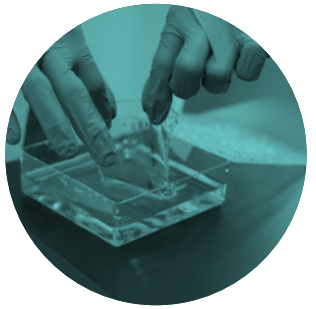
A novel anti-myostatin GLP-1RA fusion molecule to preserve muscle and improve body composition during GLP-1RA therapy

Mohammed S. Alsuraih, Justin W. Jackson, Duc Phan, Christopher D. Chapron, Meghan Martin, Narela Magrassi, Frederick C. Streich, Jr., Leslie K. Cortes, Mo Qatanani

PRESENTER DISCLOSURE

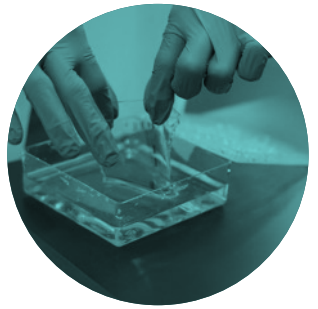
Mohammed Alsuriah

Employee and Shareholder of Scholar Rock.



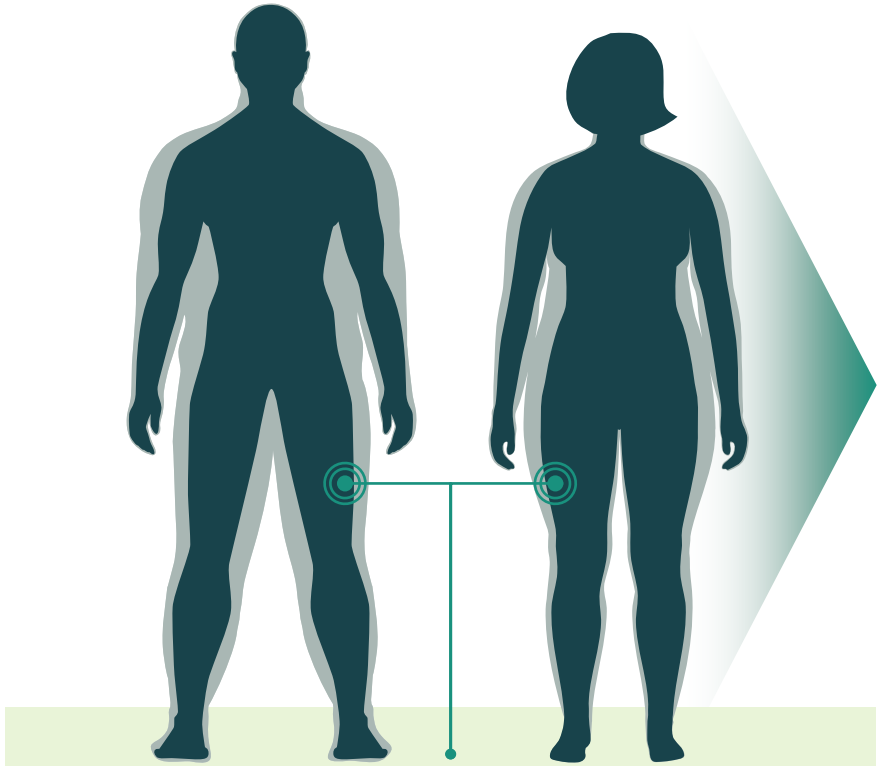
PHOTOGRAPHY PROHIBITED

PLEASE DO NOT take photos of this presentation



GLP-1 RA therapies are highly effective but loss of lean mass poses significant risk

Muscle is essential to healthy metabolic function



Significant proportion of weight loss due to loss of lean mass

Current Weight Loss Strategies
Challenged by:

- Tolerability
- Lack of durability
- **Significant muscle loss**[1-3]

Recently approved **GLP-1 RAs are highly effective** in weight loss & experiencing rapid uptake

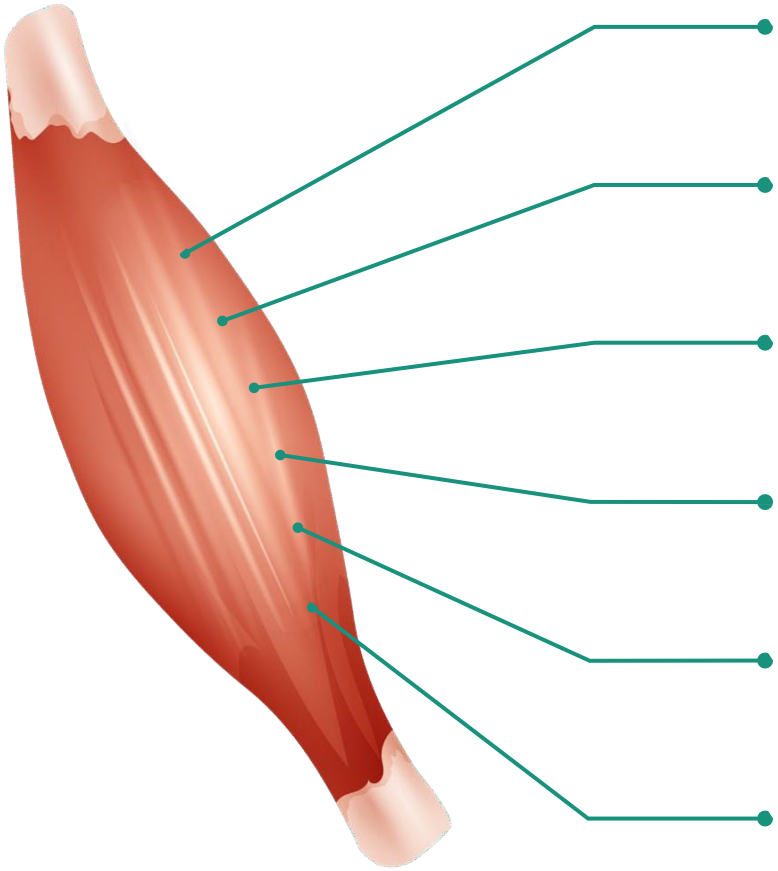
But 25%-40% of total body weight loss mediated by GLP-1 RA therapy may be attributed to **loss of lean mass**[2,3]

Preserving muscle is important to promote long-term metabolic benefits, sustainable weight management and health outcomes[4-7]

GLP-1 RA=Glucagon-like peptide-1 receptor agonists.

1. Muller TD, et al Anti-obesity drug discovery: advances and challenges. Nature Reviews Drug Discovery 2022; 21, 201–223; 2. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989-1002; 3. Jastreboff AM, et al Tirzepatide Once Weekly for the Treatment of Obesity. NEJM 2022; 387 (3): 205-216; 4. Cava et al. Preserving healthy muscle during weight loss. Adv Nutr 2017;8:511-19; 5. Lundgren JR et al. Healthy Weight Loss Maintenance with Exercise, Liraglutide or Both Combined. NEJM 2021;384:1719-30; 6. Beal JW et al. Dietary weight loss-induced improvements in metabolic function are enhanced by exercise in people with obesity and prediabetes. Nat Metab. 2022;5(7):1221-1235; 7. Dulloo AG, et al How dieting makes some fatter: from a perspective of human body composition autoregulation. Proc Nutr Soc. 2012 Aug;71(3):379-89.

Muscle is critical for overall health



- Increase basal metabolic rate (BMR)[1]
- Enhance glucose homeostasis[2] and better insulin sensitivity and lower risk of prediabetes[3]
- Signal to other systems as an endocrine organ impacting overall health[4]
- Reduce visceral fat[5]
- Increase caloric expenditure post-exercise[6]
- Increase bone density, strength, function, and longevity and decreased risk of injury and disability[7-9]

1. Aristizabal, J.C., *et al. Eur J Clin Nutr*. 2015. 2. Lindegaard, B., *et al. J Clin Endocrinol Metab*. 2008. 3. Srikanthan, P. and Karlamangla, A.S. *J Clin Endocrinol Metab*. 2011. 4. Severinsen, M.C.K. and Pedersen, B.K. *Endocr Rev*. 2020. 5. Wewege, M.A., *et al. Sport Med*. 2022. 6. Zurlo, F., *et al. J Clin Investl*. 1990. 7. Fukushima, Y., *et al. Diabetes Metab J*. 2016. 8. Roh, E. and Choi, K.M. *Front. Endocrinol (Lausanne)*. 2020. 9. Volpi, E., *et al. Curr Opin Clin Nutr Metab Care*. 2004.

Myostatin is a negative regulator of skeletal muscle mass

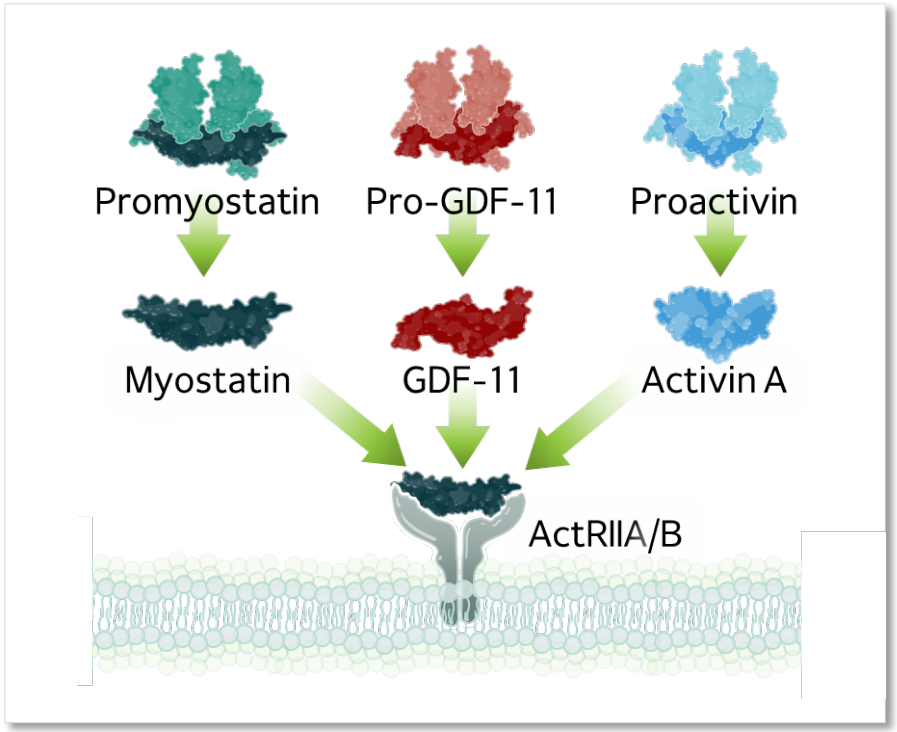
Myostatin biology

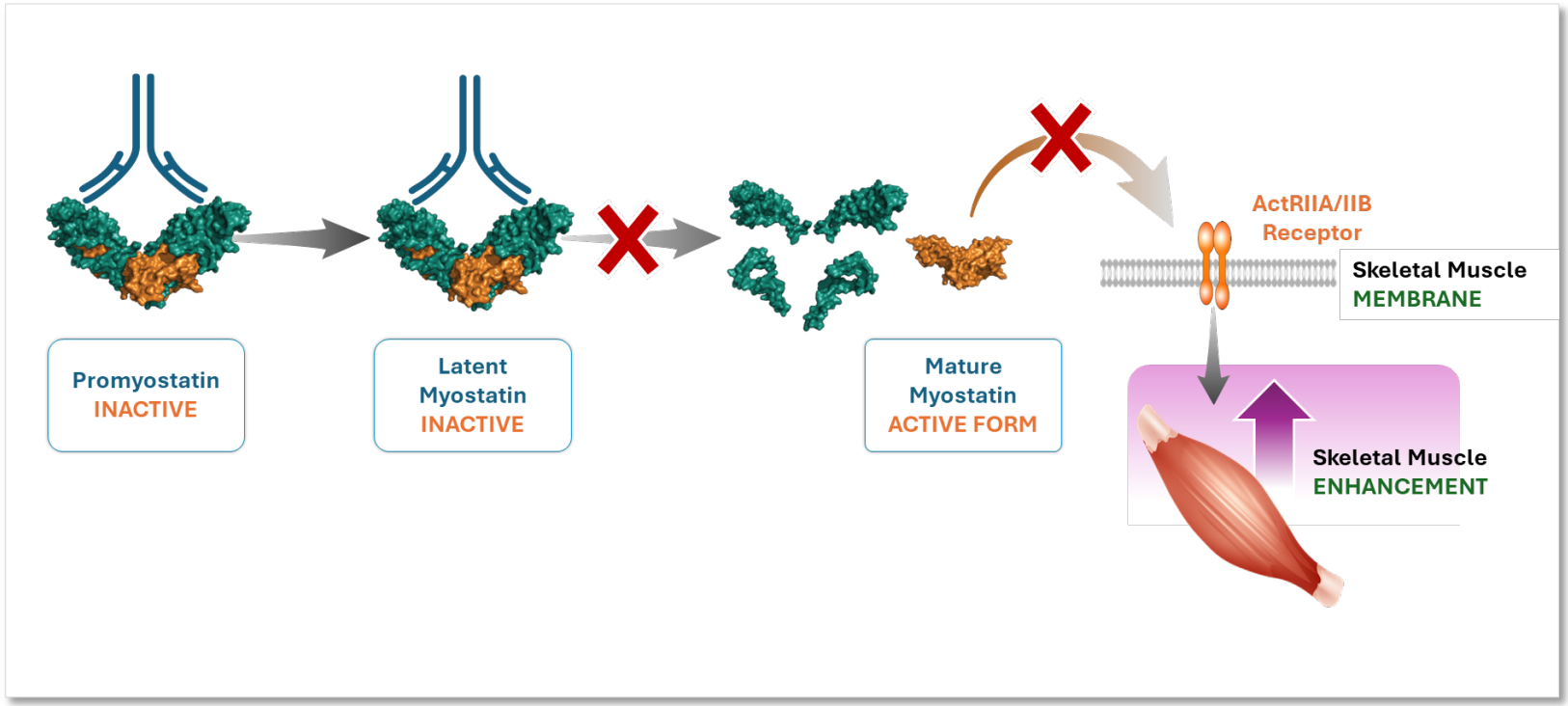
- Myostatin is a secreted growth factor which signals through the activin type II B receptor (ACVR2B) to suppress muscle hypertrophy
- Myostatin is specific to muscle[1]
- Extensive animal data demonstrate that loss of myostatin activity markedly increases muscle mass
- Validated genetically with no evident safety liabilities [1-4]
- Selective inhibition of myostatin with apitegromab has demonstrated improvements in motor function in patients with spinal muscular atrophy[5]

Pictures depict increase in muscle mass in myostatin null animals and humans

1. McPherron, A.C., et al. Nature 1997; 2. Schuelke, M., et al. NEJM 2004; 3. Kambadur, R., et al Genome Res. 1997; 4. Mosher, D.S., et al. PLoS 2007; 5. Crawford, T.O., et al. Lancet 2025.

Scholar Rock's myostatin inhibitors selectively target the pro- and latent forms of myostatin, resulting in muscle enhancement

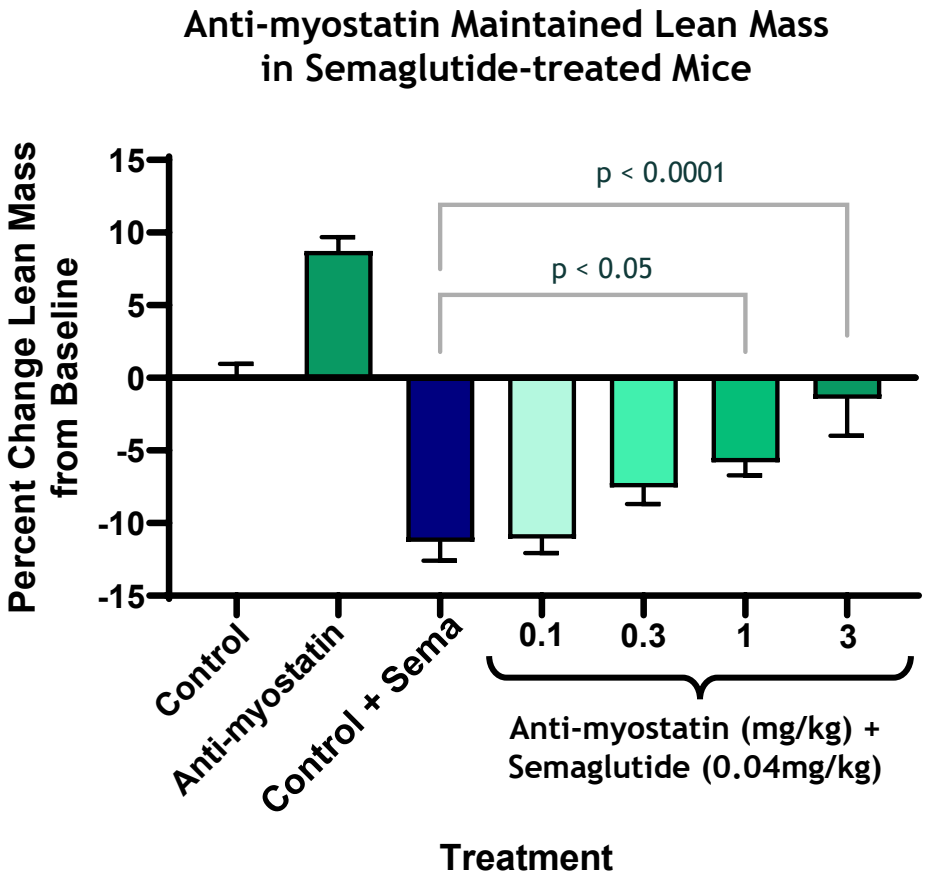




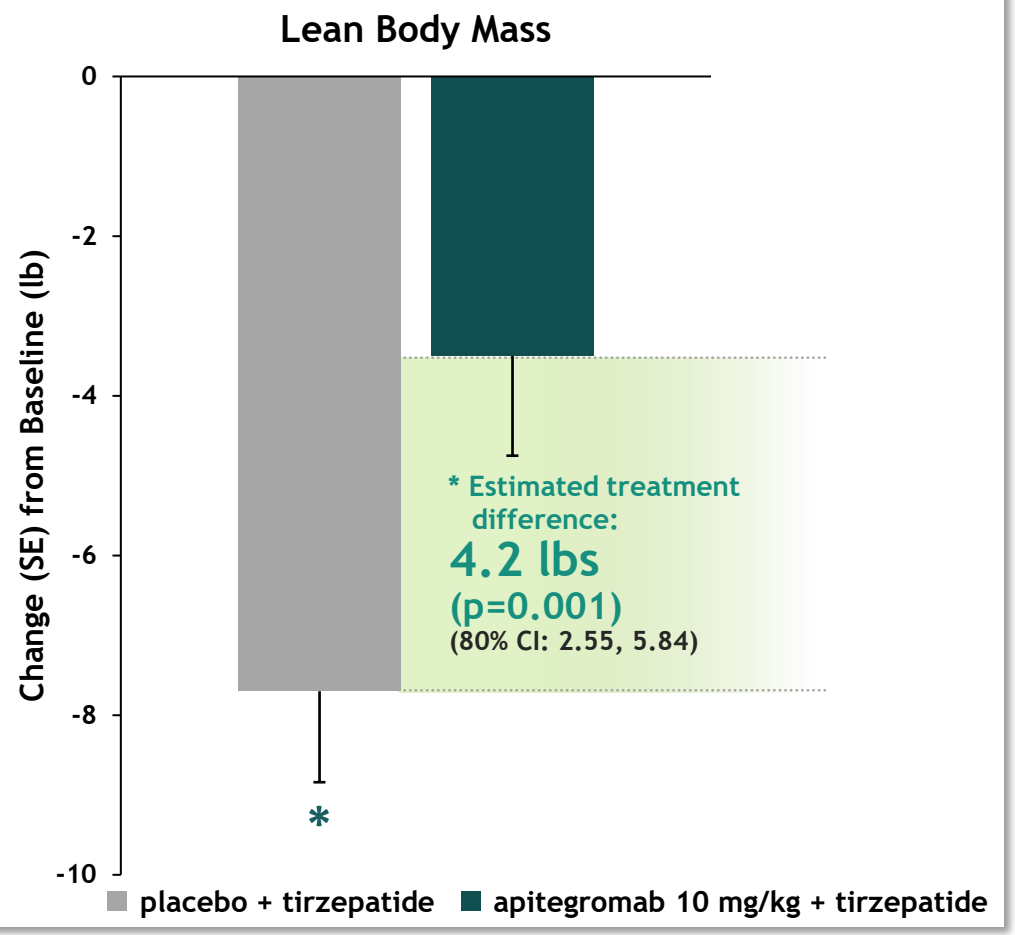
- Developing an anti-myostatin agent is difficult due to a high degree of similarity with Activin A and GDF-11
- Myostatin inhibitor binds to pro- and latent myostatin and inhibits the conversion to mature myostatin
- This approach prevents myostatin from interacting with receptors, resulting in muscle growth

Selective inhibitors of latent myostatin significantly preserved lean mass when combined with incretin-based therapeutics

Preclinical Animal Data



EMBRAZE Ph2 Trial[1]



* Analysis based on participants who completed treatment and had a Week 24 DEXA scan. Means based on a linear regression model controlling for baseline lean body mass, baseline weight, age, and sex.

[1] clinicalTrials.gov ID: NCT06445075

Anti-myostatin GLP-1RA fusion molecule

Concept & Screening workflow

Developing novel myostatin fusion therapeutics: unimolecular solutions to maintain muscle in weight loss

Anti-myostatin antibody

GLP-1RA peptide

Anti-myostatin x GLP-1RA Fusion

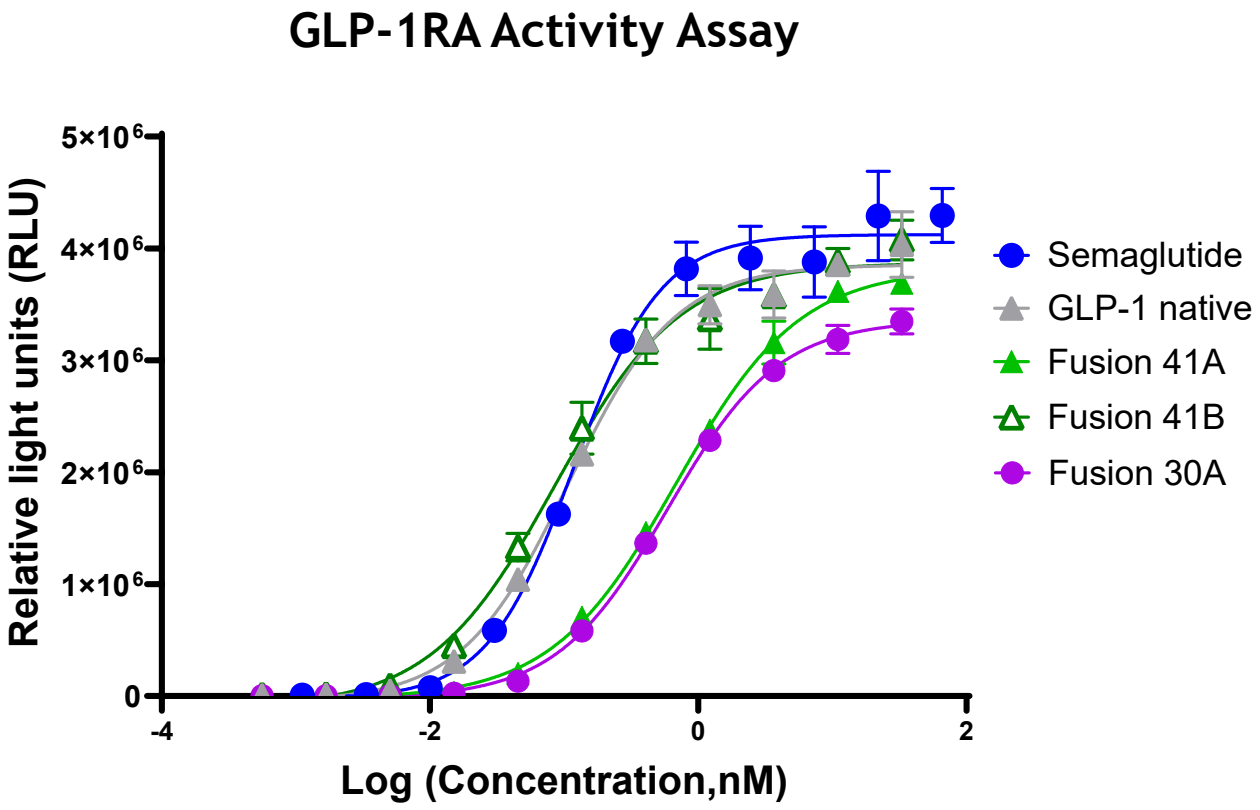
Screening Workflow

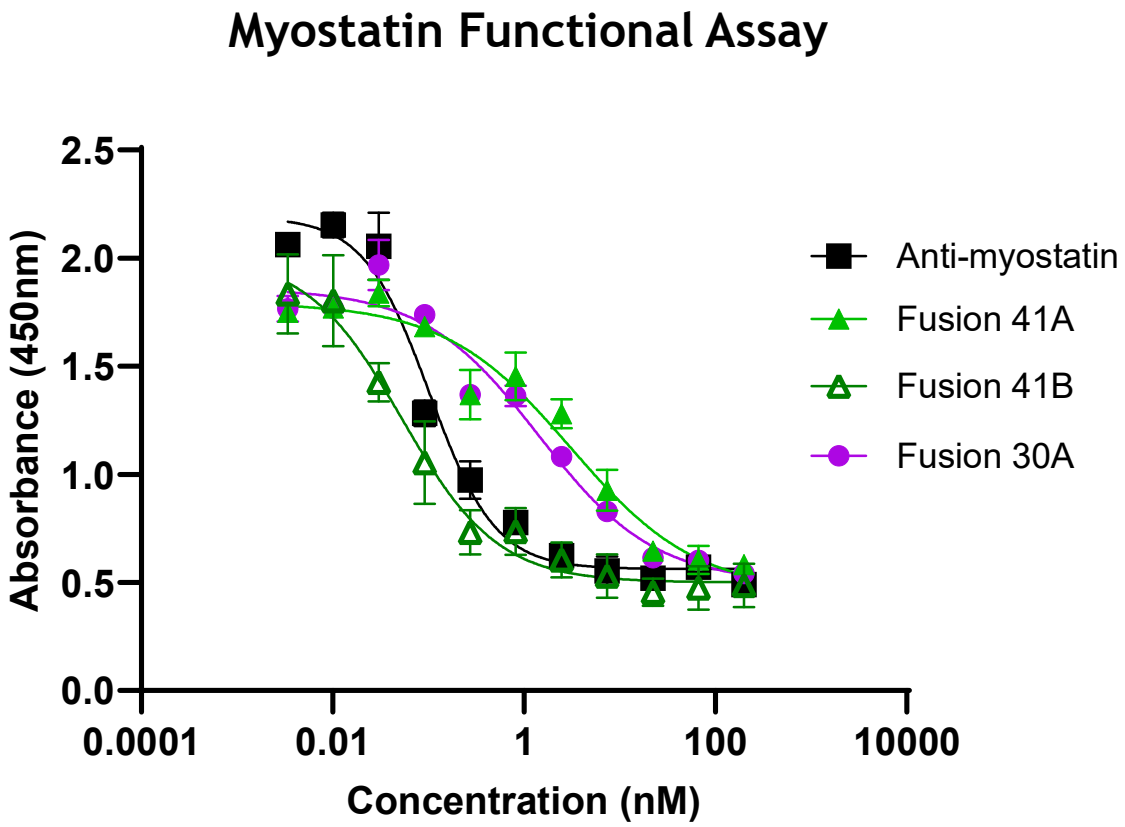
Antibody/ Peptide Engineering → GLP-1R activation assay → Myostatin binding and inhibition → *In vitro* serum stability → PK/PD and efficacy studies

Fusion molecules demonstrated agonism of the GLP-1 receptor and myostatin inhibition

Fusions activate the GLP-1R with an EC50 similar to GLP-1 native peptide and semaglutide

Fusions retain the ability to block activation of latent myostatin



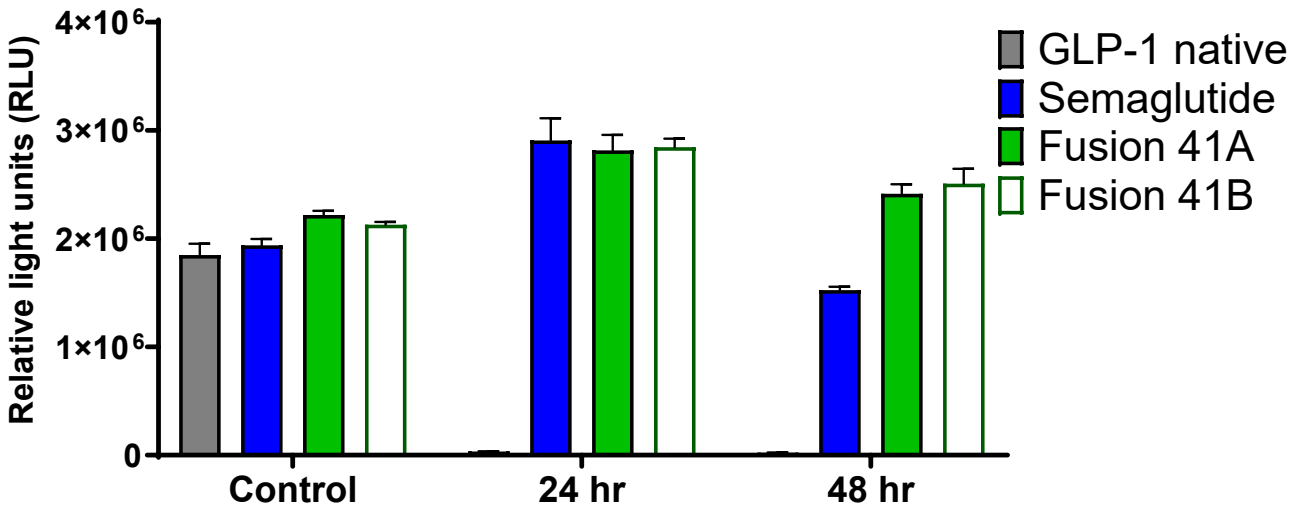


Fusions demonstrated durable *in vitro* and *in vivo* GLP-1RA activity

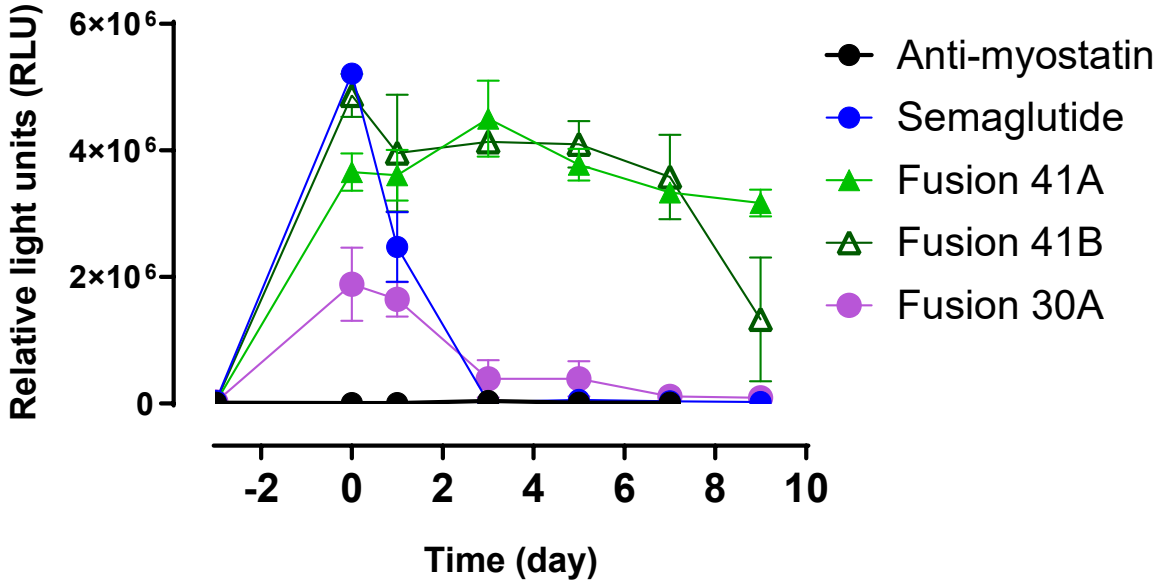
Fusions 41A and 41B maintain activity in vitro in mouse serum longer than GLP-1 native peptide and semaglutide

Fusions 41A and 41B show detectable GLP-1 activity up to 7 days after a single administration in healthy mice

In vitro Serum Stability Assay



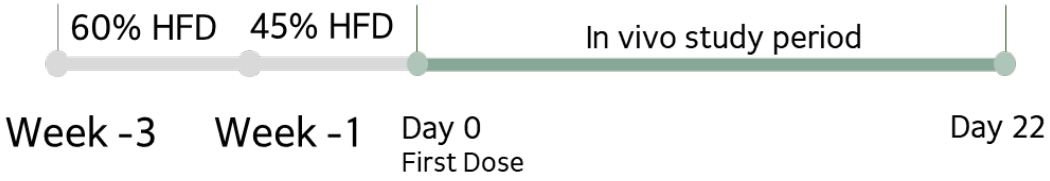
In Vivo GLP-1RA Activity



Fusion molecule 41A demonstrated GLP-1R activity *in vivo* in a model of diet-induced obesity

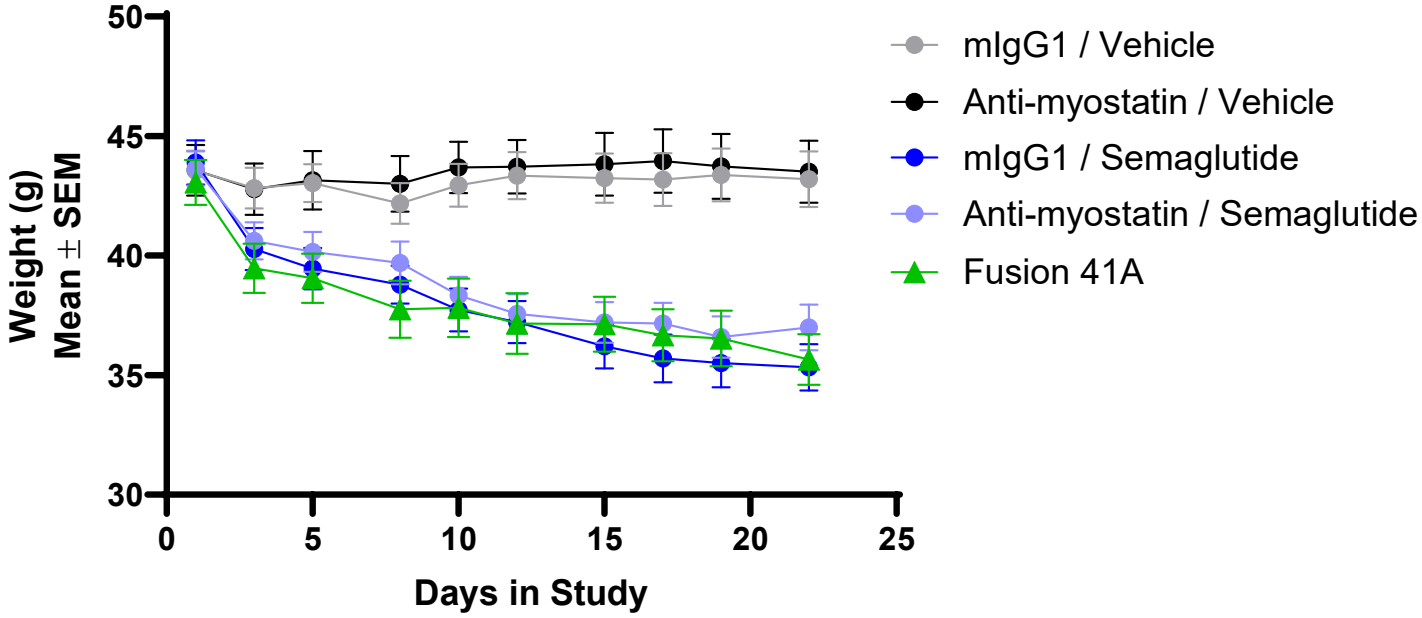
Fusion molecule 41A reduces bodyweight similarly to control semaglutide or semaglutide/anti-myostatin co-injection

Diet-Induced Obesity Efficacy Study



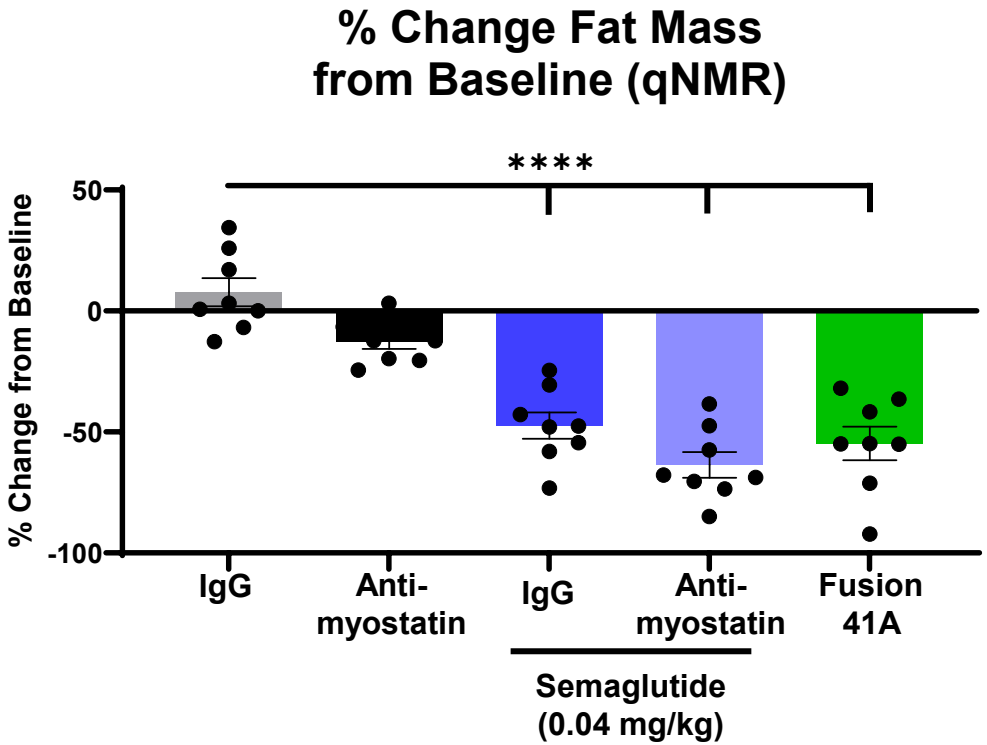
- Antibodies and fusion dosed bi-weekly 10 mg/kg
- Semaglutide dosed daily 0.04 mg/kg/day

Body Weight

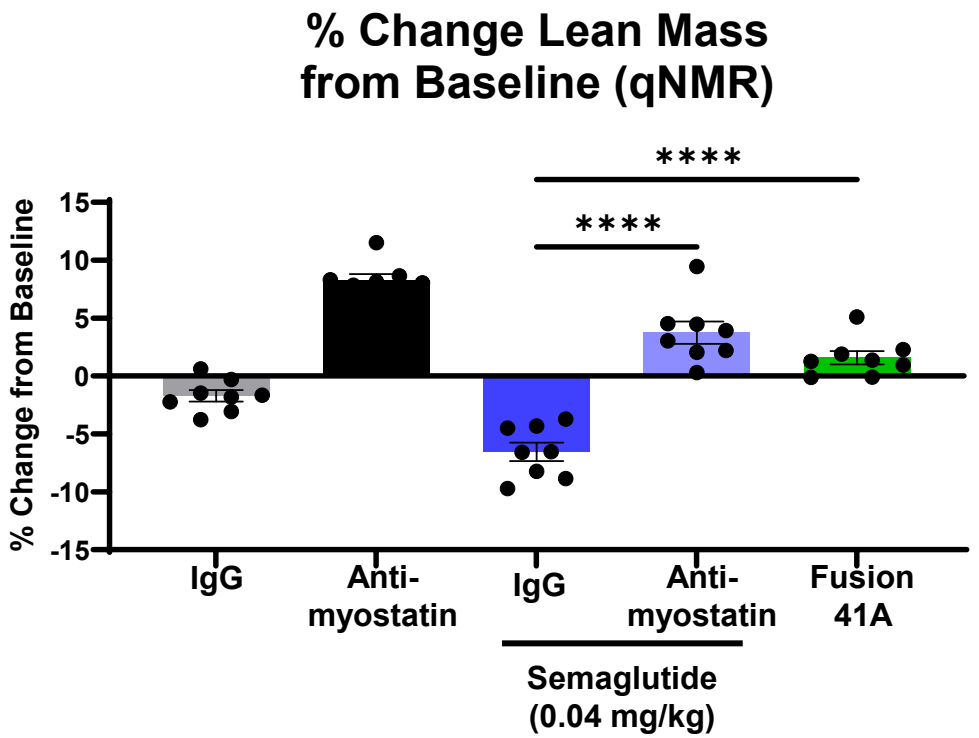


Fusion 41A drove similar weight loss to semaglutide but showed preservation of lean mass

Fusion 41A, semaglutide and the semaglutide/anti-myostatin combination drive similar fat mass loss



Fusion 41 results in 2% lean mass gain versus a 6.5% lean mass loss with semaglutide



Statistics are by 2-way ANOVA, ****p<0.0001

Summary and Conclusions

- GLP-1RAs are highly effective therapeutics for driving weight loss. However, GLP-1RAs result in a loss of a significant amount of lean mass
- Selective inhibition of latent myostatin has been demonstrated to preserve lean mass when used in combination with incretin mimetics both preclinically and clinically
- **Combining a selective anti-myostatin antibody and a GLP-1R agonist peptide represents a novel approach to weight management with improved maintenance of lean mass**
- As incretin therapies become the standard of care, understanding the functional and metabolic consequences of lean mass loss, and the benefits of lean mass preservation, will be critical to optimizing patient outcomes beyond weight loss alone

Acknowledgments

Scholar Rock, Inc.

- Co-authors
- Fusion Program Team
- Adam Rago
- Jonathan Hamm
- Atsuko Polzin

Thank You!