Control of the Appetite Through the Microbiome

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Boston, June 2017
Control the body weight (+/-)
By modulating the appetite through an intervention on microbiome
Genesis of the discovery
Strong scientific background

PNAS 2005
Autoantibodies against neuropeptides are associated with psychological traits in eating disorders.

Appetite, 2009
Emerging role of autoantibodies against appetite-regulating neuropeptides in eating disorders.

Nutrition, 2008
Autoantibodies against appetite-regulating neuropeptides and gut microflora.

Patent IP001

Psychoneuroendocrinology 2009
The putative role of neuropeptide autoantibodies in anorexia nervosa.

Curr Opin Clin Nutr Metab Care. 2008
In search of the missing link in the regulation of appetite and body weight.

Nutrition, 2009
Regulation of food intake and anxiety by α-MSH reactive autoantibodies.

Appetite 2009
Regulation of food intake and anxiety by α-MSH reactive autoantibodies.

Appetite 2011
Alpha-MSH reactive IgG are associated with delayed body weight recovery after MTX induced mucositis.

Neuropeptides, 2014
Putative modulation by gut microbiota.

Nature Medecine, 2016
Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour.

Nature Reviews, 2016
Ghrelin-reactive immunoglobulins and anxiety, depression and stress-induced cortisol response in adolescents. The TRAILS study.

Nature Medicine, 2015
Ghrelin-reactive immunoglobulins modulate ghrelin stability and its orexigenic effect in obese mice and humans.

Nutrition, 2015
Sex-related effects of nutritional supplementation of Escherichia coli: relevance to eating disorders.

Cell Metabolism 2015
Gut Commensal E.coli Proteins Activate Host Satiety Pathways Following Nutrient-Induced Bacterial Growth

Nat Commun, 2013
Anti-ghrelin immunoglobulins modulate ghrelin stability and its orexigenic effect in obese mice and humans.

Mimetic proteins

Transl Psychiatry, 2014
Bacterial CipB heat-shock protein, an antigen-mimetic of the anorexigenic peptide α-MSH, at the origin of eating disorders.

Nature, 2015
Regulation of food intake and anxiety by α-MSH reactive autoantibodies: relevance to eating disorders.
**ProbioSatys™**
for overweight

Probiotic producing α-MSH mimetic
- Strain identified
- Scale-up ongoing
- Clinical trial 2018

**ProbioNutrys™**
for elderly & cachexia

Probiotic producing ghrelin mimetic
- Strain identified
- Candidate proteins identified and currently tested

**Orexigenic**

Target:
- Elderly
- Later anorexic / cachexic population

**Anorexigenic**

Target:
- Consumers with BMI 25-35
- Obese population – 2nd step
1.4 billion people affected by overweight issues (WHO)

USA population (CDC – Center for Disease Control and Prevention)
  • 60% are concerned
  • 12% of children aged 2-5
  • 18% of children aged 6-11

By 2018 overweight and obesity will affect ¾ people in USA
- Strong homology *Enterobacteriaceae* ClpB and \(\alpha\)-MSH

- ClpB / MCR family affinity
  - Full micromolar MC1R agonist
  - Partial MC3R & MC5R agonist

- MCR are present in the gut epithelium
ClpB Protein – effect in the gut
Bacteria proteome changes: Effect on hormone release – Local effect

Bacteria growth
Proteomics
ClpB Conc.
Rat colon infusion

ClpB Protein – effect in the gut

ClpB-induced PYY secretion from rat colonic mucosa culture – Local effect

Rat colonic mucosa culture *in vitro*

- 24-well Matrigel plates
- 24 h primary culture
- 200 µL / well after removal of the medium
- 20 min incubation at 37 °C

*** One way ANOVA with Dunnett’s post-test p<0.001

Relative [PYY] change from Ctrl

Manon Dominique’s PhD thesis data (unpublished)
ClpB Protein – effect in the brain
ClpB / α-MSH Molecular mimicry – Ex-vivo Central effect

**ClpB activates Pro-opiomelanocortin (POMC) neurons**

**POMC neurons** are located in the arcuate nucleus
- When activated, they **inhibit feeding**
- Activated by circulating concentrations of leptin and insulin

POMC-eGFP neuron (arrow) visualized under infrared (A) and fluorescent light (B) during patch-clamp recording.
ClpB Protein – effect in the brain

ClpB / α-MSH Molecular mimicry – Brain injection - Central effect

ClpB injected Intracerebroventricular in rats reduces food intake

- Dose-dependent reduction of the food intake
- Higher doses stop food intake for more than 6 hours
ClpB increases Pro-opiomelanocortin (POMC) expression

Bacteria strain with and without the ClpB producing gene (∆ClpB strain)

ClpB producing strain selectively increases the production of α-MSH precursor
ClpB Protein – effect on body weight & food intake
ClpB / α-MSH Molecular mimicry – Oral gavage

Effects on body weight and food behavior are linked to the production of ClpB

POC with the same strain with and without the ClpB producing gene (ΔClpB strain) ob/ob mice fed with the ΔClpB strain behave like the control group.
ProbioSatys™
Oral gavage - High Fat Diet-induced obesity in mice

- Treatment with ProbioSatys™ significantly decreased the body weight of HFD mice
- It also prevents fat mass gain, with ProbioSatys™ mice even lose fat mass
Treatment with ProbioSatys™ induces a **significant decrease in body weight gain** as compared to untreated obese controls.

Two-way ANOVA, Bonferroni post-test, **p<0.01; *p<0.05**
• The decrease in body weight gain was associated with a decrease of cumulative food intake

• ProbioSatys™ also activates lipolysis
Preclinical proof of concept

- Lead bacteria strain is food grade
- Confirmed efficacy of the selected lead strain (experiments with 12 to 15 animals per group):
  - 2 different animal species (mice and rats)
  - 3 different animal models (ob/ob, Zucker, Diet Induced Obesity)
  - Both reduction of weight gain in developing obesity and reduction of weight in installed obesity

CMC

- Fermentation scale-up
- Formulation

Clinical trials in 2018
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