satellos

Rebuilding muscle from within™

Therapeutic restoration of muscle regeneration in Duchenne

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Acknowledgments: Ottawa Hospital Research Institute – Rudnicki Lab

Our company

Satellos has discovered that muscle stem cells are unable to adequately facilitate the repair of existing, or generate new, muscle fibers in people with certain muscular dystrophies due to an inability to correctly establish polarity prior to division. We believe this impairment is a more significant factor in progressive muscle damage than dystrophin deficiency in existing muscle fibers and have identified a protein kinase target, AAK1, that, when inhibited, promotes functional rescue of asymmetric stem cell division. Having recently announced the nomination of our lead drug candidate, SAT-3247, we present here a summary of key preclinical findings and draft clinical plans.

Re-examining dystrophin's role in muscle tissue

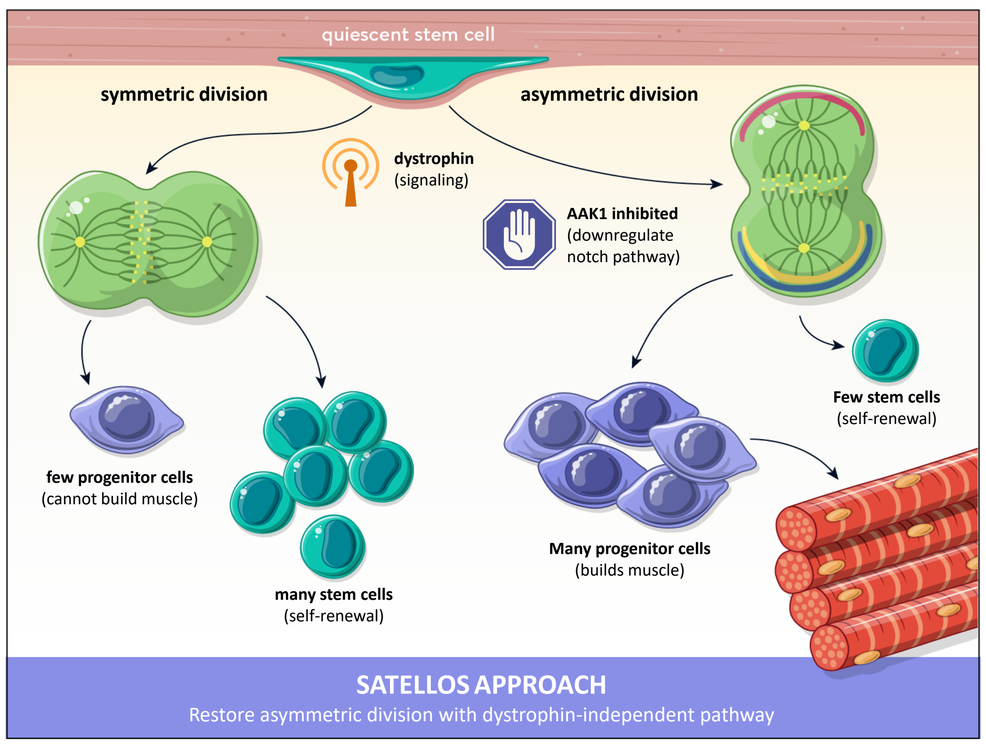
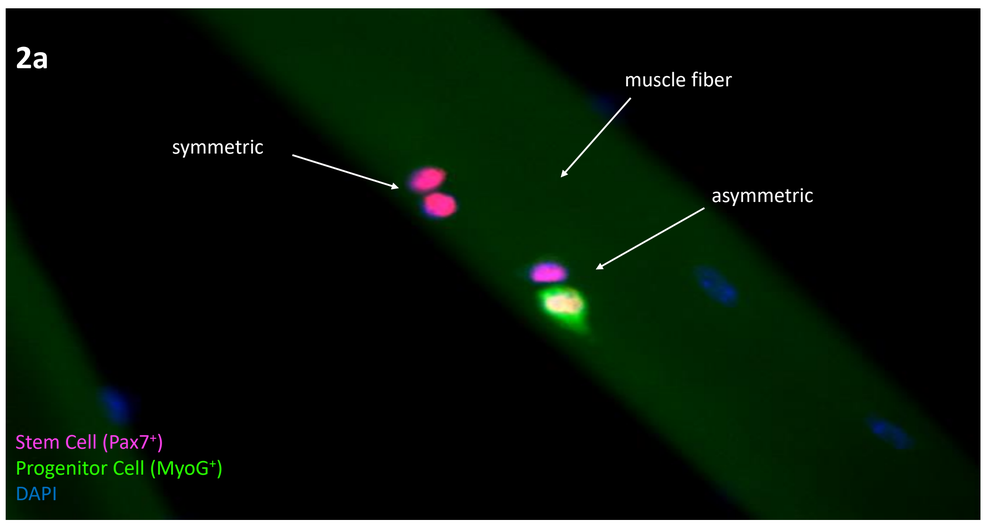


Figure 1. In addition to providing structural support to myofibers, Satellos discovered dystrophin participates in establishing the polarity in muscle stem cells (MSCs) necessary for asymmetric division. Absent dystrophin, MSCs tend to symmetrically divide, leaving an overabundance of MSCs and few progenitors (left half of figure). AAK1 inhibition promotes asymmetric division, increasing the relative amounts of progenitor cells available to create new muscle fibers (right half of figure).

Asymmetric division of stem cells in mdx muscle fibers



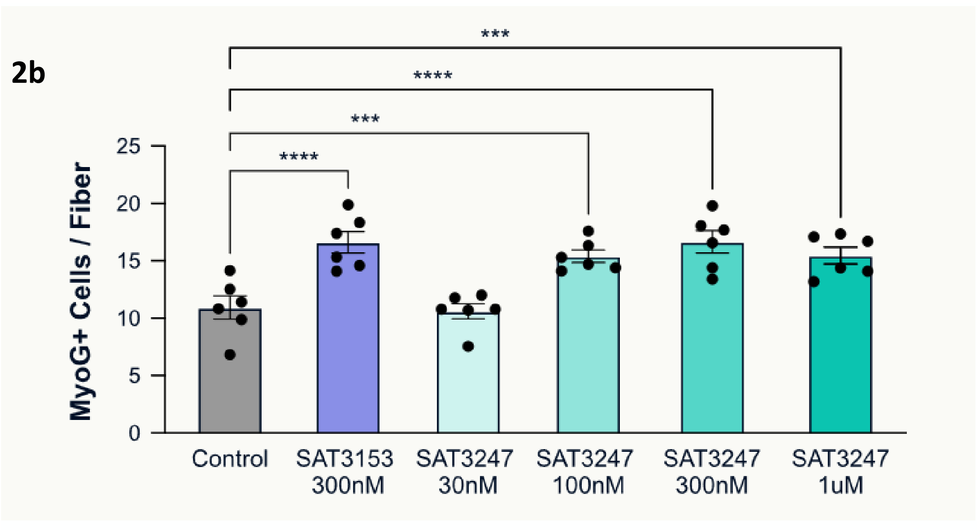
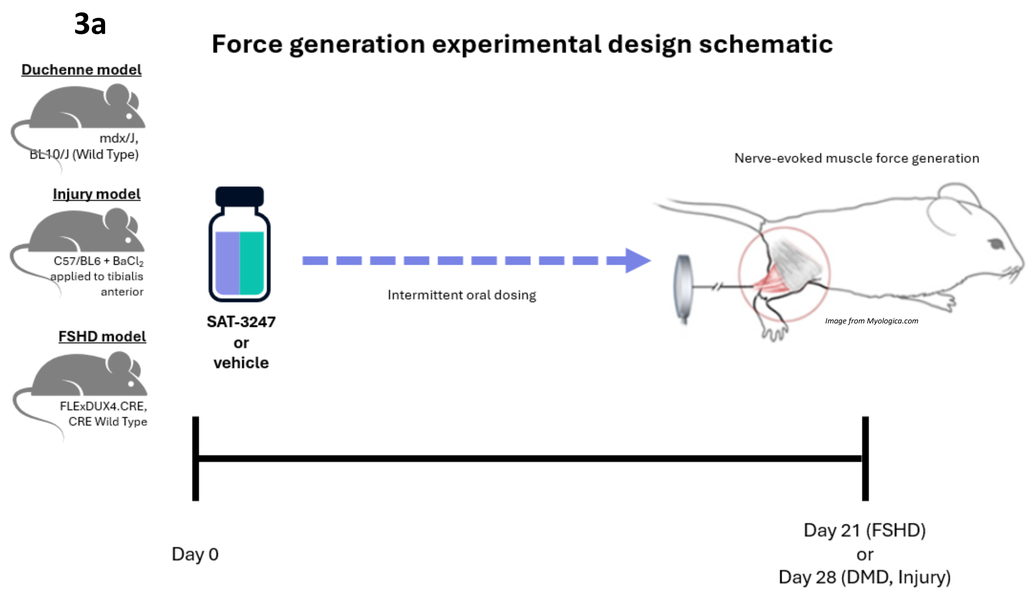
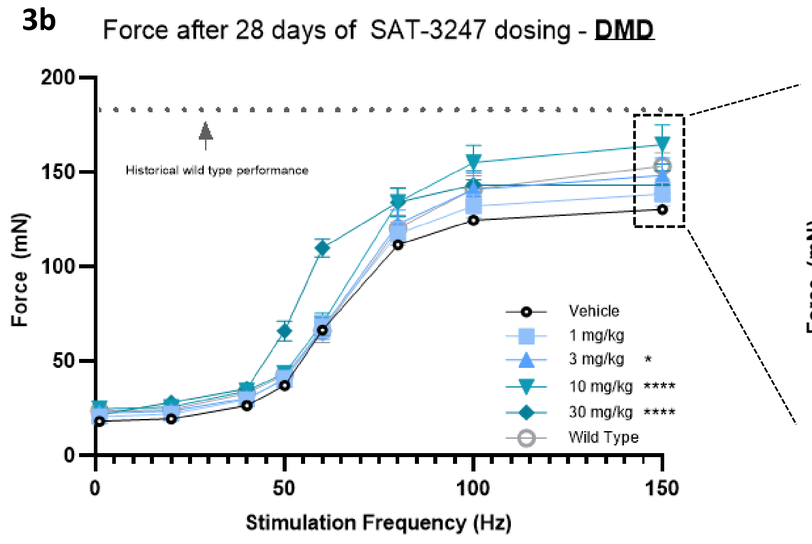
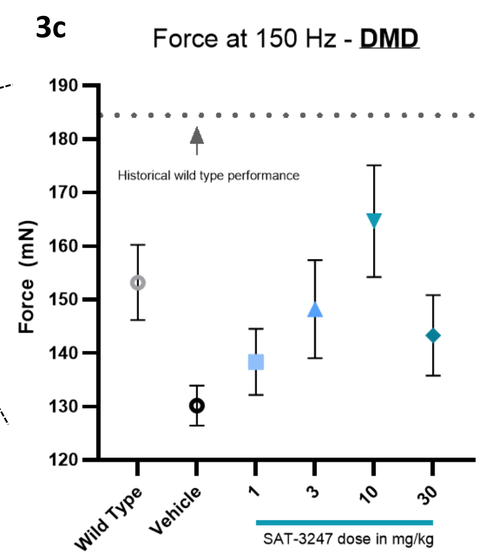


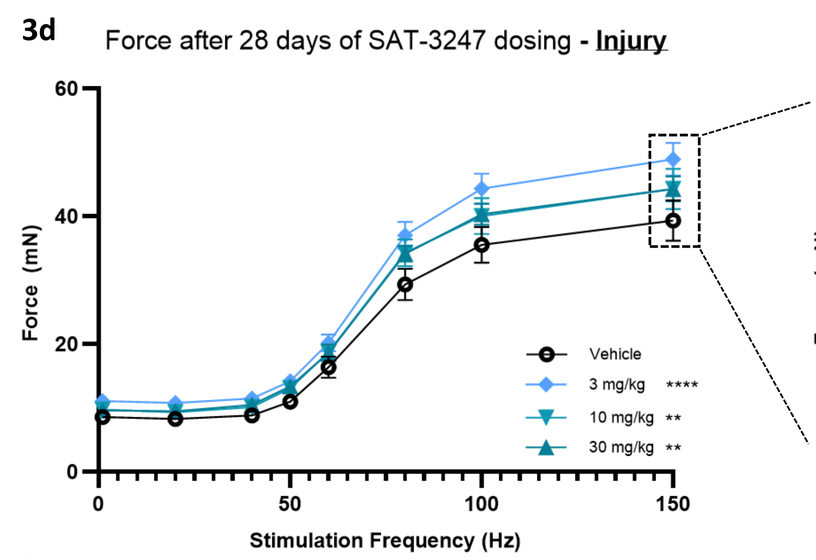
Figure 2. Symmetric versus asymmetric division of MSCs visualized using immunohistochemistry (IHC) (2a), and induction of asymmetric division of MSCs in mdx flexor digitorum brevis fibers ex vivo by SAT-3153 (also an AAK1 inhibitor) & SAT-3247 (2b) as determined by IHC. At each dose where a statistically significant change in MyoG⁺ cells/fiber is shown in the figure, a corresponding statistically significant increase in the *proportion* of MyoG⁺ to Pax7⁺ cells per fiber was also observed (data not shown). ***p < 0.001; **** p < 0.0001

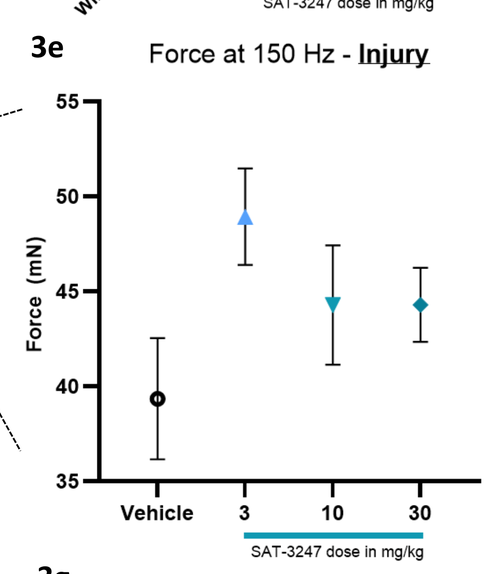
SAT-3247 increases force in preclinical models of DMD, injury, and FSHD

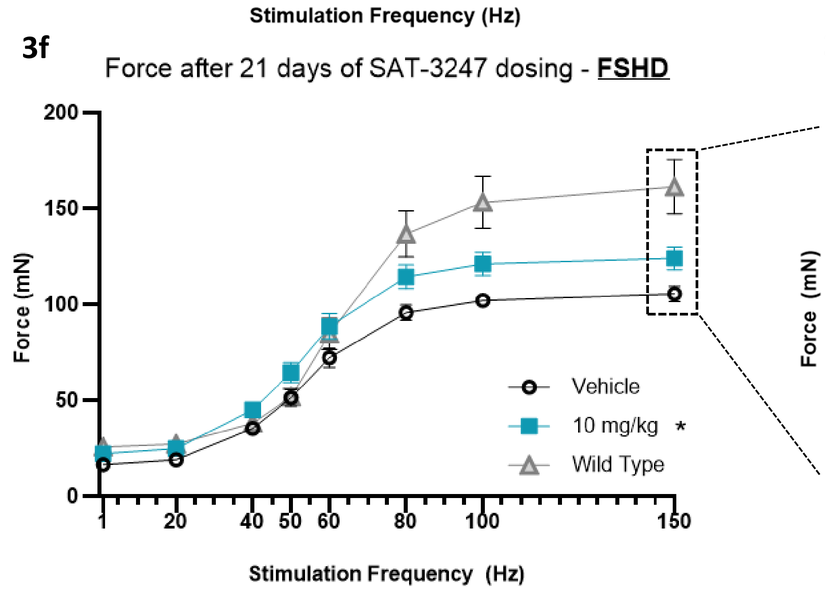












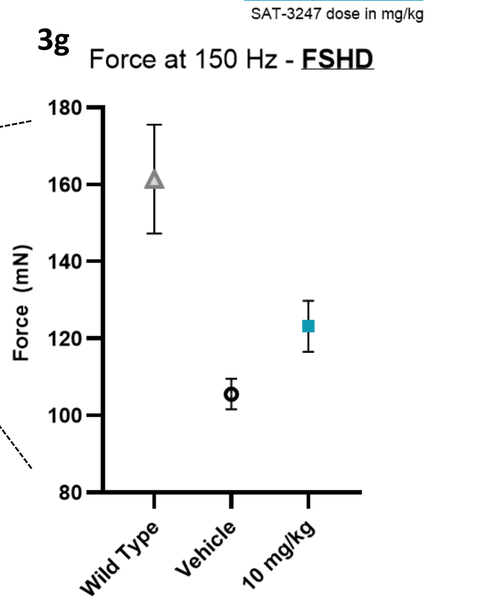


Figure 3. Force generation (mean, SEM) after treatment with SAT-3247 in mouse models of Duchenne muscular dystrophy (DMD, 3b & c), injury (3d & e), and Facioscapulohumoral dystrophy (FSHD, 3f & g). For each experiment, mice were dosed orally at an intermittent frequency, and force measurements were collected from the hindlimbs at either 21 days (FSHD) or 28 days (DMD, injury) as depicted in the schematic (3a). Injury model force was generated by ankle dorsiflexion. DMD and FSHD model force was generated by ankle plantar flexion. Statistical significance was calculated using two-way ANOVA with respect to vehicle: *p < 0.05; **p < 0.01; ****p < 0.0001

SAT-3247 development plans in Duchenne muscular dystrophy

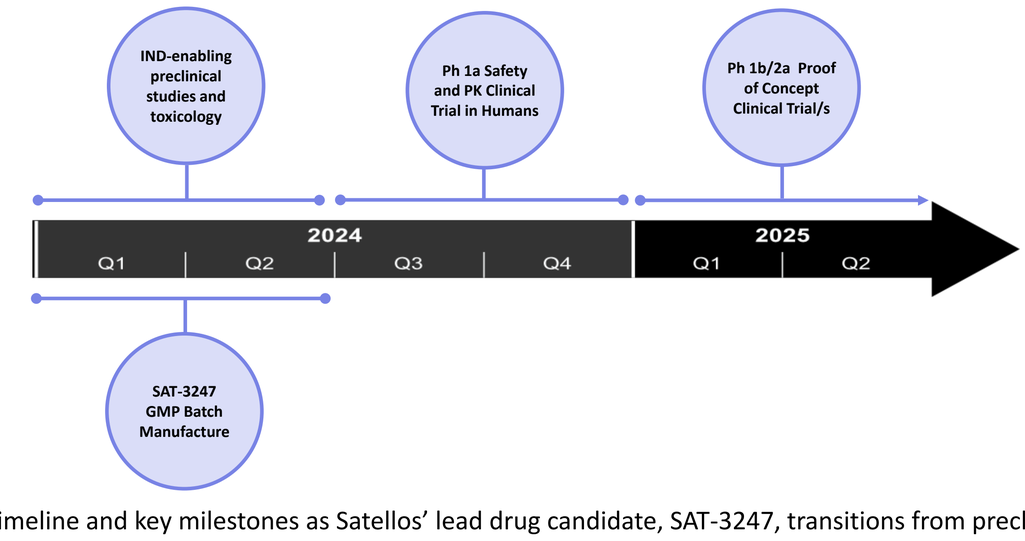


Figure 4. Planned timeline and key milestones as Satellos' lead drug candidate, SAT-3247, transitions from preclinical to clinical development