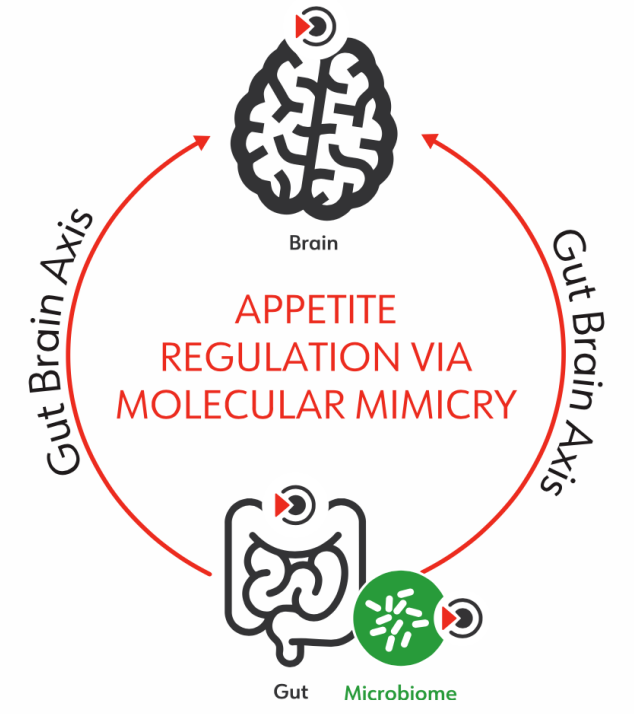
TargEDys

TARGETING EATING DYSFUNCTIONS

ProbioSatys™ – Naturally modulating the appetite via the microbiome

ADEBIOTECH, 19&20 juin 2018

Gregory Lambert, Pharm.D, Ph.D
Chief Executive Officer



Our mission

is to control body weight and metabolic disease by modulating the appetite through an intervention on the microbiome

Our approach

is to use the concept of molecular mimicry to physiologically bind well-described pharmacological targets such as melanocortin receptors (MCR) and ghrelin receptor GHS-R1a with bacterial metabolites and derived small molecules

Executive summary

- Based on **10 years of research** at **INSERM** (University of Rouen, France)
- Offices in Longjumeau, Paris area & Labs in Rouen, Normandy
- IP: 7 patent families and 6 trademarks
- Platform delivers both **therapeutic** and **nutraceutical** products
- Technologies in development
  - **ProbioSatys®**: Satiety for weight management, obesity and metabolic disease
  - **ProbioNutrys®**: Increase appetite in elderly, cachexia and anorexia

Seventure

PONTIFAX

NCI
Cultivons l'ambition

ZALUVIDA

INNOVATION 2030
CONCOURS MONDIAL D'INNOVATION

bpifrance

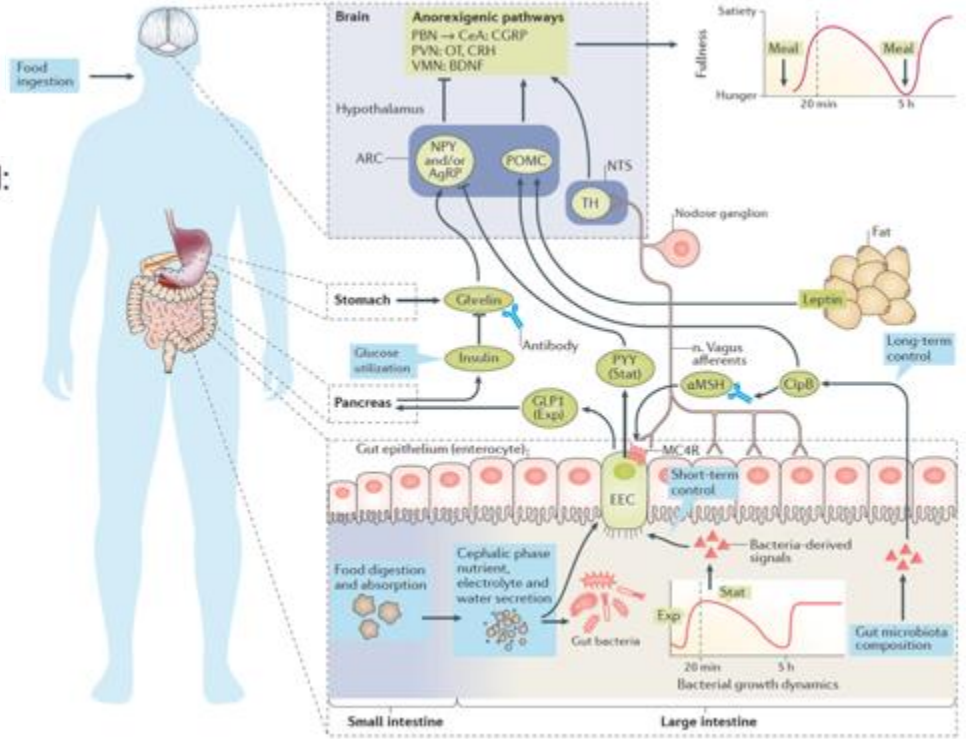
New model for gut-brain appetite regulation

nature REVIEWS ENDOCRINOLOGY

Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour

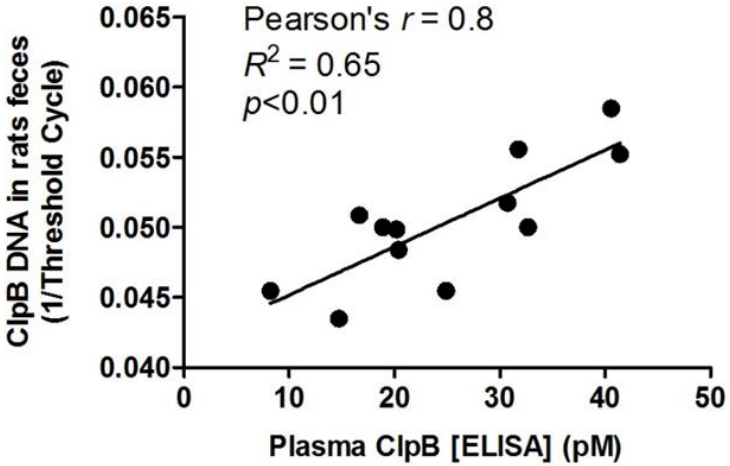
Sergueï O. Fetissov

Nature Reviews Endocrinology (2016) | doi:10.1038/nrendo.2016.150
Published online 12 September 2016

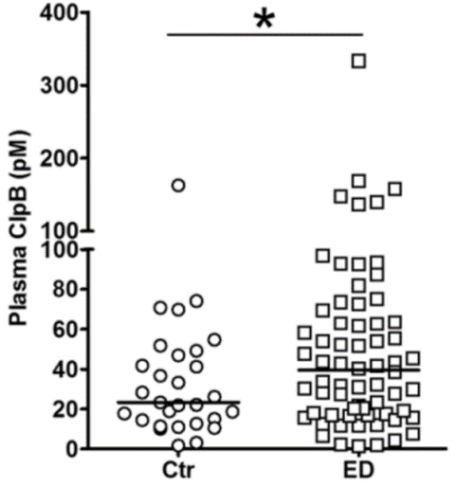


ClpB is present in blood circulation

Plasma ClpB levels correlate with ClpB DNA in gut microbiota in rats



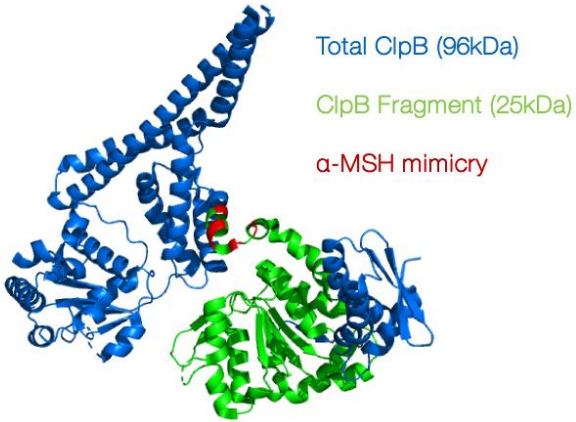
E.coli ClpB is present in human plasma



From: Breton et al., Int J Eat Dis 49: 805-808, 2016

The concept of molecular mimicry
ClpB / α-MSH Molecular mimicry

- **Strong homology** between an exposed loop on the surface of ClpB* and α-MSH[1]
- ClpB / MCR family affinity[2]
  - Full MC1R agonist
  - Partial MC3R & MC5R agonist
- MCR are present in the **gut epithelium**[3]



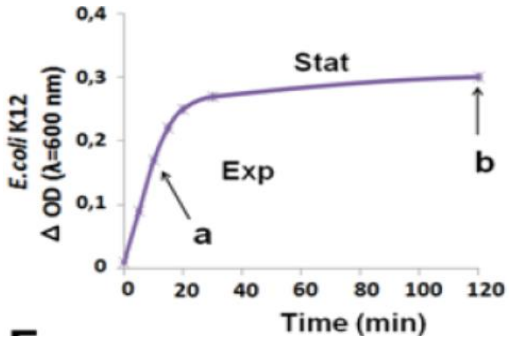
α-MSH	Ac-SYSME HFRW GKPV-NH₂	✓
ClpB E.coli	534-AEIAEVLARWTGIPV-548	✓
ClpB ProbioSatys	534-VEIAEVLARWTGIPV-548	✓
ClpX Lactobacillus casei	DVAEVVSQWTGIPV	✗
ClpC Bifidobacterium animalis	IAEV IS QS TGIPV	✗
ClpB Enterococcus fecalis	EIAQVVG RL TGIPV	✗
Hsp 104 Saccharomyces cerevisiae	ISETAA RL TGIPV	✗

1. Tennoune et al., Transl Psy, 2014
2. Ericson et al., Bioorg Med Chem Letters, 2015
3. Panaro et al., Cell metab, 2014

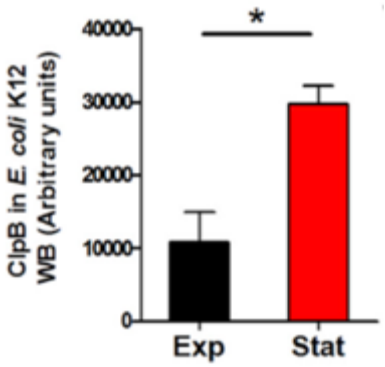
* From *Enterobacteriaceae*

ClpB – effect in the gut
Stimulation of PYY release

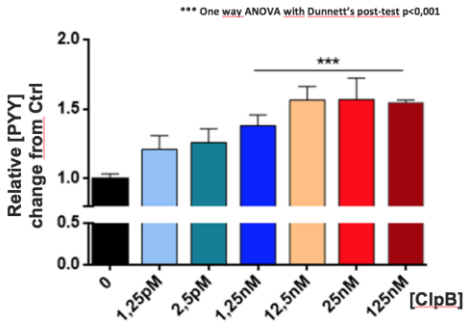
Bacterial growth



ClpB Concentration



Primary cultures
Rat colon mucosa

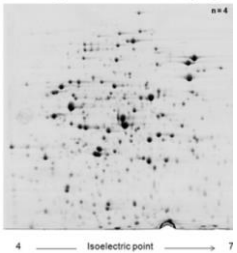


Manon Dominique's PhD thesis data (unpublished)

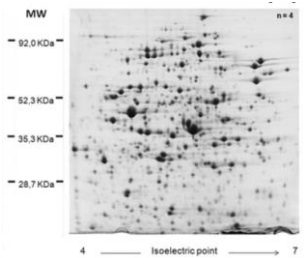
Rat colon infusion

Proteomics

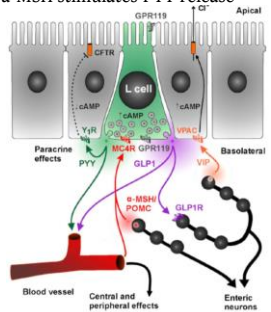
Exp. Phase (a)



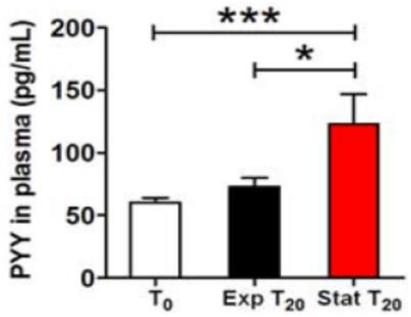
Stat. Phase (b)



a-MSH stimulates PYY release



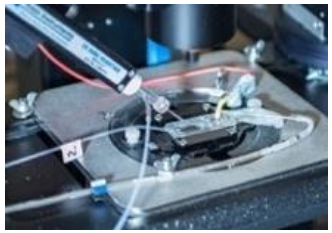
Panaro et al., Cell Metab, 20: 2014.



Breton J. et al. Cell Metab 23, 324-334, 2016

ClpB Protein – effect in the brain

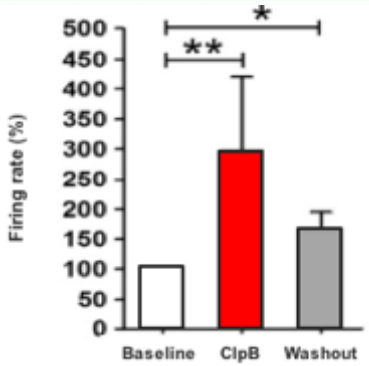
ClpB / α-MSH Molecular mimicry – Central effect

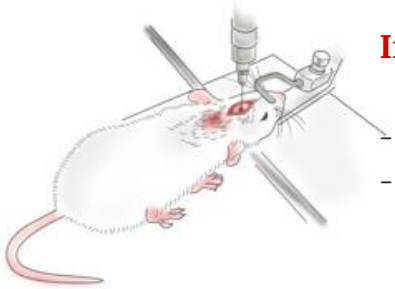


ClpB activates Pro-opiomelanocortin (POMC) neurons ex-vivo

POMC neurons are located in the arcuate nucleus

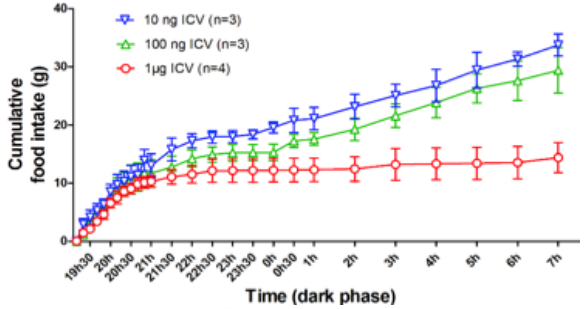
- When activated, they inhibit feeding
- Activated by circulating concentrations of leptin and insulin



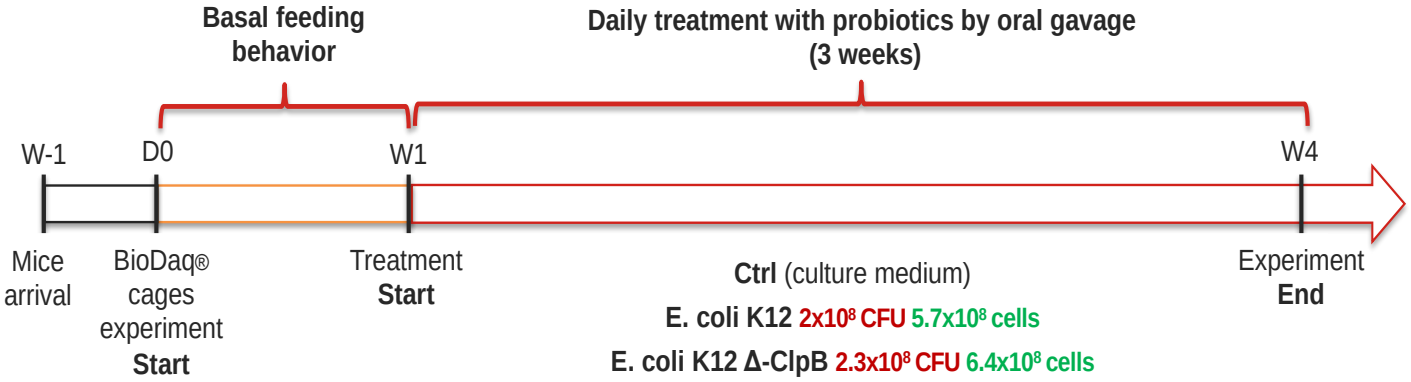


Intracerebroventricular injection of ClpB reduces food intake in-vivo

- Dose-dependant reduction of the food intake
- Higher doses stop food intake for more than 6 hours



E.coli K12 / *E.coli* K12 ΔClpB
Oral gavage - Normal mice



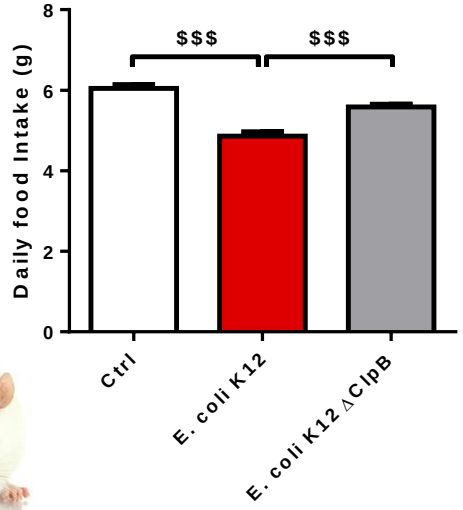
- n=8/group
- **Daily body weight follow-up**
- **Euthanasia and tissu sampling:** plasma, colic fecal content, intestine, epididymal fat
  + body composition

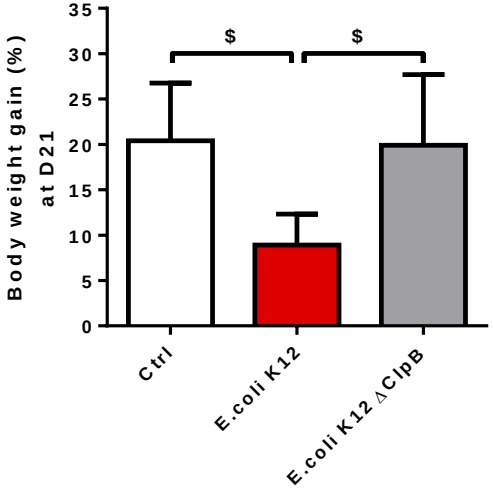
E.coli K12 / *E.coli* K12 ΔClpB
Oral gavage - Normal mice

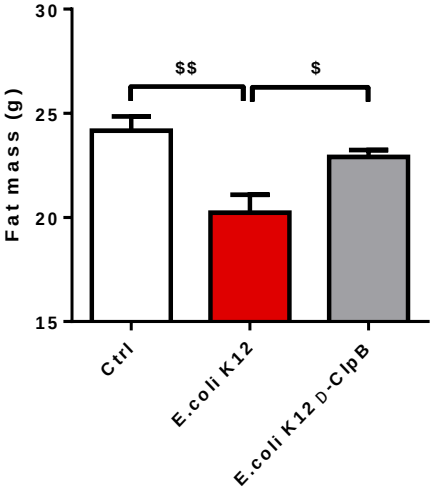
Effects on body weight and food behaviour are linked to the production of ClpB

Same strain with and without the ClpB producing gene (ΔClpB strain)

Effects on food intake, body weight and fat mass

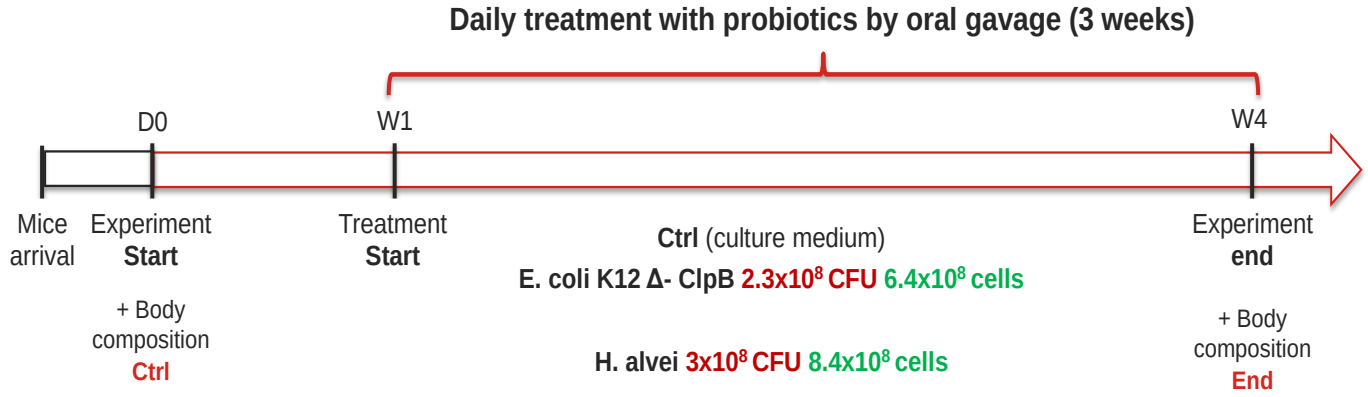






1-way ANOVA, Tukey's post-test, $p<0.05, $$$p<0.001

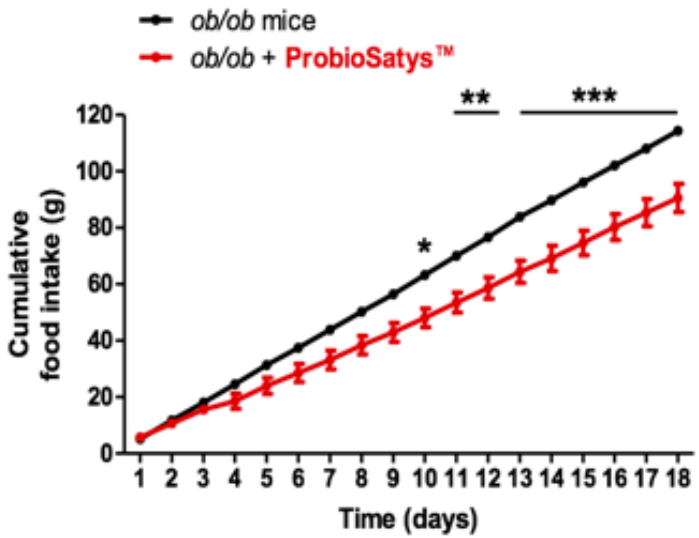
Hafnia alvei
Oral gavage - Obese ob/ob mice

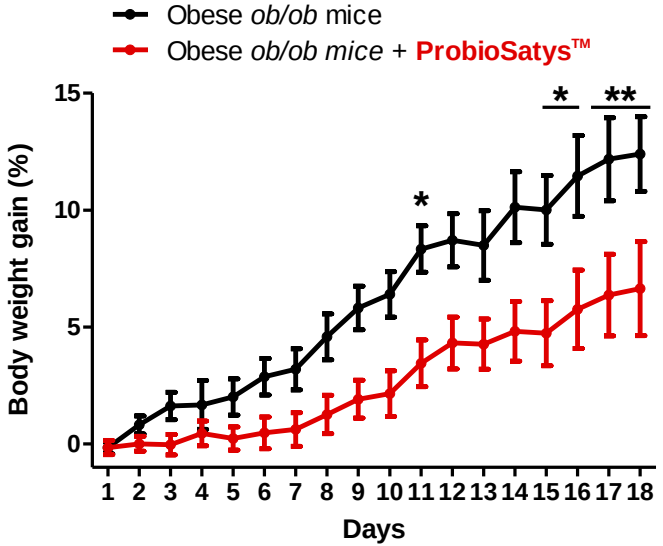


- n=12 to 15/group
- **Daily body weight follow-up**
- **Euthanasia and tissu sampling:** plasma, colic fecal content, intestine, epididymal fat

Hafnia alvei
Oral gavage - Obese ob/ob mice

Treatment with *Hafnia alvei* decreases food intake and induces a significant decrease in body weight gain as compared to untreated obese controls





Two-way ANOVA, Bonferronni post-test, **p<0.01; *p<0.05

Hafnia alvei
Oral Gavage - Ob/Ob mice

Male *ob/ob* mice
7 weeks
n=90
(*n*=3/cage)

Acclim.
W-1
SD *n*=44

D-19
D-12
Body composition
Randomization
(SD/ HFD)

D-7
Sham gavage
2 per day

D0
Body composition
Randomisation
treatments

SD Ctrl *n*=22
W1 **W2** **W3**
OGTT *n*=11
No OGTT *n*=11

SD H. alvei $2.8x10^{10}$ **CFU** $6.7x10^{10}$ **cells** *n*=22
W1 **W2** **W3**
OGTT *n*=11
No OGTT *n*=11

D22
Body composition

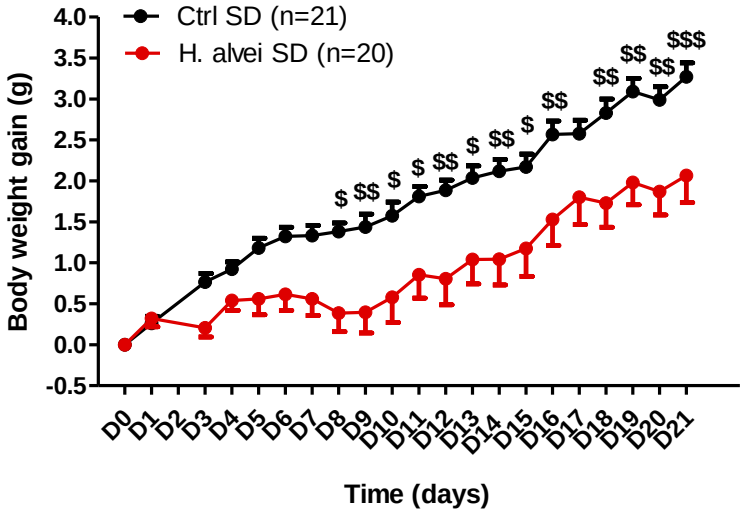
D22
Total blood dosage by IDEXX Catalyst
(without fasting)

Tissue sampling:
Adipose tissue,
Hypothalamus,
Duodenum, Jejunum,
Ileum, Colon,
Fecal colonic content,
Liver

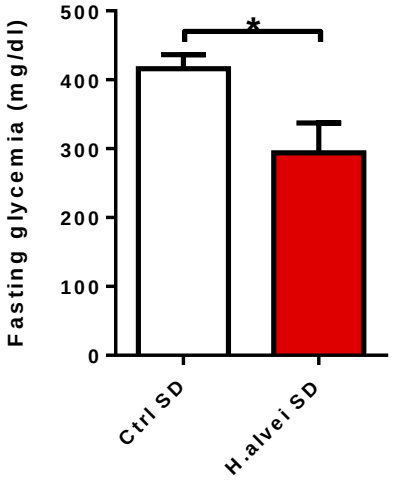
D23
OGTT
(overnight fasted)

T_0, T_{15}, T_{45},
T_{60}, T_{90}, T_{120}

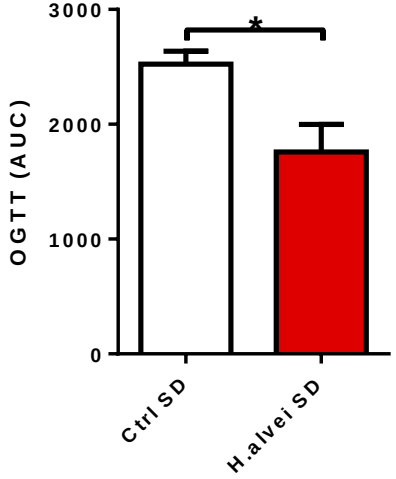
Hafnia alvei
Oral Gavage - Ob/Ob mice



2-way ANOVA, Bonferronni post-test, $$$p<0.001, $$p<0.01 , $p<0.05



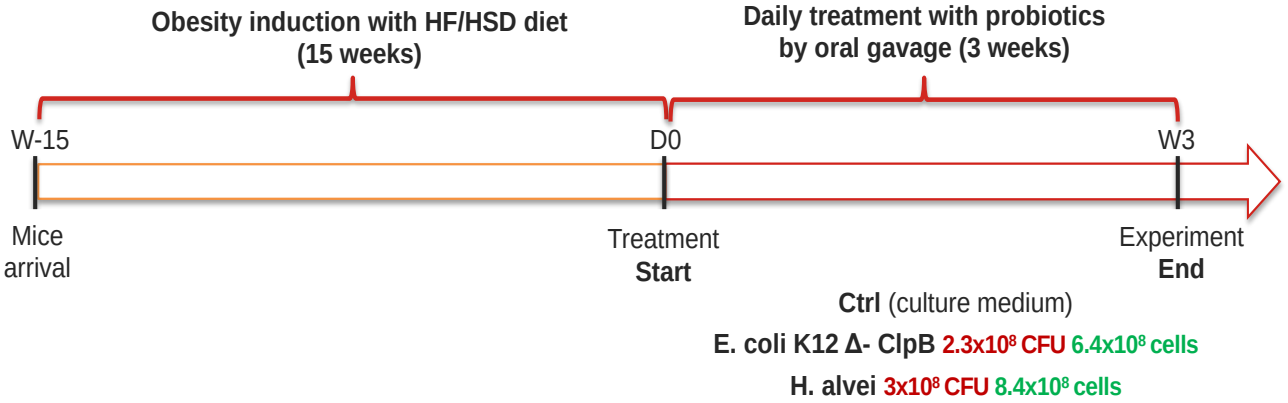
Student's t-test, *p<0.05



Student's t-test, *p<0.05

In addition to body weight, *Hafnia alvei* improves glycemia, OGTT and hepatic markers

Hafnia alvei
Oral gavage – HFD mice

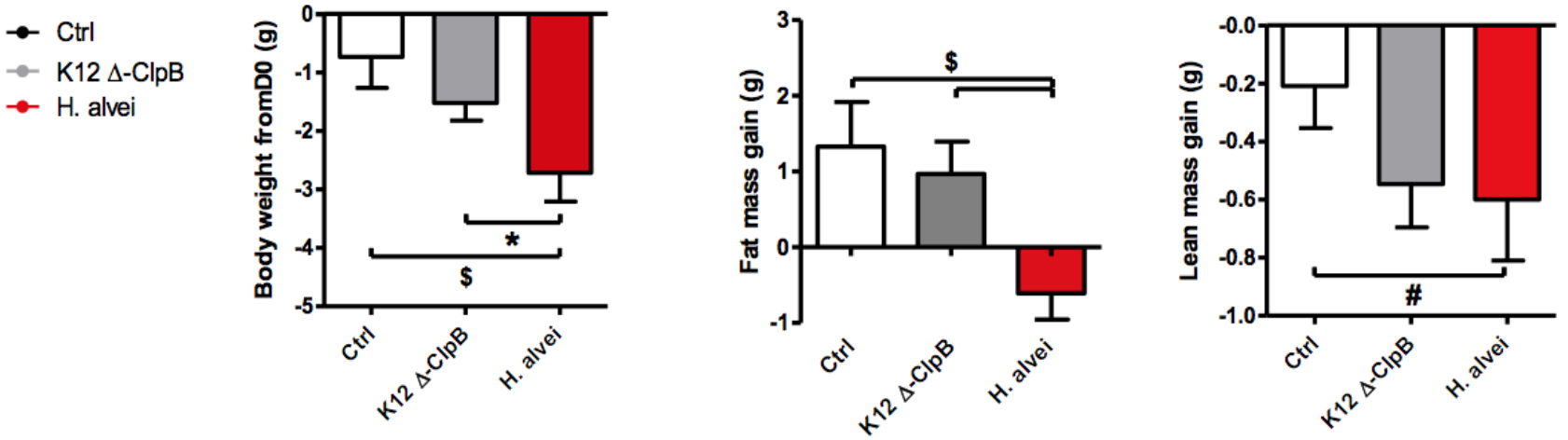


- n=13/group
- **Daily body weight follow-up**
- **Euthanasia and tissu sampling:** plasma, colic fecal content, intestine, epididymal fat
  + body composition

Hafnia alvei
Oral gavage – HFD mice

Treatment with *Hafnia alvei* significantly decreased the body weight of HFD mice

It also improves body composition



:0.05

$ One-way ANOVA, p<0.05
* Student's t-test, p<0.05

$ One-way ANOVA Tukey's post-test p<0,05

Mann-Whitney test, p<0.10

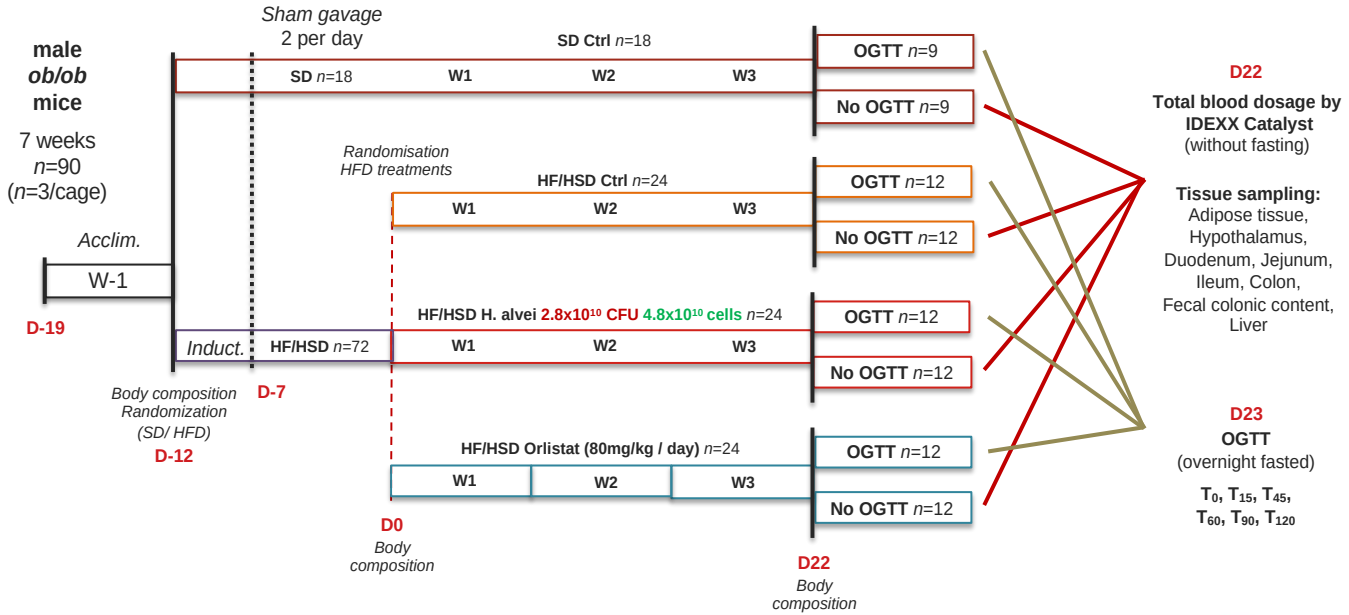
Hafnia alvei vs Orlistat
Hybrid Model HF-HSD – ob/ob

Hybrid model to reflect human causes of overweight

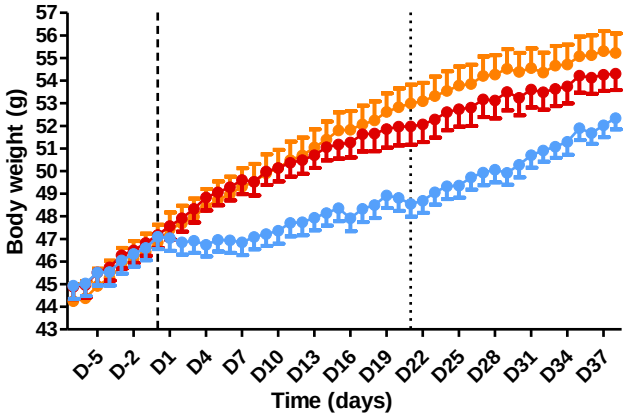
Combines inappropriate diet and hyperphagia

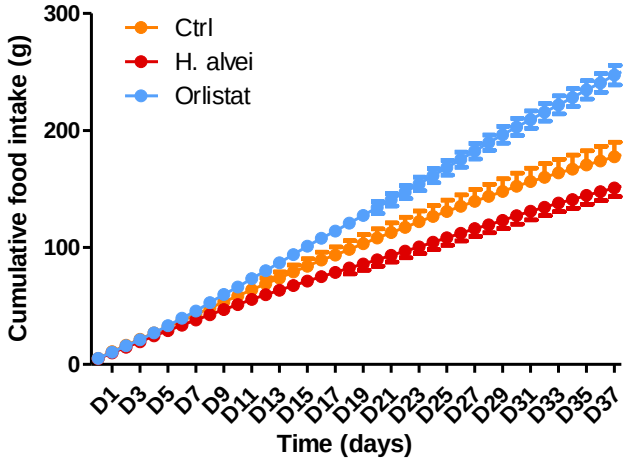
Orlistat pancreatic lipase inhibitor

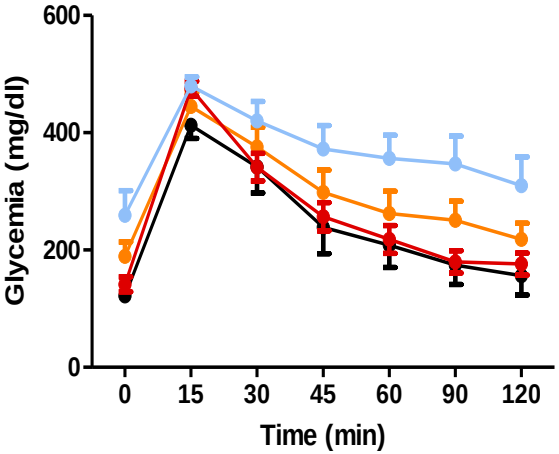
Prevents absorption of fat



Hafnia alvei vs Orlistat
Hybrid Model HF-HSD – ob/ob







Hafnia alvei has 40% of the effect of Orlistat on body weight treat & no side effects

Hafnia alvei reduced food intake while Orlistat increased it

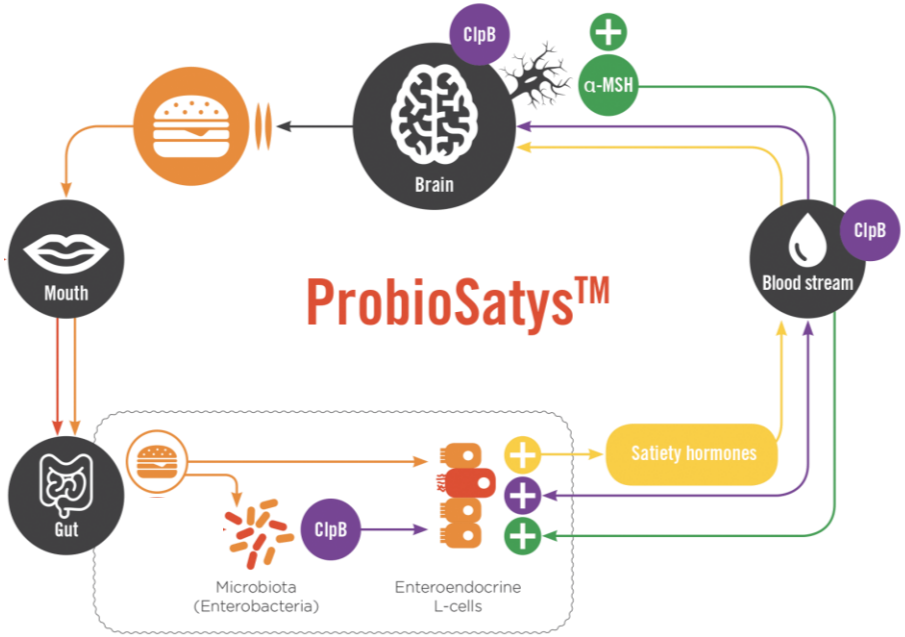
Hafnia alvei reduced fasted glycemia while Orlistat increased it

EnteroSatys™ Food supplement
Hafnia alvei

- Food grade
- Optimised fermentation process
- Optimised formulation in GI resistant capsules
- Stable at room temperature

- Based on ProbioSatys™ technology
- 60 capsules in one box
- 2 capsules per day
- Recommended treatment time: 3 months

ProbioSatys™ key benefits



- Reduction in body weight
- Reduction of food intake
- Improvement of body composition
- Activation of lipolysis
- Activation of central satiety pathways

Fetissov, Nature reviews Endocrinology, 2016

Contact information

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Proven
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PHYSIOLOGICAL