

## Emerging Therapies for Intestinal Failure - Strategies from the Distal Gut


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## Messing's Principle's for Reducing Parenteral Nutrition Dependence

1. avoid exclusive or total parenteral nutrition as much as possible, and;
2. implement enteral nutrition as much as possible.

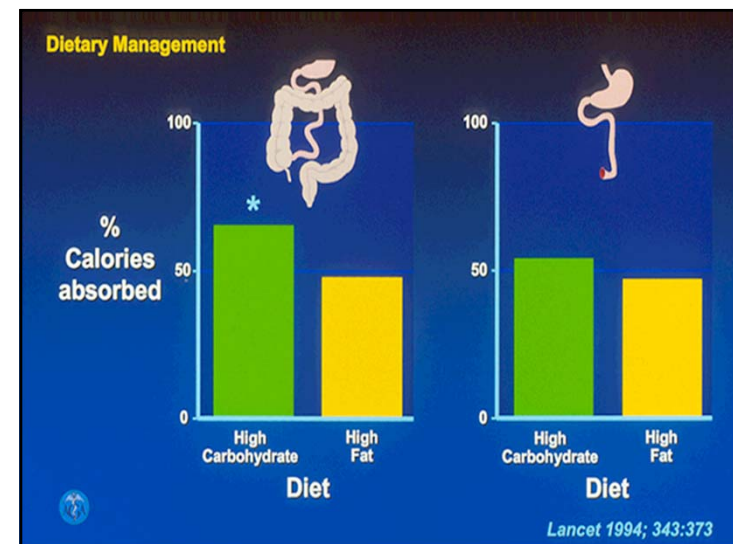
Messing and Joly, Gastro 2006;130:S43-S51.

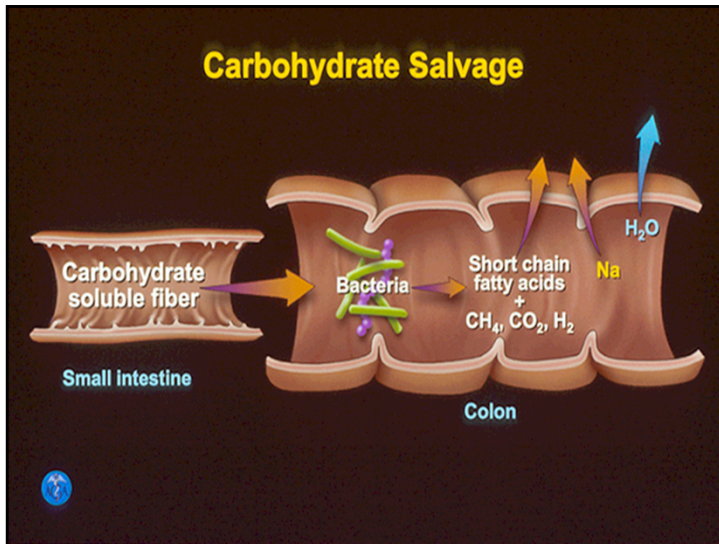


## Enteral nutrients are an important stimulus for regulating intestinal structure and function

1. Adaptive capacity of ileum > jejunum
2. Ileo-jejunal transposition induced ileal adaptation
3. Structural gradient of healthy intestine
4. Atrophy of bypassed intestine
5. Fasting impairs intestinal structure and function

How does the intestine recognize increased concentrations of specific nutrients in the intestine?  
 What is the mechanism for the 'workload hypothesis'?

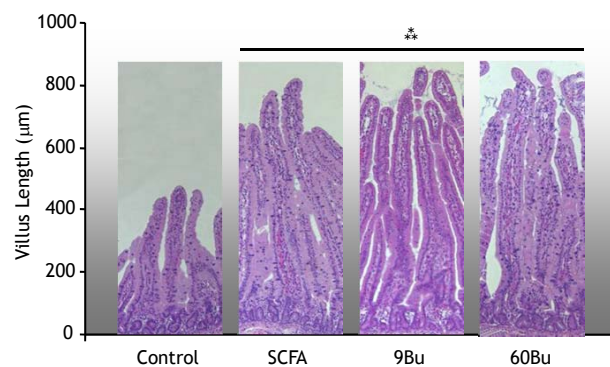




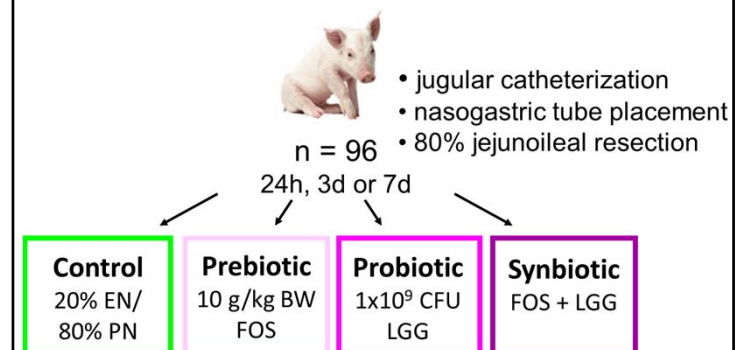
### Short Chain Fatty Acids

- Products of carbohydrate and protein fermentation
- Acetate, propionate, butyrate comprise 83% of SCFAs
- Enhance *structure* and *function* in adult rodent small intestine
  - ↑ mucosal proliferation in colon, ileum and jejunum (Sakata, 1987; Kripke et al., 1989; Koruda et al., 1990)
  - ↑ transporter activity (Tappenden et al., 1997, 1998; Tappenden and McBurney, 1998)
- PN-supplemented butyrate induced intestinal adaptation in neonatal piglets (Bartholome et al., 2004)

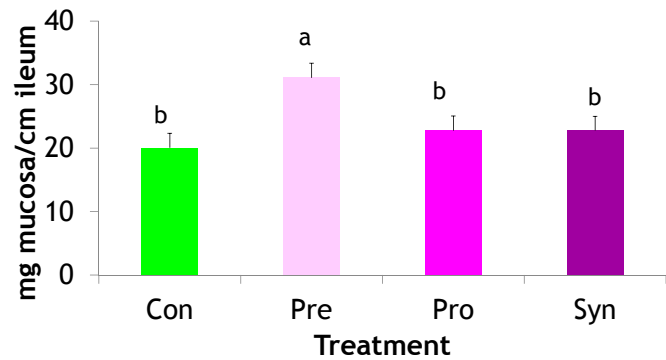
Regardless of time, ileal villus length increased by supplemented treatments.



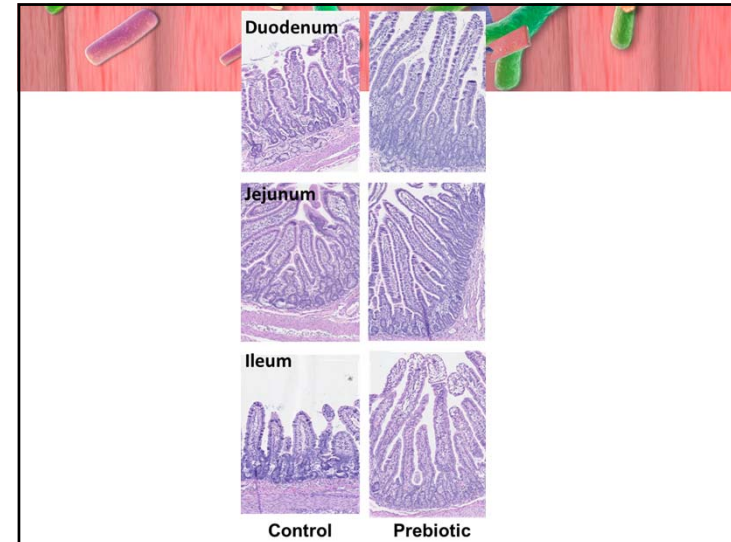
### Experimental Design



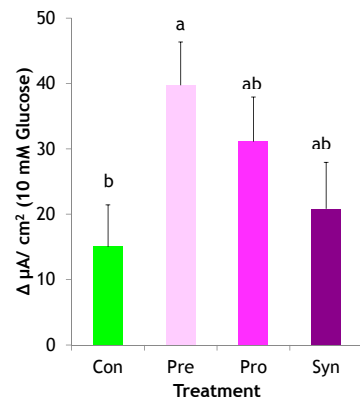
Ileum mucosal weight is increased by the prebiotic treatment, regardless of time



txt,  $p=0.005$ ; day,  $p<0.0001$ ; txt x day,  $p=0.163$

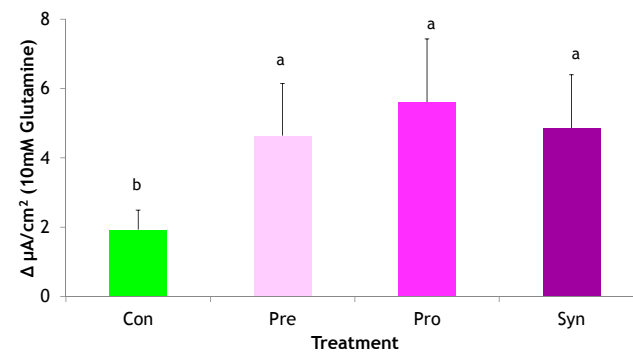


Prebiotic treatment increases glucose transport in the jejunum



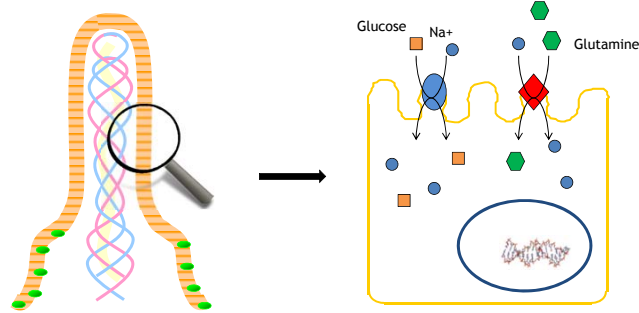
txt,  $p=0.042$ ; day,  $p=0.092$ ; txt x day,  $p=0.484$

All treatments increase glutamine transport over control in the colon



txt,  $p=0.013$ ; day,  $p=0.013$ ; txt x day,  $p=0.309$

## Summary from IF piglet work



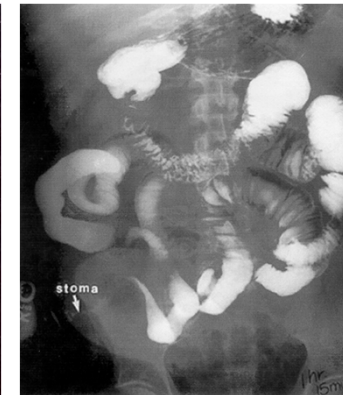
Prebiotic/Synbiotic treatment increased:

- Intestinal mass
- Mucosal weight
- DNA quantity
- Glucose and glutamine transport

## What about humans with intestinal failure?



Intact Gastrointestinal Tract

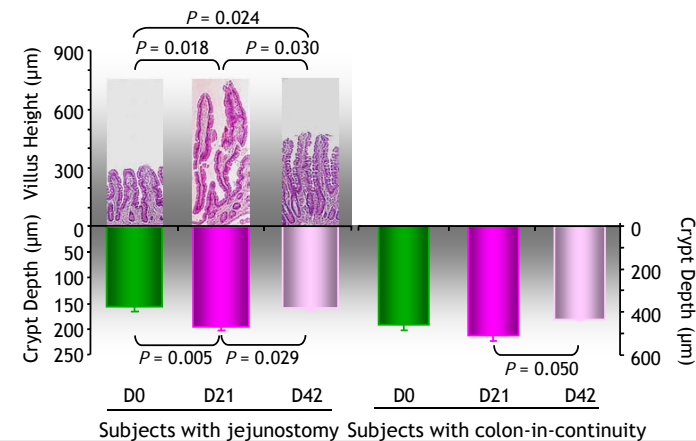


Short-Bowel Syndrome

## Glucagon-like peptide 2

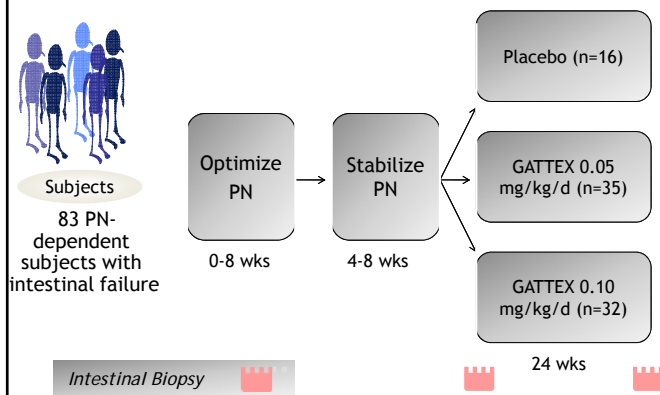
- Intestinotrophic peptide secreted from enteroendocrine L-cells (Drucker et al., 1996)
- Enhances *structural* and *functional* adaptations in adult small intestine
  - ↑ crypt-villus architecture (Drucker et al., 1996; Tsai et al., 1997)
  - ↑ enzyme and transporter activity (Brubaker et al., 1997; Cheeseman, 1997; Kato et al., 1999)
- Prevents parenteral nutrition-induced hypoplasia in adult and neonatal small intestine (Chance et al., 1997; Burrin et al., 2000; Peterson et al., 2000)
- GATTEX, a GLP-2 analog, completed Phase III clinical trials with parenteral nutrient/fluid dependent subjects with SBS

## GLP-2 analog increases jejunal villus height and crypt depth

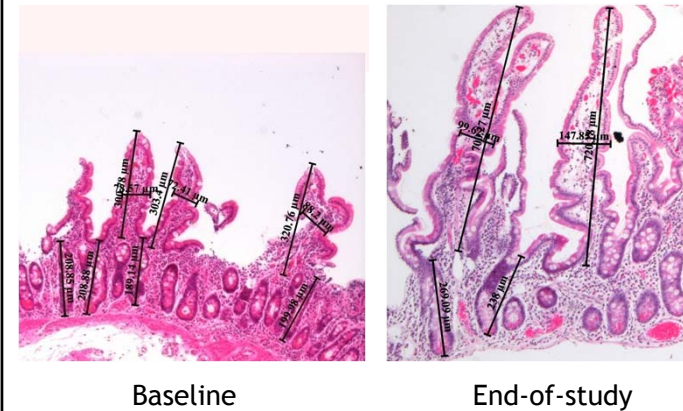




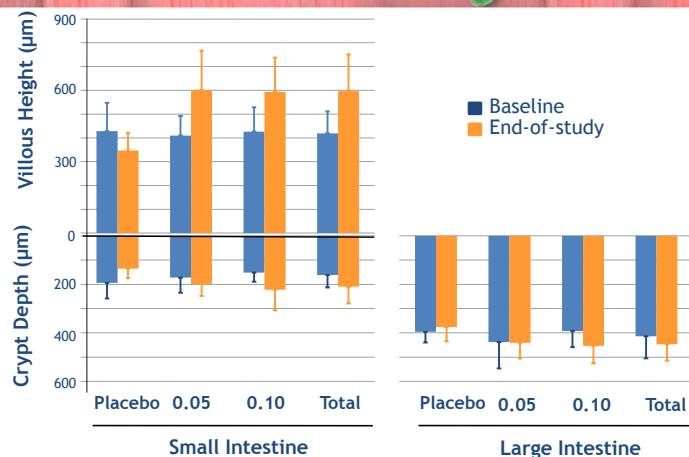
## Design of multicenter prospective, randomized double-blind, placebo-controlled study



## Representative change in small intestinal mucosa following 24 wks of 0.05 GATTEX administration.



Small intestinal villous height changed -19%, +54% and +39% in the placebo, 0.05 and 0.10 groups, respectively.



54% of patients treated with GATTEX reduced # infusion d/wk by  $\geq 1$ ; response  $\uparrow$  with time; wt stable

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**GATTEX(R) (teduglutide) Shown to Reduce Parenteral Support Volume in Patients with Adult Short Bowel Syndrome**

54% of patients treated with GATTEX reduced number of infusion days per week by one or more days

Response to GATTEX steadily increased throughout the course of the study

Patients' weight remained unchanged despite significant reductions in parenteral support

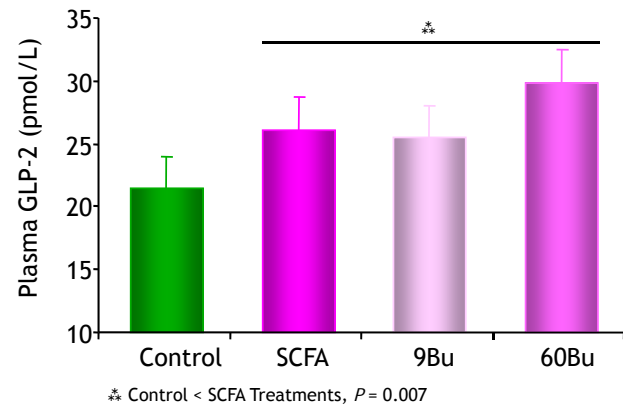
Pivotal phase 3 study results at Digestive Disease Week late-breaking oral session CHICAGO, May 10, 2011 (BUSINESS WIRE) --

NPS Pharmaceuticals, Inc. (NASDAQ: NPS), a specialty pharmaceutical company developing innovative therapeutics for rare gastrointestinal and endocrine disorders, today announced that GATTEX(R) (teduglutide), a novel, recombinant analog of human glucagon-like peptide 2, was found to effectively and safely reduce parenteral support (PS) volume in adult short bowel syndrome-intestinal failure (SBS-IF) patients. Professor Palle Bekker Jeppesen, M.D., Department of Medical Gastroenterology, Rigshospitalet, University Hospital of Copenhagen, Denmark, presented results of the 24-week, placebo-controlled Phase 3 study known as STEPS today at the Late-Breaking Abstract Session at Digestive Disease Week(R) (DDW(R)) 2011 in Chicago, IL.

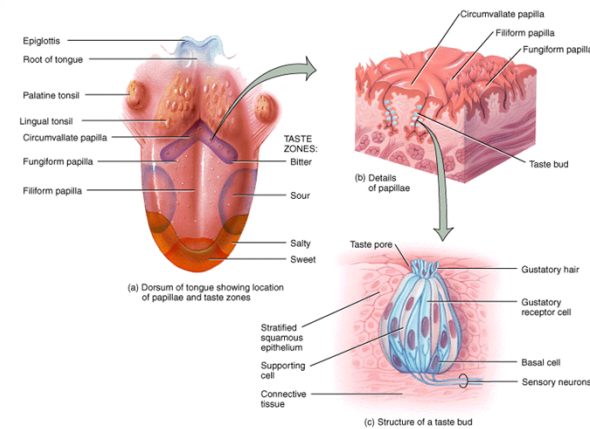
The study evaluated the ability of GATTEX to reduce the volume of PS in adult SBS-IF patients. The primary efficacy endpoint was defined as the percentage of patients who achieved a 20 to 100 percent reduction in weekly PS volume at Weeks 20 and 24, compared to baseline. In the intention-to-treat (ITT) population, 63 percent (27/43) of GATTEX-treated patients were responders versus 30 percent (13 of 43) of placebo-treated patients ( $p=0.002$ ).

Patients treated with GATTEX for 24 weeks also achieved significantly greater reductions in weekly PS volume and infusion days versus placebo. At Week 24, patients who received GATTEX experienced an average 4.4 liter

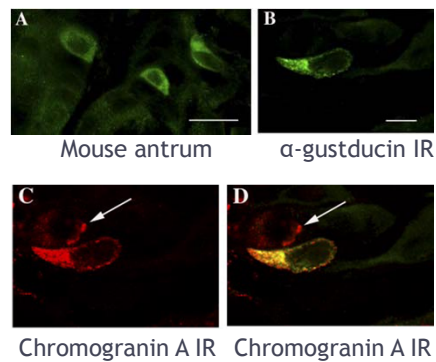
### Supplemented treatments increase plasma GLP-2 concentration at all time points



### Taste receptors essential for sensory response to nutrients in mouth

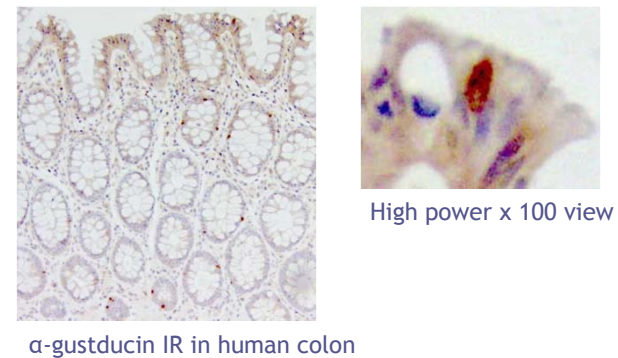


### Taste receptors throughout intestine serve as important chemosensors



Sternini C., AJP 2007;292:457-461.

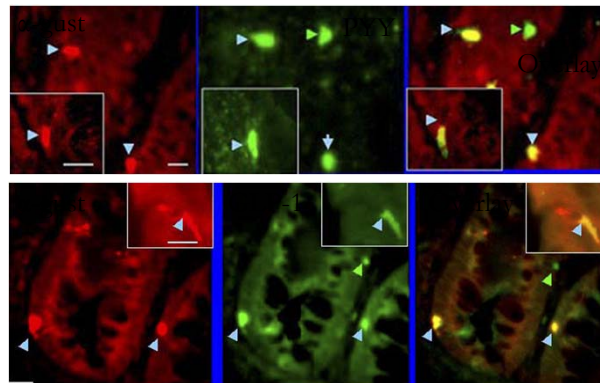
### α-gustducin expressed in human colonic mucosa



α-gustducin IR in human colon

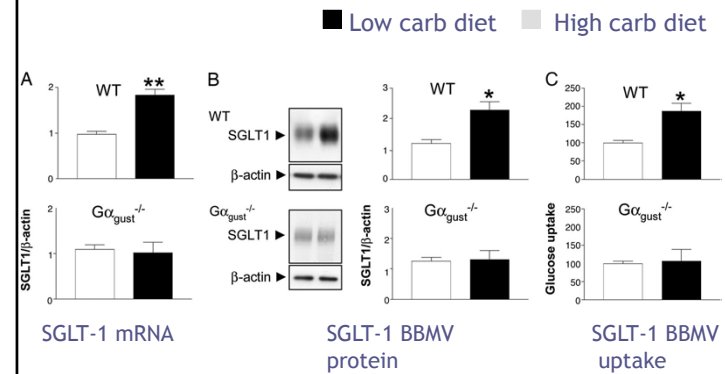
Rozengurt et al., AJP 2006; 291:792-802.

### $\alpha$ -gustducin found in L-cells that secrete GLP-2



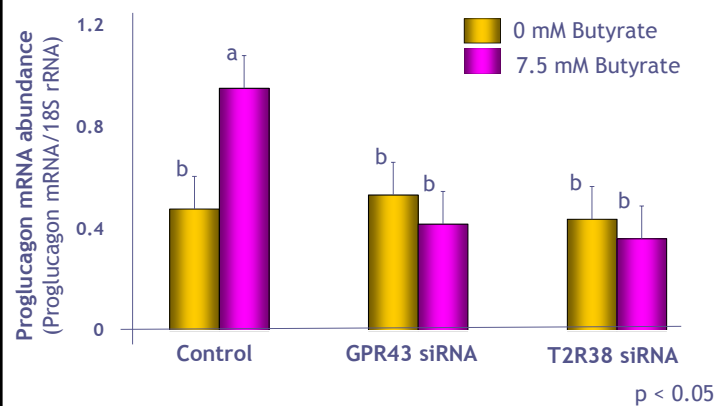
Rozengurt et al., AJP 2006; 291:792-802.

### $\alpha$ -gustducin necessary for carbohydrate induced glucose absorption



Margolskee et al., PNAS 2007;104:15075-15080.

### Silencing taste receptors prevent butyrate from increasing GLP-2



### Take Home Message

Strategies to enhance intestinal adaptation, such as short-chain fatty acids and GLP-2 therapy, promise to reduce PNin individuals with intestinal failure.

Novel taste receptors, present throughout the intestine, may provide an important mechanism mediating these effects.

## Acknowledgements

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