developability can be improved. Although an already established approach in oncology, it was only recently adapted in order to treat inflammatory disorders and autoimmunity. Several cytokines (IL-10 amongst others) and a photosensitizer were targeted to psoriatic lesions by fusion to a scFv antibody fragment specific for the extra domain B of fibronectin (Trachsel, E. et al., J. Invest. Dermatol. 127(4), 881-886 (2007). Moreover, antibody fragments specific for the extra domain A of fibronectin (F8, DEKAVIL, Philogen SpA)-IL-10 fusion proteins were used preclinically to inhibit the progression of established collagen-induced arthritis (Trachsel, E. et al., Arthritis Res. Ther. 9(1), R 9 (2007); Schwager, K. et al., Arthritis Res. Ther. 11(5), R142 (2009)) and entered clinical trials. Recently, the same F8-IL-10 fusion protein was used for targeting endometriotic lesions in a syngeneic mouse model and reduced the average lesion sizes compared to the saline control group (Schwager, K. et al., Hum. Reprod. 26(9), 2344-2352 (2011)).

The IgG-IL-10 fusion proteins of this ~~invention~~disclosure have several advantages over the known antibody fragment-based (e.g. scFv, diabody, Fab) IL-10 fusion proteins, including improved produceability, stability, serum half-life and, surprisingly, significantly increased biological activity upon binding to target antigen.

## Summary ~~of the Invention~~

In one aspect, the ~~invention~~disclosure provides a fusion protein of an IgG-class antibody and an IL-10 molecule, wherein the fusion protein comprises two identical heavy chain polypeptides and two identical light chain polypeptides. In one embodiment, each of said heavy chain polypeptides comprises an IgG-class antibody heavy chain and an IL-10 monomer. In a more specific embodiment, said IL-10 monomer is fused at its N-terminus to the C-terminus of said IgG-class antibody heavy chain, optionally through a peptide linker. In one embodiment, said heavy chain polypeptides each essentially consist of an IgG-class antibody heavy chain, an IL-10 monomer and optionally a peptide linker. In one embodiment, each of said light chain polypeptides comprises an IgG-class antibody light chain. In one embodiment, said light chain polypeptides each essentially consist of an IgG-class antibody light chain.

In some embodiments, said IL-10 monomer is a native IL-10 monomer, particularly a native human IL-10 monomer. In a specific embodiment, said IL-10 monomer comprises the polypeptide sequence of SEQ ID NO: 1. In one embodiment, said IL-10 monomers comprised in said heavy chain polypeptides form a functional homodimeric IL-10 molecule.

comprises the heavy chain CDR (HCDR) 1 of SEQ ID NO: 37, the HCDR 2 of SEQ ID NO: 41, the HCDR 3 of SEQ ID NO: 49, the light chain CDR (LCDR) 1 of SEQ ID NO: 53, the LCDR 2 of SEQ ID NO: 57 and the LCDR 3 of SEQ ID NO: 61. In an even more specific embodiment, said IgG-class antibody comprises the heavy chain variable region (VH) of SEQ ID NO: 63 and the light chain variable region (VL) of SEQ ID NO: 65. In another, particular, specific embodiment, said IgG-class antibody comprises the HCDR 1 of SEQ ID NO: 37, the HCDR 2 of SEQ ID NO: 43, the HCDR 3 of SEQ ID NO: 47, the LCDR 1 of SEQ ID NO: 51, the LCDR 2 of SEQ ID NO: 55 and the LCDR 3 of SEQ ID NO: 59. In an even more specific embodiment, said IgG-class antibody comprises the VH of SEQ ID NO: 67 and the VL of SEQ ID NO: 69.

In one embodiment, the fusion protein is capable of binding to IL-10 receptor-1 (IL-10R1) with an affinity constant ($K_D$) of smaller than 1 nM, particularly smaller than 100 pM, when measured by SPR at 25°C. In a specific embodiment, said IL-10R1 is human IL-10R1. In one embodiment, said affinity constant ($K_D$) for binding to IL-10R1 is about equal or greater than said affinity constant ($K_D$) for binding to FAP, when measured by SPR at 25°C. In a specific embodiment, said $K_D$ for binding to IL-10R1 is greater than about half of said $K_D$ for binding to FAP.

In a particular embodiment, the ~~invention~~disclosure provides a fusion protein of an IgG-class antibody and an IL-10 molecule, wherein the fusion protein comprises two identical heavy chain polypeptides and two identical light chain polypeptides; and wherein

(i) said IgG-class antibody comprises the heavy chain CDR (HCDR) 1 of SEQ ID NO: 37, the HCDR 2 of SEQ ID NO: 43, the HCDR 3 of SEQ ID NO: 47, the light chain CDR (LCDR) 1 of SEQ ID NO: 51, the LCDR 2 of SEQ ID NO: 55 and the LCDR 3 of SEQ ID NO: 59, or comprises the heavy chain variable region (VH) of SEQ ID NO: 67 and the light chain variable region (VL) of SEQ ID NO: 69;

(ii) said IgG-class antibody comprises amino acid substitutions L234A, L235A and P329G (EU numbering) in the antibody heavy chains;

(iii) said IL-10 molecule comprises the sequence of SEQ ID NO: 1; and

(iv) said heavy chain polypeptides each comprise an IgG-class antibody heavy chain and an IL-10 monomer fused at its N-terminus to the C-terminus of said IgG-class antibody heavy chain through a peptide linker.

In another embodiment, the ~~invention~~disclosure provides a fusion protein of an IgG-class antibody and an IL-10 molecule, wherein the fusion protein comprises two identical heavy chain polypeptides and two identical light chain polypeptides; and wherein

(i) said IgG-class antibody comprises the heavy chain CDR (HCDR) 1 of SEQ ID NO: 37, the HCDR 2 of SEQ ID NO: 41, the HCDR 3 of SEQ ID NO: 49, the light chain CDR (LCDR) 1 of SEQ ID NO: 53, the LCDR 2 of SEQ ID NO: 57 and the LCDR 3 of SEQ ID NO: 61, or comprises the heavy chain variable region (VH) of SEQ ID NO: 63 and the light chain variable region (VL) of SEQ ID NO: 65;

(ii) said IgG-class antibody comprises amino acid substitutions L234A, L235A and P329G (EU numbering) in the antibody heavy chains;

(iii) said IL-10 molecule comprises the sequence of SEQ ID NO: 1; and

(iv) said heavy chain polypeptides each comprise an IgG-class antibody heavy chain and an IL-10 monomer fused at its N-terminus to the C-terminus of said IgG-class antibody heavy chain through a peptide linker.

The ~~invention~~disclosure further provides, in a second aspect, a polynucleotide encoding the fusion protein of the ~~invention~~disclosure. Further provided, in a third aspect, is a vector, particularly an expression vector, comprising the polynucleotide of the ~~invention~~disclosure. In ~~another~~ a fourth aspect, the ~~invention~~disclosure provides a host cell comprising the polynucleotide or the vector of the ~~invention~~disclosure. The ~~invention~~disclosure also provides, in a fifth aspect, a method for producing a fusion protein of the ~~invention~~disclosure, comprising the steps of (i) culturing the host cell of the ~~invention~~disclosure under conditions suitable for expression of the fusion protein, and (i) recovering the fusion protein. Also provided, in a sixth aspect, is a fusion protein of an IgG-class antibody and an IL-10 molecule produced by said method.

In ~~one~~ a seventh aspect, the ~~invention~~disclosure provides a pharmaceutical composition comprising the fusion protein of the ~~invention~~disclosure and a pharmaceutically acceptable carrier. In an eighth aspect, ~~T~~the fusion protein or the pharmaceutical composition of the ~~invention~~disclosure is also provided for use as a medicament. In a ninth aspect, the fusion protein or the pharmaceutical composition of the disclosure is provided, ~~and~~ for use in the treatment or prophylaxis of an inflammatory disease. The inflammatory disease may be, specifically inflammatory bowel disease or rheumatoid arthritis, most specifically inflammatory bowel disease. Further provided, in a tenth aspect, is the use of the fusion protein of the ~~invention~~disclosure for the manufacture of a medicament for the treatment of a disease in an individual in need thereof. The present disclosure also provides, ~~and~~ a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the fusion protein of the ~~invention~~disclosure in a pharmaceutically acceptable form. In one embodiment, said disease is an inflammatory disease. In a more specific embodiment, said inflammatory disease is inflammatory bowel disease or rheumatoid arthritis. In an even more specific embodiment, said inflammatory disease is inflammatory bowel disease. In one embodiment, said individual is a mammal, particularly a human.

38. A method for producing the fusion protein of any one of claims 1-34, comprising the steps of (i) culturing the host cell of claim 37 under conditions suitable for expression of the fusion protein, and (ii) recovering the fusion protein.

39. A fusion protein of an IgG-class antibody and an IL-10 molecule, produced by the method of claim 38.

40. A pharmaceutical composition comprising the fusion protein of any one of claims 1-34 or 39 and a pharmaceutically acceptable carrier.

41. The fusion protein of any one of claims 1-34 or 39, or the pharmaceutical composition of claim 40, for use as a medicament.

42. The fusion protein of any one of claims 1-34 or 39, or the pharmaceutical composition of claim 40, for use in the treatment or prophylaxis of an inflammatory disease.

43. The fusion protein or the pharmaceutical composition of claim 42, wherein said inflammatory disease is inflammatory bowel disease or rheumatoid arthritis.

44. Use of the fusion protein of any one of claims 1-34 or 39 for the manufacture of a medicament for the treatment of a disease in an individual in need thereof.

45. The use of claim 44, wherein said disease is an inflammatory disease.

46. The use of claim 45, wherein said inflammatory disease is inflammatory bowel disease or rheumatoid arthritis.

47. The use of any one of claims 44-46, wherein said individual is a mammal, particularly a human.

~~48. A method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the fusion protein of any one of claims 1-34 or 39 in a pharmaceutically acceptable form.~~

~~49. The method of claim 48, wherein said disease is an inflammatory disease.~~

~~50. The method of claim 49, wherein said inflammatory disease is inflammatory bowel disease or rheumatoid arthritis.~~

~~51. The method of any one of claims 48-50, wherein said individual is a mammal, particularly a human.~~