Animal Models and Progress Towards Clinical Trials

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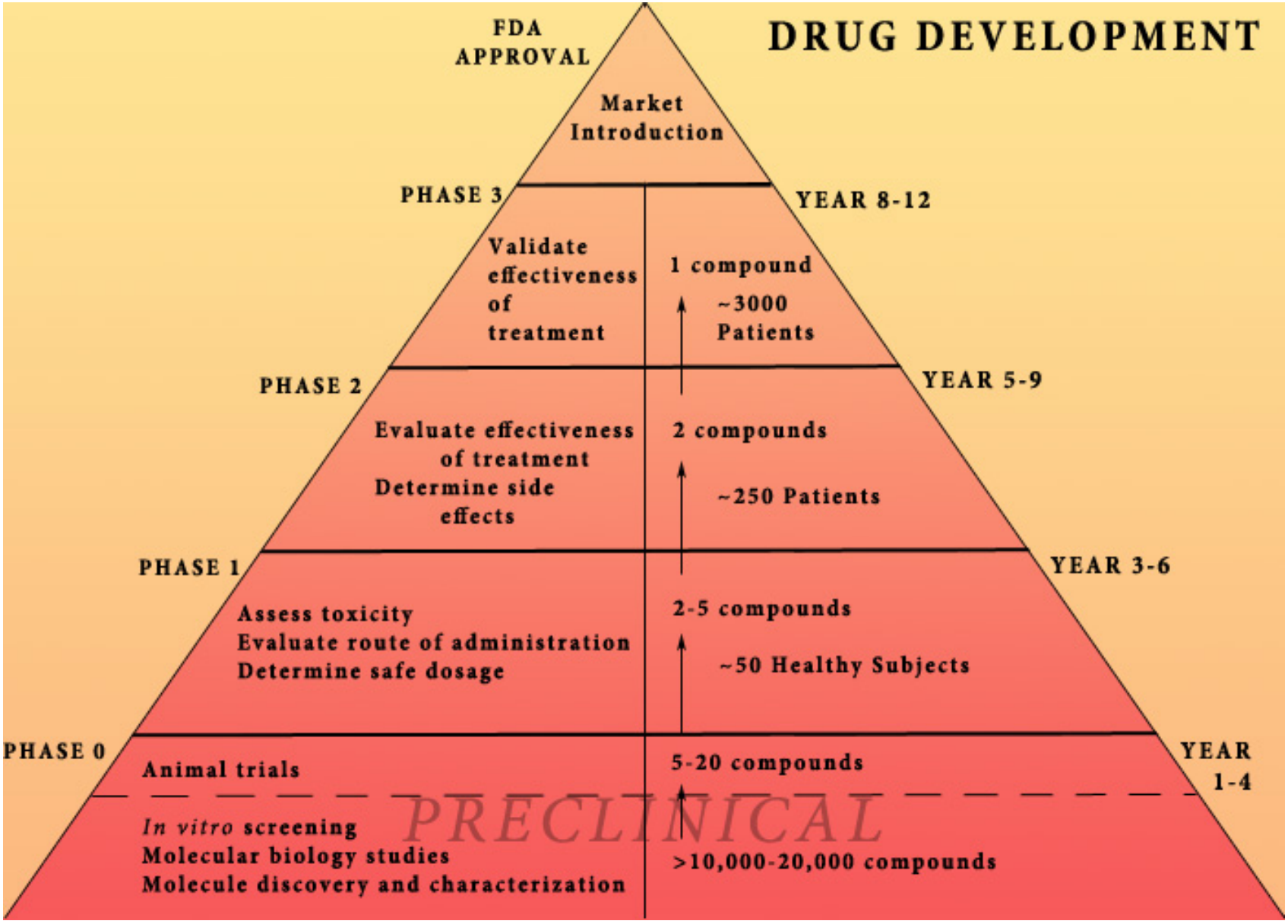
The BAD NEWS

Clinical Trials.....


DRUG DEVELOPMENT
FDA APPROVAL
Market Introduction
PHASE 3
YEAR 8-12
Validate effectiveness of treatment
1 compound
~3000 Patients
PHASE 2
YEAR 5-9
Evaluate effectiveness of treatment
Determine side effects
2 compounds
~250 Patients
PHASE 1
YEAR 3-6
Assess toxicity
Evaluate route of administration
Determine safe dosage
2-5 compounds
~50 Healthy Subjects
PHASE 0
YEAR 1-4
Animal trials
5-20 compounds
PRECLINICAL
In vitro screening
Molecular biology studies
Molecule discovery and characterization
>10,000-20,000 compounds

In 2010:

Search: "Facioscapulohumeral muscular dystrophy" clinicaltrials.gov

Rank	Status	Study
1	Not yet recruiting	Physical Training Introduction in Lifestyle of Facioscapulohumeral Dystrophy Patients Condition: Muscular Dystrophy, Facioscapulohumeral Interventions: Other: Physical training; Other: Control
2	Recruiting	Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Registry Conditions: Myotonic Dystrophy; Muscular Dystrophy, Facioscapulohumeral; Muscular Dystrophy Intervention:
3	Recruiting	Molecular Analysis of Patients With Neuromuscular Disease Conditions: Limb-Girdle Muscular Dystrophy; Duchenne Muscular Dystrophy; Becker Muscular Dystrophy; Facioscapulohumeral Muscular Dystrophy Intervention:

Total studies: 3
Total drug studies: 0

In 2012:

Search: "Facioscapulohumeral muscular dystrophy" clinicaltrials.gov

Rank	Status	Study
1	Recruiting	Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Registry Conditions: Myotonic Dystrophy; Muscular Dystrophy, Facioscapulohumeral; Muscular Dystrophy Intervention:
2	Not yet recruiting	A Multicenter Collaborative Study on the Clinical Features, Expression Profiling, and Quality of Life of Infantile Onset Facioscapulohumeral Muscular Dystrophy Condition: Facioscapulohumeral Muscular Dystrophy Intervention:
3	Recruiting	Effects Antioxidants Supplementation on Muscular Function Patients Facioscapulohumeral Dystrophy (FSHD) Condition: Facioscapulohumeral Muscular Dystrophy Interventions: Procedure: Taking of blood; Dietary Supplement: needle biopsy of the vastus lateralis muscle; Dietary Supplement: Vit C Vit E Zn Se; Dietary Supplement: Placebo Vit E Placebo Vit C Zn Se
4	Recruiting	Molecular Analysis of Patients With Neuromuscular Disease Conditions: Limb-girdle Muscular Dystrophy; Duchenne Muscular Dystrophy; Becker Muscular Dystrophy; Facioscapulohumeral Muscular Dystrophy Intervention:
5	Recruiting	Physical Training Introduction in Lifestyle of Facioscapulohumeral Dystrophy Patients Condition: Muscular Dystrophy, Facioscapulohumeral Interventions: Other: Physical training; Other: Control

Total studies: 5

Total drug studies: 1 (France and The Netherlands)

In 2014:
Search: "Facioscapulohumeral muscular dystrophy" clinicaltrials.gov

1	Recruiting	Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Registry **Conditions:** Myotonic Dystrophy; Muscular Dystrophy, Facioscapulohumeral; Muscular Dystrophy **Intervention:**
2	Recruiting	Magnetic Resonance Imaging and Spectroscopy Biomarkers for Facioscapulohumeral Muscular Dystrophy **Condition:** Facioscapulohumeral Muscular Dystrophy **Intervention:**
3	Recruiting	1 Year MRI Followup in Facioscapulohumeral Muscular Dystrophy **Condition:** FSHD - Facioscapulohumeral Muscular Dystrophy **Intervention:** Other: MRI
4	Recruiting	High Intensity Training in Patients With Facioscapulohumeral Muscular Dystrophy **Conditions:** FSHD - Facioscapulohumeral Muscular Dystrophy; Healthy Subjects **Interventions:** Other: Supervised training; Other: Unsupervised training; Other: Optional training; Other: Control
5	Recruiting	A Multicenter Collaborative Study on the Clinical Features, Expression Profiling, and Quality of Life of Infantile Onset Facioscapulohumeral Muscular Dystrophy **Condition:** Facioscapulohumeral Muscular Dystrophy **Intervention:**
6	Recruiting	Intramuscular Transplantation of Muscle Derived Stem Cell and Adipose Derived Mesenchymal Stem Cells in Patients With Facioscapulohumeral Dystrophy (FSHD) **Condition:** Dystrophy **Intervention:** Biological: Intramuscular injection
7	Not yet recruiting	Neurological and Psychiatric Comorbidities Patients With FSHD 1 and 2 **Condition:** Muscular Dystrophy, Facioscapulohumeral **Intervention:** Behavioral: Psychiatric test
8	Recruiting	Clinical, Genetic and Epigenetic Characterization of Patients With FSHD Type 1 and FSHD Type 2 **Condition:** Muscular Dystrophy, Facioscapulohumeral **Intervention:** Biological: Blood test
9	Recruiting	Molecular Analysis of Patients With Neuromuscular Disease **Conditions:** Limb-girdle Muscular Dystrophy; Duchenne Muscular Dystrophy; Becker Muscular Dystrophy; Facioscapulohumeral Muscular Dystrophy

- Total studies: 9
- Total drug studies: 0

Potential New Clinical Approaches

- 2 year time frame:
  - Nonspecific treatments to improve weakness
    - Troponin activator (Cytokinetics)
    - Myostatin inhibitors (Novartis, Pfizer, BMS, etc.)
- 3-5 year time frame
  - Specific drugs directed at FSHD pathophysiology
    - "Knock down" of Dux4 (Genzyme)
    - Targeting of other misregulated proteins in FSHD (GSK)
- 10 years or greater
  - Stem cell therapy

The GOOD NEWS

Animal and cellular models

Limitation of animal models

- Degree to which phenotype mirrors human disease:
- Unclear translation to humans
  - Currently, the only pharmacologic agent with proven benefit in muscular dystrophy (prednisone) developed initially from anecdotal observations in patients, not from animal studies
  - Conversely, several agents with promise in mice had no clear benefit in muscular dystrophy (e.g. creatine, glutamine, CoQ10)
  - Not unique to muscular dystrophy field: e.g. beneficial effects in preclinical SOD1 studies have not translated to benefit in ALS with one exception (Riluzole).

Role of Xenografts in other fields

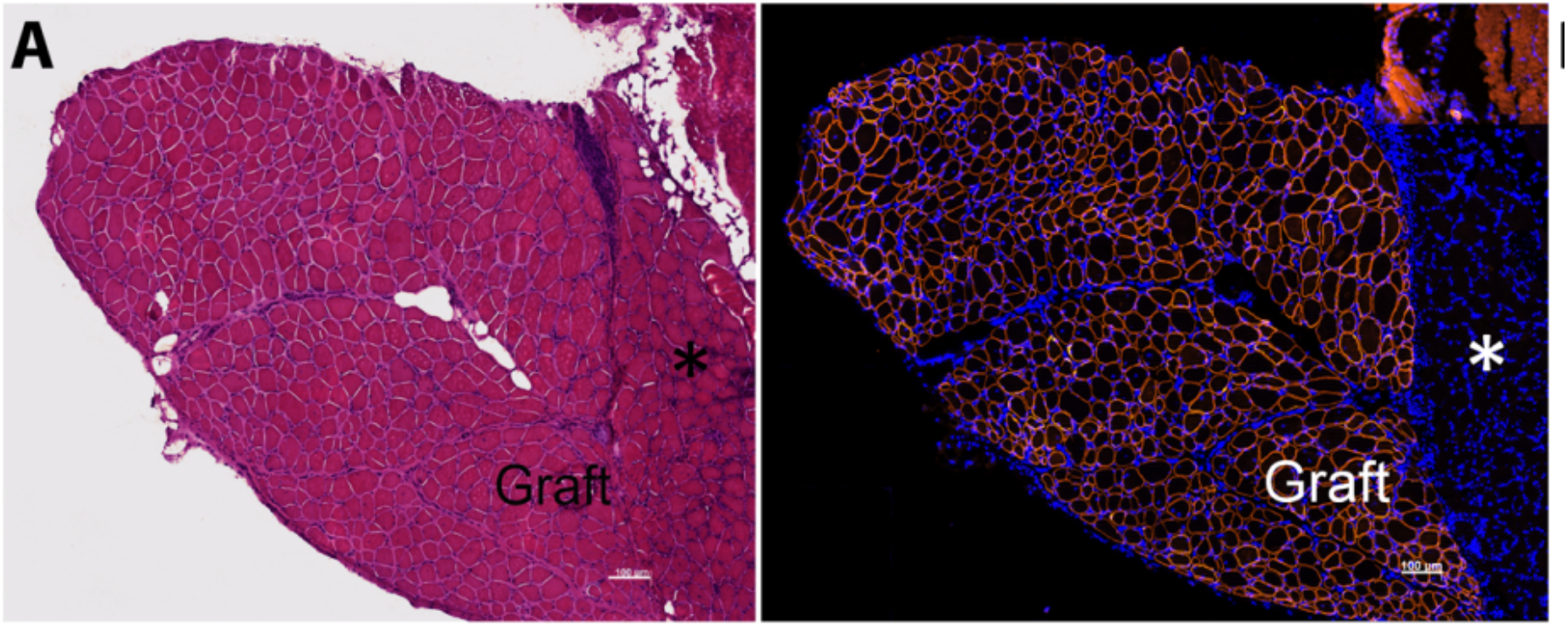
- Example : Human tumor models to assess if an individual patient's tumor will respond to a specific therapeutic regimen
- Successes: Multiple Myeloma response to proteosome inhibitor Velcade and to combination therapy Velcade and melphalen first demonstrated in xenografts and now standard of care in MM
- Limitations:
  - To more or less degree a hybrid of species
  - Meaningful outcome measures evaluating therapies are reduced compared to whole animal
  - Labor intensive preparation of animal cohort.

Transplantation of FSHD human muscle in mouse limb

20 weeks post-transplant:

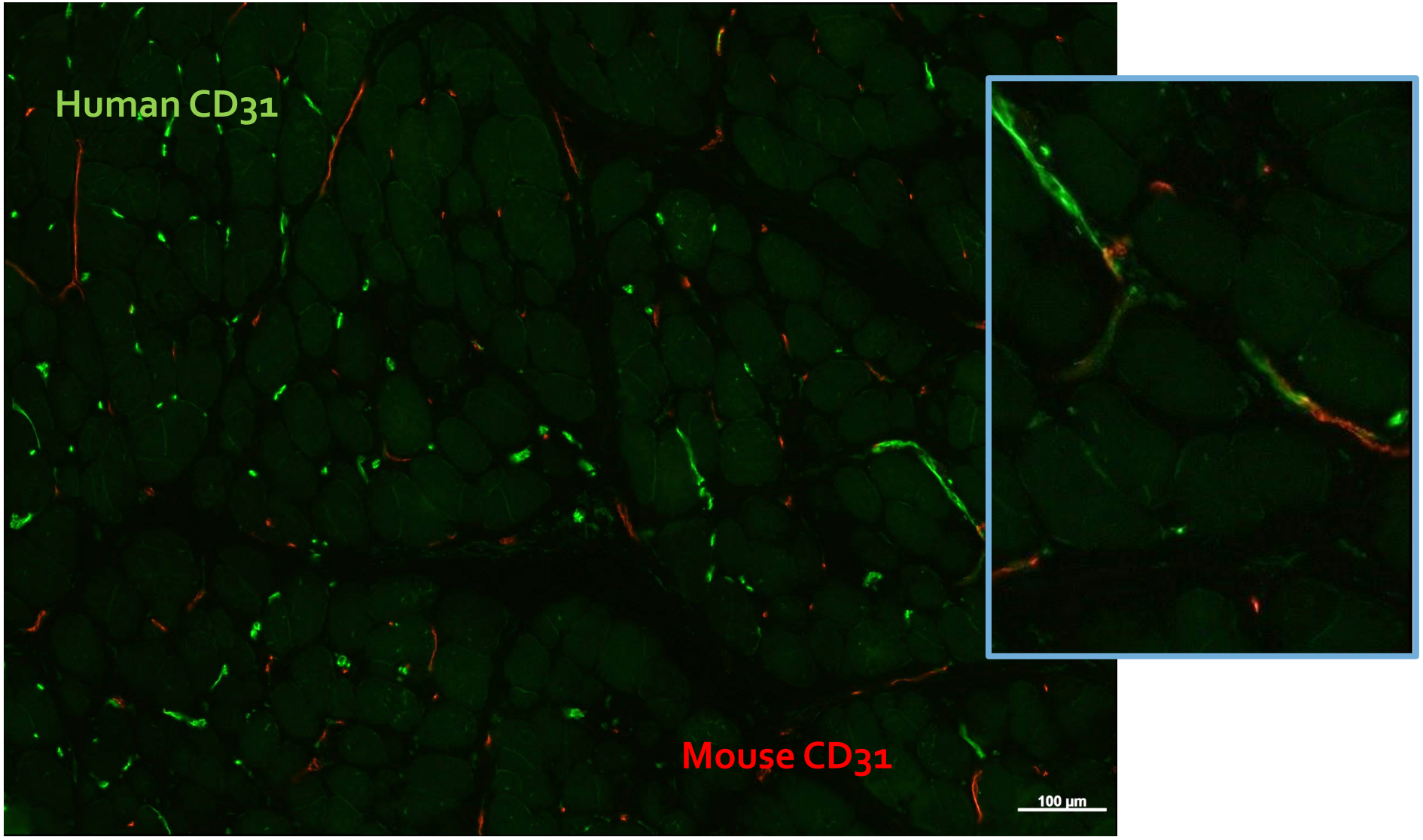
H&E

anti-human spectrin



Zhang Y, King OD, Rahimov F, Jones TI, Ward CW, Kerr JP, Liu N, Emerson CP, Kunkel LM, Partridge TA and Wagner KR. Human skeletal muscle xenograft as a new preclinical model for muscle disorders. Human Molecular Genetics, 2014.

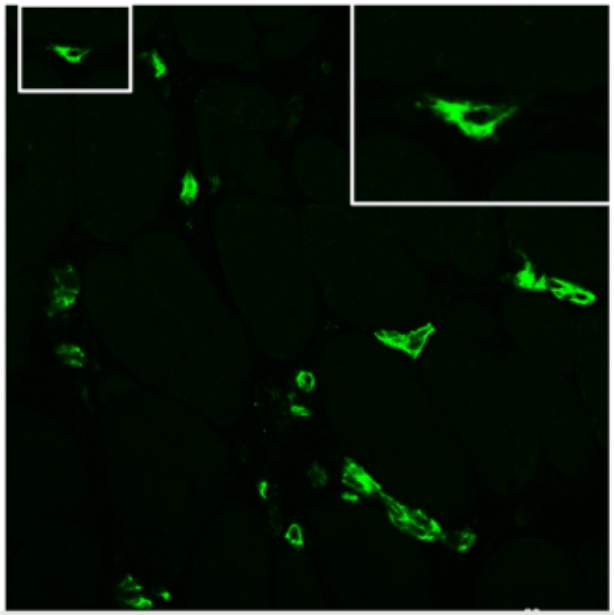
Vasculature in the xenograft: human and mouse

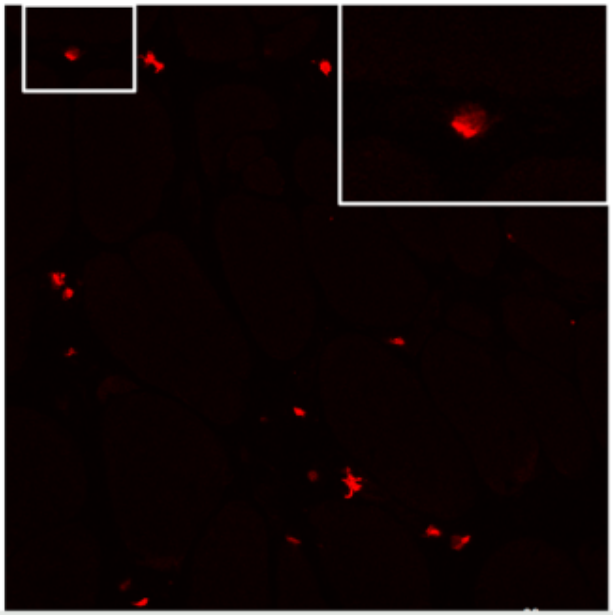


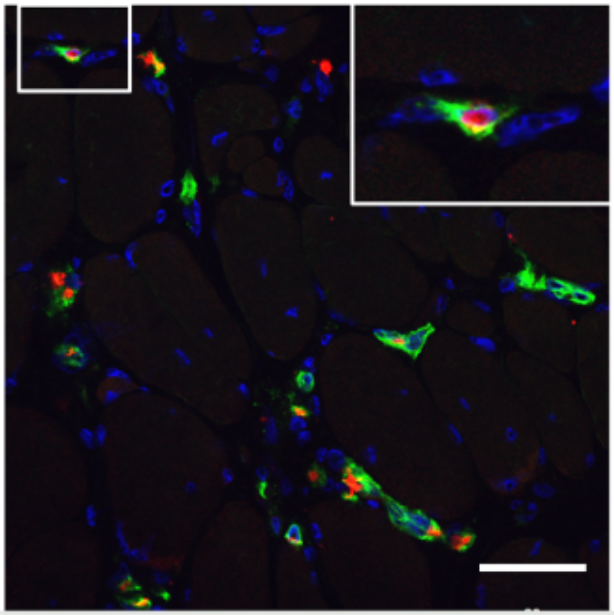
Human vasculature is functional

anti-human CD31

anti-mouse TER-119



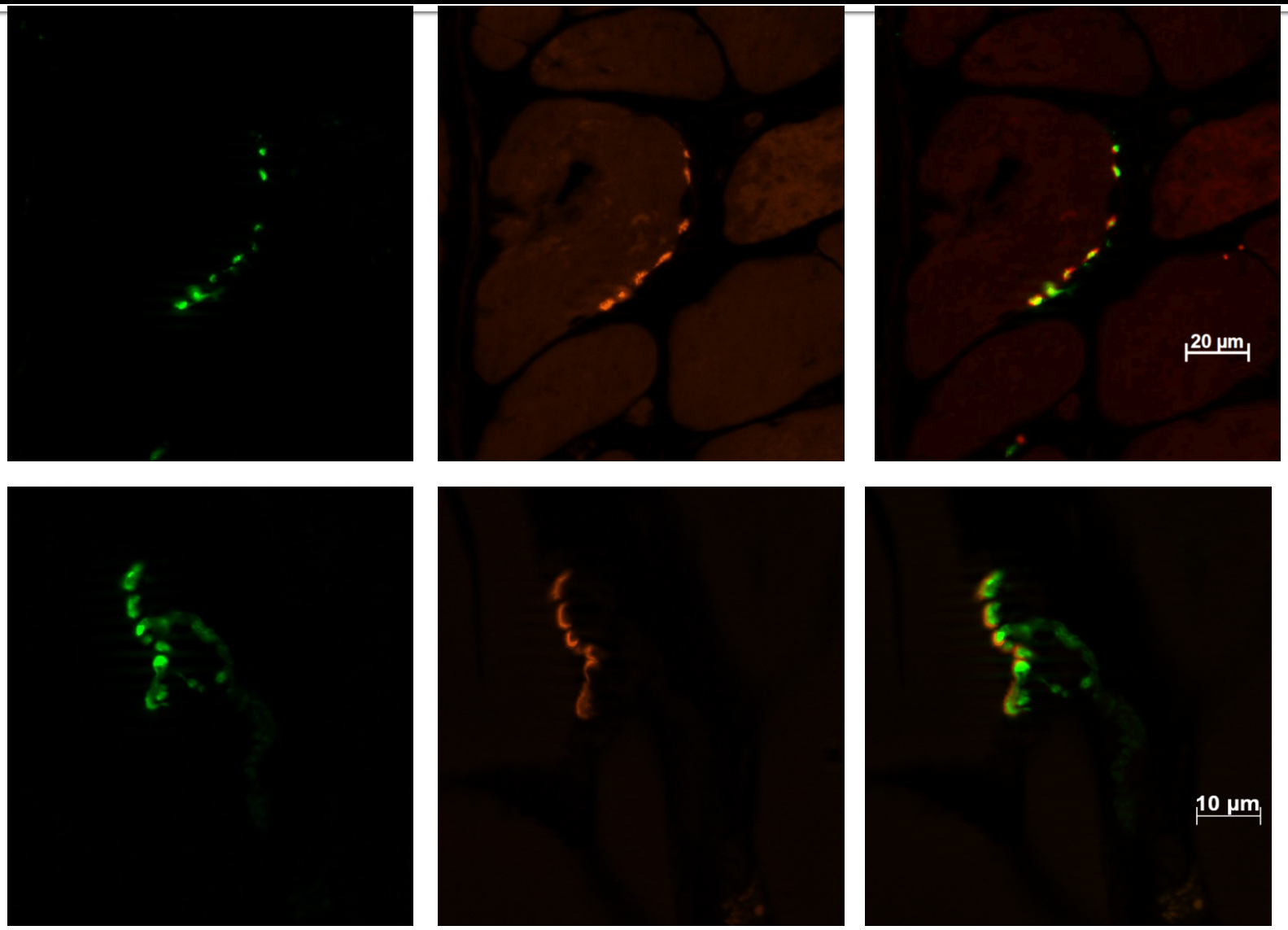




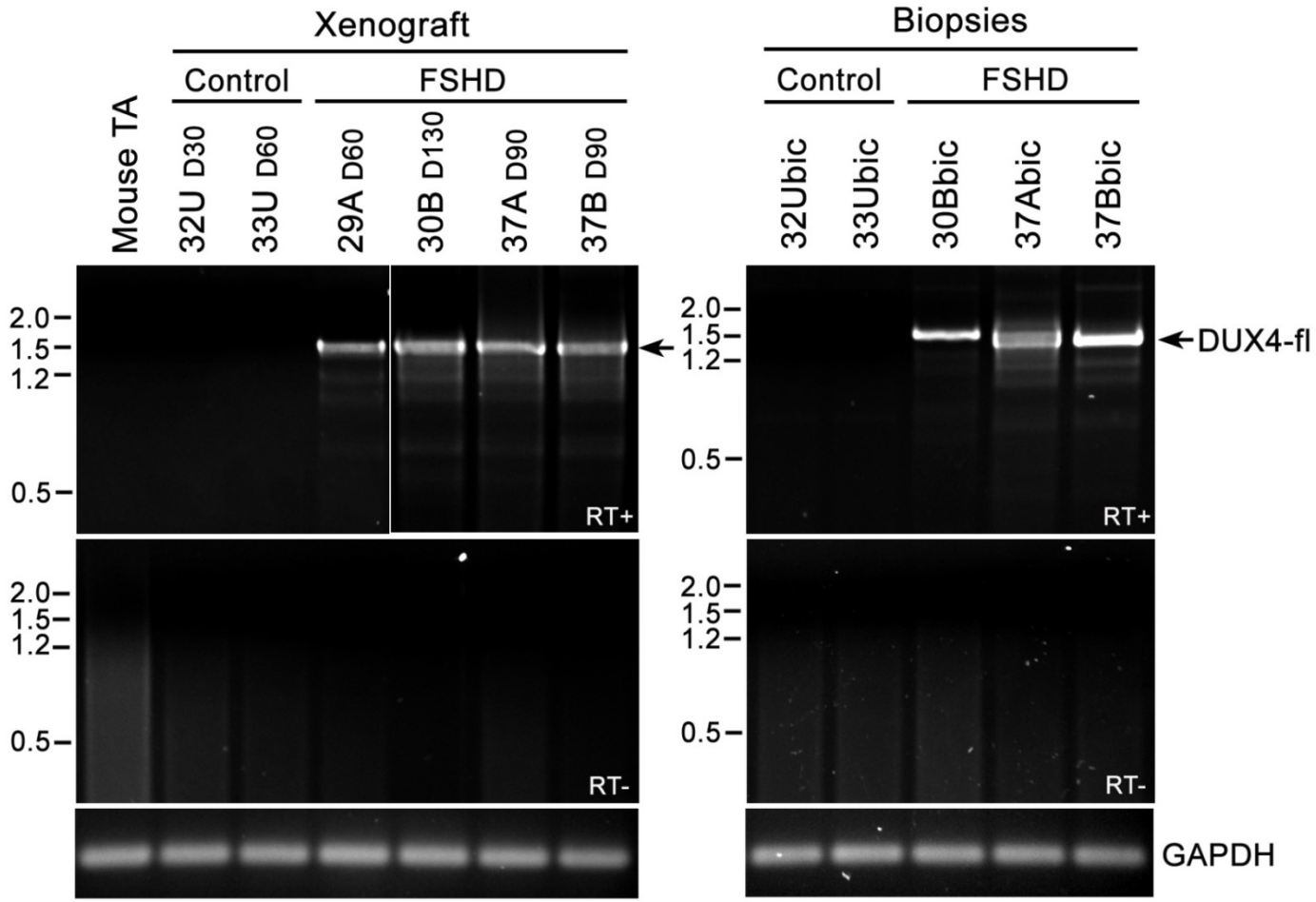
Xenografts are innervated

anti-SV2

α-bungarotoxin



Xenografts express-Dux4-fl



Potential Applications

- Study of human muscle regeneration
- Preclinical drug screening with molecular outcome measure
- Genetic modification studies
  - Dux4fl knock-down in human FSHD xenografts

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