FL-501 Is a Potential Best-in-Class GDF-15 Inhibitor with Extended Half-life and Potent Anti-cachexia Activity in Preclinical Models

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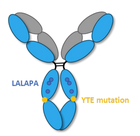
INTRODUCTION

- Cancer cachexia is a devastating syndrome characterized by unintentional weight loss, muscle wasting, fatigue, and severely reduced quality of life.
- This condition affects up to 80% of cancer patients and represents a major contributor to cancer-related mortality. [a,b]
- Despite its significant clinical impact, there are currently no approved FDA therapies for cancer cachexia.
- Growth Differentiation Factor-15 (GDF-15) is a promising therapeutic target for treating cancer cachexia. [c]

FL-501

FL-501 Is a Potential Best-in-Class Anti-GDF-15 Neutralizing Antibody

A.



B.

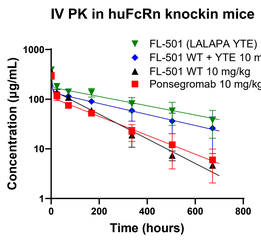
	FL-501	Visugromab	Ponsegromab
Affinity to hGDF-15	0.19 pM	~40x less	~2.5x less
Affinity to mGDF-15	0.69 pM	< 1000x less	< 100x less
GFRAL blocking	at ~1.25 nM	~2-3x less	~1.3x less

Engineered to demonstrate:
- **Extended half-life**
- **High affinity to GDF-15**
- **Silenced effector function**

Fig 1. Comparison of FL-501 with competitors.
A. Structure of FL-501 antibody with key mutations. **B.** Comparison of affinity measurements and competitive GDF-15 binding of FL-501 with benchmark antibodies, measured by SPR using Biacore 8K.

FL-501 Has an Extended Half Life in Comparison to Ponsegromab

A.



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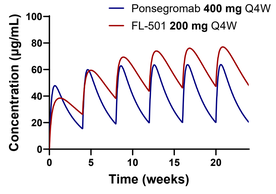


B.

	$T_{1/2}$ (days)	Cl (mL/kg/day)	V_z (mL/kg)
FL-501 (LALAPA YTE)	13.6 ± 6.1	3.0 ± 1.0	52 ± 12
FL-501 WT + YTE	12.2 ± 6.4	4.4 ± 1.6	66 ± 12
FL-501 WT	4.3 ± 1.0	8.2 ± 0.7	51 ± 10
Ponsegromab	6.2 ± 2.4	9.1 ± 2.0	77 ± 24

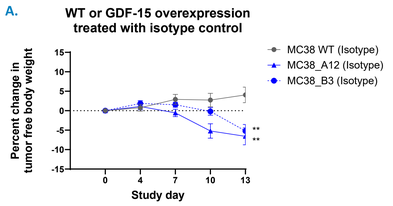
Fig 2. FL-501 has extended half-life in comparison to ponsegromab.
A. Serum concentration versus time curves following a single intravenous dose at 10 mg/kg ponsegromab (red square), FL-501 WT (black triangle), FL-501 WT + YTE (blue diamond), or FL-501 LALAPA YTE (green triangle) in humanized FcRn mice. Solid lines show the fit of the data to a 2-compartment model. **B.** Half-life ($T_{1/2}$), Clearance (Cl), and Volume of distribution (V_z) (all reported as Mean ± SD) obtained from non-compartmental fit of the mouse data. The half life of FL-501 (LALAPA YTE) compared to FL-501 WT is increased and the clearance is decreased, consistent with incorporation of the YTE mutation in the Fc region. **C.** Simulated human drug concentration versus time curves for ponsegromab dosed Q4W at 400 mg (blue) or FL-501 dosed Q4W at 200 mg (red). Simulations are based on 2-compartment models for ponsegromab and FL-501 based on data from hFcRn mice with allometric scaling of individual parameters to human.

METHODS & RESULTS

FL-501 Blocks GDF-15 Induced Body Weight Loss in a Murine Tumor Model

MC38 Clone A12 : High GDF-15 expression
MC38 Clone B3 : Moderate GDF-15 expression

A.



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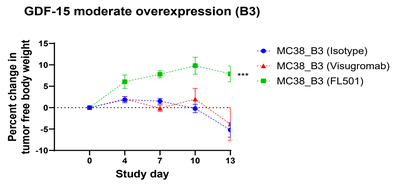

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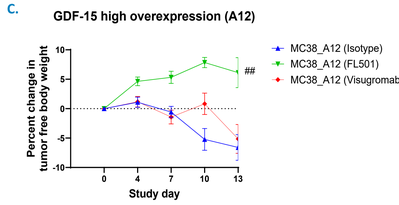
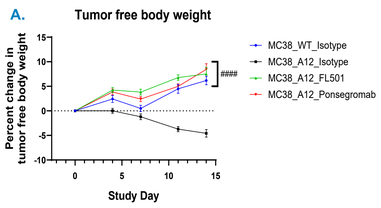


Fig 3. Human GDF-15 overexpression in murine tumors induces body weight loss which is restored by treatment with FL-501.
Murine MC38 cells were engineered to express human GDF-15, with clone A12 expressing higher levels compared to clone B3. Wild-type MC38 cells (no GDF-15 expression) were used as a control. These cells were injected subcutaneously into female C57BL/6 mice aged 6-8 weeks (n=10 per group). Treatment began when tumors reached an average volume of 50mm³ (day 0), with test articles (IgG isotype control, FL-501, or visugromab) administered intraperitoneally at 20mg/kg, twice weekly (BIW). **A.** Body weight changes in tumor-bearing mice treated with IgG isotype control. **B.** Body weight changes in mice inoculated with MC38 clone B3 tumors and treated with test articles. **C.** Changes in body weight in mice inoculated with MC38 clone A12 in response to treatment with test articles.

**p < 0.01versus MC38_WT (Isotype); ***p < 0.001 versus MC38_B3 (Isotype); ##p < 0.01 versus MC38_A12 (Isotype); Data were analyzed using ANOVA with longitudinal mixed-effects and are represented as mean ± SEM.

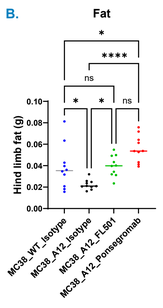
FL-501 Restores Body Composition in a Murine Tumor Model Overexpressing Human GDF-15

A.



Terminal Analysis

B.



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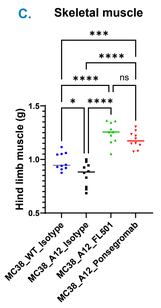

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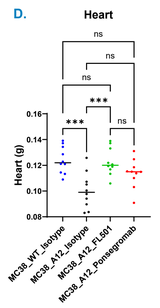
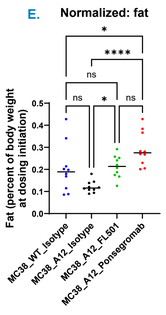


Body Weight Adjusted Terminal Analysis

E.



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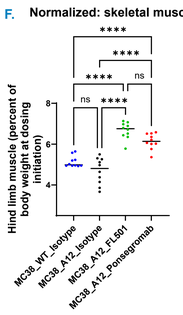

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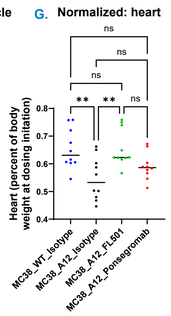
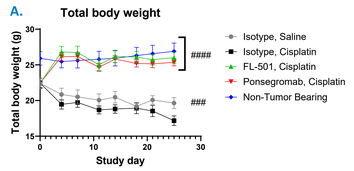


Fig 4. FL-501 demonstrates indicators of anti-cachexia activity in a murine tumor model overexpressing human GDF-15.
Murine MC38_clone A12 cells engineered to express human GDF-15 were injected subcutaneously into female C57BL/6 mice aged 6-8 weeks (n=10 per group). Treatment began when tumors reached an average volume of 50mm³ (day 0), with test articles (IgG isotype control, FL-501, or ponsegromab) administered intraperitoneally at 20mg/kg, twice weekly (BIW). **A.** Changes in tumor free body weight in animals in response to treatment. **B.** Weight of fat tissue within the hind limb of animals at time of euthanasia. **C.** Weight of hind limb skeletal muscles at time of euthanasia. **D.** Heart weight at time of euthanasia. **E-F.** Weight normalized to body weight of animals at time of dosing initiation.

p < 0.0001 versus MC38_WT_isotype; *p < 0.05, **p < 0.01,***p<0.001 ****p < 0.0001; ns= nonsignificant. Data were analyzed using ANOVA, comparison of tumor volume and body weight changes with longitudinal mixed-effects ANOVA. Data in (A and H) represent mean ± SEM. Data in (B-G) are represented as scatter plots with a line at median.

FL-501 Restores Body Composition in a Therapeutic Model of Cancer Cachexia

A.



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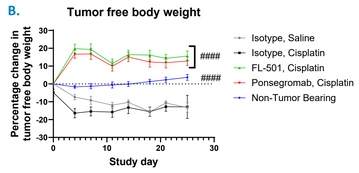

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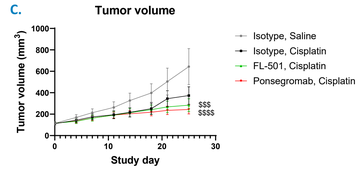
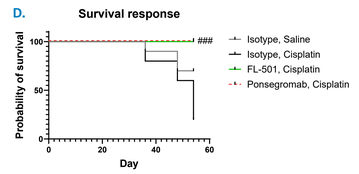
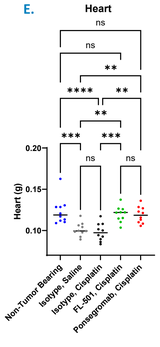


D.



Terminal Analysis

E.



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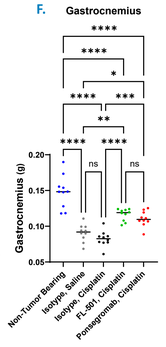

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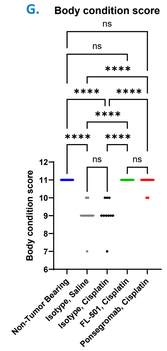
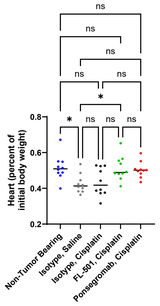
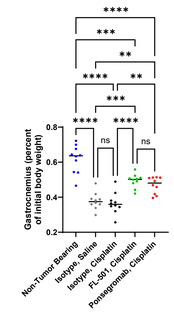


Body Weight Adjusted Terminal Analysis

H.



I.



J.

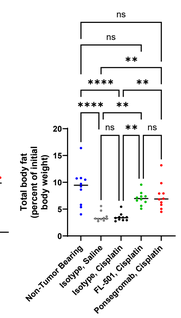


Fig 5. FL-501 reverses cachexia and improves survival in a therapeutic model of cancer cachexia.
LU5176 PDX model (Crown Biosciences) were inoculated subcutaneously into ICR scid animals. Once tumors reached a mean volume of 115mm³ and animals had lost 5-10% of body weight, the animals were randomized into treatment arms (day 0). Animals were administered IgG isotype control, FL-501, or ponsegromab intraperitoneally at 20mg/kg, twice weekly (BIW) and cisplatin was administered every 10 days at 5mg/kg. Non-tumor bearing mice were also included in the study, with each treatment group comprising of 10 animals. **A.** Total body weight of animals during the study. **B.** Changes in tumor free body weight in animals in response to treatment. **C.** Tumor volume in response to IgG, FL-501, ponsegromab and/or cisplatin treatment. **D.** Survival response in tumor-bearing mice treated with FL-501, ponsegromab, IgG, and/or cisplatin. **E.** Weight of heart at time of euthanasia. **F.** Gastrocnemius muscle weight at euthanasia. **G.** Body condition score, calculated as a score based on parameters of appearance, natural behavior, and provoked behavior. [d] **H-I.** Heart and gastrocnemius weight reported as a percent of initial body weight of the animal **J.** Total body fat measured by a DXA scan and reported as a percentage of initial body weight of the animal.

p < 0.001, #### p < 0.0001 versus Isotype, Cisplatin; $$$ p < 0.001, $$$$ p < 0.0001 versus Isotype, Saline; *p < 0.05, **p < 0.01,*** p < 0.001 ****p < 0.0001; Cisplatin; ns= nonsignificant. Data were analyzed using ANOVA, comparison of body weight changes with longitudinal mixed-effects ANOVA, and comparison of survival with Kaplan-Meier and log-rank test. Data in (A-C) represent mean ± SEM. Data in (E-F) and (H-J) are represented as scatter plots with a line at median.

CONCLUSIONS

- FL-501 is a novel GDF-15 neutralizing antibody engineered for high affinity and extended half-life. In humanized FcRn mouse studies, it demonstrated a 2-3-fold longer half-life and 50% reduced clearance compared to its wild-type precursor and ponsegromab.
- In mouse cachexia models using GDF-15-overexpressing colorectal cancer cells, FL-501 fully restored body composition, comparably or better than clinical-stage antibodies visugromab and ponsegromab.
- These results were validated in a non-small cell lung cancer xenograft model, where FL-501 effectively countered cisplatin-induced weight loss, restoring body weight, composition, and condition scores.
- These findings confirm GDF-15's role in cachexia and support FL-501's advancement to clinical development.

REFERENCES: **a.** Argiles, J. M. et al., Cancer cachexia: understanding the molecular basis. Nature Reviews Cancer, 14, 754-62 (2014). DOI: 10.1038/nrc3829 | **b.** Teunissen, S.C.C.M. et al., Symptom prevalence in patients with incurable cancer: a systematic review. Journal of Pain and Symptom Management, 34, 94–104 (2007). DOI: 10.1016/j.jpainsymman.2006.10.015 | **c.** Groarke, J.D. et. al., Ponsegromab for the treatment of cancer cachexia. The New England Journal of Medicine, 391, 2291-2303 (2014). DOI: 10.1056/NEJMoa2409515 | **d.** Rupert, J.E. et al., Tumor-derived IL-6 and trans-signaling among tumor, fat, and muscle mediate pancreatic cancer cachexia. Journal of Experimental Medicine, 218 (6): e20190450 (2021). DOI: 10.1084/jem.20190450

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