

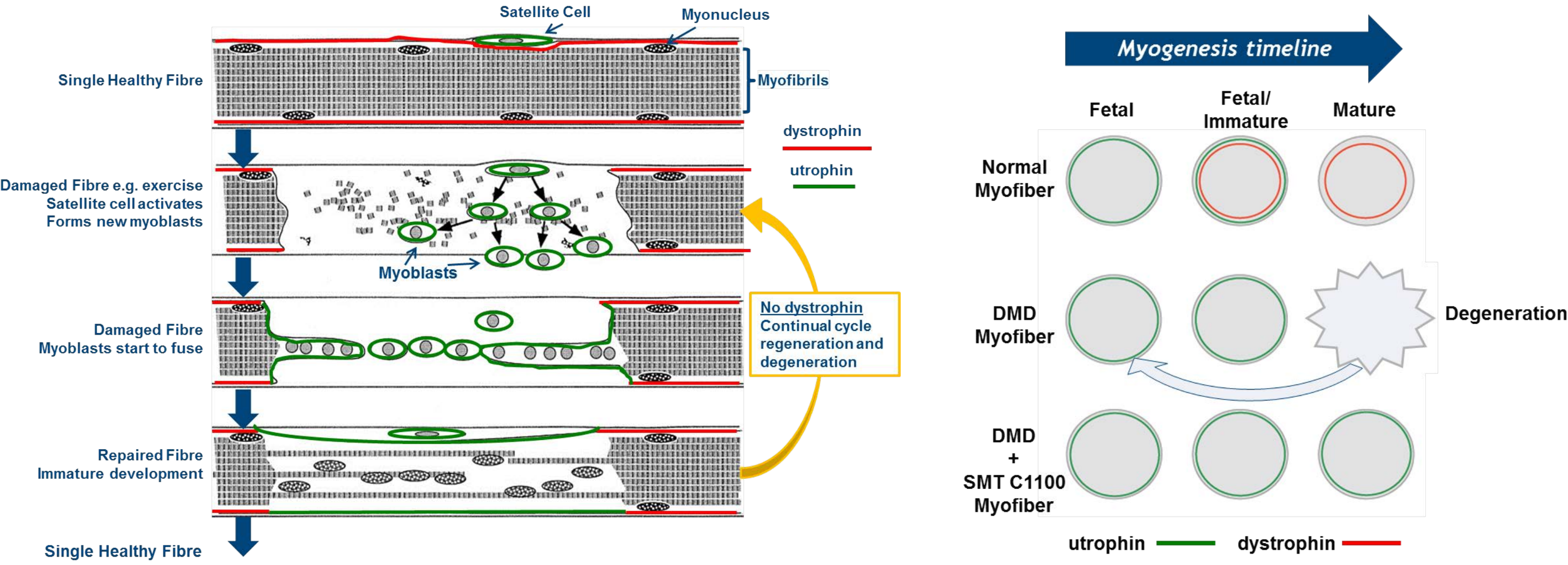
# Future clinical and biomarker development for SMT C1100, the first utrophin modulator to enter clinical trials for Duchenne Muscular Dystrophy (DMD)

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## 1. Utrophin Modulation: Disease-modifying strategy for all DMD

- DMD is a lethal, progressive muscle wasting disease caused by the loss of sarcolemmal bound dystrophin that results in the death of muscle fibres leading to the gradual depletion of skeletal muscle. There is currently no effective treatment for the disease.
- Utrophin is the functionally equivalent protein to dystrophin in foetal and regenerating muscle and its modulation offers the potential of treating all DMD patients, regardless of their underlying dystrophin defect (Tinsley *et al.* 1998: Nat Med; 4, 1441-4).



- SMT C1100 has been developed as a potential first-in-class, orally bioavailable small molecule utrophin modulator to treat DMD

## 2. Successful Phase 1 Healthy Volunteer Trial with SMT C1100

- The Phase 1 trial was a double-blind, placebo-controlled study in healthy male subjects to determine the safety, tolerability and PK of single oral ascending doses and multiple oral doses of a suspension formulation containing SMT C1100
- All doses were safe and well tolerated using the oral aqueous suspension formulation appropriate for paediatric use
- Inter-individual variation was observed
- The levels of SMT C1100 stabilised after 3- 4 days of dosing at levels around 70% of the original dose (Figure 1)
- Repeat dosing for 10 days with 100mg/kg bid results in plasma levels for at least several hours above the estimated 200nM required for utrophin modulation in a 12 hour period (Figure 2).

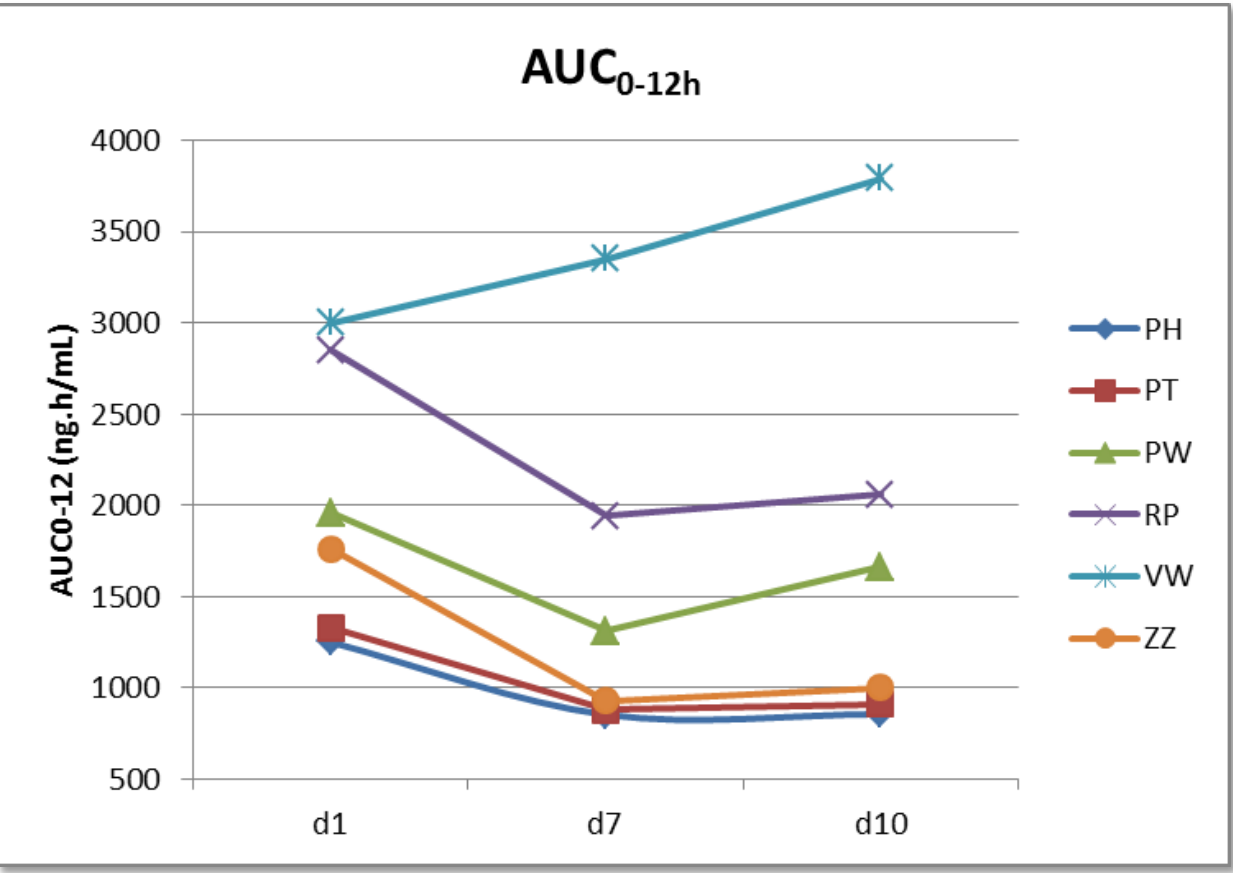


Figure 1: individual AUC at day 1, day 7 and day 10 oral dosing with 100mg/kg bid SMT C1100

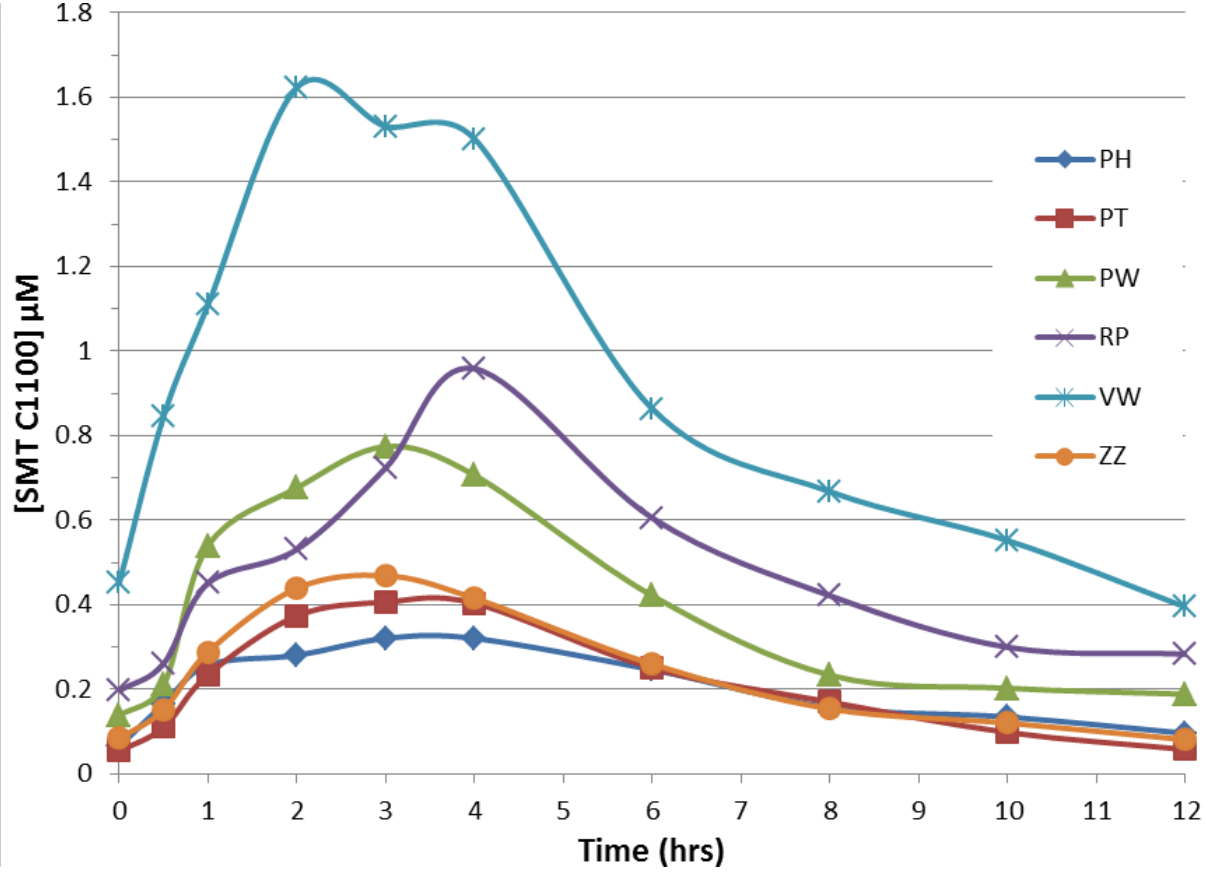


Figure 2: Individual PK at day 10 oral dosing with 100mg/kg bid SMT C1100

## 3. Proposed Clinical Development Plan to Proof of Concept in DMD patients

### Phase 1b (SAD, MAD study)

- 12 DMD patients
- 10 days of dosing
- Tolerability & Safety
- PK levels SMT C1100 and metabolites
- Identify doses for Phase 2 Proof of Concept (PoC) trial
- UK-based study

Proposed first patient dosed Q4 2013

### Phase 2 (Proof of concept)

- Double blind PoC trial
- ~40-50 ambulatory DMD patients (tbc)
- At least 24 weeks dosing (tbc)
- Primary endpoint 6 minute walk distance (6MWD) test
- Secondary endpoints muscle function tests
- Exploratory endpoints include pre and post dosing biomarker quantification (biopsy, serum)

Proposed trial expected to start mid-2014

- Trial plans currently under discussion with clinical advisors and regulatory authorities
- Development of biomarker assays to identify potential changes in muscle biopsies and serum relevant to muscle health as part of the Phase 2 exploratory outcome measures (See Section 4)

## 4. Development of biomarker strategy for PoC studies in DMD patients

- Becker patients expressing ~50% truncated dystrophin have reduced levels of regenerative fibres, inflammation and fibrosis due to dystrophin protection. Working on this assumption we are predicting at least a similar result with utrophin modulation to replace the missing dystrophin.
- Summit plans to develop exploratory endpoints to quantify increases in utrophin levels at both the RNA and protein level and reductions in functional biomarkers of muscle degeneration quantifying fibre degeneration, fibrosis and inflammation for inclusion in the Phase 2 trial.

### a) Utrophin quantification

- To quantify total utrophin protein levels, Summit is currently working with **Yetricb Hathout CNMC, Washington, US** developing Mass Spectrometry methods for sensitive quantification. This work is funded by the **Federation to Eradicate Duchenne**.
- Quantification of utrophin in muscle biopsies calculating both the percentage of utrophin positive fibres and levels per fibre of a larger number of DMD and Becker biopsies are on-going in collaboration with **J. Morgan, C. Sewry, K. Anthony, UCL ICH, London, UK**. Preliminary feasibility data is presented below.

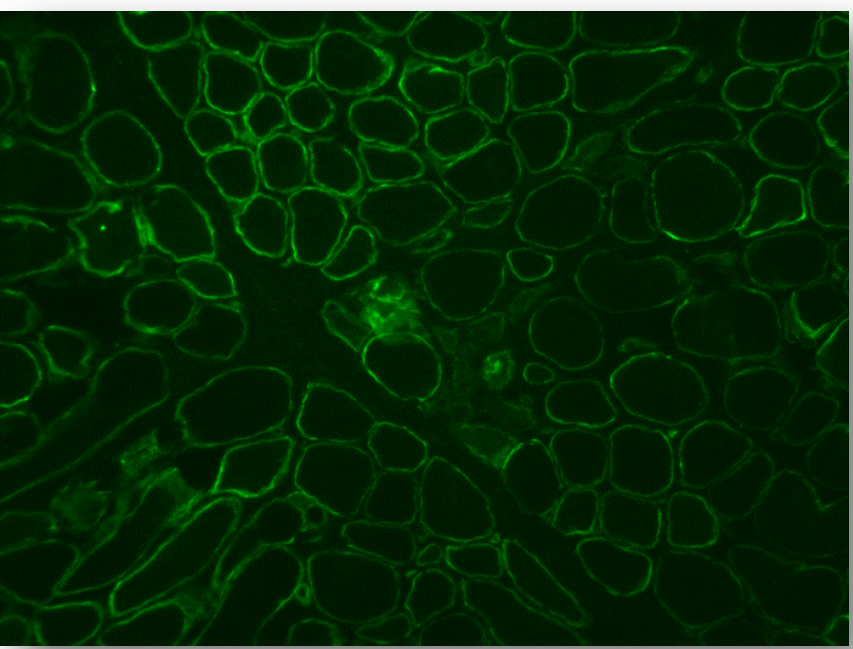


Figure 3 shows an example of the utrophin staining of biopsy from a 6year old DMD boy. Using image capture and analysis software the intensity of the staining is calculated and using a proprietary algorithm the intensity of each fibre can be calculated relative to background.

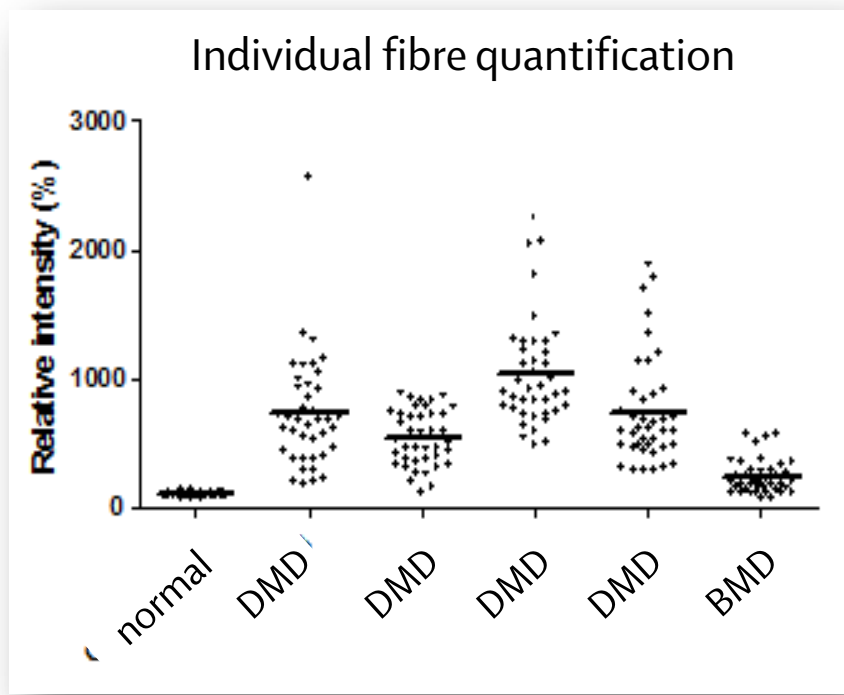


Figure 4 is an example of the individual fibre intensities from a normal muscle, 4 DMD biopsies and a Becker biopsy. This data confirms the technology can quantify the intensity of utrophin staining at the sarcolemma. Techniques are in development to quantify intensity of individual fibres in large areas of the biopsy.

### b) Quantification of Regeneration

If utrophin expression is maintained continually in muscle fibres due to SMT C1100 treatment then the numbers of regenerating fibres should fall. Using similar methods as described above, biopsies are stained using a cocktail of early myosin markers and the percentage of stained (regenerating) fibres calculated.

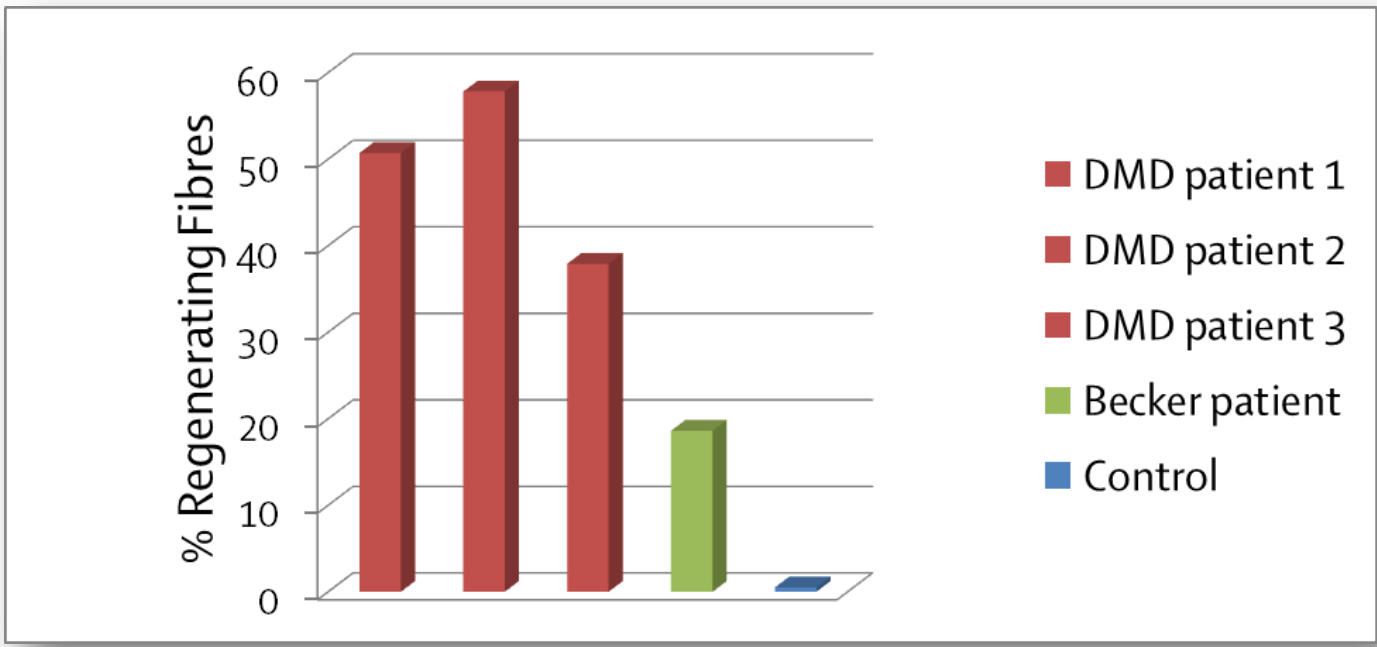
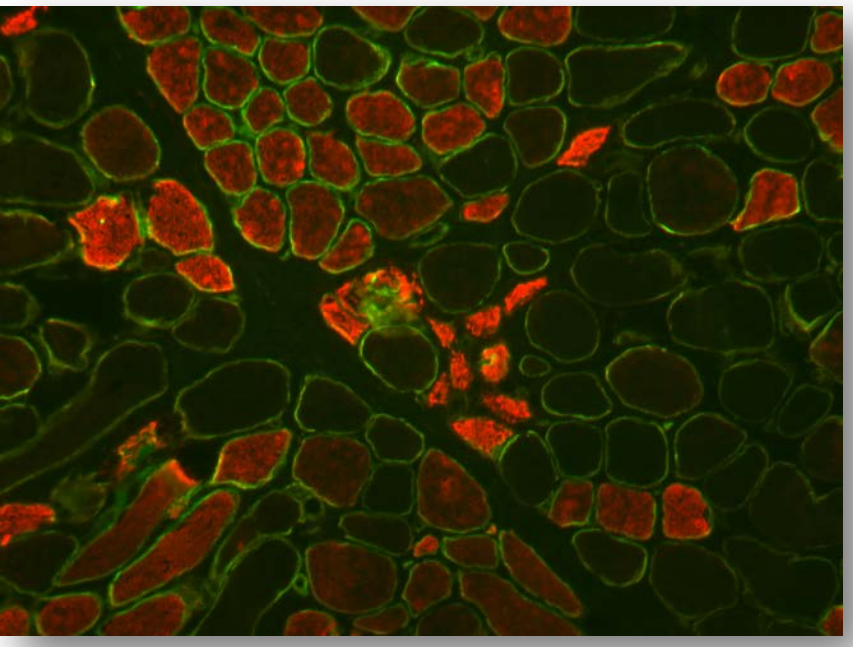


Figure 3 shows an example of a DMD biopsy stained with the regeneration marker (regenerating fibres marked red). Calculation of the percentage number of fibres stained with this marker in fields of view are shown in Figure 4. Work performed in collaboration with **J. Morgan, C. Sewry, K. Anthony, UCL ICH, London, UK**

### c) Quantification of Fibrosis Peptide Biomarkers

Studies on-going to quantify levels of collagen I peptide (P1NP) a marker of active extracellular matrix remodelling in plasma samples from DMD and Becker patients. Collaboration with **K. Henriksen, Nordic Bioscience**. DMD and Becker plasma samples kindly provided by **H. Lochmüller, M. Reza, MRC Centre for Neuromuscular Diseases, Newcastle University, UK**

## 5. Summary

- SMT C1100 has the potential to treat all DMD patients via utrophin modulation regardless of the dystrophin mutations
- SMT C1100 was found to be safe and well tolerated in a Phase 1 trial utilising an orally administered paediatric suspension formulation
  - Plasma levels of SMT C1100 above that required for activation of utrophin expression
- Phase 1b safety and PK dose finding study in DMD boys expected to start later this year
- Exploratory biomarker strategy developed to support Phase 2 proof of concept trial in DMD patients. Trial expected to commence mid-2014.

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