Cbi-Ex4 for the Treatment of Cancer Anorexia-Cachexia Syndrome

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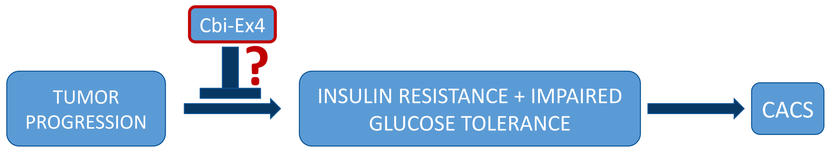
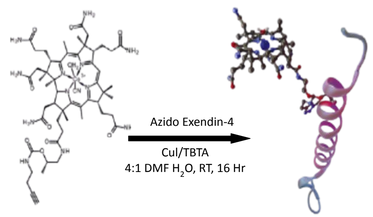
Introduction

Cancer Anorexia-Cachexia Syndrome (CACS) is highly prevalent in oncology patients but often goes untreated until closer to the end of life. CACS is characterized by many metabolic alterations including insulin resistance and reduced glucose tolerance, common in both cancer and type 2 diabetes. Due to the similarities in metabolic alterations, some FDA approved drugs could be repurposed to treat CACS.

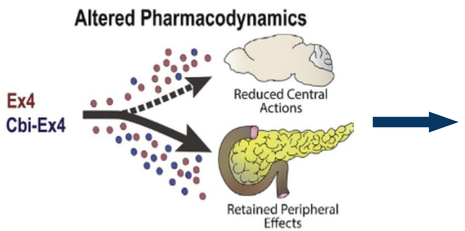


Unfortunately, one of the most efficacious drugs, Glucagon-like peptide-1 receptor (GLP-1R) agonist Exendin-4 (Ex4), causes nausea, vomiting, and unwanted anorexia that limit its applications in oncology patients. Our group developed a novel GLP-1R agonist conjugated with a precursor of vitamin B12 (Cbi-Ex4), that shows reduced brain penetrance while maintaining beneficial peripheral actions on glucose homeostasis, consequently lessening the severity and occurrence of nausea, emesis and anorexia.

Cbi-Ex4 Synthesis and Structure



Altered Pharmacodynamics



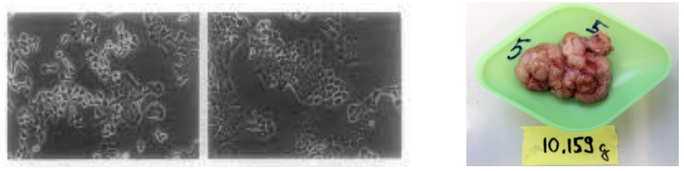
Glucoregulation
No nausea
No anorexia
No weight loss

Aims

1. Characterize the effects of chronic, daily doses of Cbi-Ex4 on malaise, anorexia, and body weight in healthy rats compared to the effects of equimolar doses of native Ex4.
2. Establish a rat tumor-bearing model to closely mimic CACS in humans.
3. Test the effects of Cbi-Ex4 on feeding and glucose metabolism in our tumor-bearing rat model *(ongoing studies)*.

Methods

- Chronic systemic injections (B.I.D., i.e. twice per day) of 3mg/kg Ex4 (positive control), Cbi-Ex4 (equimolar dose), and saline (negative control) at 0 and 6 hours post dark onset (n=7-8/group).
- Food intake, body weight, and kaolin consumption (established proxy of malaise in rats) were recorded daily.
- Glucose tolerance was assessed using the intraperitoneal glucose tolerance test (IPGTT).
- For tumor-bearing studies, in vitro cultured Morris-7777 hepatoma cells (10^7 cells/animal) were inoculated to induce subcutaneous tumor growth.



Hepatoma tumors become palpable and reach ~10-15g 3 weeks post-inoculation.

Results

Chronic delivery of Cbi-Ex4 improves glucose homeostasis without hypophagia or malaise

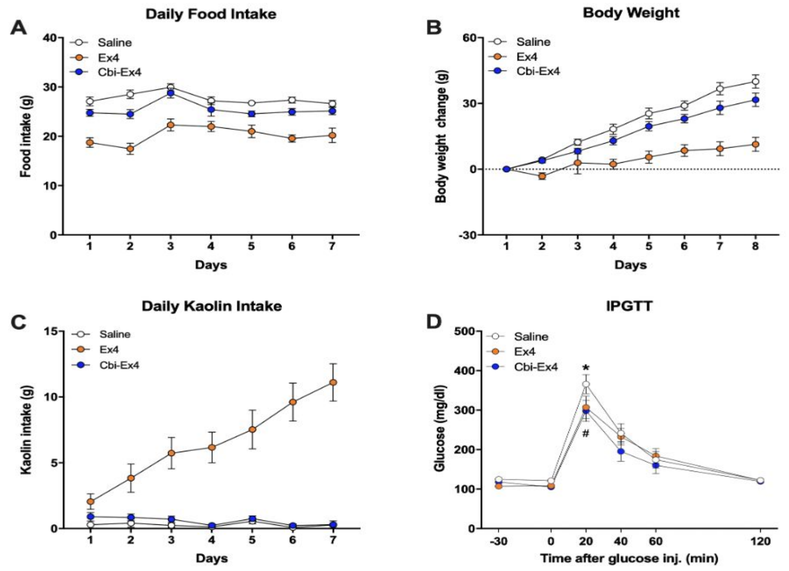


Figure 1: (A) *In contrast to Ex4 treatment, daily administrations of Cbi-Ex4 do not attenuate food intake.* ***(B)*** *Daily body weight changes during treatment show significant differences for Ex4 treated animals relative to saline and Cbi-Ex4 treated animals.* ***(C)*** *While Ex4 treatment induces profound kaolin intake (i.e. malaise), no increase in kaolin intake occurred following Cbi-Ex4 administration.* ***(D)*** *IPGTT performed on day 8 shows a similar improved glucose metabolism for both Ex4 and Cbi-Ex4, compared to saline-treated animals. n=7/8 per group. All data expressed as mean +/- SEM and analyzed with a 2-way ANOVA followed by Tukey post-hoc tests.*

Results

Tumor-bearing rats experience hypophagia, body weight loss, and reduced glucose metabolism

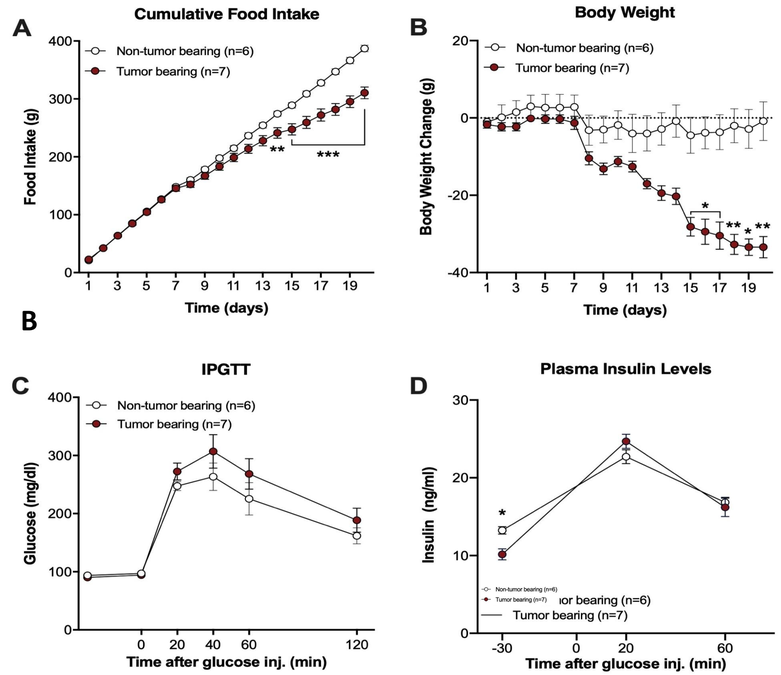


Figure 2: (A) *Tumor-bearing animals show an attenuation in food intake compared to controls ~10 days after cell inoculation.* ***(B)*** *Tumor-induced anorexia was paralleled by progressive body weight loss.* ***(C)*** *Tumor-bearing animals show a trend towards impaired glucose regulation during an IPGTT (2 g/kg, IP, injected at t = 0) compared to controls.* ***(D)*** *Tumor-bearing animals show reduced baseline insulin levels compared to controls. n=6-7 per group. All data expressed as mean ± SEM and analyzed with repeated measures two-way ANOVA followed by Siddak's post-hoc test.*

Conclusion & Outlook

Chronic Cbi-Ex4 delivery successfully mitigated hypophagia and malaise typically induced by native Ex4, while retaining its beneficial glucoregulatory properties.

- Food intake and body weight were significantly higher in the Cbi-Ex4 treated group relative to Ex4.
- In contrast to Ex4, kaolin consumption was absent following chronic delivery of Cbi-Ex4.
- These differences are not a consequence of a general lack of effect because the beneficial effects on glucose homeostasis remained, displayed by IPGTT results.

Current ongoing studies seek to investigate Cbi-Ex4's efficacy in ameliorating glucose metabolism without negative side effects in a tumor-bearing model. Further implications involve establishing a model that simulates a human model of CACS.