Development of a Novel Fusion Protein, JUV-161, that Enhances Muscle Regeneration for Treatment of Myotonic Dystrophy Type 1

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Introduction

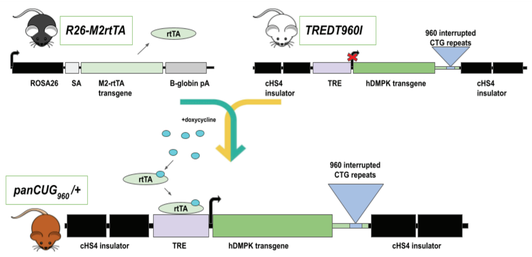
Stem cell secreted proteins are increasingly appreciated to drive regenerative effects across a multitude of tissues and cell types. An important application of these effects are leveraging them to both identify and develop biologics that elicit rejuvenation in specific biological processes and systems that undergo degeneration in aging, disease, or developmental conditions.

Utilizing this approach, Juvena Therapeutics developed JUV-161 as a recombinant fusion protein to agonistically target MAPK/ERK and PI3K/AKT regenerative cascades. These pathways are the major signaling mediators in skeletal muscle to enhance myogenesis, muscle survival, metabolism, and strength.

To advance the preclinical development of JUV-161, Juvena Therapeutics developed a pan- inducible, TREDT960I transgenic mouse model containing a human genomic segment containing exons 11-15 of DMPK gene with 960 interrupted CTG repeats (CUG960) under direction of the tetO (tet-responsive element) promoter. This panCUG960/+ murine model to encompasses the key aspects of DM1 muscle deterioration, as shown using both functional and histological testing to confirm distal muscle wasting and RNA foci accumulation in impacted tissue.

Administration of JUV-161 in this DM1 mouse model resulted in significant improvements in the grip strength, coinciding with significantly increased tibialis anterior cross-sectional area in both male and female mice. Binding assays coupled with mouse PK profiling reflected potential clinical translatability of the preclinical results obtained in the DM1 mouse model. Receptor binding along with evaluation of receptor sequence homology (>94% across all species evaluated) allowed selection of the pharmacologically relevant species (rat and dog) for the conduct of PK/PD and nonclinical safety studies. Based on the results from these studies and the promising activity of JUV-161 in preclinical and nonclinical studies, Juvena therapeutics is planning to evaluate the potential therapeutic benefit of JUV-161 in adult-onset DM1 patients in 2024. JUV-161 treatment could improve muscle strength, endurance, mass, and glucose regulation, leading to reduced atrophy together with faster walk speeds and reduced fall rates, in adult-onset DM1 patients.

Mouse Model Development



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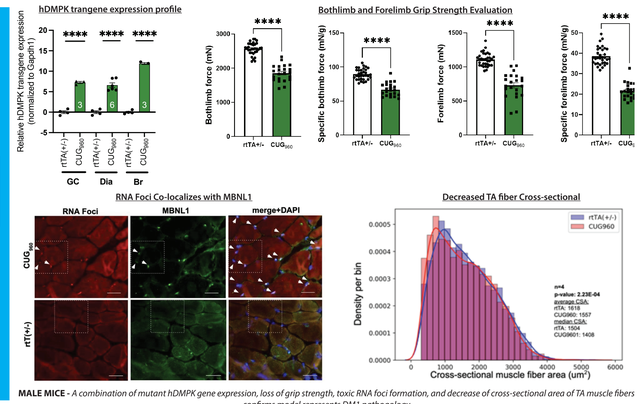

MALE MICE - *A combination of mutant hDMPK gene expression, loss of grip strength, toxic RNA foci formation, and decrease of cross-sectional area of TA muscle fibers confirms model represents DM1 pathogology*

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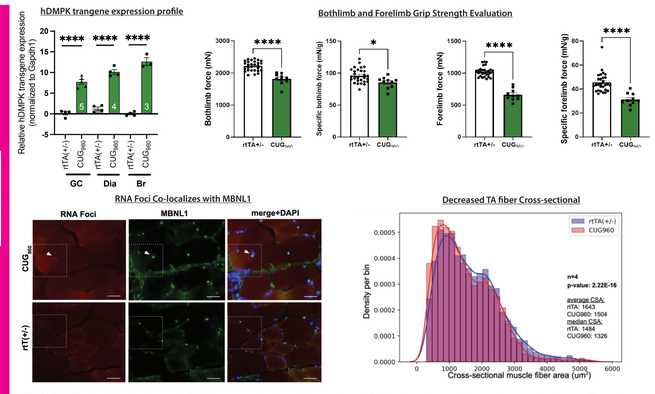
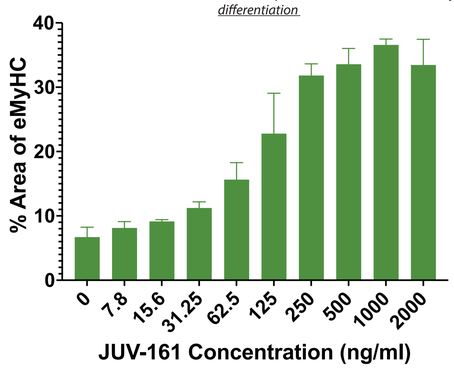


FEMALE MICE - *A combination of mutant hDMPK gene expression, loss of grip strength, toxic RNA foci formation, and decrease of cross-sectional area of TA muscle fibers confirms model represents DM1 pathogology*

Results

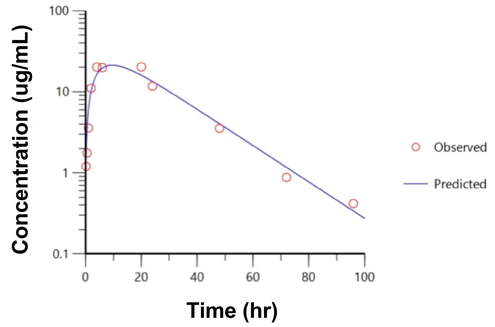
JUV-161 Treatment leads to Myogenesis in vitro

JUV-161 in vitro resulted in concentration-dependent induction of human myoblast differentiation



PK Profile of JUV-161 in panCUG960 Male MIce

Subcutaneous administraiton of JUV-161 shows predictable PK

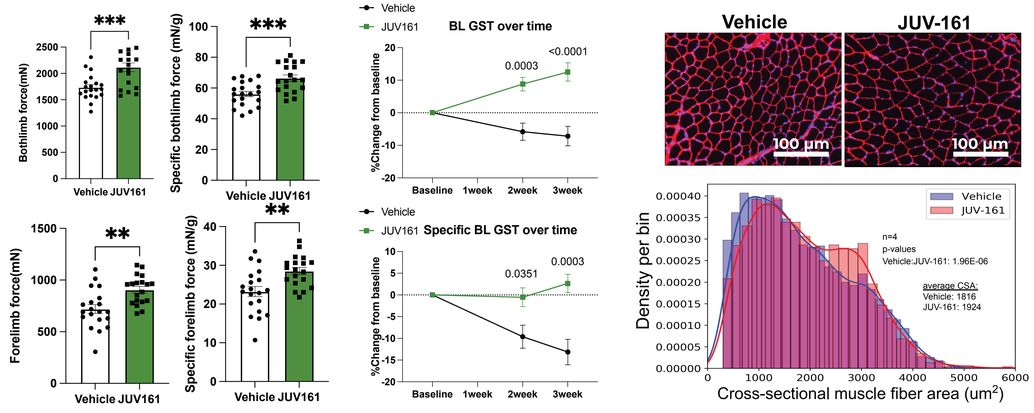


In vivo Efficacy of JUV-161

Male and Female panCUG960 Mice Treated with JUV-161 Q.O.D for 3 weeks

JUV-161 treated animals of both genders were observed to have greatly improved grip strength across multiple metrics, as well as greatly improved TA cross-sectional area

MALES



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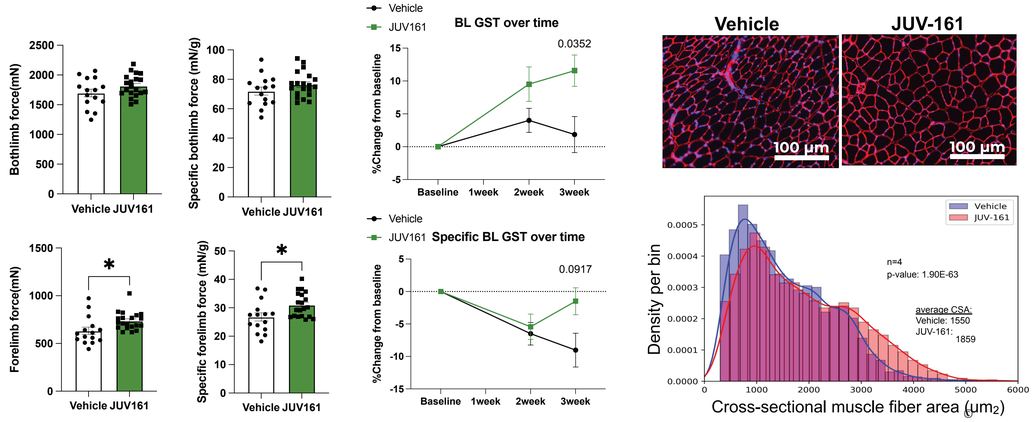
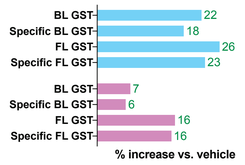


Results

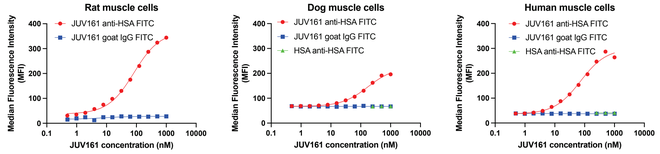
In vivo Efficacy of JUV-161: Graphic Summary

	Male		Female	
	JUV-161	Vehicle	JUV-161	Vehicle
BL GST (mN)	2117	1734	1816	1697
Specific BL GST (mN/g)	66.44	56.14	76.35	71.99
FL GST (mN)	905.7	719.3	736.5	632.4
Specific FL GST (mN/g)	28.51	23.21	30.99	26.78



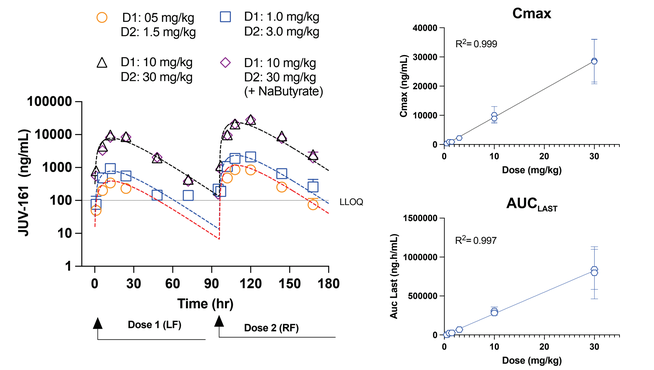
JUV-161 Binds to Rat, Dog and Human Primary Muscle Cells

JUV-161 shows specific and concentration depenedent binding to rat, dog, and human primary muscle cells



Rat PK profile following subcutaneous dosing

A 1-compartment model closely fits the data following the first dose and allowes PK profile predictions following the second dose



Conclusions

- The panCUG960/+ DM1 mouse model recapitulated myopathic and functional manifestations of DM1 consistent with defects in patients with DM1, enabling assessment of reversal and/or amelioration of these changes following administration of JUV-161 in this animal model
- Treatment with JUV-161 in vitro resulted in concentration-dependent induction of human myoblast differentiation (EC50 ~ 100ng/mL)
- SC administration of JUV-161 in panCUG960/+ mice resulted in a predictable PK profile
- In the panCUG960/+ DM1 mouse model, administration of JUV-161 was associated with increases in skeletal muscle fiber cross-sectional areas, and ultimately significant improvements in functional assessments
- JUV-161 shows specific and concentration-dependent binding to rat, dog and human primary muscle cells, supporting rat and dog as relevant species for the conduct of pharmacology/toxicology studies
- Subcutaneous administration of JUV-161 in rats resulted in dose-proportional increases in the exposure and the linear PK profiles. Additionally, the PK profile following administration of the second dose was both linear and stationary (time-independent). These results indicated no complexities in JUV-161 absorption or elimination following SC dosing in rats