

Anti-inflammatory and Immunomodulatory Activities of Parnaparin Sodium (CB-01-05)

C. Rosette¹, L. Moro², G. Celasco², R. Bozzella², M. Ajani², M. Gerloni¹
¹Cosmo Bioscience, San Diego, United States. ² Cosmo Pharmaceuticals, Lainate, Italy

1. Introduction

Phase II clinical trials with oral low molecular weight heparin, parnaparin sodium (CB-01-05) assembled with MMX[®] technology, showed promising efficacy in improving ulcerative colitis symptoms. The mechanisms of action underlying this therapeutic effect have not yet been elucidated. Since IBD is characterized by inflammation and immune dysregulation, we investigated *in vitro* whether CB-01-05 exhibits anti-inflammatory and immunomodulatory activities to account for the positive effects seen in the clinical trials.

2. Conclusions

- Sodium parnaparin inhibited TNF- α and IL-1 β -induced synthesis and secretion of the chemokine IL-8 from human intestinal epithelial cell line.
- Sodium parnaparin inhibited secretion of IL6 from human monocytes.
- Sodium parnaparin substantially inhibited cytokine secretion from activated CD4⁺ T cells: IFN- γ , IL17, TNF- α , IL6, IL-2, IL-5 and IL-10.
- Sodium parnaparin effectively prevented the differentiation of naive CD4⁺ T cells into cells characteristic of mature Th1 and Th2 cells.

3. Relevance

Reduction of synthesis of several cytokines that are known to be overexpressed in inflamed colonic mucosa of IBD patients is useful to control the inflammatory response in this chronic disease. It is anticipated that the delivery of sodium parnaparin-MMX[®] into the colon could antagonize the local inflammatory cytokine effects, without affecting the functions of these cytokines in the periphery.

Acknowledgments

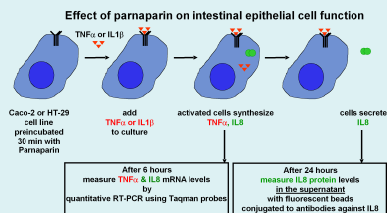
We thank Dr. R. Bacchetta for the L cells and technical guidance, K. Fontes, F.B.Laysa, M. Mascarenas, and S.Pakar for laboratory assistance.

For further information

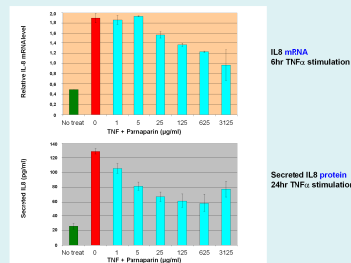
Please contact Carl Rosette: crosette@cosmobioscience.com. More information on this and related projects can be obtained at www.cosmopharmaceuticals.com.



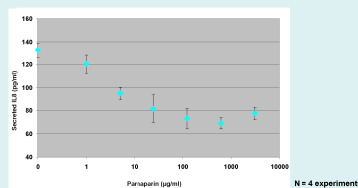
4. Activity on Epithelial Cells



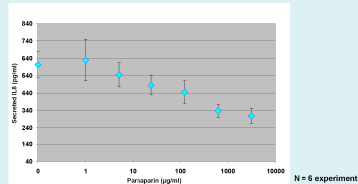
Parnaparin inhibits TNF α -induced IL8 mRNA expression and IL8 protein secretion from Caco-2 cells



Parnaparin inhibits TNF α -induced IL8 secretion from Caco-2

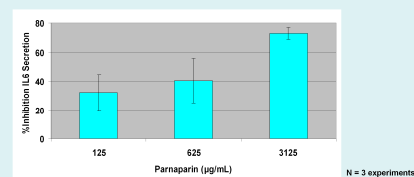


Parnaparin inhibits IL1 β -induced IL8 secretion from Caco-2



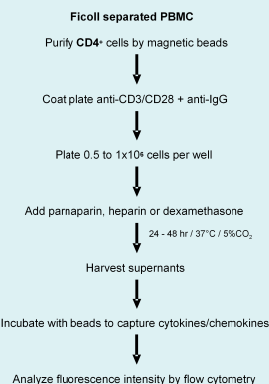
5. Activity on Monocytes

Parnaparin inhibits IL6 from Monocytes

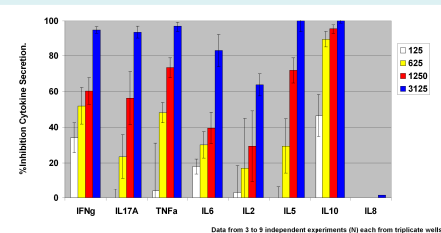


6. Activity on CD4 T Cells

Inhibition of cytokines from CD4⁺ cells

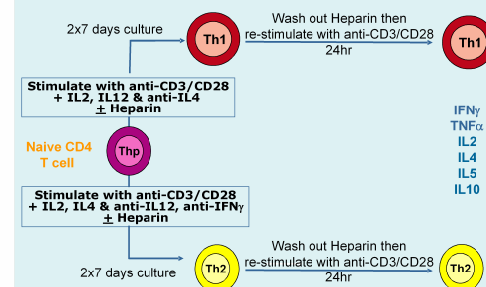


Parnaparin inhibits secretion of multiple cytokines



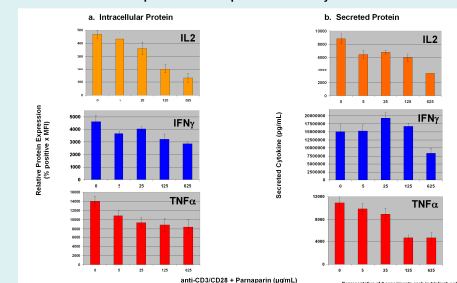
7. Activity on CD4 Polarization

Effect of Parnaparin on Th1/Th2 differentiation *in vitro*



Effect of Parnaparin on Th1/Th2 differentiation *in vitro*

Parnaparin inhibits expression of Th1 cytokines



Parnaparin inhibits CD4⁺ T Cell Polarization

