

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 July 2010 (15.07.2010)

PCT

(10) International Publication Number  
**WO 2010/081112 A1**

- (51) **International Patent Classification:**  
A61K 38/20 (2006.01) C07K 14/54 (2006.01)
- (21) **International Application Number:**  
PCT/US2010/020673
- (22) **International Filing Date:**  
11 January 2010 (11.01.2010)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**  
61/144,134 12 January 2009 (12.01.2009) US
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- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) **Title:** PREVENTION AND/OR TREATMENT OF MULTIPLE ORGAN DYSFUNCTION SYNDROME WITH INTERLEUKIN-22

(57) **Abstract:** The present invention relates to use an agent for the prevention and/or treatment of multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF) comprising interleukin-22 (IL-22) as an effective ingredient. The present invention is applicable to prevention of or therapy for diseases from sepsis, septic shock, liver failure, to multiple organ dysfunction syndromes. More particularly, the present invention is useful for an emergency medical service, for treatment of injury caused by a traffic accident, burns, heat attacks, hypercytokinemia or severe infective diseases.



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**Use of Interleukin-22 for the prevention and/or treatment of multiple organ  
dysfunction syndrome (MODS)**

**FIELD OF INVENTION**

[0001] This invention relates to the medical use of Interleukin-22 (IL-22).

**BACKGROUND OF INVENTION**

[0002] Multiple organ dysfunction syndrome (MODS), previously known as multiple organ failure (MOF), is altered organ function in an acutely ill patient such that homeostasis cannot be maintained without medical intervention. It is well established that Systemic Inflammatory Response Syndrome (SIRS) will lead to sepsis or severe sepsis and eventually lead to MODS. MODS usually results from uncontrolled inflammatory response which is triggered by infection, injury (accident or surgery), hypoperfusion and/or hypermetabolism. The uncontrolled inflammatory response will lead to SIRS or sepsis.

[0003] SIRS is an inflammatory state affecting the whole body. It is one of several conditions related to systemic inflammation, organ dysfunction, and organ failure. SIRS is a subset of cytokine storm, in which there is abnormal regulation of various cytokines. The cause of SIRS can be classified as infectious or noninfectious. SIRS is also closely related to sepsis. When SIRS is due to an infection, it is considered as sepsis. Noninfectious causes of SIRS include trauma, burns, pancreatitis, ischemia and hemorrhage. Sepsis is a serious medical condition characterized by a whole-body inflammatory state. Sepsis can lead to septic shock, multiple organ dysfunction syndrome and death. Both SIRS and sepsis could ultimately progress to MODS.

[0004] The underline mechanism of MODS is not well understood. At present there is no agent that can reverse the established organ failure. Therapy therefore is limited to

supportive care. Prevention and treatment for MODS, MOF or sepsis are important to emergency medical service, for treatment of injury caused by traffic accident, burns, heart attacks, and severe infective diseases. Therefore, the development of an effective drug is in urgent need for patients.

### **SUMMARY OF INVENTION**

[0005] It is therefore an object of the present invention to provide a therapeutic composition and method for MODS, MOF or sepsis.

[0006] Accordingly, the present invention, in one aspect, provides the use of interleukin-22 (IL-22) in manufacture of a composition for preventing and/or treating MODS, MOF, sepsis, or liver failure.

[0007] In another aspect, the present invention provides a method for the prevention and the treatment of MODS, MOF, sepsis, or liver failure in a subject, the method comprising administering a pharmaceutically effective amount of IL-22. In a further aspect, the present invention relates to the use of IL-22 in the manufacture of a medicament for preventing and treating MODS, MOF, sepsis, or liver failure. MODS, MOF or sepsis may be caused by, among other causes, trauma such as traffic accidents, burns, heart attack, and severe infective diseases.

[0008] In various aspects, IL-22 of the present invention includes but is not limited to mammal IL-22 and recombinant mammal IL-22. In a preferred embodiment, IL-22 is human IL-22.

### **BRIEF DESCRIPTION OF FIGURES**

[0009] Figure 1 shows the Murine interleukin-22 cDNA sequence.

[0010] Figure 2 shows the Human interleukin-22 cDNA sequence.

[0011] Figure 3 shows the Murine interleukin-22 amino acid sequence.

[0012] Figure 4 shows the Human interleukin-22 amino acid sequence.

[0013] Figure 5 shows that IL-22 increased animal survival in LPS-induced sepsis shock in mice.

[0014] Figure 6 shows that IL-22 protects LPS-induced multiple organ failure in rats caused by cachexia.

[0015] Figure 7 shows that IL-22 protected animal from death in LPS/GalN-induced acute liver failure in mice.

#### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

[0016] **Example 1: Human and murine IL-22 gene cloning**

[0017] Cloning of human IL-22 gene: Human peripheral blood monocytes were stimulated with anti-human CD<sub>3</sub> mAb and cultured for 24 h. Total RNA was extracted by ultracentrifugation, and cDNA was synthesized with the dT primers. Human IL-22 gene was amplified by PCR with the sense primer (5'-GCA GAA TCT TCA GAA CAG GTT C-3') and anti-sense primer (5'-GGC ATC TAA TTG TTA TTT CTA G-3'). The amplified DNA is cloned into E.coli expression vector.

[0018] Cloning of mouse IL-22 gene: C57BL/6 female mice were injected with LPS (5 mg/kg, sc). The spleen was obtained after 20 hours. Total RNA was extracted and cDNA was synthesized with the dT primers. Mouse IL-22 gene was amplified by PCR with the sense primer (5'-CTC TCA CTT ATC AAC TGT TGA C-3') and anti-sense primer (5'-GAT GAT GGA CGT TAG CTT CTC AC-3'). The amplified cDNA was cloned into E.coli expression vector pET21(+)

[0019] Both human IL-22 and murine IL-22 were verified by DNA sequencing, as shown in Fig. 1 and Fig.2.

[0020] **Example 2: human IL-22 and mouse IL-22 gene expression**

[0021] E. coli strain BL21(+) was used to express the recombinant protein. The E.coli cells were homogenized under high pressure. IL-22 inclusion bodies were obtained by centrifugation and washed with buffers (Tris-HCl 50 mM, NaCl 100 mM, EDTA 1 mM, DTT 1 mM, and sodium deoxycholate 0.5%) completely. Inclusion bodies were solubilized in 8M urea, 50 mM Mes, 10 mM EDTA, and 0.1 mM DTT, pH 6.5. Inclusion bodies was refolded 4 times for 20 hours in 100 mM Tris-HCl, 2 mM EDTA, 0.5 M L-arginine, 1 mM reduced glutathion, and 0.1mM oxidized glutathion, pH 8. The mixture was then concentrated and purified using a Superdex75 (Amersham) column chromatography. The protein was eluted with 20 mM Tris-HCl, 50 mM NaCl, pH 7. The purity of IL-22 was determined by SDS-PAGE (>95%) as shown in Fig.3 and Fig.4. IL-22 protein aliquot was stored at -80 °C.

[0022] **Example 3: Protective Effect of IL-22 on Endotoxin-induced sepsis in mice**

[0023] Female Balb/c mice, at 6 to 8 weeks, were treated with lipopolysacchride (LPS, salmonella abortus-equi (L-5886, Sigma) prepared at 1.0 mg/mL saline. 0.2 mL LPS solution was injected by i.p. to mice at dose of 10 mg/kg. Animals were divided to different treatment groups and survival was monitored for 7 days. Single dose of LPS at >12.0 mg/kg could result in 100% animal death at 48 to 72 hrs. LPS dosed at 10 mg/kg single dose resulted in 20 to 30% animal survival by day 7.

[0024] Treatment of mice started with daily subcutaneous injection of recombinant mouse IL-22, at 100 ug/kg, and 500 ug/kg. Control mice were treated with carrier, 0.5% BSA and saline. Results are shown in Fig 5. Control mice (carrier, n=10) had 20% survival by day 7. Treatment of IL-22 at 100 ug/kg and 500 ug/kg resulted in significant animal survival. These results show that IL-22 significantly protect mice from death in LPS-induced sepsis shock model.

[0025] **Example 4: Protective Effect of IL-22 on Endotoxin-induced multiple organ failure in rats.**

[0026] Animal model of multiple organ failure was established by daily injection of endotoxin (LPS-E-coli; 10 mg/kg/day, Difco) to 6 weeks old male Wister rats. Animals were divided into different treatment groups (n=8). Recombinant mouse IL-22 was administered subcutaneously at 100, 300, and 1000 ug/kg/day daily for 7 days. Control animals were injected with carrier solution only, 0.5% BSA PBS, pH7.0. Serum protein and albumin levels were measured at the end of 7 day treatment.

[0027] Results are shown in Fig 6. Serum levels of total proteins, albumin were decreased in control group, indicating that these rats were suffering from cachexia. Animals treated with rmIL-22 had significantly improved blood chemistry parameters. These data shows that IL-22 was effective in protect multiple organ failure in rats caused by endotoxin-induced cachexia.

[0028] **Example 5: Protective Effect of IL-22 on LPS/GalN-induced acute liver failure in mice.**

[0029] Lippolysaccharides (LPS, 100 ng/mL, Sigma, Cat: L2630) and D-galactosamine (D-GalN, 130 mg/mL, Sigma, Cat: G1639) were prepared in pyrogen-free saline. Female BALB/c mice, 6-8 weeks, were injected introperitoneally (i.p.) with 0.2mL solution containing 0.1mL of LPS and 0.1 mL D-GalN. The injection of LPS/GalN into mice induced acute liver failure evidenced by rapid elevation of liver enzymes (> 20-fold increase compared to control group) including a greater than 20-fold increase of alanine aminotransferase (ALT) and a greater than 40-fold increase of aspartate aminotransferase (AST) in the serum at 8 hrs. Less than 20% mice were viable at 24 hrs after LPS/GalN challenge.

[0030] Treatment of mice started with subcutaneous injection of recombinant mouse IL-22, at 100 ug/kg, and 300 ug/kg. Control mice were treated with carrier, 0.5% BSA and saline. Results are shown in Fig 7. Control mice (carrier, n=10) had 12.5% survival at 16 hrs. Treatment of IL-22 at 100 ug/kg and 300 ug/kg resulted 37.5% and 62.5% (n=10) survival, respectively. These results show that IL-22 significantly protect mice from LPS/GalN induced death mainly resulted from acute liver failure.

What is claimed is:

1. A method of prevention or treatment of multiple organ dysfunction syndromes in a subject comprising administering a pharmaceutically effective amount of IL-22.
2. The method of claim 1 wherein said IL-22 increases serum total protein in said subject suffering multiple organ dysfunction syndromes.
3. The method of claim 1 wherein said IL-22 increases serum albumin in said subject suffering multiple organ dysfunction syndromes.
4. The method of claim 1 wherein said IL-22 is mammal IL-22.
5. The method of claim 1 wherein said IL-22 is recombinant mammal IL-22.
6. The method of claim 1 wherein said pharmaceutically effective amount of IL-22 ranges from 100 to 1000 micrograms per kilogram of said subject per day.
7. A method of prevention or treatment of systemic inflammatory response syndrome in a subject comprising administering a pharmaceutically effective amount of IL-22.
8. The method of claim 7 wherein said IL-22 increases the survival rate of said subject.
9. The method of claim 7 wherein said IL-22 is mammal IL-22.
10. The method of claim 7 wherein said IL-22 is recombinant mammal IL-22.
11. The method of claim 7 wherein said pharmaceutically effective amount of IL-22 ranges from 100 to 500 micrograms per kilogram of said subject.
12. A method of prevention or treatment of liver failure in a subject comprising administering a pharmaceutically effective amount of IL-22.
13. The method of claim 12 wherein said IL-22 lowers serum AST and ALT levels in said subject.
14. The method of claim 12 wherein said IL-22 is mammal IL-22.

15. The method of claim 12 wherein said IL-22 is recombinant mammal IL-22.
16. The method of claim 12 wherein said pharmaceutically effective amount of IL-22 ranges from 100 to 300 micrograms per kilogram of said subject.

1 cgaccagggtt ctccttcccc agtcaccagt tgctcgagtt agaattgtct gcaatggccg  
61 ccctgcagaa atctgtgagc tctttcctta tggggaccct ggccaccagc tgctccttc  
121 tcttgccct cttggtacag ggaggagcag ctgcgcccac cagctccac tgcaggcttg  
181 acaagtccaa cttccagcag ccctatatca ccaaccgcac cttcatgctg gctaaggagg  
241 ctagcttggc tgataacaac acagacgttc gtctcattgg ggagaaactg ttccacggag  
301 tcagtatgag tgagcgtgc tatctgatga agcagggtct gaacttcaac cttgaagaag  
361 tgctgttccc tcaatctgat aggttccagc cttatatgca ggaggtggtg ccttctctgg  
421 ccaggctcag caacaggcta agcacatgct atattgaagg tgatgacctg catatccaga  
481 ggaatgtgca aaagctgaag gacacagtga aaaagcttgg agagagtgga gagatcaaag  
541 caattggaga actggatttg ctgtttatgt ctctgagaaa tgctgcatt tgaccagagc  
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661 aaagcgattt ttttaacca aaaggaagat ggaagccaa actccatcat gatgggtgga  
721 ttccaatga acccctgcgt tagttacaaa ggaaaccaat gccacttttg tttataagac  
781 cagaaggtag actttctaag catagatatt tattgataac atttcattgt aactggtgtt  
841 ctatacacag aaaacaattt attttttaa taattgtctt tttccataaa aaagattact  
901 ttccattcct ttaggggaaa aaaccctaa atagcttcat gttccataa tcagtacttt  
961 atatttataa atgtatttat tattattata agactgcatt ttatttatat cattttatta  
1021 atatggattt atttatagaa acatcattcg atattgctac ttgagtgtaa ggctaatatt  
1081 gatatttatg acaataatta tagagctata acatgtttat ttgacctcaa taaacacttg  
1141 gatatcc

Fig.1

1 cctaaacagg atatcatata acttatcaac tgttgacact tgtgcatct ctgatggctg  
61 tcctgcagaa atctatgagt tttccctta tggggacttt ggcggccagc tgctgcttc  
121 tcattgccct gtgggcccag gaggcaaagt cgtgcccgt caacacccgg tgcaagcttg  
181 aggtgtccaa cttccagcag ccgtacatcg tcaaccgcac ctttatgctg gccaaaggagg  
241 ccagccttgc agataacaac acagacgtcc ggtcatcgg ggagaaactg ttccgaggag  
301 tcagtgtcaa agatcagtgc tacctgatga agcaggtgct caacttcacc ctggaagacg  
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421 ccaaaactcag caatcagctc agctcctgct acatcagcgg tgacgaccag aacatccaca  
481 agaatgtcag aaggctgaag gagacagtga aaaagcttgg agagagtgga gagatcaagg  
541 cgattgggga actggacctg ctgtttatgt ctctgagaaa tgettgcgctc tgagcgagaa  
601 gaagctagaa aacgaagaac tgctccttcc tgcttctaa aaagaacaat aagatccctg  
661 aatggaacttt ttactaaaag gaaagtgaga agctaacgctc catcatcatt agaagatttc  
721 acatgaaacc tggctcagtt gaaaaagaaa atagtgtcaa gttgtccatg agaccagagg  
781 tagacttgat aaccacaaag attcattgac aatattttat tgctactgat gatacaacag  
841 aaaaataatg tactttaaaa aattgtttga aaggagggtta catatcatta ctttagaaaa  
901 aaagcttatg taacttcatt tacatataca atattttata tatgtaagtt tatttattat  
961 aagtatacat tttatttatg tcagtttatt aatatggatt tatttataga aacattatct  
1021 gctattgata tttagtataa ggcaaataat atttatgaca ataactatgg aaacaagata  
1081 tcttaggctt taataaacac atggatatca taaaaaaaa a

Fig.2

MAALQKSVSSFLMGTLATSCLL  
LLALLVQGGAAAPISSHCRLDK  
SNFQQPYITNRTFMLAKEASLA  
DNNTDVRLIGEKLFHGVSMSER  
CYLMKQVLNFTLEEVLPQSDR  
FQPYMQEVVPFLARLSNRLSTC  
HIEGDDLHIQRNVQKLKDTVKK  
LGESGEIKAIGELDLLFMSLRN  
ACI

Fig.3

MAVLQKSMFS SLMGTLAASCLL  
LIALWAQEANALPVNTRCKLEV  
SNFQQPYIVNRTFMLAKEASLA  
DNNTDVRLIGEKLEFRGVS AKDQ  
CYLMKQVLNFTLEDVLLPQSDR  
FQPYMQEVVPFLTKLSNQLSSC  
HISGDDQNIQKNVRR LKETVKK  
LGESGEKAIGELDLLFMSLRNA  
CV

Fig.4

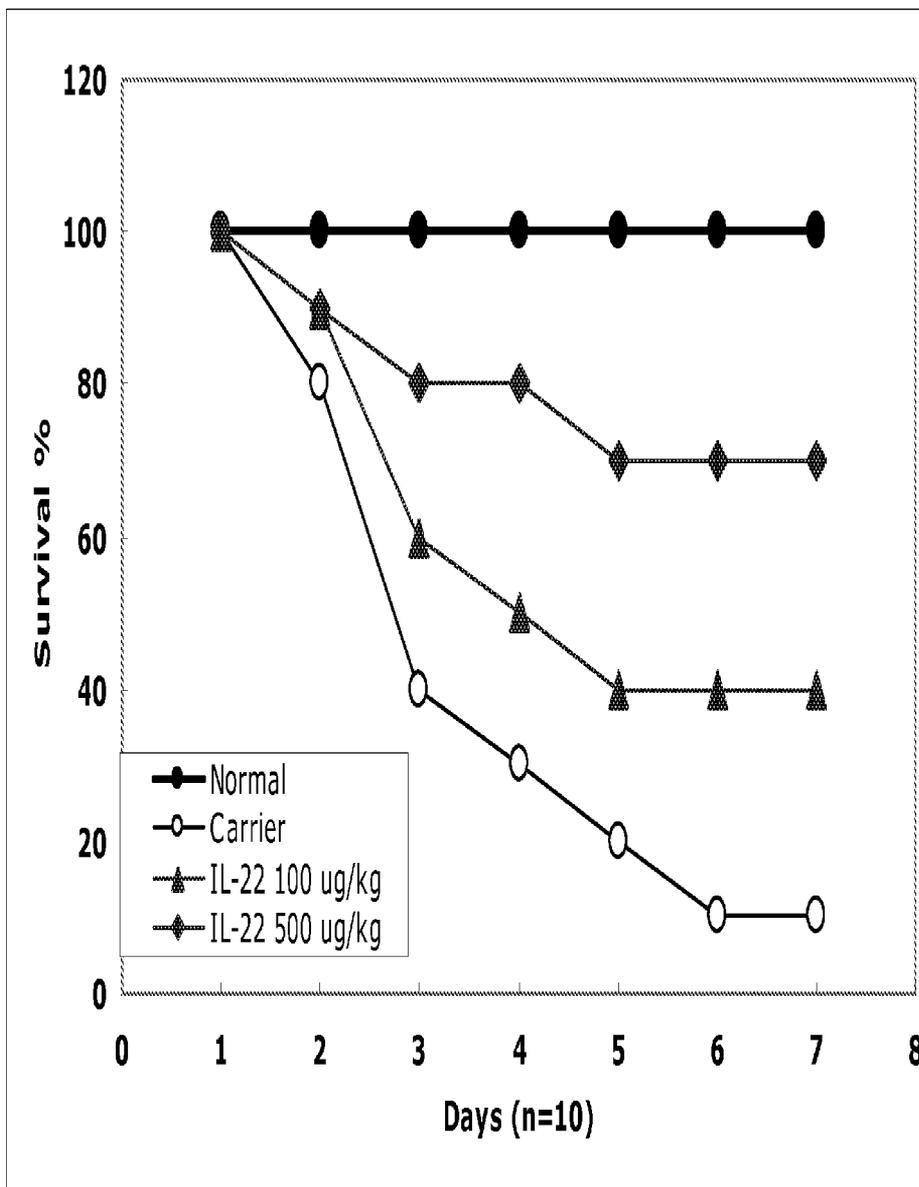


Fig.5

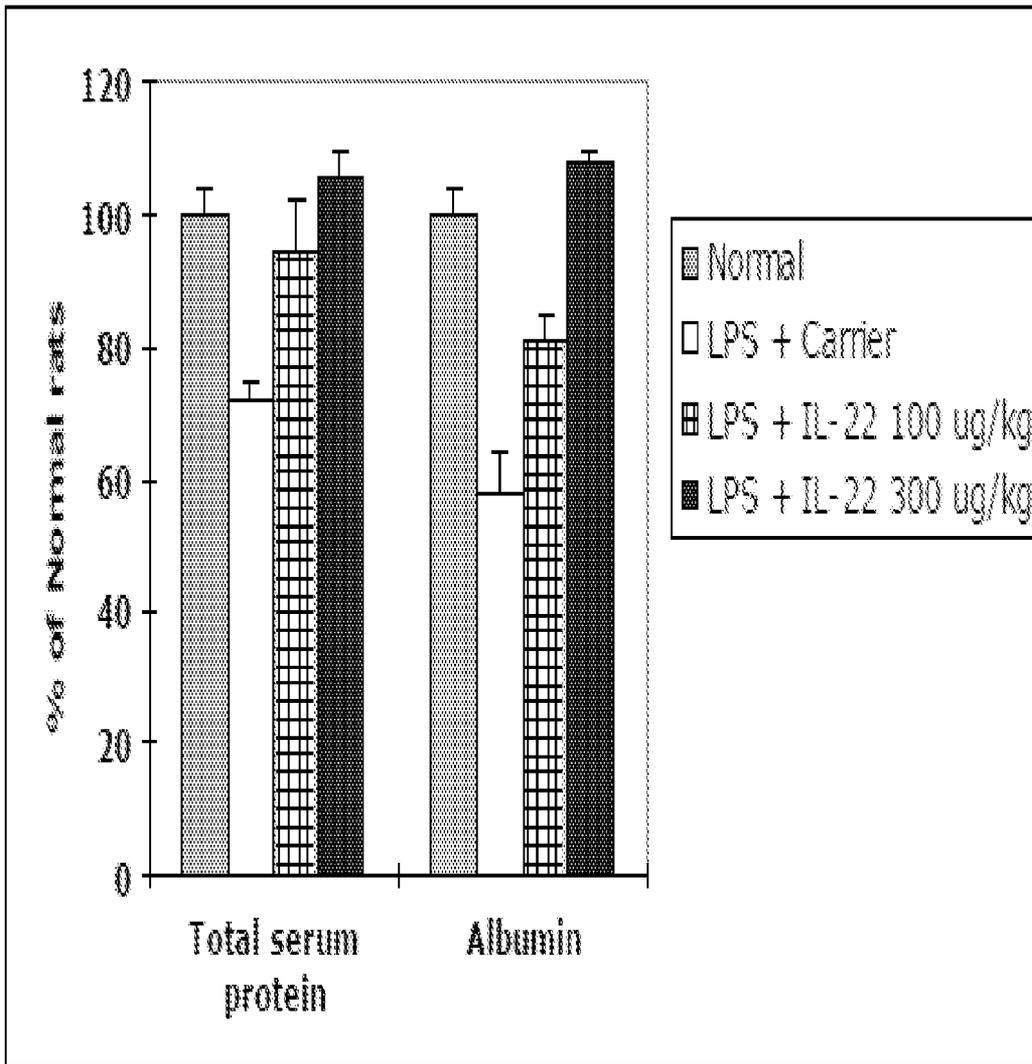


Fig.6

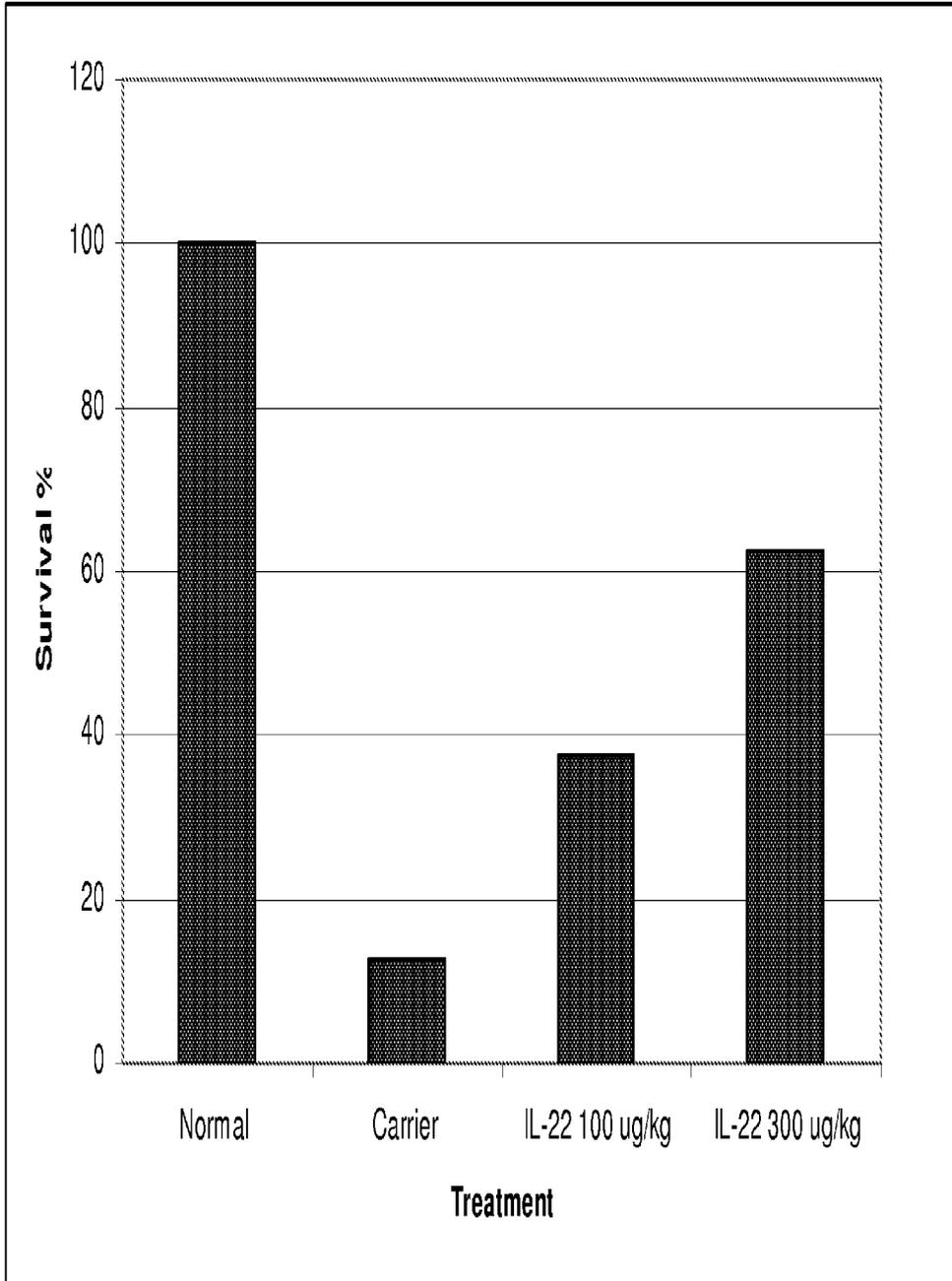


Fig.7

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/20673

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61K 38/20; C07K 14/54 (2010.01) USPC - 514/2, 530/351, 424/85.2 According to International Patent Classification (IPC) or to both national classification and IPC																									
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) USPC: 514/2, 530/351, 424/85.2 IPC(8): A61K 38/20; C07K 14/54 (2010.01) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 424/158.1, 1.41, 78.05; 435/69.52 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Electronic Databases Searched: PubWEST DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ, Google Scholar, Google Patent Search Terms Used: IL-22, interleukin-22, systemic inflammatory response syndrome, SIRS, multiple organ dysfunction, MODS, aspartate aminotransferase, alanine aminotransferase																									
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>																									
<table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X — Y</td> <td>US 2007/0207943 A1 (Ebner et al.) 6 September 2007 (06.09.2007) entire document, esp: abstract, paras [0002], [0008], [0058], [0186], [0221], [0237], [0430], [0439].</td> <td>1-5, 7-10 6, 11, 14, 15</td> </tr> <tr> <td>X — Y</td> <td>2008/0241246 A1 (Sakhivel et al.) 2 October 2008 (02.10.2008) entire document, esp: abstract, paras [0006], [0025], [0027], [0028], [0092].</td> <td>12, 13 14-16</td> </tr> <tr> <td>Y</td> <td>US 7,226,591 B2 (Gurney et al.) 5 June 2007 (05.06.2007) entire document, esp: abstract, col 68 ln 434-58.</td> <td>6, 11, 16</td> </tr> <tr> <td>A</td> <td>US 2008/0031882 A1 (Liang et al.) 7 February 2008 (07.02.2008) entire document, esp: abstract, paras [0041], [0123].</td> <td>2, 3</td> </tr> <tr> <td>A</td> <td>Zenewicz et al. Interleukin-22 but Not Interleukin-17 Provides Protection to Hepatocytes during Acute Liver Inflammation. Immunity October 2007, 27, 647-659. entire document, esp: abstract, pg 655 last paragraph second column; Fig. 3.</td> <td>7-16</td> </tr> <tr> <td>A</td> <td>US 2005/0148029 A1 (Buechler et al.) 7 July 2005 (07.07.2005) entire document.</td> <td>1-16</td> </tr> <tr> <td>A</td> <td>Radaeva et al. Interleukin 22 (IL-22) Plays a Protective Role in T Cell-mediated Murine Hepatitis: IL-22 Is a Survival Factor for Hepatocytes via STAT3 Activation. HEPATOLOGY 2004, 39:1332-1342.</td> <td>1-16</td> </tr> </tbody> </table>	Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X — Y	US 2007/0207943 A1 (Ebner et al.) 6 September 2007 (06.09.2007) entire document, esp: abstract, paras [0002], [0008], [0058], [0186], [0221], [0237], [0430], [0439].	1-5, 7-10 6, 11, 14, 15	X — Y	2008/0241246 A1 (Sakhivel et al.) 2 October 2008 (02.10.2008) entire document, esp: abstract, paras [0006], [0025], [0027], [0028], [0092].	12, 13 14-16	Y	US 7,226,591 B2 (Gurney et al.) 5 June 2007 (05.06.2007) entire document, esp: abstract, col 68 ln 434-58.	6, 11, 16	A	US 2008/0031882 A1 (Liang et al.) 7 February 2008 (07.02.2008) entire document, esp: abstract, paras [0041], [0123].	2, 3	A	Zenewicz et al. Interleukin-22 but Not Interleukin-17 Provides Protection to Hepatocytes during Acute Liver Inflammation. Immunity October 2007, 27, 647-659. entire document, esp: abstract, pg 655 last paragraph second column; Fig. 3.	7-16	A	US 2005/0148029 A1 (Buechler et al.) 7 July 2005 (07.07.2005) entire document.	1-16	A	Radaeva et al. Interleukin 22 (IL-22) Plays a Protective Role in T Cell-mediated Murine Hepatitis: IL-22 Is a Survival Factor for Hepatocytes via STAT3 Activation. HEPATOLOGY 2004, 39:1332-1342.	1-16	<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>
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Date of the actual completion of the international search 11 February 2010 (11.02.2010)	Date of mailing of the international search report <b>09 MAR 2010</b>																								
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774																								