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Targeting Prostaglandin D2 in Treating Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is characterized by progressive muscle weakness and wasting due to the lack of dystrophin protein. The acute phase of DMD is characterized by muscle necrosis and increased levels of the pro-inflammatory mediator, prostaglandin D2 (PGD2). Inhibiting the production of PGD2 by inhibiting hematopoietic prostaglandin D synthase (HPGDS) may alleviate inflammation and decrease muscle necrosis. We tested our novel HPGDS inhibitor, PK007, in the *mdx* mouse model of DMD.

Three-week-old male C75BL/10 ScSn-*mdx* (n = 12) and C75BL/10 ScSn (strain control; n = 12) mice were used in this study, sourced from the Animal Resources Centre (ARC) Perth, WA Australia. Mice were randomly allocated into two groups (n = 6) and were housed in individually ventilated cages (6 pups per cage) and were treated in a double-blind manner with vehicle (0.5% methyl cellulose, 0.1% Tween80, and MilliQ water), or HPGDS inhibitor (PK007: 10 mg/kg/day in 0.5% methylcellulose, 0.1% Tween80, and MilliQ water) via oral gavage daily. Weight and Hindlimb grip strength were measured daily, 2 h after oral gavage over the 10-day treatment period. Hindlimb Muscle strength was assessed using the IMADA® grip device. The instrument measured the highest force generated by each mouse over the course of 5 trials over a 1 min cycle and t maximum force (N) produced over the trials was selected.

At the conclusion of the 10-day treatment, postnatal (p) 28 days (p28), mice were euthanized via cervical dislocation. The gastrocnemius (GA) and tibialis anterior (TA) were dissected and fixed in 4% paraformaldehyde (PFA) and processed into paraffin blocks. Transverse sections were cut at 7 µm using a Lecia RM 2245 microtome and were collected onto Super Frost Plus microscopic slides. These slides were stained with Mayer's hematoxylin and eosin (H&E) (0.1%) and toluidine blue (acetate) stains (0.1% pH = 2.3). The stained slides were digitally imaged using a Leica Aperio slide scanner at 20× magnification for quantitative analysis. After cervical dislocation, blood was collected from the heart to assess Creatine kinase (CK-MM) levels. A colorimetric creatine kinase activity assay kit was used to determine CK-MM levels (Abcam, Melbourne, Vic. Australia Cat. No.: ab155901)

Our results show that hindlimb grip strength was two-fold greater in the PK007-treated mdx group, compared to untreated mdx mice, and displayed similar muscle strength to strain control mice (C57BL/10ScSn). Histological analyses showed a decreased percentage of regenerating muscle fibers (~20% less) in tibialis anterior (TA) and gastrocnemius muscles and reduced fibrosis in the TA muscle in PK007-treated mice. Lastly, we confirmed that the DMD blood biomarker, muscle creatine kinase activity, was also reduced by ~50% in PK007-treated mdx mice. We conclude that our HPGDS inhibitor, PK007, has effectively reduced muscle inflammation and fibrosis in a DMD mdx mouse model and shows promise in treating the acute phase of DMD.