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- (54) **DELIVERY OF TREFOIL PEPTIDES**
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- See application file for complete search history.

- (56) **References Cited**
- U.S. PATENT DOCUMENTS**
- 6,221,648 B1 \* 4/2001 Le Page et al. .... 435/252.3  
6,221,840 B1 \* 4/2001 Podolsky ..... 514/12  
6,605,286 B2 \* 8/2003 Steidler et al. .... 424/243.1
- FOREIGN PATENT DOCUMENTS**
- WO WO 82/03329 \* 10/1982  
WO WO 92/14837 9/1992  
WO WO 93/17117 \* 2/1993  
WO WO 97/09437 3/1997  
WO WO 97/14806 4/1997

- WO WO 97/38712 10/1997  
WO WO 00/23471 4/2000  
WO WO 01/21200 \* 3/2001

**OTHER PUBLICATIONS**

- Malin et al. *Ann. Nutr. Metabol.* 40: 137-145, 1996.\*  
Wells et al. *Mol. Microbiol.* 8: 1155-1162, Jun. 1993.\*  
Wells et al. *Appl. Environ. Microbiol.* 59: 3954-3959, Nov. 1993.\*  
Babyatsky et al. *Gastroenterology* 110: 489-497, 1996.\*  
Playford et al. *PNAS* 93: 2137-2142, Mar. 1996.\*  
Chinery et al. *Clin. Sci.* 88: 401-403, 1995.\*  
Tran et al. *Gut* 44: 636-642, May 1999.\*  
Robinson et al. *Nature Biotechnol.* 15: 653-657, 1997.\*  
Pouwels et al. *J. Biotechnol.* 44: 183-192, 1992.\*  
Pouwels et al. *Int. J. Food Microbiol.* 41: 155-167, 1998.\*  
Steidler L. *Nato ASI Series. vol. H98.* Springer Verlag, Berlin Heidelberg, pp. 63-79, 1996.\*  
Wells et al. *Antonie van Leeuwenhoek* 70: 317-330, 1996.\*  
Slos et al. *FEMS Microbiol. Lett.* 169: 29-36, 1998.\*  
Steidler et al. *Infect. Immun.* 66: 3183-3189, 1998.\*  
Wong et al., *Int. J. Gastroenterology and Hepatology*, 44(6): 890-895, 1999.  
Tan et al., *Biochem. and Biophys. Res. Communications*, 237: 673-677, 1997.  
Lefebvre, *J. Cell. Biol.*, 122(1): 191-198, 1993.  
Poulsen, S.S.; Thulesen, J.; Christensen, L.; Nexø, E.; and Thim, L., "Metabolism of Oral Trefoil Factor 2 (TFF2) and the Effect of Oral and Parenteral TFF2 on Gastric and Duodenal Ulcer Healing in the Rat", *Gut*, vol. 45, No. 2 (1999); pp. 516-522.

\* cited by examiner

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(57) **ABSTRACT**

The present invention relates to a microorganism, preferably a bacterial strain, preferably a non-pathogenic strain, preferably a non-invasive strain, preferably a food grade strain, preferably a gram-positive bacterial strain, delivering a trefoil peptide in vivo. Preferably said trefoil peptide is TFF1. The present invention further relates to a method for the delivery of trefoil peptide to the gastro-intestinal tract comprising the administration of such a bacterial strain. The present invention also relates to a pharmaceutical composition comprising a trefoil peptide delivering bacterium as well as methods of treatment of acute gastro-intestinal inflammatory diseases comprising administration of said transformed bacterial strains, particularly for treating acute colitis, including but not limited to acute flare-ups of Crohn's disease and ulcerative colitis in humans, as well as for treating gastro-intestinal disorders of a similar nature in other animal species.

**12 Claims, 16 Drawing Sheets**