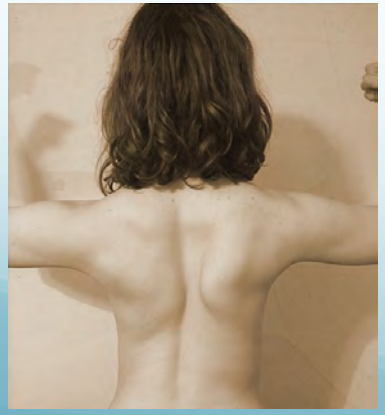
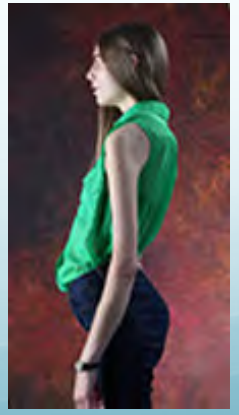
University of Nevada, Reno
School of Medicine
Department of Pharmacology

The Future of FSHD Therapies

Miami patient meeting Feb 23, 2019

Peter L. Jones, Ph.D. and Takako I. Jones, Ph.D.
Co-Principal Investigators



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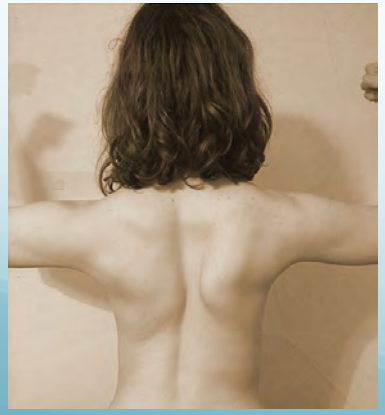
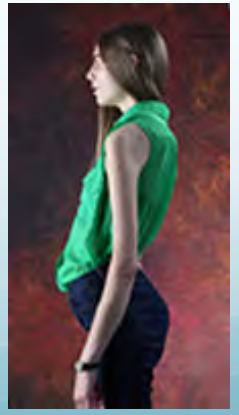
Disclosures:

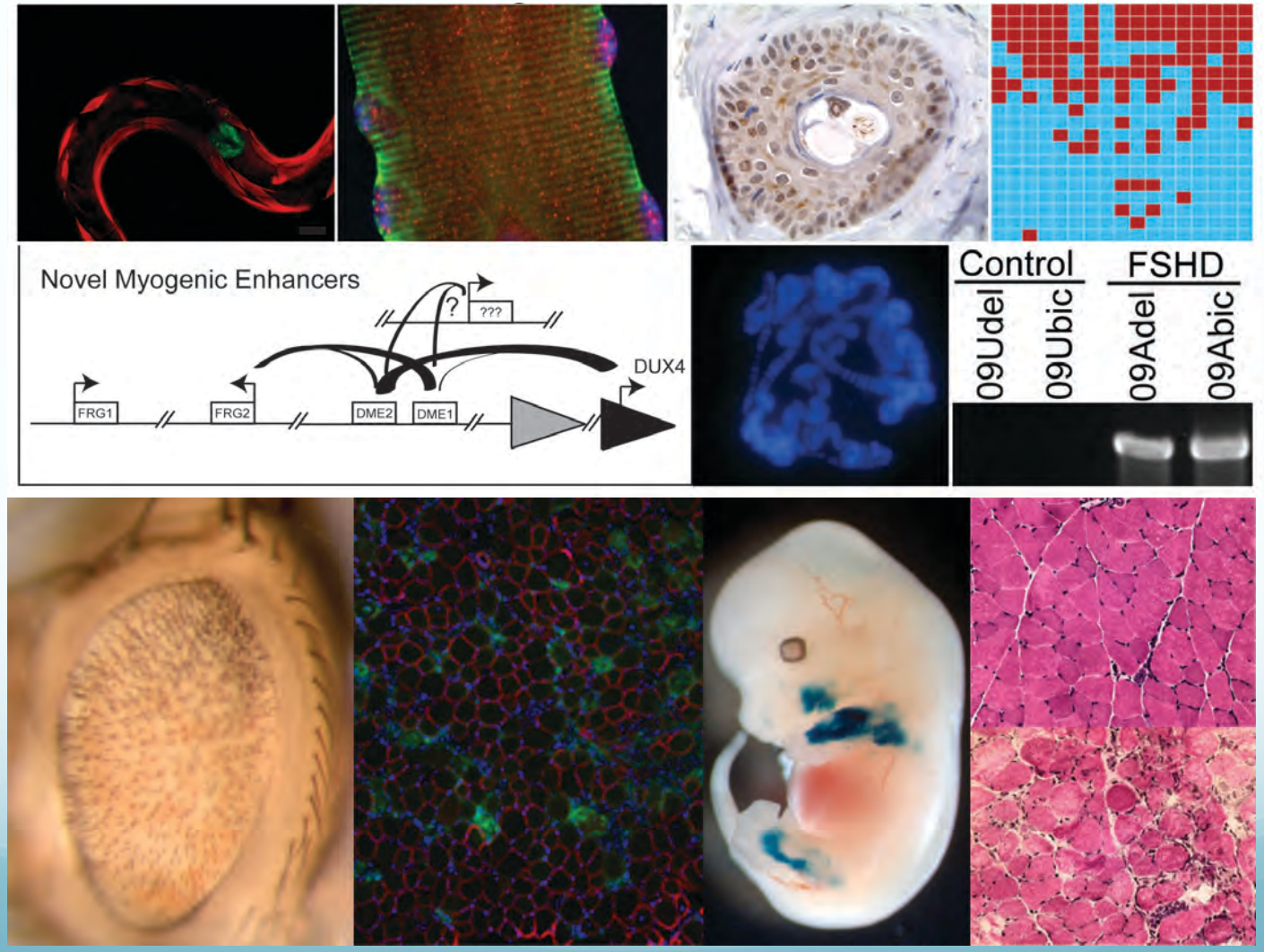
Peter Jones, Takako Jones, and Charis Himeda are listed as inventors on US patent applications for epigenetic diagnosis of FSHD (PJ, TJ), epigenetic therapeutic targets for FSHD (PJ) and CRISPR therapy for FSHD (PJ, TJ, CH).

Peter Jones is on the SAB for Fulcrum Therapeutics






Jones Lab expertise is epigenetics and developmental biology



Epigenetics refers to a mechanism for integrating signals environmental signals into the genome

Epigenetic differences can have profound long-term health consequences

Epialleles

A^{IAP} allele, methylated

Brown, normal

A^{IAP} allele, unmethylated

Yellow, obese, spontaneous tumors

Genetically identical
Epigenetically different

→ **Affects long-term health**
→ **heritable?**

Waterland and Jirtle, *Mol Cell Biol*, 2003

Epigenetic Diseases

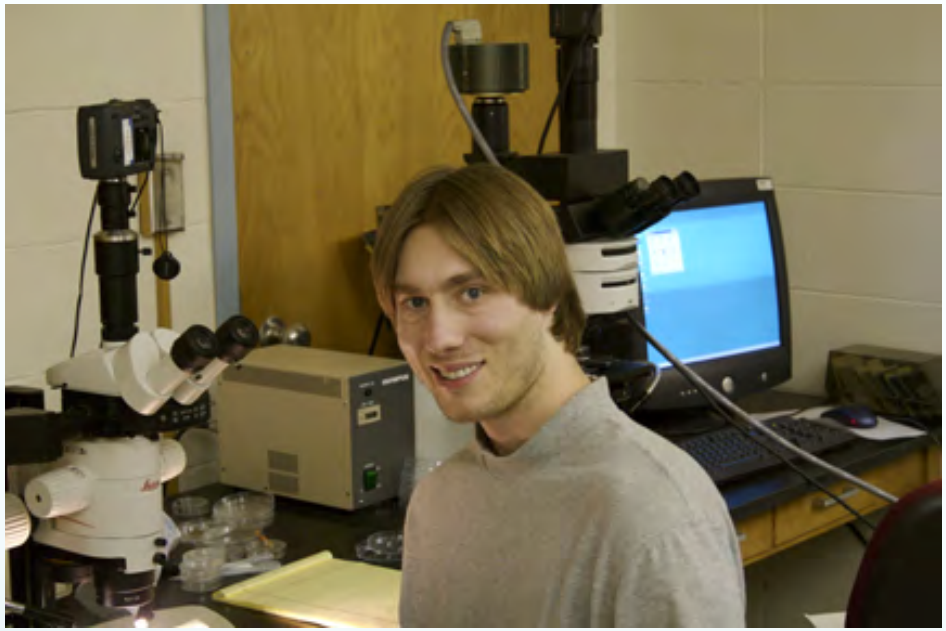
Mutations leading to aberrant epigenetic regulation

Disease	Epigenetics	Manifestation
FSHD	Chromatin structure	Progressive skeletal muscle loss
Rett Syndrome	MeCP2	Intellectual disabilities
ATR-X	Snf2 remodeling	Intellectual disabilities, α-thalassaemia
Fragile X Syndrome	DNA methylation	Intellectual disabilities
ICF Syndrome	DNA methylation	Immunodeficiency
Angelman's Syndrome	LOI	Intellectual disabilities
Prader-Willi Syndrome	LOI	Obesity, intellectual disabilities
Beckwith-Wiedemann	LOI	Organ overgrowth
Leukemia	DNA methylation	Disrupted haematopoiesis
Lupus	DNA methylation	Chronic inflammation in joints, skin
Cancer	DNA methylation	Uncontrolled cell cycle
Rubinstein-Taybi	CBP (HAT)	Intellectual disabilities
Multiple sclerosis	HDAC?	Autoimmune CNS degeneration
Spinal muscular atrophy	HDAC?	Motor neuron disease
Osteoarthritis	DNA methylation?	Destruction of articular cartilage ECM

Bipolar disorder, Autism spectrum disorders, schizophrenia, …

Coronary heart disease, congenital heart disease, anemia, atherosclerosis, and stroke

Jones Lab expertise is epigenetics and developmental biology

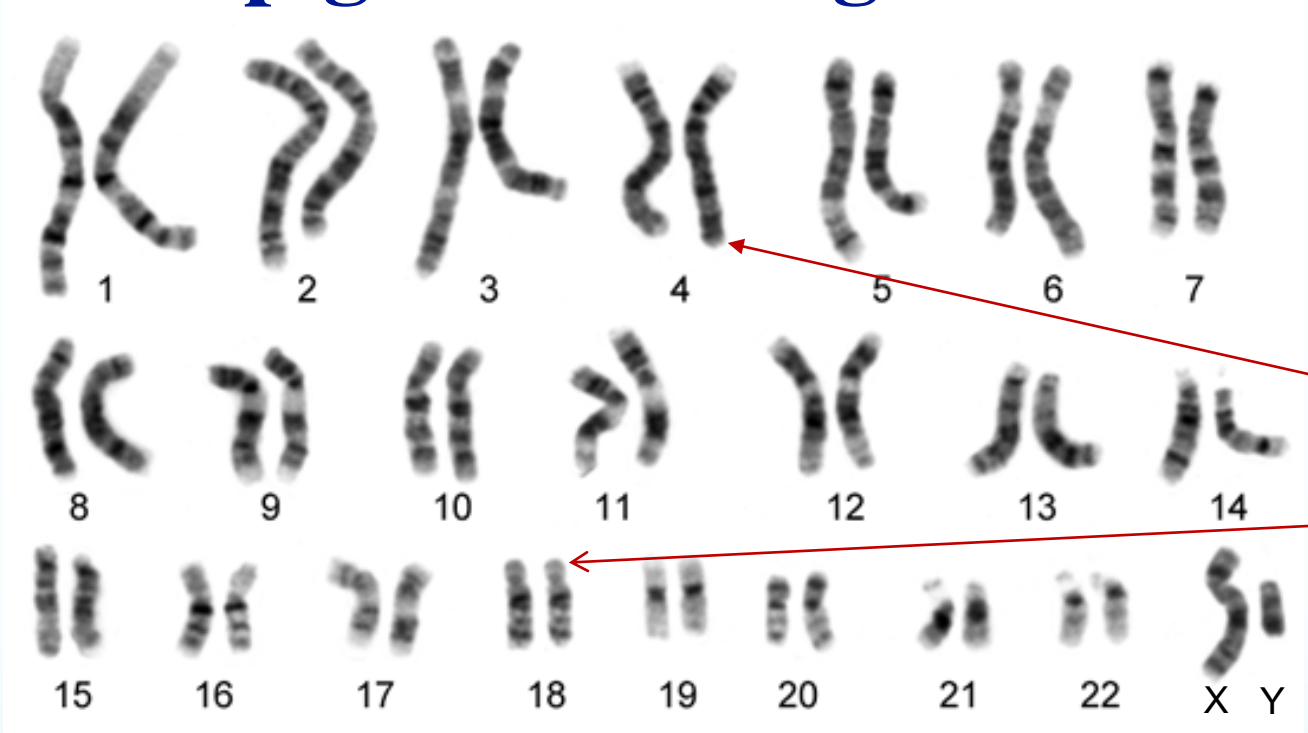


Ryan Wuebbles, Graduate student, University of Illinois at Urbana Champaign

1) 2002 Patient meeting: FSHD may have an epigenetic etiology
2) Nothing we can do for you

Introduced us to FSHD and recruited us to FSHD research

FSHD is caused by genetic changes that lead to epigenetic changes at Chr 4q35



Human haploid genome has ~3,100,000,000 base pairs of DNA (GATCs)

FSHD1 is caused by small deletions on Chr 4q

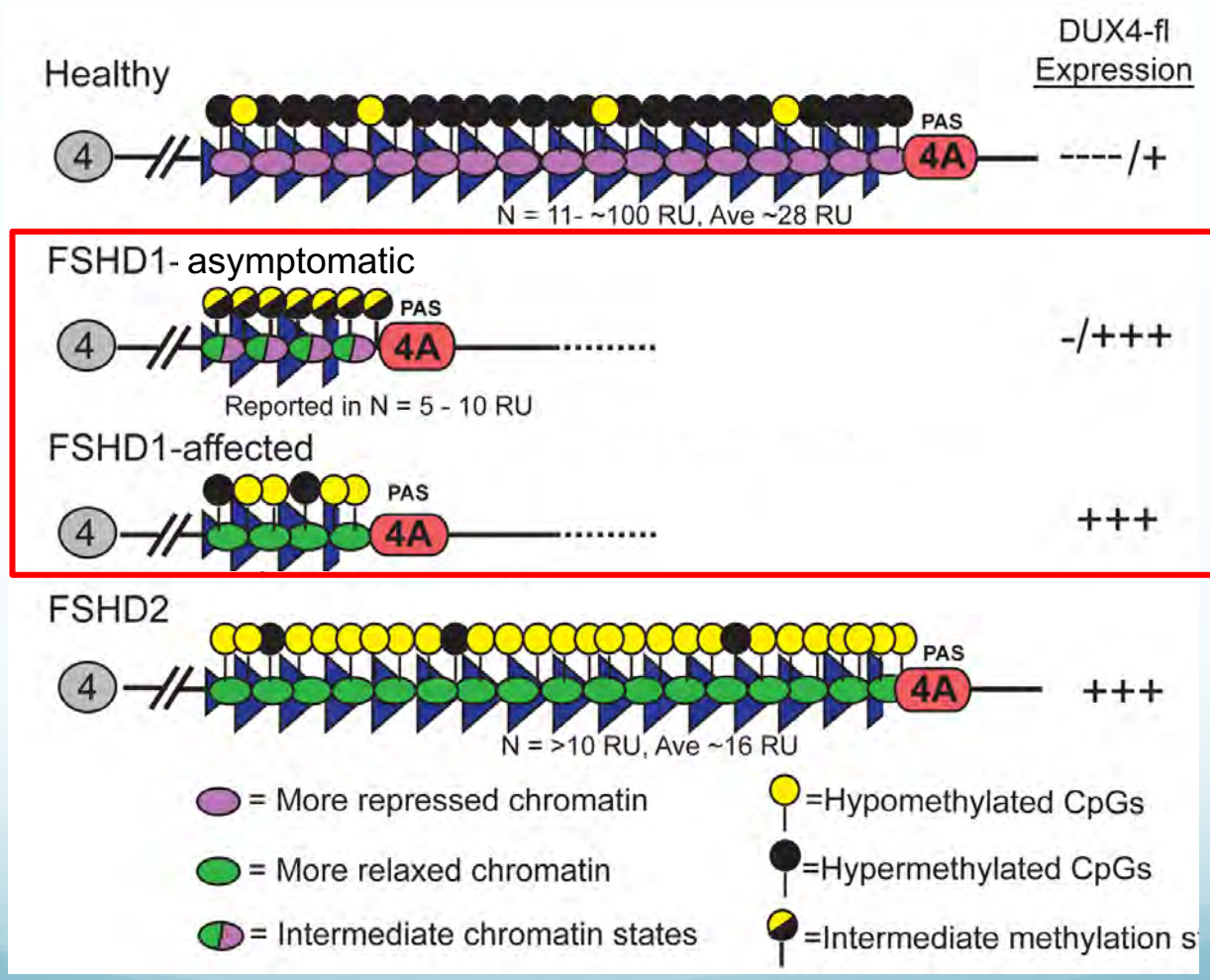
→ lead to epigenetic changes at Chr 4q

FSHD2 is usually caused my mutations on Chr 18p

→ lead to epigenetic changes at Chr 4q

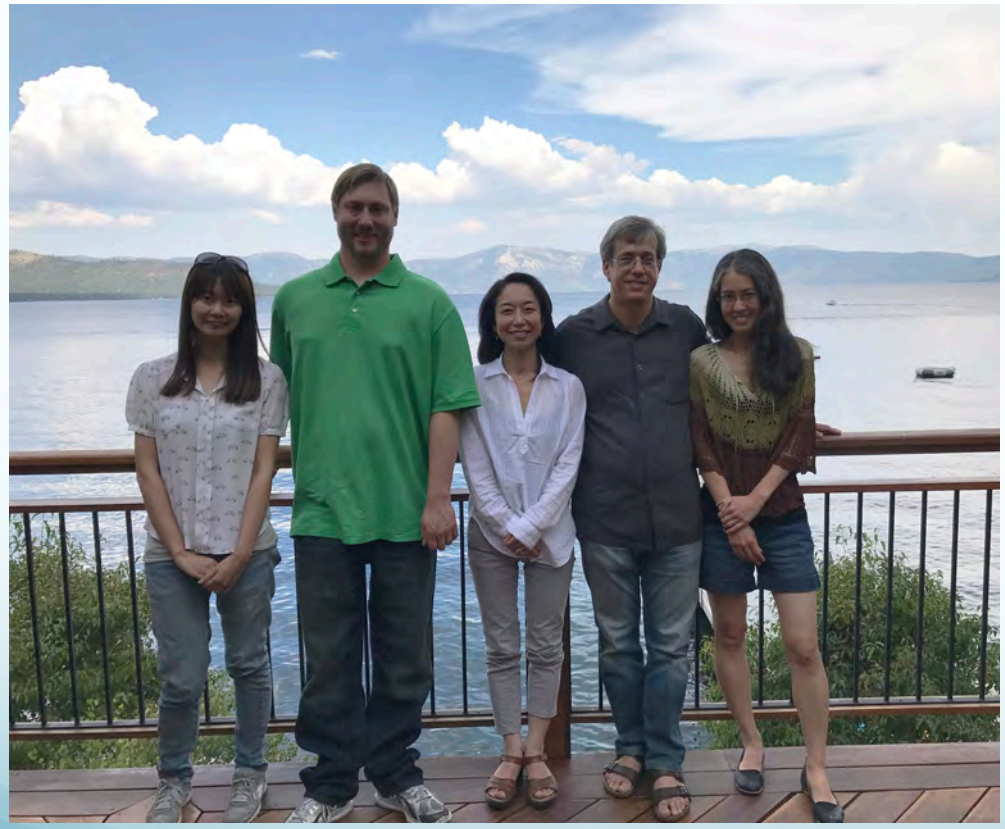
FSHD is an epigenetic disease

The FSHD gene, *DUX4*, is under epigenetic regulation
The "genetic environment" is changed in FSHD



T Jones *et al*. 2015 *Clinical Epigenetics*

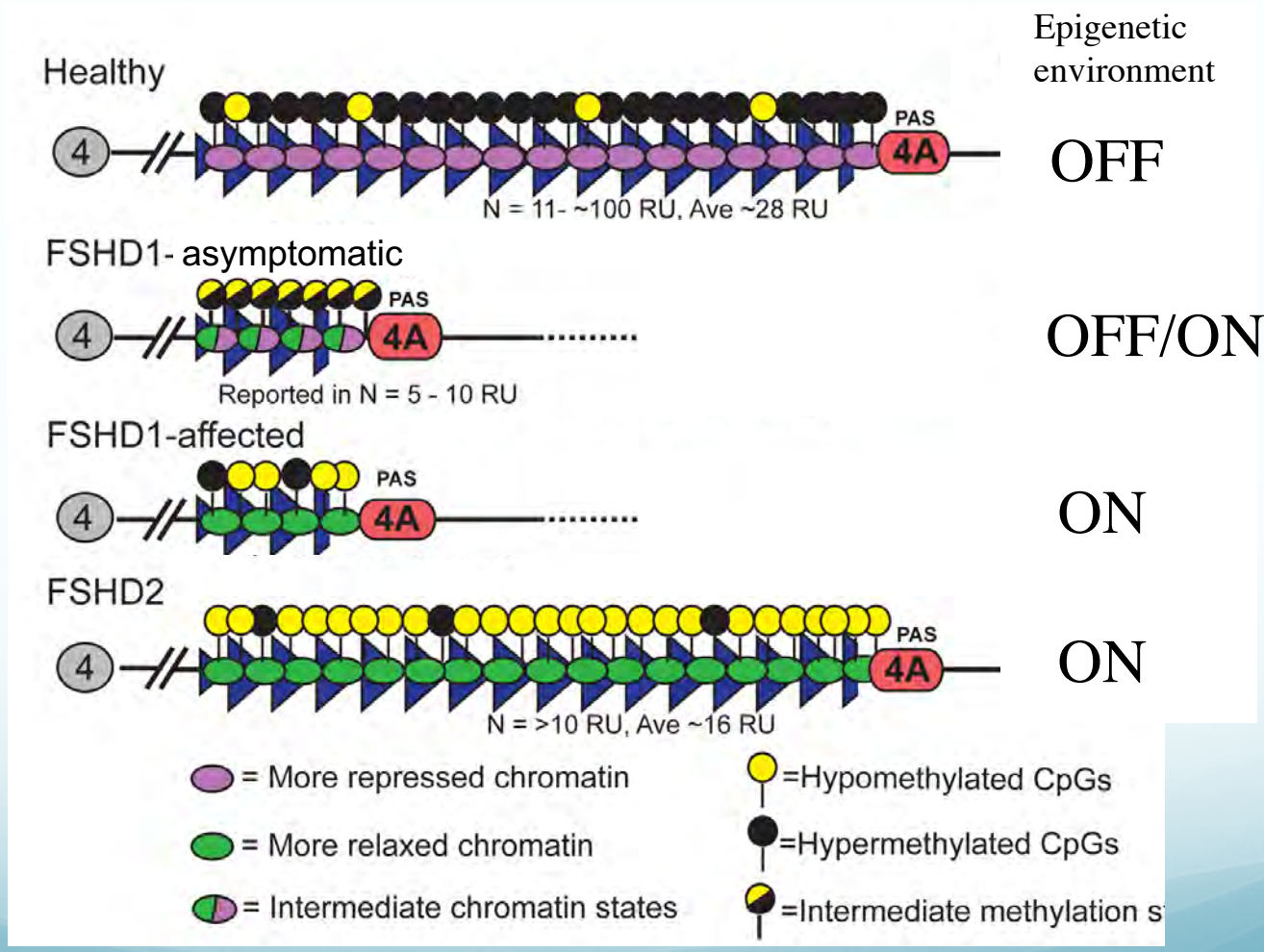
Since 2003, the Jones Lab focus has been on epigenetics of FSHD



- **FSHD pathogenic mechanisms**
- **FSHD diagnostics**
- **FSHD pre-clinical models**
- **FSHD therapeutics**

UNR FSHD group Dr. Wuebbles, Dr. T Jones, Dr. P Jones, Dr. Himeda

FSHD is an epigenetic disease



T Jones *et al*. 2015 *Clinical Epigenetics*

Current FSHD diagnostics are complex and expensive

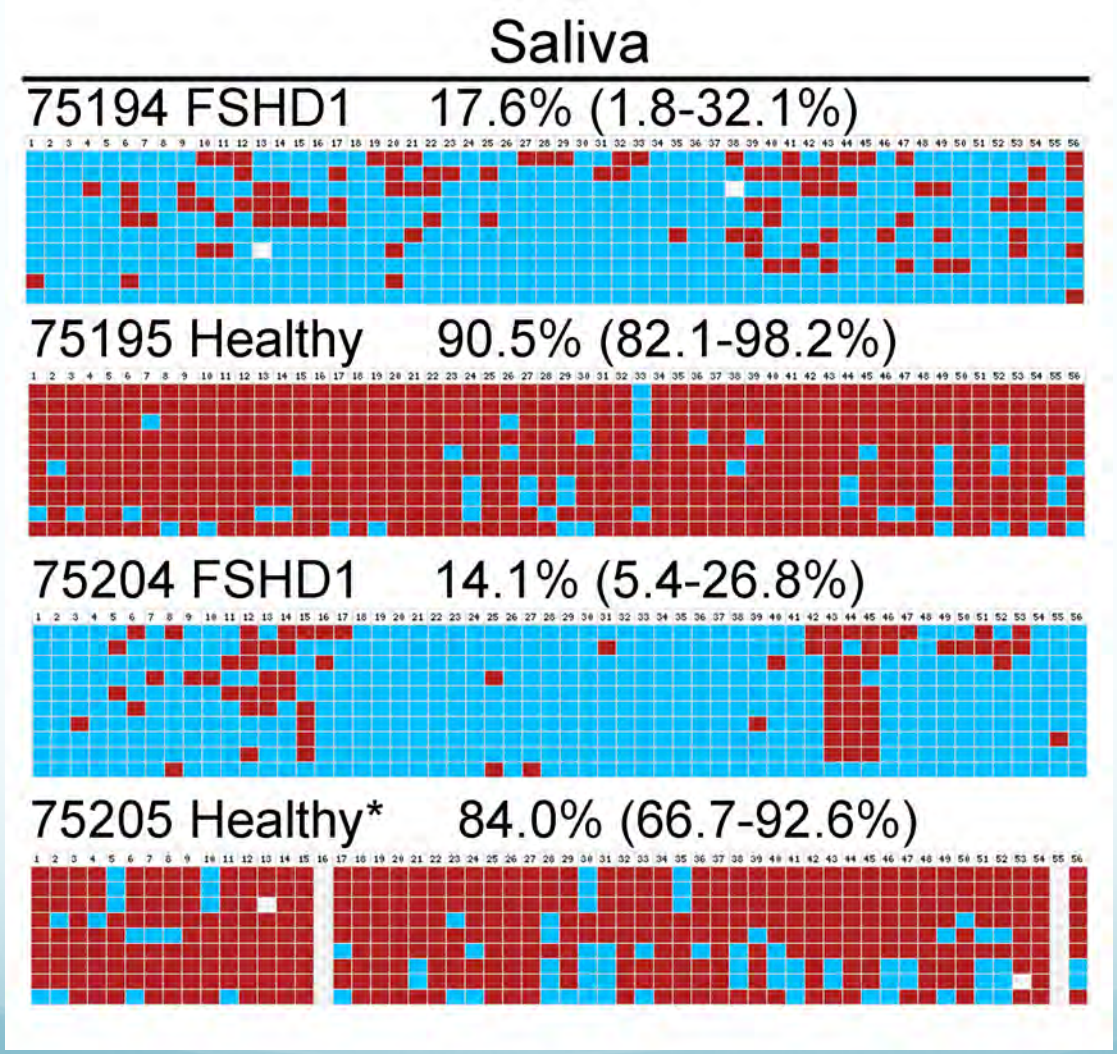
- **Clinical diagnosis is very difficult**

- **Genetic diagnosis is complicated and expensive ($3000)**
  - → **Limited availability in US and worldwide**
  - → **FSHD1 is not found by genome sequencing**
  - → **Cost is prohibitive to many**

- **~Invasive (fresh blood draw)**
  - → **Tough on children and some adults**

EPIGENETIC TESTING

Epigenetic diagnosis of FSHD using saliva

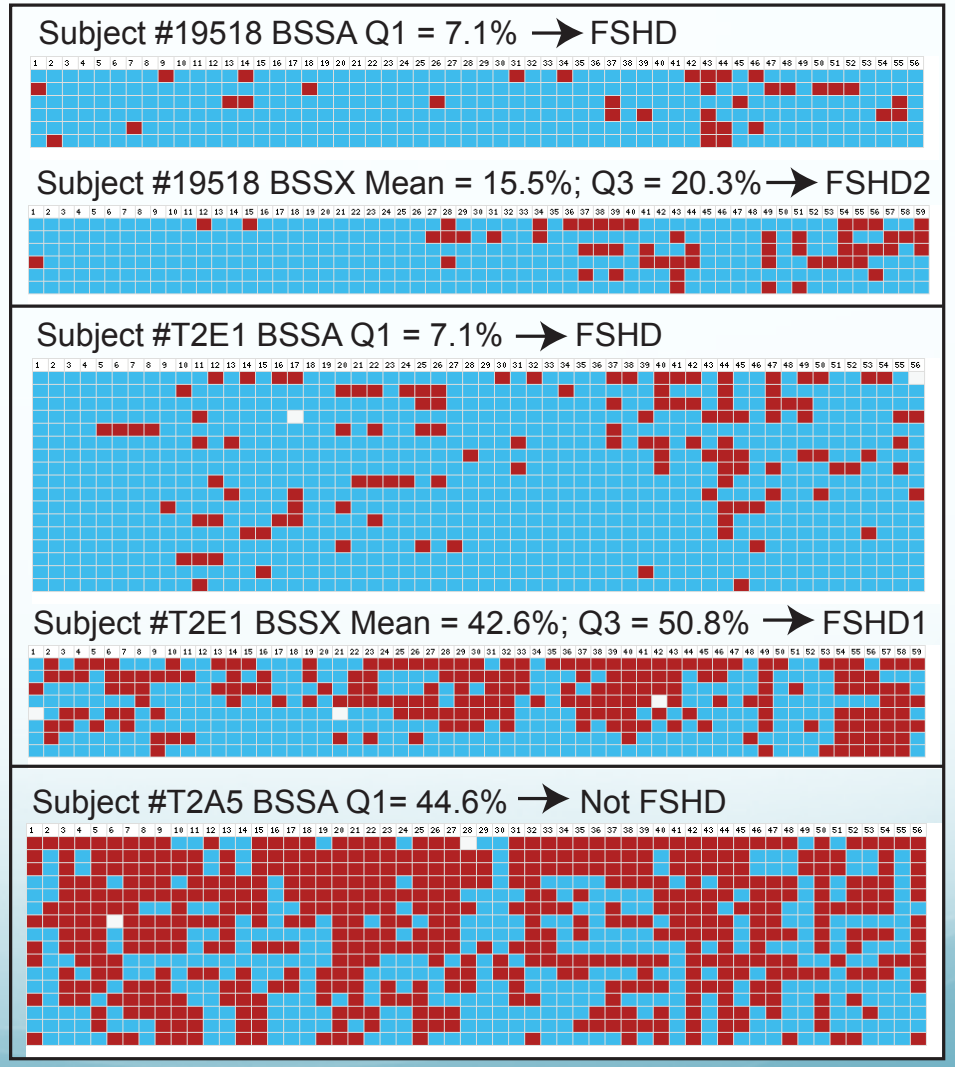


Epigenetic diagnosis of FSHD1 and FSHD2 from saliva

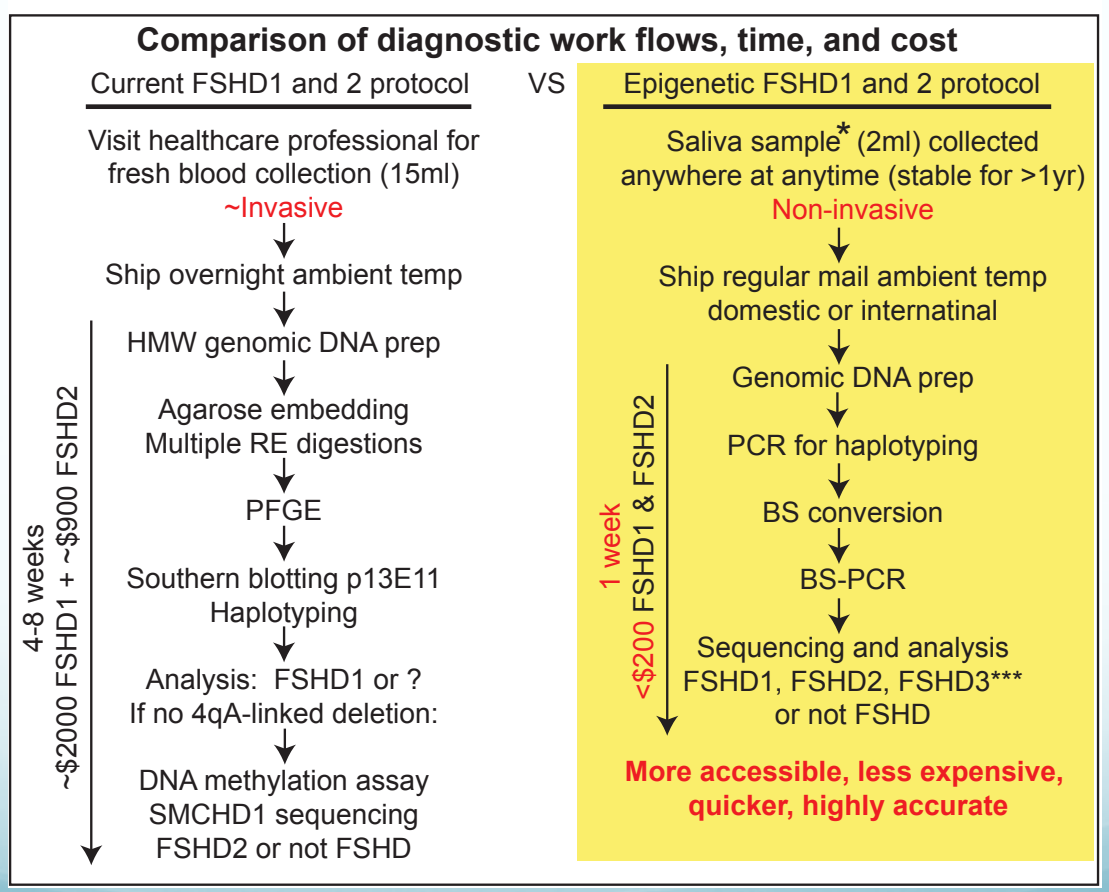
Diagnostic Biomarker

Clinical Biomarker?

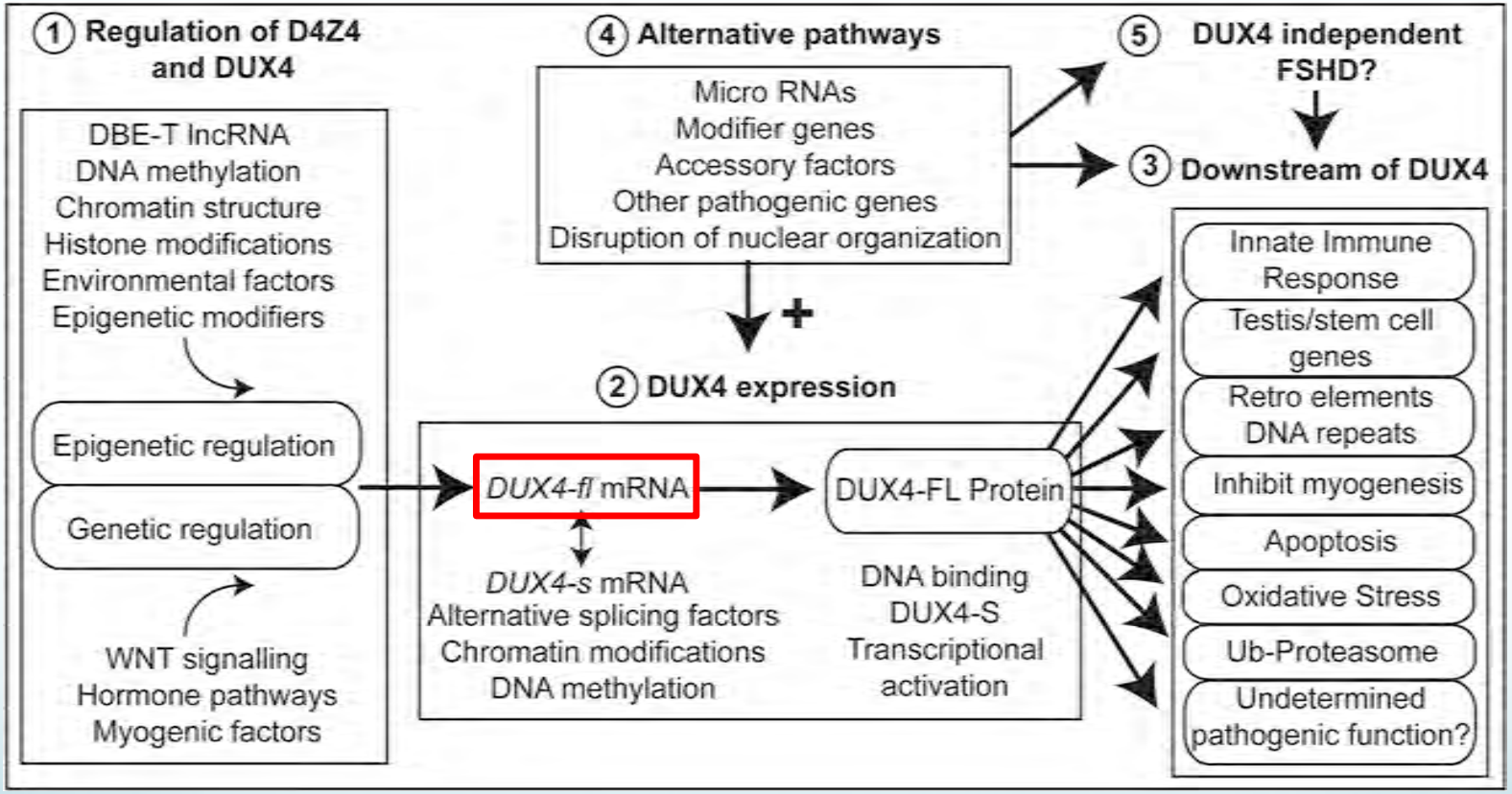
- → **epigenetics correlate with disease status**
- → **Non-invasive**
- → **Direct target**



Current diagnosis vs epigenetic diagnosis



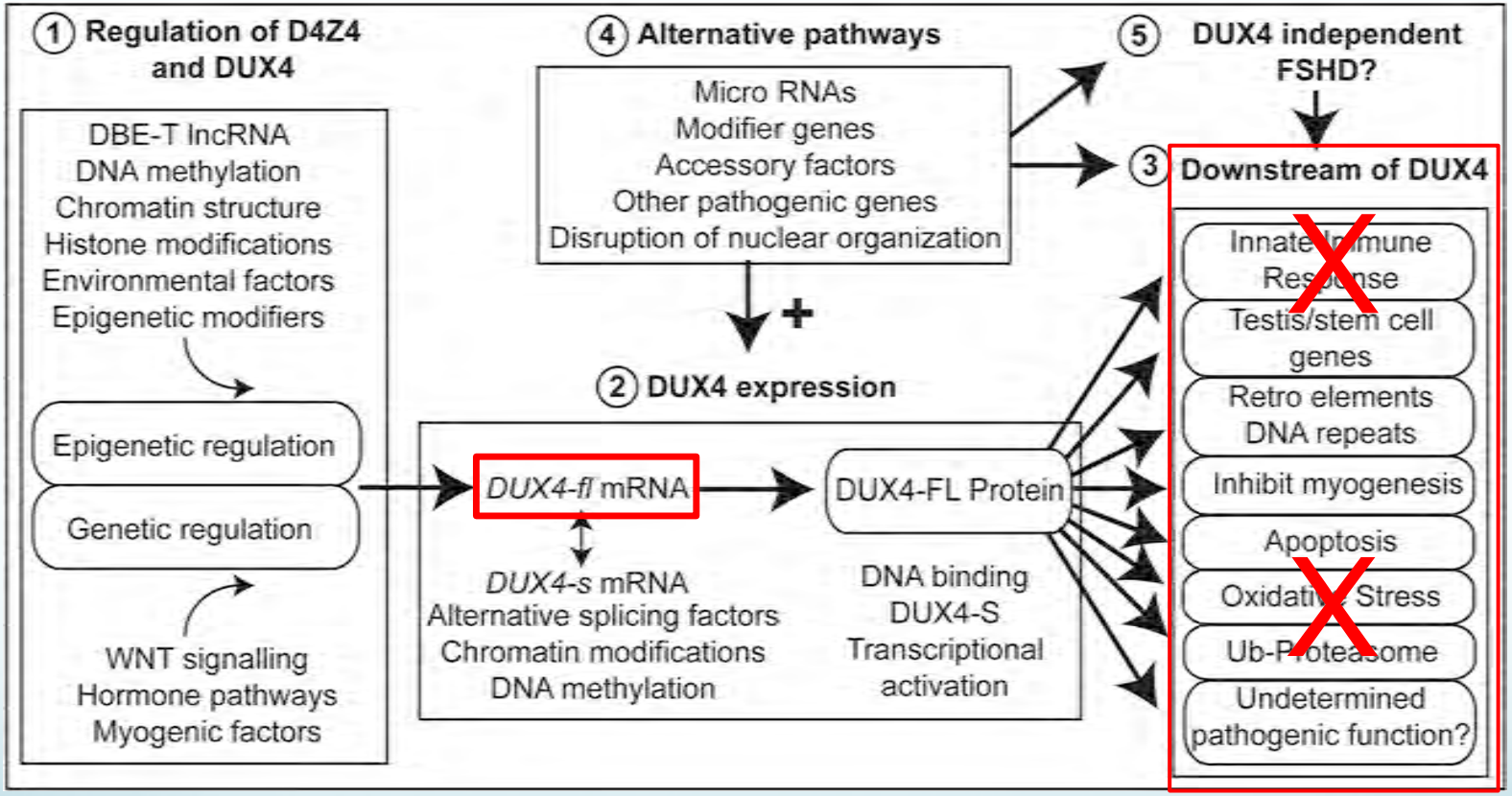
FSHD in 2019
Many viable therapeutic approaches!



DUX4-independent approaches

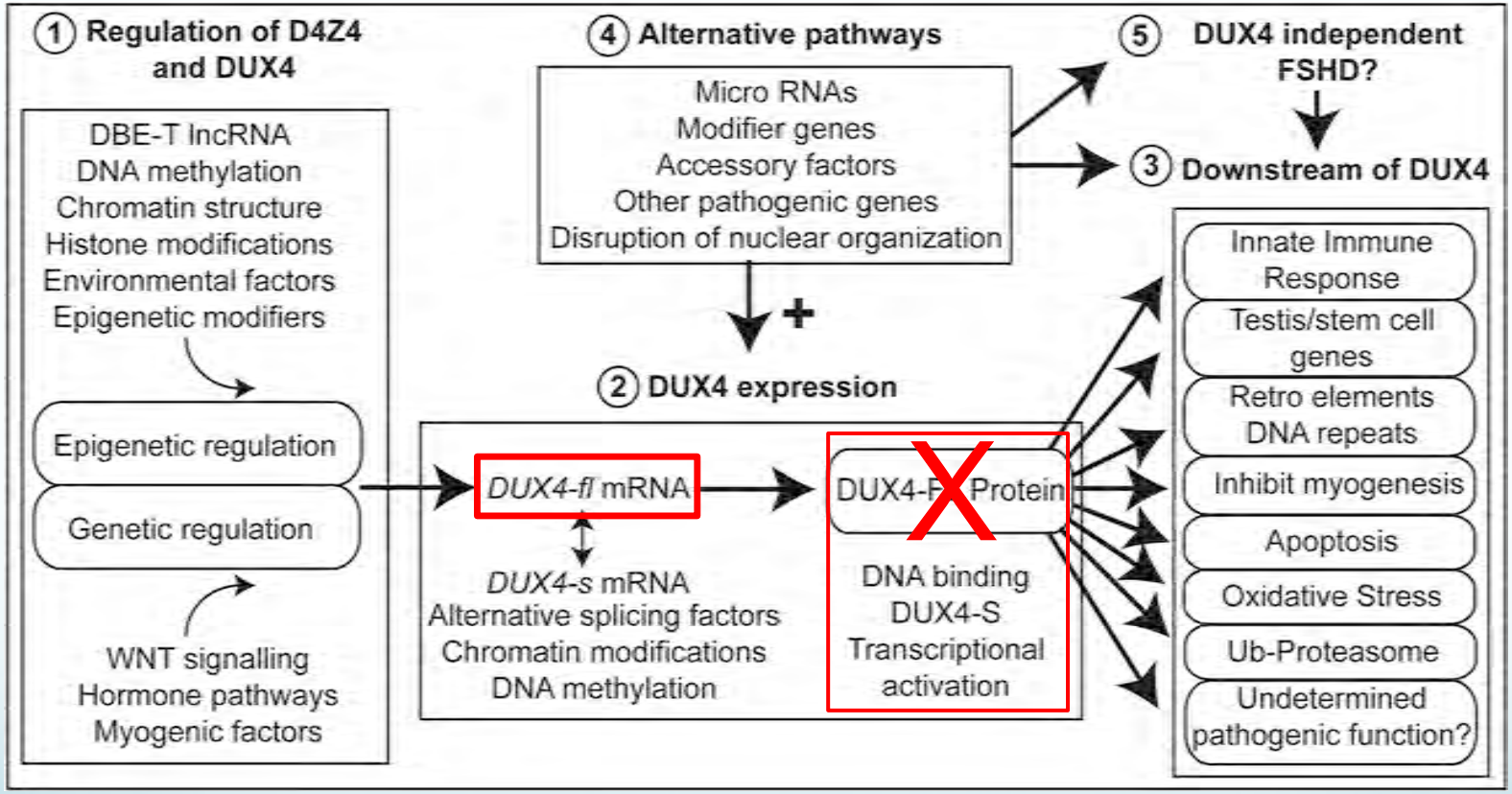
→ Myostatin inhibition (Acceleron ACE-083 trial)

FSHD in 2019
Many viable therapeutic approaches!



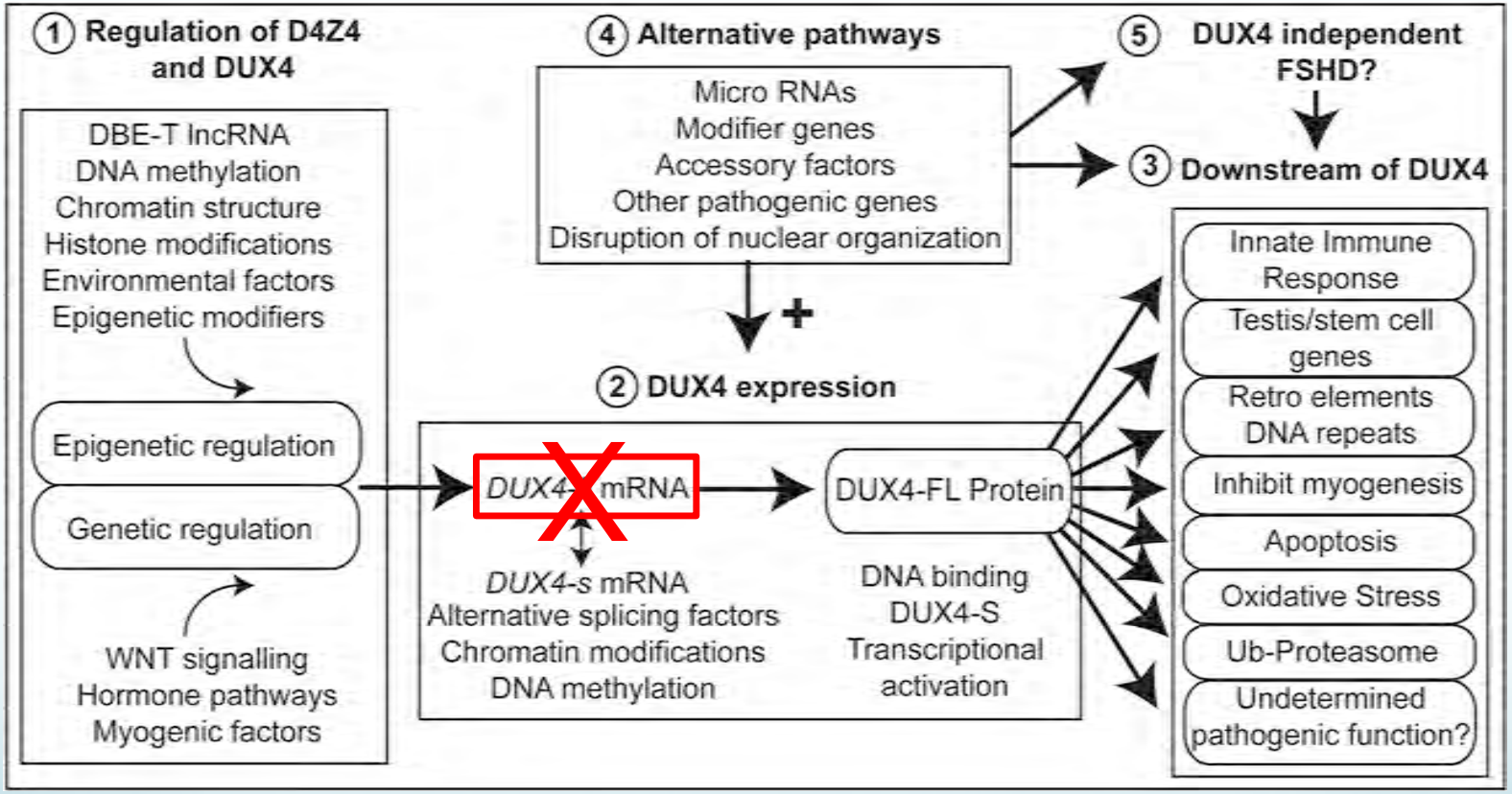
Drugs to block the pathogenic effects of DUX4-FL protein (e.g. Anti-oxidants, immune suppression; aTyr trial)

FSHD in 2019
Many viable therapeutic approaches!



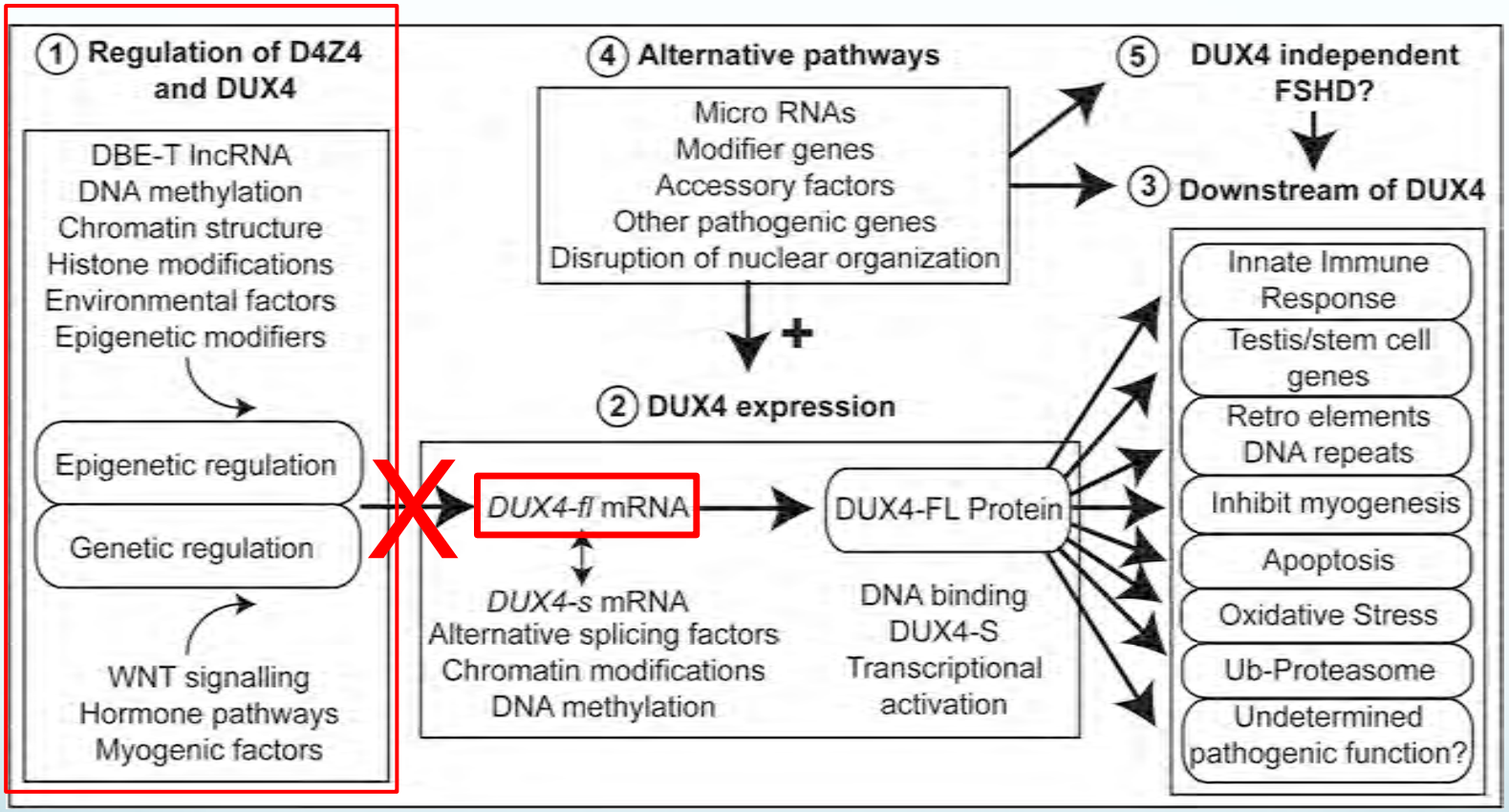
Drugs blocking DUX4 protein function (Icagen)

FSHD in 2019
Many viable therapeutic approaches!



Anti-sense technology to inactivate or destroy the DUX4-fl mRNA (Idera Pharmaceuticals and others)

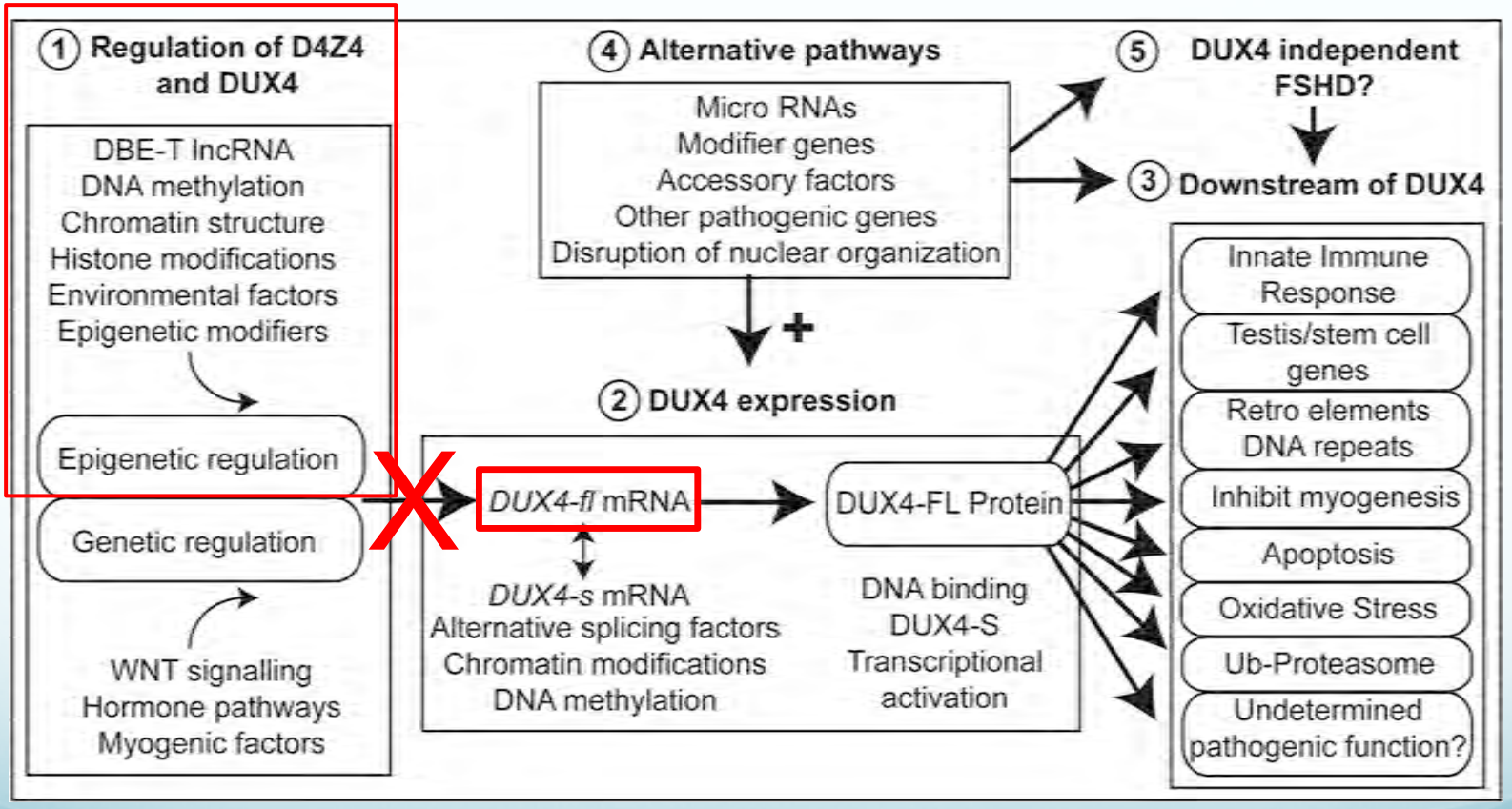
FSHD in 2019
Many viable therapeutic approaches!



Drugs to prevent expression of the *DUX4* gene
(Fulcrum Therapeutics & Novartis; clinical trials coming soon!!!)

FSHD in 2017
Many viable therapeutic approaches!

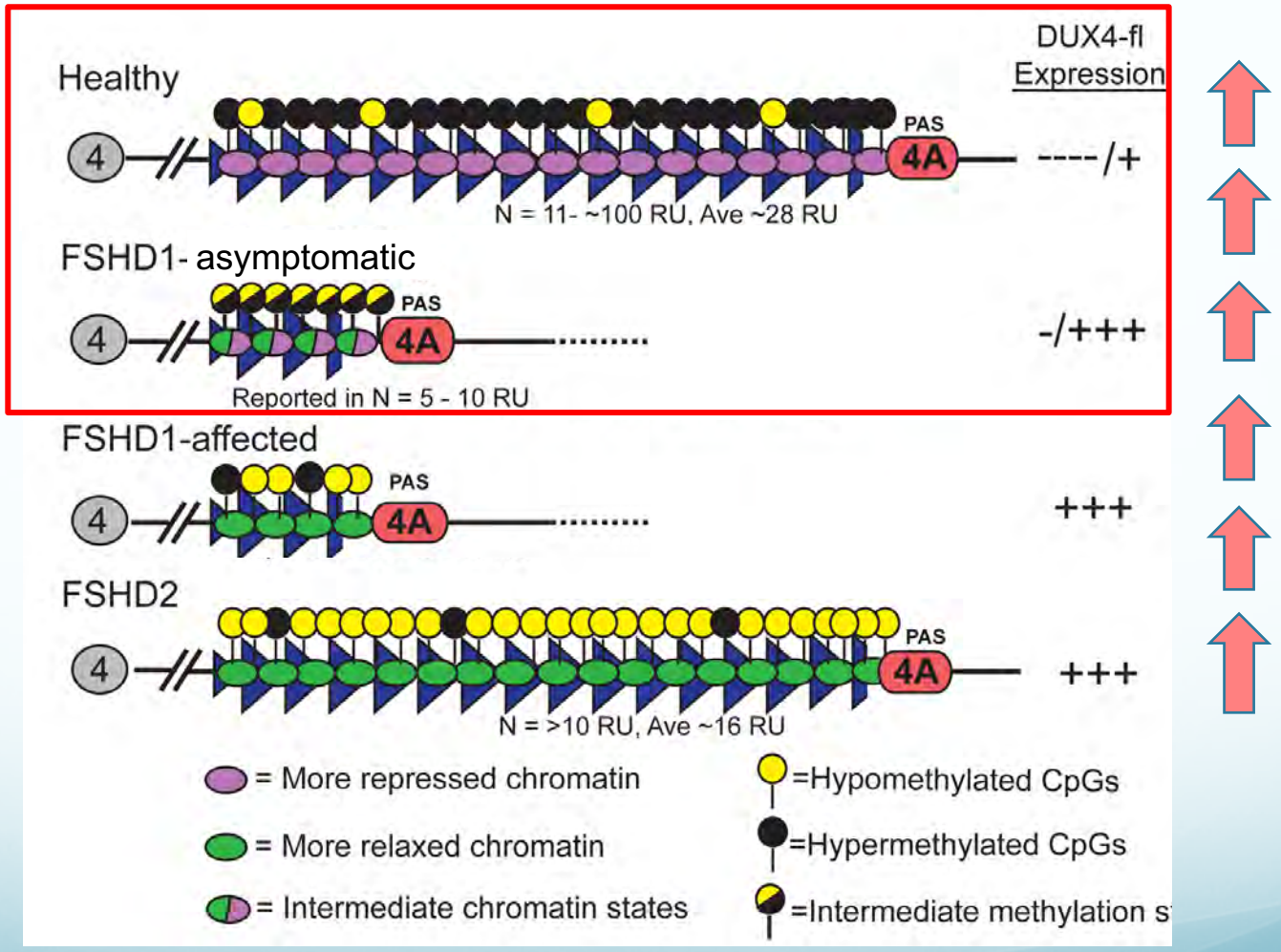
Jones Lab at UNRSOM



- **Drug development targeting FSHD epigenetics**
- **CRISPR/dCas9 silencing**

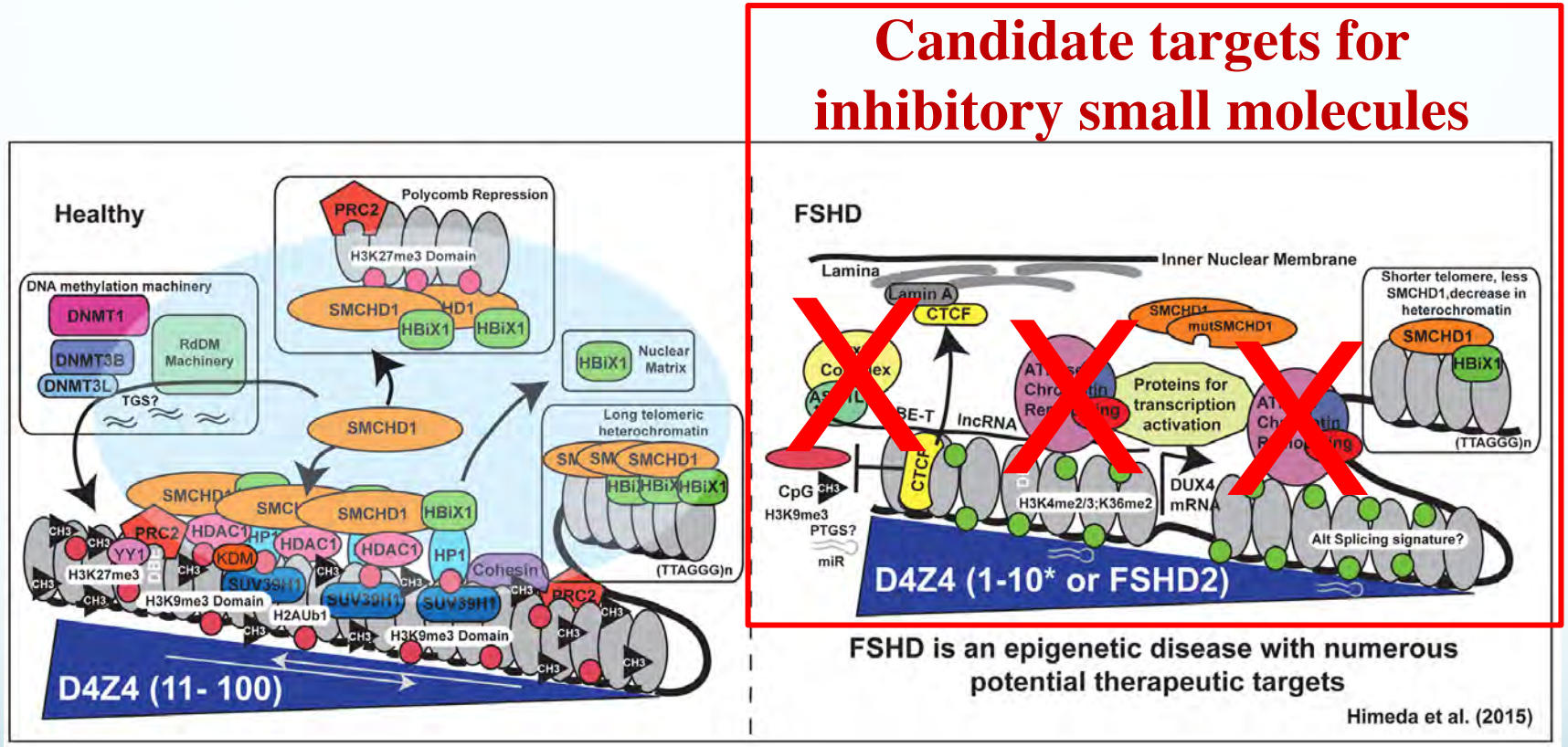
FSHD is an epigenetic disease

Can we therapeutically return to an FSHD non-affected epigenetic state?



T Jones *et al*. 2015 *Clinical Epigenetics*

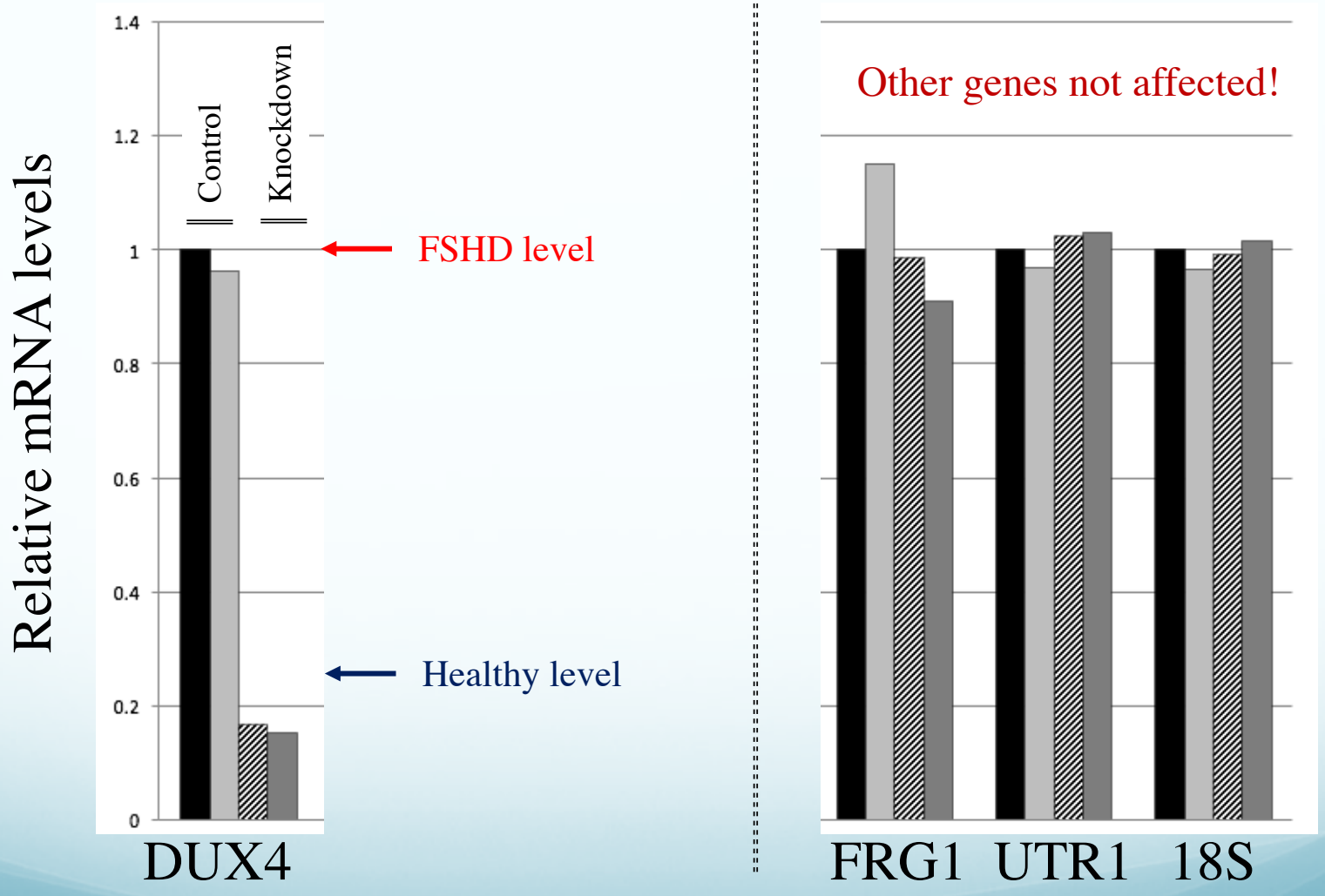
Epigenetic regulation at chrom 4q35 is distinct between healthy and FSHD



Healthy ← ← ← ← ← ← ← **FSHD**

Partnering with pharma to discover and develop drugs

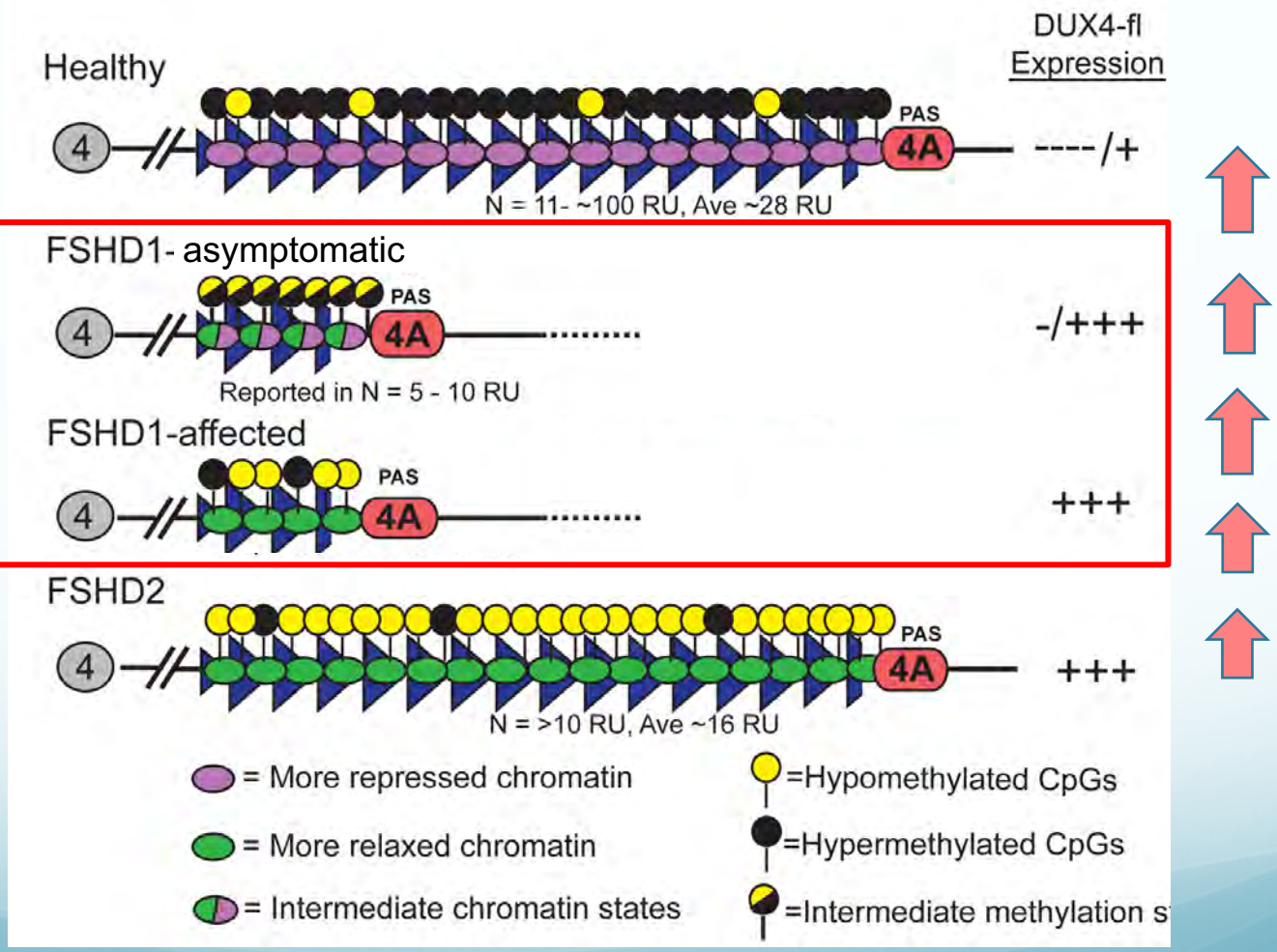
Identification of epigenetic targets for drug development



Designer drug development against FSHD therapeutic target

Targeting FSHD epigenetics

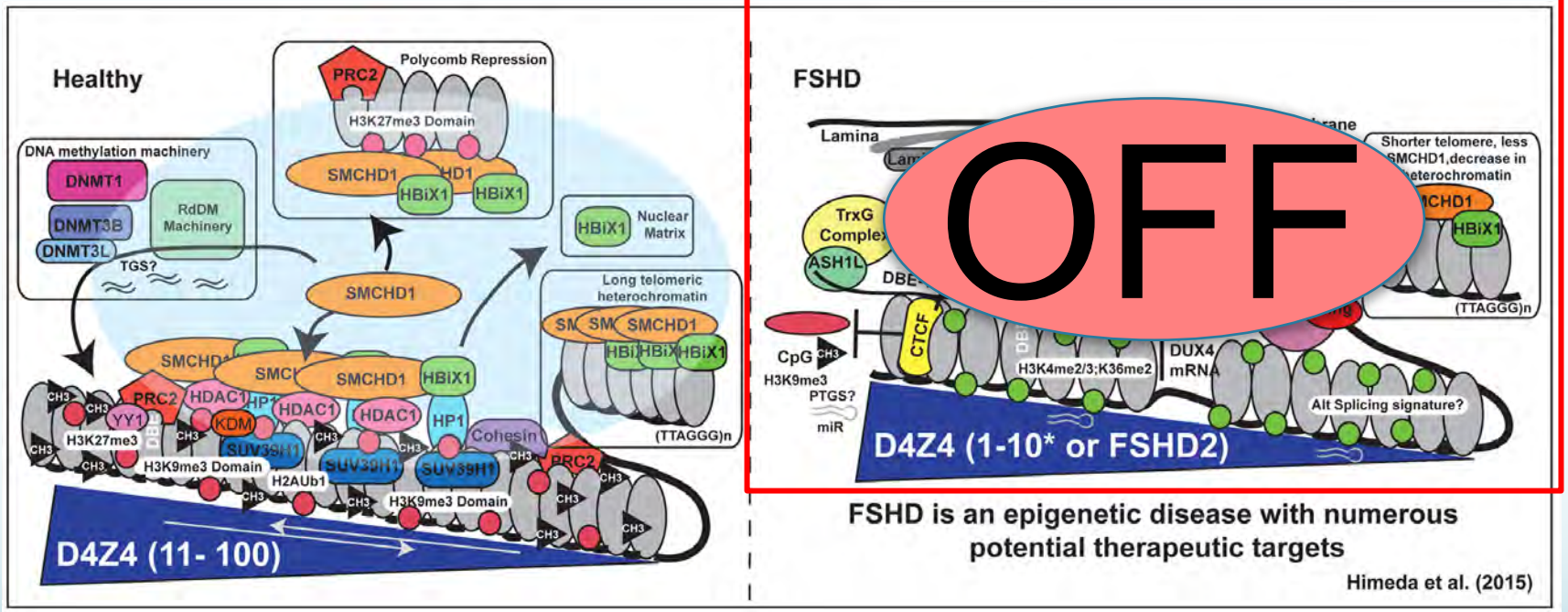
Can we therapeutically return to a non-affected epigenetic state by recruiting OFF machinery?



T Jones *et al*. 2015 *Clinical Epigenetics*

Epigenetic regulation at chrom 4q35 is a target for CRISPR therapy

Target for CRISPR-inhibition



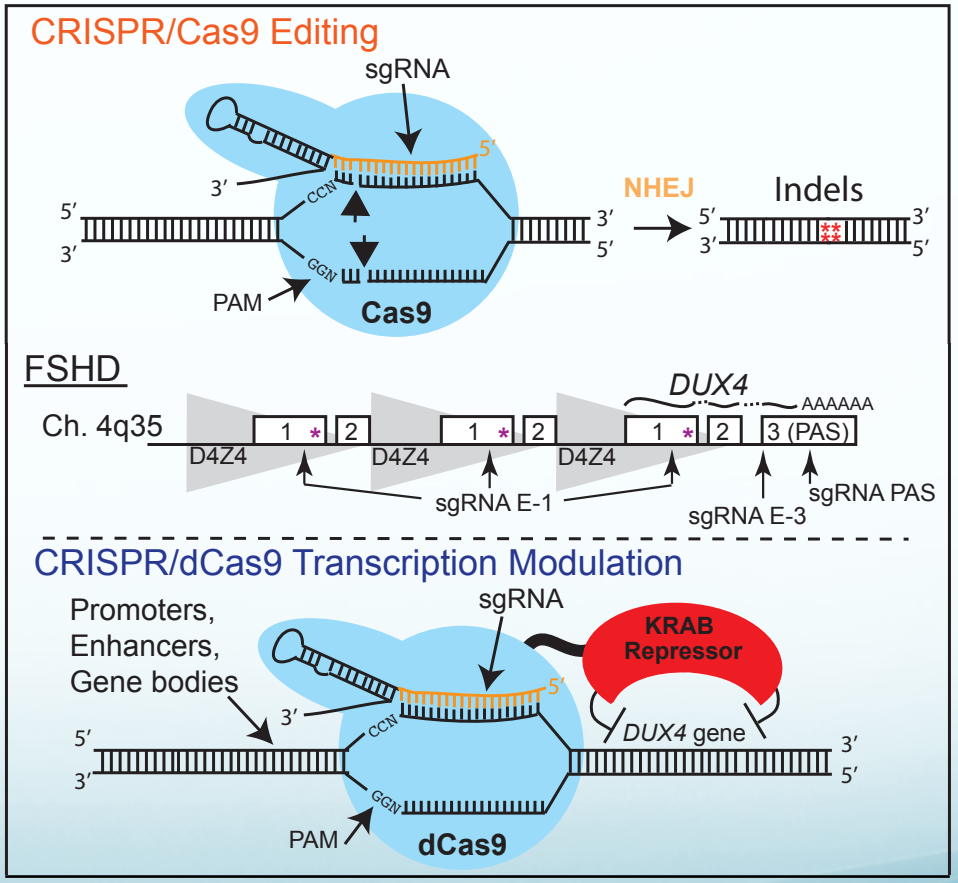
Healthy ← ← ← ← ← ← ← **FSHD**

Partnering with pharma to develop CRISPR therapy

CRISPR-mediated “genome editing” --> not what we are doing for FSHD!

Developing CRISPR-inhibition technology as a therapy for FSHD

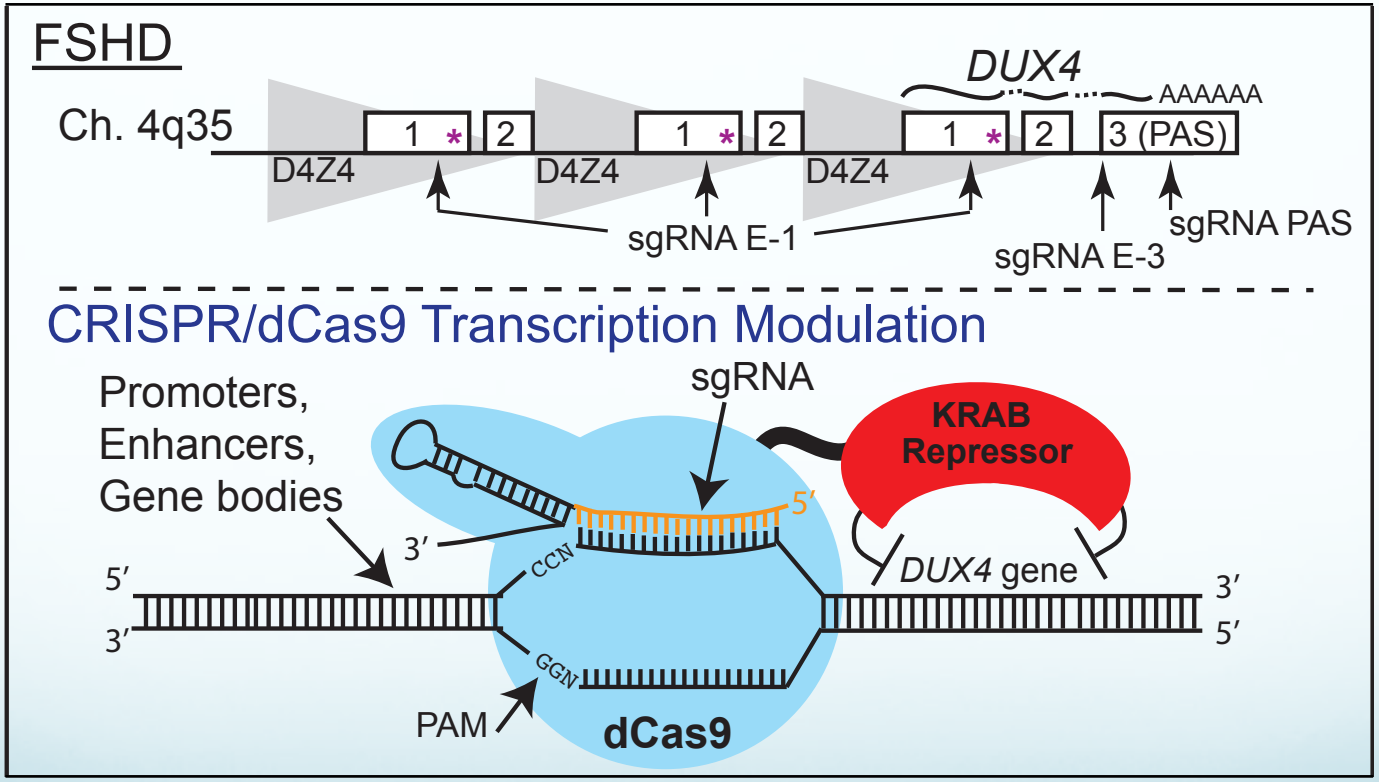
Charis Himeda, PhD



Himeda *et al*. (2015) *Mol. Therapy*
Himeda *et al*. (2016) *Trends Pharmacol*.

CRISPR/dCas9 in FSHD therapeutic development

Efficient genome targeting of a transcriptional repressor



Himeda *et al*. (2015) *Mol. Therapy*
Himeda *et al*. (2016) *Trends Pharmacol*.

original article

Mol Ther. 2016 Mar;24(3):527-35. doi: 10.1038/mt.2015.200. Epub 2015 Nov 3.

CRISPR/dCas9-mediated Transcriptional Inhibition Ameliorates the Epigenetic Dysregulation at D4Z4 and Represses *DUX4-fl* in FSH Muscular Dystrophy

Charis L Himeda[1], Takako I Jones[1] and Peter L Jones[1,2]

[1]*The Department of Cell and Developmental Biology, University of Massachusetts Medical School, Worcester, Massachusetts, USA;* [2]*The Department of Neurology, University of Massachusetts Medical School, Worcester, Massachusetts, USA*

First use of CRISPR technology for any neuromuscular disease

The Washington Post

Innovations

How CRISPR could lead to a cure for muscular dystrophy

By Dominic Basulto November 19

BOSTON BUSINESS JOURNAL

BIOFLASH

UMass researchers achieve several 'firsts' in new use for CRISPR/Cas9

Nov 16, 2015, 11:31am EST

INDUSTRIES & TAGS Technology, Health Care, Biotech, Pharmaceuticals

MOTHERBOARD Watch Machines Discoveries Space Futures Gaming Earth

CRISPR Technique Could 'Turn Off' Muscular Dystrophy Gene, Study Says

November 13, 2015 // 05:00 AM EST

Written by MELISSA CRONIN CONTRIBUTOR

How Controversial Gene Editing Could Lead To Groundbreaking Cures

This technology may change the way we think of some of the world's most challenging diseases.

Lila Shapiro
Senior Staff Reporter, The Huffington Post

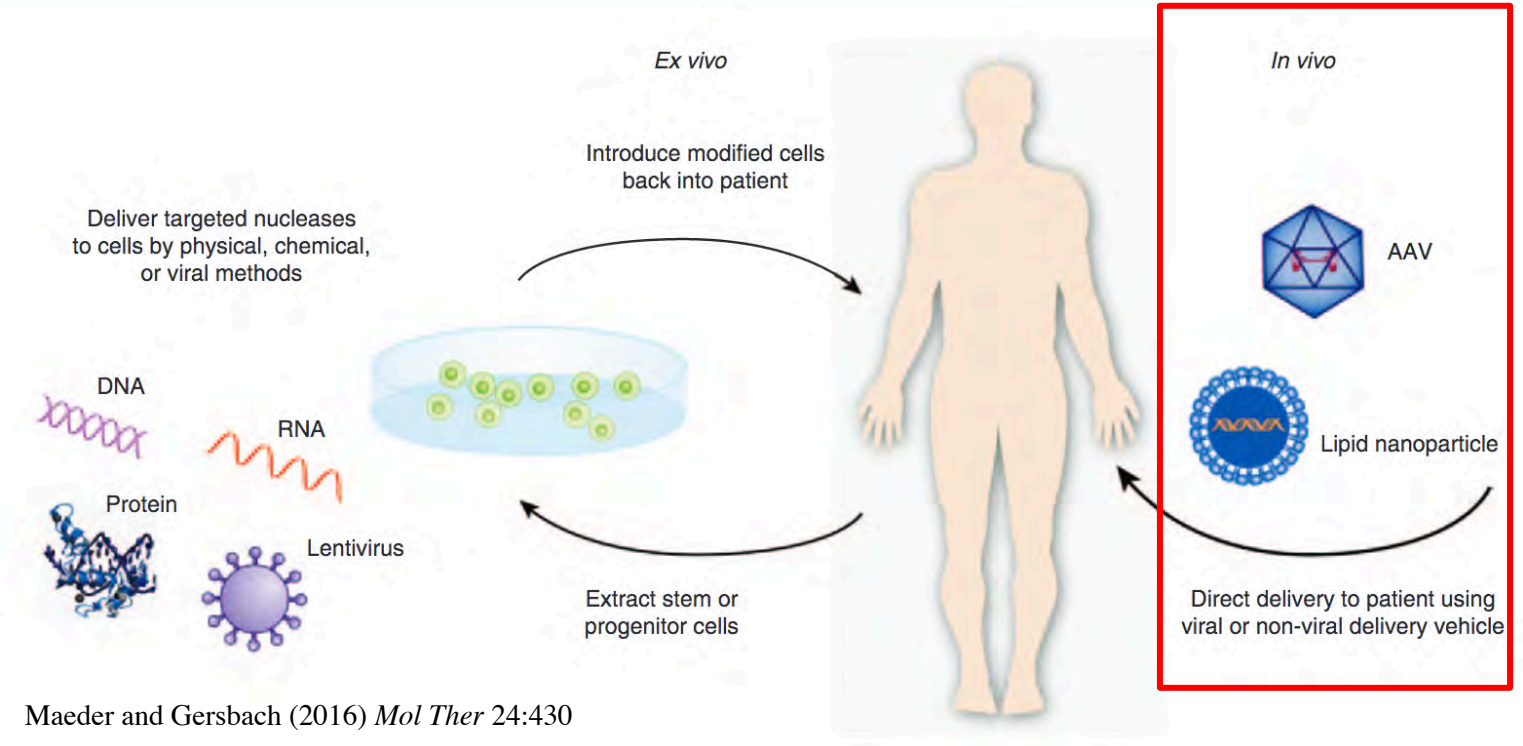
11/28/2015 07:31 am ET

Gregory Adams via Getty Images

Partnering with pharma to get into clinic

Therapeutic delivery of CRISPR/dCas9 *in vivo* is challenging

FSHD is a skeletal muscle disease

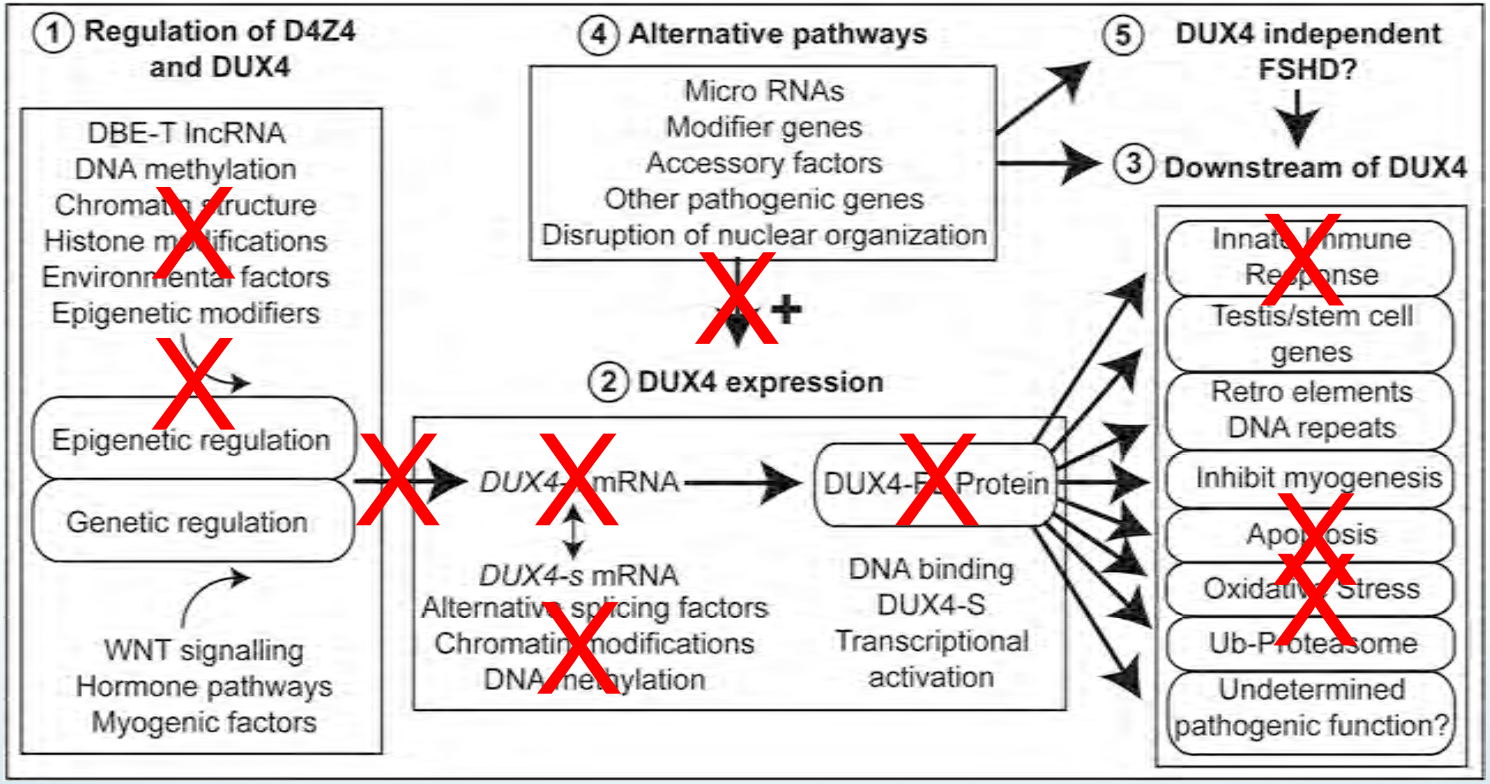


Maeder and Gersbach (2016) *Mol Ther* 24:430

Currently working on pre-clinical trials

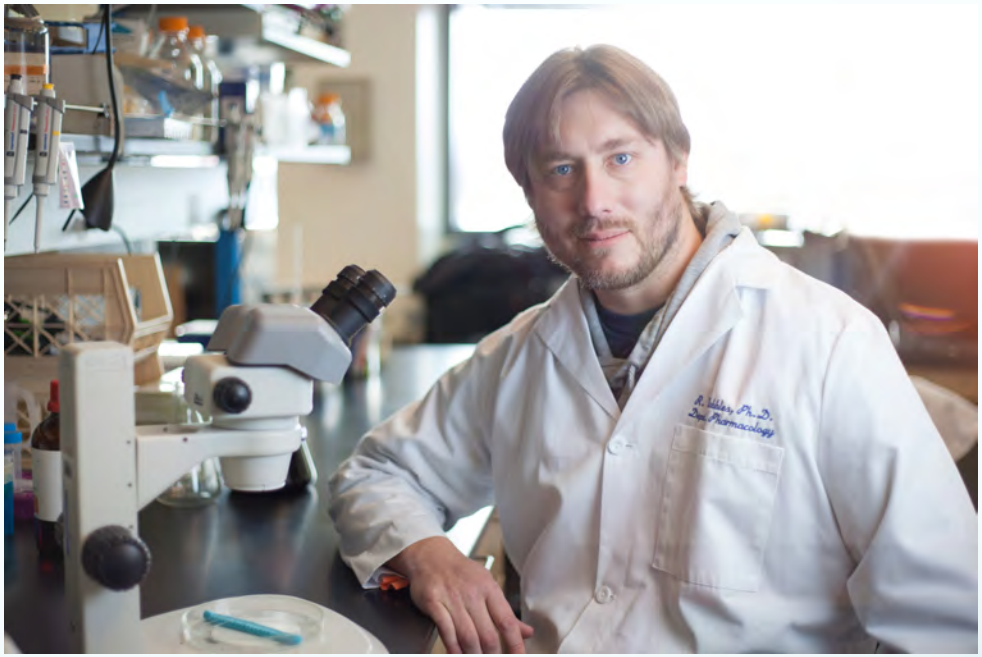
→ delivery, optimization, longevity

Our recent increased understanding of FSHD pathogenic mechanisms has led to the development of numerous therapeutic approaches and tools



CRISPRi/dCas9-KRAB; CRISPR/Cas9; Myostatin inhibition Morpholinos/PMOs/shRNAs; miRNAs; Anti-inflammatory Small molecules targeting epigenetic regulators; more…

What can you do as patients, family members, friends?



Ryan Wuebbles, PhD; UNR Med Faculty; CSO StrykaGen Corp

Participate in research and clinical trials
Advocate for FSHD (and biomedical research) funding
Promote FSHD awareness

University of Nevada, Reno
School of Medicine

Gait analysis as a potential metric for FSHD clinical trials

Drs. Nicholas Murray and Ryan Wuebbles working with Bob Rosania

Ongoing and upcoming clinical trials: https://clinicaltrials.gov/

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Effect of Creatine Monohydrate on Functional Muscle Strength in Children With **FSHD**	• **Facio-Scapulo-Humeral Dystrophy** • **FSHD2** • **FSHD1**	• Dietary Supplement: Creatine Monohydrate • Dietary Supplement: Placebo	• The Royal Children's Hospital Melbourne, Victoria, Australia
2	☐	Recruiting	Clinical Trial Readiness to Solve Barriers to Drug Development in **FSHD**	• **Facioscapulohumeral Muscular Dystrophy**	• Diagnostic Test: FSHD-specific functional rating scale • Device: Electrical Impedance Myography	• University of California Los Angeles Los Angeles, California, United States • University of Kansas Medical Center Kansas City, Kansas, United States • Kennedy Krieger Institute Baltimore, Maryland, United States • (and 5 more...)
3	☐	Recruiting	Study of Testosterone and rHGH in **FSHD**	• **Facioscapulohumeral Muscular Dystrophy**	• Drug: Testosterone Enanthate • Drug: Somatropin	• University of Rochester Rochester, New York, United States
4	☐	Recruiting	Magnetic Resonance Imaging and Spectroscopy Biomarkers for **Facioscapulohumeral Muscular Dystrophy**	• **Facioscapulohumeral Muscular Dystrophy**		• Doris Leung Baltimore, Maryland, United States
5	☐	Recruiting	Intramuscular Transplantation of Muscle Derived Stem Cell and Adipose Derived Mesenchymal Stem Cells in Patients With Facioscapulohumeral Dystrophy (**FSHD**)	• Dystrophy	• Biological: Intramuscular injection	• Royan Institute Tehran, Iran, Islamic Republic of
6	☐	Recruiting	Neurological and Psychiatric Comorbidities Patients With **FSHD** 1 and 2	• Muscular Dystrophy, Facioscapulohumeral	• Behavioral: Psychiatric test	• Hôpital Pasteur Nice, France
7	☐	Recruiting	Myotonic Dystrophy and **Facioscapulohumeral Muscular Dystrophy** Registry	• Myotonic Dystrophy • **Facioscapulohumeral Muscular Dystrophy** • Muscular Dystrophy • (and 6 more...)		• University of Rochester Medical Center, Department of Neurology Rochester, New York, United States
8	☐	Recruiting	Acceptance and Commitment Therapy for Muscle Disease	• Muscle Diseases	• Behavioral: Acceptance and Commitment Therapy (ACT)	• King's College Hospital; The Royal London Hospital; University Hospital Southampton; King's College London London, United Kingdom

Additional clinical trials planned for 2019

Fulcrum Therapeutics FSHD Preparatory Studies

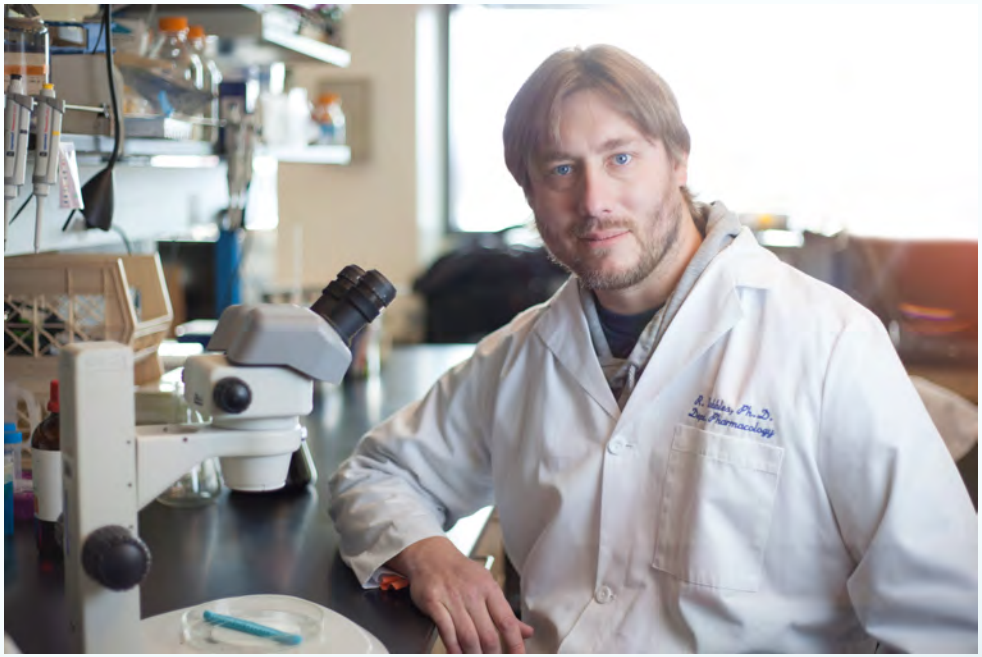
1. **FSHD mobility function (TUG= Time Up and Go)**
   - Single site at UCI-Irvine open; 20 HVs completed, 21/20 FSHD completed, still looking for 3 more patients (low disability).
2. **FSHD Shoulder/proximal arm function (RWS=**Reachable Work Space)
   - U01 NIH collaboration study- 11 sites activated, 110/220 subjects enrolled; looking for 110 more.
3. **FSHD Longitudinal muscle MRI and muscle biopsy biomarker study**
   - 6 sites activated, 6 patients enrolled, looking for 14 more.
4. **FSHD patient input in ph2 study design (Survey)**
   - 7 sites in the US, Canada and EU
   - Looking for 40-80 patients in the US

Fulcrum Therapeutics FSHD Preparatory Studies

	SRA-003-2017 (RWS)	SRA-003-2018 (TUG)	SRA-004-2018 (survey)	FTX-002-2018 (biomarker)
URMC/Rochester, NY	X		X	X
Uwashington/Seatte	X			X
UCLA/Los Angeles	X			X
UKMC/Kansas City	X			X
KKI/Baltimore	X		X	X
VCU/Richmond, VA	X		X	X
OSU, Columbus, OH	X			
UOU/Salt Lake City	X			
UC Irvine		X		
Radboudumc, Netherlands	X			X
CHU de Nice Hôpital, France	X		X	
Centro Clinico Nemo Milano, Italy	X			
Montreal Neurological Institute and Hospital/Canada			X	
Newcastle University/UK			X	

Contact the sites directly for participation

We are very near being able to do something for you, and you can help



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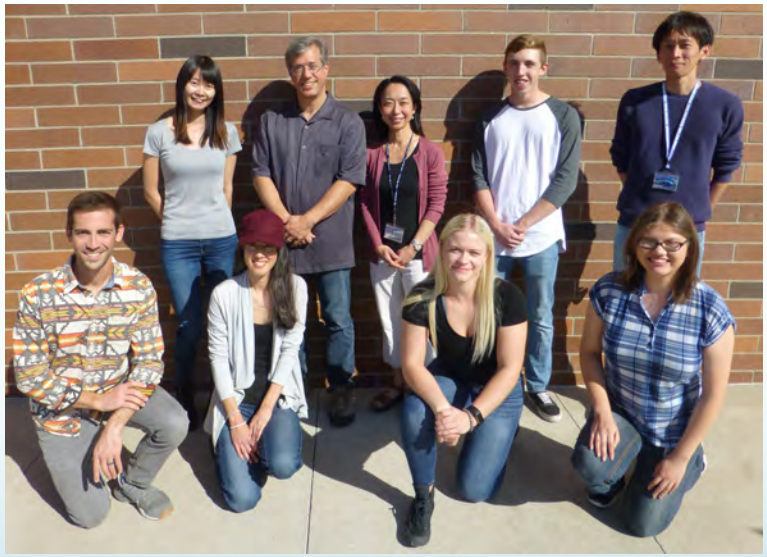
Acknowledgements

Mick Hitchcock, PhD Endowed Chair in Medical Biochemistry

NYC

A Voice for FSHD
The Chris Carrino Foundation for FSHD



France

AFM
Association Française contre les Myopathies

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Australia

FSHD
Global Research Foundation Ltd

Eunice Kennedy Shriver
NICHD
National Institute of Child Health & Human Development

USA

FSH SOCIETY
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

FSHD CANADA FOUNDATION
Curing the #1 Form of Muscular Dystrophy

USA

MDA

Contact: peterjones@med.unr.edu
https://med.unr.edu/jones-lab

Let us know if visiting Reno/Tahoe area

→ lab tour, meet with researchers, option to participate in research studies

- **Gait analysis for clinical trial endpoints**
- **Improving FSHD diagnostics by epigenetic testing**