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LET003: AI-Enabled Next Generation of ACVR2A/2B Antibody for Obesity

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Harbour BioMed

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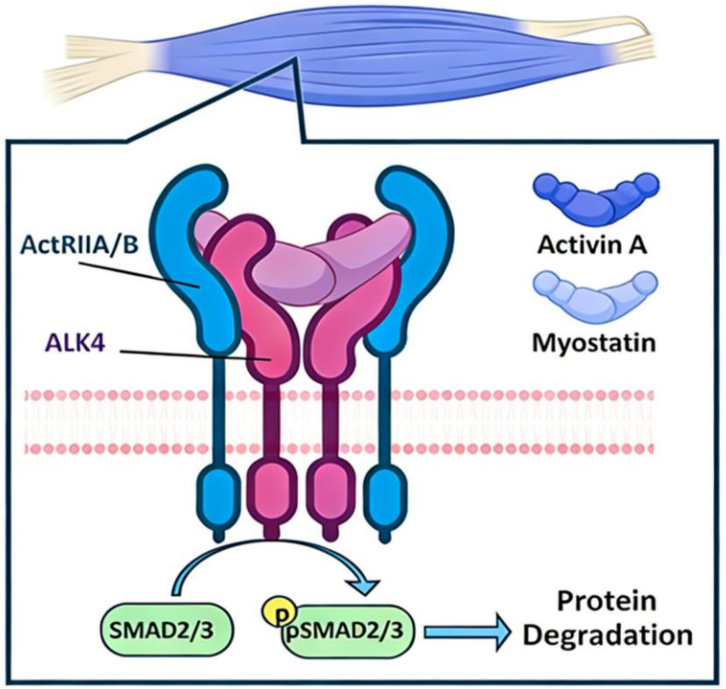
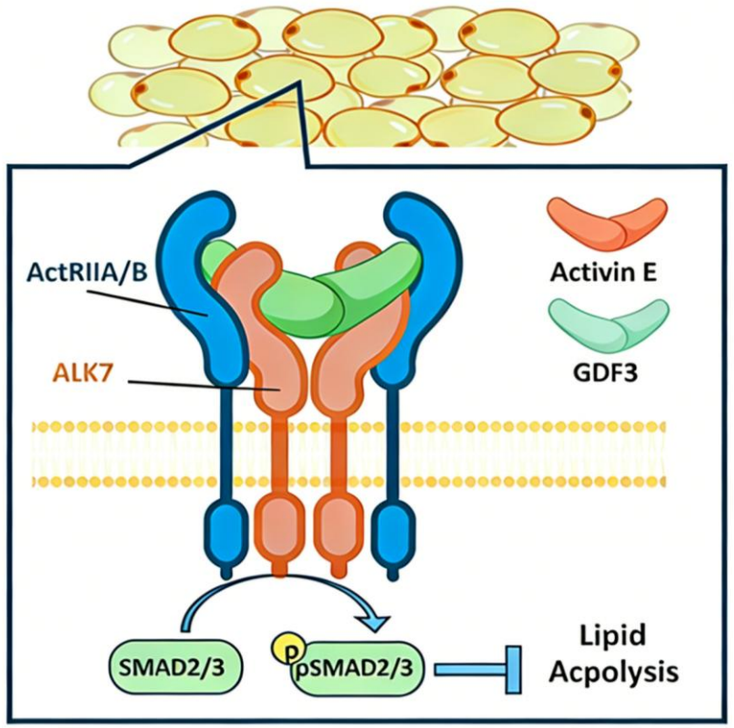
ACVR2A/2B Plays an Important Role in the Balance between Fat and Muscle

Skeletal Muscle Myotubes	Adipose Tissue Adipocytes
Activin A/Myostatin bind ActRIIA/B-ALK4, phosphorylate SMAD2/3, drive protein degradation, and cause muscle atrophy	Activin E/GDF3 bind ActRIIA/B-ALK7, phosphorylate SMAD2/3, inhibit lipolysis, and result in lipid accumulation



Muscle Atrophy



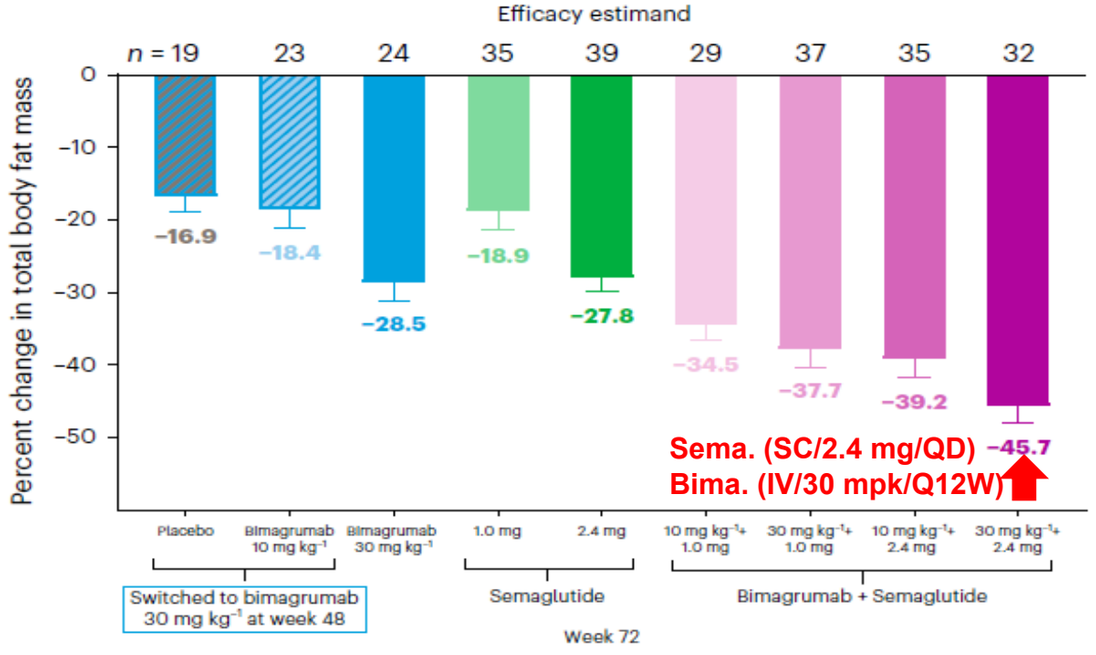
Lipolysis Accumulation

Source: American Diabetes Association 85th Scientific Session, June 20-23, 2005

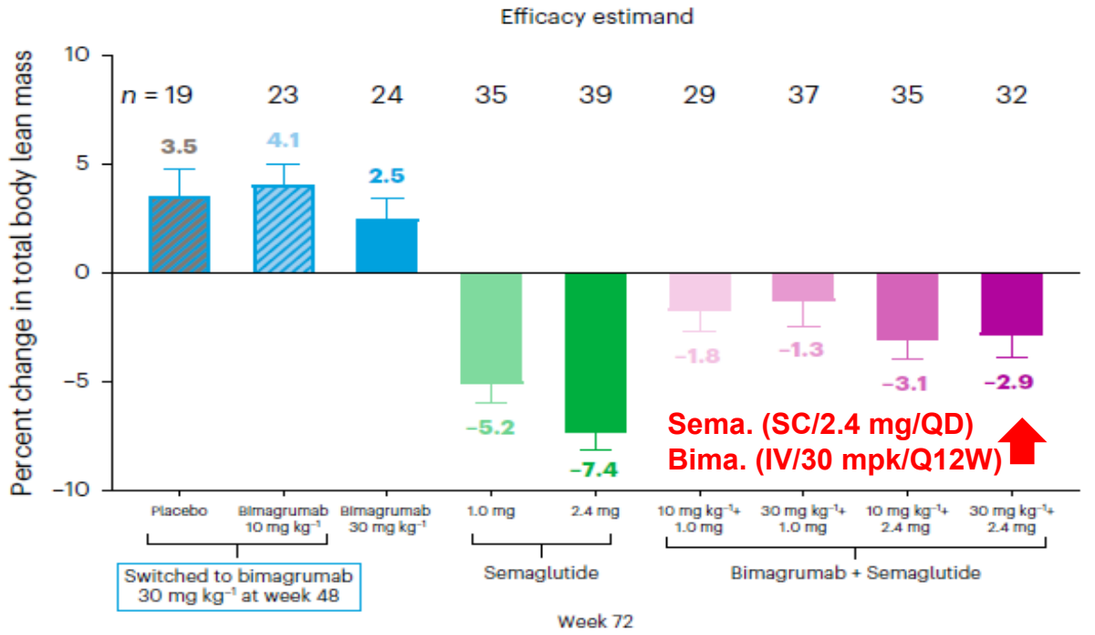
Bimagrumab, the First Dual ACVR2A/2B Blocker, Has Delivered Promising Clinical Results

48W Double Blind + 24W Open Label Data (Extra Loading Dose of Bima at W1 and W4)

Percent Change in Total Body Fat Mass



Percent Change in Total Body Lean Mass



Limitation of Bimagrumab

- Intravenous (IV) injections administered in a hospital setting may lead to poor patient adherence
- Very high dosage (30 mg/kg)
- Adverse events for Bimagrumab included muscle spasms, diarrhea and acne

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Source: Nat Med. 2026 Mar 2. Bimagrumab plus semaglutide alone or in combination for the treatment of obesity: a randomized phase 2 trial

AEs and Safety through Week 48

AE	Placebo (*N*=55)	Bimagrumab		Placebo + semaglutide		Bimagrumab + semaglutide			
		10 mg kg^{-1} (*N*=56)	30 mg kg^{-1} (*N*=57)	1.0 mg (*N*=55)	2.4 mg (*N*=56)	10 mg kg^{-1} + 1.0 mg (*N*=56)	10 mg kg^{-1} + 2.4 mg (*N*=55)	30 mg kg^{-1} + 1.0 mg (*N*=56)	30 mg kg^{-1} + 2.4 mg (*N*=55)
AEs during treatment that occurred in ≥10% of participants in any treatment group									
Muscle spasms	3 (5.5)	26 (46.4)	42 (73.7)	7 (12.7)	5 (8.9)	32 (57.1)	35 (63.6)	35 (62.5)	35 (63.6)
Diarrhea	3 (5.5)	23 (41.1)	28 (49.1)	19 (34.5)	20 (35.7)	24 (42.9)	30 (54.5)	24 (42.9)	27 (49.1)
Nausea	7 (12.7)	14 (25.0)	7 (12.3)	25 (45.5)	26 (46.4)	23 (41.1)	34 (61.8)	21 (37.5)	27 (49.1)
Acne	2 (3.6)	19 (33.9)	25 (43.9)	6 (10.9)	5 (8.9)	24 (42.9)	25 (45.5)	31 (55.4)	29 (52.7)
Upper respiratory tract infection	9 (16.4)	12 (21.4)	11 (19.3)	11 (20.0)	12 (21.4)	8 (14.3)	7 (12.7)	11 (19.6)	11 (20.0)
COVID-19	8 (14.5)	14 (25.0)	11 (19.3)	12 (21.8)	16 (28.6)	10 (17.9)	3 (5.5)	3 (5.4)	9 (16.4)
Headache	6 (10.9)	11 (19.6)	6 (10.5)	10 (18.2)	10 (17.9)	9 (16.1)	12 (21.8)	12 (21.4)	9 (16.4)
Constipation	3 (5.5)	2 (3.6)	2 (3.5)	11 (20.0)	16 (28.6)	8 (14.3)	15 (27.3)	15 (26.8)	9 (16.4)
Fatigue	2 (3.6)	4 (7.1)	4 (7.0)	12 (21.8)	14 (25.0)	5 (8.9)	12 (21.8)	7 (12.5)	12 (21.8)
Blood creatine phosphokinase increased	6 (10.9)	8 (14.3)	7 (12.3)	3 (5.5)	1 (1.8)	6 (10.7)	9 (16.4)	8 (14.3)	7 (12.7)
Decreased appetite	2 (3.6)	4 (7.1)	4 (7.0)	6 (10.9)	7 (12.5)	10 (17.9)	6 (10.9)	8 (14.3)	7 (12.7)
Vomiting	1 (1.8)	4 (7.1)	3 (5.3)	5 (9.1)	9 (16.1)	6 (10.7)	10 (18.2)	6 (10.7)	7 (12.7)
Abdominal pain	3 (5.5)	1 (1.8)	3 (5.3)	3 (5.5)	6 (10.7)	8 (14.3)	8 (14.5)	5 (8.9)	8 (14.5)
Rash	3 (5.5)	7 (12.5)	1 (1.8)	4 (7.3)	2 (3.6)	8 (14.3)	5 (9.1)	5 (8.9)	5 (9.1)
Gastroesophageal reflux disease	1 (1.8)	0 (0.0)	3 (5.3)	5 (9.1)	3 (5.4)	3 (5.4)	8 (14.5)	5 (8.9)	6 (10.9)
Nasopharyngitis	3 (5.5)	6 (10.7)	2 (3.5)	4 (7.3)	5 (8.9)	4 (7.1)	2 (3.6)	4 (7.1)	2 (3.6)
Back pain	2 (3.6)	2 (3.6)	0	2 (3.6)	6 (10.7)	5 (8.9)	5 (9.1)	4 (7.1)	2 (3.6)
Arthralgia	4 (7.3)	1 (1.8)	6 (10.5)	5 (9.1)	3 (5.4)	1 (1.8)	0	4 (7.1)	3 (5.5)
Lipase increased	0	2 (3.6)	3 (5.3)	5 (9.1)	6 (10.7)	1 (1.8)	5 (9.1)	3 (5.4)	2 (3.6)
Dizziness	2 (3.6)	4 (7.1)	2 (3.5)	2 (3.6)	7 (12.5)	1 (1.8)	1 (1.8)	3 (5.4)	4 (7.3)
Dyspepsia	0	0	1 (1.8)	3 (5.5)	6 (10.7)	4 (7.1)	5 (9.1)	3 (5.4)	3 (5.5)
Abdominal pain upper	0	3 (5.4)	2 (3.5)	2 (3.6)	3 (5.4)	2 (3.6)	8 (14.5)	2 (3.6)	3 (5.5)
Abdominal distension	0	0	2 (3.5)	3 (5.5)	9 (16.1)	1 (1.8)	6 (10.9)	2 (3.6)	1 (1.8)

A Superior ACVR2A/2B Blocker to Bimagrumab is Valuable

- **Using lower dosage**
- **SC injections and self-administration at home can significantly improve patient adherence**
- **Reduce side effects included muscle spasms, diarrhea and acne**

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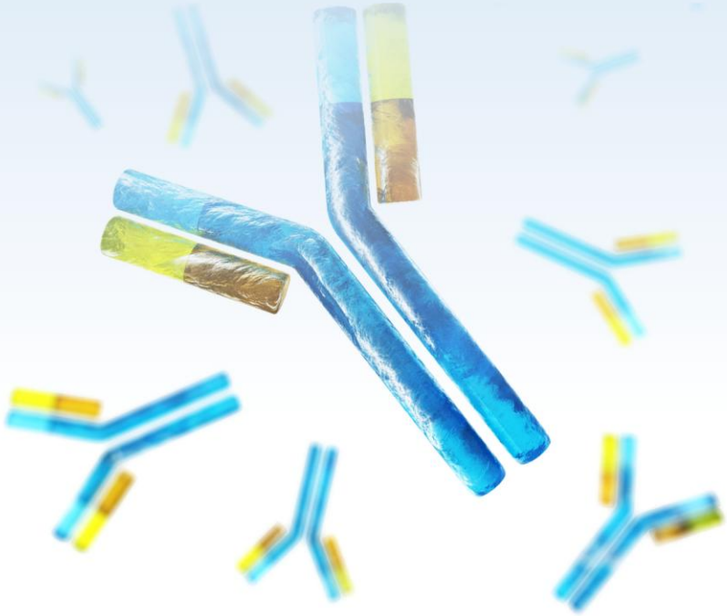
Source: Nat Med. 2026 Mar 2. Bimagrumab plus semaglutide alone or in combination for the treatment of obesity: a randomized phase 2

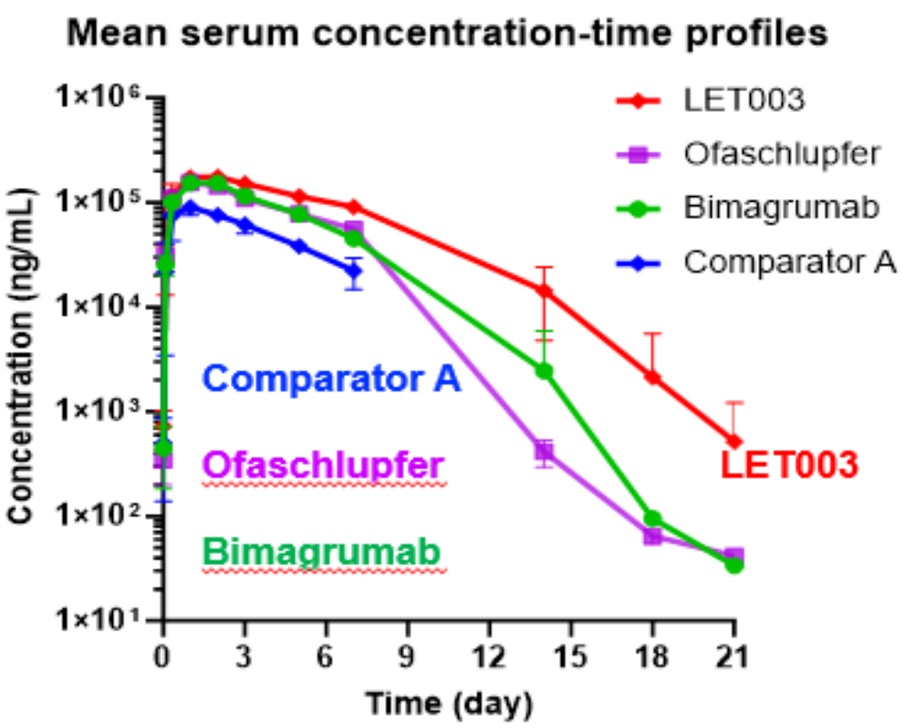
LET003 Has the Potential to Be the BIC ACVR2A/2B Blocker

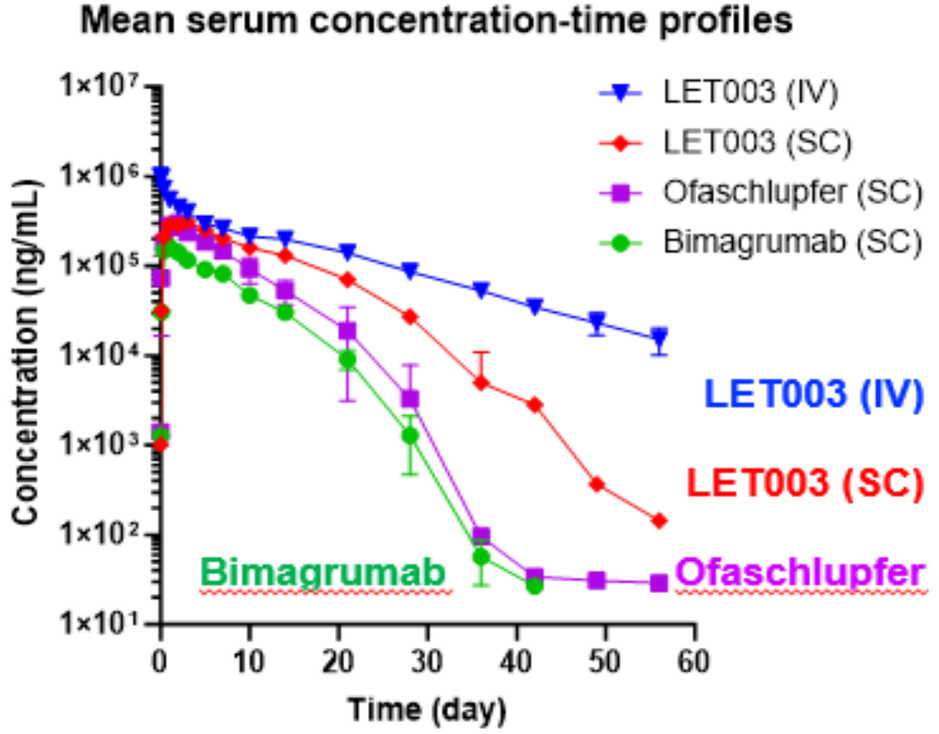
- **Extensive structure-based and Hu-mAtrIx™ AI platform-driven engineering**
- **Superior PK profile to Bimagrumab (Eli Lilly), Ofaschlupfer (Sixpeaks) and Comparator A in wild type mice, human FcRn mice, and cynomolgus monkeys**
- **Superior fat reduction or lean mass preservation in DIO mice and lean mice**



LET003 Has the Best PK Profile among All Tested ACVR2A/2B Blockers

Human FcRn KI Mouse	Cynomolgus PK





- The clearance rate of LET003 is the slowest among all disclosed ACVR2A/2B binders

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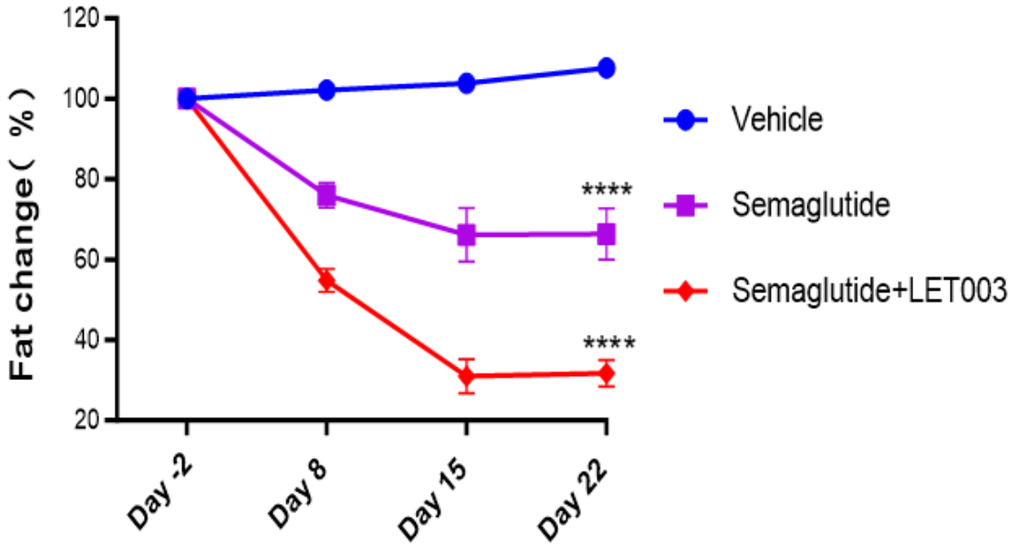
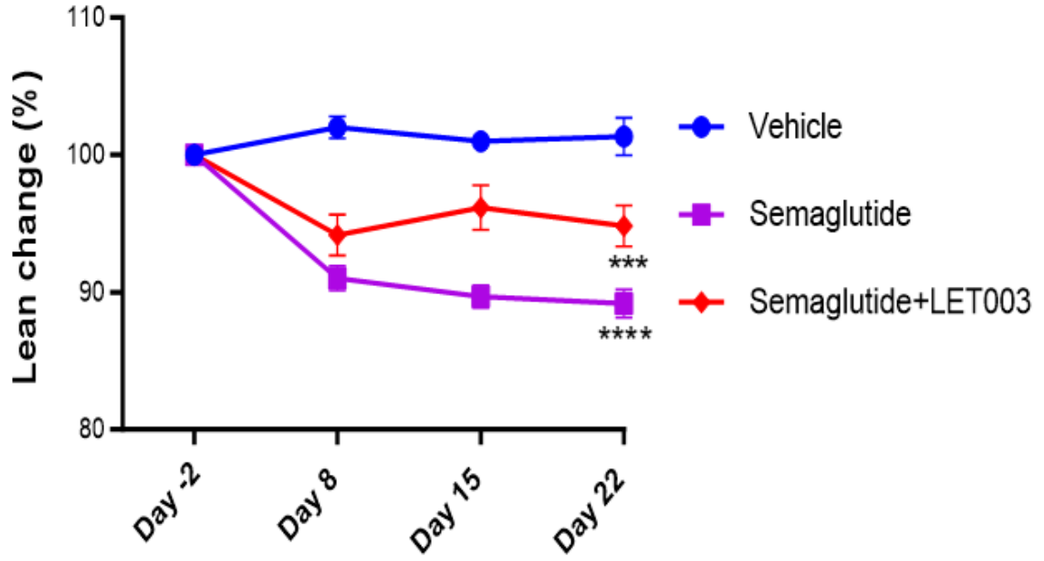
LET003 Shows Potent Efficacy when combining with Semaglutide in Reducing Fat Mass and Preserving Lean Mass

% Change of Fat Mass	% Change of Lean Mass





- Wild type mice received 30nmol/kg Semaglutide and 20 mg/kg antibody treatment via weekly subcutaneous injection
- Fat Mass decreased by 76.0% versus Vehicle (P<0.0001) and by 34.7% versus Semaglutide monotherapy (P<0.0001)
- Lean Mass decreased by 6.5% versus Vehicle (P=0.0001) but increased by 5.7% versus Semaglutide monotherapy (P=0.0007)

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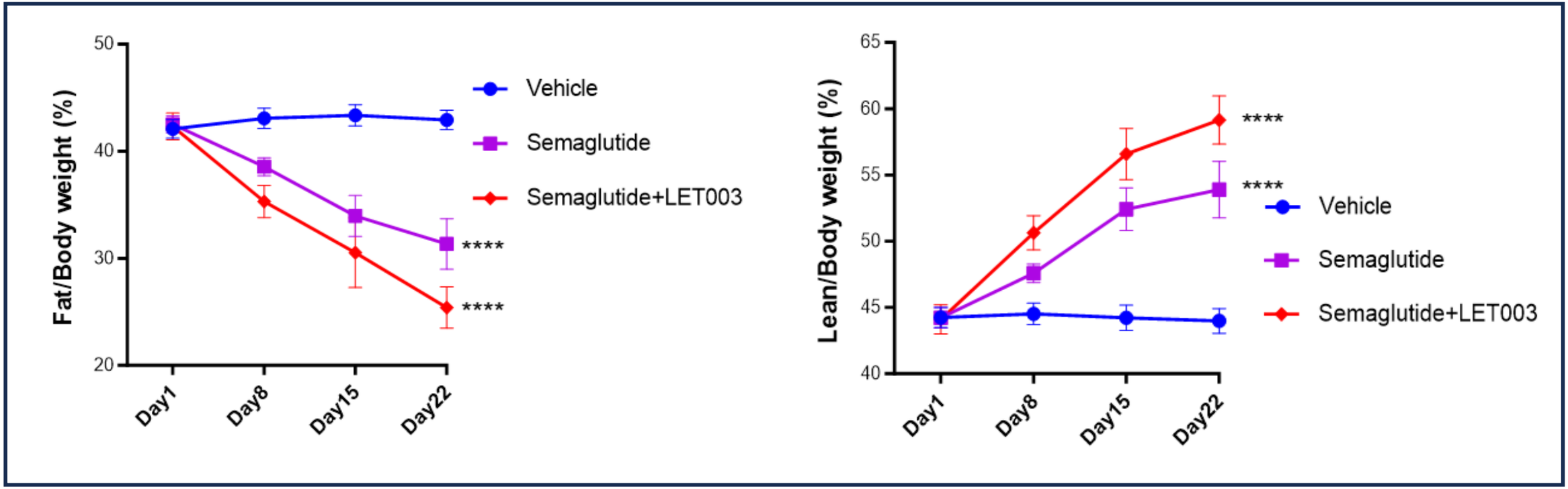
LET003 Shows Potent Efficacy when combining with Semaglutide in Reducing Fat Mass and Preserving Lean Mass

Fat Mass/Body Weight (%)	Lean Mass/Body Weight (%)



- hFcRn DIO mice received 30nmol/kg Semaglutide and 20 mg/kg antibody treatment via weekly subcutaneous injection
- Fat/body ratio decreased by 17.5% versus Vehicle (P<0.0001) and by 6.0% versus Semaglutide monotherapy (P=0.0127)
- Lean/body ratio increased by 15.2% versus Vehicle (P<0.0001) and by 5.3% versus Semaglutide monotherapy (P=0.0194)

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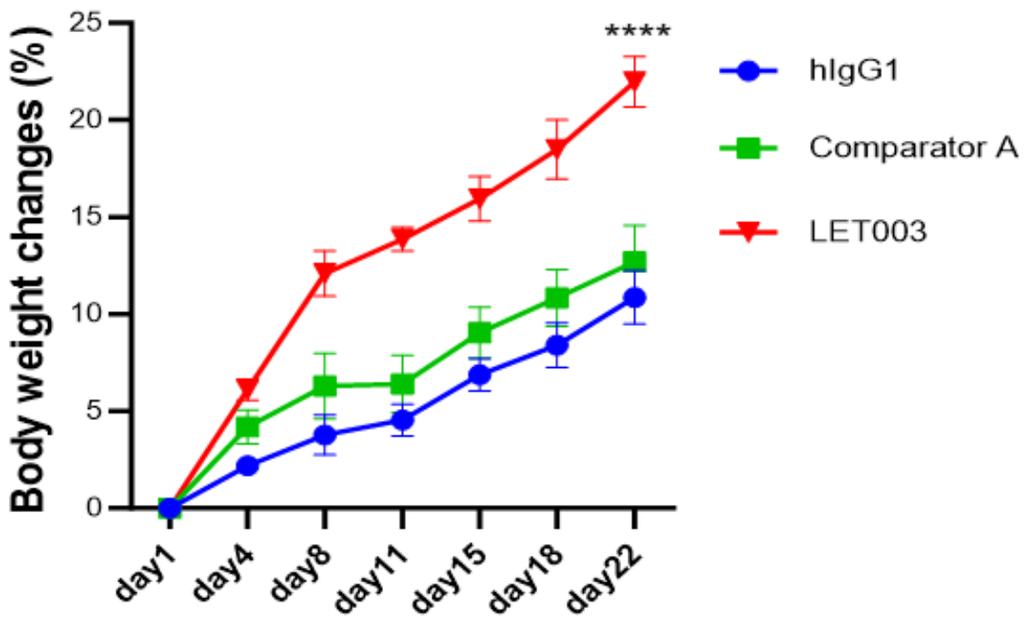
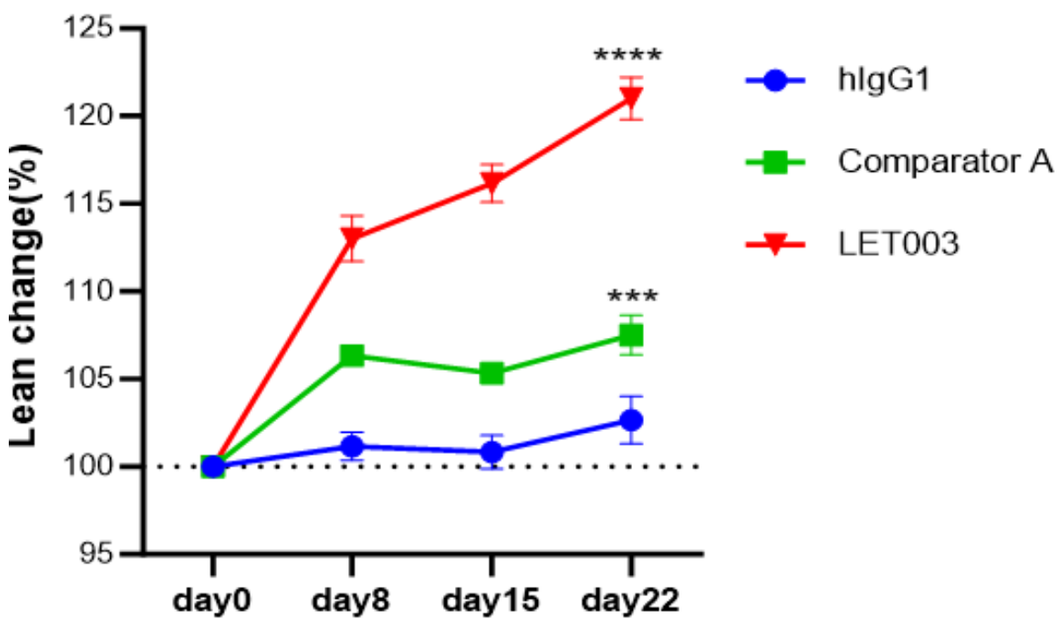
Note: Human FcRn Knock-In Mouse DIO Model

LET003 Shows Potent Lean Mass-Promoting Activity

% Change of Body Weight	% Change of Lean Mass





- Mice received 20 mg/kg treatment via weekly subcutaneous injection
- With normal diet feeding, lean mass growth contributes more than fat accumulation
- Body weight increased by 11.1% versus Isotype (P<0.0001) and by 9.3% versus comparator A molecule (P<0.0001)
- Lean mass increased by 18.3% versus Isotype (P<0.0001) and by 13.5% versus comparator A molecule (P<0.0001)

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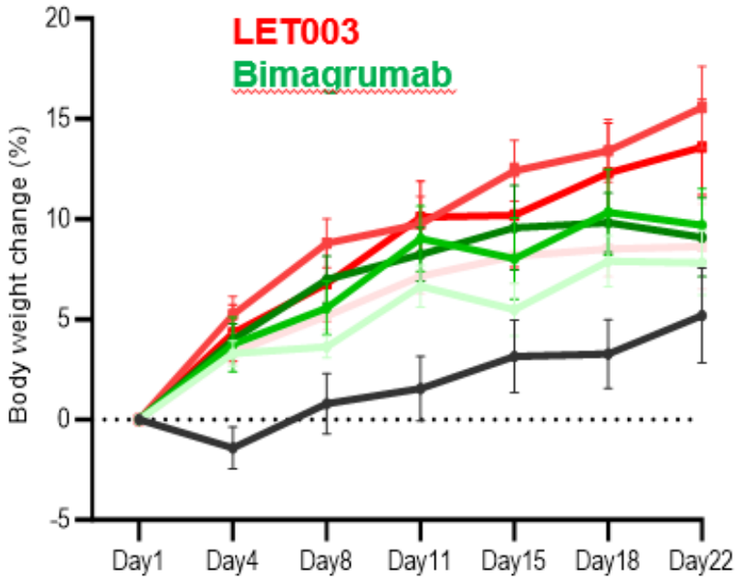
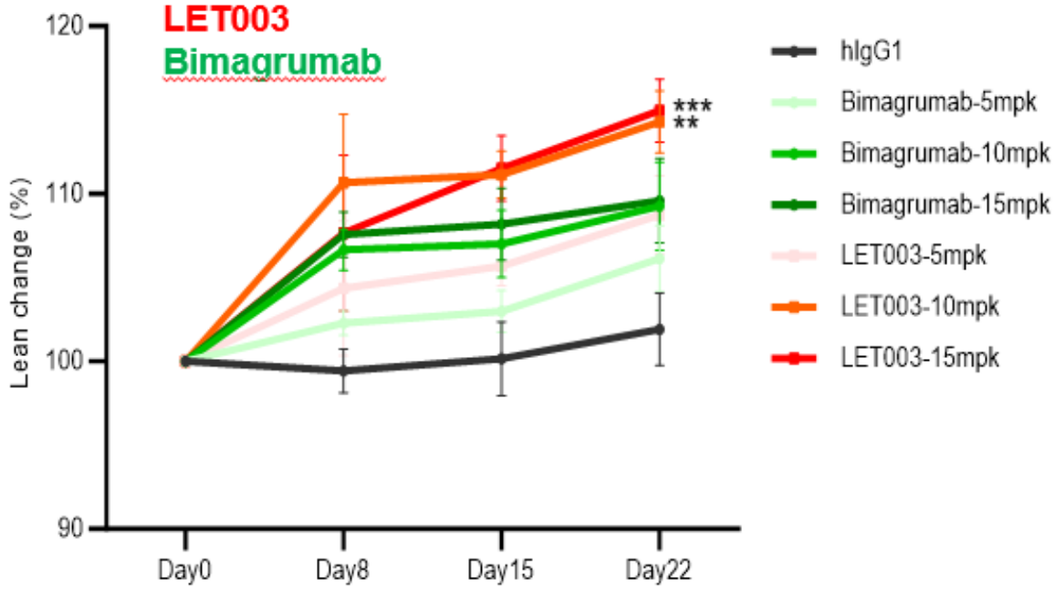
Note: Lean Mice, ie, Not DIO Mouse Model

LET003 Shows Potent Lean Mass-Promoting Activity

% Change of Body Weight	% Change of Lean Mass





- Mice received weekly subcutaneous injection at different dose levels
- With normal diet feeding, lean mass growth contributes more than fat accumulation
- Treatment with 5 mpk LET003 promoted lean mass to a comparable extent as 15 mpk Bimagrumab

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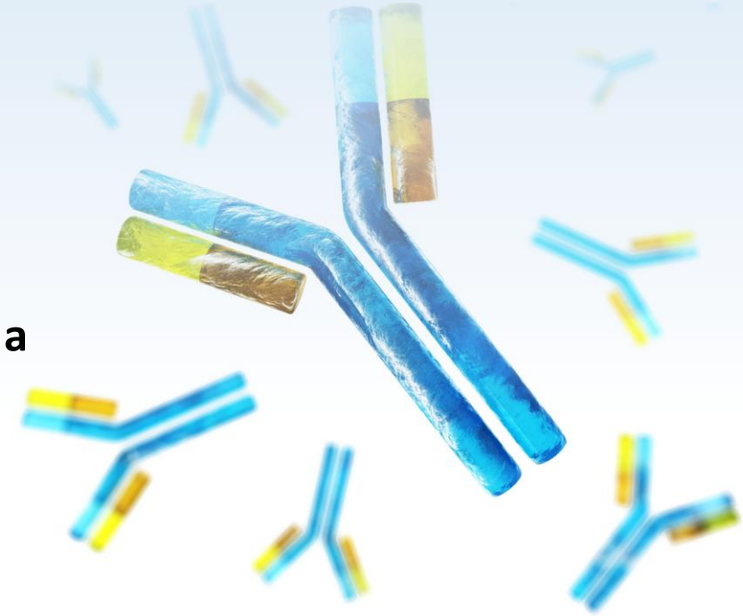
Note: Lean Mice, ie, Not DIO Mouse Model

Summary of LET003 Pre-clinical Data Readout

- LET003 shows a significantly improved PK profile in wild-type, hFcRn mice and cynomolgus monkeys, compared with competitors including Bimagrumab, Ofaschlupfer, Comparator A, etc.
- LET003 promotes more effectively gain of lean mass in lean mice fed on a normal diet
- LET003 exhibits superior efficacy in fat reduction and lean mass preservation in wild-type and hFcRn DIO mice
- LET003 exhibits superior developability
- LET003 is well tolerated in Rat and Monkey



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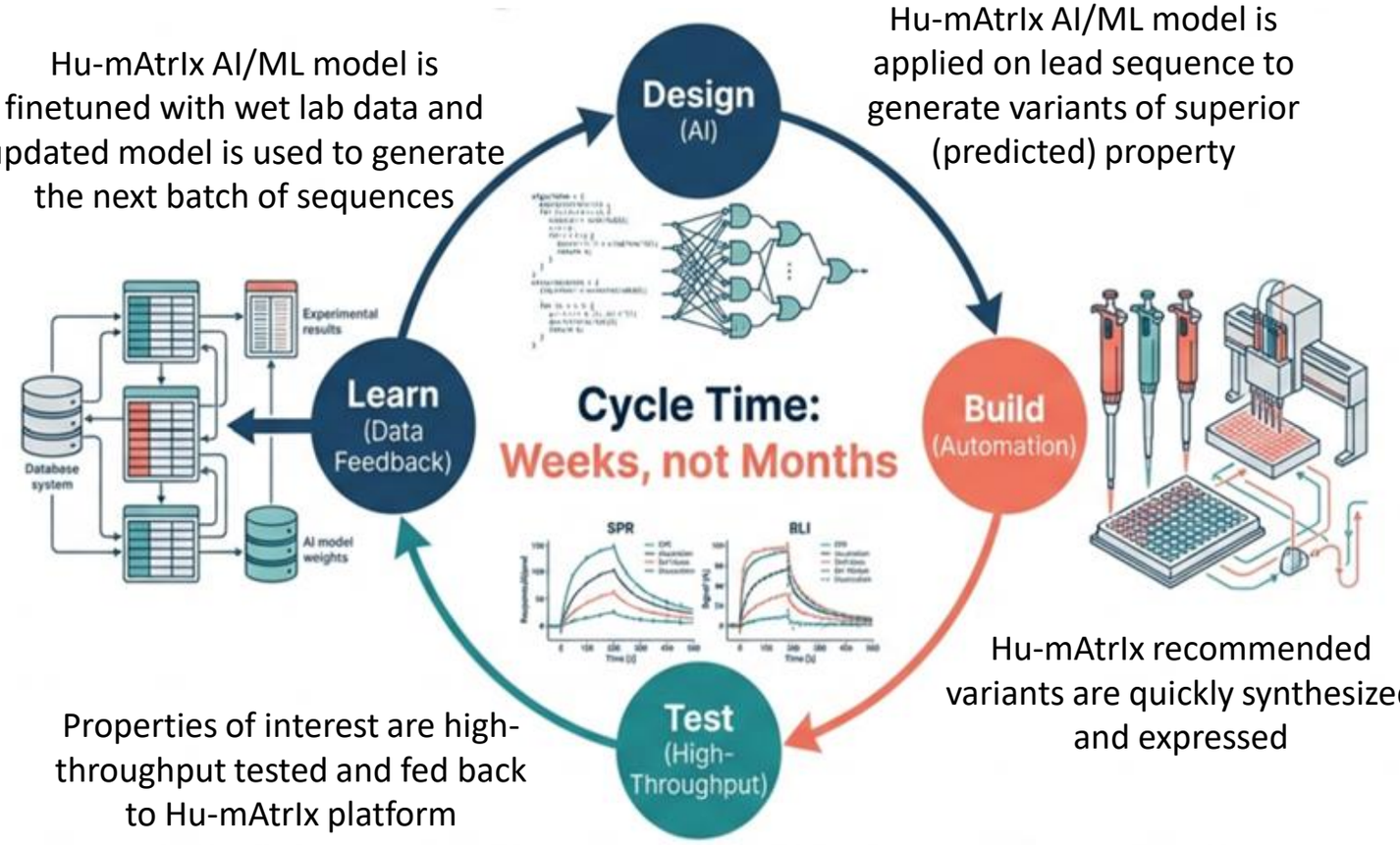
Hu-mAtrIx Engineering, Lab-in-the-loop Optimization

Hu-mAtrIx AI/ML model is finetuned with wet lab data and updated model is used to generate the next batch of sequences

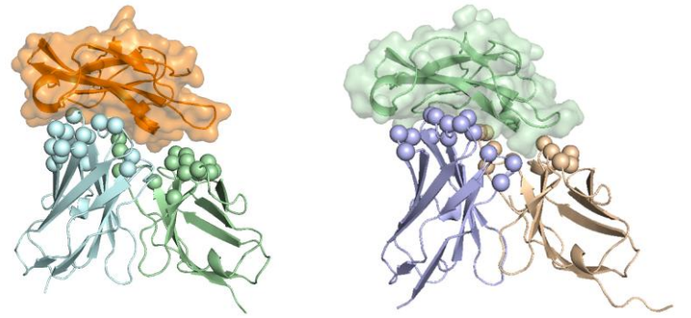
Hu-mAtrIx AI/ML model is applied on lead sequence to generate variants of superior (predicted) property



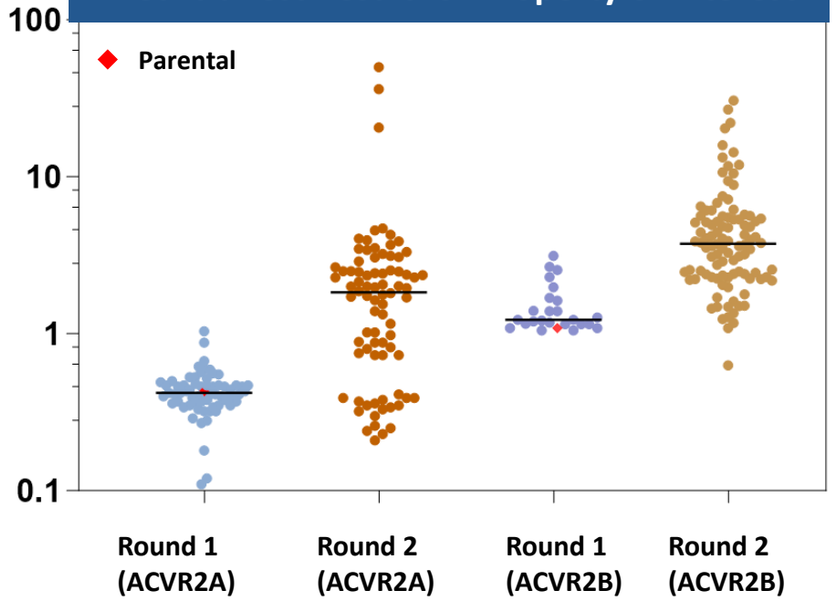
Hu-mAtrIx recommended variants are quickly synthesized and expressed

Properties of interest are high-throughput tested and fed back to Hu-mAtrIx platform

Structural Information Available



Wet Lab Test Result for Property of Interest



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