Design and Evaluation of a Dual Mechanism GLP-1R Agonist-Antibody Fusion for Weight Loss with Lean Mass Preservation

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

Scholar Rock, Inc., Cambridge, MA USA

Abstract

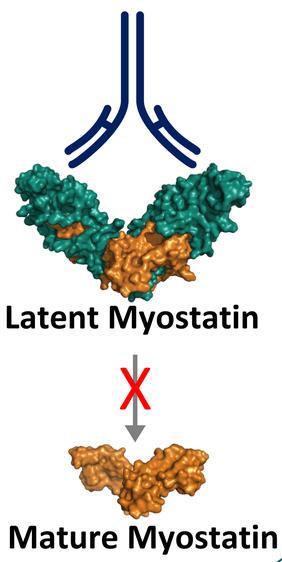
The treatment of obesity and type 2 diabetes has been transformed by incretin-based therapeutics such as glucagon-like peptide-1 receptor (GLP-1R) and dual GLP-1R/glucose-dependent insulinotropic polypeptide receptor (GIPR) agonists. However, a major limitation of these therapies is the accompanying loss of lean mass, which can account for up to 40% of total body mass lost during treatment. This has created strong interest in new therapeutic approaches that preserve lean mass. Scholar Rock has developed antibodies highly selective for the precursor forms of myostatin, a negative regulator of muscle mass. These antibodies inhibit the proteolytic activation of latent myostatin into its mature growth factor form, thereby blocking myostatin signaling. Apitegromab is one such antibody in development for the treatment of spinal muscular atrophy (SMA) and has demonstrated functional benefit for SMA patients in both the TOPAZ and SAPPHIRE clinical trials. Additionally, in the EMBRAZE trial for the treatment of adults who are overweight or obese, apitegromab combined with tirzepatide resulted in greater than 50% preservation of lean mass compared to tirzepatide alone, demonstrating that myostatin inhibition has the potential to improve the quality of weight loss. Building on this platform, we sought to engineer fusion molecules combining anti-myostatin and GLP-1R agonist activities. Fusion molecules were evaluated using a suite of *in vitro* assays. Across the molecules tested, GLP-1RA potency and molecular stability varied from sub-nanomolar to double-digit nanomolar EC50s, while inhibition of myostatin activation remained comparable to the parental antibody. In a proof-of-concept diet-induced obesity mouse model, an anti-myostatin GLP-1R agonist fusion molecule produced weight loss comparable to semaglutide while preserving lean mass.

Scholar Rock anti-myostatin antibodies

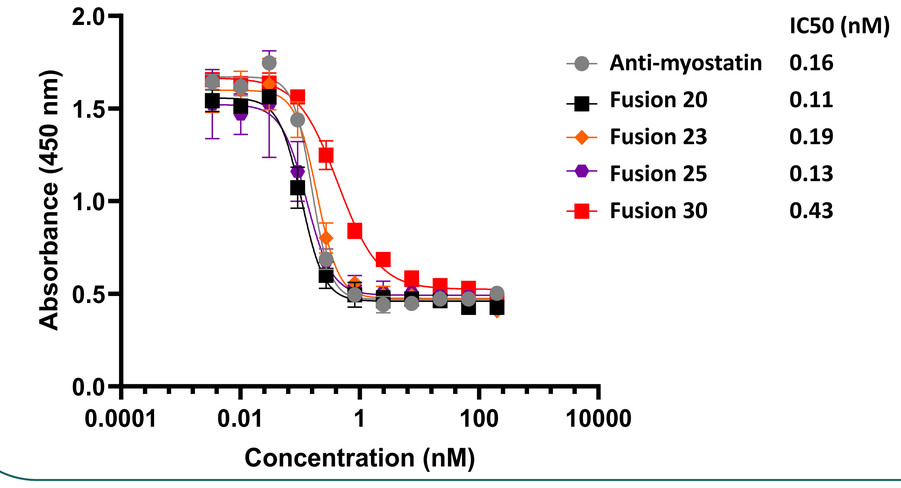
- Target latent myostatin, preventing proteolytic cleavage into mature myostatin

Apitegromab

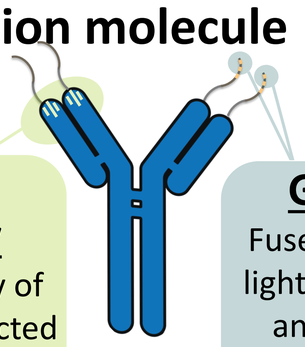
- First anti-myostatin to demonstrate clinically-meaningful functional effect in SMA patients in phase 2 and phase 3 clinical trials (TOPAZ, SAPPHIRE)
- EMBRAZE Phase 2 trial – Patients receiving apitegromab with tirzepatide showed >50% lean mass preservation compared to tirzepatide alone



Fusion molecules potently inhibit the proteolytic activation of latent myostatin



Engineering an anti-myostatin GLP-1R agonist fusion molecule



Anti-Myostatin Inhibitory Antibody

Binding and inhibitory activity of the antibody should be unaffected by the fusion to a peptide

GLP-1R Agonist

Fused to the heavy and/or light chain. Must be potent and stable to maximize efficacy

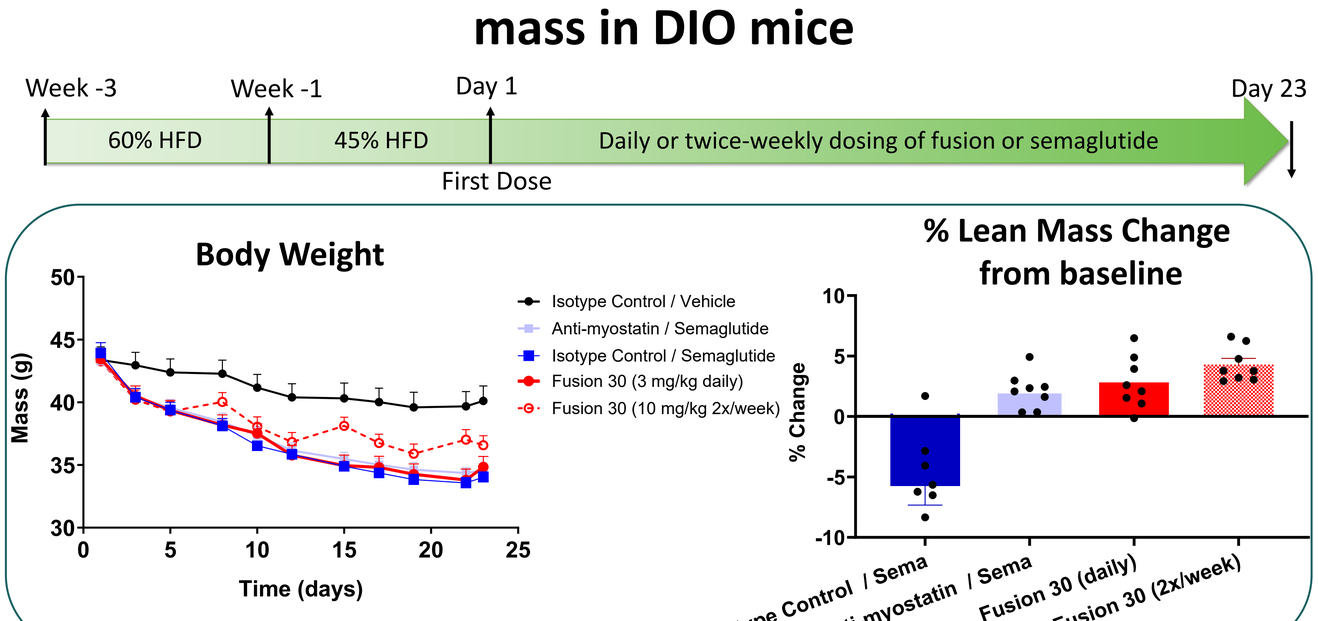
Objective:

Engineer a unimolecular anti-myostatin/GLP-1R agonist fusion that retains potency, stability, and promising developability characteristics

Screening Workflow

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

Fusion molecules have extended stability profile in mouse serum



- Select fusion molecules retained GLP-1R activation following 48-hour mouse serum incubation, unlike semaglutide and native GLP-1

Fusion molecules potently activate GLP-1R

- A diverse set of fusion peptides and linkers were assessed in both HEK293 GLP-1R and GIPR reporter cells
- Some fusions activate GLP-1R similar to native GLP-1 and semaglutide
- GLP-1/GIP multi-agonist fusions were explored, but showed decreased potency

Fusion 30 reduces body mass while maintaining lean mass in DIO mice

- Isotype control and anti-myostatin antibodies dosed at 3 mg/kg weekly; semaglutide dosed at 0.04 mg/kg daily
- Treatment with a fusion molecule resulted in comparable weight loss to daily semaglutide, although administration twice weekly resulted in less weight loss than daily administration
- Semaglutide treatment alone resulted in lean mass loss
- Semaglutide + anti-myostatin rescued loss of lean mass, and the fusion molecule achieved comparable results

Conclusion

The unimolecular fusion molecule combining a selective anti-myostatin antibody and a GLP-1R agonist peptide potently activates GLP-1R with an extended stability profile and inhibits proteolytic activation of latent myostatin *in vitro*. In a DIO mouse model, this molecule preserved lean mass while reducing body weight comparable to a current leading therapeutic, and further engineering may enable lower and less frequent dosing. This unimolecular strategy may provide a basis for future therapeutics aimed at weight management with improved quality of weight loss.

Acknowledgements

The authors thank and acknowledge the *in vivo* team at Charles River for conducting the diet-induced obesity mouse study, and the team at ATUM for their support with codon optimization, expression, and purification of fusion constructs.