SAT-3247: An oral small molecule inhibitor targeting AAK1, a critical effector of skeletal muscle regeneration

satellos
Rebuilding muscle from within™

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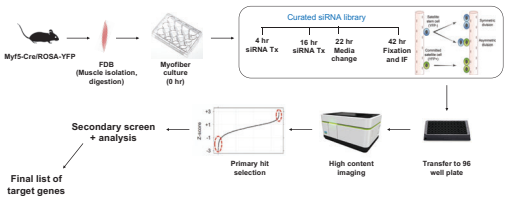
The Ottawa Hospital Research Institute | L'Hôpital d'Ottawa Institut de recherche

Satellos Bioscience Inc. is developing the world's first drug specifically designed to target the innate process of muscle regeneration, through regulation of muscle stem cell polarity. Dystrophin protein is expressed in activated muscle stem cells where it is required for establishing apical-basal polarity. In the absence of dystrophin, muscle stem cells undergo reduced numbers of asymmetric divisions and increased numbers of symmetric divisions resulting in a stem cell hyperplasia and reduced numbers of progenitor cells to match the ongoing muscle damage found in Duchenne Muscular Dystrophy (DMD). This deficiency is a significant factor contributing to the progressive muscle loss experienced by people living with DMD. Through the use of an in-situ muscle stem cell screening platform, a highly druggable protein kinase target called adapter associated kinase 1 (AAK1) was identified. The inhibition of AAK1 promotes functional rescue of asymmetric stem cell divisions, resulting in the robust production of progenitors *in vitro* and *in vivo*. Satellos' lead drug candidate, SAT-3247, is a potent, orally available, muscle penetrant small molecule inhibitor of AAK1. SAT-3247 is efficacious in both mouse and dog pre-clinical models of DMD and has recently completed a phase 1a/b clinical trial in healthy human volunteers and adult Duchenne patients. SAT-3247 was found to be safe, well tolerated and demonstrated potential early signs of impact on improving muscle strength.

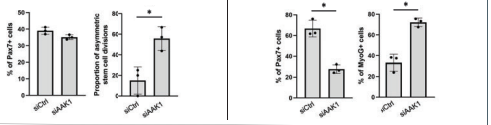
Screen for polarity targets using MyoReGenX™



Notch prioritized and protein target **AAK1** identified

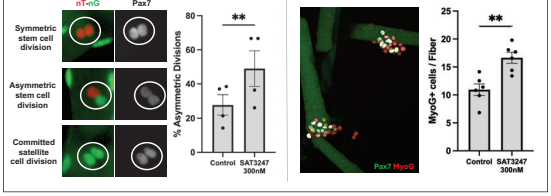
Increased progenitors with AAK1 knock-down

Cultured mdx EDL myofiber at 42h | *Cultured mdx EDL myofiber at 72h*

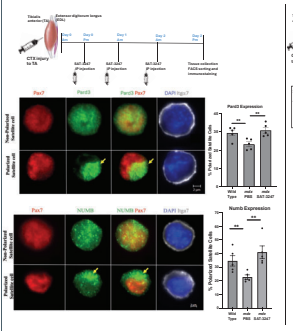


SAT-3247: An AAK1 inhibitor developed by Satellos

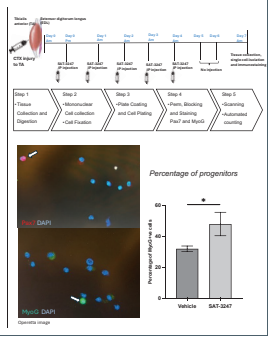
Increased asymmetric divisions at 42h | *Increased MyoG+ progenitors at 72h*



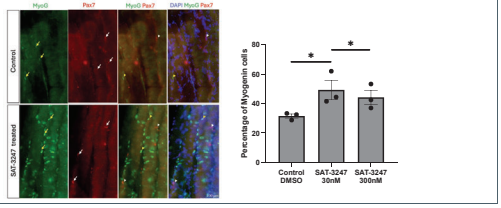
SAT-3247 increases polarization 2d after CTX



SAT-3247 increases progenitors 7d after CTX

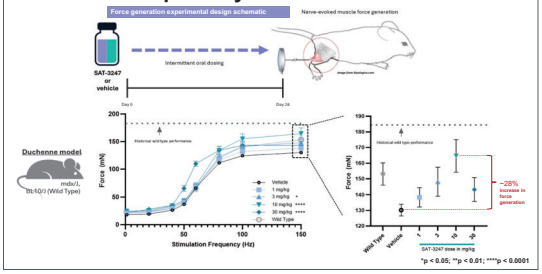


8-day Human Psoas muscle bundles with SAT-3247



*p < 0.05; **p < 0.01; ****p < 0.0001

Proof of concept study in the DMD mouse model



Pilot proof of concept study in the canine model

Multi-parameter pilot study using 2 affected dogs

Duchenne Canine

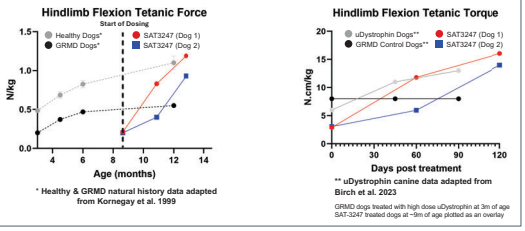
Natural DMD mutation

Weekly	Monthly	Every 2 Months	Study End
9 datapoints	*5 datapoints*	*3 datapoints*	*1 datapoint*
Body weight	Gait analysis	Force evaluation	ECG/Echo
Clin Chem and Hematology	Overnight activity	Muscle biopsy	ECU function
	Cytokine panel		Necropsy

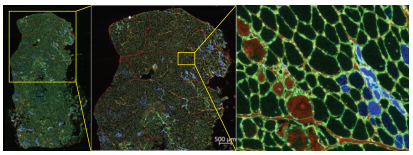
~9 months of age → Intermittent oral dosing → ~13 months of age

Scaled dose and matching schedule selected from efficacy studies in Mdx mice

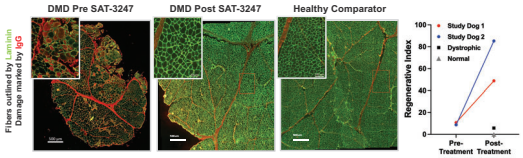
Critical functional measures return to healthy levels and benchmark favorably vs gene therapy

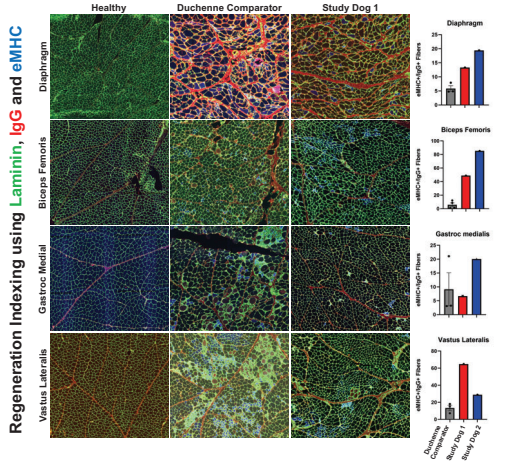


Regeneration measured with Regenerative Index

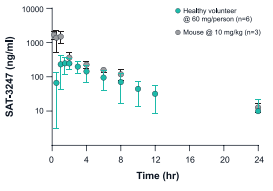


Increased RI in the canine model with SAT-3247





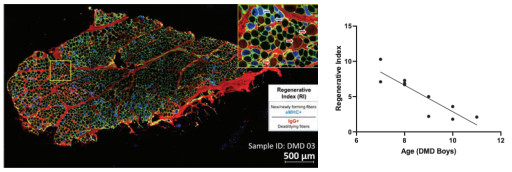
SAT-3247 Exposure in Human Consistent with Preclinical Efficacious Dose and displayed encouraging results in Phase 1b study



Clinical Data Highlights

- ✓ Safe and Well tolerated
- ✓ **SAT-3247** met desired PK profile regardless of concomitant steroid
- ✓ Potential trend to improved grip strength
- ✓ **Average strength** doubled from ~2kg to ~4kg

A significant negative correlation between RI and age in DMD boys (7 to 11yrs)



Regenerative Index to be evaluated as a measure of SAT-3247 activity in human clinical samples

Conclusions

- Inhibition of AAK1 by siRNA or SAT-3247 increases polarization, the number of asymmetric divisions and myogenic progenitors
- SAT-3247 enhances muscle regeneration in the DMD mouse model and in the dystrophic dog, showing a dramatic increase in Regenerative Index
- SAT-3247 has shown encouraging results in DMD patients including a potential improvement in grip strength