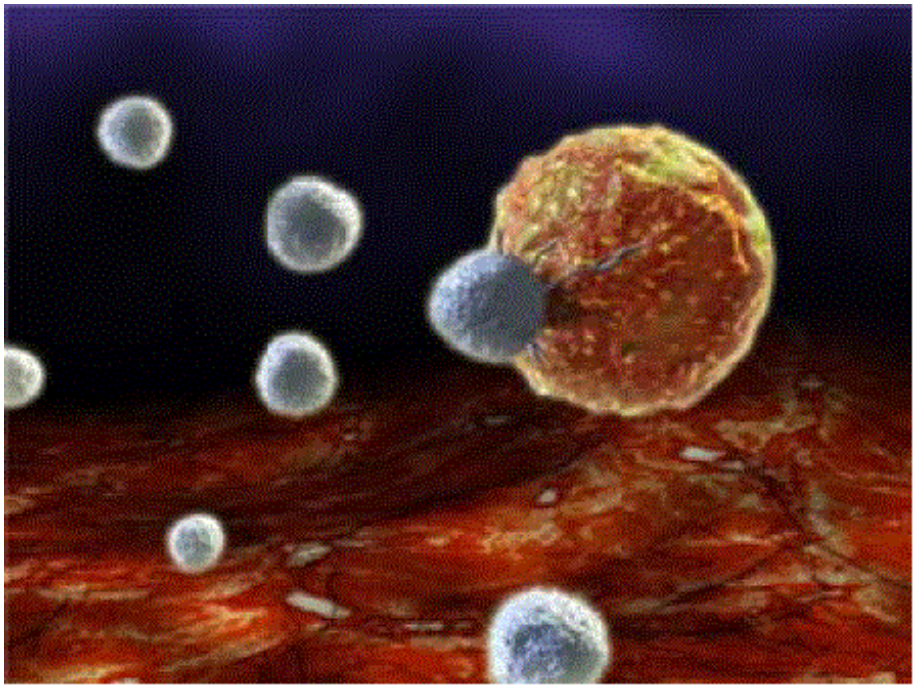

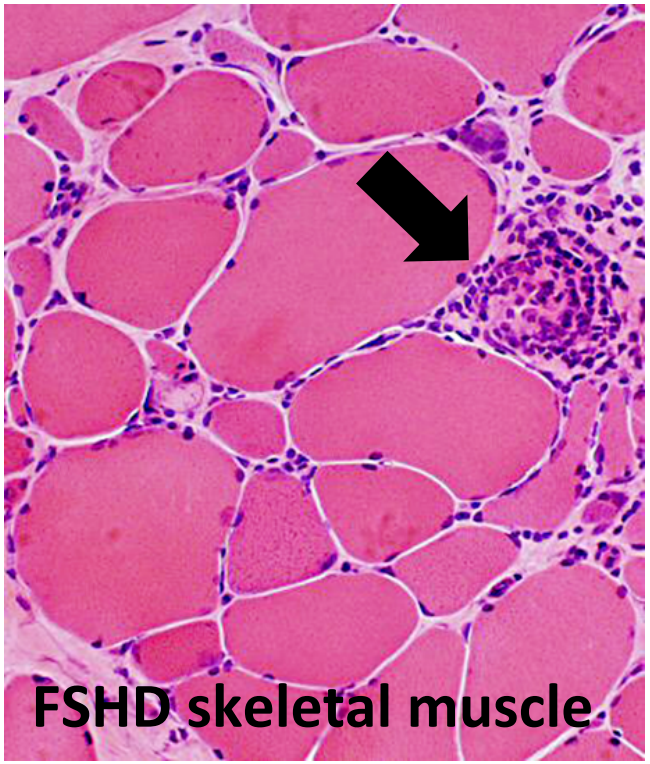

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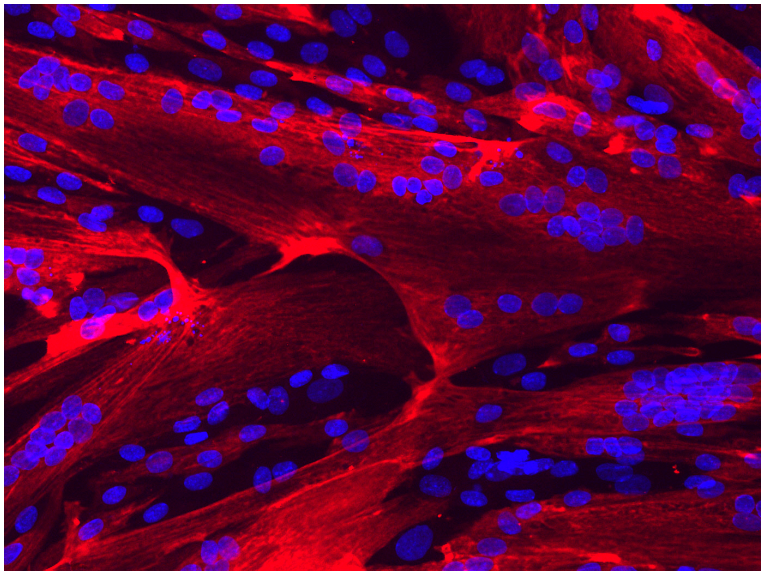

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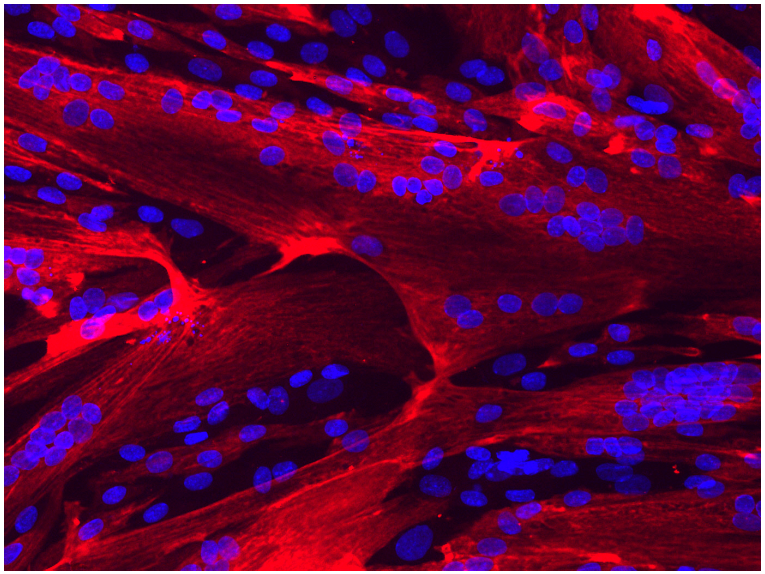

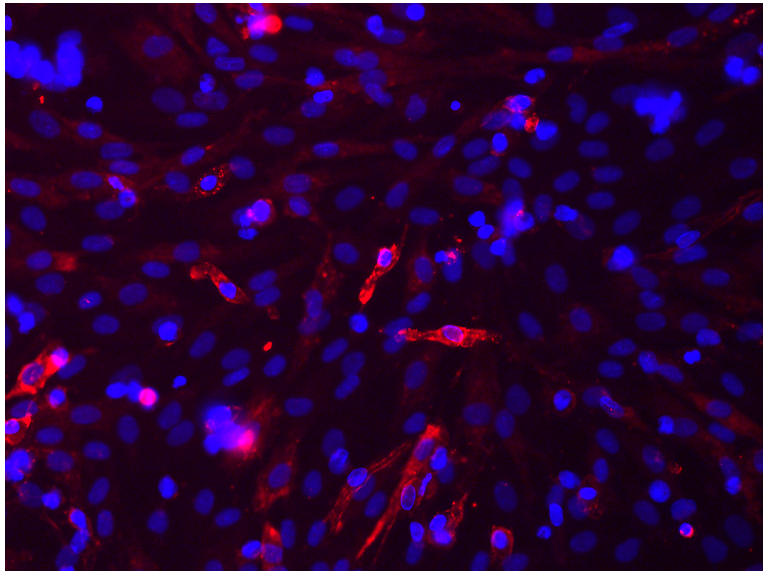

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- **And more ….**

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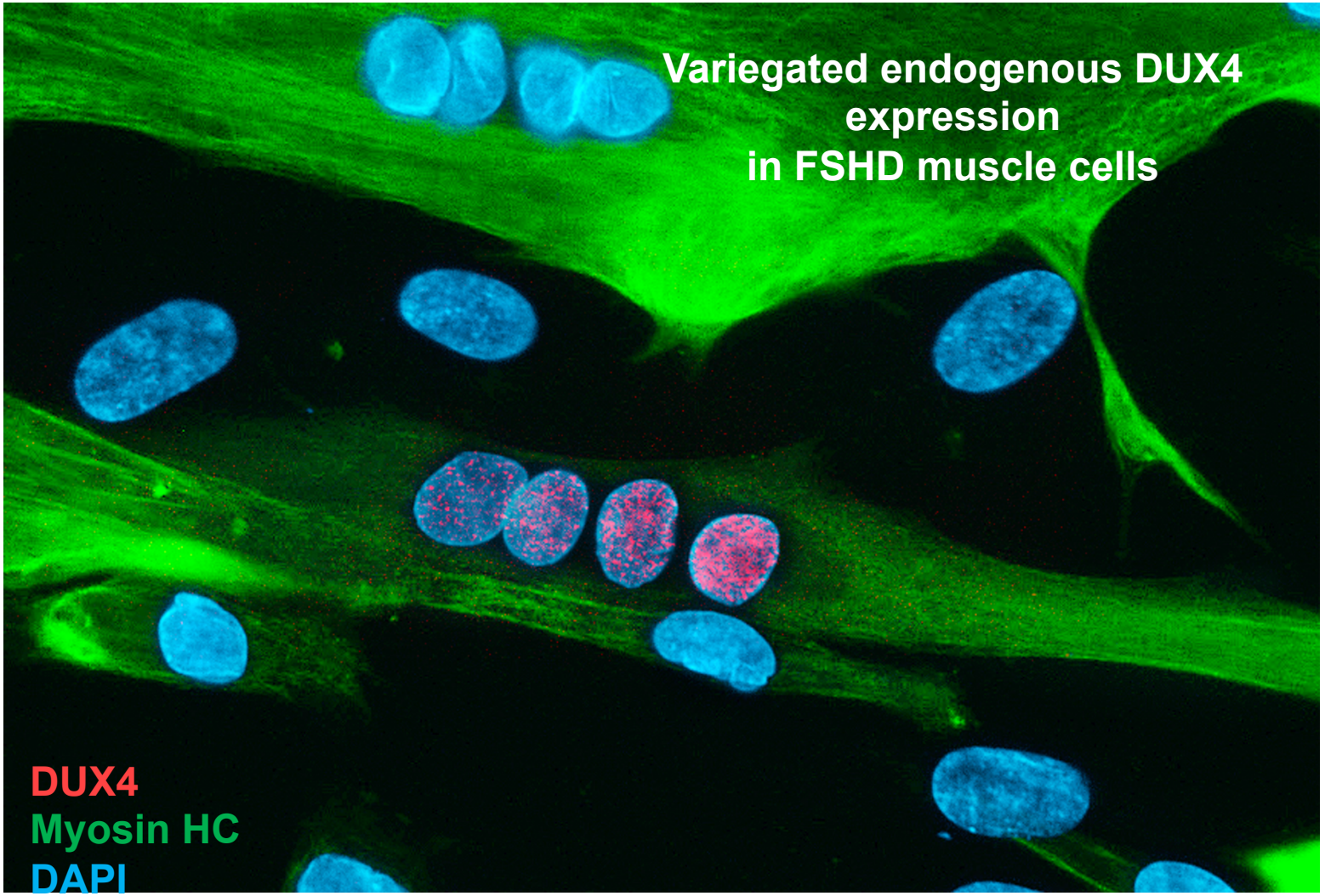

Snider et al, PLoS Genet 2010; Geng et al, Dev Cell 2012

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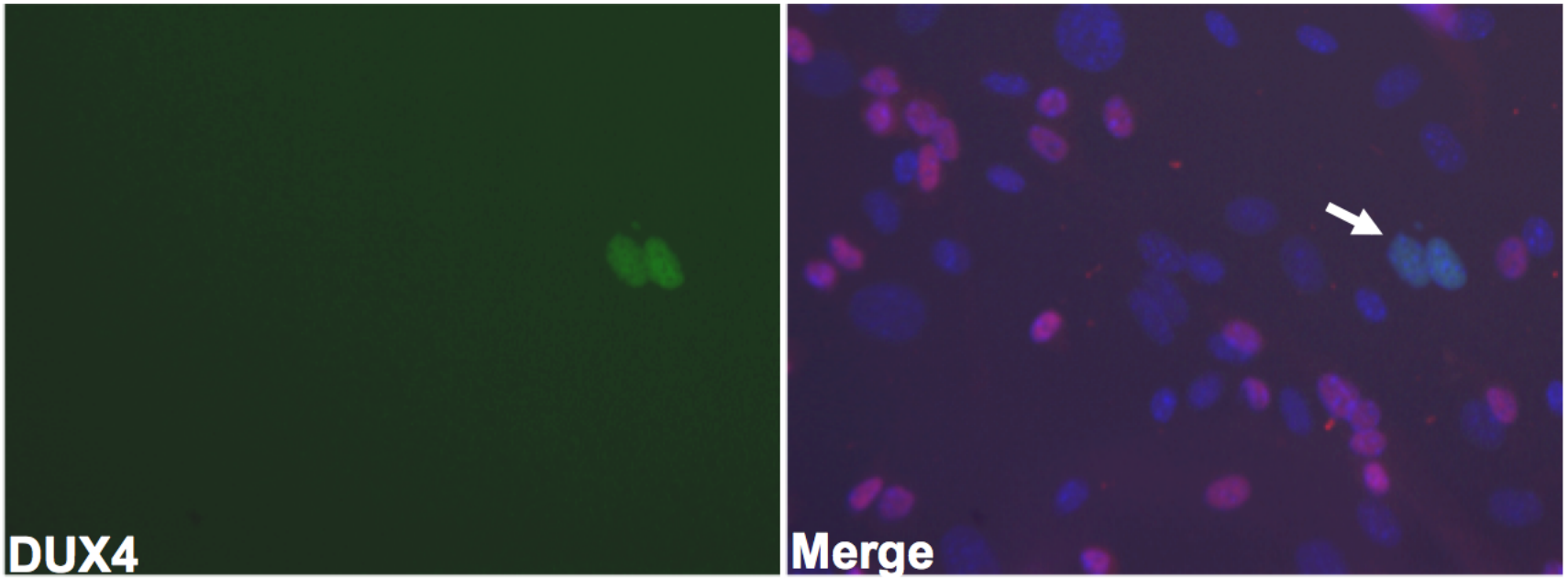

Krom et al, PLoS Genet 2013

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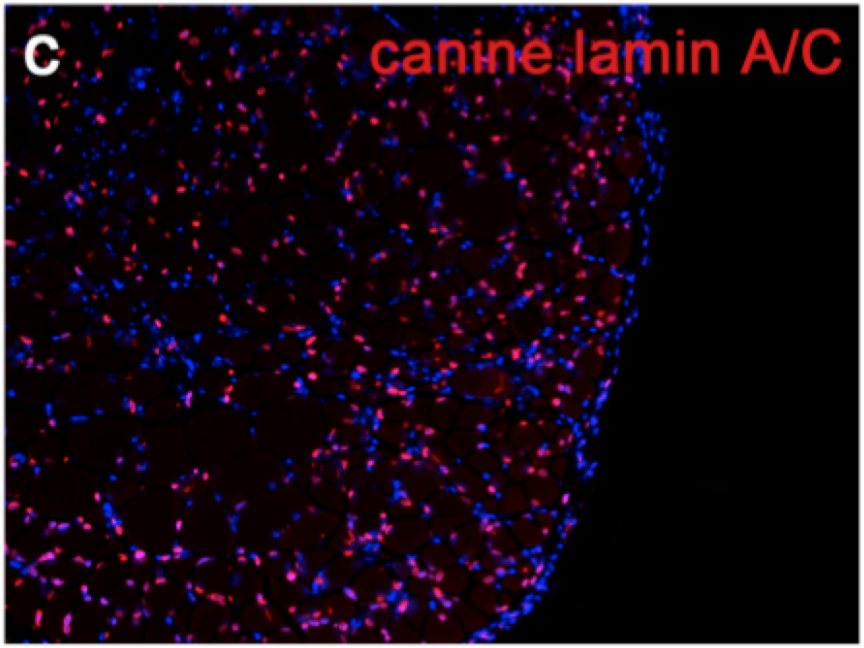

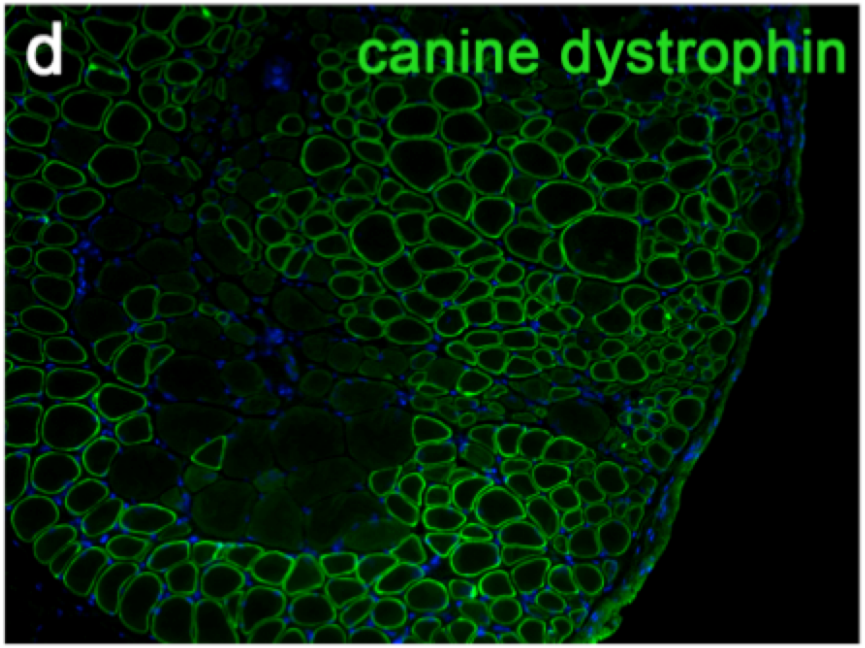

Parker et al Skeletal Muscle 2012
Parker et al Stem Cells 2012

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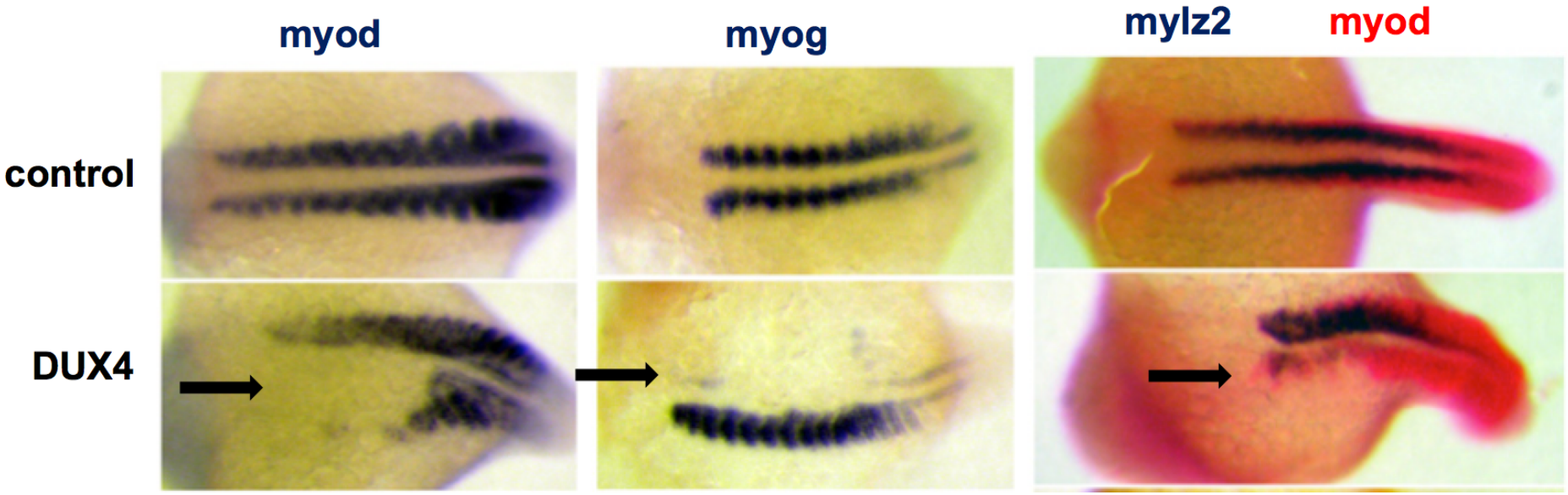

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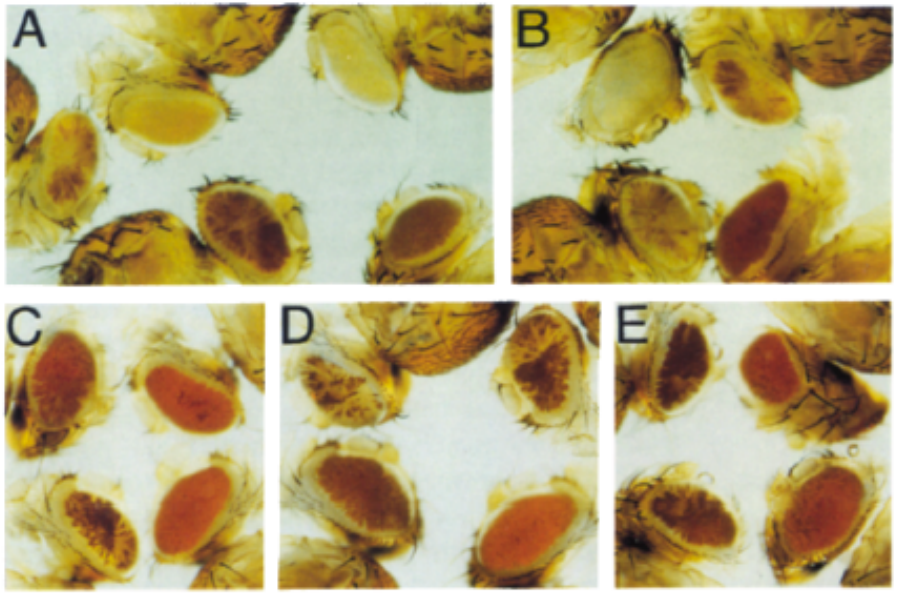

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  - Slowly progressive disease
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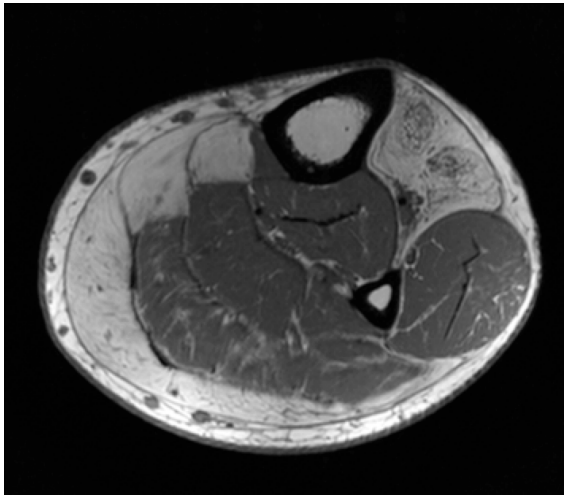

Milestones for Success

Small numbers of participants
Short-term studies
Prioritize candidate therapies

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Large numbers of participants
Long-term studies
Outcome studies for FDA approval

How long will it take?

- Within a few years if … ?
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- Within a decade if … ?
  - New drug development
  - Progressively more effective drugs

When will we start?

- We have, thanks to you!
  - Consensus model of disease
  - Candidate biomarkers
  - Clinical natural history studies
  - Multiple efforts at drug development

Tawil et al, Skeletal Muscle 2014

And thanks to the groups providing funding and inspiration

friends of FSH research

STICHTING FSHD

Geraldi Norton Foundation
& the Eklund Family

George & Jack Shaw
& the Shaw Family Foundation