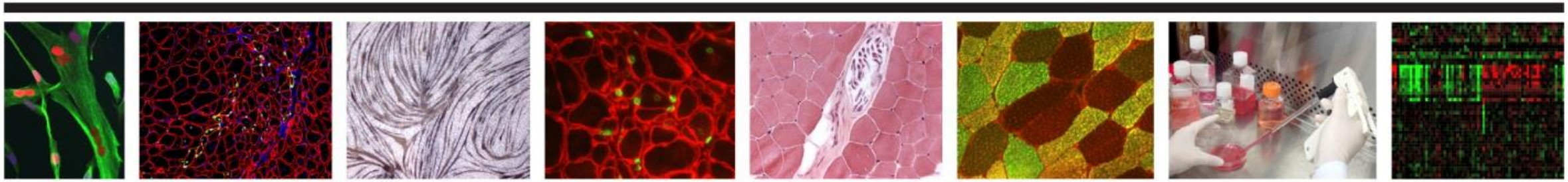
Welcome

New England FSHD Patient Luncheon



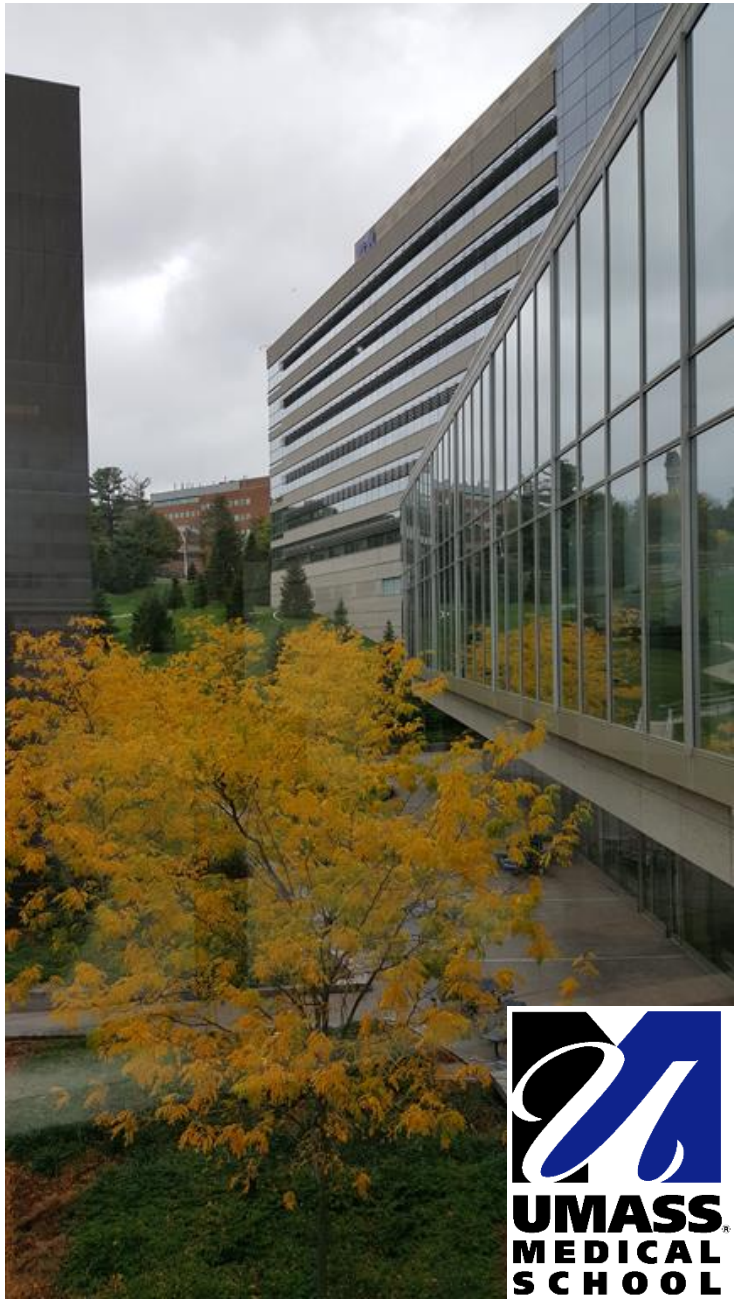
November 4, 2018

Overview of the Wellstone Research Program and FSHD Clinic at UMMS

Lawrence Hayward, M.D., Ph.D.
Professor of Neurology
UMass Medical School, Worcester, MA
November 4, 2018

Mission of the Wellstone Centers
Wellstone Investigators and Organization
Wellstone Projects and Recent Accomplishments

FSHD Clinic at UMass Medical School
FSHD Biomarker Study



The NIH Wellstone Centers Program

Translational Research Centers for Muscular Dystrophy Therapeutics

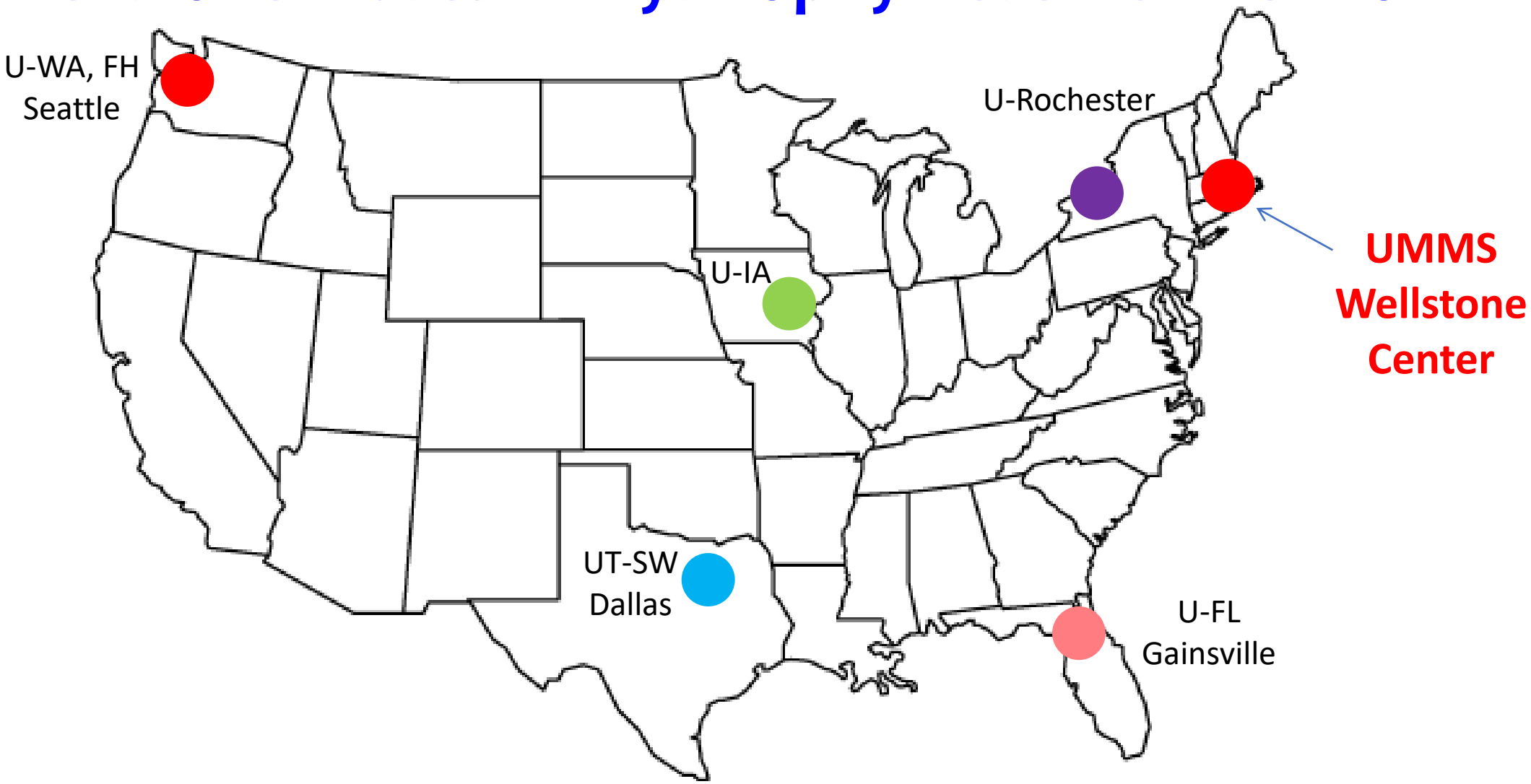
Paul D. Wellstone Muscular Dystrophy Community Assistance, Research and Education Amendments (MD-CARE Act)

Public Law 107-84 of 2001 and 110-361 of 2008

Paul D. Wellstone
1944-2002
Senator from MN
1991-2002

Glen Nuckolls, NIAMS

Wellstone Muscular Dystrophy Research Network

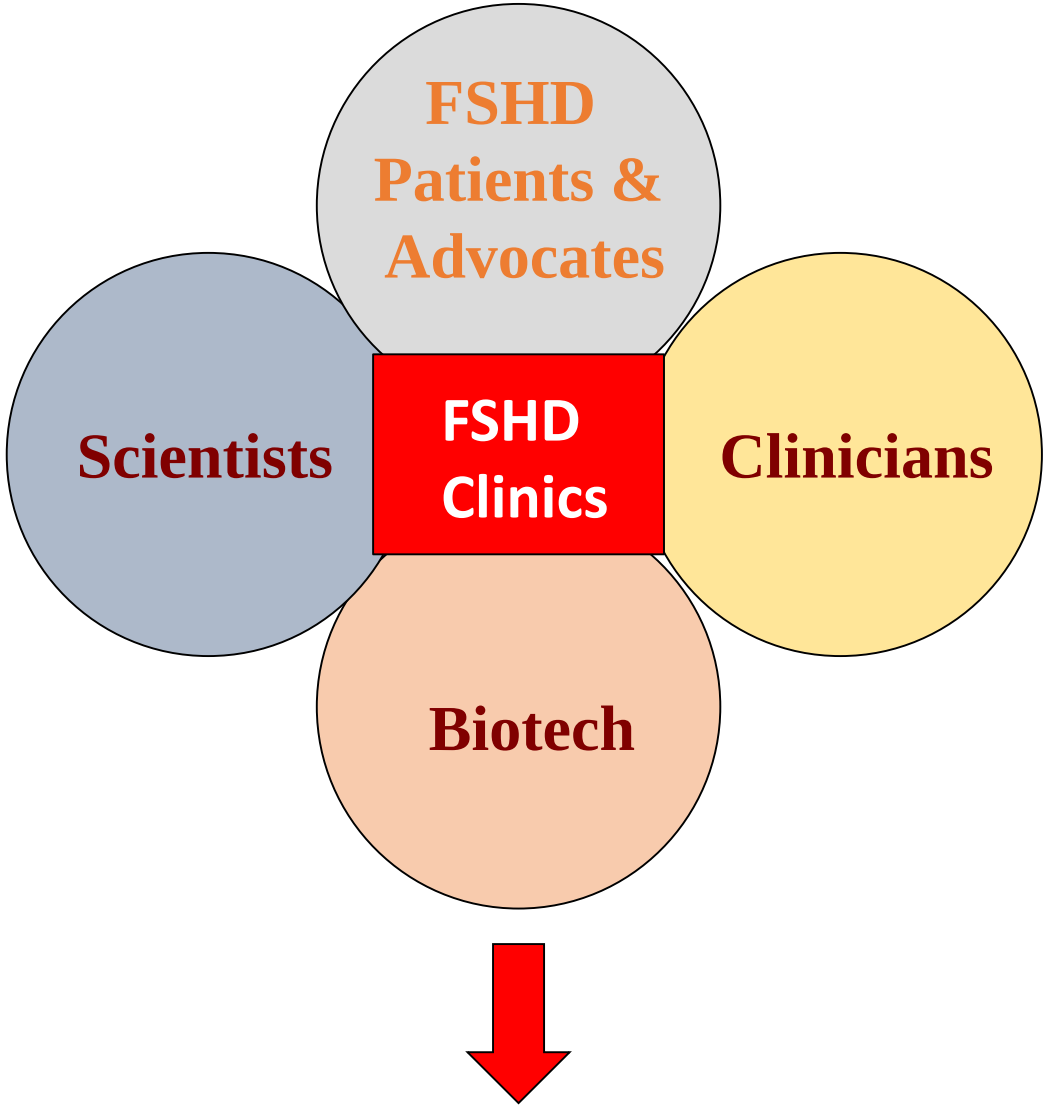


THE UMMS WELLSTONE IS SINGULARLY FOCUSED ON FSHD

Glen Nuckolls, NIAMS

Mission of UMMS Wellstone Center

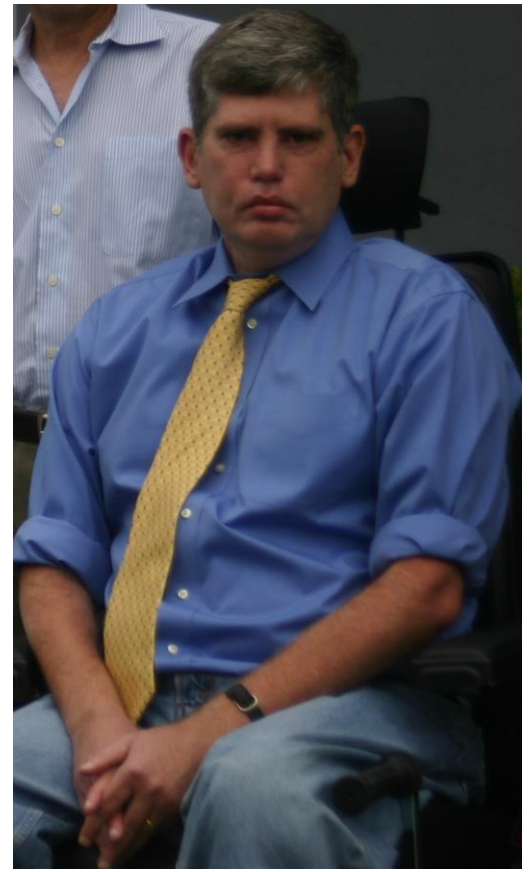
The UMMS Wellstone Center focuses on the molecular, genetic and epigenetic pathologies of facioscapulohumeral muscular dystrophy with the goal of developing potential therapies that can be tested clinically.



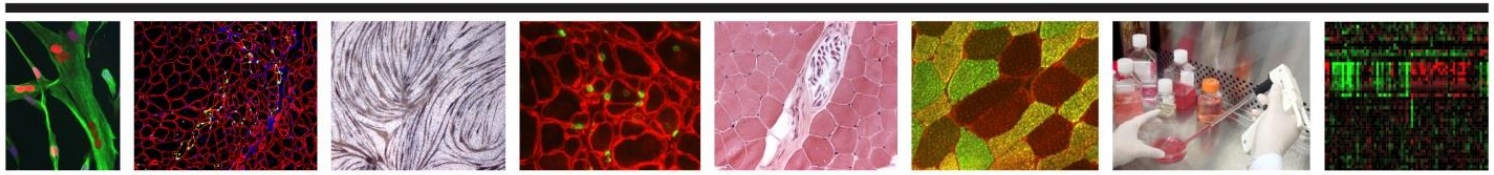
Biologics **FSHD Therapeutics** **Training**

OUR WELLSTONE TEAM

Annual UMMS Wellstone Retreat



Daniel Perez and the FSH Society



Wellstone Principal Investigators

An exceptional multidisciplinary team dedicated to collaborative research for FSHD therapies

NIH UMMS Wellstone Center for FSHD Principal Investigators

UMASS	**Charles P. Emerson, PhD (Director)** **Oliver D. King, PhD** **Anastasia Khvorova, PhD** **Jonathan K. Watts, PhD** **Lawrence J. Hayward, MD, PhD**	Myogenesis and Disease Mechanisms Cellular and Xenograft Modeling Genome Biology and Bioinformatics Oligonucleotide-based Therapeutics FSHD Clinic and Biomarkers Single-cell Biology in FSHD
Boston Children's Hospital	**Louis Kunkel, PhD (Co-Director)** **Angela Lek, PhD (now at Yale)**	Human Genetics and Disease Modifiers Zebrafish Modeling and Therapeutics Genetic Pathway Screening
Kennedy Krieger Institute	**Kathryn Wagner, MD, PhD (Co-Director)**	FSHD Clinic and Therapeutics Muscle Biopsy and Xenograft Model Imaging and Genetic Modifiers in FSHD
The University of Utah	**Nicholas Johnson, MD** **Robert Weiss, PhD**	Population-based Genetics Disease Modifiers Clinical Trials
Nationwide Children's	**Scott Q. Harper, PhD**	Gene-based Therapies Inducible Mouse Model for FSHD DUX4 Functions and Modifications

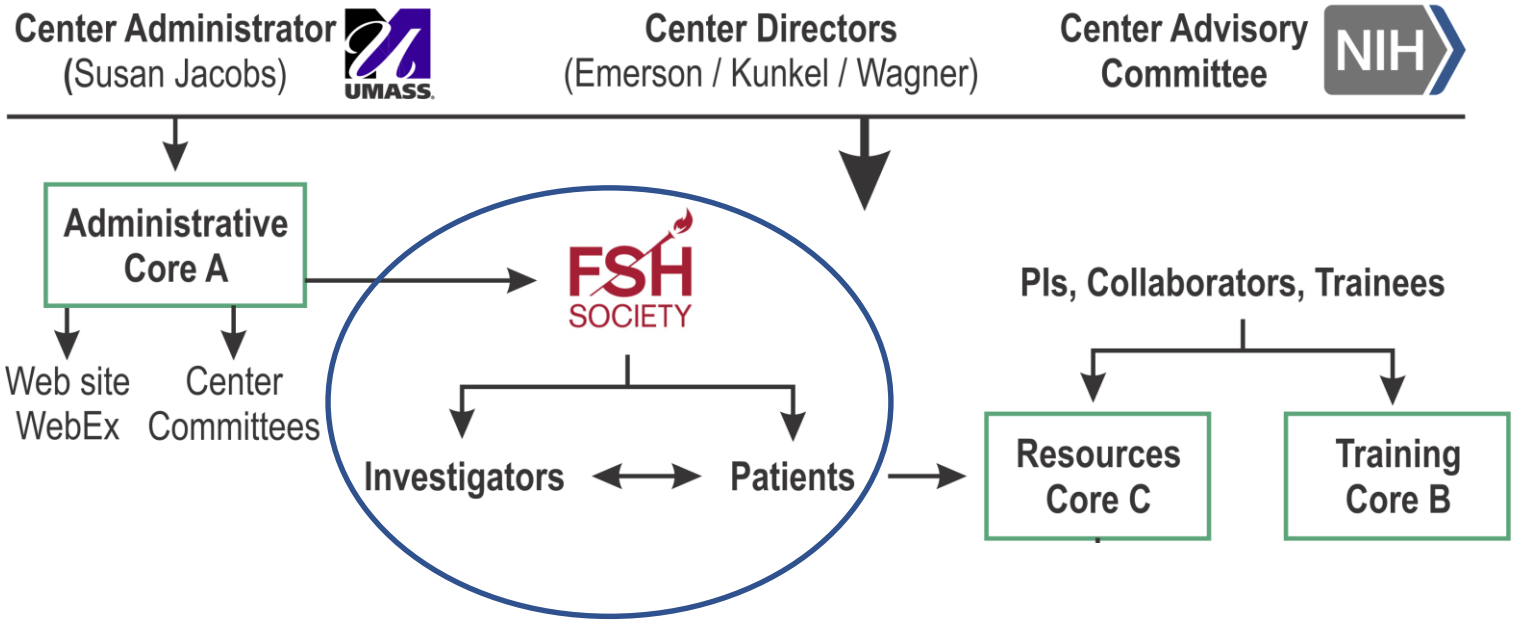
NIH Seattle-Rochester Wellstone CRC Collaborators

Stephen J. Tapscott, MD, PhD **Rabi Tawil, MD**	Molecular Genetics and Biology of FSHD Clinical Trials and Muscle Pathology

FSHD patients and family members are the backbone of our Wellstone Center

- Blood and muscle biopsies for FSHD research and therapeutic development;
- Participation in future FSHD clinical trials;
- Inspiration for our scientists, clinicians and trainees.

Novel Therapeutics for FSHD



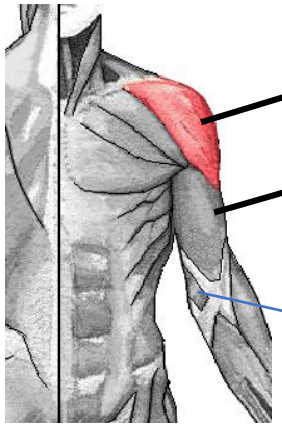
FSHD Blood, Muscle Biopsy and Cell Repository

FSHD1 Family Cohorts: consented 197 individuals from 84 FSHD families

63 family cohorts:
FSHD1 subject (6-10 D4Z4)
(moderate weakness)
&
Unaffected First Degree Relative

+

21 family cohorts:
Clinically Divergent



Deltoid muscle – Less affected

Biceps muscle – More affected

Muscle biopsies from 56 families

Blood DNA → Genotyping → Genome sequencing

Cells
Primary myogenic
Immortalized iPSCs

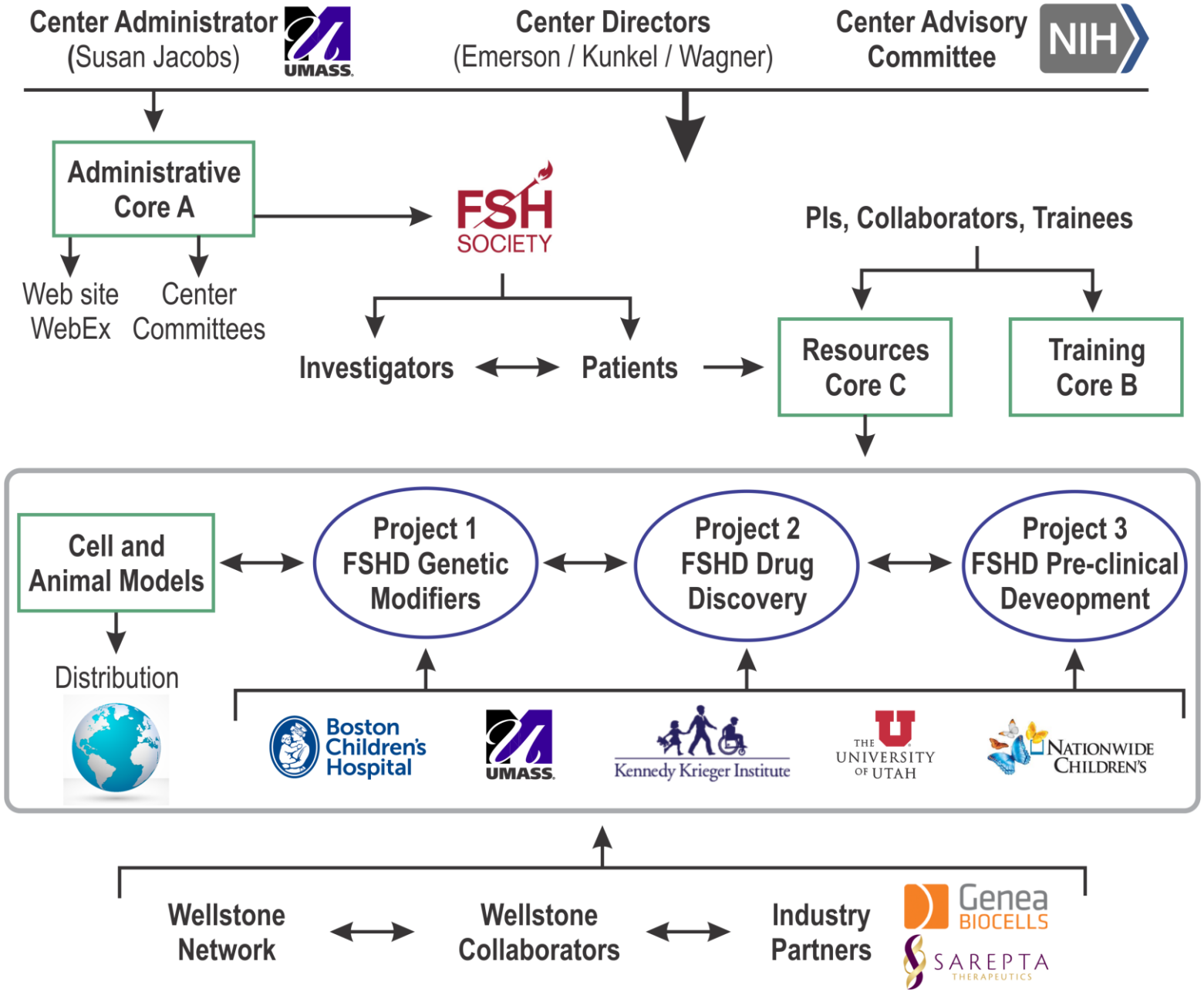
Muscle Fibers
Fiber xenografts
SF physiology

RNA biomarkers
RNA-Seq

Proteomics

Histopathology

Novel Therapeutics for FSHD



Recent Findings from Wellstone Investigations

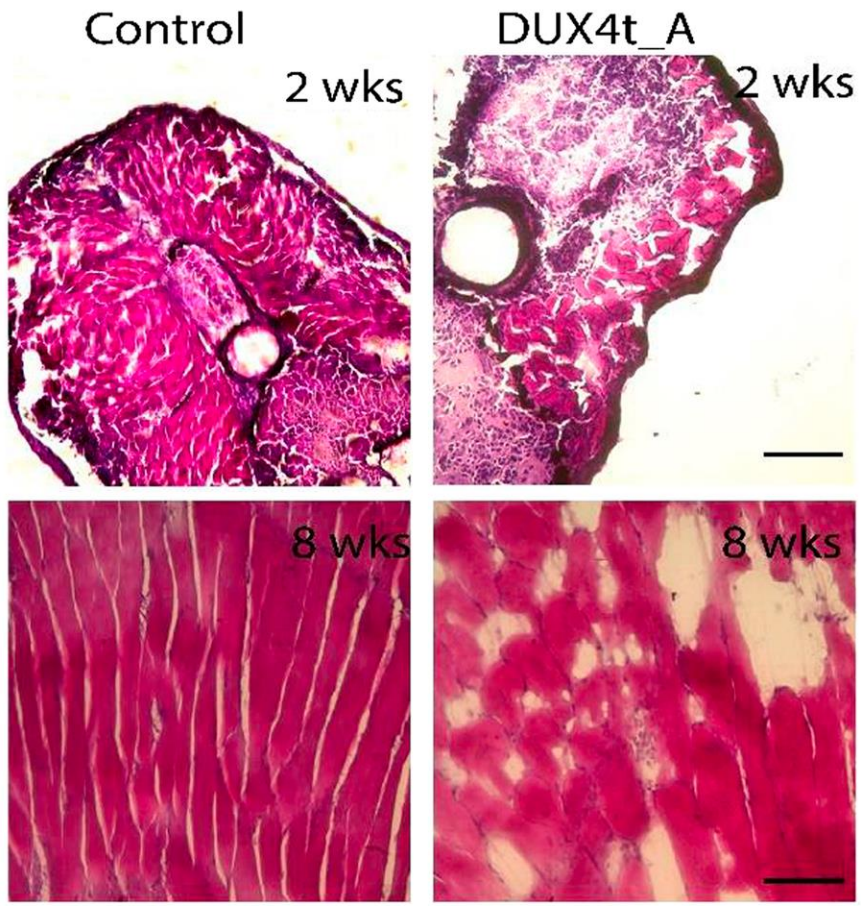
Consequences of early DUX4 expression in zebrafish may manifest later in adulthood

GENERAL ARTICLE

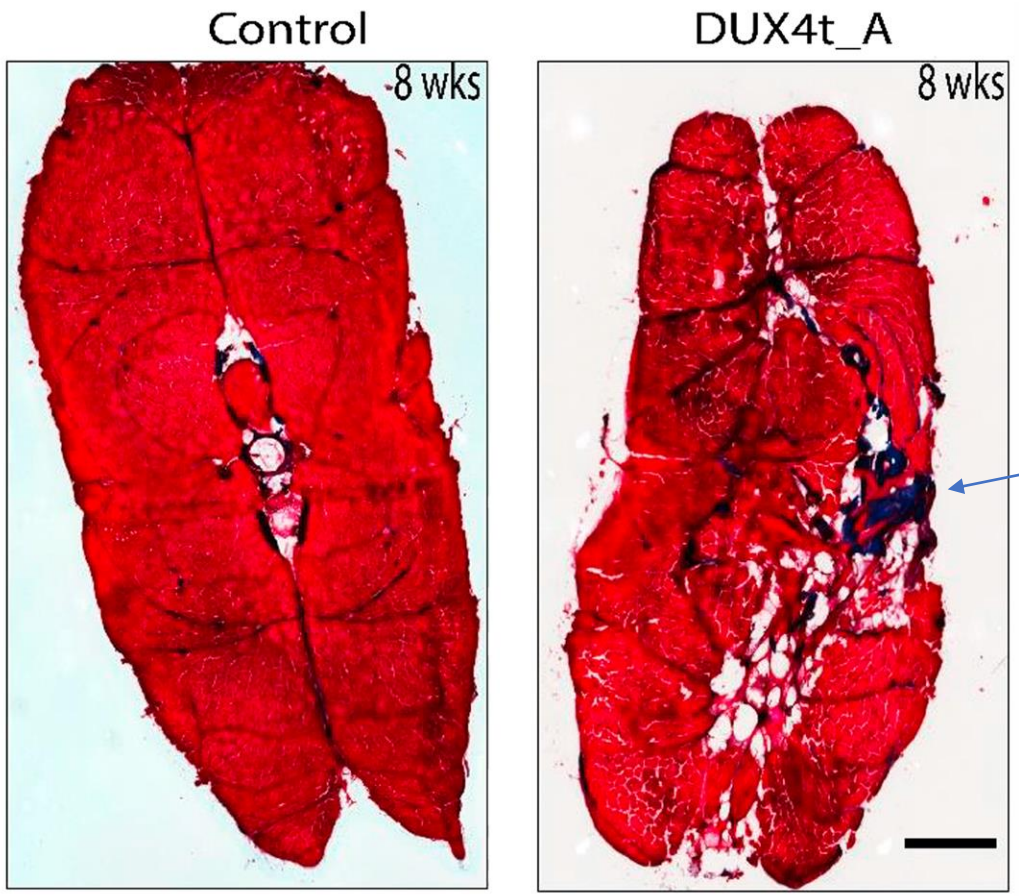
Transgenic zebrafish model of DUX4 misexpression reveals a developmental role in FSHD pathogenesis

Anna Pakula[1,2,3,†], Angela Lek[1,2,3,4,†], Jeffrey Widrick[1,3], Hiroaki Mitsuhashi[1,2,3], Katlynn M. Bugda Gwilt[1,5], Vandana A. Gupta[3,5], Fedik Rahimov[1,3], June Criscione[1,3], Yuanfan Zhang[1,2,3], Devin Gibbs[1,3], Quinn Murphy[1,3], Anusha Manglik[1,3], Lillian Mead[1,3] and Louis Kunkel[1,2,3,*]

Human Molecular Genetics (in press, 2018)



Muscle replacement by fat or collagen



Asymmetrical collagen accumulation

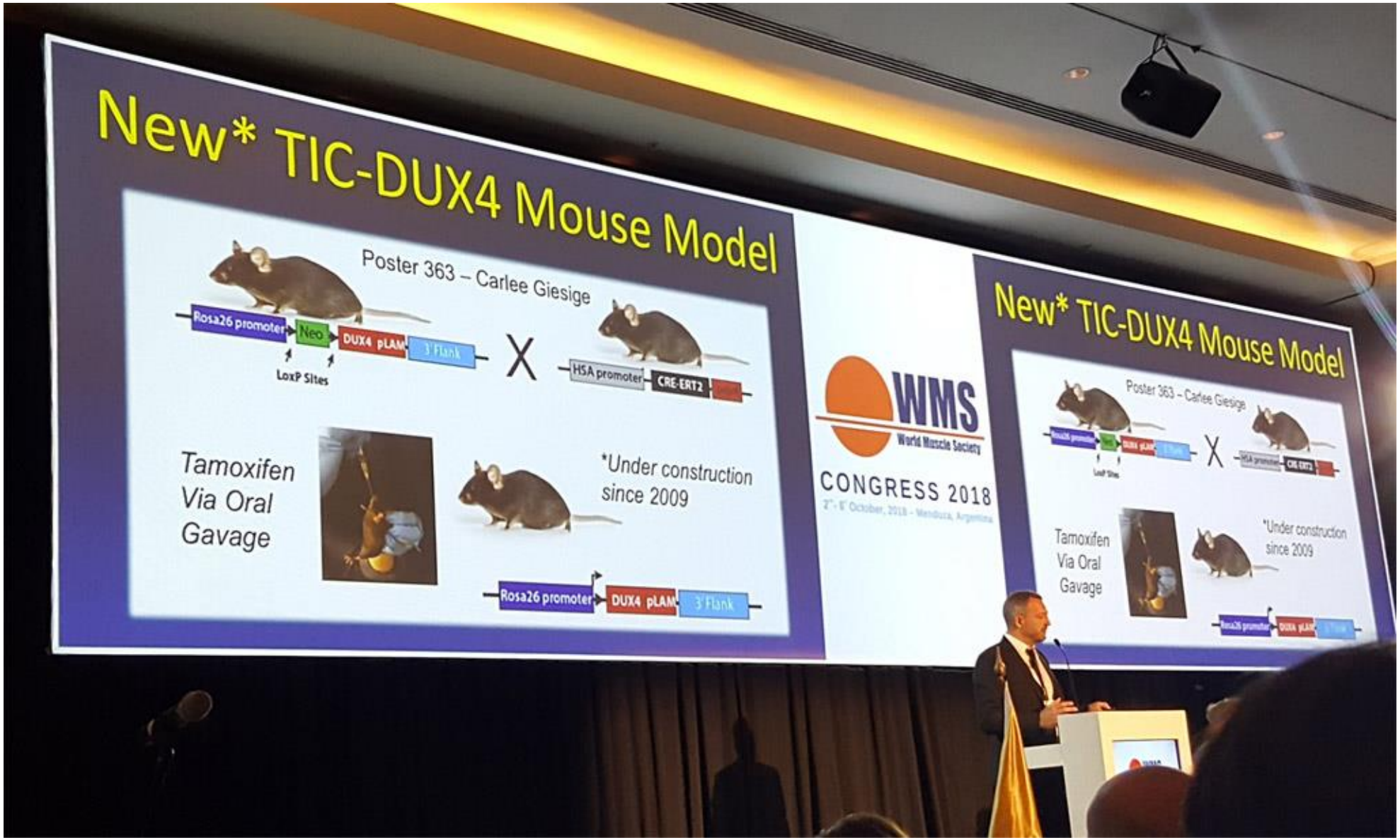
Recent Findings from Wellstone Investigations

CRISPR Library Screen for Drug Targets Downstream of DUX4

Dr. Lou Kunkel (Boston Children's) and Dr. Angela Lek (Yale)

1. Used novel genetic method to randomly knock out single genes in a population of cells
2. Turned on DUX4 gene in the cells and then allowed the cells that could resist DUX4 toxicity to grow
3. Sequenced the DNA of the resistant cells to identify genes that influence DUX4 toxicity
4. Identified specific pathways important for cell survival when DUX4 is expressed
5. Interrogate these pathways further and test drugs in the zebrafish model

Recent Findings from Wellstone Investigations



Scott Q. Harper, PhD

Recent Findings from Wellstone Investigations

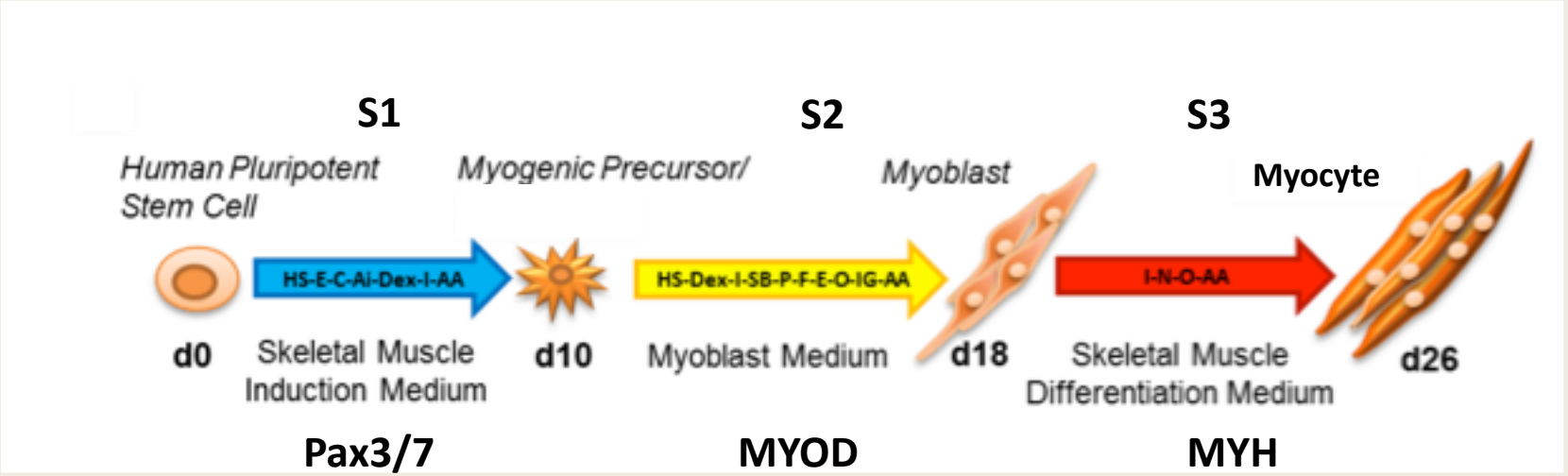
Emerson Lab at UMass:

1. Dr. Alec DeSimone
   Novel Druggable Pathways for FSHD Therapeutics
2. Dr. Katelyn Daman
   Next-generation RNA Therapeutics for FSHD
3. Dr. Dongsheng Guo
   Induction of human muscle cells from pluripotent stem cells

Gene-free iPSC induction of human myogenic progenitors

Genea ESC Myogenesis Protocol

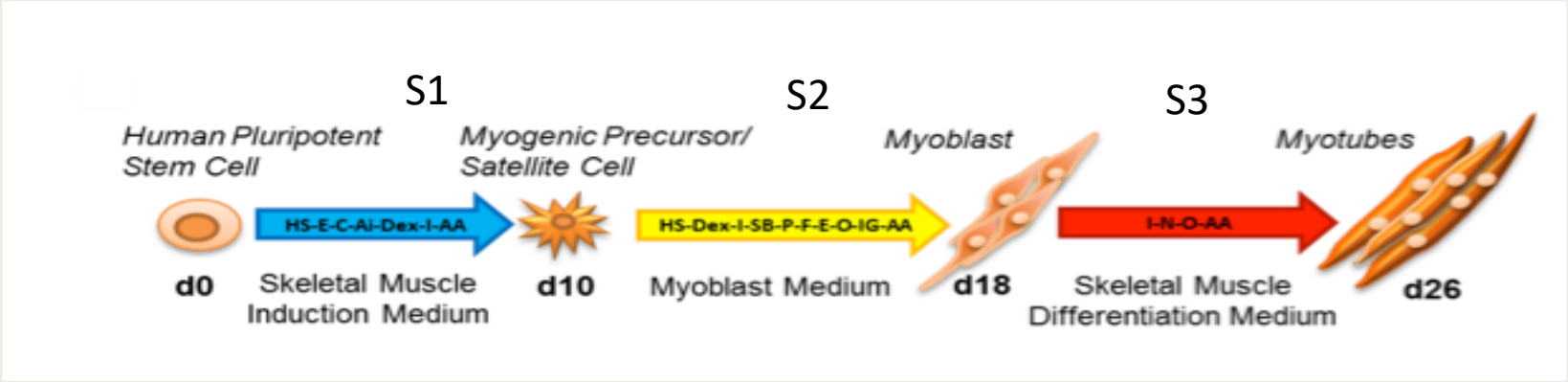
Stem Cells Translational Medicine, 2016

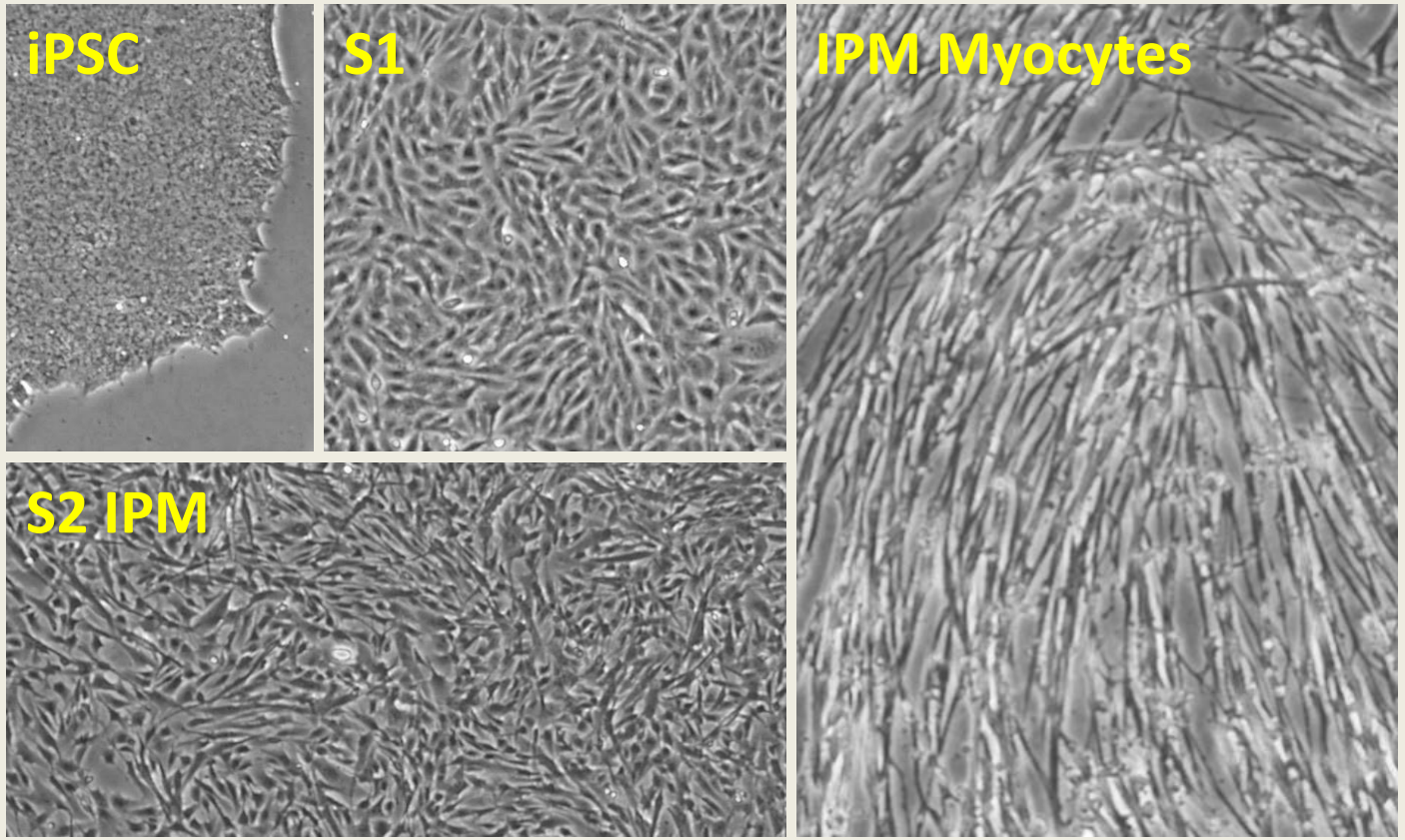


- **Rational protocol based on developmental signaling**
- **Optimized for human ESC**

from Charlie Emerson

iPSC Induction of primary myoblasts





- Rapid
- Monolayer
- Staged
- Efficient
- Reproducible

from Charlie Emerson

Recent Developments Toward Therapies for FSHD

Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD

U01 program (Dr. Jeff Statland, Kansas and Dr. Rabi Tawil, Rochester)

Adjunct therapies to improve muscle function

rHGH and testosterone clinical trial (Dr. Chad Heatwole, Univ. of Rochester)

Myostatin inhibition (Acceleron small molecule clinical trial ACE-083)

Strategies targeting DUX4 or its downstream effects

FSHD Clinic at UMass Medical School

- 1st and 3rd Thursdays each month
  8:30 am – 12:30 pm

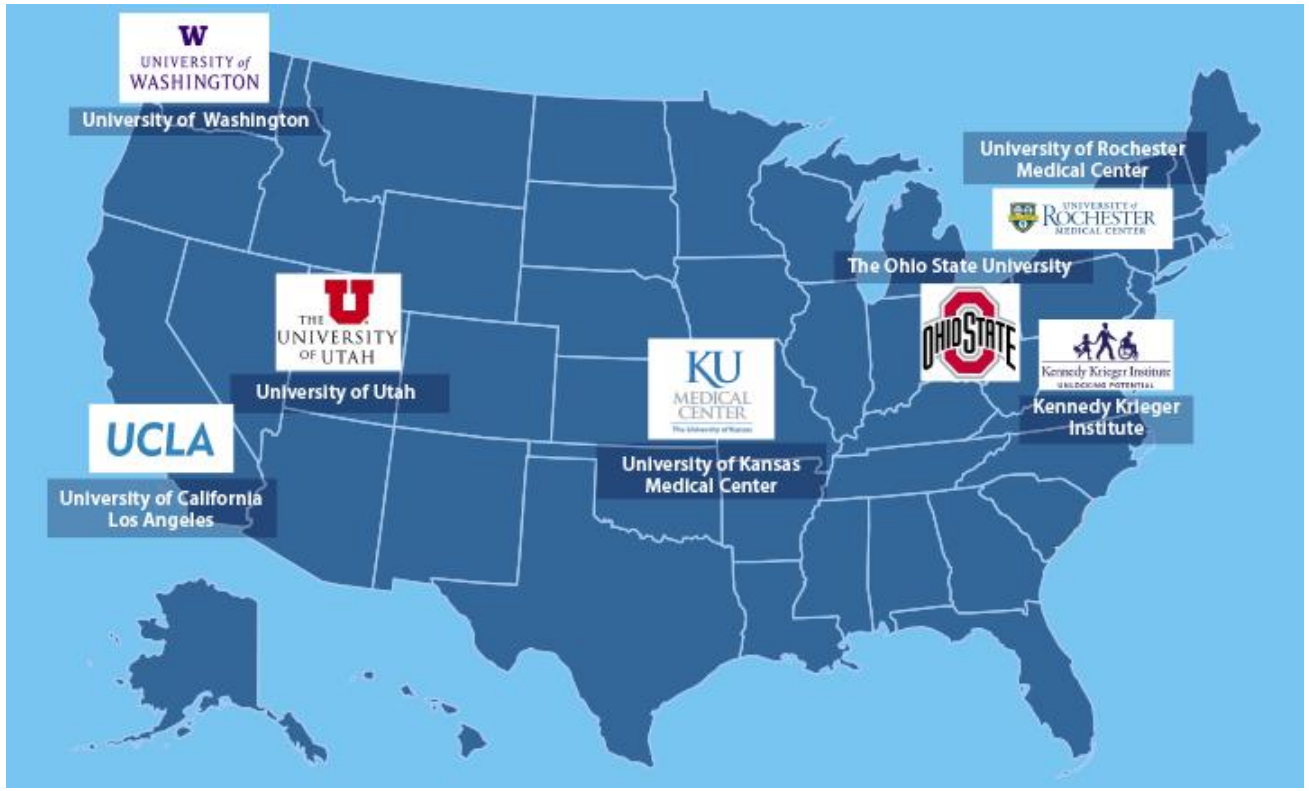
- Lawrence Hayward, MD, PhD
  Kate Daniello, MD

- UMMS/UMMHC Neurology Clinic
  University Campus - A Level
  55 Lake Avenue North
  Worcester, Massachusetts

- To make clinical appointments please contact:
  FSHD - Neurology Clinic
  Phone (508) 334-2527
  Fax (774)441-9091

FSHD Clinic at UMass Medical School

- Expanding to include patients across New England
- Genetic testing and Biomarker Study
- Physical therapy referral available to Fairlawn Rehabilitation Hospital
- Referral for genetic counseling, vision screening, and pulmonary function
- Standardizing the evaluation to participate in the FSHD Clinical Trial Research Network (CTRN)



Requirements for participation:

To become involved, you must:

- Be diagnosed with Facioscapulohumeral muscular dystrophy (FSHD) or be a family member of someone with FSHD
- **OR** Be a control participant with no family history of FSHD
- Be willing to give a blood sample (approximately 8 teaspoons), or in some cases a saliva sample
- Be willing to consider giving a muscle and/or skin sample
- Be willing to complete questionnaires about your general medical/ family history

UMASS MEDICAL SCHOOL

University of Massachusetts Medical School
Department of Neurology, Rm S5-710
55 Lake Ave. North
Worcester, MA 01655
Phone: (508) 856-4697
Fax: (508) 856-4675
diane.mckenna-yasek@umassmed.edu

FSHD Biomarker Study

at the

University of Massachusetts Medical Center

Study Docket #H000006581

UMASS MEDICAL SCHOOL

NIH National Institutes of Health

FSHD Biomarker Study

Physicians and researchers at the University of Massachusetts Medical School (UMMS) seek individuals with facioscapulohumeral muscular dystrophy (FSHD) to participate in an FSHD Biomarker Study. This will be conducted by Dr. Robert H. Brown, Jr. and Lawrence J. Hayward, M.D., Ph.D. This study focuses on explaining the variability of FSHD, especially within the same families, through examination of both genetics and other biomarkers.

Purpose:

The purpose of this study is to identify and understand genes that may explain why people with FSHD have different amounts of weakness in different muscles (different phenotypes). We also aim to identify biological markers that will enable us to follow and predict disease progression or indicate possible responses to treatment in upcoming FSHD clinical trials.

Participation:

Blood, saliva, muscle and/or skin samples from individuals with FSHD, some family members, and population controls are being accepted for this research study. Participants will be asked to complete a brief medical/family history questionnaire. Also, the clinicians will ask for permission to review the medical records of those with FSHD to understand the onset and progression of their disease.

The University of Massachusetts Medical School will cover costs of the sample collection for participation, except for travel and housing. We are happy to help to make arrangements for the blood and saliva samples to be collected locally.

UMMS Wellstone Center for FSHD:

This study is an integral component of the Senator Paul D. Wellstone Cooperative Research Center for FSHD, sponsored by the National Institutes of Health. The overriding goal of the Center is to develop innovative therapies for FSHD. Research projects are conducted by an exceptional team of collaborative investigators led by Charles P. Emerson, Ph.D. (UMMS), Louis Kunkel, Ph.D. (Children's Hospital of Boston), and Kathryn Wagner, M.D., Ph.D. (Kennedy Krieger Institute at Johns Hopkins School of Medicine). The Center also provides outreach to academic and industry partners and to patient advocacy groups such as the FSH Society to share research materials and to connect with individuals affected by FSHD.

Further information about the Center:
https://www.umassmed.edu/wellstone/

Benefits:

Although there are no direct benefits for those involved in this research, we believe that understanding FSHD will lead to more effective screening, diagnosis, treatments, and ultimately a cure for this disease.

We greatly look forward to speaking with you to answer any questions you may have and to describe this study in more detail.

For more information, please contact:

Diane McKenna-Yasek, RN, BSN
Neuromuscular Research Coordinator
Phone: (508) 856-4697
diane.mckenna-yasek@umassmed.edu

or

Catherine Douthwright, PhD
Neurology Research Coordinator
Phone: (508) 856-6491
catherine.douthwright@umassmed.edu

Brown Neuromuscular Laboratory
University of Massachusetts Medical School
Room S5-710
55 Lake Ave. North
Worcester, MA 01655
Fax: (508) 856-4675

Muscle ultrasound may provide an accessible biomarker for FSHD clinical trials

Safe, fast, and patient-friendly

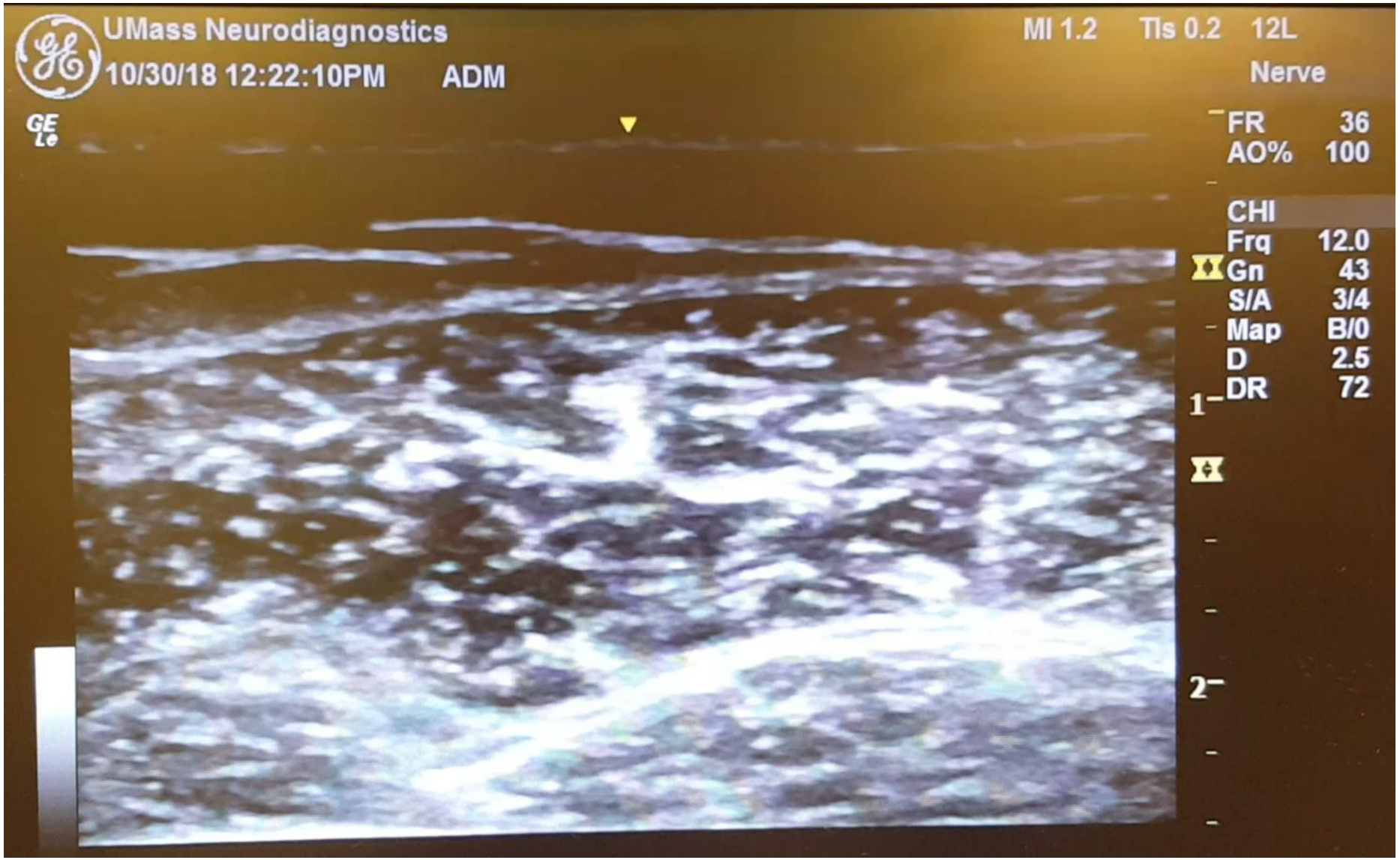
Sensitive to detect early fibrosis

Also detects fatty infiltration and edema (like MRI)

Increased echogenicity correlates well with decreased muscle strength

Unable to measure deep layers of muscle

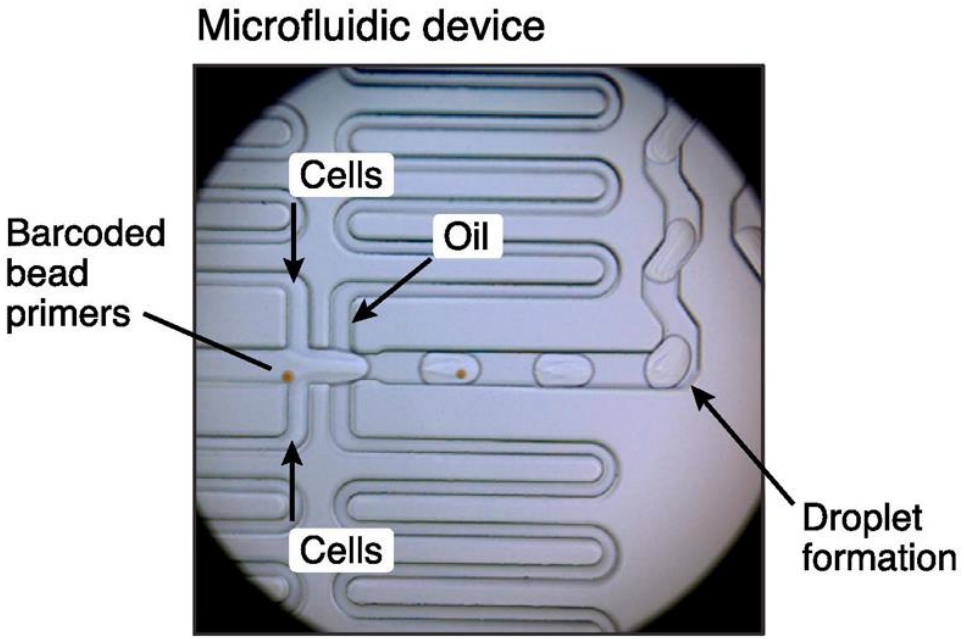
Muscle ultrasound may provide an accessible biomarker for FSHD clinical trials

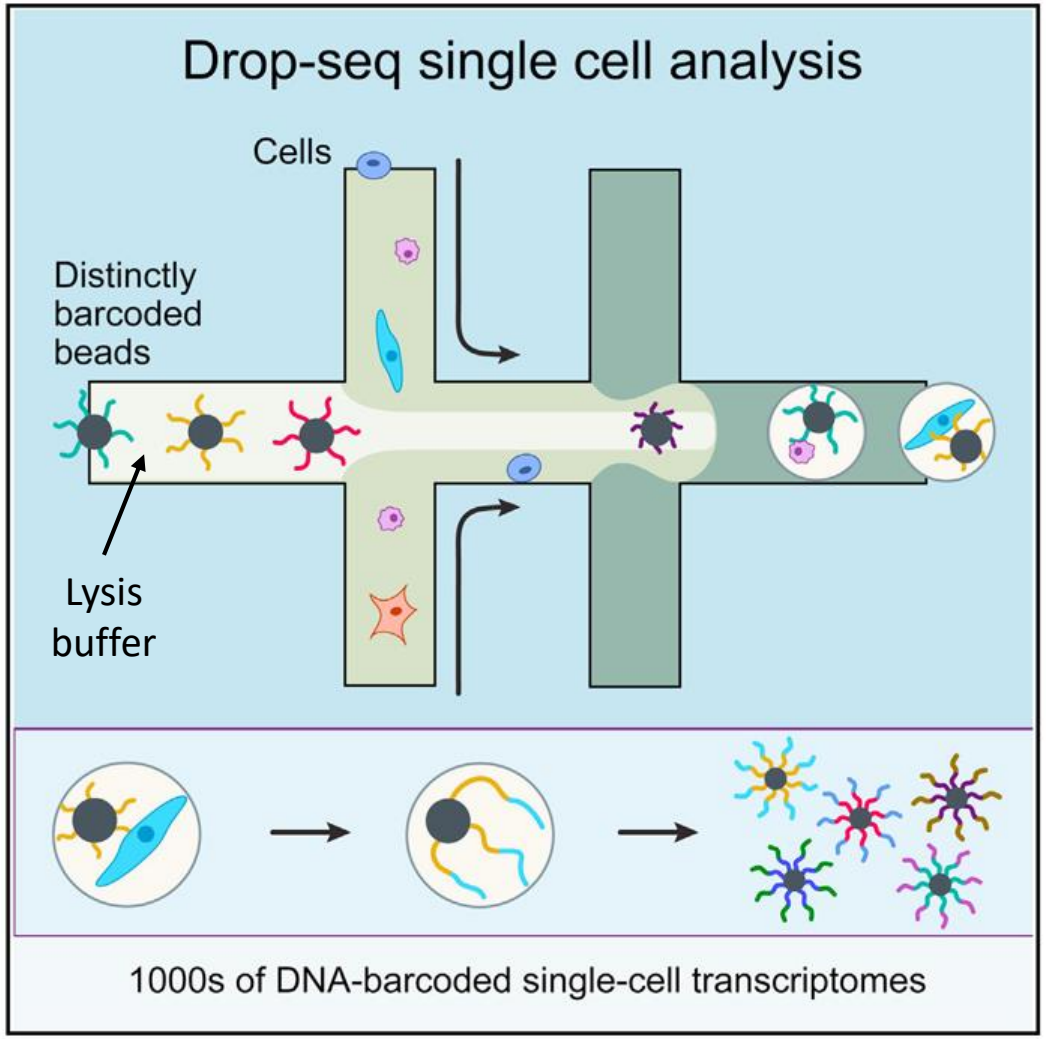


Single-cell Gene Expression Detected in Droplets

Each cell is unique!

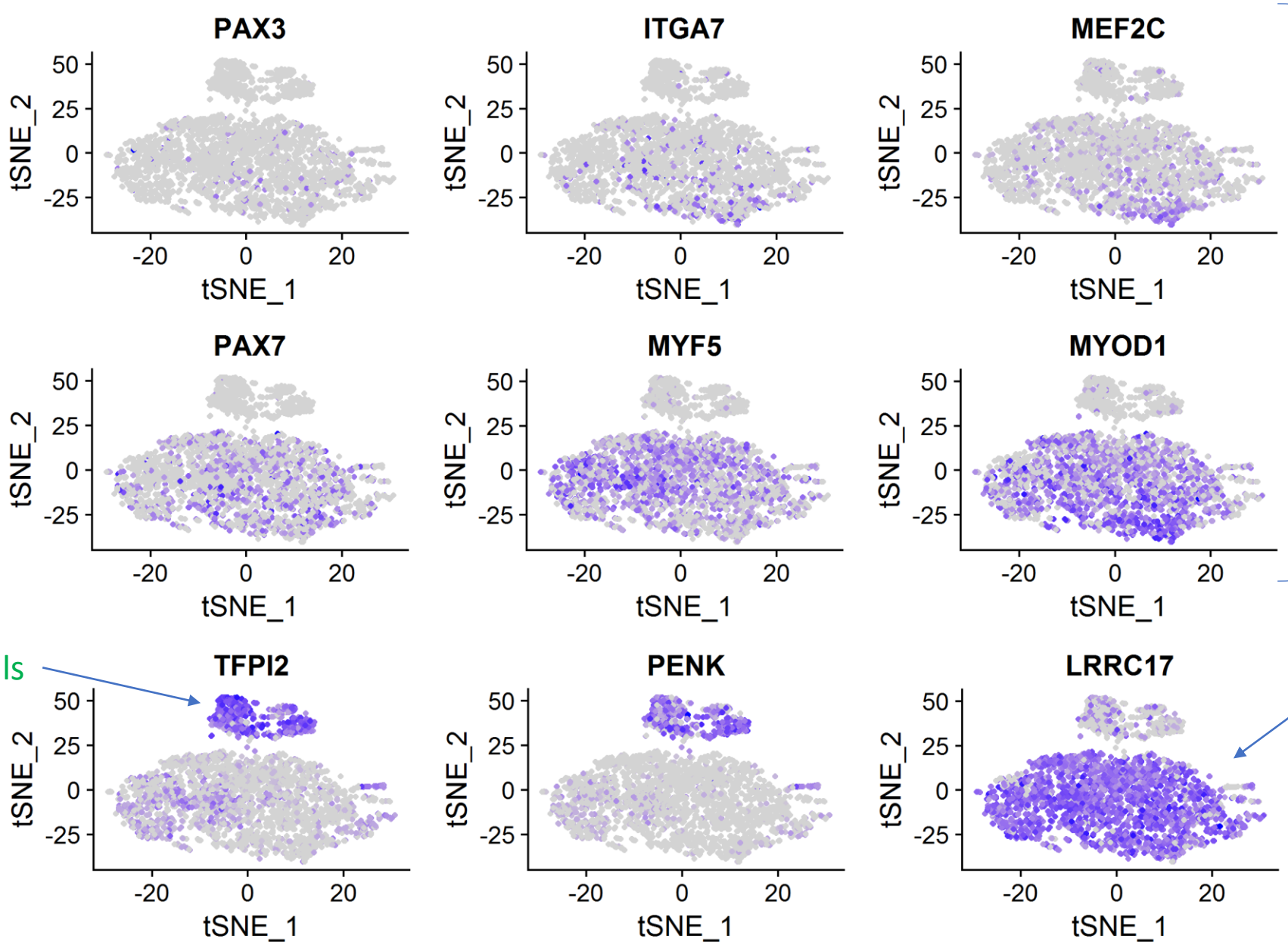
Drop-seq employs a microfluidic device to capture single-cell transcriptomes.





Macosko EZ, ..., McCarroll SA, *Cell* 161: 1202-14 (2015)

Cells Arranged According to Similarity of Single-cell Gene Expression



Myogenic regulators and marker genes

Non-myogenic cells

Marker gene enriched in myogenic cells

THANK YOU to our Sponsors

SEN. PAUL D. WELLSTONE MD COOPERATIVE RESEARCH CENTER

NIH National Institutes of Health

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

friends of FSH research

FSH SOCIETY
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases

UMASS CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

MDA Muscular Dystrophy Association

SPECIAL THANKS

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