(1996) Arthritis Rheum. 39: 1535-1544); Fernandes et al. (1999) Am. J. Pathol. 154: 11590-11690); Zhang et al. (2006) Biochem. Biophys. Res. Commun. 341 : 202-208). In addition, IL-1 knockout (KO) mice were found to be resistant to surgically induced cartilage damage when compared to their wild-type counterparts (Glasson et al. (2009) Osteoarthritis Cartilage, 18: 572-580).

Both IL-1α and IL-1β are expressed in synovial membranes, cartilage, and synovial fluid of human OA patients (see, e.g., Farahat et al. (1993) Ann. Rheum. Dis. 52: 870-875). The IL-1 antagonist, Anakinra, which is an IL-1 receptor antagonist, and AMG-108, which is an IL-1 receptor monoclonal antibody, have demonstrated some efficacy in OA trials with respect to symptoms and chondroprotection ("Results from a Randomized Controlled Trial of AMG 108 (a fully human monoclonal antibody to IL-1R type I) in Patients With Osteoarthritis of the Knee" Cohen et al., ACR2007). Both of these proposed therapies await additional studies to demonstrate clear and robust clinical efficacy.

A need remains for new and effective methods and compositions for treating individuals afflicted with osteoarthritis.

Summary of the Invention

The invention provides methods for treating osteoarthritis (OA) and for treating pain. Such methods comprise administering to an individual (human or other mammal) one or more binding proteins that bind IL-1α and IL-1β.

In one aspect, there is provided the use of a binding protein that binds both IL-1α and IL-1β, in the manufacture of a medicament for treating pain in an individual suffering from osteoarthritis, wherein the individual suffers from a pain condition selected from the group consisting of allodynia, hyperalgesia, and a combination of allodynia and hyperalgesia.

In one aspect, there is provided the use of a binding protein that binds both IL-1α and IL-1β, in the manufacture of a medicament for treating osteoarthritis, wherein the binding protein further treats pain, wherein the pain is selected from the group consisting of allodynia, hyperalgesia, and a combination of allodynia and hyperalgesia.

In an aspect of the invention, a method for treating osteoarthritis in an individual (human or other mammal) comprises the step of administering to the individual a binding protein that binds IL-1α in combination with (e.g., in a mixture, by successive administration, or by concurrent administration with) a binding protein that binds IL-1β or administering to the individual a binding protein that binds both IL-1α and IL-1β.

In an embodiment, a method for treating osteoarthritis in an individual comprises administering to the individual a binding protein that binds IL-1α, wherein the binding protein is an antibody to IL-1α, for example, a monoclonal antibody to IL-1α. In another

embodiment, a method for treating osteoarthritis in an individual comprises administering to the individual a binding protein that binds IL-Iβ, wherein the binding protein is an antibody that binds IL-Iβ, for example, a monoclonal antibody that binds IL-1β.

In another aspect of the invention, a method of treating osteoarthritis in an individual (human or other mammal) comprises the step of administering to the individual a binding protein that binds both IL-1α and IL-1β. Preferably, the binding protein is a dual variable domain immunoglobulin binding protein (also referred herein as "DVD-Ig™" or "DVD-Ig" binding protein or molecule) that comprises at least one binding site that binds IL-1α and at least one binding site

CLAIMS

1. Use of a binding protein that binds both IL-1α and IL-1β, in the manufacture of a medicament for treating pain in an individual suffering from osteoarthritis.

2. The use for treating pain according to claim 1, wherein the individual suffers from a pain condition selected from the group consisting of allodynia, hyperalgesia, and a combination of allodynia and hyperalgesia.

3. The use according to claim 1, wherein said binding protein that binds both IL-1α and IL-1β is a bispecific antibody or a dual variable domain immunoglobulin (DVD-Ig) binding protein.

4. The use according to claim 1, wherein said binding protein that binds both IL-1α and IL-1β is formulated in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

5. The use according to 1, wherein said binding protein that binds both IL-1α and IL-1β is crystallized.

6. The use according to claim 5, wherein said crystallized binding protein that binds both IL-1α and IL-1β is formulated in a composition further comprising a polymeric carrier.

7. The use according to claim 6, wherein said polymeric carrier is a polymer selected from one or more of the group consisting of: a poly (acrylic acid), a poly (cyanoacrylate), a poly (amino acid), a poly (anhydride), a poly (depsipeptide), a poly (ester), a poly (lactic acid), a poly (lactic-co-glycolic acid), a poly (b-hydroxybutryate), a poly (caprolactone), a poly (dioxanone); a poly (ethylene glycol), a poly ((hydroxypropyl) methacrylamide, a poly [(organo)phosphazene], a poly (ortho ester), a poly (vinyl alcohol), a poly (vinylpyrrolidone), a maleic anhydride- alkyl vinyl ether copolymer, a pluronic polyol, an albumin, an alginate, a cellulose, a cellulose derivative, a collagen, a fibrin, a gelatin, a hyaluronic acid, an oligosaccharide, a glycaminoglycan, a sulfated polysaccharide, a blend, and a copolymer thereof.

8. The use according to claim 6 further comprising an ingredient selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol, and polyethylene glycol.

9. The use according to claim 1 further comprising a biologically active second agent that provides a desirable property.

10. The use according to claim 9, wherein said second agent is one or more compounds in the group consisting of budenoside, epidermal growth factor, corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxygenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1β monoclonal antibodies, anti-IL-6 monoclonal antibodies, growth factors, elastase inhibitors, pyridinyl-imidazole compounds, antibodies of TNF, LT, IL-2, IL-6, IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-23, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD-19, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα converting enzyme inhibitors, T-cell signalling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, anti-inflammatory cytokines, IL-4, IL-10, IL-11, IL-13, and TGFβ.

11. The use according to any one of claims 1-10, wherein said medicament is to be administered by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intra-articular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

12. Use of a binding protein that binds both IL-1α and IL-1β, in the manufacture of a medicament for treating osteoarthritis.

13. The use according to claim 12, wherein said binding protein that binds both IL-1α and IL-1β is a dual variable domain immunoglobulin (DVD-Ig) binding protein.

14. The use according to claim 12, wherein said binding protein that binds both IL-1α and IL-1β is formulated in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

15. The use according to 12, wherein said binding protein that binds both IL-1α and IL-1β is crystallized.

16. The use according to claim 15, wherein said crystallized binding protein is formulated in a composition further comprising a polymeric carrier.

17. The use according to claim 16, wherein said polymeric carrier is a polymer selected from one or more of the group consisting of: a poly (acrylic acid), a poly (cyanoacrylate), a poly (amino acid), a poly (anhydride), a poly (depsipeptide), a poly (ester), a poly (lactic acid), a poly (lactic-co-glycolic acid), a poly (b-hydroxybutryate), a poly (caprolactone), a poly (dioxanone); a poly (ethylene glycol), a poly ((hydroxypropyl) methacrylamide, a poly [(organo)phosphazene], a poly (ortho ester), a poly (vinyl alcohol), a poly (vinylpyrrolidone), a maleic anhydride- alkyl vinyl ether copolymer, a pluronic polyol, an albumin, an alginate, a cellulose, a cellulose derivative, a collagen, a fibrin, a gelatin, a hyaluronic acid, an oligosaccharides, a glycaminoglycan, a sulfated polysaccharide, a blend, and a copolymer thereof.

18. The method according to claim 16 further comprising an ingredient selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol, and polyethylene glycol.

19. The use according to claim 12 further comprising a biologically active second agent that provides a desirable property.

20. The use according to claim 19, wherein said second agent is one or more compounds in the group consisting of budenoside, epidermal growth factor, corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxygenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1β monoclonal antibodies, anti-IL-6 monoclonal antibodies, growth factors, elastase inhibitors, pyridinyl-imidazole compounds, antibodies of TNF, LT, IL-2, IL-6, IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-23, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD-19, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα converting enzyme inhibitors, T-cell signalling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, anti-inflammatory cytokines, IL-4, IL-10, IL-11, IL-13, and TGFβ.

21. The use according to any one of claims 12-16, 19 and 20, wherein said medicament is to be administered by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intra-articular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

22. The use according to claim 12, wherein the osteoarthritis comprises an osteoarthritis lesion.

23. The use according to claim 12, wherein the osteoarthritis comprises an injury to an anterior cruciate ligament.

24. The use according to claim 12, wherein osteoarthritis comprises cartilage degeneration and expression of IL-6.

25. The use according to claim 24, wherein the cartilage degeneration comprises femoral cartilage degeneration or tibial cartilage degeneration.

26. The use according to claim 12, wherein administering the binding protein produces an antinociceptive effect.

27. The use according to claim 12, wherein the binding protein further treats pain.

28. The use according to claim 27, wherein the pain is selected from the group consisting of allodynia, hyperalgesia, and a combination of allodynia and hyperalgesia.

CLAIMS

1. Use of a binding protein that binds both IL-1α and IL-1β, in the manufacture of a medicament for treating pain in an individual suffering from osteoarthritis, wherein the individual suffers from a pain condition selected from the group consisting of allodynia, hyperalgesia, and a combination of allodynia and hyperalgesia.

2. The use according to claim 1, wherein said binding protein that binds both IL-1α and IL-1β is a bispecific antibody or a dual variable domain immunoglobulin (DVD-Ig) binding protein.

3. The use according to claim 1, wherein said binding protein that binds both IL-1α and IL-1β is formulated in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

4. The use according to claim 1 further comprising a biologically active second agent that provides a desirable property.

5. The use according to claim 4, wherein said second agent is one or more compounds in the group consisting of budenoside, epidermal growth factor, corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxygenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1β monoclonal antibodies, anti-IL-6 monoclonal antibodies, growth factors, elastase inhibitors, pyridinyl-imidazole compounds, antibodies of TNF, LT, IL-2, IL-6, IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-23, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD-19, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα converting enzyme inhibitors, T-cell signalling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors,

soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, anti-inflammatory cytokines, IL-4, IL-10, IL-11, IL-13, and TGFβ.

6. The use according to any one of claims 1-5, wherein said medicament is to be administered by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intra-articular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

7. Use of a binding protein that binds both IL-1α and IL-1β, in the manufacture of a medicament for treating osteoarthritis, wherein the binding protein further treats pain, wherein the pain is selected from the group consisting of allodynia, hyperalgesia, and a combination of allodynia and hyperalgesia.

8. The use according to claim 7, wherein said binding protein that binds both IL-1α and IL-1β is a dual variable domain immunoglobulin (DVD-Ig) binding protein.

9. The use according to claim 7, wherein said binding protein that binds both IL-1α and IL-1β is formulated in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

10. The use according to claim 7 further comprising a biologically active second agent that provides a desirable property.

11. The use according to claim 10, wherein said second agent is one or more compounds in the group consisting of budenoside, epidermal growth factor, corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxygenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1β monoclonal antibodies, anti-IL-6 monoclonal antibodies, growth factors, elastase inhibitors, pyridinyl-imidazole compounds, antibodies of TNF, LT,

IL-2, IL-6, IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-23, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD-19, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα converting enzyme inhibitors, T-cell signalling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, anti-inflammatory cytokines, IL-4, IL-10, IL-11, IL-13, and TGFβ.

12. The use according to any one of claims 7-11, wherein said medicament is to be administered by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intra-articular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

13. The use according to claim 7, wherein the osteoarthritis comprises an osteoarthritis lesion.

14. The use according to claim 7, wherein the osteoarthritis comprises an injury to an anterior cruciate ligament.

15. The use according to claim 7, wherein osteoarthritis comprises cartilage degeneration and expression of IL-6.

16. The use according to claim 15, wherein the cartilage degeneration comprises femoral cartilage degeneration or tibial cartilage degeneration.