An innovative therapeutic biopharma solution to achieve peripheral and central protection during colitis

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Enteric glia activation has been reported to amplify intestinal inflammation during colitis and molecules inhibiting enteric activation might mitigate the course of inflammatory bowel diseases (IBD). Palmitoylethanolamide (PEA) is an *N*-acylethanolamide produced on-demand by the enzyme *N*-acylphosphatidylethanolamine-preferring phospholipase D (NAPE-PLD). Being a key member of the larger family of bioactive autacoid local injury antagonist amides (ALIAmides), PEA significantly improves the clinical and histopathological stigmata in models of ulcerative colitis (UC). Despite its safety profile, high PEA doses are required *in vivo* to exert its therapeutic activity; therefore, PEA has been tested only in animals or human biopsy samples, to date. To overcome these limitations, we developed a NAPE-PLD-expressing *Lactobacillus paracasei F19* (pNAPE-LP), able to produce PEA under the boost of ultra-low palmitate supply, and investigated its therapeutic potential in a murine model of UC. The co-administration of pNAPE-LP and palmitate led to a time-dependent release of PEA, resulting in a significant amelioration of the clinical and histological damage score, with a significantly reduced neutrophil infiltration, lower expression and release of pro-inflammatory cytokines and oxidative stress markers, and a markedly improved epithelial barrier integrity. The effect of pNAPE-LP with ultra-low palmitate supply treatment caused a consequent reduction of enteric glia activation induced by DSS, and a parallel decrease expression of S100B, GFAP, TLR-4 and iNOS was also observed, suggesting that the pNAPE-LP bacteria was also able to moderate the enteric neuroinflammation featuring colitis. We concluded that pNAPE-LP with ultra-low palmitate supply stands as a new method to increase the *in situ* intestinal delivery of PEA representing a new therapeutic able of controlling intestinal inflammation in inflammatory bowel disease and targeting the enteric glia activation by genetically-modified probiotics.