

PRE-CLINICAL STUDIES OF A NOVEL ORALLY DELIVERED ANOREXIGENIC PEPTIDE

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Unigene Business Models Are Driven By Peptide Expertise: Parallel Pathways To Success

Unigene Dual Business Model

Peptide Technology Platforms

- **Secrapep™**
 - r-DNA Peptide Manufacturing
- **Enteripep™**
 - Solid Dosage Oral Peptide Delivery
- **Nasapep™**
 - Nasal Peptide Delivery

Therapeutic Product Programs

- **Obesity**
- **Oral PTH (1-31)NH₂**
- **Oral Calcitonin**
 - Osteoporosis
 - Osteoarthritis
 - Rheumatoid Arthritis
- **Site Directed Bone Growth**
- **Annexin Peptides**

Multiple Unigene Strategic Partnerships



Unigene Technology Platforms Are Complimentary To Each Other

Enteripep™

Unigene's proprietary oral peptide delivery technology

Secrapep™

Unigene's proprietary recombinant peptide manufacturing process

Oral Peptide Products

PTH Analogs, Salmon Calcitonin, Satiety Peptides, Glucose Regulatory Peptides, etc.

Unigene's Enteripep™ Technology

Challenges for Oral Peptide Delivery

- Low absorption through the GI tract
 - Molecules with molecular mass greater than 300 (more than 2-3 amino acids) have limited bioavailability
 - Hydrophilic nature of peptides inhibits absorption
 - Mucosal layer of GI tract binds charged molecules such as peptides, inhibiting absorption
- Degradation of peptide in the digestive tract



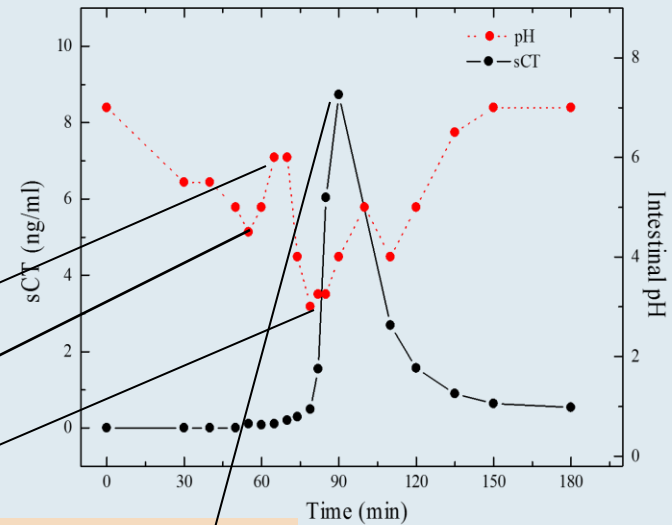
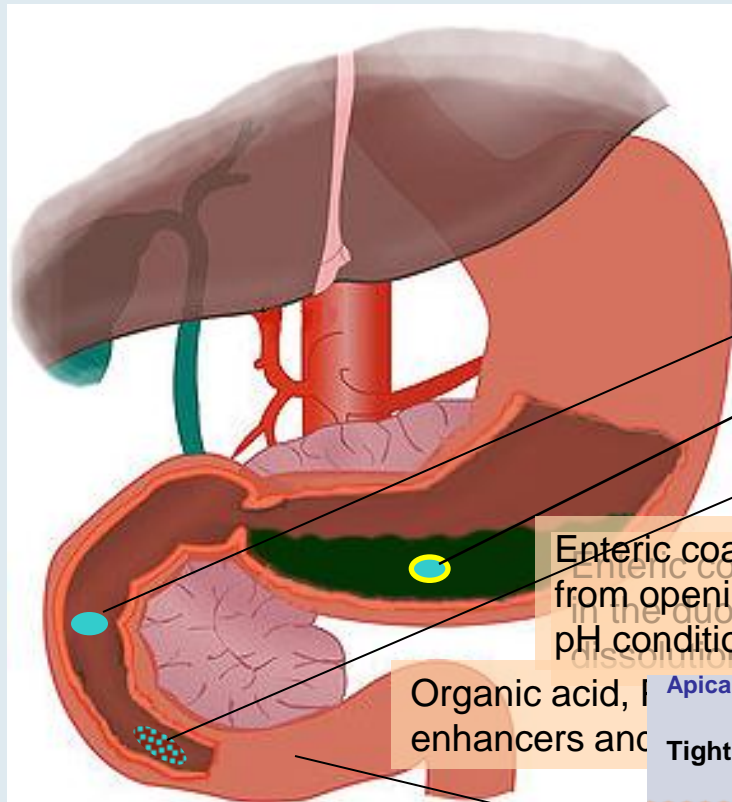
Oral Peptide Delivery with Enteripep™

- Enteric-coating permits passage through the stomach into the small intestine
- Organic acid inhibits proteases
- Absorption enhancer facilitates the uptake of the peptide by a paracellular transport mechanism
- Absolute bioavailability ranging from 1% to greater than 20% depending upon the peptide

Components of Unigene's Solid Dosage Oral Delivery Formulation

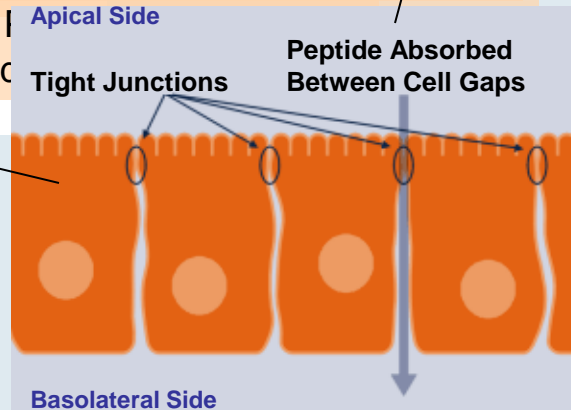
EXCIPIENT	FUNCTION
Satiety Peptide	Active Ingredient
Coated Citric Acid	Protease Inhibitor
Lauroylcarnitine	Absorption Enhancer
Nonionic Polymer	Subcoat
Eudragit L30D-55	Enteric Coat

Enteripep™ Oral Delivery Methodology

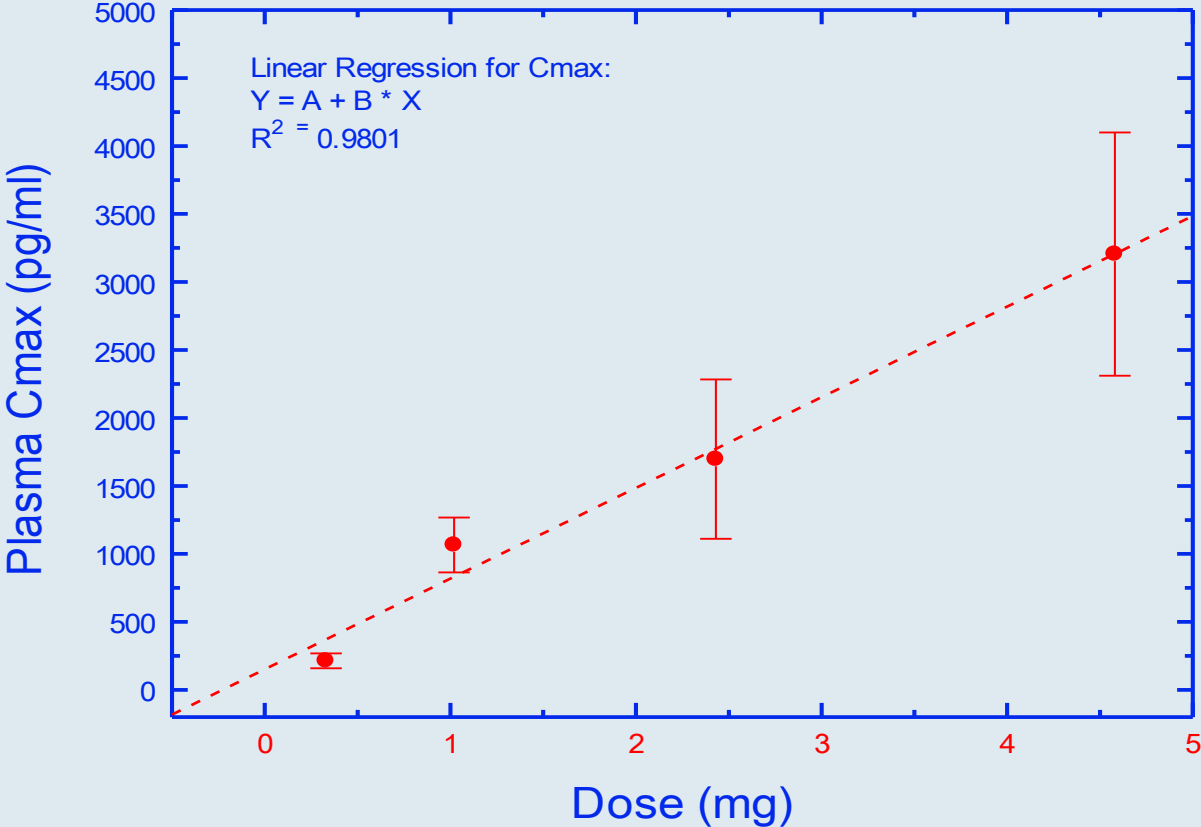


Enteric coated capsule prevented from opening in stomach under low pH conditions

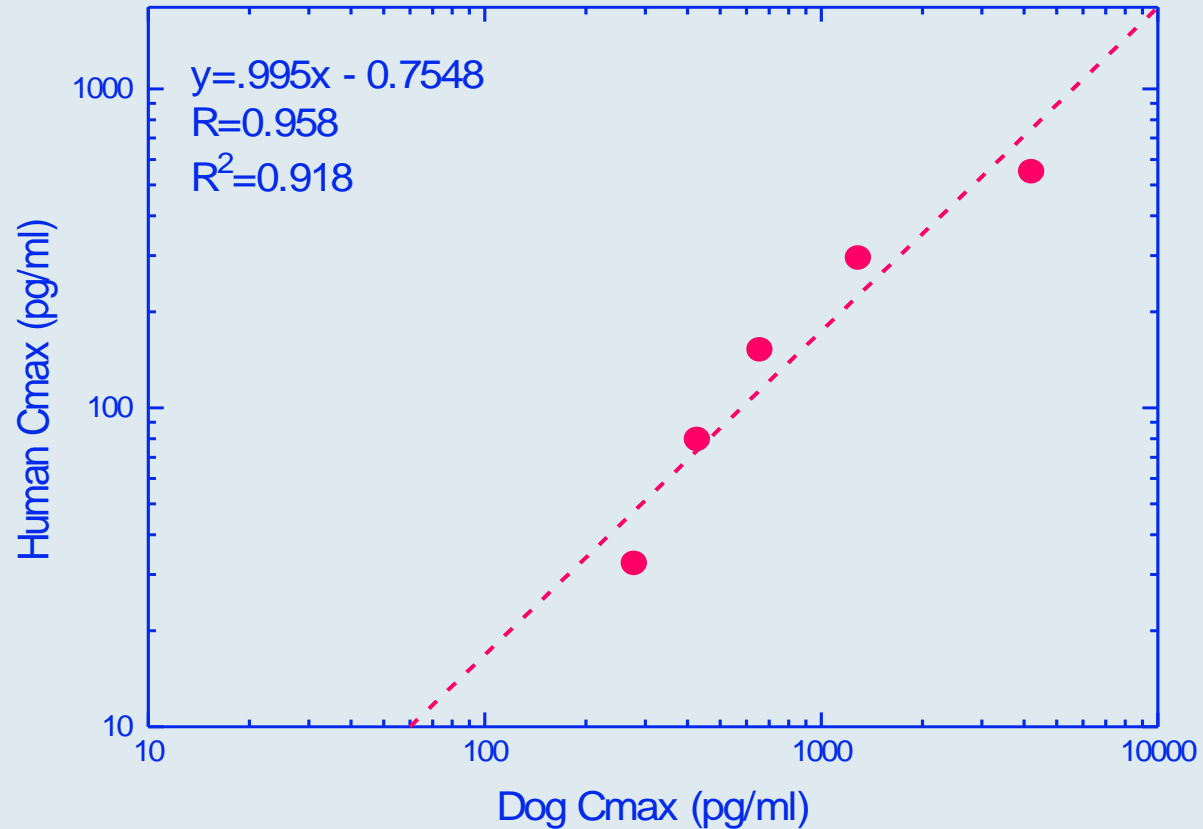
Organic acid, I
enhancers and



Oral Dosing in Dogs: Demonstration of Linearity with Respect to Peptide Dose



Correlation of Dog and Human Plasma sCT Levels

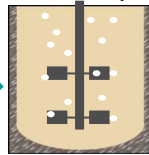


The Secrapep™ Peptide Manufacturing Platform

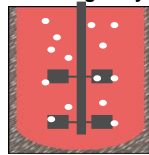
Secrapep™ Recombinant Peptide Manufacturing

Product of Interest is Secreted Directly into the Culture Medium

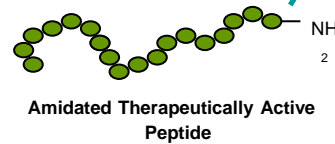
E. coli Expression of Glycine Extended Peptide



CHO Expression of α -Amidating Enzyme

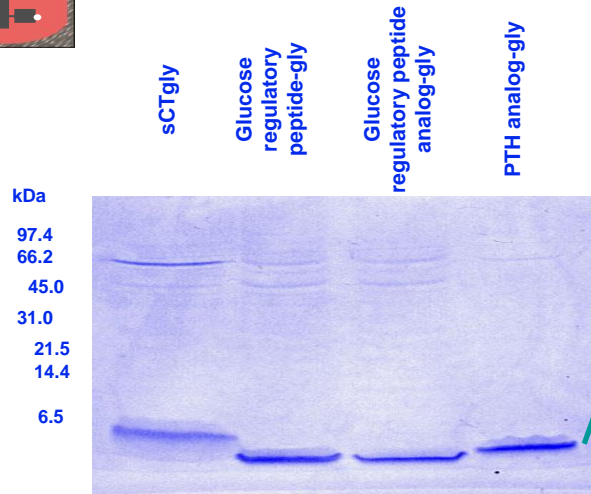


In-vitro Amidation of peptide



In-vitro Amidation

- Required for peptides that need C-terminal amide for activity
- Can enhance bioavailability for non-amidated peptides



SDS PAGE of Crude Medium

- Enriched Starting Material
- Extracellular yields of 400 to 1300 mg/L
- Reduced purification steps



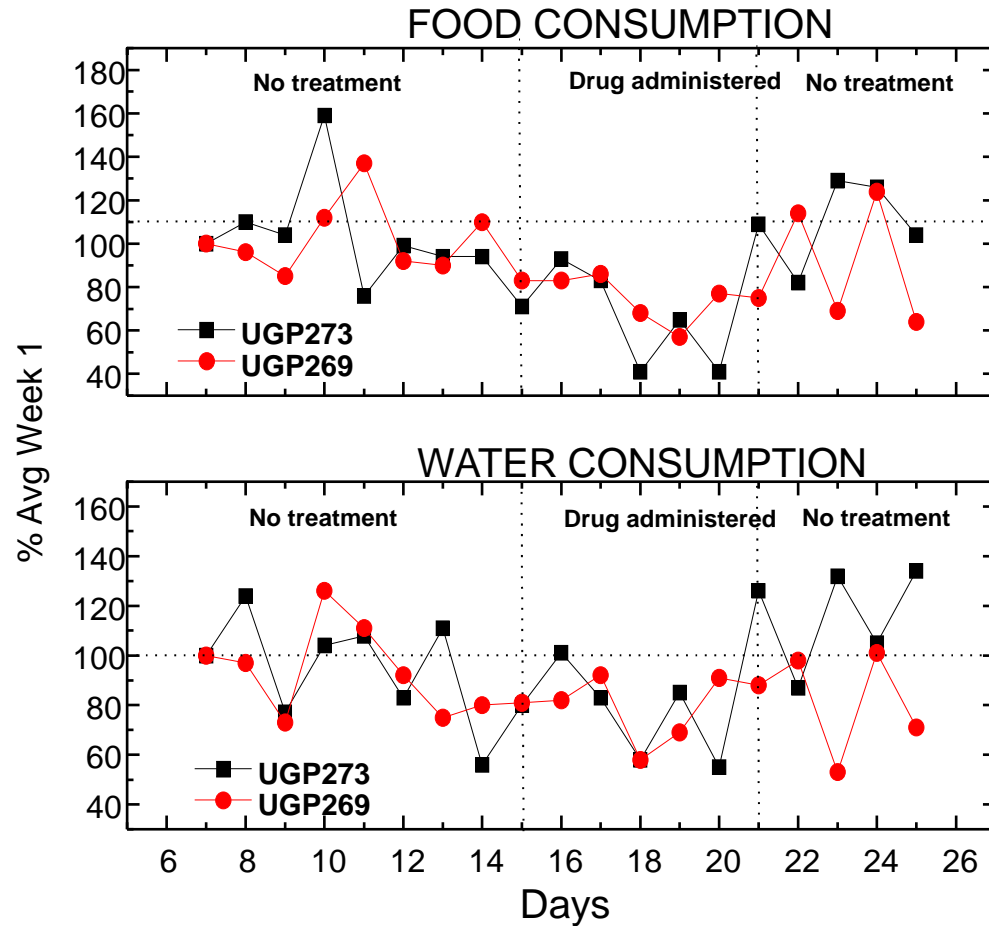
Unigene Satiety Peptide Program

- Unigene peptides are 30-40 amino acid analogs of naturally occurring peptides
- The peptides are agonists of a Class B GPCR
- The peptides contain all natural amino acids and can be made recombinantly using Unigene's Secrapep[®] recombinant expression system
- Unigene's Enteripep[®] oral delivery technology is applicable to these peptides and enables oral formulations of these peptides to increase patient acceptance and compliance
- Studies with first generation analogs (UGP269 and UGP273) demonstrated both decreased food consumption and weight reduction in dogs following oral administration
- Subsequent studies with additional analogs have been done primarily by intramuscular injections in a rat model

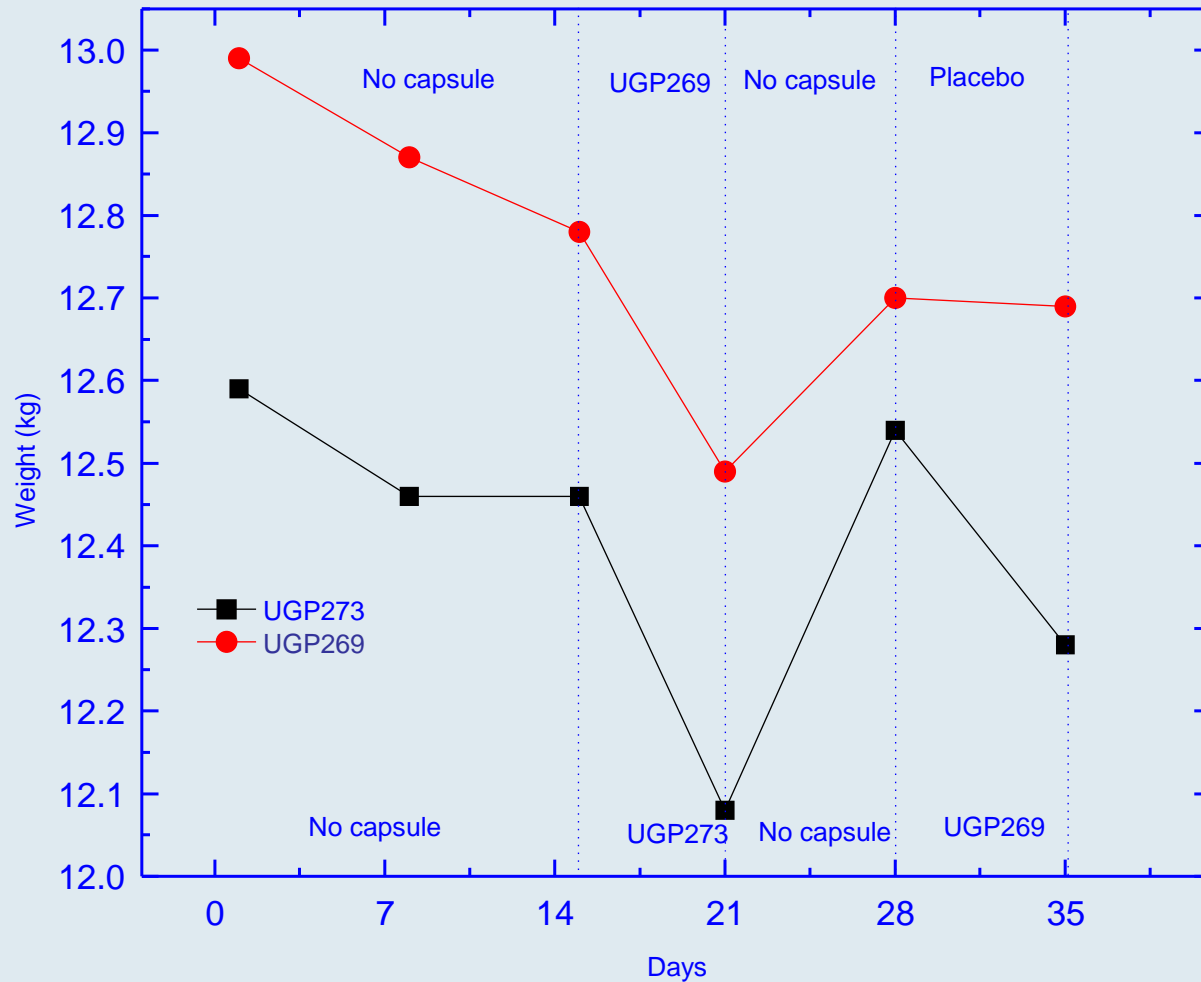
Dog Model to Study Feeding Behavior

- Dogs acclimated for at least 1 week to feeding from a bowl with 400 grams dried food in a bowl
- Dogs weigh between 10 and 14 kg and 1 dog is housed per cage
- Dogs fed between 8AM and 5PM
- For water consumption, dogs trained to drink from a bowl containing 1000 ml
- Water and food consumption monitored on a daily basis
- Dogs weighed once per week
- Each study used an equal number of male and female dogs.

Food and Water Consumption Following Oral Capsule Administration of UGP273 or UGP269 in Beagle Dogs



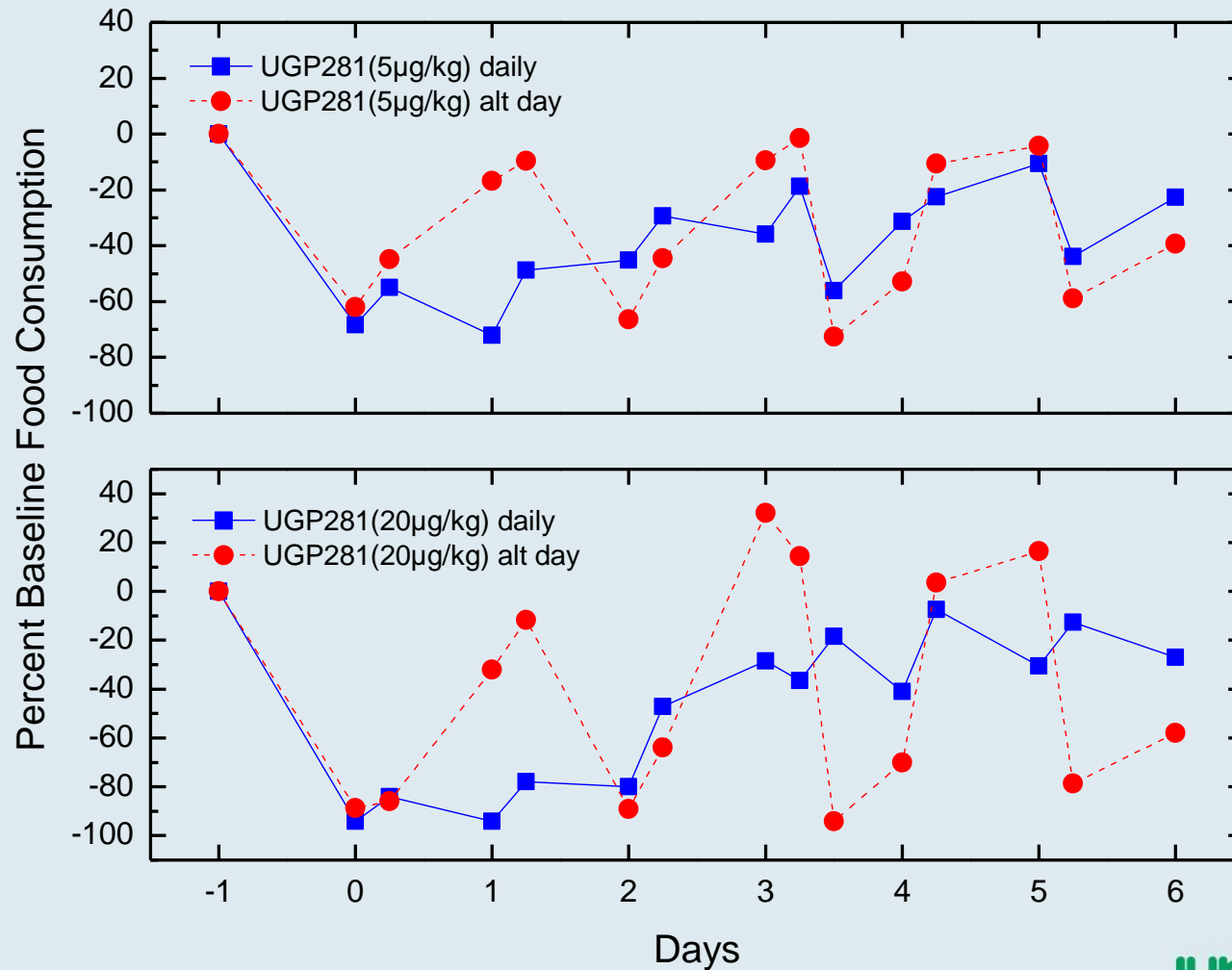
Weight Change Following Oral Capsule Administration of UGP273 or UGP269 in Beagle Dogs



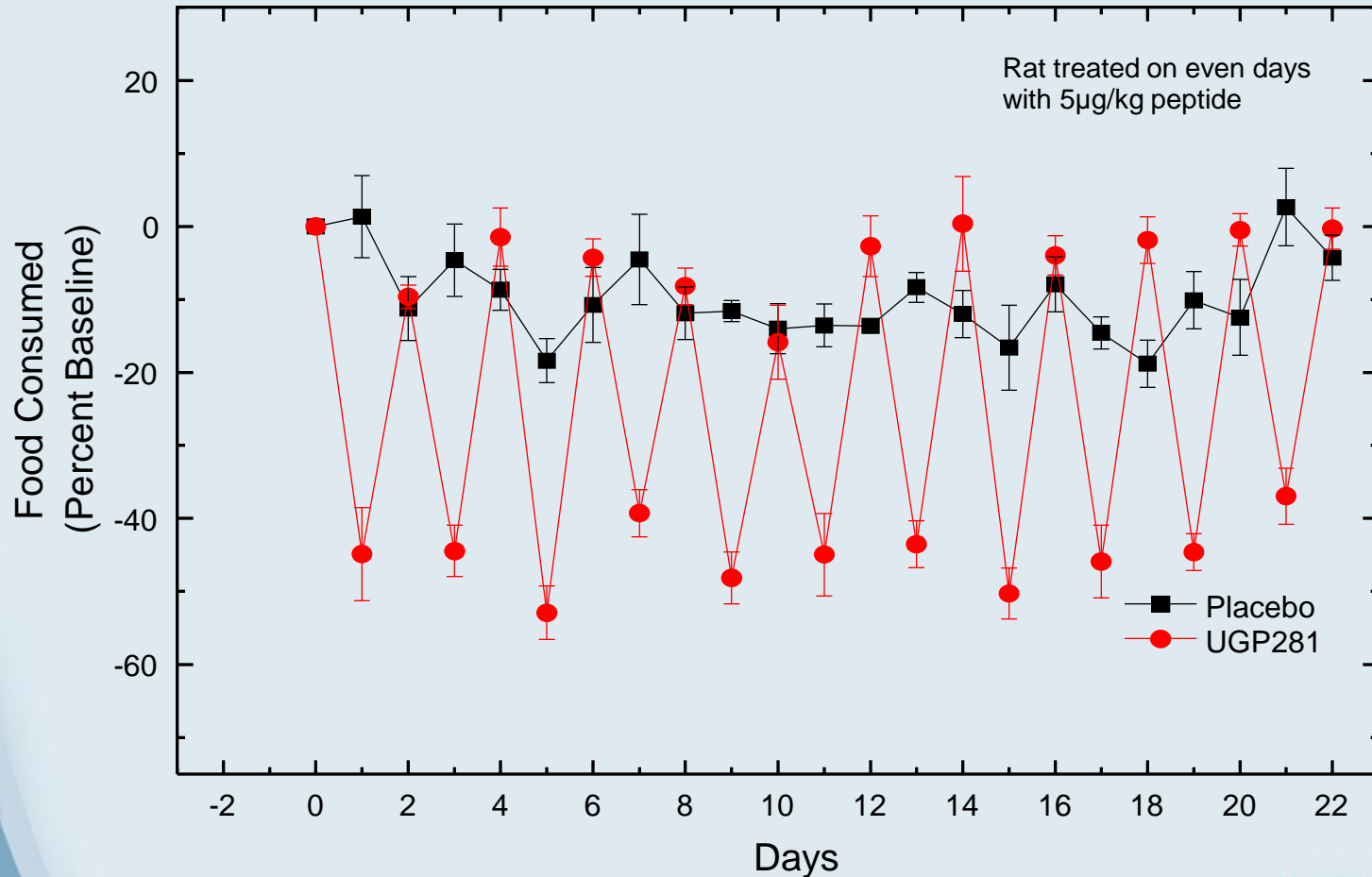
Rat Model to Study Feeding Behavior

- Sprague-Dawley rats with a mean weight of 206 grams were used at the beginning of the studies
- Rats acclimated to feed during the day
- Rats kept in individual cages
- Rats dosed by intramuscular injection in the morning
- Food and water consumption are monitored on a daily basis
- Rats are weighed daily or weekly depending on study
- Each group consists of 5 rats
- All studies have a placebo group that is injected with the vehicle

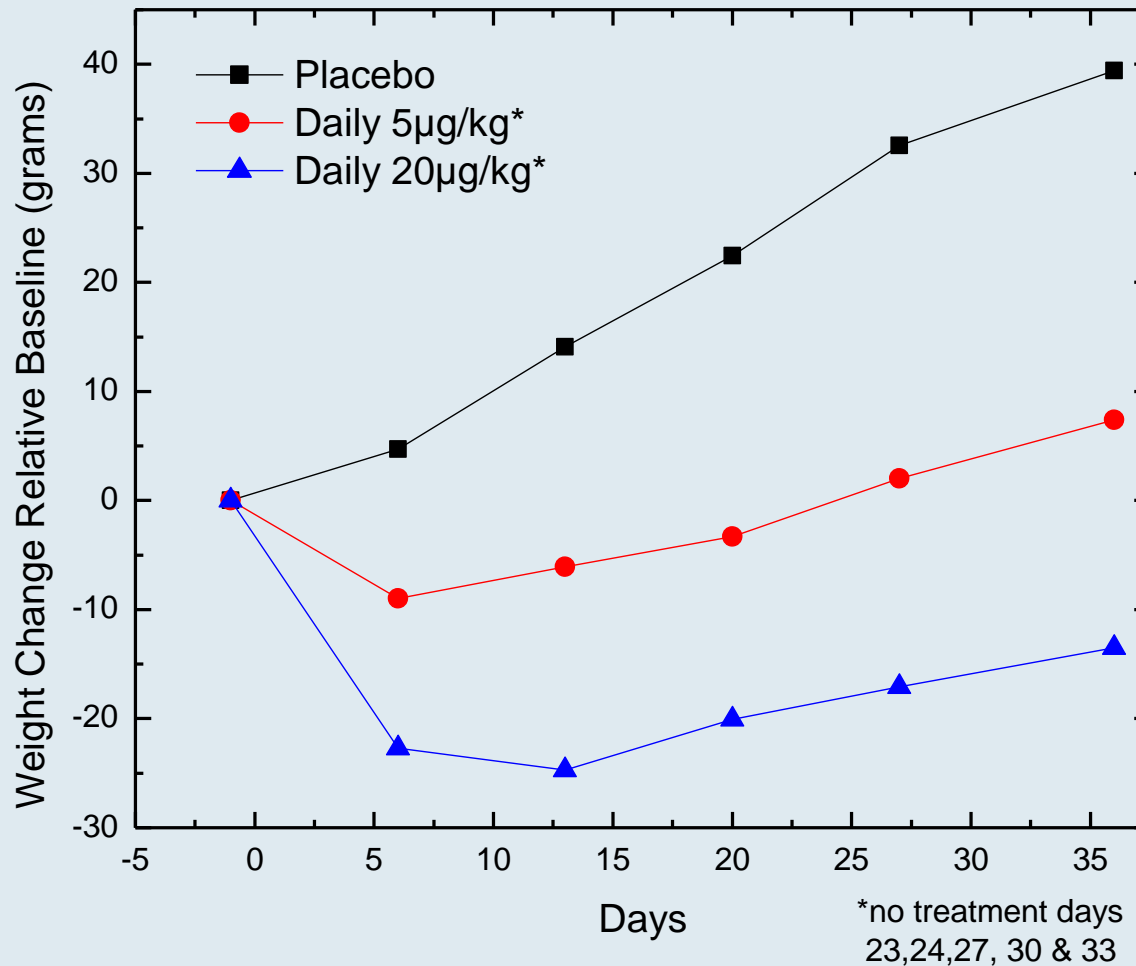
Daily or Alternate Day i.m. Administration of UGP281 on 6 and 24 Hr Food Consumption



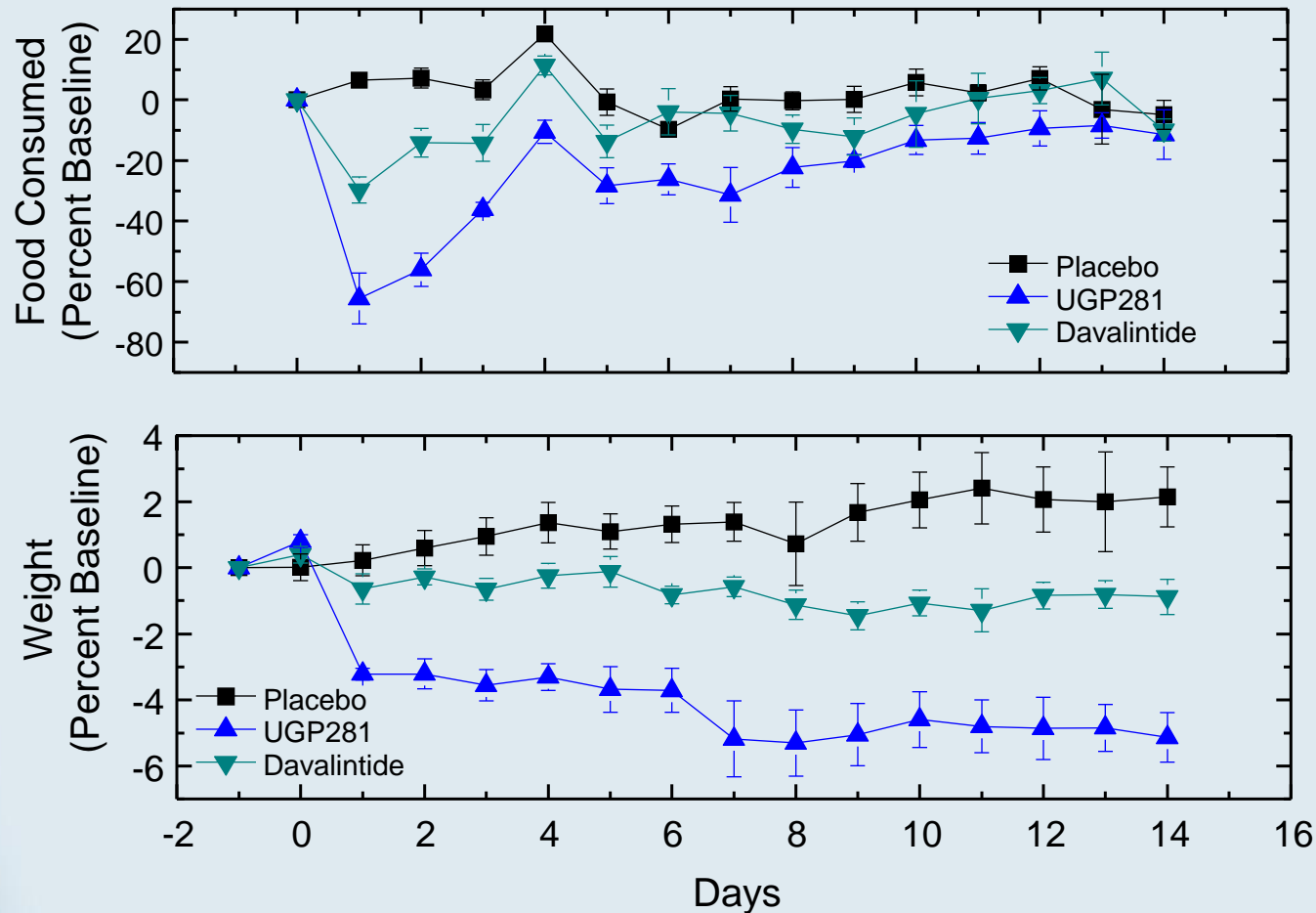
Effect of Low Dose (5 $\mu\text{g}/\text{kg}$), Alternate Day Injections of UGP281 on Food Consumption



Effect of UGP281 on Rat Body Weight After 36 Days of Daily i.m. Dosing



Effect of UGP281 and Davalintide on Food Consumption and Weight of Rats: Daily i.m. Dosing for 14 Days at 10 $\mu\text{g}/\text{kg}$



Summary of Obesity Program

- UGP281 is currently the lead compound, and in the rat model, has shown efficacy that is greater than that of Davalintide
- Daily dosing shows some evidence of tolerance after multiple days as far as reduction in food intake
- Weight loss remains consistent for the 4 week duration of the longest study
- Preliminary evidence suggests that oral dosing may show less evidence of tolerance
- Longer term oral studies with UGP281 in dog models have been initiated

Acknowledgements

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