SELECTED OPPORTUNITY IN ONCOLOGY

Ox1R agonists for the treatment of cancer (pancreas, colon, liver, prostate…) BIO14361 & BIO14365

OX1R AGONISTS FOR THE TREATMENT OF CANCER (PANCREAS, COLON, LIVER, PROSTATE…) BIO14361 & BIO14365

Product factsheet

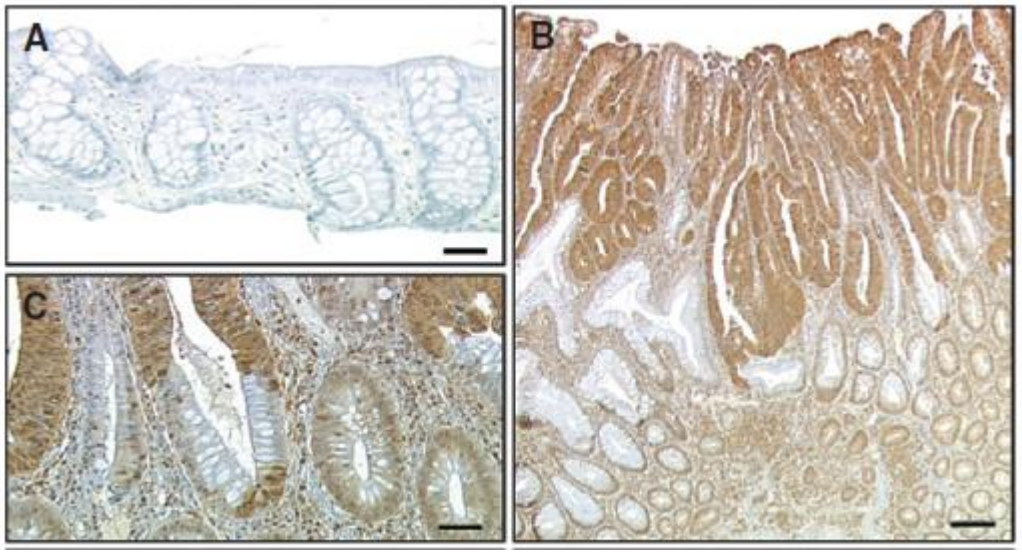
In vivo POC
Biomarker in human

- **Target** : Ox1R Orexin Receptor
  - 7A 7TM/GPCR known to be involved in the control of circadian cycle and food intake (CNS) – no peripheral expression in normal tissues.
  - A tumor associated antigen in pancreatic, prostate and colon cancer (all stages including cancers resistant to chemotherapy).
  - At central level, it's activation via it's natural ligands, hypothalamic neuropeptides Orexin A & B, induces cellular calcium transient (canonic pathway).
  - In cancer cells Orexins promotes apoptosis through an Ox1R mediated novel signaling pathway via phosphatase SHP-2 recruitment and caspases induction.
- **Product candidates** : proprietary anti-Ox1R agonist hmAb, Orexin based fusion protein and derived peptides and Ox1R specific small molecules (second use).
- **POC** :
  - Orexin derived peptides, anti-Ox1R agonist hmAb and Ox1R specific small molecule induces apoptosis *in vitro* and reduce tumor growth *in vivo* (xenograft mouse models & pdx).
- **Publications** :
  - *In vitro, in vivo* and *ex vivo* demonstration of the antitumoral role of hypocretin-1/orexin-A and Almorexant in pancreatic ductal adenocarcinoma. Dayot S. *et al*, **Oncotarget 2018.**
  - Impact of Orexin-A Treatment on Food Intake, Energy Metabolism and Body Weight in Mice. Blais A *et al*, **PLoS One 2017.**
  - Aberrant expression of OX1R for orexins in colon cancers and liver metastasis: an openable gate to apoptosis, Voisin T *et al*, **Cancer Res. 2011**.
- **Patent applications** : cover the target, orexin peptides and orexin based fusion proteins, anti-Ox1R proprietary human mAb candidates, second use of known small molecules.

OX1R AGONISTS FOR THE TREATMENT OF CANCER

Proof of concept

Ectopic expression of Orexin Receptor in human colon tumors

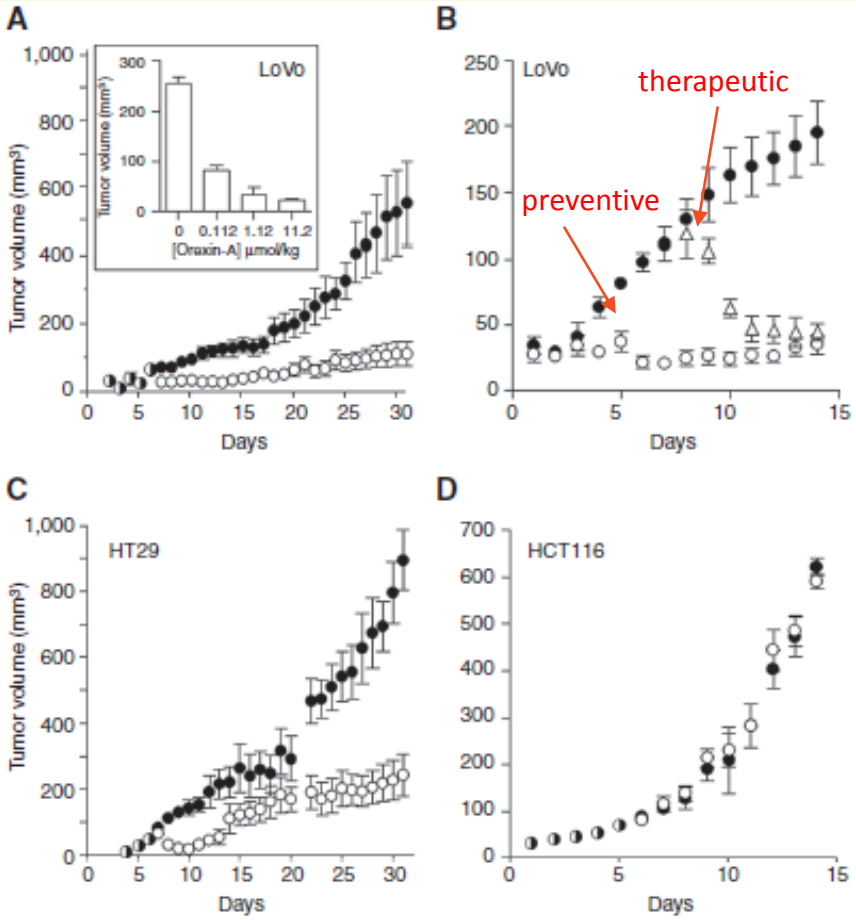


Indirect immunostaining of OX1R in human colon tumors.
A, paraformaldehyde-fixed sigmoid from a patient with irritable bowel. No immunoreactive signal was observed.
B–C, paraformaldehyde-fixed colon tumors :
B, strong immunostaining in neoplastic glands, whereas normal glands remained negative.
C, detail of this tumor showing the difference of immunostaining in the same glands between neoplastic cells and still normal colonocytes.

Proof of concept

Orexin A reduces tumour growth in mouse xenografted with cancer cells expressing OX1R

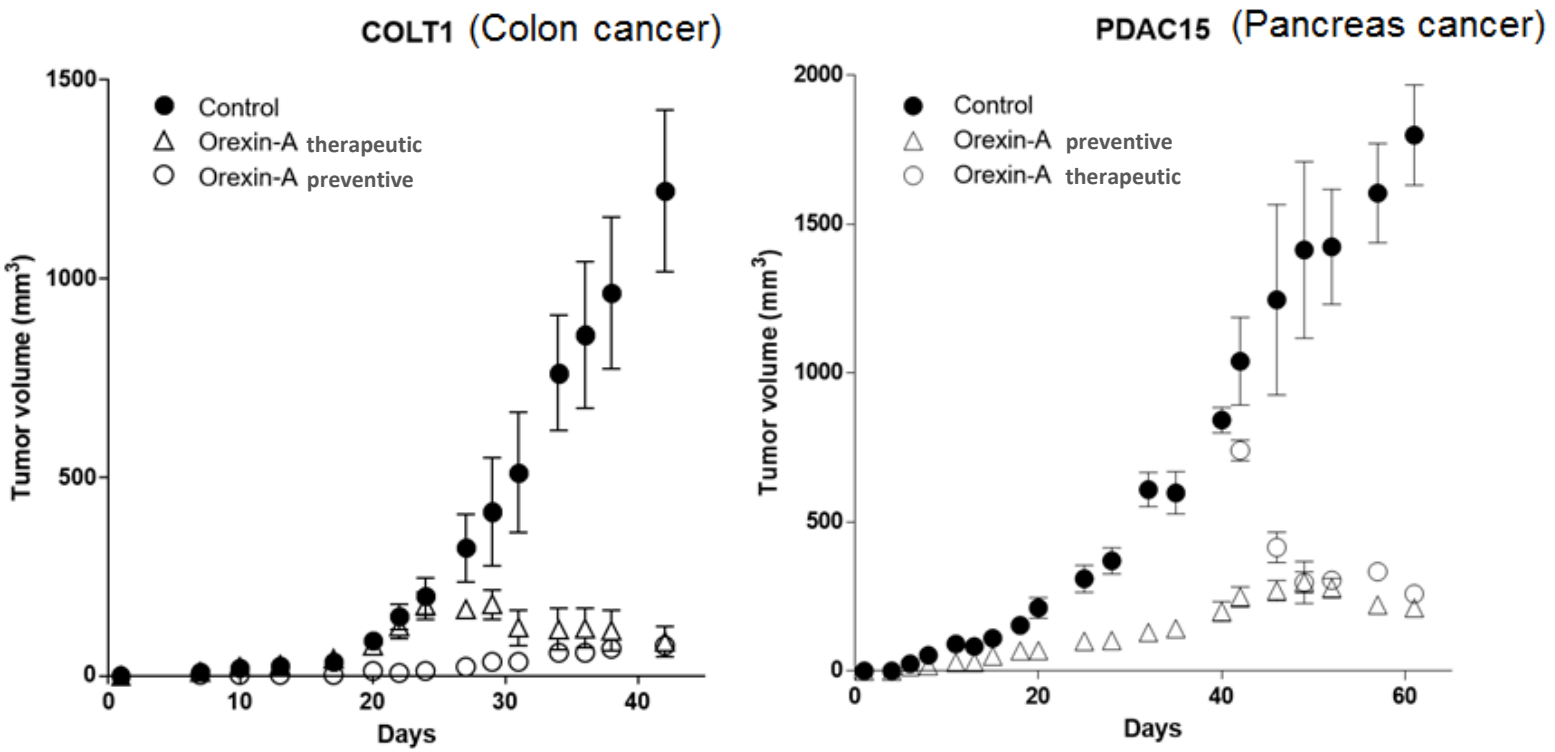
LoVo cells (A and B), HT-29 cells (C), or HCT116 cells (negative for Orexin receptor expression, D) were inoculated in the flank of nude mice at day 0. Mice were daily injected intraperitoneally with 1.12 µmoles of **orexin-A**/kg starting at day 0 (○) or day 7 (triangle) or with PBS (•) for control. The development of tumors was followed by caliper measurement.



OX1R AGONISTS FOR THE TREATMENT OF CANCER

Proof of concept

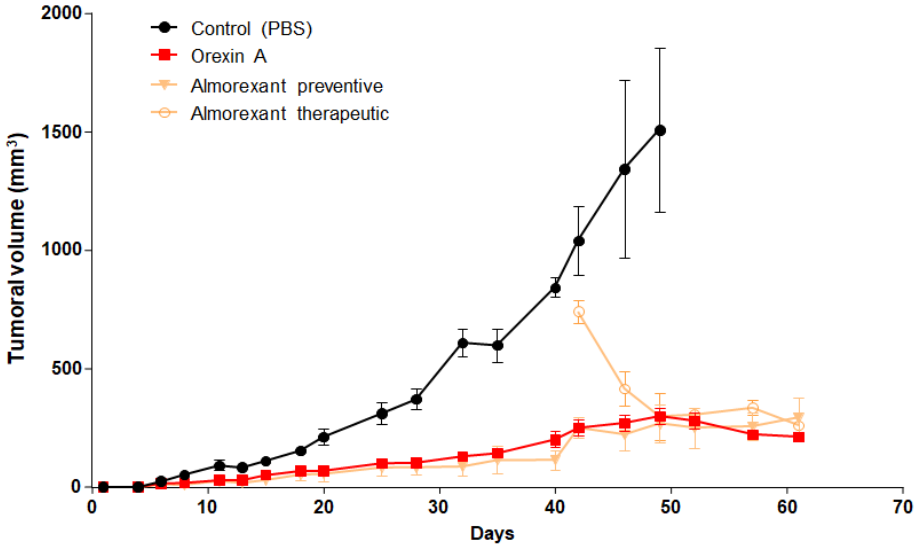
Orexin A reduces tumour growth in preclinical animal models using colonic & pancreatic PDX

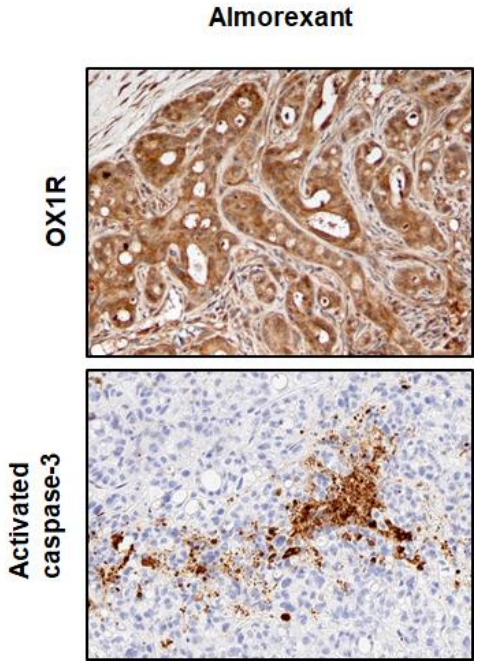


Colon and **pancreas tumor patient derived xenograft (pdx)** were inoculated in the flank of nude mice at day 0. Mice were intraperitoneally injected twice a week with 0,22 µmoles/kg of orexin-A preventive or therapeutic or with PBS (•) for control. The development of tumors was followed by caliper measurement.

Proof of concept

OX1R small molecules agonists reduces tumor growth *in vivo* in PDAC xenograft mouse models



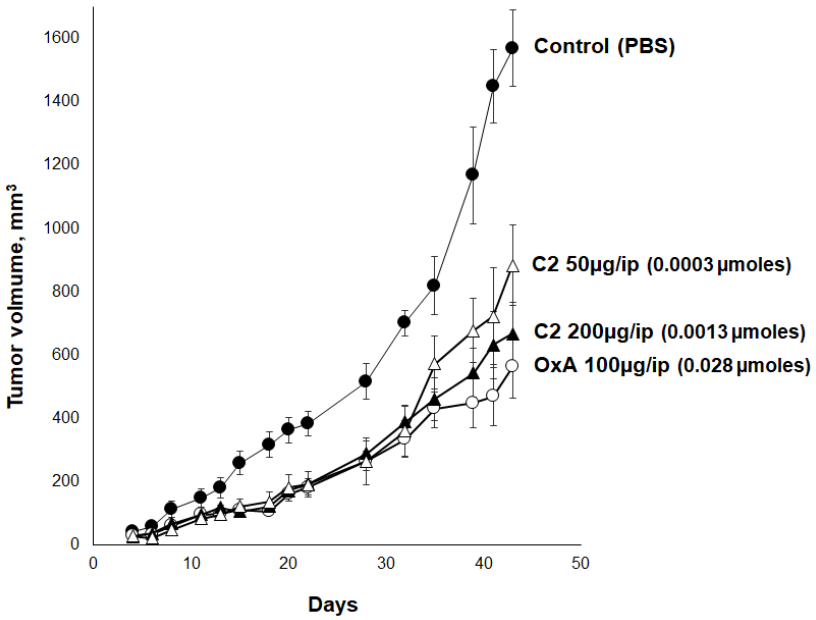


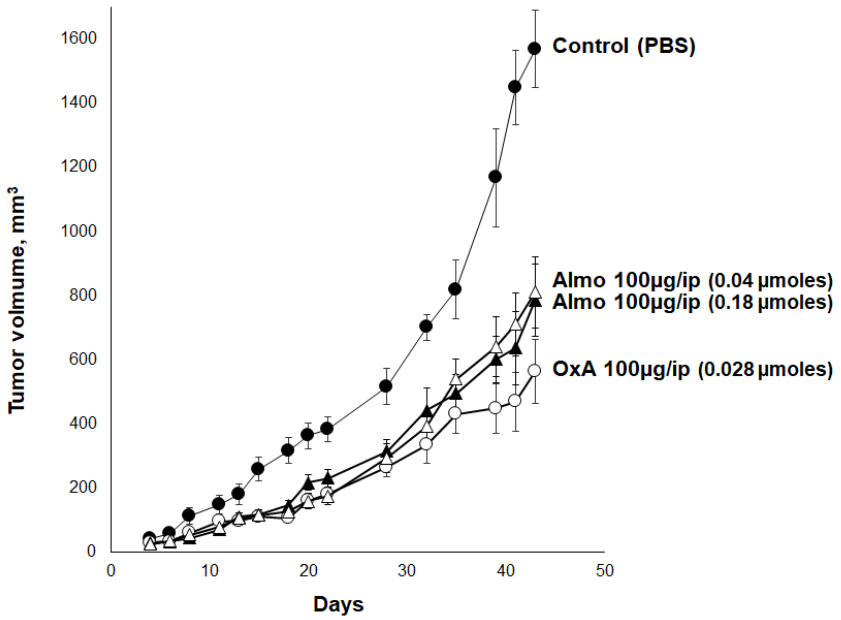
Human Pancreatic cancer cell line (AsPC-1) were xenografted in the flank of nude mice at day 0. Mice were intraperitoneally injected 3 times a week with 100µl of **Almorexant** (1,8µmol/kg) starting at day 0 or at day 38, or of **orexin-A** (1,4 µmol/kg) or with PBS for control. The development of tumors was followed by caliper measurement.
Indirect immunostaining of OX1R (top) and activated caspase-3 (bottom) in xenografted AsPC-1 tumors resected from nude mice.

OX1R AGONISTS FOR THE TREATMENT OF CANCER

Proof of concept

Ox1R hmAb and specific small molecules reduces tumour growth *in vivo* in colonic xenograft mouse models



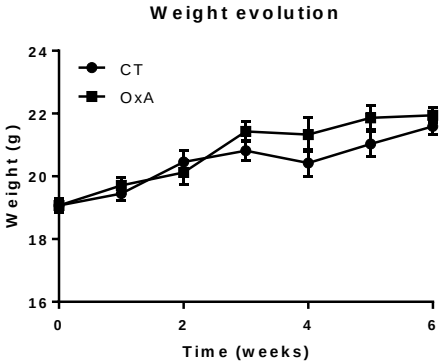


Human colonic cancer cell line (HT-29) were xenografted in the flank of nude mice at day 0. Mice were intraperitoneally injected 3 times a week starting at day 0 either with different doses of : - C2, an anti-Ox1R agonist hmAb, or
- Almorexant,

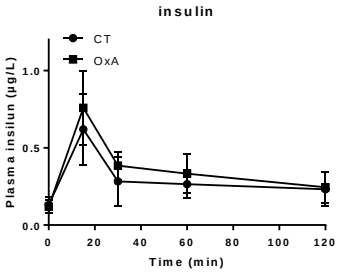
compared to orexin-A and to PBS for control.
The development of tumors was followed by caliper measurement.

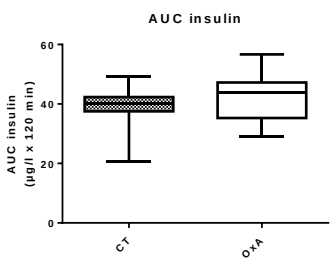
Proof of concept

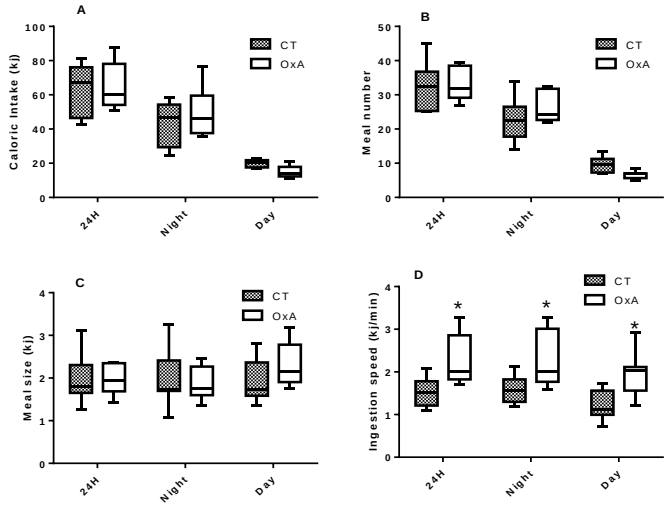
Chronic OxA treatment has not a major impact on the physiology of mice

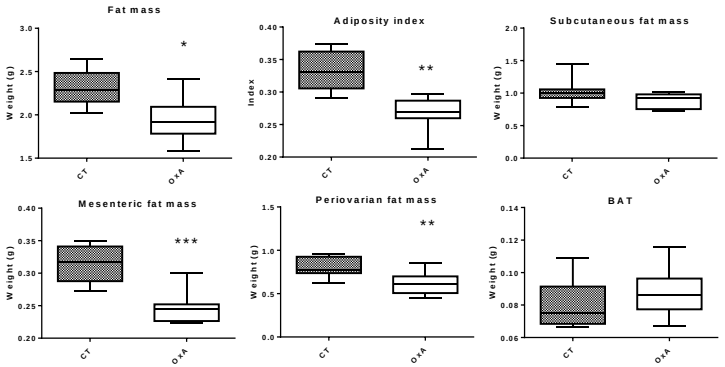


Mice were orally treated during 6 weeks









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