PROTECTIVE EFFECT OF LEUPRORELIN ACETATE ON ACUTE RADIATION-INDUCED INTESTINAL DAMAGE

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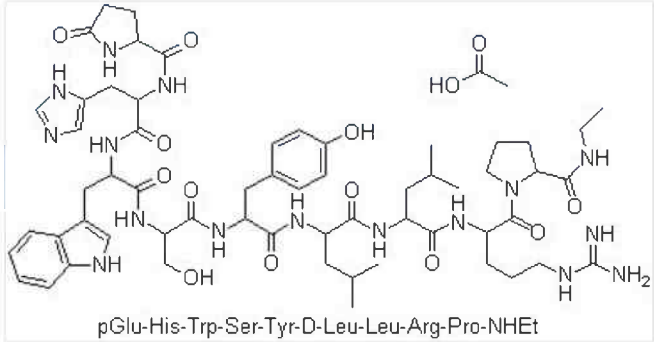
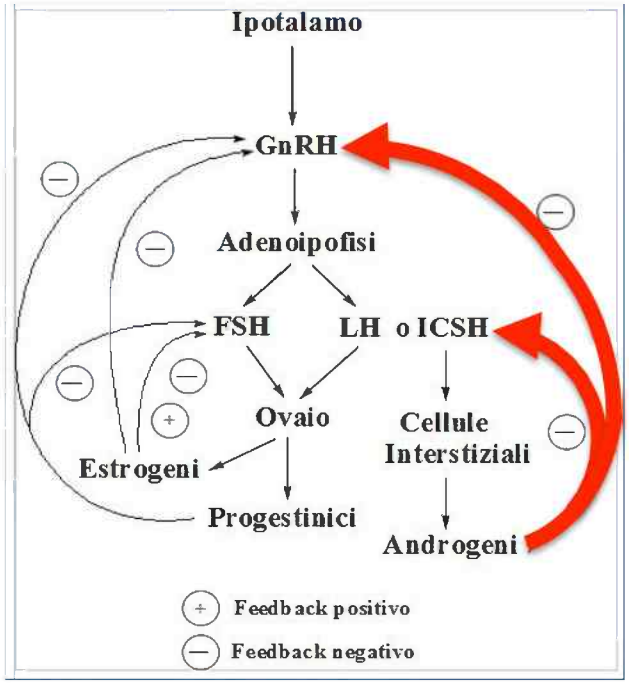
Mechanism of action of Enantone® (Leuprorelin acetate)



Synthetic agonist of GnRH



Therapy

Men: prostate cancer

Women: breast cancer, endometriosis, uterine fibroids

Dose: 3,75 mg/month for 3 months
11.25 mg every 3 months

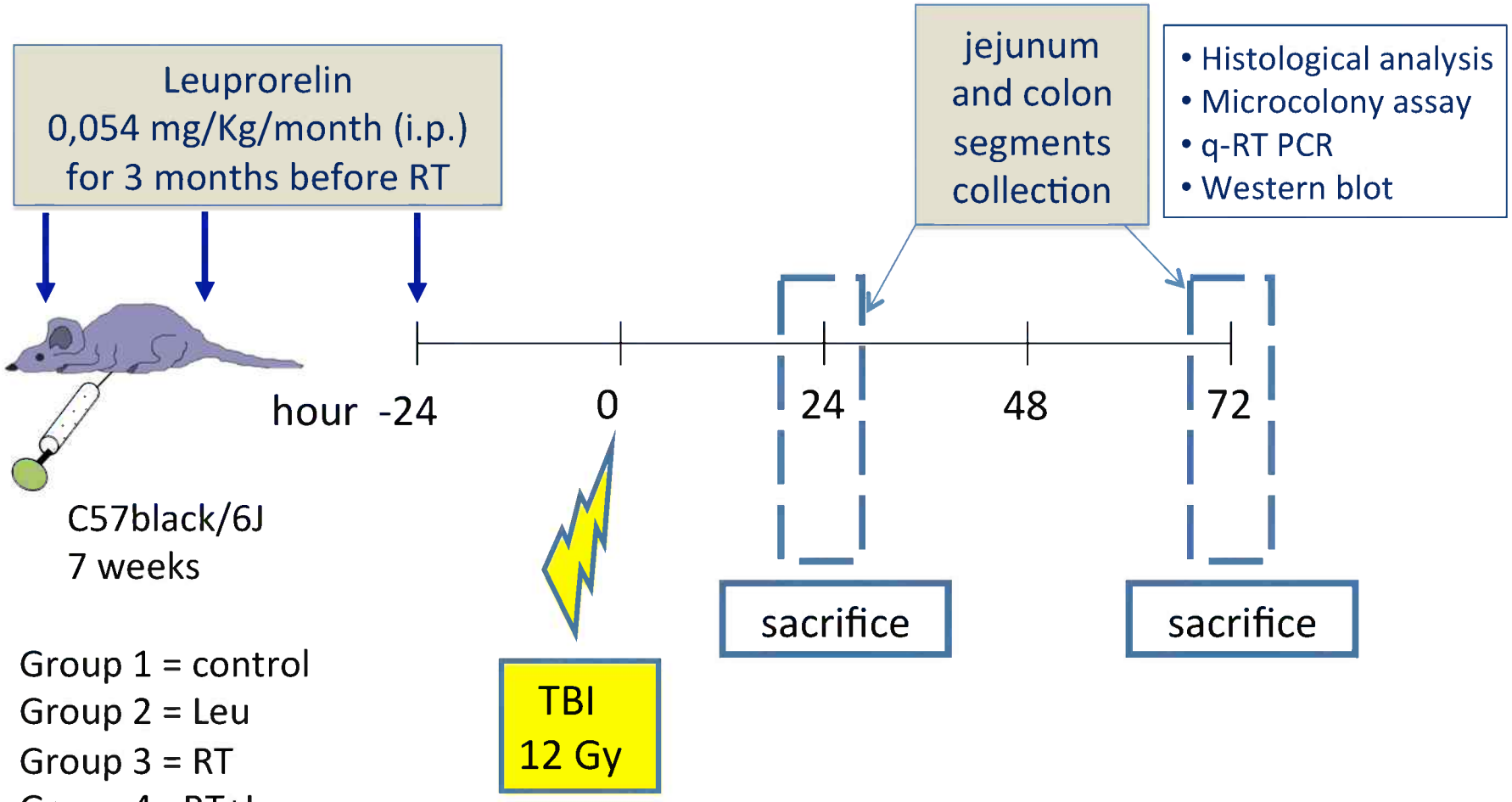
Aim of the study

82 patients treated with neoadjuvant androgenic ablation for prostate cancer experienced less radiation-induced intestinal toxicity

Size reduction of bulky prostatic tumors and optimization of the target volume

Does leuprorelin exert itself a protective effect on irradiated bowel?

Leuprorelin prevents acute radiation-induced intestinal damage



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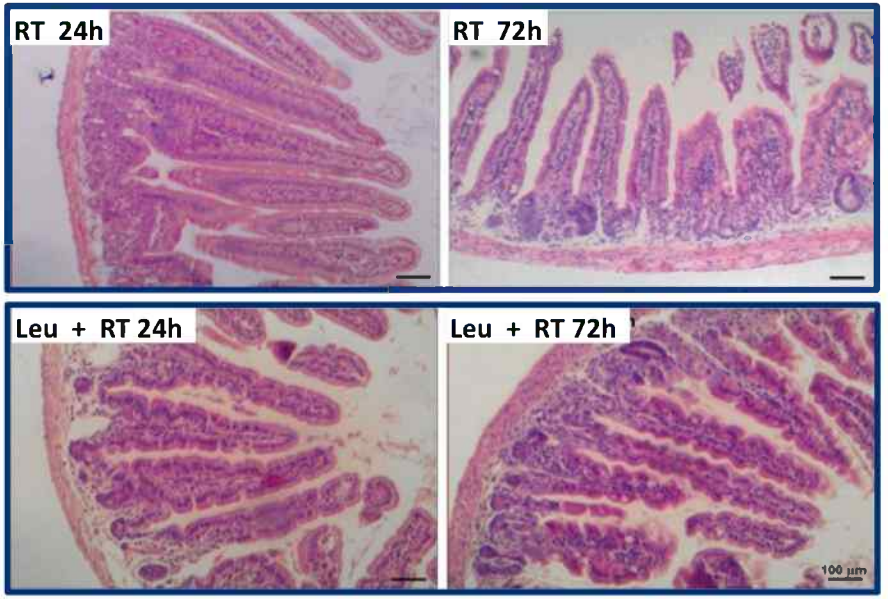
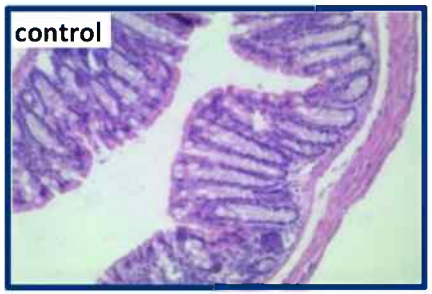
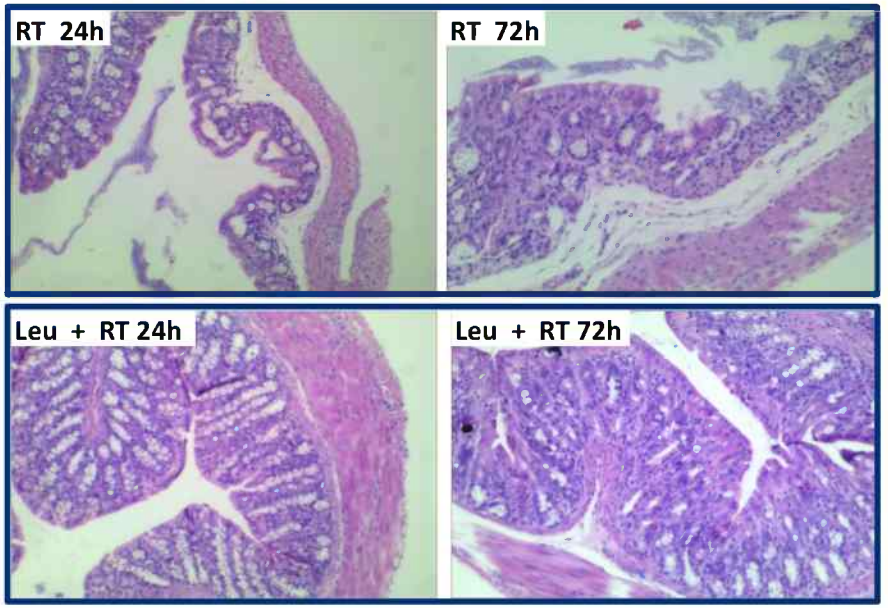
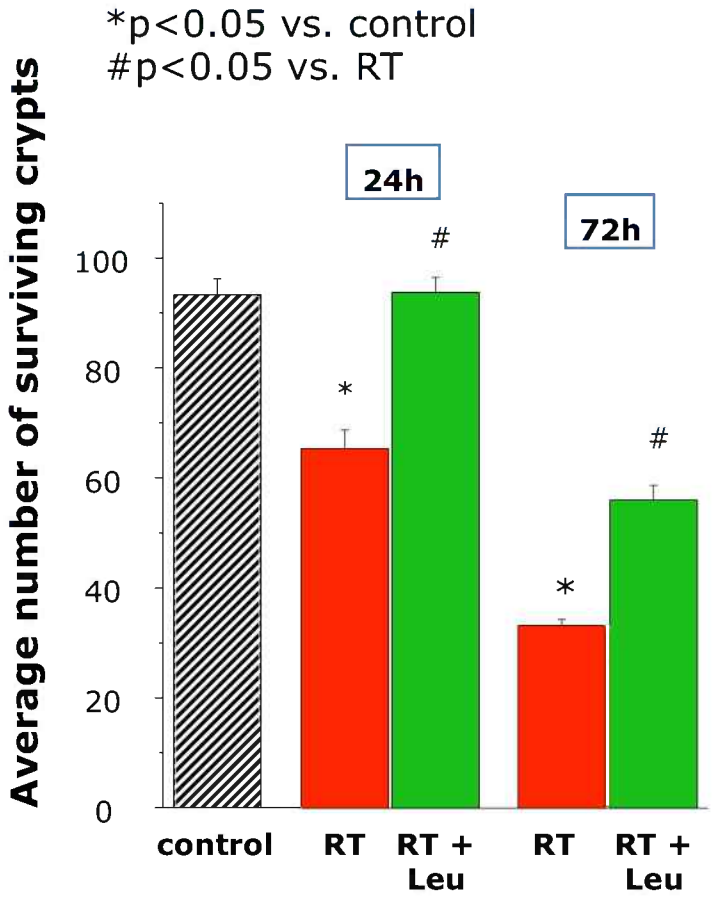


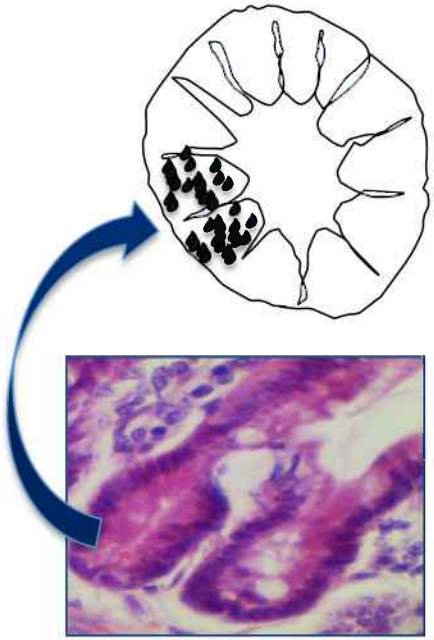
COLON





Microcolony assay





Expression of radio-induced injury markers

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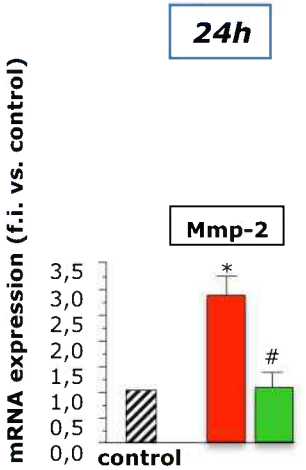
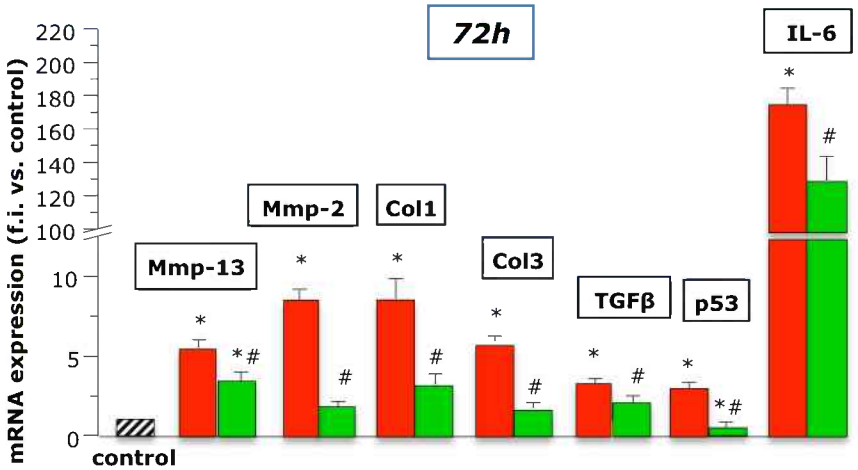
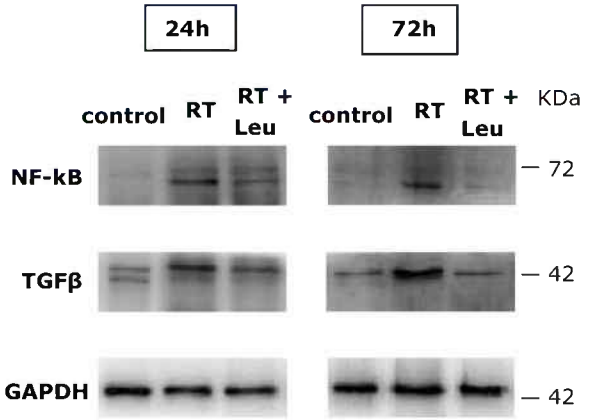
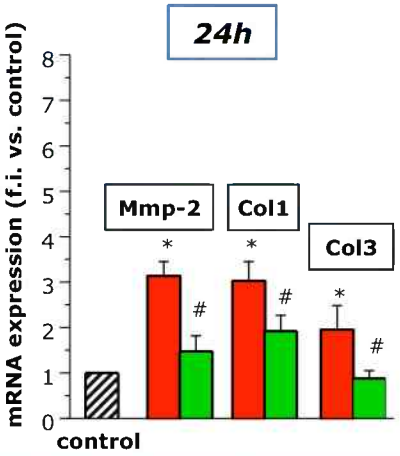


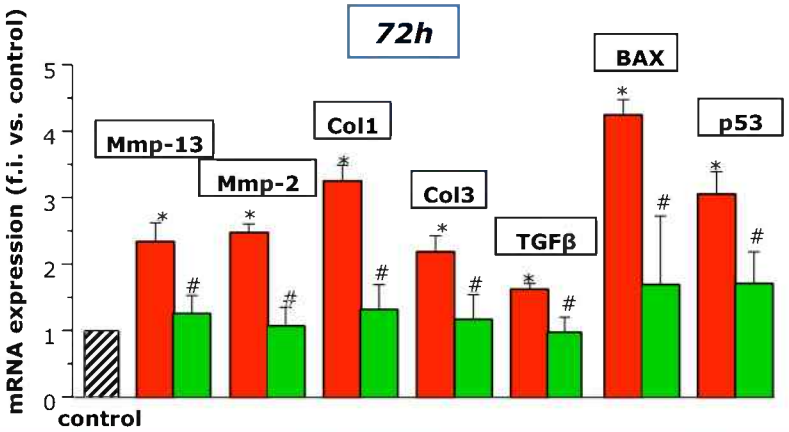


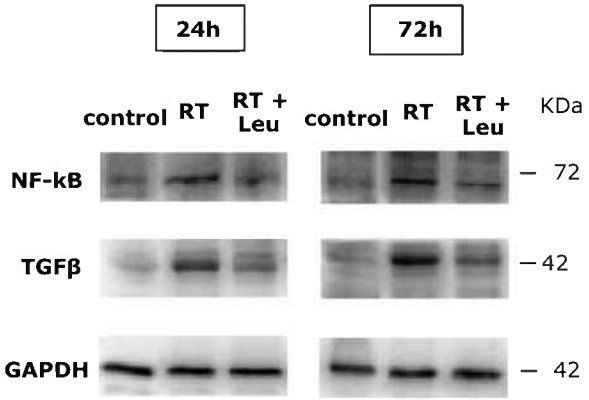


*p<0.05 vs. control
#p<0.05 vs. RT
RT
RT+ Leu

COLON







Mechanisms ???

H-mediated

PRO

LH receptors on cells of the intestinal wall (myenteric neurons, glial cells, neutrophils, endothelial cells, mast-cells) → immunological, circulatory and neuroprotective effects.

Leuprorelin reduces the symptoms in patients affected by irritable bowel syndrome, chronic intestinal pseudo-obstructions, functional intestinal disorders.
(unknown mechanism, an hypothesis is that leuprorelin acts trough the down-regulation of LH secretion, hormone with antagonist effects on gastrointestinal motility).

Palomba S, Fertil Steril. 2005
Hammar O, et al. Drug Target Insights 2012
Mathias JR, et al. Dig Dis Sci. 1994

Not H-mediated
Oxidative Stress Reduction?

PRO

- GnRH agonists inhibit Nitric Oxide synthesis in the corpus luteum of pregnant rats.
  Yang H, et al. Biol Reprod. 2003
- Leuprorelin reduces oxidative stress and cytotoxicity on Alzheimer's Disease.
  Bowen RL, J. Biol. Chem. 2004
  Casadesus G, Biophys. Acta 2006
  Wilson AC, J. Endocrinol. 2006

H-mediated mechanism?

Study repeated on:

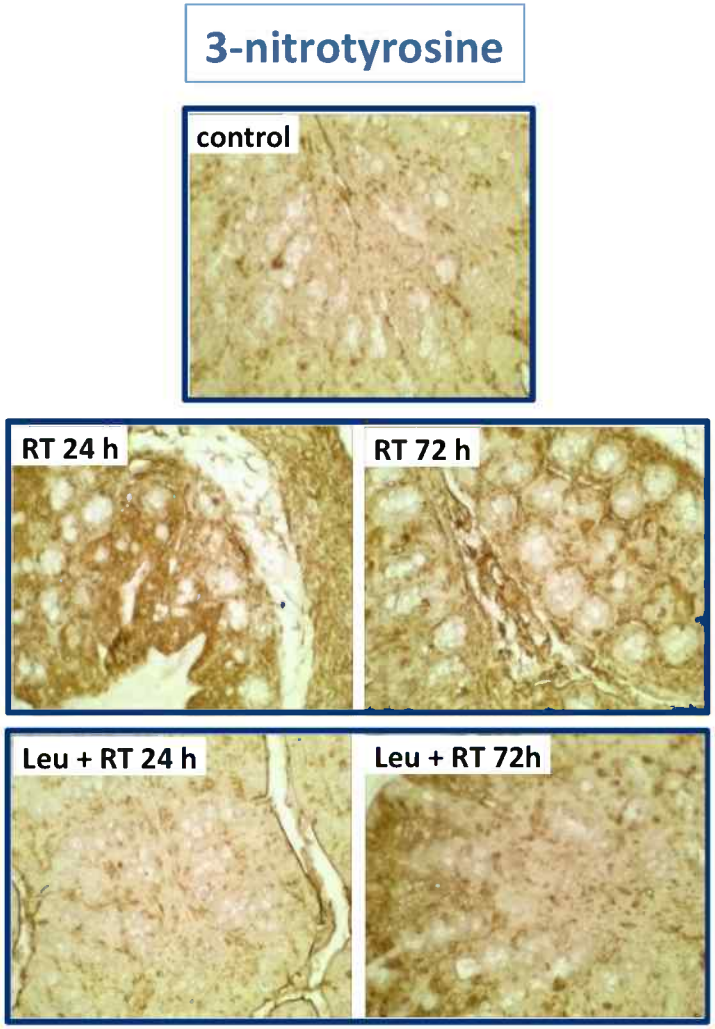
- Female mice
- Male mice
- Surgically castrated male mice

No significant histological or molecular differences between leuprorelin-treated groups

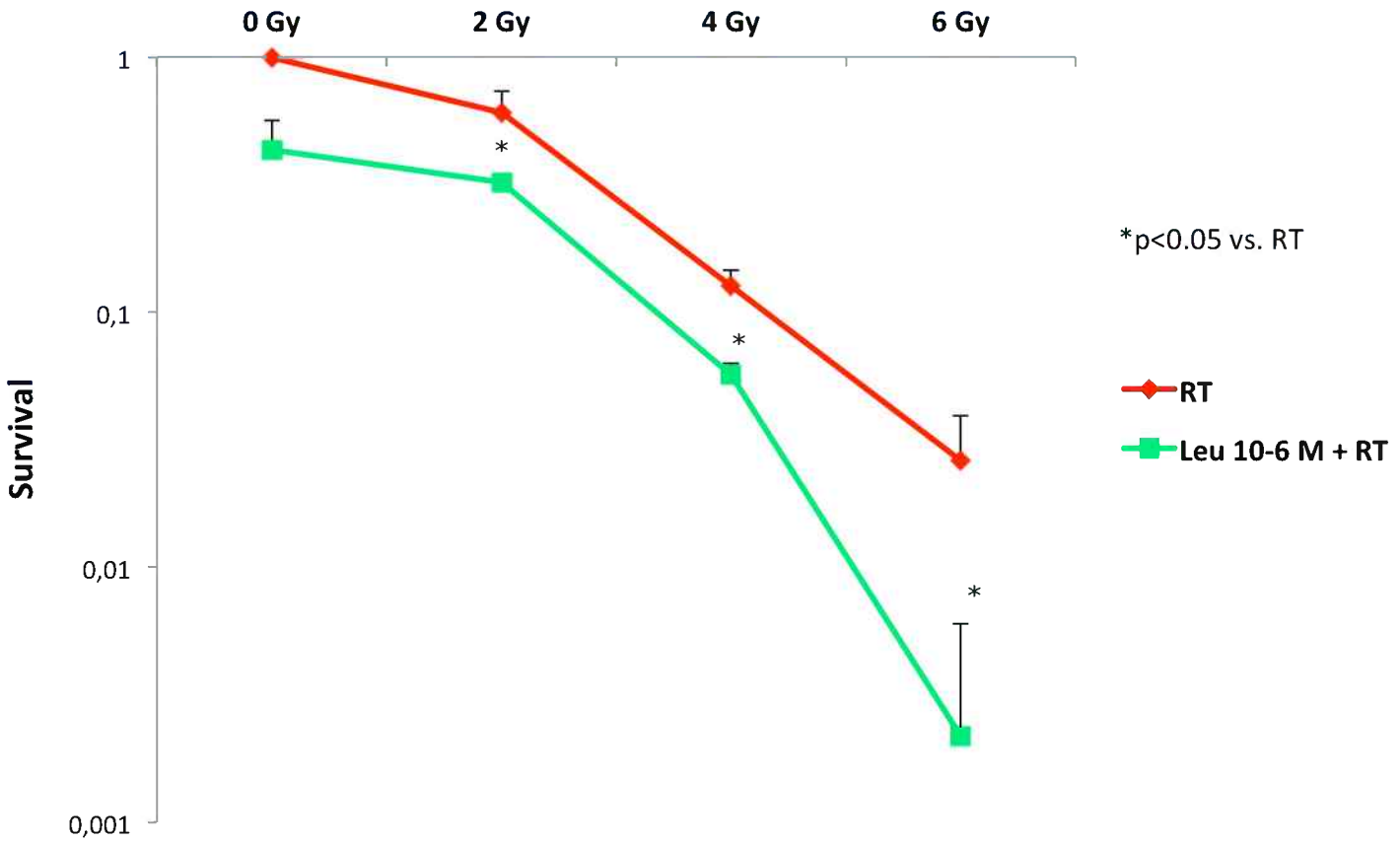
Leuprorelin substituted with a GnRH antagonist

Lack of protective effect

Effect of Leuprorelin on oxidative stress



Clonogenic assay on prostate cancer cells (PC3)



Conclusions

- ✓ Pretreatment with leuprorelin exerts a protective effect against radiation-induced intestinal injury in mice.
- ✓ Leuprorelin doesn't protect prostate cancer cells from radiotherapy.
- ✓ These data suggest that the radioprotective effect intrinsic to the molecule adds to the decrease in treatment volume, reducing intestinal toxicity.
- ✓ More investigations are needed to confirm and to study in deep the way(s) of action for the reported effect of leuprorelin on irradiated intestinal mucosa.

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