SELECTED OPPORTUNITIES IN PAIN

LIPOPEPTIDE COMPOUND AND TREATMENT OF PAIN DISORDER (BIO16070)

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Product factsheet

Stage: pre-clinical, in vivo model

- **Target:**
  - $GABA_B$ receptor
- **Product:**
  - Lipopeptide compound with C12-Asn-γ-aminobutyric acid (C12AsnGABA*OH*) structure derived from a *Escherichia coli* Nissle product
- **Application:**
  - Treatment of visceral pain resulting from gastrointestinal disorders (Inflammatory bowel disorder (IBD), irritable bowel syndrome (IBS), functional abdominal pain syndrome (FAPS), Crohn's disease…)
- **Technology:**
  - Synthetic lipopeptide
- **Rational / POC:**
  - Probiotic *Escherichia coli* strain Nissle 1917 (EcN) is known to be effective for the treatment of abdominal pain in IBS patients. However, little is known about the specific mechanism through which EcN exerts its effects. The inventors have identified a non-genotoxic metabolite, produced by EcN, with analgesic properties in visceral pain.
  - *In vitro* POC: C12AsnGABA*OH* crosses the epithelial barrier and inhibits neuronal activity without modifying the physiology of the intestinal epithelium
  - *In vivo* POC: intracolonic administration leads to increased concentrations of C12AsnGABA*OH* in colonic tissue and blood, and decrease of visceral hypersensitivity in mice.
- **Patent and publication:**
  - Identification of an analgesic lipopeptide produced by the probiotic Escherichia coli strain Nissle 1917. Pérez-Berezo T et al. Nat Commun 2017 Nov 3;8(1):1314. doi: 10.1038/s41467-017-01403-9
  - Patent EP17305481

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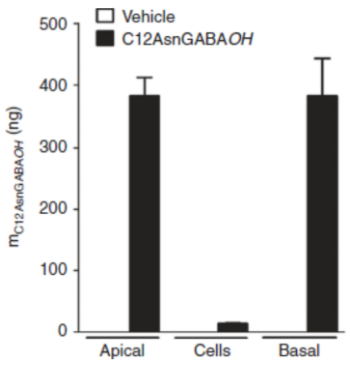
Proof of concept: *in vitro*

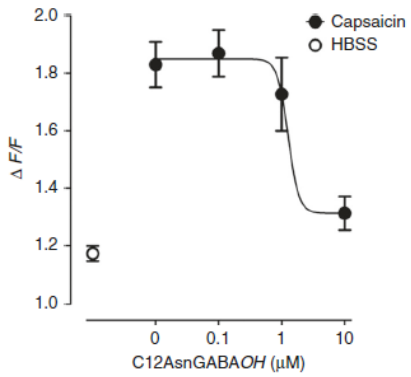
C12AsnGABAOH crosses the epithelial barrier and inhibits neuronal activation via the $GABA_B$ receptor

- **Transport of C12AsnGABAOH across human epithelial cells monolayers**



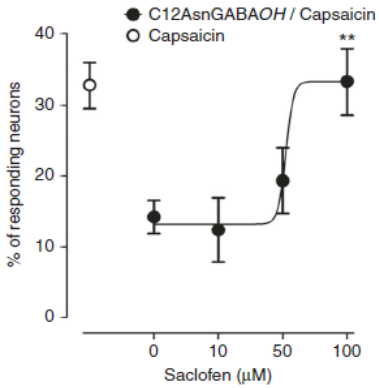
Caco-2 cells were cultivated in transwell chambers. After 24h treatment with C12AsnGABAOH (800 ng) at the apical side, C12AsnGABAOH was quantified inside the cells and in both the apical and basolateral compartments by LC-MS/MS.

- **Dose-dependent decrease of calcium flux induced by C12AsnGABAOH**



Amplitude of intracellular calcium mobilization (ΔF/F) in mouse sensory neurons pretreated with increasing amounts of C12AsnGABAOH (black circle) or vehicle (HBSS; white circle) and treated with capsaicin (125 nM).

- **Saclofen abolishes the inhibitory effect of C12AsnGABAOH**



Percentage of responding neurons pretreated with increasing amounts of saclofen (black circle), a competitive antagonist of the $GABA_B$ receptor, or vehicle (HBSS; white circle) and treated with C12AsnGABAOH (10 µM) and capsaicin (125 nM).

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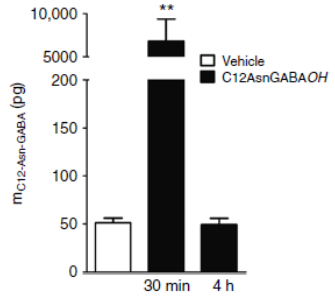
Proof of concept: *in vivo*

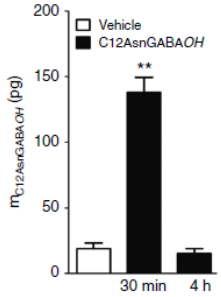
C12AsnGABA*OH* decreases visceral hypersensitivity *in vivo*

- **Intracolonic administration of C12AsnGABAOH increases concentrations of the compound in colonic tissue and blood**

a.



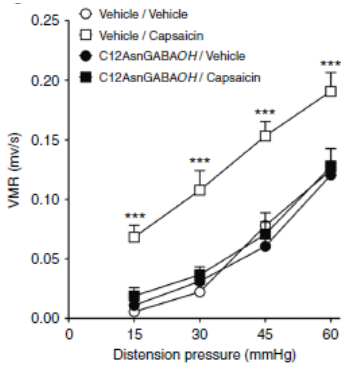
b.



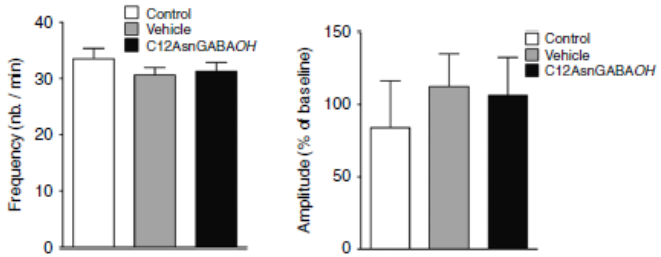
Mice received intracolonic administration of C12AsnGABAOH (10 µM; black bars) or vehicle (40% ethanol; white bars) and 30 min or 4 h later colon (a) and blood (b) were harvested in order to quantify C12AsnGABAOH by LC-MS/MS.

- **C12AsnGABAOH inhibits capsaicin-induced visceral hypersensitivity without altering intestinal contraction**

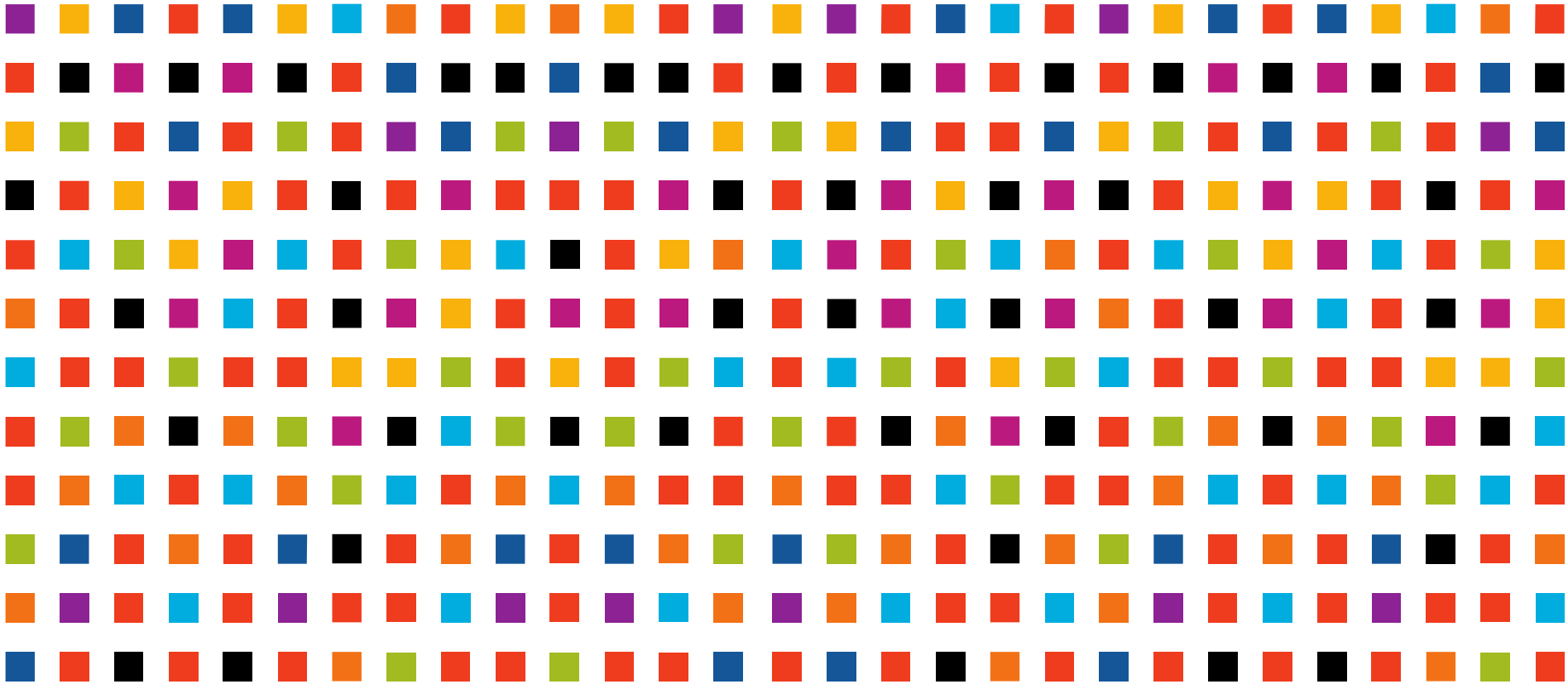
c.



d.



Mice received intracolonic administration of C12AsnGABAOH (10 µM; black symbols) or vehicle (40% ethanol; white symbols) and 30 min or 4 h later an intracolonic administration of capsaicin (100 µg per mouse; square) or its vehicle (40% ethanol; circle). Fifteen minutes after capsaicin or vehicle treatment, VMR to increasing pressures of CRD was performed (c). Ex vivo measurement of duodenal mechanical contraction frequency (d, left panel) and amplitude (d, right panel) in response to Krebs–Ringer solution (control; white bar), DMSO 0.2% (vehicle; gray bar), or to C12AsnGABAOH (10 µM; black bar).



ANNE.COCHI@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr