

and EDB domains of fibronectin, respectively, and anti-tenascin C antibody F16 (Brack *et al.* 2006, Villa *et al.*, 2008, Viti *et al.*, 1999), have been employed for the development of armed antibodies, some of which have begun clinical testing in oncology and in rheumatology (Eigentler *et al.*, 2011; Papadia *et al.*, 2012). The tumour targeting properties of these antibodies have also been documented in mouse models of cancer and in patients

Interleukin 22 (IL22) is a 17 kDa globular cytokine belonging to the IL-10 family, which is mainly secreted by NK cells, dendritic cells and T-cells (Murphy 2012). It contains two intramolecular disulfide bonds and three N-linked glycosylation sites. Biological functions of IL22 include involvement in tissue protection, autoimmunity and inflammation. Secreted by lamina propria effector T-cells in the intestine, it induces mucin production, antimicrobial, proliferative and antiapoptotic pathways, which prevent tissue damage and promote epithelial repair. (Li *et al.* 2014). We investigated whether IL22 could be successfully fused to a vascular targeting antibody.

Cytokines can be conjugated to antibody molecules to produce immunocytokines as mentioned above. However, not all immunocytokines retain, for example, the *in vivo* targeting properties of the parental antibody (Pasche & Neri 2012) or expected activities. The preparation of immunocytokines with therapeutic effects, such as anti-inflammatory activity, is therefore far from straightforward.

The preparation of conjugates comprising a mouse IgG1 Fc fused to the N-terminus or C-terminus of mouse IL-22 is described in Smith *et al.* 2013. These conjugates were prepared with a view to providing a more potent and longer-lasting IL-22R agonist compared with rIL-22. The purpose of the Fc region in this instance was therefore not to target IL22 to regions of disease as was the case with the immunocytokines described in the preceding paragraph.

## **Summary**

In one aspect, there is provided a conjugate comprising interleukin-22 (IL22) and an antibody molecule, or antigen-binding fragment thereof, which binds an antigen associated with angiogenesis.

In another aspect, there is provided a nucleic acid molecule encoding a conjugate as described herein.

In another aspect, there is provided an expression vector comprising the nucleic acid as described herein.

In another aspect, there is provided a host cell comprising the vector as described herein.

In another aspect, there is provided a method of producing a conjugate as described herein, the method comprising culturing the host cell as described herein under conditions for expression of the conjugate.

In another aspect, there is provided the conjugate as described herein for use in therapy of the human body.

In another aspect, there is provided the conjugate as described herein for use in the treatment of an autoimmune disease in a patient.

In another aspect, there is provided the conjugate as described herein for use in the delivery of IL22 to sites of autoimmune disease in a patient.

In another aspect, there is provided use of a therapeutically effective amount of a conjugate as described herein in the manufacture of a medicament for treating an autoimmune disease in a patient.

In another aspect, there is provided use of the conjugate as described herein in the manufacture of a medicament for delivering IL22 to sites of autoimmune disease in a patient.

In another aspect, there is provided the conjugate as described herein for use in the treatment of inflammation in a patient.

In another aspect, there is provided the conjugate as described herein for use in the delivery of IL22 to sites of inflammation in a patient.

In another aspect, there is provided use of a therapeutically effective amount of a conjugate as described herein in the manufacture of a medicament for treating inflammation in a patient.

In another aspect, there is provided use of the conjugate as described herein in the manufacture of a medicament for delivering IL22 to sites of inflammation in a patient.

### **Statements of Invention**

The present inventors have shown that IL22 can be conjugated to antibodies, which bind ED-A, while retaining not only the targeting properties of the unconjugated antibody but also the biological activity of IL22.

In one aspect, the present invention therefore relates to a conjugate comprising interleukin-22 (IL22) and an antibody molecule, or antigen-binding fragment thereof, which binds an antigen associated with angiogenesis. The present invention also relates to a nucleic acid

22. A method of producing a conjugate according to any one of claims 1 to 17, the method comprising culturing the host cell of claim 21 under conditions for expression of the conjugate.

23. The method of claim 22 further comprising isolating and/or purifying the conjugate following expression.

24. The conjugate according to any of claims 1 to 17 for use in therapy of the human body.

25. The conjugate according to any one of claims 1 to 17 for use in the treatment of an autoimmune disease in a patient.

26. The conjugate according to any one of claims 1 to 17 for use in the delivery of IL22 to sites of autoimmune disease in a patient.

27. Use of a therapeutically effective amount of a conjugate according to any one of claims 1 to 17 in the manufacture of a medicament for treating an autoimmune disease in a patient.

28. Use of the conjugate according to any one of claims 1 to 17 in the manufacture of a medicament for delivering IL22 to sites of autoimmune disease in a patient.

29. The conjugate for use according to claim 25 or 26, or the use according to claim 27 or 28, wherein the autoimmune disease is selected from the group consisting of: bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis (MS), endometriosis, autoimmune diabetes (such as diabetes mellitus type 1), psoriasis, psoriatic arthritis, periodontitis and atherosclerosis.

30. The conjugate for use or the use according to claim 29, wherein the autoimmune disease is bowel disease.

31. The conjugate for use or the use according to claim 30, wherein the bowel disease is ulcerative colitis or Crohn's disease.

32. The conjugate according to any one of claims 1 to 17 for use in the treatment of inflammation in a patient.

33. The conjugate according to any one of claims 1 to 17 for use in the delivery of IL22 to sites of inflammation in a patient.

34. Use of a therapeutically effective amount of a conjugate according to any one of claims 1 to 17 in the manufacture of a medicament for treating inflammation in a patient.

35. Use of the conjugate according to any one of claims 1 to 17 in the manufacture of a medicament for delivering IL22 to sites of inflammation in a patient.

36. The conjugate for use according to claim 32 or 33, or the use according to claim 34 or 35, wherein the inflammation is the result of an inflammatory disease and/or disorder.

37. The conjugate for use according to claim 36, or the use according to claim 36, wherein the inflammatory disease and/or disorder is selected from the group consisting of: graft versus host disease; wound healing; and ulcers, in particular diabetic foot ulcers.