The present invention is directed to therapeutic methods using antibodies and fragments thereof having binding specificity for IL-6 to prevent or treat cachexia, fever, weakness and/or fatigue in a patient in need thereof. In preferred embodiments, the anti-IL-6 antibodies will be humanized and/or will be aglycosylated. Also, in preferred embodiments these patients will comprise those exhibiting (or at risk of developing) an elevated serum C-reactive protein level. In another preferred embodiment, the patient’s survivability or quality of life will preferably be improved.
FIG. 3
FIG. 10D

AL2 INHIBITS CP30 BINDING

CONTROL ANTIBODY

AL2

BINDING [mm]

0.000
0.200
0.400
0.600
0.800
1.000
1.200
1.400
1.600
1.800
2.000

TIME (SECONDS)
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Ab1</th>
<th>Ab2</th>
<th>Ab3</th>
<th>Ab4</th>
<th>Ab5</th>
<th>Ab6</th>
<th>Ab7</th>
<th>Ab8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks IL6 binding to GP130</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blocks IL6 binding to R1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**FIG. 11**
FIG. 15

A. Surface Plasmon Resonance: Averaged binding constants determined at 25 °C for Ab1 to IL-6.

<table>
<thead>
<tr>
<th>Species (IL-6)</th>
<th>( K_{A} ) (M(^{-1})s(^{-1}))</th>
<th>( K_{D} ) (s(^{-1}))</th>
<th>( K_{D} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>1.6e6</td>
<td>2.2e-3</td>
<td>1.4 nM</td>
</tr>
<tr>
<td>Mouse</td>
<td>1.1e6</td>
<td>4.0e-4</td>
<td>0.4 nM</td>
</tr>
<tr>
<td>Dog</td>
<td>Below LOQ(^a)</td>
<td>Below LOQ(^a)</td>
<td>Below LOQ(^a)</td>
</tr>
<tr>
<td>Human</td>
<td>1.6e5</td>
<td>5e-7</td>
<td>4 pM</td>
</tr>
<tr>
<td>Cynomolgus monkey</td>
<td>9.6e4</td>
<td>3e-6</td>
<td>31 pM</td>
</tr>
</tbody>
</table>

\( a \). Below Limit of Quantitation

B. IC50 values for Ab1 against human, cynomolgus monkey, mouse, rat and dog IL-6 in the T1165 assay.

<table>
<thead>
<tr>
<th>IL-6 Species</th>
<th>IC50 (pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>13</td>
</tr>
<tr>
<td>Cynomolgus monkey</td>
<td>12</td>
</tr>
<tr>
<td>Mouse</td>
<td>1840</td>
</tr>
<tr>
<td>Rat</td>
<td>2060</td>
</tr>
<tr>
<td>Dog</td>
<td>No inhibition of cell proliferation</td>
</tr>
</tbody>
</table>
FIG. 16

Mean Plasma Concentration of Ab1 in Healthy Male Subjects

Plasma Concentration Ab1 (μg/ml)

Time (h)
<table>
<thead>
<tr>
<th>Dose of Ab1</th>
<th>$T_{1/2}$ (days)</th>
<th>AUC (µg·h/mL)</th>
<th>$C_{max}$ (µg/mL)</th>
<th>$T_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mg</td>
<td>10.3</td>
<td>35</td>
<td>0.1</td>
<td>8</td>
</tr>
<tr>
<td>3mg</td>
<td>11.6</td>
<td>229</td>
<td>0.7</td>
<td>4</td>
</tr>
<tr>
<td>10mg</td>
<td>22.4</td>
<td>1473</td>
<td>4.0</td>
<td>4</td>
</tr>
<tr>
<td>30mg</td>
<td>25.1</td>
<td>9076</td>
<td>19.4</td>
<td>4</td>
</tr>
<tr>
<td>100mg</td>
<td>30.3</td>
<td>26128</td>
<td>48.0</td>
<td>12</td>
</tr>
<tr>
<td>300mg</td>
<td>30.3</td>
<td>92891</td>
<td>188.0</td>
<td>12</td>
</tr>
<tr>
<td>640mg</td>
<td>30.2</td>
<td>175684</td>
<td>306.0</td>
<td>12</td>
</tr>
</tbody>
</table>
FIG. 20
Pharmacokinetics of Ab1 in Patients with Advanced Cancer

Elimination half-life: 31 days

Mean plasma concentration of Ab1 given as a single IV infusion of 80 mg (n=2) or 160 mg (n=3) (Mean +/- SEM)
<table>
<thead>
<tr>
<th></th>
<th>Ab1</th>
<th>Actemra (Tocilizumab)</th>
<th>Remicade</th>
<th>Synagis</th>
<th>Erbitux</th>
<th>Zenapax</th>
<th>Avastin</th>
<th>Pertuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human</strong></td>
<td>15-21</td>
<td>~31</td>
<td>6</td>
<td>8-9.5</td>
<td>20</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>Cynomolgus Monkey</strong></td>
<td>15-21</td>
<td>7</td>
<td>5</td>
<td>8.6</td>
<td>3-7</td>
<td>7</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Unprecedented Elimination Half-life of Ab1

**FIG. 21**
FIG. 22

Ab1 Increases Hemoglobin Concentration in Patients with Advanced Cancer

Hemoglobin concentration (g/dl)

Time (weeks)

Single IV infusion of 80 mg, 160 mg, or 320 mg Ab1 (n=8) (Mean +/- SEM)
FIG. 25

Ab1 Suppresses Serum CRP in Healthy Volunteers

Placebo i.v. (n=14)
Ab1 1mg i.v. (n=6)
Ab1 3mg i.v. (n=6)
Ab1 10mg i.v. (n=5)
Ab1 30mg i.v. (n=5)
Ab1 100mg i.v. (n=5)

Medium serum CRP concentration (1ug/ml)

Time (h)
FIG. 26B

Ab1 Suppresses Serum CRP in Patients with Advanced Cancer

Patient A

Patient B

Serum CRP conc (ug/ml)

Time (weeks)

80mg as a Single IV Infusion
FIG. 27

Ab1 Prevents Weight Loss in a Mouse Cancer Cachexia Model

Polynonal IgG
Ab1: 30mg/kg day 1
Ab1: 10mg/kg day 1
PFA, control

Ab1 Dosing

p<0.0001
p<0.0005

Time (days)

Mean Percent Body Weight
FIG. 28
Ab1 Prevents Weight Loss in a Mouse Cancer Cachexia Model

Control (PBS)

Ab1 Treated (30 mg/kg)

3 - 8
FIG. 29

Ab1 Promotes Weight Gain in Patients with Advanced Cancer

Single IV Infusion of 60 mg or 160 mg Ab1 (n=5)
Ab1 Reduces Fatigue in Patients with Advanced Cancer

Single IV infusion of 80 mg or 160 mg Ab1 (n=5) Mean score for U.S. general population = 40.1

Mean Fatigue FS Subscale score vs. Time (weeks)
Ab1 Promotes Hand Grip Strength (L+R) in Patients with Advanced Cancer

Response considered clinically significant

Single IV infusion of 80 mg or 160 mg Ab1

Percentage change in mean hand grip strength
Ab1 Increases Plasma Albumin Concentration in Patients with Advanced Cancer

Fig. 33

Time (weeks)

Plasma Albumin Concentration (g/L)

Single IV infusion of 80 mg or 160 mg Ab1 (n=5)
FIGURE 36A - Alignment of Ab1 light chains

<table>
<thead>
<tr>
<th>SEQ ID NO:2</th>
<th>FR1</th>
<th>CDR1</th>
<th>FR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDTRAPTQLGLLLMLWLPGRAC</td>
<td>AYDMTQTPASCASAVGGTVTIC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
<tr>
<td>SEQ ID NO:20</td>
<td>IGMTQSPSSLSAVGGTVTITC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
<tr>
<td>SEQ ID NO:647</td>
<td>AYDMTQTPASCASAVGGTVTIC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
<tr>
<td>SEQ ID NO:651</td>
<td>AGMTQSPSLSAVGGTVTITC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
<tr>
<td>SEQ ID NO:660</td>
<td>MDTRAPTQLGLLLMLWLPGRAC</td>
<td>AYDMTQTPASCASAVGGTVTIC</td>
<td>QASQINNELS</td>
</tr>
<tr>
<td>SEQ ID NO:666</td>
<td>IGMTQSPSSLSAVGGTVTITC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
<tr>
<td>SEQ ID NO:699</td>
<td>AGMTQSPSLSAVGGTVTITC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
<tr>
<td>SEQ ID NO:702</td>
<td>AGMTQSPSLSAVGGTVTITC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
<tr>
<td>SEQ ID NO:706</td>
<td>MKWVTFLSLFLFSSAYS</td>
<td>A GMTQSPSSLSAVGGTVTITC</td>
<td>QASQINNELS</td>
</tr>
<tr>
<td>SEQ ID NO:709</td>
<td>A GMTQSPSSLSAVGGTVTITC</td>
<td>QASQINNELS</td>
<td>WYQQKPGQRPKLIY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDR2</th>
<th>FR3</th>
<th>CDR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>SEQ ID NO:20</td>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
</tr>
<tr>
<td>SEQ ID NO:647</td>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
</tr>
<tr>
<td>SEQ ID NO:651</td>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
</tr>
<tr>
<td>SEQ ID NO:660</td>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
</tr>
<tr>
<td>SEQ ID NO:666</td>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
</tr>
<tr>
<td>SEQ ID NO:699</td>
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<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
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</tr>
<tr>
<td>SEQ ID NO:706</td>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
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<tr>
<td>SEQ ID NO:709</td>
<td>RASLTAS</td>
<td>GVSSRFKGSGGSTETCTLISLEDCAATYYC</td>
</tr>
</tbody>
</table>
FIGURE 36B - Alignment of Ab1 light chains (continued)

**kappa constant light chain**

**FR4**

| SEQ ID NO: 2 | FGGTTEVVVKR T VAAPSVFIPPSDEQLKSGTASVCLLNN |
| SEQ ID NO: 20 | FGGTTEVVVKR |
| SEQ ID NO: 647 | FGGTTEVVVKR |
| SEQ ID NO: 661 | FGGTKEIKR |
| SEQ ID NO: 660 | FGGTKEIKR |
| SEQ ID NO: 666 | FGGTKEIKR T VAAPSVFIPPSDEQLKSGTASVCLLNNFYPREAVQWKNVDALQSGN |
| SEQ ID NO: 699 | FGGTKEIKR T |
| SEQ ID NO: 702 | FGGTKEIKR T VAAPSVFIPPSDEQLKSGTASVCLLNNFYPREAVQWKNVDALQSGN |
| SEQ ID NO: 706 | FGGTKEIKR T VAAPSVFIPPSDEQLKSGTASVCLLNNFYPREAVQWKNVDALQSGN |
| SEQ ID NO: 709 | FGGTKEIKR |

**kappa constant light chain (continued)**

| SEQ ID NO: 2 | SQESVTEQDSKDSTYSLSTTLKADYEKHYACEVTHQGLSSPVTSPFRGEC |
| SEQ ID NO: 20 | |
| SEQ ID NO: 647 | |
| SEQ ID NO: 661 | |
| SEQ ID NO: 666 | SQESVTEQDSKDSTYSLSTTLKADYEKHYACEVTHQGLSSPVTSPFRGEC |
| SEQ ID NO: 699 | |
| SEQ ID NO: 702 | SQESVTEQDSKDSTYSLSTTLKADYEKHYACEVTHQGLSSPVTSPFRGEC |
| SEQ ID NO: 706 | SQESVTEQDSKDSTYSLSTTLKADYEKHYACEVTHQGLSSPVTSPFRGEC |
| SEQ ID NO: 709 | |
FIGURE 37A - Alignment of Ab1 heavy chains

<table>
<thead>
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<th>SEQUENCE</th>
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<tbody>
<tr>
<td>3</td>
<td>METGLRWLLLAVLKVQG</td>
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<tr>
<td>18</td>
<td>EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>19</td>
<td>EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>652</td>
<td>QSLEESGGRGVRGPGLTVLTCASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>656</td>
<td>EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>657</td>
<td>EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>658</td>
<td>QSLEESGGRGVRGPGLTVLTCASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>661</td>
<td>QSLEESGGRGVRGPGLTVLTCASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>664</td>
<td>EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>665</td>
<td>EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>704</td>
<td>EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
</tr>
<tr>
<td>708</td>
<td>MKWVTISLLFLFSSAYE EVQILVESGGGLVQPGSRLSCLASGFSLS NYVT WVRQAPGKLEGWIG</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SEQ ID NO:</th>
<th>SEQUENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>IIGS-SDEYATWAIG RFTISKTST - TDNLKMTSLLTAADTATYFCAR CDR2</td>
</tr>
<tr>
<td>18</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN WGQTLTVVSS</td>
</tr>
<tr>
<td>19</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>652</td>
<td>IIGS-SDEYATWAIG RFTISKTST - TDNLKMTSLLTAADTATYFCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>656</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>657</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN</td>
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<td>658</td>
<td>IIGS-SDEYATWAIG RFTISKTST - TDNLKMTSLLTAADTATYFCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>661</td>
<td>IIGS-SDEYATWAIG RFTISKTST - TDNLKMTSLLTAADTATYFCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>664</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>665</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>704</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN</td>
</tr>
<tr>
<td>708</td>
<td>IIGS-SDEYATWAIG RFTISDNSKTLYLQMNLSRAEDTAYYCAR CDR3 DDSSDNDKFLN</td>
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</tbody>
</table>

FR3

<table>
<thead>
<tr>
<th>SEQ ID NO:</th>
<th>SEQUENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>RFTISKTST - TDNLKMTSLLTAADTATYFCAR</td>
</tr>
<tr>
<td>18</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
<tr>
<td>19</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
<tr>
<td>652</td>
<td>RFTISKTST - TDNLKMTSLLTAADTATYFCAR</td>
</tr>
<tr>
<td>656</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
<tr>
<td>657</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
<tr>
<td>658</td>
<td>RFTISKTST - TDNLKMTSLLTAADTATYFCAR</td>
</tr>
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<td>661</td>
<td>RFTISKTST - TDNLKMTSLLTAADTATYFCAR</td>
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<tr>
<td>664</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
<tr>
<td>665</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
<tr>
<td>704</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
<tr>
<td>708</td>
<td>RFTISDNSKTLYLQMNLSRAEDTAYYCAR</td>
</tr>
</tbody>
</table>

FR4
Mean (±SD) plasma C-reactive protein concentration ALDS18 80mg, 160mg, and 320mg as a single i.v. infusion in patients with advanced cancer (n=8)
Mean (±SD) C-reactive protein concentration versus time: Ab1 versus placebo in rheumatoid arthritis patients with an inadequate response to methotrexate.
Mean (±SD) hemoglobin concentration (g/dl): Ab1 versus placebo in NSCLC patients

Figure 42
Mean (±SEM) hemoglobin concentration (g/dl) in NSCLC patients with a baseline hemoglobin below 11 g/l at baseline versus time:

- Ab1 320mg (n=11)
- Ab1 160mg (n=8)
- Ab1 80mg (n=10)
- Placebo (n=6)

Time (weeks)

Hemoglobin Concentration (g/l)
Mean (±SEM) Hemoglobin concentration: Ab1 versus placebo in patients with rheumatoid arthritis who have an inadequate response to methotrexate

Figure 45
Mean ±SD change from baseline in plasma albumin concentration (g/L) versus time: Ab1 versus placebo in NSCLC patients.
Mean (±SEM) albumin concentration in NSCLC patients with a baseline albumin ≤35 g/l at baseline versus time: Ab1 versus placebo
Percentage change in mean (±SEM) lean body mass (kg) over time using DEXA.

Abi versus placebo in NSCLC patients.

Time (weeks)

Abi 160 mg (n=10)
Abi 180 mg (n=12)
Abi 320 mg (n=20)
Placebo (n=20)

Figure 51
Figure S3

Mean (±SD) change from baseline FACT-F fatigue subscale score versus time: Ab1 versus placebo in NSCLC patients.

Time (weeks)

Ab1 320mg (n=32)
Ab1 160mg (n=31)
Placebo (n=31)

Mean change from baseline FACT-F fatigue subscale score
Median D-dimer concentration (ng/ml) versus time: Ab1 versus placebo in NSCLC patients.

- Placebo (n=31)
- Ab1 80mg (n=20)
- Ab1 160mg (n=32)
- Ab1 320mg (n=32)

Time (weeks)

Figure 54
<table>
<thead>
<tr>
<th>Responder Imputation</th>
<th>Placebo (n=33)</th>
<th>Ab1 80mg (n=32)</th>
<th>Ab1 160mg (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 20</td>
<td>36%</td>
<td>75%</td>
<td>65% (p=0.0025)</td>
</tr>
<tr>
<td>ACR 50</td>
<td>15%</td>
<td>41%</td>
<td>41% (p=0.0281)</td>
</tr>
<tr>
<td>ACR 70</td>
<td>6%</td>
<td>22%</td>
<td>18% (p=0.0084)</td>
</tr>
</tbody>
</table>

Figure 56
Percentage patients achieving a good/moderate EULAR response versus time:

Ab1 versus placebo in rheumatoid arthritis patients with an inadequate response to methotrexate.
Percentage patients achieving an ACR50 score versus time - Ab1 versus placebo MTT in rheumatoid arthritis patients with an inadequate response to methotrexate.
Percentage patients achieving an ACR70 score versus time - Ab1 versus placebo MITT in rheumatoid arthritis patients with an inadequate response to methotrexate
Mean ±SEM change from baseline in HAQ-DI score versus time:
Ab1 versus placebo in patients with rheumatoid arthritis with an inadequate response to methotrexate.

Figure 61
Mean (±SD) DAS28-CRP score versus time: Ab1 versus placebo in rheumatoid arthritis patients with an inadequate response to methotrexate.
Percentage patients achieving a good/moderate EULAR response versus time:
Ab1 versus placebo in rheumatoid arthritis patients with an inadequate response to methotrexate

Figure 63
Figure 64. Study Design

Healthy male subjects, 18-45 years old (N=27)

- Ab1 SC 100 mg (n=6)
- Placebo SC (n=6)
- Ab1 SC 50 mg (n=6)
- Placebo SC (n=6)
- Ab1 IV 100 mg (n=6)
- Placebo IV (n=6)

- Randomized and single dose administered
- Day -21 Screening
- Day 0 Randomized
- Week 12 Follow-up
- Week 24 Follow-up

Subjects: Randomized to placebo were followed for 12 weeks after which they discontinued from the study.

SC = subcutaneous, IV = intravenous
<table>
<thead>
<tr>
<th>Subjects with an AE</th>
<th>Dose</th>
<th>AE severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50mg</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>100mg</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>50mg</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>100mg</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>50mg</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>100mg</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Figure 67 Adverse Events
**Figure 67 (continued)**

<table>
<thead>
<tr>
<th>AEs reported in ≥2 subjects in any group</th>
<th>1</th>
<th>2</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site erythema</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection site pruriitss</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>URTI</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Skin laceration</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Patients randomized to placebo (IV or SC) discontinued at Week 12 and are not included in Week 24 analyses; AE=adverse event; SC=subcutaneous; IV=intravenous; URTI=upper respiratory tract infection.
<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>Placebo SC</th>
<th>Phaleno IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>100 mg</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>150 mg</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>200 mg</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total subjects with injection site reactions**

<table>
<thead>
<tr>
<th>Injection site reaction</th>
<th>Placebo</th>
<th>Placebo SC</th>
<th>Phaleno IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reddening</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection site rash</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All injection site reactions were reported in the first 12 weeks of the study. SC = subcutaneous, IV = intravenous.*
Figure 69. Clinical Laboratory Evaluations Over 24 Weeks (Ab1)

<table>
<thead>
<tr>
<th></th>
<th>SC 50 mg n=6</th>
<th>SC 100 mg n=6</th>
<th>IV 100 mg n=6</th>
<th>Placebo n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ALT</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Elevated total bilirubin</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Elevated direct bilirubin</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low neutrophil count</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Low platelet count</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*SC and IV groups combined up to Week 12 only, after which placebo-treated patients discontinued. **Below the lower limit of normal; SC=suspected; IV=intravenous; ALT=alanine aminotransferase; AST=aspartate aminotransferase.
Figure 70. Ab1 Plasma Pharmacokinetic Parameters to Week 24

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T=0 (day)</th>
<th>T=14 (day)</th>
<th>T=28 (week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0 (log10 (mg/L))</td>
<td>5.87 (24%)</td>
<td>6.19 (34%)</td>
<td>6.52 (28%)</td>
</tr>
<tr>
<td>T1/2 (days)</td>
<td>0.14</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>AUC [day (mg*day/mL)]=0 mg/L]</td>
<td>2.85 (10%)</td>
<td>4.95 (19%)</td>
<td>7.52 (22%)</td>
</tr>
<tr>
<td>AUC [day (mg*day/mL)]=0 mg/L]</td>
<td>2.24 (35%)</td>
<td>4.44 (29%)</td>
<td>7.48 (22%)</td>
</tr>
<tr>
<td>t1/2 (days)</td>
<td>3.1 (19%)</td>
<td>31 (45%)</td>
<td>20.7 (5.9)</td>
</tr>
<tr>
<td>CL (ml/day)</td>
<td>223 (32%)</td>
<td>225 (32%)</td>
<td>194 (27%)</td>
</tr>
</tbody>
</table>

Data are geometric mean coefficient of variation %. CV% for data are median (interquartile range). AUC is area under the curve, 1SD=standard deviation. CLT=apparent total body clearance, t1/2=terminal half-life.
FIGURE 71

Impact of SC and IV ALD518 on serum CRP levels.

Graph showing the effect of SC and IV ALD518 on serum CRP levels over time. The graph includes various lines representing different conditions and dosages.
ANTAGONISTS OF IL-6 TO RAISE ALBUMIN AND/OR LOWER CRP

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to provisional application Ser. No. 61/410,169, filed on Nov. 4, 2010; provisional application Ser. No. 61/358,615, filed on Jun. 25, 2010; provisional application Ser. No. 61/355,819, filed on Jun. 17, 2010 and provisional application Ser. No. 61/325,547, filed on Apr. 19, 2010. This application further claims priority to U.S. Ser. No. 12/624,965; 12/624,830; 12/624,816 and 12/624,788 all filed on Nov. 24, 2009. The disclosures of each of the aforementioned provisional and non-provisional applications including all the sequence information is incorporated by reference in its entirety herein.

[0002] The sequence listing in the file named “6785607020006.txt” having a size of 331,894 bytes that was created Nov. 23, 2009 is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0003] 1. Field of the Invention

[0004] This invention is an extension of Applicants’ prior invention disclosed in the above-referenced patent applications relating to novel anti-IL-6 antibodies and novel therapies and therapeutic protocols using anti-IL-6 antibodies, preferably those described herein. In particular, this invention pertains to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an IL-6 antagonist, whereby the patient’s C-reactive protein (“CRP”) level is lowered, and/or the patient’s albumin level is raised.

[0005] In one aspect, this invention relates to methods of lowering the C-reactive protein level in a patient in need thereof, comprising administering to the patient an IL-6 antagonist, whereby the patient’s CRP level is lowered, and monitoring the patient to assess the CRP level. In one embodiment, the IL-6 antagonist comprises an anti-IL-6 antibody or antibody fragment, such as an anti-IL-6 antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and humanized, human, chimeric or single chain versions thereof that specifically bind human IL-6.

[0006] In another aspect, this invention relates to methods of raising the albumin level in a patient in need thereof, comprising administering to the patient an IL-6 antagonist, whereby the patient’s serum albumin level is raised, and monitoring the patient to assess the albumin level. In one embodiment, the IL-6 antagonist comprises an anti-IL-6 antibody or antibody fragment, such as an anti-IL-6 antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and humanized, human, chimeric or single chain versions thereof that specifically bind human IL-6.

[0007] In another aspect the invention provides novel combination therapies wherein the CRP level is lowered and/or albumin level is raised in a patient in need thereof by the administration of at least one IL-6 antagonist and at least one other therapeutic compound e.g., a statin compound, including but not limited to atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

[0008] This invention further pertains to novel methods of lowering the CRP level and/or raising the albumin level in a patient in need thereof using anti-IL-6 antibodies, preferably aglycosylated and/or humanized antibodies possessing an elimination half-life which is at least about 25 days.

[0009] 2. Description of Related Art

[0010] Interleukin-6 (hereinafter “IL-6”) (also known as interferon-β2; B-cell differentiation factor; B-cell stimulatory factor-2; hepatocyte stimulatory factor; hybridoma growth factor; and plasmacytoma growth factor) is a multifunctional cytokine involved in numerous biological processes such as the regulation of the acute inflammatory response, the modulation of specific immune responses including T- and B-cell differentiation, bone metabolism, thrombopoiesis, epidermal proliferation, menses, neuronal cell differentiation, neuroprotection, aging, cancer, and the inflammatory reaction occurring in Alzheimer’s disease. See A. Papassotiropoulos et al, Neurobiology of Aging, 22:863-871 (2001).

[0011] IL-6 is a member of a family of cytokines that promote cellular responses through a receptor complex consisting of at least one subunit of the signal-transducing glycoprotein gp130 and the IL-6 receptor (“IL-6R”) (also known as gp80). The IL-6R may also be present in a soluble form (“sIL-6R”). IL-6 binds to IL-6R, which then dimerizes the signal-transducing receptor gp130. See Jones, S A, J. Immunology, 175:3463-3468 (2005).

[0012] In humans, the gene encoding IL-6 is organized in five exons and four introns, and maps to the short arm of chromosome 7 at 7p21. Translation of IL-6 RNA and post-translational processing result in the formation of a 21 to 28 kDa protein with 184 amino acids in its mature form. See A. Papassotiropoulos, et al, Neurobiology of Aging, 22:863-871 (2001).

[0013] As set forth in greater detail herein IL-6 is believed to play a role in the development of a multitude of diseases and disorders, including but not limited to fatigue, cachexia, autoimmune diseases, diseases of the skeletal system, cancer, heart disease, obesity, diabetes, asthma, alzheimer’s disease and multiple sclerosis. Due to the perceived involvement of IL-6 in a wide range of diseases and disorders, there remains a need in the art for compositions and methods useful for preventing or treating diseases associated with IL-6, as well as methods of screening to identify patients having diseases or disorders associated with IL-6. Particularly preferred anti-IL-6 compositions are those having minimal or minimizing adverse reactions when administered to the patient. Compositions or methods that reduce or inhibit diseases or disorders associated with IL-6 are beneficial to the patient in need thereof.

[0014] The function of IL-6 is not restricted to the immune response as it acts in hematopoiesis, thrombopoiesis, osteoclast formation, elicitation of hepatic acute phase response
resulting in the elevation of C-reactive protein (CRP) and serum amyloid A (SAA) protein. It is known to be a growth factor for epidermal keratinocytes, renal mesangial cells, myeloma and plasmacytoma cells (Grossman et al., 1989 Prot Natl Acad Sci., 86, (16) 6367-6371; Horii et al., 1989, J Immunol, 143, 12, 3949-395; Kawano et al., 1988, Nature 332, 6159, 83-85). IL-6 is produced by a wide range of cell types including monocytes/macrophages, fibroblasts, epidermal keratinocytes, vascular endothelial cells, renal mesangial cells, gland cells, condrocytes, T and B-cells and some tumor cells (Akira et al, 1990, FASEBJ, J, 4, 11, 2860-2867). Except for tumor cells that constitutively produce IL-6, normal cells do not express IL-6 unless appropriately stimulated. [0015] Elevated IL-6 levels have been observed in many types of cancer, including breast cancer, leukemia, ovarian cancer, prostate cancer, pancreatic cancer, lymphoma, lung cancer, renal cell carcinoma, colorectal cancer, and multiple myeloma (e.g., Chopra et al., 2004, MIAFI 60:45-49; Songur et al., 2004, Tumor 90:196-200; Blay et al., 1992, Cancer Research 52:3317-3322; Nikiteas et al., 2005, World J. Gastroenterol. 11:1639-1643; reviewed in Heikkila et al., 2008, Eur J Cancer, 44:937-945). As noted above, IL-6 is known or suspected to play a role in promoting proliferation or survival of at least some types of cancer. Moreover, some of these studies have demonstrated correlation between IL-6 levels and patient outcome. Together, these results suggest the possibility that inhibition of IL-6 can be therapeutically beneficial. Indeed, clinical studies reviewed in (Trikha et al., 2003, Clinical Cancer Research 9:4653-4665) have shown some improvement in patient outcomes due to administration of various anti-IL-6 antibodies, particularly in those cancers in which IL-6 plays a direct role promoting cancer cell proliferation or survival. [0016] As noted above, IL-6 stimulates the hepatic acute phase response, resulting in increased production of CRP and elevated serum CRP levels. For this reason, C-reactive protein (CRP) has been reported to comprise a surrogate marker of IL-6 activity. Thus, elevated IL-6 activity can be detected through measurement of serum CRP. Conversely, effective suppression of IL-6 activity, e.g., through administration of a neutralizing anti-IL-6 antibody, can be detected by the resulting decrease in serum CRP levels. [0017] A recent clinical trial demonstrated that administration of rosuvastatin to apparently healthy individuals having elevated CRP (greater than 2.0 mg/dl) reduced their CRP levels by 57% and greatly decreased the incidence of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Ridker et al., N Engl J Med. 2008 Nov. 9 [Epub ahead of print]. [0018] In addition to its direct role in pathogenesis of some cancers and other diseases, chronically elevated IL-6 levels appear to adversely affect patient well-being and quality of life. For example, elevated IL-6 levels have been reported to be associated with cachexia and fever, and reduced serum albumin. Gauldie et al., 1987, PNAS 84:7251-7253; Heinrich et al., 1990, 265:621-636; Zamir et al., 1993, Metabolism 42:204-208; Zamir et al., 1992, Arch Surg, 127:170-174. Inhibition of IL-6 by a neutralizing antibody has been reported to ameliorate fever and cachexia in cancer patients, though improvement in these patients’ serum albumin level has not been reported (Emille et al., 1994, Blood, 84:2472-2479; Blay et al., 1992, Cancer Research 52:3317-3322; Bataille et al., 1995, Blood, 86: 685-691). [0019] Numerous studies have suggested that CRP is a valuable prognostic factor in cancer patients, with elevated CRP levels predicting poor outcome. See, e.g., Helter et al., Clin Cancer Res, 2008 Feb; 14(3):710-4; Nagao et al., Liver Int, 2007 October; 27(8):1091-7; Heikikila et al, J Epidemiol Community Health, 2007 September; 61(9):824-33, Review; Han et al, Anticancer Res, 2007 July-August; 27(4):3001-4; Polterauer et al, Gynecol Oncol, 2007 October; 107(1):114-7, Epub 2007 Jul 6; Tingstedt et al, Scand J Gastroenterol, 2007 June; 42(6):754-9; Suhi et al, Support Care Cancer, 2007 June; 15(6):613-20, Epub 2007 Jan 18; Gerhardt et al, World J Gastroenterol, 2006 Sep; 12(34); 5495-500; Mc Ardle et al, Urol Int, 2006; 77(2):127-9; Guille et al, Dis Esophagus, 2005; 18(3):146-50; Brown et al, Cancer, 2005 Jan; 15; 103(2):377-82. Decreased serum albumin (hypoalbuminemia) is also associated with increased morbidity and mortality in many critical illnesses, including cancers (e.g., Vignali et al., Arch Intern Med, 2000 Mar; 160(6):861-8; Hauser et al, Support Care Cancer, 2006 October; 14(10):999-1011; Seve et al., Cancer, 2006 Dec; 1; 107 (11):2698-705). The apparent link between hypoalbuminemia and poor patient outcome suggests that restoring albumin levels through direct albumin infusion could promote patient survival, however, albumin infusion has not improved survival of patients with advanced cancer (Demirkazik et al., Proc Am Soc Clin Oncol 21: 2002 (abstr 2092)) or other critically ill patients groups reviewed in Wilkus et al., Ann Intern Med. 2005 Aug 7; 143(3):149-64. [0020] The Glasgow Prognostic Score (GPS) is an inflammation-based prognostic score that combines levels of albumin (<35 mg/L–1 point) and CRP (>10 mg/L–1 point) (Forrest et al., Br J Cancer, 2004 May 4; 90(9):1704-6). Since its introduction in 2004, the Glasgow Prognostic Score has already been shown to have prognostic value as a predictor of mortality in numerous cancers, including gastro-esophageal cancer, non-small-cell lung cancer, colorectal cancer, breast cancer, ovarian cancer, bronchogenic cancer, and metastatic renal cancer (Forrest et al., Br J Cancer, 2004 May 4; 90(9):1704-6; Sharma et al., Clin Colorectal Cancer, 2008 September; 7(5):331-7; Sharma et al., Eur J Cancer, 2008 January; 44(2):251-6; McMillan et al., Nutr Cancer, 2001; 41(1-2):64-9; McMillan, Proc Nutr Soc, 2008 August; 67(3):257-62; Ramsey et al., Cancer, 2007 Jan; 15; 109(2):205-12). [0021] U.S. patent application publication no. 20080081041 (relating to treatment of cancer using an anti-IL-6 antibody) discloses that since IL-6 is associated with disease activity and since CRP is a surrogate marker of IL-6 activity, sustained suppression of CRP by neutralization of IL-6 by their anti-IL-6 antibody (CNTO 328, Zaki et al., Int J Cancer, 2004 Sep; 10: 111(4):592-5) may be assumed necessary to achieve biological activity. The same patent application indicates that the relationship between IL-6 and CRP in patients with benign and malignant prostate disease was previously examined by Mc Ardle (Mc Ardle et al. 2004 Br J Cancer 91(10):1755-1757). Mc Ardle reportedly found no significant differences between the concentrations of IL-6 and CRP in the patients with benign disease compared with prostate cancer patients, in the cancer patients there was a significant increase in both IL-6 and CRP concentration with increasing tumor grade. The median serum CRP value for the 86 subjects with prostate cancer was 1.8 mg/L. Based thereon the inventors in this patent application postulate a proposed dose and schedule wherein 0.1 mg/kg of an anti-IL-6 antibody (CNTO 328) is administered every 2 weeks and allege that
this is likely to achieve sustained suppression of CRP in subjects with metastatic HRPC.

[0022] IL-6 signaling is mediated by the Jak-Tyk family of cytoplasmic tyrosine kinases, including JAK1, JAK2, and JAK3 (reviewed in Murray J Immunol. 2003 Mar; 170(5): 2623-9). Sivash et al. report abrogation of IL-6-mediated Jak signaling by the cyclopentenone prostaglandin 15d-PGJ2 in oral squamous carcinoma cells. British Journal of Cancer (2004) 91, 1074-1080. These results suggest that inhibitors of JAK1, JAK2, or JAK3 could be employed as antagonists of IL-6.

[0023] Ulanova et al. report that inhibition of the nonreceptor protein tyrosine kinase Syk (using siRNA) decreased production of IL-6 by epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2005 March; 288(3):L497-507. These results suggest that an inhibitor of Syk could be employed as an antagonist of IL-6.

[0024] Kedar et al. report that treatment with thalidomide significantly reduced serum levels of CRP and IL-6 to normal or near normal levels in a substantial fraction of renal cell carcinoma patients. Int J Cancer. 2004 Jun; 109(2):260-5. These results suggest that thalidomide, and possibly derivatives thereof, such as lenalidomide, may be useful antagonists of IL-6.

[0025] In addition, another published patent application, US 20070292420 teaches a Phase I dose escalating study using an anti-IL-6 (cCLB-8) antibody for treating refractory patients with advanced stage multiple myeloma (N=12) and indicate that this study demonstrated that some patients had disease stabilization. The application also reports that after discontinuation of treatment there was acceleration in the increase of M protein levels, suggesting disease re-bound after the withdrawal of therapy. Anti-IL-6 cCLB-8 antibody inhibited free circulating IL-6.

[0026] The application also indicates that this antibody trial resulted in no toxicity (except transient thrombocytopenia in two heavily pretreated patients) or allergic reactions were observed and that C-reactive protein (CRP) decreased below detection level in all patients. Their antibody (cCLB-8 antibody) reportedly possessed a circulating half-life of 17.8 days, and that there was no human anti-chimeric antibody (HACA) immune response observed (van Zaalen et al. 1998). They allege that the administration of NT29 528 did not cause changes in blood pressure, pulse rate, temperature, hemoglobin, liver functions and renal functions. Except for transient thrombocytopenia in two heavily pretreated patients, no toxicity or allergic reactions allegedly were observed, and there was no human anti-chimeric antibody (HACA) immune response observed. Three patients in their study reportedly developed infection-related complications during therapy, however, a possible relation with anti-IL-6 cCLB-8 antibody was concluded by the inventors to be unlikely because infectious complications are reportedly common in end stage multiple myeloma and are a major cause of death. They conclude based on their results that this anti-IL-6 cCLB-8 antibody was safe in multiple myeloma patients.

**BRIEF SUMMARY OF THE INVENTION**

[0027] The present invention is an extension of Applicants' previous inventions directed to specific antibodies, humanized or chimeric or single chain antibodies and fragments thereof having binding specificity for IL-6, in particular antibodies having specific epitopic specificity and/or functional properties and novel therapies using these and other anti-IL-6 antibodies. One embodiment of the invention encompasses specific humanized antibodies and fragments thereof capable of binding to IL-6 and/or the IL-6/IL-6R complex. These antibodies may bind soluble IL-6 or cell surface expressed IL-6. Also, these antibodies may inhibit the formation or the biological effects of one or more of IL-6, IL-6/IL-6R complexes, IL-6/IL-6R/gp130 complexes and/or multimers of IL-6/IL-6R/gp130. The present invention relates to novel therapies and therapeutic protocols using anti-IL-6 antibodies, preferably those described herein. In particular, the present invention pertains to methods of improving survivability or quality of life of a patient in need thereof, e.g., a patient showing elevated CRP levels and/or lowered albumin levels, comprising administering to the patient an IL-6 antagonist, such as those identified infra, e.g., an anti-IL-6 antibody or antibody fragment, whereby the patient's C-reactive protein ("CRP") level is lowered, and/or the patient's albumin level is raised. In some embodiments these methods may further include the administration of other actives such as statins that may further help (synergize) with the IL-6 antagonist and thereby more effectively treat the patient.

[0028] In a preferred embodiment this is effected by the administration of the antibodies described herein, comprising the sequences of the V\_p, V\_l and CDR polypeptides described herein, or humanized or chimeric or single chain versions thereof containing one or more of the CDRs of the exemplified anti-IL-6 antibody sequences and the polynucleotides encoding them. Preferably these antibodies will be glycosylated. In more specific embodiments of the invention these antibodies will block gp130 activation and/or possess binding affinities (K\_d) less than 50 picomolar and/or K\_p values less than or equal to 10^{-4} S\(^{-1}\).

[0029] In another embodiment of the invention these antibodies and humanized versions will be derived from rabbit immune cells (B lymphocytes) and may be selected based on their homology (sequence identity) to human germ line sequences. These antibodies may require minimal or no sequence modifications, thereby facilitating retention of functional properties after humanization. In exemplary embodiments these humanized antibodies will comprise human frameworks which are highly homologous (possess high level of sequence identity) to that of a parent (e.g. rabbit) antibody as described infra.

[0030] In another embodiment of the invention the subject antibodies may be selected based on their activity in functional assays such as IL-6 driven T1165 proliferation assays, IL-6 stimulated HepG2 hepatocarcinoma production assays, and the like. A further embodiment of the invention is directed to fragments from anti-IL-6 antibodies encompassing V\_p, V\_l and CDR polypeptides or variants or fragments thereof, e.g., derived from rabbit immune cells and the polynucleotides encoding the same, as well as the use of these antibody fragments and the polynucleotides encoding them in the creation of novel antibodies and polypeptide compositions capable of recognizing IL-6 and/or IL-6/IL-6R complexes or IL-6/IL-6R/gp130 complexes and/or multimers thereof.

[0031] The invention also contemplates the administration of conjugates of anti-IL-6 antibodies and humanized, chimeric or single chain versions thereof and other binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates methods of making said humanized anti-IL-6 or anti-IL-6/IL-6R complex antibodies and binding fragments thereof. In one
embodiment, binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, Fv and scFv fragments.

Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient diagnosed with cancer, comprising administering to the patient an anti-IL-6 antibody or antibody fragment, whereby the patient’s serum C-reactive protein (“CRP”) level is stabilized and preferably reduced, and monitoring the patient to assess the reduction in the patient’s serum CRP level, wherein the anti-IL-6 antibody or antibody fragment may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies or those depicted in FIGS. 34-37 that specifically bind IL-6, which preferably are aglycosylated.

Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an anti-IL-6 antagonist, whereby the patient’s serum CRP level is reduced, and monitoring the patient to assess the reduction in the patient’s serum CRP level.

Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an anti-IL-6 antagonist, whereby the patient’s serum albumin level is increased, and monitoring the patient to assess the increase in the patient’s serum albumin level.

Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an anti-IL-6 antagonist, whereby the patient’s serum CRP level is reduced and the patient’s serum albumin level is increased, and monitoring the patient to assess the reduction in the patient’s serum CRP level and the increase in the patient’s serum albumin level.

In an embodiment of the invention, the patient may have an elevated serum CRP level prior to treatment.

In an embodiment of the invention, the patient may have a reduced serum albumin level prior to treatment.

In an embodiment of the invention, the patient’s Glasgow Prognostic Score (GPS) may be improved following the treatment.

In an embodiment of the invention, the IL-6 antagonist may target IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

In an embodiment of the invention, the IL-6 antagonist may comprise an antibody, an antibody fragment, a pep-
tide, a glycoalkoid, an antisense nucleic acid, a ribozyme, a retinoid, a viburnum, a small molecule, or any combination thereof.

[0045] In an embodiment of the invention, the IL-6 antagonist may comprise an anti-IL-6R, anti-gp130, anti-p38 MAP kinase, anti-JAK1, anti-JAK2, anti-JAK3, or anti-SYK antibody or antibody fragment.

[0046] In one embodiment of the invention, the IL-6 antagonist may comprise a small molecule comprising thalidomide, lenalidomide, or any combination thereof.

[0047] In an embodiment of the invention, the antagonist may comprise an anti-IL-6 antibody or antibody fragment.

[0048] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated. As discussed infra in a preferred exemplary embodiment the anti-IL-6 antibody will comprise a humanized antibody containing the CDRs of Ab1 and more preferably will comprise the variable heavy and light chain in SEQ ID NO:657 and SEQ ID NO:709 respectively and the constant regions in SEQ ID NO:588 and 586 respectively or one comprising any of the VH and VL sequences contained in FIGS. 34-37 and variants thereof wherein one or more amino acids are modified by substitution or deletion without substantially disrupting IL-6 binding affinity.

[0049] In an embodiment of the invention, the anti-IL-6 antibody may bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as Ab1.

[0050] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may specifically bind to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or antibody thereof as an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated.

[0051] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may specifically bind to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as Ab1 or a humanized or chimeric antibody comprising all or most of the same CDRs as Ab1 or in particular an antibody comprising one or several of the VH and VL sequences depicted in FIGS. 34-37 that specifically binds IL-6.

[0052] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may specifically bind to the same linear or conformational epitope(s) on an intact IL-6 polypeptide or fragment thereof that is (are) specifically bound by Ab1 and wherein said epitope(s) when ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide includes one or more residues comprised in IL-6 fragments selected from those respectively encompassing amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72.

[0053] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may comprise at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 or a combination of CDRs from one or several of said antibodies.

[0054] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may comprise at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in Ab1.

[0055] In an embodiment of the invention, all of the CDRs in the anti-IL-6 antibody or antibody fragment may be identical to the CDRs contained in an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated.

[0056] In an embodiment of the invention, all of the CDRs in the anti-IL-6 antibody or antibody fragment may be identical to one or more of the CDRs contained in Ab1 in particular antibodies having the VH and VL sequences depicted in FIGS. 34-37.

[0057] Another embodiment of the invention relates to Ab1, including rabbit and humanized forms thereof, as well as heavy chains, light chains, fragments, variants, and CDRs thereof. In the human clinical trials presented in the Examples, a humanized form of Ab1 was administered.

[0058] In a preferred exemplary embodiment, the anti-IL-6 antibody will comprise all the CDRs in Ab1. In a more preferred embodiment, the anti-IL-6 antibody will comprise the variable heavy chain sequence in SEQ ID 2 or 709 and the light chain sequence in SEQ ID 3 or 657 or variants thereof.

[0059] In a preferred embodiment the humanized anti-IL-6 antibody will comprise the variable heavy and variable light chain sequences respectively contained in SEQ ID NO:657 and SEQ ID NO:709, and preferably further comprising the heavy chain and light chain constant regions respectively contained in SEQ ID NO:588 and SEQ ID NO:586, and variants thereof comprising one or more amino acid substitutions or deletions that do not substantially affect IL-6 binding and/or desired effector function. This embodiment also contemplates polynucleotides comprising, or alternatively consisting of, one or more of the nucleic acids encoding the variable heavy chain (SEQ ID NO: 700) and variable light chain (SEQ ID NO:723) sequences and the constant region heavy chain (SEQ ID NO: 589) and constant region light chain (SEQ ID NO:587) sequences. This embodiment further
contemplates nucleic acids encoding variants comprising one or more amino acid substitutions or deletions to the variable heavy and variable light chain sequences respectively contained in SEQ ID NO: 657 and SEQ ID NO: 709 and the heavy chain and light chain constant regions respectively contained in SEQ ID NO: 588 and SEQ ID NO: 586, that do not substantially affect I£-6 binding and/or desired effector function.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be aglycosylated.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation. Preferably the Fc region is modified to eliminate glycosylation.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be a human, humanized, single chain or chimeric antibody.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be a humanized antibody derived from a rabbit (parent) anti-IL-6 antibody.

In an embodiment of the invention, the framework regions (FRs) in the variable light region and the variable heavy regions of said anti-IL-6 antibody or antibody fragment respectively may be human FRs which are unmodified or which have been modified by the substitution of at most 2 or 3 human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and the human FRs may have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library. As disclosed in detail infra in a preferred embodiment the antibody will comprise human FRs which are selected based on their high level of homology (degree of sequence identity) to that of the parent antibody that is humanized.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be administered to the patient with a frequency at most once per period of approximately four weeks, approximately eight weeks, approximately twelve weeks, approximately sixteen weeks, approximately twenty weeks, or approximately twenty-four weeks.

In an embodiment of the invention, the patient’s serum CRP level may remain decreased and/or serum albumin level may remain raised for an entire period intervening two consecutive anti-IL-6 antibody administrations.


In an embodiment of the invention, the patient may have been diagnosed with a cancer selected from Colorectal Cancer, Non-Small Cell Lung Cancer, Cholangiocarcinoma, Mesothelioma, Castleman’s disease, Renal Cell Carcinoma, or any combination thereof.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may comprise a VH polypeptide sequence comprising: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 652, 656, 657, 658, 661, 664, 665, 668, 672, 676, 680, 684, 688, 691, 692, 704, or 708 or the VH sequences contained in the antibodies depicted in FIGS. 34-37, and may further comprise a VL polypeptide sequence comprising: SEQ ID NO: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 262, 298, 314, 330, 346, 362, 378, 392, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or 709 or the VH sequences contained in the antibodies depicted in FIGS. 34-37 or a variant thereof wherein one or more of the framework residues (FR residues) in said VH or VL polypeptide may have been substituted with another amino acid residue resulting in an anti-IL-6 antibody or antibody fragment that specifically binds human IL-6. Preferably the variable heavy and light sequences comprise those in SEQ ID NO:657 and 709.

In an embodiment of the invention, one or more of said FR residues may be substituted with an amino acid present at the corresponding site in a parent rabbit anti-IL-6 antibody from which the complementarity determining regions (CDRs) contained in said VH or VL polypeptides have been derived or by a conservative amino acid substitution.

In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment may be humanized.

In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment may be chimeric.

In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment may further comprise a human Fe, e.g., an Fe region comprised of the variable heavy and light chain constant regions contained in SEQ ID NO:704 and 702.

In an embodiment of the invention, the human Fe may be derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19.


In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may have an elimination half-life of at least about 22 days, at least about 25 days, or at least about 30 days.

In an embodiment of the invention, the IL-6 antagonist may be co-administered with a chemotherapeutic agent, including without limitation thereto: VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcetabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids (e.g., vinblastine, vincristine, vinbesine and vinorelbine), mustard, tyrosine kinase inhibitors,
radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, IL-1 antagonists, interleukins (e.g. IL-12 or IL-2), IL-12R antagonists, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux™, Avastin™, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be directly or indirectly attached to a detectable label or therapeutic agent.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be Ab1 or a humanized, chimeric, single chain or fragment thereof comprising all or most of the CDRs of Ab1, or in particular an antibody that comprises the VH and VL polypeptides in SEQ ID NO:657 and 709.

In an embodiment of the invention, the IL-6 antagonist may be an antisense nucleic acid, for example comprising at least approximately 10 nucleotides of a sequence encoding IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, SYK.

In an embodiment of the invention, the antisense nucleic acid may comprise DNA, RNA, peptide nucleic acid, locked nucleic acid, morpholino (phosphorodiamidate morpholino oligo), glycerol nucleic acid, threose nucleic acid, or any combination thereof.

In an embodiment of the invention, the IL-6 antagonist may comprise Actemra™ (Tocilizumab), Remicade®, Zenapax™ (daclizumab), or any combination thereof.

In an embodiment of the invention, the IL-6 antagonist may comprise a polypeptide having a sequence comprising a fragment of IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof, such as a fragment or full-length polypeptide that is at least 40 amino acids in length.

In an embodiment of the invention, the IL-6 antagonist may comprise a soluble IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

In an embodiment of the invention, the IL-6 antagonist may be coupled to a half-life increasing moiety.

In an embodiment of the invention, the method may include measuring the patient’s serum CRP level prior to administration of the anti-IL-6 antibody, and administering the anti-IL-6 antibody or antibody fragment if the patient’s serum CRP level is at least approximately 5 mg/L.

In an embodiment of the invention, the patient’s serum CRP level may be reduced to less than approximately 5 mg/L within 1 week of administration of the IL-6 antagonist.

In an embodiment of the invention, the patient’s serum CRP level may be reduced to below 1 mg/L within 1 week of administration of the IL-6 antagonist.

In an embodiment of the invention, treatment may result in a prolonged reduction in serum CRP level of the patient.

In an embodiment of the invention, the patient’s serum CRP level may be reduced to below 10 mg/L within about 1 week of IL-6 antagonist administration.

In an embodiment of the invention, 14 days after IL-6 antagonist administration the patient’s serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 21 days after IL-6 antagonist administration the patient’s serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 28 days after IL-6 antagonist administration the patient’s serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 35 days after IL-6 antagonist administration the patient’s serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 42 days after IL-6 antagonist administration the patient’s serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 49 days after IL-6 antagonist administration the patient’s serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 56 days after IL-6 antagonist administration the patient’s serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, the patient’s survivability is improved.

In an embodiment of the invention, the method may include measuring the patient’s serum albumin level prior to administration of the IL-6 antagonist, and administering the IL-6 antagonist if the patient’s serum albumin level is less than approximately 35 g/L.

In an embodiment of the invention, the patient’s serum albumin level may be increased to more than approximately 55 g/L within about 5 weeks of administration of the IL-6 antagonist.

In an embodiment of the invention, treatment may result in a prolonged increase in serum albumin level of the patient.

In an embodiment of the invention, 42 days after IL-6 antagonist administration the patient’s serum albumin level may remain above 35 g/L.

In an embodiment of the invention, 49 days after IL-6 antagonist administration the patient’s serum albumin level may remain above 35 g/L.

In an embodiment of the invention, 56 days after IL-6 antagonist administration the patient’s serum albumin level may remain above 35 g/L.

In an embodiment of the invention, the patient’s serum albumin level may be increased by about 5 g/L within approximately 5 weeks of administering the IL-6 antagonist.

In an embodiment of the invention, the patient may have been diagnosed with rheumatoid arthritis, cancer, advanced cancer, liver disease, renal disease, inflammatory bowel disease, celiac’s disease, trauma, burns, other diseases associated with reduced serum albumin, or any combination thereof.

In an embodiment of the invention, the patient may have been diagnosed with rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, systemic lupus erythematosus, Crohn’s disease, ulcerative colitis, pemphigus, dermatomyositis, polymyositis, polymyalgia rheumatica, giant cell arteritis, vasculitis, polyarteritis nodosa, Wegener’s granulomatosis, Kawasaki disease, isolated CNS vasculitis, Churg-Strauss arteritis, microscopic polyarteritis, microscopic polyangiitis, Henoch-Schonlein purpura, essential cryoglobulinemic vasculitis, rheumatoid vasculitis, cryoglobulinemia, relapsing polyarthritis, Behcet’s disease, Takayasu’s arteritis, ischemic heart disease, stroke, multiple sclerosis, sepsis, vasculitis secondary to viral infection (e.g., hepatitis B, hepatitis C, HIV,
cytomegalovirus, Epstein-Barr virus, Parvo B19 virus, etc.), Buerger's Disease, cancer, advanced cancer, Osteoarthristis, systemic sclerosis, CREST syndrome, Reiter's disease, Paget's disease of bone, Sjogren's syndrome, diabetes type 1, diabetes type 2, familial Mediterranean fever, autoimmune thrombocytopenia, autoimmune hemolytic anemia, autoimmune thyroid diseases, pernicious anemia, vitiligo, alopecia areata, primary biliary cirrhosis, autoimmune chronic active hepatitis, alcoholic cirrhosis, viral hepatitis including hepatitis B and C, other organ-specific autoimmune diseases, burns, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, allergic asthma, other allergic conditions or any combination thereof.

[0108] In an embodiment of the invention, the method may further comprise administration of one or more statins to the patient, including without limitation thereto atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosvastatin, simvastatin, or any combination thereof.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0109] FIG. 1 shows that a variety of unique epitopes were recognized by the collection of anti-IL-6 antibodies prepared by the antibody selection protocol. Epitope variability was confirmed by antibody-IL-6 binding competition studies (FortBio Octet).

[0110] FIG. 2 shows alignments of variable light and variable heavy sequences between a rabbit antibody variable light and variable heavy sequences and homologous human sequences and the humanized sequences. Framework regions are identified FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3. Amino acid residues are numbered as shown. The initial rabbit sequences are called RbtVL and RbtVH for the variable light and variable heavy sequences respectively. Three of the most similar human germline antibody sequences, spanning from Framework 1 through to the end of Framework 3, are aligned below the rabbit sequences. The human sequence that is considered the most similar to the rabbit sequence is shown first. In this example those most similar sequences are L12A for the light chain and 3-64-64 for the heavy chain. Human CDR3 sequences are not shown. The closest human Framework 4 sequence is aligned below the rabbit Framework 4 sequence. The vertical dashes indicate a residue where the rabbit residue is identical with one or more of the human residues at the same position. The bold residues indicate that the human residue at that position is identical to the rabbit residue at the same position. The final humanized sequences are called VLH and VHb for the variable light and variable heavy sequences respectively. The underlined residues indicate that the residue is the same as the rabbit residue at that position but different than the human residues at that position in the three aligned human sequences.

[0111] FIG. 3 demonstrates the high correlation between the IgG produced and antigen specificity for an exemplary IL-6 protocol. 9 of 11 wells showed specific IgG correlation with antigen recognition.

[0112] FIG. 4 provides the α-2-Macroglobulin (AZM) dose response curve for antibody Ab1 administered intravenously at different doses one hour after a 100 μg/kg s.c. dose of human IL-6.

[0113] FIG. 5 provides survival data for the antibody Ab1 progression groups versus control groups.

[0114] FIG. 6 provides additional survival data for the antibody Ab1 progression groups versus control groups.

[0115] FIG. 7 provides survival data for polyclonal human IgG at 10 mg/kg i.v. every three days (270-320 mg tumor size) versus antibody Ab1 at 10 mg/kg i.v. every three days (270-320 mg tumor size).

[0116] FIG. 8 provides survival data for polyclonal human IgG at 10 mg/kg i.v. every three days (400-527 mg tumor size) versus antibody Ab1 at 10 mg/kg i.v. every three days (400-527 mg tumor size).

[0117] FIG. 9 provides a pharmacokinetic profile of antibody Ab1 in cynomolgus monkey. Plasma levels of antibody Ab1 were quantitated through antigen capture ELISA. This protein displays a half life of between 12 and 17 days consistent with other full length humanized antibodies.

[0118] FIGS. 10(A-D) provides binding data for antibodies Ab4, Ab3, Ab8 and Ab2, respectively. FIG. 10 E provides binding data for antibodies Ab1, Ab6 and Ab7.

[0119] FIG. 11 summarizes the binding data of FIGS. 10 (A-D) in tabular form.

[0120] FIG. 12 presents the sequences of the 15 amino acid peptides used in the peptide mapping experiment of Example 14.

[0121] FIG. 13 presents the results of the blot prepared in Example 14.

[0122] FIG. 14 presents the results of the blots prepared in Example 14.

[0123] FIG. 15A shows affinity and binding kinetics of Ab1 for IL-6 of various species.

[0124] FIG. 15B demonstrates inhibition of IL-6 by Ab1 in the T1615 cell proliferation assay.

[0125] FIG. 16 shows the mean plasma concentration of Ab1 resulting from a single administration of Ab1 to healthy male subjects in several dosage groups.

[0126] FIG. 17 shows mean area under the plasma Ab1 concentration time curve (AUC) for the dosage groups shown in FIG. 16.

[0127] FIG. 18 shows mean peak plasma Ab1 concentration (Cmax) for the dosage groups shown in FIG. 16.

[0128] FIG. 19 summarizes Ab1 pharmacokinetic measurements of the dosage groups shown in FIG. 16.

[0129] FIG. 20 shows the mean plasma concentration of Ab1 resulting from a single administration of Ab1 to patients with advanced cancer.

[0130] FIG. 21 illustrates the unprecedented elimination half-life of Ab1 compared with other anti-IL-6 antibodies.

[0131] FIG. 22 shows increased hemoglobin concentration following administration of Ab1 to patients with advanced cancer.

[0132] FIG. 23 shows mean plasma lipid concentrations following administration of Ab1 to patients with advanced cancer.

[0133] FIG. 24 shows mean neutrophil counts following administration of Ab1 to patients with advanced cancer.

[0134] FIG. 25 demonstrates suppression of serum CRP levels in healthy individuals.

[0135] FIGS. 26(A-B) demonstrates suppression of serum CRP levels in advanced cancer patients.

[0136] FIG. 27 shows prevention of weight loss by Ab1 in a mouse cancer cachexia model.

[0137] FIG. 28 shows the physical appearance of representative Ab1-treated and control mice in a cancer cachexia model.
Fig. 29 demonstrates that Ab1 promotes weight gain in advanced cancer patients. Fig. 30 demonstrates that Ab1 reduces fatigue in advanced cancer patients. Fig. 31 demonstrates that Ab1 promotes hand grip strength in advanced cancer patients. Fig. 32 demonstrates that Ab1 suppresses an acute phase protein (Serum Amyloid A) in mice. Fig. 33 demonstrates that Ab1 increases plasma albumin concentration in advanced cancer patients. Figs. 34 and 35 show alignments between a rabbit antibody light and variable heavy sequences and homologous human sequences and the final humanized sequences. Framework regions are identified as FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3. Figs. 36 (A-B) and 37 (A-B) shows alignments between light and variable heavy sequences, respectively, of different forms of Ab1. Framework regions are identified as FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3. Sequence differences within the CDR regions are highlighted.

Fig. 38 shows the mean CRP values for each dosage concentration (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody. Fig. 39 shows the change in median values of CRP from each dosage concentration group corresponding to Fig. 38.

Fig. 40 shows a reduction in serum CRP levels in patients with various cancers after dosing at 80, 160 or 320 mg for 12 weeks.

Fig. 41 shows a reduction in serum CRP levels in the patient population with rheumatoid arthritis after dosing at 80, 160 and 320 mg for 12 weeks.

Fig. 42 demonstrates that Ab1 increases mean hemoglobin at 80, 160 and 320 mg after 12 weeks of dosing.

Fig. 43 demonstrates mean change from baseline hemoglobin for the data presented in Fig. 42.

Fig. 44 demonstrates that Ab1 increases mean hemoglobin at 160 and 320 mg after 12 weeks of dosing in patients having baseline hemoglobin below 11 g/l.

Fig. 45 demonstrates that Ab1 increases mean hemoglobin at 80, 160 and 320 mg after 16 weeks of dosing.

Fig. 46 demonstrates that Ab1 increases mean albumin concentration at 80, 160 and 320 mg after 12 weeks of dosing.

Fig. 47 demonstrates the change from baseline for mean albumin concentration from each dosage concentration group corresponding to Fig. 46.

Fig. 48 demonstrates that Ab1 provides sustained increases in mean albumin concentration at 160 and 320 mg after 12 weeks of dosing in patients having baseline albumin below 35 g/l.

Fig. 49 demonstrates the averaged weight change data from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody over 12 weeks.

Fig. 50 demonstrates the averaged percent change in body weight from each dosage concentration group corresponding to Fig. 49.

Fig. 51 demonstrates the change in averaged lean body mass data for the dosage concentration groups corresponding to Fig. 49.

Fig. 52 demonstrates increases in the mean Facit-F FS subscale score for some of the dosage concentration groups in the patient population after dosing at 80, 160 and 320 mg after 8 weeks.

Fig. 53 demonstrates the change from baseline Facit-F FS subscale score corresponding to Fig. 52.

Fig. 54 demonstrates that Ab1 drops D-dimer levels over placebo at 80, 160 and 320 mg after 16 weeks of dosing. Fig. 55 demonstrates the percent change from baseline in D-dimer concentration from each dosage concentration group corresponding to Fig. 54.

Fig. 56 demonstrating that treatment of patients with rheumatoid arthritis produced significant improvement over placebo based upon ACR metrics.

Fig. 57 demonstrates patients achieving ACR 20 over placebo at 80, 160, and 320 mg after 16 weeks of dosing.

Fig. 58 demonstrates patients achieving ACR 50 over placebo at 80, 160, and 320 mg after 16 weeks of dosing.

Fig. 59 demonstrates patients achieving ACR 70 over placebo at 80, 160, and 320 mg after 16 weeks of dosing.

Fig. 60 demonstrates the change from baseline for the components of the ACR metric for placebo, 80, 160, and 320 mg dosage concentration groups.

Fig. 61 demonstrates the change in HAQ-DI scores for placebo, 80, 160, and 320 mg dosage concentration groups.

Fig. 62 demonstrates the change in DAS28 scores for placebo, 80, 160, and 320 mg dosage concentration groups.

Fig. 63 demonstrates the change in percentage of patients achieving EULAR good or moderate responses for placebo, 80, 160, and 320 mg dosage concentration groups.

Fig. 64 schematically shows a clinical study relating to the use of humanized Ab1 for treatment of rheumatoid arthritis.

Fig. 65 shows plasma concentrations of humanized Ab1 in rheumatoid arthritis patients after subcutaneous (SC) or intravenous (IV) dosing with humanized Ab1.

Fig. 66 shows plasma CRP level concentrations after subcutaneous or intravenous dosing of humanized Ab1.

Fig. 67 contains a table enumerating adverse events in patients administered humanized Ab1 through week 24.

Fig. 68 contains a Table enumerating injection site reactions to humanized Ab1 through week 12 after antibody administration.

Fig. 69 tabulates clinical laboratory evaluations (ALT, AST, bilirubin, neutrophil counts, and platelet counts) for patients subcutaneously or intravenously administered humanized Ab1 and controls through week 12 after humanized Ab1 administration.

Fig. 70 tabulates plasma pharmacokinetic parameters in patients through week 24 after subcutaneous or intravenous administration of humanized Ab1.

Fig. 71 shows the effect of subcutaneous and intravenous administration of ALD518 through week 12 after antibody, dosing at 50 or 100 mg.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may
vary. It is also understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0179] As used herein the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the protein" includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

[0180] Interleukin-6 (IL-6): As used herein, interleukin-6 (II-6) encompasses not only the following 212 amino acid sequence available as GenBank Protein Accession No. NP_000591:

MNSSFITSAFGPVAPFLGLLVLPAAAPAV-PPVPGEDSKVAAPHPKLLSERSIKY IQYILDGHS-ALRKTCKSNMCMCESSKEALENNLIQP-KMAEKGDCFQSGFNEETC
LVKIHGGLLFEEVFLEQLYNRFESE- EQRARAVQSMRTKVLQFIQQKAKNLDAITTP DPTT- NASLLTQLAQQNQLQMCTMLRSL- FKEFQSSRLRQM (SEQ ID NO: 1), but also any pro-, pre- and mature forms of this IL-6 amino acid sequence, as well as mutants and variants including allelic variants of this sequence.

[0181] IL-6 antagonist: As used herein, the terms "IL-6 antagonist," and grammatical variants thereof include any composition that prevents, inhibits, or lessens the effect(s) of IL-6 signaling. Generally, such antagonists may reduce the levels or activity of IL-6, IL-6 receptor alpha, gp130, or a molecule involved in IL-6 signal transduction, or may reduce the levels or activity complexes between the foregoing (e.g., reducing the activity of an IL-6/IL-6 receptor complex). Antagonists include antisense nucleic acids, including DNA, RNA, or a nucleic acid analogue such as a peptide nucleic acid, locked nucleic acid, morpholin (phosphorodiamidate morpholino oligo), glycerol nucleic acid, or threon nucleic acid. See Heasman, Dev Biol. 2002 Mar. 15; 243(2):209-14; Hamon and Rossi, Nature. 2004 Sep. 16; 431(7006):371-8; Paul et al., Nat Biotechnol. 2002 May; 20(5):505-8; Zhang et al., J Am Chem Soc. 2005 Mar. 30; 127(12):4174-5; Wahlstedt et al., Proc Natl Acad Sci USA. 2000 May 9; 97(10):5633-8; Hanvey et al., 1992 Nov. 27; 258(5087):1481-5; Braesch et al., Biochemistry. 2002 Apr. 9; 41(14):4503-10; Schoning et al., Science. 2000 Nov. 17; 290(5495):1347-51.

In addition IL-6 antagonists specifically include peptides that block IL-6 signaling such as those described in any of U.S. Pat. Nos. 6,599,875; 6,172,042; 6,838,433; 6,841,533; 5,210,075 et al. Also, IL-6 antagonists according to the invention may include p38 MAP kinase inhibitors such as those reported in US20070010529 et al. given this kinase’s role in cytokine production and more particularly IL-6 production. Further, IL-6 antagonists according to the invention include the glycoalkaloid compounds reported in US20050090453 as well as other IL-6 antagonist compounds isolatable using the IL-6 antagonist screening assays reported therein. Other IL-6 antagonists include antibodies, such as anti-IL-6 antibodies, anti-IL-6 receptor alpha antibodies, anti-gp130 antibodies, and anti-p38 MAP kinase antibodies including (but not limited to) the anti-IL-6 antibodies disclosed herein, Actemra™ (Tocilizumab), Remicade®; Zenapax™ (daclizumab), or any combination thereof. Other IL-6 antagonists include portions or fragments of molecules involved in IL-6 signaling, such as IL-6, IL-6 receptor alpha, and gp130, which may be native, mutant, or variant sequence, and may optionally be coupled to other moieties (such as half-life-increasing moieties, e.g., an Fe domain). For example, an IL-6 antagonist may be a soluble IL-6 receptor or fragment, a soluble IL-6 receptor:Fc fusion protein, a small molecule inhibitor of IL-6, an anti-IL-6 receptor antibody or antibody fragment, antisense nucleic acid, etc. Other IL-6 antagonists include avemurs, such as C326 (Silverman et al., Nat Biotechnol. 2005 December; 23(12):1556-61) and small molecules, such as synthetic retinoid AM80 (taminbarotene) (Takeda et al., Arterioscler Thromb Vasc Biol. 2006 May; 26(5):1177-83). Such IL-6 antagonists may be administered by any means known in the art, including contacting a subject with nucleic acids which encode or cause to be expressed any of the foregoing polypeptides or antisense sequences.

[0182] Disease or condition: As used herein, “disease or condition” refers to a disease or condition that a patient has been diagnosed with or is suspected of having, particularly a disease or condition associated with elevated IL-6. A disease or condition encompasses, without limitation thereto, the side-effects of medications or treatments (such as radiation therapy), as well as idiopathic conditions characterized by symptoms that include elevated IL-6.

[0183] Cachexia: As used herein, cachexia, also known as wasting disease refers to any disease marked especially by progressive emaciation, weakness, general ill health, malnutrition, loss of body mass, loss of muscle mass, or an accelerated loss of skeletal muscle in the context of a chronic inflammatory response (reviewed in Kotler, Ann Intern Med. 2000 Oct. 17; 133(8):622-34). Diseases and conditions in which cachexia is frequently observed include cancer, rheumatoid arthritis, AIDS, heart disease, dehydration, malnutrition, lead exposure, malaria, respiratory disease, old age, hypothyroidism, tuberculosis, hypopituitarism, neurothennia, hypohypertension, hyperotension, renal disease, splenecic, ankylosing spondylitis, failure to thrive (faltering growth) and other diseases, particularly chronic diseases. Cachexia may also be idiopathic (arising from an uncertain cause). Weight assessment in a patient is understood to exclude growths or fluid accumulations, e.g. tumor weight, extravascular fluid accumulation, etc. Cachexia may be assessed by measurement of a patient’s total body mass (exclusive of growths or fluid accumulations), total lean (fat-free) body mass, lean mass of the arms and legs (appendicular lean mass, e.g. measured using dual-energy x-ray absorptiometry or bioelectric impedance spectroscopy), and/or lean body mass index (lean body mass divided by the square of the patient’s height). See Kotler, Ann Intern Med. 2000 Oct. 17; 133(8):622-34; Marcora et al., Rheumatology (Oxford). 2006 November; 45(11): 1385-8.

[0184] Weakness: As used herein, weakness refers physical fatigue, which typically manifests as a loss of muscle strength and/or endurance. Weakness may be central (affecting most or all of the muscles in the body) or peripheral (affecting a subset of muscles). Weakness includes “true weakness,” in which a patient’s muscles have a decrease in some measure of peak and/or sustained force output, and “perceived weakness,” in which a patient perceives that a greater effort is required for performance of a task even though objectively
measured strength remains nearly the same, and may be objectively measured or self-reported by the patient. For example, weakness may be objectively measured using the hand grip strength test (a medically recognized test for evaluating muscle strength), typically employing a handgrip dynamometer.


[0186] Fever: As used herein, “fever” refers to a body temperature set-point that is elevated by at least 1 to 2 degrees Celsius. Fever is often associated with a subjective feeling of hypothermia exhibited as a cold sensation, shivering, increased heart rate and respiration rate by which the individual’s body reaches the increased set-point. As is well understood in the medical arts, normal body temperature typically varies with activity level and time of day, with highest temperatures observed in the afternoon and early evening hours, and lowest temperatures observed during the second half of the sleep cycle, and temperature measurements may be influenced by external factors such as mouth breathing, consumption of food or beverage, smoking, or ambient temperature (depending on the type of measurement). Moreover, the normal temperature set point for individuals may vary by up to about 0.5 degrees Celsius, thus a medical professional may interpret an individual’s temperature in view of these factors to diagnose whether a fever is present. Generally speaking, a fever is typically diagnosed by a core body temperature above 38.0 degrees Celsius, an oral temperature above 37.5 degrees Celsius, or an axillary temperature above 37.2 degrees Celsius.

[0187] Improved: As used herein, “improved,” “improvement,” and other grammatical variations, includes any beneficial change resulting from a treatment. A beneficial change is any way in which a patient’s condition is better than it would have been in the absence of the treatment. “Improved” includes prevention of an undesired condition, slowing the rate at which a condition worsens, delaying the development of an undesired condition, and restoration to an essentially normal condition. For example, improvement in cachexia encompasses any increase in patient’s mass, such as total body mass (excluding weight normally excluded during assessment of cachexia, e.g. tumor weight, extracellular fluid accumulation, etc.), lean body mass, and/or appendicular lean mass, as well as any delay or slowing in the rate of loss of mass, or prevention or slowing of loss of mass associated with a disease or condition with which the patient has been diagnosed. For another example, improvement in weakness encompasses any increase in patient’s strength, as well as any delay or slowing in the rate of increase of fatigue, or prevention or slowing of increase in fatigue associated with a disease or condition with which the patient has been diagnosed. For still another example, improvement in fever encompasses any decrease in patient’s fever, as well as any delay or slowing in the rate of increase of fatigue, or prevention or slowing of increase in fatigue associated with a disease or condition with which the patient has been diagnosed.

[0188] C-Reactive Protein (CRP): As used herein, C-Reactive Protein (CRP) encompasses not only the following 224 amino acid sequence available as GenBank Protein Accession No. NP_000558: MEKKLCHVLTSLSIHAGFTMQMSRKAFILEVFPSKEDDSYSLKAPLTLKPLKAFTVCL...HFFYLESSRTDRGYSIFSSTAYKRFQDNEILFWSKDJIGYFTVGGESEILFEVPEVTVAPV HICTSWESASGIVFMDGKPVSRK- SLKKGITYVGEASILQEQDSFHGNGFEQGQLVQGDIYIYDNLQPSPEIINTYILGYPSPS NVLLNRLARKYEYEVQGGEFTPKQLPW (SEQ ID NO: 72), but also any pre-pro, pro- and mature forms of this CRP amino acid sequence, as well as mutants and variants including allelic variants of this sequence. CRP levels, e.g. in the serum, liver, tumor, or elsewhere in the body, can be readily measured using routine methods and commercially available reagents, e.g. ELISA, antibody test strip, immunoturbidimetry, rapid immunofluorescence, visual agglutination, Western blot, Northern blot, etc.

[0189] Interleukin-6 receptor (IL-6R); also called IL-6 receptor alpha (IL-6RA): As used herein, “interleukin-6 receptor” (“IL-6R”; also “IL-6 receptor alpha” or “IL-6RA”) encompasses not only the following 468 amino acid sequence available as Swiss-Prot Protein Accession No. P08887: MALTQGCAAALLAAPGAAPCRCPAQVEARGVLTSLPGDSVTFTCPGVEDEDATNVHWV- LRKPAAGHPSRWAGMGRPSLRSVQL-HDSGNYSYCRAIRGAPGTVHLIVDDVPPEEPQQLSCFRKSLPLNV- VCEWGRSTPSLTQKAVLILRKFQSNPSEAEDFQEPQCYSQSEQSKFCQIALPEGIDDSSFYIVSMECVASSVGSKFKSTQTPFQCGIQLDPHANEITVAVARPWNLSTWQDPH- SWNSSFYRLFERLVRYAERSKFTFTTWVKDLQHHCVHIDAWGLRHVVQLRAGQEEFGQGQWS- EWSPEAMGTPWESRSPPPANEVSTPMPMQALTNKDDNDLRDSANATSLPVQDSSTPPFLTVAGGSLAFTTLCLIAVLR- FKKTWKRLKLEGHTSMHPYPS-LQLQVYPERPRPTPTVLPPLZIPPPVSPSSLGSDNTSHHRPRDPARDPSPSYPEISNTDYFPPR (SEQ ID NO: 72), but also any pre-pro, pro- and mature forms of this amino acid sequence, as well as mutants and variants including allelic variants of this sequence.

[0190] gp130: As used herein, gp130 (also called Interleukin-6 receptor subunit beta) encompasses not only the following 918 precursor amino acid sequence available as Swiss-Prot Protein Accession No. P40189: NLIIPQWWTQVQLFIHFLITTELGPDFGIESPESVPVLHINFTACVCLKEKCMDFYHNAV- NYTVIWKTNHEQIKPEQYHTNRAAVTFDIAHNLNQETCMLTFQGQLEQNYVGITIILPKEKPKLCS- CIVVNEGKMKRCEWDGGRETHLETNKELSEWATH
KFADCKAKRDTPTSCTVDYSTVY-FVNIEVWWEAENAL.GKTVSDHNFDPVYVKVKPNP-PHNLSVESELILKTWNPSKSVIILKYNQYRTICADSTWSQIPPEPDTAS TRSSFTVQDLKPTFYEVIRRC-MKEDGQGYSDWEASEAGIYEDPSCPAPSFW YKIDPSHTQGTYRTQVLWKLTP-PFEANGKLIDYTEVLTIRWKSII.QNYTVNATKL TVN-LINDAYLALTVRNQGSADAALVLT-PCADQAFTHPVMDLAKPDCNDMLW VETWTPRESVICKYLEWCILSDC-CAPCITDQWQEDGTVHRTYLGNLASEKICYLTVTPYDVADPSGESPISKAY-LKQAPPSKGPRTTVKKVGKEA.ELWDQLPVDVQ NGFIRNTITYFYRTIGNETAYNVDSSHI-TEYTLDSLITDLYMVRMAAYTEGGIDC GPEPETITIPFQAAEIAVPPV-CLALFLLITLGVLFCFNIRCLDLKHIVPNVPDSPS KSHIAQWSHPHTPPRNFNSQDKOMYSQDGNFDTDYSPVEITANDKKPPEDLKSLDLF KKEKIN-TEGHSSGGSCSSRSSPSSSSSENESSQNTSSTVIPQSYVTHSISGYRHQVPSVQVF3R5E5STQPLLLDSEER-PEDQLVQDVLVDGDGILPQAQQYFKQCNQHCESSPDHSHEIRSKVQSVNEEDFVR.LKQIIS-DHISQSCGCSQKMFQVEASADAFPGTQGQVEFETVGMEMAEATIDEMKPSYQPTVRQGGYMPQ (SEQ ID NO: 728), but also any pre-pro, pro- and mature forms of this amino acid sequence, such as the mature form encoded by amino acids 23 through 916 of the sequence shown, as well as mutants and variants including allelic variants of this sequence.

[0191] Glasgow Prognostic Score (GPS): As used herein, Glasgow Prognostic Score (GPS) refers to an inflammation-based prognostic score that assigns one point for a serum albumin level less than <35 mg/L and one point for a CRP level above 10 mg/L. Thus, a GPS of 0 indicates normal albumin and CRP, a GPS of 1 indicates reduced albumin or elevated CRP, and a GPS of 2 indicates both reduced albumin and elevated CRP.

[0192] Effective amount: As used herein, “effective amount,” “amount effective to,” “amount of X effective to” and the like, refer to an amount of an active ingredient that is effective to relieve or reduce to some extent one or more of the symptoms of the disease in need of treatment, or to retard initiation of clinical markers or symptoms of a disease in need of prevention, when the compound is administered. Thus, an effective amount refers to an amount of the active ingredient which exhibit effects such as (i) reversing the rate of progress of a disease; (ii) inhibiting to some extent further progress of the disease; and/or, (iii) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the disease. The effective amount may be empirically determined by experimenting with the compounds concerned in known in vivo and in vitro model systems for a disease in need of treatment. The context in which the phrase “effective amount” is used may indicate a particular desired effect. For example, “an amount of an anti-IL-6 antibody effective to reduce serum CRP levels” and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable increase in serum albumin levels, or prevent, slow, delay, or arrest, a decrease in serum albumin levels for which the subject is at risk. An effective amount will vary depending on the weight, age, and medical history of the individual, as well as the severity of the patient’s condition(s), the type of disease(s), mode of administration, and the like. An effective amount may be readily determined using routine experimentation, e.g., by titration (administration of increasing dosages until an effective dosage is found) and/or by reference to amounts that were effective for prior patients. Generally, the anti-IL-6 antibodies of the present invention will be administered in dosages ranging between about 0.1 mg/kg and about 20 mg/kg of the patient’s body-weight.

[0193] Prolonged reduction in serum CRP: As used herein, “prolonged reduction in serum CRP” and similar phrases refer to a measurable decrease in serum CRP level relative to the initial serum CRP level (i.e. the serum CRP level at a time before treatment begins) that is detectable within about a week from when a treatment begins (e.g. administration of an anti-IL-6 antibody) and remains below the initial serum CRP level for an prolonged duration, e.g. at least about 14 days, at least about 21 days, at least about 28 days, at least about 35 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 11 weeks, or at least about 12 weeks from when the treatment begins.

[0194] Prolonged increase in serum albumin: As used herein, “prolonged increase in serum albumin” and similar phrases refer to a measurable decrease in serum albumin level relative to the initial serum albumin level (i.e. the serum albumin level at a time before treatment begins) that is detectable within about a week from when a treatment begins (e.g. administration of an anti-IL-6 antibody) and remains above the initial serum albumin level for a prolonged duration, e.g. at least about 14 days, at least about 21 days, at least about 28 days, at least about 35 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 11 weeks, or at least about 12 weeks from when the treatment begins.

[0195] Prolonged improvement in cachexia: As used herein, “prolonged improvement in cachexia” refers to a measurable improvement patient’s body mass, lean body mass, appendicular lean body mass, and/or lean body mass index, relative to the initial level (i.e. the level at a time before treatment begins) that is detectable within about 4 weeks and remains improved for a prolonged duration, e.g. at least about 35 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 11 weeks, or at least about 12 weeks from when the treatment begins.

[0196] Prolonged improvement in weakness: As used herein, “prolonged improvement in weakness” refers to a measurable improvement in muscular strength, relative to the initial level (i.e. the level at a time before treatment begins) that is detectable within about 2 weeks and remains improved for a prolonged duration, e.g. at least about 21 days, at least about 28 days, at least about 35 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 11 weeks, or at least about 12 weeks from when the treatment begins.

[0197] Prolonged improvement in fatigue: As used herein, “prolonged improvement in fatigue” refers to a measurable improvement in fatigue, relative to the initial level (i.e. the level at a time before treatment begins) that is detectable
within about 1 week and remains improved for a prolonged duration, e.g., at least about 14 days, at least about 21 days, at least about 28 days, at least about 35 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 11 weeks, or at least about 12 weeks from when the treatment begins.

Prolonged improvement in fever. As used herein, "prolonged improvement in fever" refers to a measurable decrease in fever (e.g., peak temperature or amount of time that temperature is elevated, relative to the initial level (i.e. the level at a time before treatment begins)) that is detectable within about 1 week and remains improved for a prolonged duration, e.g., at least about 14 days, at least about 21 days, at least about 28 days, at least about 35 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 11 weeks, or at least about 12 weeks from when the treatment begins.

Mating competent yeast species: In the present invention this is intended to broadly encompass any diploid or tetraploid yeast which can be grown in culture. Such species of yeast may exist in a haploid, diploid, or tetraploid form. The cells of a given ploidy may, under appropriate conditions, proliferate for indefinite number of generations in that form. Diploid cells can also sporulate to form haploid cells. Sequential mating can result in tetraploid strains through further mating or fusion of diploid strains. In the present invention the diploid or polyplloid yeast cells are preferably produced by mating or spheroplast fusion.

In one embodiment of the invention, the mating competent yeast is a member of the Saccharomycetaceae family, which includes the genera Arxiozyma; Ascobotryozyma; Citeromyces; Debaromyces; Dekkera; Eremothecium; Issatchenkia; Kazachstania; Kluyveromyces; Kodamaea; Lodderomyces; Pachysolen; Pichia; Saccharomyces; Saccharomycodes; Sataniopsis; Tetraplops; Torulaspora; Williopsis; and Zygosaccharomyces. Other types of yeast potentially useful in the invention include Jarrovia, Rhodosporidium, Candida, Hansenula, Filobasidium, Filobasidilla, Sporidiobolus, Bullera, Leucosporidium and Filobasidilla.

In a preferred embodiment of the invention, the mating competent yeast is a member of the genus Pichia. In a further preferred embodiment of the invention, the mating competent yeast of the genus Pichia is one of the following species: Pichia pastoris, Pichia methanolica, and Hansenula polymorpha (Pichia angusta). In a particularly preferred embodiment of the invention, the mating competent yeast of the genus Pichia is the species Pichia pastoris.

Haploid Yeast Cell: A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

Polyploid Yeast Cell: A cell having more than one copy of its normal genomic (chromosomal) complement.

Diploid Yeast Cell: A cell having two copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (matting) of two haploid cells.

Tetraploid Yeast Cell: A cell having four copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (matting) of two haploid cells. Tetraploids may carry two, three, four, or more different expression cassettes. Such tetraploids might be obtained in S. cerevisiae by selective mating homozygotic heterothallic a/a and alpha/alpha diploids and in Pichia by sequential mating of haploids to obtain auxotrophic diploids. For example, a [met his] haploid can be mated with [ade his] haploid to obtain diploid [his]; and a [met arg] haploid can be mated with [ade arg] haploid to obtain diploid [arg]; then the diploid [his]diploid [arg] to obtain a tetraploid prototroph. It will be understood by those of skill in the art that reference to the benefits and uses of diploid cells may also apply to tetraploid cells.

Yeast Mating: The process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

Meiosis: The process by which a diploid yeast cell undergoes reductive division to form four haploid spore products. Each spore may then germinate and form a haploid vegetatively growing cell line.

Selectable Marker: A selectable marker is a gene or gene fragment that confers a growth phenotype (physical growth characteristic) on a cell receiving that gene as, for example through a transformation event. The selectable marker allows that cell to survive and grow in a selective growth medium under conditions in which cells that do not receive that selectable marker gene cannot grow. Selectable marker genes generally fall into several types, including positive selectable marker genes such as a gene that confers on a cell resistance to an antibiotic or other drug, temperature when two ts mutants are crossed or a ts mutant is transformed; negative selectable marker genes such as a biosynthetic gene that confers on a cell the ability to grow in a medium without a specific nutrient needed by all cells that do not have that biosynthetic gene, or a mutated biosynthetic gene that confers on a cell inability to grow by cells that do not have the wild type gene; and the like. Suitable markers include but are not limited to: ZEO; G418; LYS3; MET1; MET3; ADE1; ADE3; URA3; and the like.

Expression Vector: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, e.g. E. coli, and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Stearns, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

Expression vectors for use in the methods of the invention will further include yeast specific sequences, including a selectable auxotrophic or drug marker for identifying transformed yeast strains. A drug marker may further be used to amplify copy number of the vector in a yeast host cell.

The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in yeast cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be
included, e.g. a signal sequence, and the like. A yeast origin of replication is optional, as expression vectors are often integrated into the yeast genome.

[0212] In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

[0213] Nucleic acids are “operably linked” when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, “operably linked” means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway® Technology; Invitrogen, Carlsbad Calif.). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0214] Promoters are untranslated sequences located upstream (5′) to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, e.g., the presence or absence of a nutrient or a change in temperature.

[0215] The yeast promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the yeast genome; alternatively a selectable marker is used as the site for homologous recombination. *Pichia* transformation is described in Cregg et al. (1985) *Mol. Cell. Biol.* 5:3376-3385.


[0217] Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and cimeric promoter’s derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile, amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

[0218] The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, e.g. a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pro-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P. pastoris*. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Other secretion signals of interest also include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, e.g., K28 pre-protoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto et al. *Protein Eng.* 11(2) 75 (1998), and Kobayashi et al. *Therapeutic Apheresis* 2(4) 257 (1998).

[0219] Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5′ or 3′ to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5′ or 3′ to the coding sequence, but is preferably located at a site 5′ from the promoter.

[0220] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3′ to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

[0221] Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and religated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin™ (phleomycin)) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

[0222] As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) *Ann. Rev. Biochem.* 58:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E. coli*—encoded recombination proteins. Recombination occurs between specific attachment (att) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) *Site-Specific Recombination in*
Phage Lambda, in *Lambda II*, Weisberg, ed. (Cold Spring Harbor, N.Y.:Cold Spring Harbor Press), pp. 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the att sites are hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

Att sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing att sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites; and the like.

Folding, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. While non-covalent interactions are important in determining structure, usually the proteins of interest will have intra- and/or intermolecular covalent disulfide bonds formed by two cysteine residues. For naturally occurring proteins and polypeptides or derivatives and variants thereof, the proper folding is typically the arrangement that results in optimal biological activity, and can conveniently be monitored by assays for activity, e.g. ligand binding, enzymatic activity, etc.

In some instances, for example where the desired product is of synthetic origin, assays based on biological activity will be less meaningful. The proper folding of such molecules may be determined on the basis of physical properties, energetic considerations, modeling studies, and the like.

The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, i.e. foldases, chaperonins, etc. Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, etc. as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin, and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, e.g. one strain may express BIP, and the other strain may express PDI or combinations thereof.

The terms “desired protein” or “target protein” are used interchangeably and refer generally to a humanized antibody or a binding portion thereof described herein. The term “antibody” is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetype antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be “antibodies.”


For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (e.g., a functional domain, catalytic amino acid residues, etc). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for in vitro mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.
[0231] Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions ($V_L$ and $V_H$), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, e.g., in U.S. Pat. No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, IgG4, IgG5, IgM, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions.

[0232] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hypervariable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. Although facially complex, the process is straightforward in practice. See, e.g., U.S. Pat. No. 6,187,287, incorporated fully herein by reference. In a preferred embodiment, humanization may be effected as disclosed in detail infra. This scheme grafts CDRs onto human FR's highly homologous to the parent antibody's FR's.

[0233] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab, Fab', or other fragments) may be synthesized. “Fragment,” or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance “Fv” immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest, e.g., diabodies, which comprise two distinct Fv specificities. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), cell membranes, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

[0234] Immunoglobulins and fragments thereof may be modified post-translationally, e.g., to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of additional effector molecules are provided infra.

[0235] The term “polyploid yeast that stably expresses or expresses a desired secreted heterologous polypeptide for prolonged time” refers to a yeast culture that secretes said polypeptide for at least several days to a week, more preferably at least a month, still more preferably at least 1-6 months, and even more preferably for more than a year at threshold expression levels, typically at least 10-25 mg/liter and preferably substantially greater.

[0236] The term “polyploid yeast culture that secretes desired amounts of recombinant polypeptide” refers to cultures that stably or for prolonged periods secrete at least 10-25 mg/liter of heterologous polypeptide, more preferably at least 50-500 mg/liter, and most preferably 500-1000 mg/liter or more.

[0237] A polynucleotide sequence “corresponds” to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (i.e., the polynucleotide sequence “encodes” the polypeptide sequence), one polynucleotide sequence “corresponds” to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

[0238] A “heterologous” region or domain of a DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

[0239] A “coding sequence” is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A “promoter sequence” is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is “under the control” of the promoter sequence or “operatively linked” to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

[0240] Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes (for polypeptides). A “DNA vector” is a replicon, such as a plasmid, phage or cosmid, which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An “expression vector” is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypeptide encoded by said polynucleotide sequence. Exemplary expression vectors and techniques for their use are described in the following publications: Old et al., Principles of Gene Manipulation: An Introduction to Genetic Engineering, Blackwell Scientific
[0241] For example, a lipoprotein or other lipid aggregate may comprise a lipid such as phosphatidylethanolamine (lecithin) (PC), phosphatidylethanolamines (PE), lyssolecithins, lysophosphatidylethanolamines, phosphatidylserines (PS), phosphatidylglycerols (PG), phosphatidylinositol (PI), sphingomyelins, cardiolipin, phosphatidic acids (PA), fatty acids, gangliosides, glycolipids, glycolipids, mono-, di- or triglycerides, ceramides, cerebrosides and combinations thereof; a cationic lipid (or other cationic amphiphile) such as 1,2-dioleoyl-3-(trimethylamino) propane (DOTAP); N-cholesteryloxy carbaryl-1,3,7,12-tetrazapentadecane-1,15-diamine (CTAP); N-[1-(2,3-dioleyloxy)propyl]-N,N-dimethyl-N-hydroxyethylammonium bromide (DMRIE); N-[1-(2,3-dioleoyloxy)propyl]-N,N-dimethyl-N-hydroxy ethylammonium bromide (DORIE); N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA); 3 beta [N-[(N',N'-dimethylaminoethyle)carbamoylo] cholesterol (DC-Chol); and dimethyldioctadecylammonium (DDAB); dioleoylphosphatidyl ethanolamine (DOPE), cholesterol-containing DOPE; and combinations thereof; and/or a hydrophilic polymer such as polyvinylpyrrolidone, polyvinylmethyl ether, poly vinyl monochloride, polylactioxazoline, polyoxyhydroxypropylxazoline, polyoxyhydroxypropylethamaryclamide, polyoxyhydroxypropylacrylamide, polyoxyhydroxyethylacrylamide, polyoxyhydroxyethylacrylate, polyoxyhydroxyethylcelullose, hydroxyethylcellulose, polyethylenglycol, polyaspartamide and combinations thereof. Other suitable cationic lipids are described in Miller, Angew. Chem. Int. Ed. 37:1768 1785 (1998), and Cooper et al., Chem. Eur. J. 4(1): 137 151 (1998). Liposomes can be crosslinked, partially crosslinked, or free from crosslinking. Crosslinked liposomes can include crosslinked as well as non-crosslinked components. Suitable cationic liposomes or cationic lipids are commercially available and can also be prepared as described in Sipkens et al., Nature Medicine, 1998, 4(5)(1998), 623-626 or as described in Miller, supra. Exemplary liposomes include a polymericzable zwitterionic or neutral lipid, a polyetherizable integrin targeting lipid and a polymerizable cationic lipid suitable for binding a nucleic acid. Liposomes can optionally include peptides that provide increased efficiency, for example as described in U.S. Pat. No. 7,297,759. Additional exemplary liposomes and other lipid aggregates are described in U.S. Pat. No. 7,166,298.

[0242] “Amplification” of nucleonucleotide sequences is the in vitro production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, Bio/Technol., 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

[0243] The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., Ann. N.Y. Acad. Sci., 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 daltons (the “light chain”), and two identical heavy chains of molecular weight 53,000-70,000 (the “heavy chain”). The four chains are joined by disulfide bonds in a “Y” configuration wherein the light chains bracket the heavy chains starting at the mouth of the “Y” configuration. The “branch” portion of the “Y” configuration is designated the Fv region; the stem portion of the “Y” configuration is designated the Fe region. The amino acid sequence orientation runs from the N-terminal end at the top of the “Y” configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

[0244] The variable region is linked to each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (i.e., the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE) corresponding to γ, μ, α, δ, and ε (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., Structural Concepts in Immunology and Immunchemistry, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., et al., Clinical Immunobiology, p p 1-18, W. B. Saunders (1980); Kohl, S., et al., Immunochemistry, 48: 187 (1985)). While the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or λ (lambda). Each heavy chain class can be paired with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the “tail” portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

[0245] The expression “variable region” or “VR” refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain (VL) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0246] The expressions “complementarity determining region,” “hypervariable region,” or “CDR” refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (See Kabat, E. A. et al., Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat et al. (“Sequences of Proteins of Immunological Interest,” Kabat E., et al., US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, J Mol. Biol. 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the
critical contact residues used by the CDR in the antibody-
antigen interaction (Kashmiri, S., Methods, 36:25-34
(2005)). CDRs for exemplary anti-IL-6 antibodies are pro-
vided herein.

[0247] The expressions “framework region” or “FR” refer
to one or more of the framework regions within the variable
regions of the light and heavy chains of an antibody (See
Kabat, E. A. et al., Sequences of Proteins of Immunological
Interest, National Institutes of Health, Bethesda, Md.,
(1987)). These expressions include those amino acid
sequence regions interposed between the CDRs within the
variable regions of the light and heavy chains of an anti-
body. As mentioned in the preferred embodiments, the FR’s will
comprise human FR’s highly homologous to the parent
antibody (e.g. rabbit antibody).

Anti-IL-6 Antibodies and Binding Fragments Thereof

[0248] The invention includes antibodies having binding
specificity to IL-6 and possessing a variable light chain
sequence comprising the sequence set forth below:

(SEQ ID NO: 2)

MTGTRAPQLLGLLWLPLGAKCAWMYQSFASAVAVGTVTICCAQSG
INRELSWYQSMQPKMLLYRATLASSVSRRPSGEGSSTFTLLTSDL
ECDAATYCYQQGYSLLHIDNAGGQGEVVVKEVRVAAPSVFIPPSDEQL
KSGTASVCCILIN

(SEQ ID NO: 709)

AIGMTQSPSSLSASDVSDFVTTCASQSIMNELSWYQSMQPKMLLYR
ASTLASQVPSQSGGOTDFTLTISLQLQDFTLATYQCYQQGSLNIMD
FPGETTVKIR.

[0249] The invention also includes antibodies having bind-
ing specificity to IL-6 and possessing a variable heavy chain
sequence comprising the sequence set forth below:

(SEQ ID NO: 3)

METGRELWLLVLVAKVQQCLESBSGSLVTPGFLTCTAASSLSNY
YTVVWRQAPKGMHGEIIGIYSGDLETAYTNAIGRPTSKSTTVYLDAMTS
LTATATYPCARDSSDMDAKHLWQGQTLTVSSAATKPSVPPAPS
SKTSGTGAALCGVK

(SEQ ID NO: 657)

EVQIERSQSSGLVQLPQPSLRLACASGFSLSHYYTVKQAGPKGILEWGVII
YGSDLETAYTNAIGRPTSKSTTVYLDAMTS
SDMDASKHNLWQGQTLTVSS.

[0250] The invention further contemplates antibodies com-
prising one or more of the polypeptide sequences of SEQ
ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which corre-
pond to the complementarity-determining regions (CDRs, or
hypervariable regions) of the variable light chain sequence of
SEQ ID NO: 2 or 709, and/or one or more of the polypeptide
sequences of SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO:
9 which correspond to the complementarity-determining
regions (CDRs, or hypervariable regions) of the variable
heavy chain sequence of SEQ ID NO: 3 or SEQ ID NO: 657 or
those contained in FIGS. 34-37, or combinations of these
polypeptide sequences. In another embodiment of the inven-
tion, the antibodies of the invention include combinations of
the CDRs and the variable heavy and light chain sequences set
forth above.

[0251] In another embodiment, the invention contemplates
other antibodies, such as for example chimeric antibodies,
comprising one or more of the polypeptide sequences of SEQ
ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which corre-
pond to the complementarity-determining regions (CDRs, or
hypervariable regions) of the variable light chain sequence
of SEQ ID NO: 2 or 709 or the other humanized VL sequences
contained in FIGS. 34-37, and/or one or more of the polypep-
tide sequences of SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID
NO: 9 which correspond to the complementarity-determining
regions (CDRs, or hypervariable regions) of the variable
heavy chain sequence of SEQ ID NO: 3 or 657, or combina-
tions of these polypeptide sequences. In another embodiment
of the invention, the antibodies of the invention include com-
binations of the CDRs and humanized versions of the variable
heavy and light chain sequences set forth above.

[0252] The invention also contemplates fragments of the
antibody having binding specificity to IL-6. In one embo-
diment of the invention, antibody fragments of the invention
comprise, or alternatively consist of, humanized versions of
the polypeptide sequence of SEQ ID NO: 2 or 709. In another
embodiment of the invention, antibody fragments of the inven-
tion comprise, or alternatively consist of, the humanized
versions of polypeptide sequence of SEQ ID NO: 3 or 657.

[0253] In a further embodiment of the invention, fragments
of the antibody having binding specificity to IL-6 comprise,
or alternatively consist of, one or more of the polypeptide
sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO:
6 which correspond to the complementarity-determining
regions (CDRs, or hypervariable regions) of the variable
light chain sequence of SEQ ID NO: 2 or SEQ ID NO: 709.

[0254] In another embodiment of the invention, fragments
of the antibody having binding specificity to IL-6 comprise,
or alternatively consist of, one or more of the polypeptide
sequences of SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO:
9 which correspond to the complementarity-determining
regions (CDRs, or hypervariable regions) of the variable
heavy chain sequence of SEQ ID NO: 3 or SEQ ID NO: 657
and the VH sequences in FIGS. 34-37.

[0255] The invention also contemplates antibody frag-
ments which include one or more of the antibody fragments
described herein. In one embodiment of the invention, frag-
ments of the antibodies having binding specificity to IL-6
comprise, or alternatively consist of, one, two, three or more,
including all of the following antibody fragments: the vari-
able light chain region of SEQ ID NO: 2 or 709; the variable
heavy chain region of SEQ ID NO: 3 or 657; the complemen-
tarity-determining regions (SEQ ID NO: 4; SEQ ID NO: 5;
and SEQ ID NO: 6) of the variable light chain region of SEQ
ID NO: 2 or 709; and the complementarity-determining
regions (SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO: 9)
of the variable heavy chain region of SEQ ID NO: 3 and SEQ
ID NO: 657 and the VH sequences in FIGS. 34-37.

[0256] The invention also contemplates variants wherein
either of the heavy chain polypeptide sequences of SEQ ID
NO: 18 or SEQ ID NO: 19 is substituted for the heavy chain
polypeptide sequence of SEQ ID NO: 3 or SEQ ID NO: 657 or
the other VH sequences in FIGS. 34-37, the light chain
polypeptide sequence of SEQ ID NO: 20 is substituted for the
light chain polypeptide sequence of SEQ ID NO: 2 or SEQ ID NO: 709 or the other VL sequences in FIGS. 34-37; and the heavy chain CDR sequence of SEQ ID NO: 120 is substituted for the heavy chain CDR sequence of SEQ ID NO: 8.

**[0257]** In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab1, comprising SI:EQ ID NO: 2 and SEQ ID NO: 3, or more particularly an antibody comprising SEQ ID NO: 657 and SEQ ID NO: 709 (which are respectively encoded by the nucleic acid sequences in SEQ ID NO: 700 and SEQ ID NO: 723) or one comprised of the alternative SEQ ID NOs set forth in the preceding paragraph, and having at least one of the biological activities set forth herein. In a preferred embodiment, the anti-IL-6 antibody will comprise at least one humanized sequence as shown in FIGS. 34-37.

**[0258]** In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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MDTAPRTQLLGLLLLLLPQGRCAYDNTQIQPASVEVAVGQTVTINQCSLET
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**[0259]** The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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SEQ ID NO: 21
MDTAPRTQLLGLLLLLLPQGRCAYDNTQIQPASVEVAVGQTVTINQCSLET
IYWSLWYQQEPPQKPKILVQASDASGVPSRGSSGSRGSLTLTISGV
QCDDAATYCCQYSGNVDFQGTEVVKRTVAAPSVFIPPSDEQKL
KSQTASVCCILKHPY.
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**[0260]** The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21, and/or one or more of the polypeptide sequences of SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

**[0261]** In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21, and/or one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

**[0262]** The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 21. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 22.

**[0263]** In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21.

**[0264]** In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22.

**[0265]** The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 21; the variable heavy chain region of SEQ ID NO: 22; the complementarity-determining regions (SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25) of the variable light chain region of SEQ ID NO: 21; and the complementarity-determining regions (SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28) of the variable heavy chain region of SEQ ID NO: 22.

**[0266]** In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab2, comprising SEQ ID NO: 21 and SEQ ID NO: 22, and having at least one of the biological activities set forth herein.

**[0267]** In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
SEQ ID NO: 37
MDTAPRTQLLGLLLLLLPQGRCAYDNTQIQPASVEVAVGQTVTINQCSLET
IYWSLWYQQEPPQKPKILVQASDASGVPSRGSSGSRGSLTLTISGV
QCDDAATYCCQYSGNVDFQGTEVVKRTVAAPSVFIPPSDEQKL
KSQTASVCCILKHPY.
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**[0268]** The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:
The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37, and/or one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37, and/or one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 37. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 38.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38.

The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 37; the variable heavy chain region of SEQ ID NO: 38; the complementarity-determining regions (SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41) of the variable light chain region of SEQ ID NO: 37; and the complementarity-determining regions (SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44) of the variable heavy chain region of SEQ ID NO: 38.
embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 53. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 54.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 53.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 54.

The invention also contemplates antibodies having binding specificity to IL-6 which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 53; the variable heavy chain region of SEQ ID NO: 54; the complementarity-determining regions (SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57) of the variable light chain region of SEQ ID NO: 53; and the complementarity-determining regions (SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60) of the variable heavy chain region of SEQ ID NO: 54.

In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab4, comprising SEQ ID NO: 53 and SEQ ID NO: 54, and having at least one of the biological activities set forth herein.

In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

-continued

FTTEDATYPCARGGPGKMGDIWQGTVVLTVSSASTKPSYFPLLPAKSKTSQGTAALCCLVKKD.

The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69, and/or one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69, and/or one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 69. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 70.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70.

The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 69; the variable heavy
chain region of SEQ ID NO: 70; the complementarity-determining regions (SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73) of the variable light chain region of SEQ ID NO: 69; and the complementarity-determining regions (SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76) of the variable heavy chain region of SEQ ID NO: 70.

[0293] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab5, comprising SEQ ID NO: 69 and SEQ ID NO: 70, and having at least one of the biological activities set forth herein.

[0294] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

\[
\text{MDTRAPQLGGLLLNLGPAGATPAVLQTPSPVPPVQGVTQICQSEQS}
\]

\[
\text{VYENFSLWYQKQFPQKLLKLQYASKLGAAPRPQGSPASSQGQPQLTISG}
\]

\[
\text{VQDEDAATYYCGLQYDDADNAPGGGSTEVVKKVPAAPSVPFPSSDEQL}
\]

\[
\text{KSETASVQCLWDF.}
\]

[0295] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[
\text{MDTLRQQLLLLWLRQAVLQYYQQVQCGQEMSQRPLVTCSQPITLTYSG}
\]

\[
\text{AMLRWIRQGKGLEWIGZIGYASASWTYAYNKAQRFTESKTTTQVTLKQT}
\]

\[
\text{SPAEDTATYPARQGDYQDGDPLRLDNAQPGTLVTVSASTQGSVPPL}
\]

\[
\text{APSSKSTGGTAAQCLVKE.}
\]

[0296] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85, and/or one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0297] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85, and/or one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0298] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 85. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 86.

[0299] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85.

[0300] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86.

[0301] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 85; the variable heavy chain region of SEQ ID NO: 86; the complementarity-determining regions (SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89) of the variable light chain region of SEQ ID NO: 85; and the complementarity-determining regions (SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92) of the variable heavy chain region of SEQ ID NO: 86.

[0302] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab6, comprising SEQ ID NO: 85 and SEQ ID NO: 86, and having at least one of the biological activities set forth herein.

[0303] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

\[
\text{MDTRAPQLGGLLLNLGPAGATPAVLQTPSPVPPVQGVTQICQSEQS}
\]

\[
\text{INNLHRYQKQFPKLLKLYRAYASSTLAGVSSRFKQGGSTFELTLITSDL}
\]

\[
\text{ECADATYYCQQGTSRLHIDNAPGGGSTEVVKKVPAAPSVPFPSSDEQL}
\]

\[
\text{KSETASVQCLWDF.}
\]

[0304] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[
\text{MDTLRQQLLLLWLRQAVLQYYQQVQCGQEMSQRPLVTCSQPITLTYSG}
\]

\[
\text{YNMTRQAPGKMLEWIGZIGYASASWTYAYNKAQRFTESKTTTQVTLKQT}
\]

\[
\text{LTAEDTATYPARQGDYQDGDPLRLDNAQPGTLVTVSASTQGSVPPLAPS}
\]

\[
\text{SKSTSGTAALGCLVKE.}
\]
[0305] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101, and/or one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0306] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101, and/or one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0307] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 101. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 102.

[0308] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101.

[0309] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102.

[0310] The invention also contemplates antibodies comprising one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 101; the variable heavy chain region of SEQ ID NO: 102; the complementarity-determining regions (SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105) of the variable light chain region of SEQ ID NO: 101; and the complementarity-determining regions (SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108) of the variable heavy chain region of SEQ ID NO: 102.

[0311] The invention also contemplates variants wherein either of the heavy chain polypeptide sequences of SEQ ID NO: 117 or SEQ ID NO: 118 is substituted for the heavy chain polypeptide sequence of SEQ ID NO: 102; the light chain polypeptide sequence of SEQ ID NO: 119 is substituted for the light chain polypeptide sequence of SEQ ID NO: 101; and the heavy chain CDR sequence of SEQ ID NO: 121 is substituted for the heavy chain CDR sequence of SEQ ID NO: 107.

[0312] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab7, comprising SEQ ID NO: 101 and SEQ ID NO: 102, or the alternative SEQ ID NOs set forth in the preceding paragraph, and having at least one of the biological activities set forth herein.

[0313] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
MTGRAPYQLLWLWPLGAPATLVISGQPGVSTPVSARQGVTTSIQGQGS
VWHQGLSLWQPQRQPKLLILYIEKLESGVFRSF5GSGSSGTHTLTIS
GVCDDAAYTLYCQYGDGADDNA.
```

[0314] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MTGLQKLLVAVLKVQGQHVEEQGKLVTRTPGTLTTCTVSGFSLSSR
TM5WQRAPQGWEWIGTWWGGSTTYATWAKRFITKSTTIVDULKT
PTTEDATATFCARLQDTSQRHAYATRNL.
```

[0315] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122, and/or one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0316] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122, and/or one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention
include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0317] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 122. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 123.

[0318] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122.

[0319] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123.

[0320] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 122; the variable heavy chain region of SEQ ID NO: 123; the complementarity-determining regions (SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126) of the variable light chain region of SEQ ID NO: 122; and the complementarity-determining regions (SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129) of the variable heavy chain region of SEQ ID NO: 123.

[0321] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab8, comprising SEQ ID NO: 122 and SEQ ID NO: 123, and having at least one of the biological activities set forth herein.

[0322] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
MDTAPRLQLIIILPLGATFAAVLTQFSSSARSGTVSISQGSGG
YVSHYQAVQQPWQPPLLYWTSELQGAPDFSNGSSTQFPLTLTI
GVQCDADATTTYCGADDADNA.
```

[0323] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
(MEQ NO: 138)
METGLNLLLYVAVLGGQGVQGVQGSGRLEKPDTE7TCLTCTASQFSGISG
YTMKVRQAPGGSLHIGISYDSTSYAAGKRFPTIHSSTTVLDMT
SLTEDTATYFCVRSLKYPFTSDDL.
```

[0324] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138, and/or one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0325] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138, and/or one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0326] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 138. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 139.

[0327] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138.

[0328] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139.

[0329] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 138; the variable heavy chain region of SEQ ID NO: 139; the complementarity-determining regions (SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142) of the variable light chain region of SEQ ID NO: 138; and the complementarity-determining regions (SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145) of the variable heavy chain region of SEQ ID NO: 139.
[0330] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab9, comprising SEQ ID NO: 138 and SEQ ID NO: 139, and having at least one of the biological activities set forth herein.

[0331] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

\[
\text{MTARptQQLLGLLWLVSPVAVLTVTPSVPVAAVGTVTI9CQS\text{SEQ}}
\]

\[
\text{VTNNDLAOfWQEQKQPQKLLLYVATLSGVPSRFKGSSHGQTPLTLTIS}
\]

\[
\text{GVQCDAAAAYCQLGDYDDADDLN}
\]

[0332] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[
\text{MTAPRQQLLGLLWLVSPVAVLTVTPSVPVAAVGTVTI9CQS\text{SEQ}}
\]

\[
\text{TDNLRQPQPKLEHGLGYYIVSGSVSTSSGVSNGPTISKTSTDTVLKTS}
\]

\[
\text{PTEKADAYFCARGSYGAGTPYATRDL}
\]

[0333] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable light chain sequence of SEQ ID NO: 154, and/or one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable heavy chain sequence of SEQ ID NO: 155, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0334] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable light chain sequence of SEQ ID NO: 154, and/or one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable heavy chain sequence of SEQ ID NO: 155, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0335] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 154. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 155.

[0336] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable light chain sequence of SEQ ID NO: 154.

[0337] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable heavy chain sequence of SEQ ID NO: 155.

[0338] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 154; the variable heavy chain region of SEQ ID NO: 155; the complementarity-determining regions (SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158) of the variable light chain region of SEQ ID NO: 154; and the complementarity-determining regions (SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161) of the variable heavy chain region of SEQ ID NO: 155.

[0339] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab10, comprising SEQ ID NO: 154 and SEQ ID NO: 155, and having at least one of the biological activities set forth herein.

[0340] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

\[
\text{MTAPRQQLLGLLWLVSPVAVLTVTPSVPVAAVGTVTI9CQS\text{SEQ}}
\]

\[
\text{VTNNDLAOfWQEQKQPQKLLLYVATLSGVPSRFKGSSHGQTPLTLTIS}
\]

\[
\text{GVQCDAAAAYCQLGDYDDADDLN}
\]

[0341] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[
\text{MTAPRQQLLGLLWLVSPVAVLTVTPSVPVAAVGTVTI9CQS\text{SEQ}}
\]

\[
\text{TDNLRQPQPKLEHGLGYYIVSGSVSTSSGVSNGPTISKTSTDTVLKTS}
\]

\[
\text{PTEKADAYFCARGSYGAGTPYATRDL}
\]

[0342] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable light chain sequence of SEQ ID NO: 170, and/or one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable heavy chain sequence of SEQ ID NO: 171, or combinations of these polypeptide sequences. In another
embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0343] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170, and/or one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0344] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 170. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 171.

[0345] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170.

[0346] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171.

[0347] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 170; the variable heavy chain region of SEQ ID NO: 171; the complementarity-determining regions (SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174) of the variable light chain region of SEQ ID NO: 170; and the complementarity-determining regions (SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177) of the variable heavy chain region of SEQ ID NO: 171.

[0348] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab1, comprising SEQ ID NO: 170 and SEQ ID NO: 171, and having at least one of the biological activities set forth herein.

[0349] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
MTTRAPQQLGQLLLLWLPLQRCDVDYVQTASVEAVGTTTITDQSKET
IGNALAWYQKESQPPPSSLICLLYAASKLASHVPGFBFGSGETYLTLTISDL
ECABAPYYQMQCTGSDL
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[0350] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
METGKHLWLLTQLXQVQGKQEVSGGQLQVFPESSITLTCTASQPDFFSS
GYMCMWRVARQPGELWIAACITTTNTNYAEAWKSRPTITSKTSSTTVTL
QMTSLTADFTYLFARCQIVDDNYAL
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[0351] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186, and/or one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0352] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186, and/or one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0353] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 186. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 187.

[0354] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186.

[0355] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise,
or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187.

[0356] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 186; the variable heavy chain region of SEQ ID NO: 187; the complementarity-determining regions (SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190) of the variable light chain region of SEQ ID NO: 186; and the complementarity-determining regions (SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193) of the variable heavy chain region of SEQ ID NO: 187.

[0357] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab12, comprising SEQ ID NO: 186 and SEQ ID NO: 187, and having at least one of the biological activities set forth herein.

[0358] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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MTTRAQLQGILLLILILGPGCVDVNTQPSVADEAVGVTVTTICQASSE
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[0359] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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MTGRLWLLLLWALEVKLQVEGGGVKPGSLTQCTASGFFS
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[0360] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202, and/or one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0361] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202, and/or one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0362] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 202. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 203.

[0363] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202.

[0364] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203.

[0365] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 202; the variable heavy chain region of SEQ ID NO: 203; the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206) of the variable light chain region of SEQ ID NO: 202; and the complementarity-determining regions (SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209) of the variable heavy chain region of SEQ ID NO: 203.

[0366] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab13, comprising SEQ ID NO: 202 and SEQ ID NO: 203, and having at least one of the biological activities set forth herein.

[0367] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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MTTRAQLQGILLLILILGPGCVDVNTQPSVADEAVGVTVTTICQASSE
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[0368] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:
[0369] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218, and/or one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0370] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218, and/or one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0371] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 218. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 219.

[0372] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218.

[0373] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219.

[0374] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 218; the variable heavy chain region of SEQ ID NO: 219; the complementarity-determining regions (SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222) of the variable light chain region of SEQ ID NO: 218; and the complementarity-determining regions (SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225) of the variable heavy chain region of SEQ ID NO: 219.

[0375] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab14, comprising SEQ ID NO: 218 and SEQ ID NO: 219, and having at least one of the biological activities set forth herein.

[0376] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0377] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

[0378] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234, and/or one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0379] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234, and/or one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0380] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodi-
ment of the invention, antibody fragments of the invention comprise, or alternatively consist of, polypeptide sequence of SEQ ID NO: 234. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, polypeptide sequence of SEQ ID NO: 235.

[0381] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234.

[0382] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235.

[0383] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 234; the variable heavy chain region of SEQ ID NO: 235; the complementarity-determining regions (SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238) of the variable light chain region of SEQ ID NO: 234; and the complementarity-determining regions (SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241) of the variable heavy chain region of SEQ ID NO: 235.

[0384] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab15, comprising SEQ ID NO: 234 and SEQ ID NO: 235, and having at least one of the biological activities set forth herein.

[0385] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 250)

MDTAPTQLQLLWLLGPOSTPAWTVQQP2VPVAVGTVSVIS取决于QASQS

[0386] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 251)

METGRLKNLLLAFAKSWQCSQLESQGLRVTIPPTPLFTLCTLSLDSLSAY

[0387] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250, and/or one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0388] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250, and/or one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0389] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 250. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 251.

[0390] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250.

[0391] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251.

[0392] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 250; the variable heavy chain region of SEQ ID NO: 251; the complementarity-determining regions (SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254) of the variable light chain region of SEQ ID NO: 250; and the complementarity-determining regions (SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257) of the variable heavy chain region of SEQ ID NO: 251.

[0393] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab16, comprising SEQ ID NO: 250 and SEQ ID NO: 251, and having at least one of the biological activities set forth herein.
[0394] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

(seq id no: 266)
MTRAPVQQLLQLGGGSLGATPAVLQPUQSPSLVAAGAVTTVSQCQASQS
YSGQELWQLQGSQPKFLLYWASTLSGVSFSRGSQSGSTQPLTVS
GVCQDDAYTCLGQFFDDADNA.

[0395] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(seq id no: 267)
MTEGLRKLLLLALVLEKVLQSVSRESGRLVTGPTFLTLCTAGSPLSYY
SYMTNVRQAPGKGLYEGVGCTGGSYTYNYAWNKRPTIQSKSTTVLAKITS
PTTEDATYPFVCRESLSTTLPL.

[0396] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266, and/or one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of these CDRs and the variable heavy and light chain sequences set forth above.

[0397] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266, and/or one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0398] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 266. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 267.

[0399] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266.

[0400] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267.

[0401] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 266; the variable heavy chain region of SEQ ID NO: 267; the complementarity-determining regions (SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270) of the variable light chain region of SEQ ID NO: 266; and the complementarity-determining regions (SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273) of the variable heavy chain region of SEQ ID NO: 267.

[0402] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab17, comprising SEQ ID NO: 266 and SEQ ID NO: 267, and having at least one of the biological activities set forth herein.

[0403] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

(seq id no: 282)
MTRAPVQQLLQLGGGSLGATPAVLQPUQSPSLVAAGAVTTVSQCQASQS
YSGQELWQLQGSQPKFLLYWASTLSGVSFSRGSQSGSTQPLTVS
GVCQDDAYTCLGQFFDDADNA.

[0404] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(seq id no: 283)
MTEGLRKLLLLALVLEKVLQSVSRESGRLVTGPTFLTLCTAGSPLSYY
SYMTNVRQAPGKGLYEGVGCTGGSYTYNYAWNKRPTIQSKSTTVLAKITS
PTTEDATYPFVCRESLSTTLPL.

[0405] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282, and/or one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0406] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies,
comprising one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282, and/or one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0407] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, the antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 282. In another embodiment of the invention, the antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 283.

[0408] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282.

[0409] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283.

[0410] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 282; the variable heavy chain region of SEQ ID NO: 283; the complementarity-determining regions (SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286) of the variable light chain region of SEQ ID NO: 282; and the complementarity-determining regions (SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289) of the variable heavy chain region of SEQ ID NO: 283.

[0411] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab18, comprising SEQ ID NO: 282 and SEQ ID NO: 283, and having at least one of the biological activities set forth herein.

[0412] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
SEQUENCE ID NO: 299
MTRLRLLWLLLAVLKQVCQVQAESQRLVPTCPPTLTLCTASGPESLY
YNSWQRGAPKXGWNLWIG1TSQONTFASWAKRLTISRSTTVLXKTS
PFTEEATYYCQSWK5TSIDNRA.
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[0413] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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SEQUENCE ID NO: 299
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[0414] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298, and/or one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0415] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298, and/or one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0416] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, the antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 298. In another embodiment of the invention, the antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 299.

[0417] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298.

[0418] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299.

[0419] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, frag-
ments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 298; the variable heavy chain region of SEQ ID NO: 299; the complementarity-determining regions (SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302) of the variable light chain region of SEQ ID NO: 298; and the complementarity-determining regions (SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305) of the variable heavy chain region of SEQ ID NO: 299.

[0420] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab19, comprising SEQ ID NO: 298 and SEQ ID NO: 299, and having at least one of the biological activities set forth herein.

[0421] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
(QEQ ID NO: 314)
MRTAPaqQQLLGLLKLGLPQGATFAMVLTQEGSPGVAANVVTNIOEOQGS
YVQEDLAWFQOPQPPKLLKFLYASATLSGVPFRSGSGSGLTELITTS
GQVQEDATYCYLQAFFDDADNT.
```

[0422] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
(TM EQ ID NO: 321)
METGLKLLGLLLAVKLQVGPQGPQGRGAVLPTPGTLTLCTSGSFTSH
AIVWQAPGPAGLEHIGCIGNQGLQTTYWAKRFTSTSKTVTDEIIT
PPTEGATAPGCVPVQIGTVAYPFTGLDL.
```

[0423] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314, and/or one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0424] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314, and/or one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0425] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 314. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 315.

[0426] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314.

[0427] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315.

[0428] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, the fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 314; the variable heavy chain region of SEQ ID NO: 315; the complementarity-determining regions (SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318) of the variable light chain region of SEQ ID NO: 314; and the complementarity-determining regions (SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321) of the variable heavy chain region of SEQ ID NO: 315.

[0429] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab20, comprising SEQ ID NO: 314 and SEQ ID NO: 315, and having at least one of the biological activities set forth herein.

[0430] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
(QEQ ID NO: 330)
MRTAPaqQQLLGLLKLGLPQGATFAMVLTQEGSPGVAANVVTNIOEOQGS
YVQEDLAWFQOPQPPKLLKFLYASATLSGVPFRSGSGSGLTELITTS
GQVQEDATYCYLQAFFDDADNT.
```

[0431] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
(TM EQ ID NO: 331)
METGLKLLGLLLAVKLQVGPQGPQGRGAVLPTPGTLTLCTSGSFTSH
AIVWQAPGPAGLEHIGCIGNQGLQTTYWAKRFTSTSKTVTDEIIT
PPTEGATAPGCVPVQIGTVAYPFTGLDL.
```

[0432] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth above.
[0432] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable light chain sequence of SEQ ID NO: 330, and/or one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable heavy chain sequence of SEQ ID NO: 331, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0433] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable light chain sequence of SEQ ID NO: 330, and/or one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable heavy chain sequence of SEQ ID NO: 331, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0434] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 330. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 331.

[0435] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable light chain sequence of SEQ ID NO: 330.

[0436] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions of the variable heavy chain sequence of SEQ ID NO: 331.

[0437] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 330; the variable heavy chain region of SEQ ID NO: 331; the complementarity-determining regions (SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334) of the variable light chain region of SEQ ID NO: 330; the complementarity-determining regions (SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337) of the variable heavy chain region of SEQ ID NO: 331.
In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more or the polypeptide sequences of SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 346.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more or the polypeptide sequences of SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347.

The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 346; the variable heavy chain region of SEQ ID NO: 347; the complementarity-determining regions (SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350) of the variable light chain region of SEQ ID NO: 346; and the complementarity-determining regions (SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353) of the variable heavy chain region of SEQ ID NO: 347.

In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab22, comprising SEQ ID NO: 346 and SEQ ID NO: 347, and having at least one of the biological activities set forth herein.

In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

\[\text{MDTAPQQLLLMLLPQATFAQLTQPSTPSVSAVVGTVTVYINCAQMS}
\]

\[\text{VYQNYLWKQPPQKVLHNYGATLASGVPFKEGSGSTQPTLTIS}
\]

\[\text{DLBCDDAATYCNAGIRDVS} \]

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[\text{MTGLPKLLLLVAVKCVQCSLHESGDLVKPSNLTLCTTASQFPTST}
\]

\[\text{YIYWYQAPQKGLMHCIDAGQSGSTYTATKWNGRTFTISKSTSTTVL}
\]

\[\text{QMTSLTADTATYPACWYGVKNVWYDOL} \]

The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362, and/or one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362, and/or one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 362. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 363.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362.

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363.

The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 362; the variable heavy chain region of SEQ ID NO: 363; the complementarity-determining regions (SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366) of the variable light chain region of SEQ ID NO: 362; and the complementarity-determining regions (SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369) of the variable heavy chain region of SEQ ID NO: 363.

In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab23, comprising SEQ ID NO: 362 and SEQ ID NO: 363, and having at least one of the biological activities set forth herein.

In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:
The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
[SEQ ID NO: 378]
MDTRAPTQQLLMLLWLGARCAFDLTQFSSVBAAGSTTVTCQCAQGS
ISSLYANHQQPKQPPKFLYRATLSASQPSRPGSKGSSGTRPTLTIQSL
ECADAATYYQCYDVSLSNP.

[0458]
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The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378, and/or one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0460]

In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378, and/or one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0461]

The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 378. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 379.

[0462]

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378.

[0463]

In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379.

[0464] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 378; the variable heavy chain region of SEQ ID NO: 379; the complementarity-determining regions (SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382) of the variable light chain region of SEQ ID NO: 378; and the complementarity-determining regions (SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385) of the variable heavy chain region of SEQ ID NO: 379.

[0465] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab24, comprising SEQ ID NO: 378 and SEQ ID NO: 379, and having at least one of the biological activities set forth herein.

[0466] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
[SEQ ID NO: 394]
MDTRAPTQQLLMLLWLGARCAFDLTQFSSVBAAGSTTVTCQCAQGS
VYKMWLSWQQKQPPKQLLIYQAMASLAGVPSRPKEGSSTGPTLTIS
DVQCCDAATTYYQCYDVSLSNP.

[0467] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
[SEQ ID NO: 395]
MDTRAPTQQLLMLLWLGARCAFDLTQFSSVBAAGSTTVTCQCAQGS
VYKMWLSWQQKQPPKQLLIYQAMASLAGVPSRPKEGSSTGPTLTIS
MTSLTAATYQCYDVSLSNP.

[0468] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394, and/or one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0469] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain
sequence of SEQ ID NO: 394, and/or one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0470] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 394. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 395.

[0471] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394.

[0472] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395.

[0473] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 394; the variable heavy chain region of SEQ ID NO: 395; the complementarity-determining regions (SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398) of the variable light chain region of SEQ ID NO: 394; and the complementarity-determining regions (SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401) of the variable heavy chain region of SEQ ID NO: 395.

[0474] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab25, comprising SEQ ID NO: 394 and SEQ ID NO: 395, and having at least one of the biological activities set forth herein.

[0475] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

```
MDTAPQQLLWLVLVKGQVCQSESGRLVTGTPPLTLTCTVGSPSLEEY
```

[0476] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
METGLOQWLLLNVAVLQKVQCSVEEGSLVTGTPPLTLTCTVGSPSLEEY
```

[0477] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410, and/or one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0478] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410, and/or one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0479] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 410. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 411.

[0480] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410.

[0481] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411.

[0482] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the vari-
able light chain region of SEQ ID NO: 410; the variable heavy chain region of SEQ ID NO: 411; the complementarity-determining regions (SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414) of the variable light chain region of SEQ ID NO: 410; and the complementarity-determining regions (SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417) of the variable heavy chain region of SEQ ID NO: 411.

[0483] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab26, comprising SEQ ID NO: 410 and SEQ ID NO: 411, and having at least one of the biological activities set forth herein.

[0484] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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[0485] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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[0486] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426, and/or one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0487] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426, and/or one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0488] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 426. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 427.

[0489] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426.

[0490] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427.

[0491] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 426; the variable heavy chain region of SEQ ID NO: 427; the complementarity-determining regions (SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430) of the variable light chain region of SEQ ID NO: 426; and the complementarity-determining regions (SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433) of the variable heavy chain region of SEQ ID NO: 427.

[0492] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab27, comprising SEQ ID NO: 426 and SEQ ID NO: 427, and having at least one of the biological activities set forth herein.

[0493] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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[0494] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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[0495] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain
sequence of SEQ ID NO: 442, and/or one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0496] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442, and/or one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0497] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 442. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 443.

[0498] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442.

[0499] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443.

[0500] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 442; the variable heavy chain region of SEQ ID NO: 443; the complementarity-determining regions (SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446) of the variable light chain region of SEQ ID NO: 442; and the complementarity-determining regions (SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449) of the variable heavy chain region of SEQ ID NO: 443.

[0501] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab28, comprising SEQ ID NO: 442 and SEQ ID NO: 443, and having at least one of the biological activities set forth herein.

[0502] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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(METAPRTOQLGLLLLIMGPATAVISQTTPVSVASAVGQTVSIECQSQGQ
VYNNMLSWFQKEQFVPSYKLLIKYKSLALGSVRSFGSFLQTLTMS
DVQDDAVATYCAOGYDSVII.
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[0503] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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(METOLKLLLUVXLGVQCGSVSEGSRLVTSGPLTLTCTVSGFLSTY
SIMVRQAPKOWNJNFTIAFWAKGRFTVSKSTTTVDLKIITS
PTTDDATYPACREGGMTHYCRFII.
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[0504] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458, and/or one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0505] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458, and/or one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0506] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 458. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 459.

[0507] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining-
ing regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458.

[0508] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459.

[0509] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 458; the variable heavy chain region of SEQ ID NO: 459; the complementarity-determining regions (SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462) of the variable light chain region of SEQ ID NO: 458; and the complementarity-determining regions (SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465) of the variable heavy chain region of SEQ ID NO: 459.

[0510] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab29, comprising SEQ ID NO: 458 and SEQ ID NO: 459, and having at least one of the biological activities set forth herein.

[0511] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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MTTRAPQQLGGLLLLWLGARCAEDMTQTPSSVSAAVGTVTITHQASRN
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[0512] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
IYSLFAYQKKQPKKLLIFKASTLASGNSRPFEGMGSGQTQFLTILSDL
```

[0513] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474, and/or one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0514] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474, and/or one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0515] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 474. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 475.

[0516] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474.

[0517] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475.

[0518] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 474; the variable heavy chain region of SEQ ID NO: 475; the complementarity-determining regions (SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478) of the variable light chain region of SEQ ID NO: 474; and the complementarity-determining regions (SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481) of the variable heavy chain region of SEQ ID NO: 475.

[0519] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab30, comprising SEQ ID NO: 474 and SEQ ID NO: 475, and having at least one of the biological activities set forth herein.

[0520] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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MTTRAPQQLGGLLLLWLGARCAEDMTQTPSSVSAAVGTVTITHQASRN
IYSLFAYQKKQPKKLLIFKASTLASGNSRPFEGMGSGQTQFLTILSDL
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ECDQATYYCGQATGVYIDINN.
[0521] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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MEGGLAVALLLVFVQGQGQGLNLEEGRLVTPEGPLTLCVGSQILAY
AKWGVQAGPEGLGHEIITYDPIRTYATAWAKGRFTSVKSTKAMKLEIS
PTTEDATYFPCARGSGGGADRVGNYGVENV.
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[0522] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490, and/or one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0523] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490, and/or one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0524] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 490. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 491.

[0525] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490.

[0526] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491.

[0527] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 490; the variable heavy chain region of SEQ ID NO: 491; the complementarity-determining regions (SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494) of the variable light chain region of SEQ ID NO: 490; and the complementarity-determining regions (SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497) of the variable heavy chain region of SEQ ID NO: 491.

[0528] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab31, comprising SEQ ID NO: 490 and SEQ ID NO: 491, and having at least one of the biological activities set forth herein.

[0529] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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MEGGLAVALLLVFVQGQGQGLNLEEGRLVTPEGPLTLCVGSQILAY
AKWGVQAGPEGLGHEIITYDPIRTYATAWAKGRFTSVKSTKAMKLEIS
PTTEDATYFPCARGSGGGADRVGNYGVENV.
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[0530] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MEGGLAVALLLVFVQGQGQGLNLEEGRLVTPEGPLTLCVGSQILAY
AKWGVQAGPEGLGHEIITYDPIRTYATAWAKGRFTSVKSTKAMKLEIS
PTTEDATYFPCARGSGGGADRVGNYGVENV.
```

[0531] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506, and/or one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0532] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506, and/or one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention
include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0533] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 506. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 507.

[0534] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506.

[0535] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507.

[0536] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 506; the variable heavy chain region of SEQ ID NO: 507; the complementarity-determining regions (SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510) of the variable light chain region of SEQ ID NO: 506; and the complementarity-determining regions (SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513) of the variable heavy chain region of SEQ ID NO: 507.

[0537] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab32, comprising SEQ ID NO: 506 and SEQ ID NO: 507, and having at least one of the biological activities set forth herein.

[0538] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

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[SEQ ID NO: 522]
MDTRAPTQLLGLLIMLPQATFAQQLTVQTASSVSAAVGQIVTVINCOGSSQ
YVNYNLSVQKPCQPQPKLL1YTASSLAVCQVPKRQSGCTQTPLT1SE
VCDDAAATTCQGGTSGPIIT7.
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[0539] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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[SEQ ID NO: 523]
METGLRNLALLVAVLQVQCSLVEDEQGLLTQPGFLITLLCTAS6GLHNY
YIQ6VRQAGBQEHMG11YLAQGAYATWNGRPTIAKSTSTV1DHTMT
SLTEDTATYFCARGT7DGAYL.
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[0540] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522, and/or one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0541] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522, and/or one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0542] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 522. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 523.

[0543] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522.

[0544] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523.

[0545] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 522; the variable heavy chain region of SEQ ID NO: 523; the complementarity-determining regions (SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526) of the variable light chain region of SEQ ID NO: 522; and the complementarity-determining regions (SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529) of the variable heavy chain region of SEQ ID NO: 523.
[0546] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab33, comprising SEQ ID NO: 522 and SEQ ID NO: 523, and having at least one of the biological activities set forth herein.

[0547] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 538)
MDTRAPQNLGLLLLMLPQAVSLQTVVPSVFLVIFTTQTSQCSFRE
YTENLNVQWSQFQPKQFKLLEYIYSAANASGVPKRFSGSGQLFQTLTIS
GAGCDDAATYYCQVYGVSQVIN

[0548] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 539)
MERTQLKNNLLLAVLNGVQCSGVEESQSRVTPLTLCTTVGSGLSFV
FNGSWVRQAPGGEVLYIGPINQGSAVNASGGLTISTTVDLLKTS
PTTDEATYFCARILIVSGAPT

[0549] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538, and/or one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0550] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538, and/or one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0551] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 538. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 539.

[0552] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538.

[0553] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539.

[0554] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 538; the variable heavy chain region of SEQ ID NO: 539; the complementarity-determining regions (SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542) of the variable light chain region of SEQ ID NO: 538; and the complementarity-determining regions (SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545) of the variable heavy chain region of SEQ ID NO: 539.

[0555] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab34, comprising SEQ ID NO: 538 and SEQ ID NO: 539, and having at least one of the biological activities set forth herein.

[0556] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 554)
MDTRAPQNLGLLLLMLPQAVSLQTVVPSVFLVIFTTQTSQCSFRE
IGNELNWSQFQPKLLEIYSAANASGVPKRFSGSGQLFQTLTGV
ECDDAAATYFCARILIVSGAP

[0557] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 555)
MERTQLKNNLLLAVLNGVQCSGVEESQSRVTPLTLCTTVGSGLSFV
YNGSWVRQAPGGEVLYIGPINQGSAVNASGGLTISTTVDLLKTS
SPTTDEATYFCARILIVSGAP

[0558] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554, and/or one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555, or combinations of these polypeptide sequences. In another
embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0559] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs), or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554, and/or one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0560] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 554. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 555.

[0561] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554.

[0562] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555.

[0563] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 554; the variable heavy chain region of SEQ ID NO: 555; the complementarity-determining regions (SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558) of the variable light chain region of SEQ ID NO: 554; and the complementarity-determining regions (SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561) of the variable heavy chain region of SEQ ID NO: 555.

[0564] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab35, comprising SEQ ID NO: 554 and SEQ ID NO: 555, and having at least one of the biological activities set forth herein.

[0565] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

\[
\text{(SEQ ID NO: 570)}
\begin{array}
\text{MTTRAPQOLLGLLLWLLPLGACAYDQTPSVEVAVGGTYTTECQARIES} \\
\text{IGNELGWYQQFQAPKLLYSEASALASGKYVPEFKGCGGCTQFTLTITGV} \\
\text{CEDDAATYYCQOGSSAHIDNA.}
\end{array}
\]

[0566] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[
\text{(SEQ ID NO: 571)}
\begin{array}
\text{MTGQLWLWLLLWAVLKQPGQSLLRRGFLVTPGPLTLCVTSGFSLSTY} \\
\text{NKGWVRQAPGKELWIGEITCIDGTRXASWAKGERFTFVSKXSTTVLDMTS} \\
\text{LTGQDTATYFCARILIVSGQAPTI.}
\end{array}
\]

[0567] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570, and/or one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0568] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570, and/or one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0569] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 570. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 571.

[0570] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570.

[0571] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise,
or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571.

[0572] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 570; the variable heavy chain region of SEQ ID NO: 571; the complementarity-determining regions (SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574) of the variable light chain region of SEQ ID NO: 570; and the complementarity-determining regions (SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577) of the variable heavy chain region of SEQ ID NO: 571.

[0573] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab36, comprising SEQ ID NO: 570 and SEQ ID NO: 571, and having at least one of the biological activities set forth herein.

[0574] Sequences of anti-IL-6 antibodies of the present invention are shown in Table 1. Exemplary sequence variants other alternative forms of the heavy and light chains of Ab1 through Ab7 are shown. The antibodies of the present invention encompass additional sequence variants, including conservative substitutions, substitution of one or more CDR sequences and/or FR sequences, etc.

[0575] Exemplary Ab1 embodiments include an antibody comprising a variant of the light chain and/or heavy chain. Exemplary variants of the light chain of Ab1 include the sequence of any of the Ab1 light chains shown (i.e., any of SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709) wherein the entire CDR1 sequence is replaced or wherein one or more residues in the CDR1 sequence is substituted in the residue in the corresponding position of any of the other light chain CDR1 sequences set forth (i.e., any of SEQ ID NO: 23, 39, 55, 71, 87, 103, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 322, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, 524, 540, 556, or 572); and/or wherein the entire CDR2 sequence is replaced or wherein one or more residues in the CDR2 sequence is substituted in the residue in the corresponding position of any of the other light chain CDR2 sequences set forth (i.e., any of SEQ ID NO: 24, 40, 56, 72, 88, 104, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, 349, 365, 381, 397, 413, 429, 445, 461, 477, 493, 509, 525, 541, 557, or 573); and/or wherein the entire CDR3 sequence is replaced or wherein one or more residues in the CDR3 sequence is substituted in the residue in the corresponding position of any of the other light chain CDR3 sequences set forth (i.e., any of SEQ ID NO: 25, 41, 57, 73, 89, 105, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 398, 414, 430, 446, 462, 478, 494, 510, 526, 542, 558, or 574).

[0576] Exemplary variants of the heavy chain of Ab1 include the sequence of any of the Ab1 heavy chains shown (i.e., any of SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708) wherein the entire CDR1 sequence is replaced or wherein one or more residues in the CDR1 sequence is substituted in the residue in the corresponding position of any of the other heavy chain CDR1 sequences set forth (i.e., any of SEQ ID NO: 26, 42, 58, 74, 90, 106, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, 287, 303, 319, 335, 351, 367, 383, 399, 415, 431, 447, 463, 479, 495, 511, 527, 543, 559, or 575); and/or wherein the entire CDR2 sequence is replaced or wherein one or more residues in the CDR2 sequence is substituted by the residue in the corresponding position of an Ab1 heavy chain CDR2, such as those set forth in Table 1 (i.e., any of SEQ ID NO: 8, or 120) or any of the other heavy chain CDR2 sequences set forth (i.e., any of SEQ ID NO: 27, 43, 59, 75, 91, 107, 121, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, 528, 544, 560, or 576); and/or wherein the entire CDR3 sequence is replaced or wherein one or more residues in the CDR3 sequence is substituted by the residue in the corresponding position of any of the other heavy chain CDR3 sequences set forth (i.e., any of SEQ ID NO: 28, 44, 60, 76, 92, 108, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 369, 385, 401, 417, 433, 449, 465, 481, 497, 513, 529, 545, 561, or 577).

[0577] In another embodiment, the invention contemplates other antibodies, such as for example chimeric or humanized antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2; and/or one or more of the polypeptide sequences of SEQ ID NO: 7 (CDR1); SEQ ID NO: 8 (CDR2); SEQ ID NO: 120 (CDR2); and SEQ ID NO: 9 (CDR3) which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or SEQ ID NO: 19, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above including those set forth in FIGS. 2 and 34-37, and those identified in Table 1.

[0578] In another embodiment the anti-IL-6 antibody of the invention is one comprising at least one of the following: a CDR1 light chain encoded by the sequence in SEQ ID NO: 12 or SEQ ID NO: 694; a light chain CDR2 encoded by the sequence in SEQ ID NO: 13; a light chain CDR3 encoded by the sequence in SEQ ID NO: 14 or SEQ ID NO: 695; a heavy chain CDR1 encoded by the sequence in SEQ ID NO: 15; a heavy chain CDR2 encoded by SEQ ID NO: 16 or SEQ ID NO: 696 and a heavy chain CDR3 encoded by SEQ ID NO: 17 or SEQ ID NO: 697. In addition the invention embraces such nucleic acid sequences and variants thereof.

[0579] In another embodiment the invention is directed to amino acid sequences corresponding to the CDRs of said anti-IL-6 antibody which are selected from SEQ ID NO: 4 (CDR1), SEQ ID NO: 5 (CDR2), SEQ ID NO: 6 (CDR3), SEQ ID NO: 7, SEQ ID NO: 120 and SEQ ID NO: 9.

[0580] In another embodiment the anti-IL-6 antibody of the invention comprises a light chain nucleic acid sequence of SEQ ID NO: 10, 662, 698, 701, 705, 720, 721, 722, or 723; and/or a heavy chain nucleic acid sequence of SEQ ID NO: 11, 663, 700, 703, 707, 724, or 725. In addition the invention is directed to the corresponding polypeptides encoded by any of the foregoing nucleic acid sequences and combinations thereof.

[0581] In a specific embodiment of the invention the anti-IL-6 antibodies or a portion thereof will be encoded by a nucleic acid sequence selected from those comprised in SEQ ID NO: 10, 12, 13, 14, 662, 694, 695, 698, 701, 705, 720, 721,
722, 723, 11, 15, 16, 17, 663, 696, 697, 700, 703, 707, 724, and 725. For example the CDR1 in the light chain may be encoded by SEQ ID NO: 12 or 694, the CDR2 in the light chain may be encoded by SEQ ID NO: 13, the CDR3 in the light chain may be encoded by SEQ ID NO: 14 or 695; the CDR1 in the heavy chain may be encoded by SEQ ID NO: 15, the CDR2 in the heavy chain may be encoded by SEQ ID NO: 16 or 696, the CDR3 in the heavy chain may be encoded by SEQ ID NO: 17 or 697. As discussed infra antibodies containing these CDRs may be constructed using appropriate human frameworks based on the humanization methods disclosed herein.

[0582] In another specific embodiment of the invention the variable light chain will be encoded by SEQ ID NO: 10, 602, 698, 701, 705, 720, 721, 722, or 723 and the variable heavy chain of the anti-IL-6 antibodies will be encoded by SEQ ID NO: 11, 663, 700, 703, 707, 724, or 725.

[0583] In a more specific embodiment variable light and heavy chains of the anti-IL-6 antibody respectively will be encoded by SEQ ID NO: 10 and 11, or SEQ ID NO: 698 and SEQ ID NO: 700, or SEQ ID NO: 701 and SEQ ID NO: 703 or SEQ ID NO: 705 and SEQ ID NO: 707.

[0584] In another specific embodiment the invention covers nucleic acid constructs containing any of the foregoing nucleic acid sequences and combinations thereof as well as recombinant cells containing these nucleic acid sequences and constructs containing wherein these nucleic acid sequences or constructs may be extrachromosomal or integrated into the host cell genome.

[0585] In another specific embodiment the invention covers polypeptides containing any of the CDRs or combinations thereof recited in SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 120, SEQ ID NO: 9 or polypeptides comprising any of the variable light polypeptides comprised in SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709 and/or the variable heavy polypeptides comprised in SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708. These polypeptides optionally may be attached directly or indirectly to other immunoglobulin polypeptides or effector moieties such as therapeutic or detectable entities.

[0586] In another embodiment the anti-IL-6 antibody is one comprising at least one of the following: a variable light chain encoded by the sequence in SEQ ID NO: 10 or SEQ ID NO: 698 or SEQ ID NO: 701 or SEQ ID NO: 705 and a variable chain encoded by the sequence in SEQ ID NO: 11 or SEQ ID NO: 700 or SEQ ID NO: 703 or SEQ ID NO: 707.

[0587] In another embodiment the anti-IL-6 antibody is a variant of the foregoing sequences that includes one or more substitution in the framework and/or CDR sequences and which has one or more of the properties of Ab1 in vitro and/or upon in vivo administration.

[0588] These in vitro and in vivo properties are described in more detail in the examples below and include: competing with Ab1 for binding to IL-6 and/or peptides thereof; having a binding affinity (Kd) for IL-6 of less than about 50 picomolar, and/or a rate of dissociation (Kd) from IL-6 of less than or equal to 10^-8 S^-1; having an in-vivo half-life of at least about 22 days in a healthy human subject; ability to prevent or treat hypoaalbuminemia; ability to prevent or treat elevated CRP; ability to prevent or treat abnormal coagulation; and/or ability to decrease the risk of thrombosis in an individual having a disease or condition associated with increased risk of thrombosis. Additional non-limiting examples of anti-IL-6 activity are set forth herein, for example, under the heading “Anti-IL-6 Activity.”

[0589] In another embodiment the anti-IL-6 antibody includes one or more of the Ab1 light-chain and/or heavy chain CDR sequences (see Table 1) or variant(s) thereof which has one or more of the properties of Ab1 in vitro and/or upon in vivo administration (examples of such properties are discussed in the preceding paragraph). One of skill in the art would understand how to combine these CDR sequences to form an antigen-binding surface, e.g. by linkage to one or more scaffold which may comprise human or other mammalian framework sequences, or their functional orthologs derived from a SMIP, camelbody, nanobody, IgNAR or other immunoglobulin or other engineered antibody. For example, embodiments may specifically bind to human IL-6 and include one, two, three, four, five, six, or more of the following CDR sequences or variants thereof:

[0590] a polypeptide having at least 72.7% (i.e., 8 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0591] a polypeptide having at least 81.8% (i.e., 9 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0592] a polypeptide having at least 90.9% (i.e., 10 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0593] a polypeptide having 100% (i.e., 11 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0594] a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;

[0595] a polypeptide having 100% (i.e., 7 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;

[0596] a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0597] a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0598] a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0599] a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0600] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0601] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0602] a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0603] a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;

[0604] a polypeptide having 100% (i.e., 5 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;
[0605] a polypeptide having at least 50% (i.e., 8 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0606] a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0607] a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0608] a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0609] a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0610] a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0611] a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0612] a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0613] a polypeptide having 100% (i.e., 16 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0614] a polypeptide having at least 33.3% (i.e., 4 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0615] a polypeptide having at least 41.6% (i.e., 5 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0616] a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0617] a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0618] a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0619] a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0620] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0621] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0622] a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0623] a polypeptide having at least 90.9% (i.e., 10 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;

[0624] a polypeptide having 100% (i.e., 11 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;

[0625] a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;

[0626] a polypeptide having 100% (i.e., 7 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;

[0627] a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0628] a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0629] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0630] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0631] a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0632] a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0633] a polypeptide having 100% (i.e., 5 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0634] a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0635] a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0636] a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0637] a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0638] a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0639] a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0640] a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0641] a polypeptide having 100% (i.e., 16 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0642] a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0643] a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0644] a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0645] a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0646] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;
[0647] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;
[0648] a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;
[0649] Other exemplary embodiments include one or more polynucleotides encoding any of the foregoing, e.g., a polynucleotide encoding a polypeptide that specifically binds to human IL-6 and includes one, two, three, four, five, six, or more of the following CDRs or variants thereof:
[0650] a polynucleotide encoding a polypeptide having at least 72.7% (i.e., 8 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;
[0651] a polynucleotide encoding a polypeptide having at least 81.8% (i.e., 9 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;
[0652] a polynucleotide encoding a polypeptide having at least 90.9% (i.e., 10 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;
[0653] a polynucleotide encoding a polypeptide having 100% (i.e., 11 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;
[0654] a polynucleotide encoding a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;
[0655] a polynucleotide encoding a polypeptide having 100% (i.e., 7 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;
[0656] a polynucleotide encoding a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;
[0657] a polynucleotide encoding a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;
[0658] a polynucleotide encoding a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;
[0659] a polynucleotide encoding a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;
[0660] a polynucleotide encoding a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;
[0661] a polynucleotide encoding a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;
[0662] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;
[0663] a polynucleotide encoding a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;
[0664] a polynucleotide encoding a polypeptide having 100% (i.e., 5 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;
[0665] a polynucleotide encoding a polypeptide having at least 50% (i.e., 8 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0666] a polynucleotide encoding a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0667] a polynucleotide encoding a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0668] a polynucleotide encoding a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0669] a polynucleotide encoding a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0670] a polynucleotide encoding a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0671] a polynucleotide encoding a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0672] a polynucleotide encoding a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0673] a polynucleotide encoding a polypeptide having 100% (i.e., 16 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
[0674] a polynucleotide encoding a polypeptide having at least 33.3% (i.e., 4 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0675] a polynucleotide encoding a polypeptide having at least 41.6% (i.e., 5 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0676] a polynucleotide encoding a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0677] a polynucleotide encoding a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0678] a polynucleotide encoding a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0679] a polynucleotide encoding a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0680] a polynucleotide encoding a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0681] a polynucleotide encoding a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0682] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;
[0683] a polynucleotide encoding a polypeptide having at least 90.9% (i.e., 10 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;
[0684] a polynucleotide encoding a polypeptide having 100% (i.e., 11 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;
[0685] a polynucleotide encoding a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;
[0686] a polynucleotide encoding a polypeptide having 100% (i.e., 7 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;
[0687] a polynucleotide encoding a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;
[0688] a polynucleotide encoding a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0689] a polynucleotide encoding a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

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[0691] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0692] a polynucleotide encoding a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0693] a polynucleotide encoding a polypeptide having 100% (i.e., 5 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0694] a polynucleotide encoding a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0695] a polynucleotide encoding a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0696] a polynucleotide encoding a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0697] a polynucleotide encoding a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0698] a polynucleotide encoding a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0699] a polynucleotide encoding a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0700] a polynucleotide encoding a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0701] a polynucleotide encoding a polypeptide having 100% (i.e., 16 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0702] a polynucleotide encoding a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 9;

[0703] a polynucleotide encoding a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 9;

[0704] a polynucleotide encoding a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 9;

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[0708] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 9.

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* Exemplary sequence variant forms of heavy and light chains are shown on separate lines.

PRT.: Polypeptide sequence.
Nuc.: Exemplary coding sequence.

[0709] For reference, sequence identifiers other than those included in Table 1 are summarized in Table 2.

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<td>kappa constant light chain polynucleotide sequence</td>
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<td>gamma-1 constant heavy chain polypeptide sequence (differs from SEQ ID NO: 518 at two positions)</td>
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<td>C-reactive protein polypeptide sequence</td>
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[0710] Such antibody fragments may be present in one or more of the following non-limiting forms: Fab, Fab', F(ab')2, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-IL-6 antibodies described herein further comprises the kappa constant light chain sequence comprising the sequence set forth below:

```
ASTKGPSVPLPSSTSGTALGCLVLDSKPPDFPVPVISNSQALTSSV
```

[SEQ ID NO: 586]

```
HTPPAVLQSSGLYSVSVTVSESSLQTYICVNHKPENNTKVDKDKEV
KSCDKHTHTCPAPSPQPSLQPPLPPKPSLTMSTPEEVTVCQVYES
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[SEQ ID NO: 518]

```
HEPDKEKPRIVYDDG/EVHIACTKPRERKASTYVVSVLTVHQNLK
```

[SEQ ID NO: 719]

```
EVYKCWSKNLAPFLAPEKTSKAQQPREPQYTLPPPSEENTHQVSLTC
```

[SEQ ID NO: 590-646]

```
LVKGEYFPSDLASWEHNOSQPHENYKYPFPVLDGDSFGFLYSKLTVDSR\nQQGQVPSVCSWMEALWNYTHQKSLLSLPGK
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[SEQ ID NO: 518]

[0711] In another preferred embodiment, the anti-IL-6 antibodies described herein further comprises the gamma-1 constant heavy chain polypeptide sequence comprising one of the sequences set forth below:

```
VAPSVFIPPSQDEQLKSGTAVCCLNNFYPPREAV/KQRVHDNLQGGS
```

[SEQ ID NO: 586]

[SEQ ID NO: 719]

[SEQ ID NO: 590-646]

[0712] Embodiments of antibodies described herein may include a leader sequence, such as a rabbit Ig leader, albumin pre-peptide, a yeast mating factor pre pro secretion leader sequence (such as P. pastoris or Saccharomyces cerevisiae α or alpha factor), or human HAS leader. Exemplary leader sequences are shown offset from FR1 at the N-terminus of polypeptides shown in FIGS. 36A and 37A as follows: rabbit Ig leader sequences in SEQ ID Nos. 2 and 660 (MD . . . ) and SEQ ID Nos.: 3 and 661 (ME . . . ); and an albumin prepeptide in SEQ ID Nos. 706 and 708, which facilitates secretion. Other leader sequences known in the art to confer desired
properties, such as secretion, improved stability or half-life, etc. may also be used, either alone or in combinations with one another, on the heavy and/or light chains, which may optionally be cleaved prior to administration to a subject. For example, a polypeptide may be expressed in a cell or cell-free expression system that also expresses or includes (or is modified to express or include) a protease, e.g., a membrane-bound signal peptidase, that cleaves a leader sequence.

[0713] In another embodiment, the invention contemplates an isolated anti-II-6 antibody comprising a V_\text{\textsubscript{H}} polypeptide sequence comprising: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 652, 656, 657, 658, 661, 664, 665, 668, 672, 676, 680, 684, 688, 691, 692, 704, or 708; and further comprising a V_\text{\textsubscript{L}} polypeptide sequence comprising: SEQ ID NO: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 454, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or 709 or a variant thereof wherein one or more of the framework residues (FR residues) in said V_\text{\textsubscript{H}} or V_\text{\textsubscript{L}} polypeptide has been substituted with another amino acid residue resulting in an anti-II-6 antibody that specifically binds II-6. The invention also contemplates humanized and chimeric forms of these antibodies, preferably wherein the FR will comprise human FR’s highly homologous to the parent antibody. The chimeric antibodies may include an Fe derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions and in particular a variable heavy and light chain constant region as contained in SEQ ID NO:588 and SEQ ID NO:586.

[0714] In one embodiment of the invention, the antibodies or V_\text{\textsubscript{H}} or V_\text{\textsubscript{L}} polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

[0715] In another embodiment of the invention, the anti-II-6 antibodies and fragments thereof have binding specificity for primate homologs of the human II-6 protein. Non-limiting examples of primate homologs of the human II-6 protein are II-6 obtained from Macaca fascicularis (also known as the cynomolgus monkey) and the Rhesus monkey. In another embodiment of the invention, the anti-II-6 antibodies and fragments thereof inhibits the association of II-6 with IL-6R, and/or the production of IL-6/II-6R/ gp130 complexes and/or the production of IL-6/II-6R/130 multimers and/or antagonizes the biological effects of one or more of the foregoing.

[0716] As stated above, antibodies and fragments thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[0717] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylicholinesterase, alkaline phosphatase, beta-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and acquisorin. Further exemplary radioactive materials include, but are not limited to, Iodine 125 (125I), Carbon 14 (14C), Sulfur 35 (35S), Trinitritium (3H) and Phosphorus 32 (32P).

[0718] Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluouracil decarbazine; alkylating agents such as mechlorethamine, thiopeta chlorambucil, melphalan, carmustine (BCNU), mitomycin C, lomustine (CCNU), 1-methyllytrosoxurea, cyclophosphamide, mechlorothamine, busulfan, dibromomannitol, streptonizotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, caminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include actinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthracyclin (AMC); and antimycotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, pseudomonas exotoxin, gemicitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, purocin, procarbazine, hydroxyurea, asparaginase, corticosteroids, myotone (O.P. (D.D.D)), interferons, and mixtures of these cytotoxic agents.

[0719] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemicitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine, bleomycin, VEGF antagonists, EGF-F antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemicytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids (e.g., vinblastine, vincristine, vindesine and vinorelbine), mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, II-1 antagonists, interleukins (e.g. II-12 or II-12), II-12R antagonists, Toxin conjugated monoclonal antibodies, tamor antigen specific monoclonal antibodies, Erbitux™, Avastin™, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL 625, Herceptin®, or any combination thereof. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and Pseudomonas toxin may be conjugated to the humanized antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents (Youse, et al., Proc. Nat’l Acad. Sci. USA 77:5483 (1980); Gilliland, et al., Proc. Nat’l Acad. Sci. USA 77:4539 (1980); Kroll, et al., Proc. Nat’l Acad. Sci. USA 77:5419 (1980)).

[0720] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653, 104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionucleides include beta-emitters such as Phosphorus-32 (32P), Scandium-47 (47Sc), Copper-67 (67Cu), Gallium-67 (67Ga), Yttrium-88 (88Y), Yttrium-90 (90Y), Iodine-125 (125I), Iodine-131 (131I), Samarium-153 (153Sm),
Lutetium-177 (177Lu), Rhenium-186 (186Re) or Rhenium-188 (188Re), and alpha-emitters such as Astatine-211 (211At), Lead-212 (212Pb), Bismuth-212 (212Bi) or -213 (213Bi) or Actinium-225 (225Ac).

[0721] Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter et al, Nature 144:945 (1962); David et al, Biochemistry 13:1014 (1974); Pain et al, J. Immunol. Meth. 40:219 (1981); and Nygren, J., Histochem. and Cytochem. 30:407 (1982).

[0722] Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camelodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth therein. These may contain, e.g., conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, e.g., one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

[0723] In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

[0724] In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-II-6 activity. Non-limiting examples of anti-II-6 activity are set forth herein, for example, under theheading “Anti-II-6 Activity,” infra.

[0725] In another embodiment, the invention further contemplates the generation and use of anti-idiotypic antibodies that bind any of the foregoing sequences. In an exemplary embodiment, such an anti-idiotypic antibody could be administered to a subject who has received an anti-II-6 antibody to modulate, reduce, or neutralize, the effect of the anti-II-6 antibody. Such anti-idiotypic antibodies could also be useful for treatment of an autoimmune disease characterized by the presence of anti-II-6 antibodies. A further exemplary use of such anti-idiotypic antibodies is for detection of the anti-II-6 antibodies of the present invention, for example to monitor the levels of the anti-II-6 antibodies present in a subject’s blood or other bodily fluids.

[0726] The present invention also contemplates anti-II-6 antibodies comprising any of the polypeptide or polynucleotide sequences described herein substituted for any of the other polynucleotide sequences described herein. For example, without limitation thereto, the present invention contemplates antibodies comprising the combination of any of the variable light chain and variable heavy chain sequences described herein, and further contemplates antibodies resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein.

Additional Exemplary Embodiments of the Invention

[0727] In another embodiment, the invention contemplates one or more anti-II-6 antibodies or antibody fragment which specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human II-6 polypeptide or fragment thereof as an anti-II-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind II-6, which preferably are aglycosylated. In a preferred embodiment, the anti-II-6 antibody or fragment may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human II-6 polypeptide or a fragment thereof as Ab1 or an antibody comprising the CDRs of Ab1.

[0728] In another embodiment of the invention, the anti-II-6 antibody which may specifically bind to the same linear or conformational epitopes on an intact II-6 polypeptide or fragment thereof that is (are) specifically bound by Ab1 may bind to a II-6 epitope(s) ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human II-6 polypeptide. In one embodiment of the invention, the II-6 epitope comprises, or alternatively consists of, one or more residues comprised in II-6 fragments selected from those respectively encompassing amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and or amino acid residues 58-72.

[0729] The invention is also directed to an anti-II-6 antibody that binds with the same II-6 epitope and/or competes with an anti-II-6 antibody for binding to II-6 as an antibody or antigen fragment disclosed herein, including but not limited to an anti-II-6 antibody selected from Ab1, Ab2, Ab3, AM, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, and Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind II-6, which preferably are aglycosylated.

[0730] In another embodiment, the invention is also directed to an isolated anti-II-6 antibody or antibody fragment comprising one or more of the CDRs contained in the VH polypeptide sequences comprising: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 652, 656, 657, 658, 661, 664, 665, 668, 672, 676, 680, 684, 688, 691, 692, 704, or 708 and/or one or more of the CDRs contained in the VH polypeptide sequence consisting of: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or
709 and the VH and VL sequences depicted in the antibody alignments comprised in FIGS. 34-37 of this application.

[0731] In one embodiment of the invention, the anti-IL-6 antibody discussed in the two prior paragraphs comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated.

[0732] In a preferred embodiment, the anti-IL-6 antibody discussed above comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in Ab1. In another embodiment, all of the CDRs of the anti-IL-6 antibody discussed above are identical to the CDRs contained in an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated. In a preferred embodiment of the invention, all of the CDRs of the anti-IL-6 antibody discussed above are identical to the CDRs contained in Ab1, e.g., an antibody comprised of the VH and VL sequences comprised in SEQ ID NO:657 and SEQ ID NO:709 respectively, or antibodies comprising any combination of the humanized sequence comprised in FIGS. 34-37.

[0733] The invention further contemplates that the one or more anti-IL-6 antibodies discussed above are aglycosylated; that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-IL-6 antibody. Extrapolated constant regions that provide for the productivity of the antibodies in Pichia are comprised in SEQ ID NO:588 and SEQ ID NO:589 which respectively are encode by the nucleic acid sequences in SEQ ID NO:589 and SEQ ID NO:587.

[0734] The invention further contemplates one or more anti-IL-6 antibodies wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of at most 2 or 3 human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs have been derived from human variable heavy and light chain sequences which have been selected from a library of human germine antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germine antibody sequences contained in the library.

[0735] In one embodiment of the invention, the anti-IL-6 antibody or fragment may specifically bind to IL-6 expressing human cells and/or to circulating soluble IL-6 molecules in vivo, including IL-6 expressed on or by human cells in a patient with a disease associated with cells that express IL-6.

[0736] In another embodiment, the disease is selected from general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, fibromyalgia, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren’s syndrome, acute lupus erythematosus, Still’s disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget’s disease of bone, osteoarthritis, multiple myeloma, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman’s disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer’s disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thromboembolism, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperation injury, transplant rejection, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS). In a preferred embodiment, the disease is selected from a cancer, inflammatory disorder, viral disorder, or autoimmune disorder. In a particularly preferred embodiment, the disease is arthritis, cachexia, and wasting syndrome.

[0737] The invention further contemplates anti-IL-6 antibodies or fragments directly or indirectly attached to a detectable label or therapeutic agent.

[0738] The invention also contemplates one or more nucleic acid sequences which result in the expression of an anti-IL-6 antibody or antibody fragment as set forth above, including those comprising, or alternatively consisting of, yeast or human preferred codons. The invention also contemplates vectors (including plasmids or recombinant viral vectors) comprising said nucleic acid sequence(s). The invention also contemplates host cells or recombinant host cells expressing at least one of the antibodies set forth above, including a mammalian, yeast, bacterial, and insect cells. In a preferred embodiment, the host cell is a yeast cell. In a further preferred embodiment, the yeast cell is a diploid yeast cell. In a more preferred embodiment, the yeast cell is a Pichia yeast.

[0739] The invention also contemplates a method of treatment comprising administering to a patient with a disease or condition associated with IL-6 expressing cells a therapeutically effective amount of at least one anti-IL-6 antibody or fragment. The diseases that may be treated are presented in the non-limiting list set forth above. In a preferred embodiment, the disease is selected from a cancer, autoimmune disease, or inflammatory condition. In a particularly preferred embodiment, the disease is cancer or viral infection. In another embodiment the treatment further includes the
administration of another therapeutic agent or regimen selected from chemotherapy, radiotherapy, cytokine administration or gene therapy.

[0740] The invention further contemplates a method of in vivo imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective amount of at least one anti-IL-6 antibody. In one embodiment, said administration further includes the administration of a radionuclide or fluorophore that facilitates detection of the antibody at IL-6 expressing disease sites. In another embodiment of the invention, the method of in vivo imaging is used to detect IL-6 expressing tumors or metastases or is used to detect the presence of sites of autoimmune disorders associated with IL-6 expressing cells. In a further embodiment, the results of said in vivo imaging method are used to facilitate design of an appropriate therapeutic regimen, including therapeutic regimens including radiotherapy, chemotherapy or a combination thereof.

Polynucleotides Encoding Anti-IL-6 Antibody Polypeptides

[0741] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 2:

(SEQ ID NO: 10)
ATGACACGAGGGCCCGCCACTCACGTGGGTGGGTCCCTCTCCTGTCTCTCTGTCTGGCT
CCCAGTTGGCAAGATGGTCCATAATAGCTGACTACAGACCCATCGACCTGGTGG
CTGCAGCTGGGCAAGCCCACTACCATGACTGAGCTGGCTGGATGACCTGG
ATTTAAGAAGTATGATCTGGTTACAGGAACCTGGCAAGCTCCCA
GCTCTGTACTTAAATGCATTCCACTCCTCGATGCGACTGCTGCCTCTCTCTGG
TCGAAAGCCTGGGGAAGCTCTGCTGAGCTCACATCCACGACCTGGTGGGTGG
GAGTGGCGGTTGGCTCGGTCTTCTCAACACGCTGGATTTAGCCAGGTAAGCT
GATATGAGTTGTTAATCTCCGGCCGGGCAGCGGGGTGTGGATGGTCAAGGCGT
CGTTAGGAGCCCATCTCGTCTTCCCTTTCCCCGGTGAATTGCTTGG
AAAATGGGATGCTGGCTCTGGTGGCTCCTGTAGAATTCTT.

[0742] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 3:

(SEQ ID NO: 11)
ATGGGACCTGCGTTGGCTCCTGCTCTTCTCTGGTCTCTGCTGAAAGCTT
CCAGTGGCTGACTCGTGGGTGGGCTCAGCCTGGTGGGGA
CACTCCTGCCAAAATCAAGAGCATCCACTGGTGAATTCTCTGCTCTCTCTGG
TACCTTGGGCAAGCTGGGCAAGCGGGGAGGCTGaCTGACTGGTCAAGGCGT
AAATCTTATGGTAGTGGTGAAGAGGAGCTTCTGGCCAGCGGGGAGGAGGC
GATACCTACCTTCCTCGAGGAGCCTGTTGACATCTGAGGAAATATGTGAGCT
CTGCCAGGGGCGACACGGGCGCACCTCTTTTGCGGCGGATGGTAGGAGCTGAGTAC

[0743] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 12; SEQ ID NO: 13; and SEQ ID NO: 14 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 2.

[0744] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 3.

[0745] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 10 encoding the light chain variable region of SEQ ID NO: 2; the polynucleotide SEQ ID NO: 11 encoding the heavy chain variable region of SEQ ID NO: 3; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 12; SEQ ID NO: 13; and SEQ ID NO: 14) of the light chain variable region of SEQ ID NO: 10; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17) of the heavy chain variable region of SEQ ID NO: 11; and polynucleotides encoding the variable heavy and light chain sequences in SEQ ID NO:657 and SEQ ID NO:709 respectively, e.g., the nucleic acid sequences in SEQ ID NO:700 and SEQ ID NO:723 and fragments or variants thereof, e.g., based on codon degeneracy. These nucleic acid sequences encoding variable heavy and light chain sequences may be expressed alone or in combination and these sequences preferably are fused to suitable variable constant sequences, e.g., those in SEQ ID NO:589 and SEQ ID NO:587.

[0746] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 21:

(SEQ ID NO: 29)
ATGGACACGAGGGCCCGCCACTCACGTGGGTGGGTCCCTCTCCTGTCTCTCTGTCTGGCT
TCCAGTGCGCCAGATGGTCCATAATAGCTGACTACAGACCCATCGACCTGGTGG
GAGTGGCGGTTGGCTCGGTCTTCTCAACACGCTGGATTTAGCCAGGTAAGCT
GATATGAGTTGTTAATCTCCGGCCGGGCAGCGGGGTGTGGATGGTCAAGGCGT
CGTTAGGAGCCCATCTCGTCTTCCCTTTCCCCGGTGAATTGCTTGG
AAAATGGGATGCTGGCTCTGGTGGCTCCTGTAGAATTCTT.
region of SEQ ID NO: 22; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 31; SEQ ID NO: 32; and SEQ ID NO: 33) of the light chain variable region of SEQ ID NO: 29; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 34; SEQ ID NO: 35; and SEQ ID NO: 36) of the heavy chain variable region of SEQ ID NO: 30.

[0751] The invention is further directed to polynucleotides encoding antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 37:

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(SEQ ID NO: 45)
ATGGACACGAGGGCCCCACCTCACTGCGGATGCTCGCTCAGGGCTGCT
CTCCAGGCTCAGATTCTGGCGCGGCGGCTGACACTCTCTCCCCTCGT
GTCTCAGGTCGCGGCTGACCTCCACGGCACTCTGTCCAGAGCTGGGTT
AGGTGGCAGAACCTGCTTGGAGATGAGGATTATCTTTCACTTTGCT
GGGCGCTCCAGTTGAACTCTTGGGACTCGACCAGGGTGGGTGGT
CCGCTGACCGGCGCTGCTGGCGGCGGCAGAGGCAGCGCTTTCCCCCT
CTGCCGCACCTTCCTCAAGAGCAGCCTCTGGGGGCAAGGCTCGCTGGT
GCTCGTTCAGAG.
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[0752] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 38:

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(SEQ ID NO: 46)
ATGGACACTGCGCTCAGGATTCCTGGCGGCTGATGCTCGCTCAGGGCTGCT
CTCCAGGCTCAGATTCTGGCGCGGCGGCTGACACTCTCTCCCCTCGT
GTCTCAGGTCGCGGCTGACCTCCACGGCACTCTGTCCAGAGCTGGGTT
AGGTGGCAGAACCTGCTTGGAGATGAGGATTATCTTTCACTTTGCT
GGGCGCTCCAGTTGAACTCTTGGGACTCGACCAGGGTGGGTGGT
CCGCTGACCGGCGCTGCTGGCGGCGGCAGAGGCAGCGCTTTCCCCCT
CTGCCGCACCTTCCTCAAGAGCAGCCTCTGGGGGCAAGGCTCGCTGGT
GCTCGTTCAGAG.
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[0748] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 31; SEQ ID NO: 32; and SEQ ID NO: 33 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 21.

[0749] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 34; SEQ ID NO: 35; and SEQ ID NO: 36 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 22.

[0750] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide sequences encoding antibody fragments: the polynucleotide SEQ ID NO: 29 encoding the light chain variable region of SEQ ID NO: 21; the polynucleotide SEQ ID NO: 30 encoding the heavy chain variable region of SEQ ID NO: 22; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 31; SEQ ID NO: 32; and SEQ ID NO: 33) of the light chain variable region of SEQ ID NO: 29; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 34; SEQ ID NO: 35; and SEQ ID NO: 36) of the heavy chain variable region of SEQ ID NO: 30.
regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 37.

[0754] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 50; SEQ ID NO: 51; and SEQ ID NO: 52 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 38.

[0755] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, or three, or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 45 encoding the light chain variable region of SEQ ID NO: 37; the polynucleotide SEQ ID NO: 46 encoding the heavy chain variable region of SEQ ID NO: 38; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 47; SEQ ID NO: 48; and SEQ ID NO: 49) of the light chain variable region of SEQ ID NO: 37; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 50; SEQ ID NO: 51; and SEQ ID NO: 52) of the heavy chain variable region of SEQ ID NO: 38.

[0756] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 53:

```
AGGGACACGGGGCCCCACACTCAGCTTCGGGCCTCGTGGCTCTG

[SEQ ID NO: 61]
```

[0757] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 54:

```
AGGGACACGGGGCCCCACACTCAGCTTCGGGCCTCGTGGCTCTG

[SEQ ID NO: 62]
```

[0758] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 63; SEQ ID NO: 64; and SEQ ID NO: 65 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 53.

[0759] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 66; SEQ ID NO: 67; and SEQ ID NO: 68 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 54.

[0760] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three, or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 61 encoding the light chain variable region of SEQ ID NO: 53; the polynucleotide SEQ ID NO: 62 encoding the heavy chain variable region of SEQ ID NO: 54; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 63; SEQ ID NO: 64; and SEQ ID NO: 65) of the light chain variable region of SEQ ID NO: 53; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 66; SEQ ID NO: 67; and SEQ ID NO: 68) of the heavy chain variable region of SEQ ID NO: 54.

[0761] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 69:

```
AGGGACACGGGGCCCCACACTCAGCTTCGGGCCTCGTGGCTCTG

[SEQ ID NO: 77]
```
region of SEQ ID NO: 70; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81) of the light chain variable region of SEQ ID NO: 69; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84) of the heavy chain variable region of SEQ ID NO: 70.

The invention is further directed to polynucleotides encoding peptides of the antibodies having binding specificity to II.6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 85:

(SEQ ID NO: 93)

```
AGGCCACAGGGGCCCCACCTCAGCTGCTGGCTCCTTCCTCCCTGGCTCGAGTAC
```

[0767] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 86:

(SEQ ID NO: 94)

```
AGGCCACAGGGGCCCCACCTCAGCTGCTGGCTCCTTCCTCCCTGGCTCGAGTAC
```

[0768] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to II.6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 69.

[0764] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to II.6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 70.

[0765] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to II.6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide encoding antibody fragments: the polynucleotide SEQ ID NO: 77 encoding the light chain variable region of SEQ ID NO: 69; the polynucleotide SEQ ID NO: 78 encoding the heavy chain variable region of SEQ ID NO: 70; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81) of the light chain variable region of SEQ ID NO: 69; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84) of the heavy chain variable region of SEQ ID NO: 70.

The invention is further directed to polynucleotides encoding peptides of the antibodies having binding specificity to II.6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 85:

```
AGGCCACAGGGGCCCCACCTCAGCTGCTGGCTCCTTCCTCCCTGGCTCGAGTAC
```

[0766] The invention is further directed to polynucleotides encoding peptides of the antibodies having binding specificity to II.6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 85:

```
AGGCCACAGGGGCCCCACCTCAGCTGCTGGCTCCTTCCTCCCTGGCTCGAGTAC
```

[0763] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to II.6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 69.

[0762] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 70:

(SEQ ID NO: 78)

```
AGGCCACAGGGGCCCCACCTCAGCTGCTGGCTCCTTCCTCCCTGGCTCGAGTAC
```

[0767] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 86:

```
AGGCCACAGGGGCCCCACCTCAGCTGCTGGCTCCTTCCTCCCTGGCTCGAGTAC
```

[0764] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to II.6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 70.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to II.6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide encoding antibody fragments: the polynucleotide SEQ ID NO: 77 encoding the light chain variable region of SEQ ID NO: 69; the polynucleotide SEQ ID NO: 78 encoding the heavy chain variable region of SEQ ID NO: 70; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81) of the light chain variable region of SEQ ID NO: 69; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84) of the heavy chain variable region of SEQ ID NO: 70.

[0765] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to II.6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide encoding antibody fragments: the polynucleotide SEQ ID NO: 77 encoding the light chain variable region of SEQ ID NO: 69; the polynucleotide SEQ ID NO: 78 encoding the heavy chain variable region of SEQ ID NO: 70; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81) of the light chain variable region of SEQ ID NO: 69; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84) of the heavy chain variable region of SEQ ID NO: 70.
regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 85.

[0769] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding
specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO:
98; SEQ ID NO: 99; and SEQ ID NO: 100 which correspond to polynucleotides encoding the complementarity-determining
regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 86.

[0770] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences
described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 93 encoding the light chain variable region of SEQ ID NO: 85; the polynucleotide SEQ ID NO: 94 encoding the heavy chain variable region of SEQ ID NO: 86; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97) of the light chain variable region of SEQ ID NO: 85; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100) of the heavy chain variable region of SEQ ID NO: 86.

[0771] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 101:

```
ATGGAACGAGGCCCACACTCACTGCCAATGGGCTCCTGTCTCTGCT
TCCAGGTGCCCCGAGGATGCTATGATGACGAGCTGAGCTGACCTCG
GAGCTGCTAGAGAGCTAATGCCCAGCTCCGACTGAGAGATG
CCAGGTGGGCTCAGGAGGTCCGACTGAGAGATG
GACGATTGTAATTTAGCTGGATGACAGCCTAGCAGCTGAGAGATG
```

[0772] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 102:

```
ATGGAACGAGGCCCACACTCACTGCCAATGGGCTCCTGTCTCTGCT
TCCAGGTGCCCCGAGGATGCTATGATGACGAGCTGAGCTGACCTCG
GAGCTGCTAGAGAGCTAATGCCCAGCTCCGACTGAGAGATG
CCAGGTGGGCTCAGGAGGTCCGACTGAGAGATG
GACGATTGTAATTTAGCTGGATGACAGCCTAGCAGCTGAGAGATG
```

[0773] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 111; SEQ ID NO: 112; and SEQ ID NO: 113 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 101.

[0774] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 114; SEQ ID NO: 115; and SEQ ID NO: 116 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 102.

[0775] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 109 encoding the light chain variable region of SEQ ID NO: 101; the polynucleotide SEQ ID NO: 109 encoding the heavy chain variable region of SEQ ID NO: 102; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 111; SEQ ID NO: 112; and SEQ ID NO: 113) of the light chain variable region of SEQ ID NO: 101; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 114; SEQ ID NO: 115; and SEQ ID NO: 116) of the heavy chain variable region of SEQ ID NO: 102.

[0776] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 122:

```
ATGGAACGAGGCCCACACTCACTGCCAATGGGCTCCTGTCTCTGCT
TCCAGGTGCCCCGAGGATGCTATGATGACGAGCTGAGCTGACCTCG
GAGCTGCTAGAGAGCTAATGCCCAGCTCCGACTGAGAGATG
CCAGGTGGGCTCAGGAGGTCCGACTGAGAGATG
GACGATTGTAATTTAGCTGGATGACAGCCTAGCAGCTGAGAGATG
```
[0777] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 123:

(SEQ ID NO: 131)
AGCGAGACTGGGCCGCTGCGGCTCTCTCTGGCTGCTGCATCTAGGTT
TGGCTGGATACTCGTGGATTTGATTGAGCAGAGCTCGGCTCGGCT
GACACCGCTGACATCTCCTCAGGATCTTCTGGAATTTCCCTCTAGTGT
CGTGACGACGGTGGTACGATGCGACATCTCCTCAGGATCTTCTGGA
TGGCTGGATACTCGTGGATTTGATTGAGCAGAGCTCGGCTCGGCT
AGCGAGACTGGGCCGCTGCGGCTCTCTCTGGCTGCTGCATCTAGGTT
TGGCTGGATACTCGTGGATTTGATTGAGCAGAGCTCGGCTCGGCT

[0778] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 132; SEQ ID NO: 133; and SEQ ID NO: 134 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 122.

[0779] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 123.

[0780] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 130 encoding the light chain variable region of SEQ ID NO: 122; the polynucleotide SEQ ID NO: 131 encoding the heavy chain variable region of SEQ ID NO: 123; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 132; SEQ ID NO: 133; and SEQ ID NO: 134) of the light chain variable region of SEQ ID NO: 122; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137) of the heavy chain variable region of SEQ ID NO: 123.

[0781] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides encoding, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 138:

(SEQ ID NO: 146)

[0782] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 139:

(SEQ ID NO: 147)

[0783] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 138.

[0784] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 151; SEQ ID NO: 152; and SEQ ID NO: 153 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 139.

[0785] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 146 encoding the light chain variable region of SEQ ID NO: 138; the polynucleotide SEQ ID NO: 147 encoding the heavy chain
variable region of SEQ ID NO: 139; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150) of the light chain variable region of SEQ ID NO: 138; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 151; SEQ ID NO: 152; and SEQ ID NO: 153) of the heavy chain variable region of SEQ ID NO: 139.

[0786] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 154:

```
ATGGACACGAGGGCCACCACACTCTGCGCTTCGGGTCCTCTCTGAGCT
CCAGGTCGCACATTACGACGCGTGCGACGACCACACATCTGCGCTGGAT
CTCGAGCTTGCCGCGACGACCACACATCTGCGCTGGAT
GGTATTACGACGCGTGCGACGACCACACATCTGCGCTGGAT
GGTATTACGACGCGTGCGACGACCACACATCTGCGCTGGAT
CGGCGGCGAGG GCCCGAGG GCCCGAGG GCCCGAGG GCCCGAGG GCCCGAGG
```

[0787] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 155:

```
ATGGGAGCTGGGCTGGCTCGCTCCGGGCTCCTCTGCTGGAT
CCATTGTCGCCGCTCGCTCCGGGCTCCTCTGCTGGAT
CCATTGTCGCCGCTCGCTCCGGGCTCCTCTGCTGGAT
AAAATTTGGAGCTGGGCTCGCTCCGGGCTCCTCTGCTGGAT
GAATCTCCAGGGCCACGACGAGG GCCACGACGAGG GCCACGACGAGG
```

[0788] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 164; SEQ ID NO: 165; and SEQ ID NO: 166 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 154.

[0789] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 167; SEQ ID NO: 168; and SEQ ID NO: 169 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 155.

[0790] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 162 encoding the light chain variable region of SEQ ID NO: 154; the polynucleotide SEQ ID NO: 163 encoding the heavy chain variable region of SEQ ID NO: 155; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 164; SEQ ID NO: 165; and SEQ ID NO: 166) of the light chain variable region of SEQ ID NO: 154; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 167; SEQ ID NO: 168; and SEQ ID NO: 169) of the heavy chain variable region of SEQ ID NO: 155.

[0791] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 170:

```
ATGGGAGCTGGGCTGGCTCGCTCCGGGCTCCTCTGCTGGAT
CCATTGTCGCCGCTCGCTCCGGGCTCCTCTGCTGGAT
CCATTGTCGCCGCTCGCTCCGGGCTCCTCTGCTGGAT
AAAATTTGGAGCTGGGCTCGCTCCGGGCTCCTCTGCTGGAT
GAATCTCCAGGGCCACGACGAGG GCCACGACGAGG GCCACGACGAGG
```

[0792] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 171:

```
ATGGGAGCTGGGCTGGCTCGCTCCGGGCTCCTCTGCTGGAT
CCATTGTCGCCGCTCGCTCCGGGCTCCTCTGCTGGAT
CCATTGTCGCCGCTCGCTCCGGGCTCCTCTGCTGGAT
AAAATTTGGAGCTGGGCTCGCTCCGGGCTCCTCTGCTGGAT
GAATCTCCAGGGCCACGACGAGG GCCACGACGAGG GCCACGACGAGG
```

[0793] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 180; SEQ ID NO: 181; and SEQ ID NO: 182 which correspond to polynucleotides encoding the complementarity-de-
terminating regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 170.

[0794] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 183; SEQ ID NO: 184; and SEQ ID NO: 185 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 171.

[0795] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 178 encoding the light chain variable region of SEQ ID NO: 170; the polynucleotide SEQ ID NO: 179 encoding the heavy chain variable region of SEQ ID NO: 171; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 180; SEQ ID NO: 181; and SEQ ID NO: 182) of the light chain variable region of SEQ ID NO: 170; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 183; SEQ ID NO: 184; and SEQ ID NO: 185) of the heavy chain variable region of SEQ ID NO: 171.

[0796] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide encoding the variable light chain polypeptide sequence of SEQ ID NO: 186:

(SEQ ID NO: 194)
ATGGCACGAGGAGCCCCACACTCACTGCTCGGGTCCCTGGGCTCCTGCTCTGCTCCTGCT
CCAGGTCAGTCAAGTGTAGATGATGATGATCAAGCCACACTCCAGCCTCCTGCT
AGCAGCTCTCTGGGAGCACACTCCAATCAGTGACGAGGGACGACGCGGAC
ATGGGCAATCAGTCTACCCGGAACTCAGAATGACGAGGGACGACGCGGAC
GCTCTGATCTACAGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
TCACAGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
GATGCGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
TAGGTT

[0797] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 187:

(SEQ ID NO: 195)
ATGGGACGAGGAGCCCCACACTCACTGCTCGGGTCCCTGGGCTCCTGCTCTGCTCCTGCT
CCAGGTCAGTCAAGTGTAGATGATGATGATCAAGCCACACTCCAGCCTCCTGCT
AGCAGCTCTCTGGGAGCACACTCCAATCAGTGACGAGGGACGACGCGGAC
ATGGGCAATCAGTCTACCCGGAACTCAGAATGACGAGGGACGACGCGGAC
GCTCTGATCTACAGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
TCACAGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
GATGCGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
TAGGTT

[0798] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 196; SEQ ID NO: 197; and SEQ ID NO: 198 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 186.

[0799] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 199; SEQ ID NO: 200; and SEQ ID NO: 201 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 187.

[0800] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 194 encoding the light chain variable region of SEQ ID NO: 186; the polynucleotide SEQ ID NO: 195 encoding the heavy chain variable region of SEQ ID NO: 187; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 196; SEQ ID NO: 197; and SEQ ID NO: 198) of the light chain variable region of SEQ ID NO: 186; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 199; SEQ ID NO: 200; and SEQ ID NO: 201) of the heavy chain variable region of SEQ ID NO: 187.

[0801] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 202:

(SEQ ID NO: 210)
ATGGGACGAGGAGCCCCACACTCACTGCTCGGGTCCCTGGGCTCCTGCTCTGCTCCTGCT
CCAGGTCAGTCAAGTGTAGATGATGATGATCAAGCCACACTCCAGCCTCCTGCT
AGCAGCTCTCTGGGAGCACACTCCAATCAGTGACGAGGGACGACGCGGAC
ATGGGCAATCAGTCTACCCGGAACTCAGAATGACGAGGGACGACGCGGAC
GCTCTGATCTACAGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
TCACAGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
GATGCGGAGTCTCAAGAATGACGAGGGACGACGCGGAC
TAGGTT

[0802] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of,
the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 203:

(SEQ ID NO: 221)

ATGGAGAGCTGGGCTGCGTCTTCTCTTGTGTGCTGCTGCTGCTGAGTGT
CCAGGTGTAGCGTACGATGGTGGAGGGCTGCCGCTCCCGGTCAAGCGG
GGCCCTCTGCTGACTCTCTCTGTCGCTGCGTCTGCTGCTGCTGCTGAGTGT
GATCGCATTGGTTTATTATTTAATATATCGATACGGAAGCTCAGG
GCGAGAAAGGCGTACTCTCATCTTCAAGACTCTCTCTGCGTGGCAGCTTCTGT
CAATGAGACAGCTGGAGCGGCGCCAGCGCAGCCATATTCTCTGGCAG
GGGATATTCTCTGCTGAAATATTATGATGTTGCTGCTGCTGCTGAGTGT

[0803] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 212; SEQ ID NO: 213; and SEQ ID NO: 214 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 202.

[0804] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 203.

[0805] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide sequences encoding antibody fragments: the polynucleotide SEQ ID NO: 210 encoding the light chain variable region of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 211 encoding the heavy chain variable region of SEQ ID NO: 203; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 212; SEQ ID NO: 213; and SEQ ID NO: 214) of the light chain variable region of SEQ ID NO: 202; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217) of the heavy chain variable region of SEQ ID NO: 203.

[0806] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 218:

(SEQ ID NO: 222)

ATGGACACCAAGGCGCCACTCACTGCTGGGCTGCTGCTGCTGCTGAGTGT
CCAGGTGTAGCGTACGATGGTGGAGGGCTGCCGCTCCCGGTCAAGCGG
GGCCCTCTGCTGACTCTCTCTGTCGCTGCGTCTGCTGCTGCTGCTGAGTGT
GATCGCATTGGTTTATTATTTAATATATCGATACGGAAGCTCAGG
GCGAGAAAGGCGTACTCTCATCTTCAAGACTCTCTCTGCGTGGCAGCTTCTGT
CAATGAGACAGCTGGAGCGGCGCCAGCGCAGCCATATTCTCTGGCAG
GGGATATTCTCTGCTGAAATATTATGATGTTGCTGCTGCTGCTGAGTGT

[0807] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 219:

(SEQ ID NO: 227)

ATGGGACAGCTGGGCTGCGTCTTCTCTTGTGTGCTGCTGCTGCTGAGTGT
CCAGGTGTAGCGTACGATGGTGGAGGGCTGCCGCTCCCGGTCAAGCGG
GGCCCTCTGCTGACTCTCTCTGTCGCTGCGTCTGCTGCTGCTGCTGAGTGT
GATCGCATTGGTTTATTATTTAATATATCGATACGGAAGCTCAGG
GCGAGAAAGGCGTACTCTCATCTTCAAGACTCTCTCTGCGTGGCAGCTTCTGT
CAATGAGACAGCTGGAGCGGCGCCAGCGCAGCCATATTCTCTGGCAG
GGGATATTCTCTGCTGAAATATTATGATGTTGCTGCTGCTGCTGAGTGT

[0808] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 218.

[0809] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 231; SEQ ID NO: 232; and SEQ ID NO: 233 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 219.

[0810] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide sequences encoding antibody fragments: the polynucleotide SEQ ID NO: 226 encoding the light chain variable region of SEQ ID NO: 218; the polynucleotide SEQ ID NO: 227 encoding the heavy chain variable region of SEQ ID NO: 219; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230) of the light chain variable region of SEQ ID NO: 218; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 231; SEQ ID NO: 232; and SEQ ID NO: 233) of the heavy chain variable region of SEQ ID NO: 219.
[0811] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 234:

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ATGGAACACAGAGGCCCACACTGCTGGGCTTCTGCTCTCTGCT
TCCAGGGCTTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGT
CTGAGTGTGTCATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
GTTTATGAGCCAGATCTTATGTCTAGTTAGTACGCTCTAGTTAG
TGAAGATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
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[0812] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 235:

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ATGGAACACAGAGGCCCACACTGCTGGGCTTCTGCTCTCTGCT
TCCAGGGCTTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGT
CTGAGTGTGTCATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
GTTTATGAGCCAGATCTTATGTCTAGTTAGTACGCTCTAGTTAG
TGAAGATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
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[0813] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 244; SEQ ID NO: 245; and SEQ ID NO: 246 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 234.

[0814] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 247; SEQ ID NO: 248; and SEQ ID NO: 249 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 235.

[0815] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 242 encoding the light chain variable region of SEQ ID NO: 234; the polynucleotide SEQ ID NO: 243 encoding the heavy chain variable region of SEQ ID NO: 235; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 244; SEQ ID NO: 245; and SEQ ID NO: 246) of the light chain variable region of SEQ ID NO: 234; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 247; SEQ ID NO: 248; and SEQ ID NO: 249) of the heavy chain variable region of SEQ ID NO: 235.

[0816] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 250:

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ATGGAACACAGAGGCCCACACTGCTGGGCTTCTGCTCTCTGCT
TCCAGGGCTTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGT
CTGAGTGTGTCATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
GTTTATGAGCCAGATCTTATGTCTAGTTAGTACGCTCTAGTTAG
TGAAGATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
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[0817] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 251:

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ATGGAACACAGAGGCCCACACTGCTGGGCTTCTGCTCTCTGCT
TCCAGGGCTTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGTCCAGT
CTGAGTGTGTCATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
GTTTATGAGCCAGATCTTATGTCTAGTTAGTACGCTCTAGTTAG
TGAAGATGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTGCTGTG
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[0818] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 260; SEQ ID NO: 261; and SEQ ID NO: 262 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 250.

[0819] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 263; SEQ ID NO: 264; and SEQ ID NO: 265 which corre-
spond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 251. 

[0820] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide sequences encoding antibody fragments: the polynucleotide SEQ ID NO: 258 encoding the light chain variable region of SEQ ID NO: 250; the polynucleotide SEQ ID NO: 259 encoding the heavy chain variable region of SEQ ID NO: 251; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 260; SEQ ID NO: 261; and SEQ ID NO: 262) of the light chain variable region of SEQ ID NO: 250; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 263; SEQ ID NO: 264; and SEQ ID NO: 265) of the heavy chain variable region of SEQ ID NO: 251. 

[0821] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 266:

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ATGGAACACGAGGGGGCCCCCACCTCAGCTGGGCTCCTGCTTCATGGCT
CCCGAGTTCACACATCCACAGGGCTGACCGCGCTCTGCTCTGCTCTGCT
CTGGCCCTCGGGAGCGAGCTTAGACACCATCATGGGGTCGAGTCAAGAT
GTTTAACACGACACAAAATATGCGGTATCGACGCGAAGTACGGAGCC
TCGCAAGCTCGTACATACGAGGCGACACTCGCTCGTTGGGCTCTGCT
CGAGGCAACGAGGGGGCCACGGGCAACACTTACCTACTGCTGGGCTCTGCT
GATGAGCTGATATGCT.
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[0822] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 267:

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ATGGAACACGAGGGGGCCCCCACCTCAGCTGGGCTCCTGCTTCATGGCT
CCCGAGTTCACACATCCACAGGGCTGACCGCGCTCTGCTCTGCTCTGCT
CTGGCCCTCGGGAGCGAGCTTAGACACCATCATGGGGTCGAGTCAAGAT
GTTTAACACGACACAAAATATGCGGTATCGACGCGAAGTACGGAGCC
TCGCAAGCTCGTACATACGAGGCGACACTCGCTCGTTGGGCTCTGCT
GATGAGCTGATATGCT.
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[0823] In a further embodiment of the invention, polynucleotides encoding polypeptides of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 276; SEQ ID NO: 277; and SEQ ID NO: 278 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 266. 

[0824] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 279; SEQ ID NO: 280; and SEQ ID NO: 281 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 267. 

[0825] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide sequences encoding antibody fragments: the polynucleotide SEQ ID NO: 274 encoding the light chain variable region of SEQ ID NO: 266; the polynucleotide SEQ ID NO: 275 encoding the heavy chain variable region of SEQ ID NO: 267; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 276; SEQ ID NO: 277; and SEQ ID NO: 278) of the light chain variable region of SEQ ID NO: 266; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 282; and SEQ ID NO: 282) of the heavy chain variable region of SEQ ID NO: 267. 

[0826] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 282:

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ATGGAACACGAGGGGGCCCCCACCTCAGCTGGGCTCCTGCTTCATGGCT
CCCGAGTTCACACATCCACAGGGCTGACCGCGCTCTGCTCTGCTCTGCT
CTGGCCCTCGGGAGCGAGCTTAGACACCATCATGGGGTCGAGTCAAGAT
GTTTAACACGACACAAAATATGCGGTATCGACGCGAAGTACGGAGCC
TCGCAAGCTCGTACATACGAGGCGACACTCGCTCGTTGGGCTCTGCT
GATGAGCTGATATGCT.
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[0827] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 283:

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ATGGAACACGAGGGGGCCCCCACCTCAGCTGGGCTCCTGCTTCATGGCT
CCCGAGTTCACACATCCACAGGGCTGACCGCGCTCTGCTCTGCTCTGCT
CTGGCCCTCGGGAGCGAGCTTAGACACCATCATGGGGTCGAGTCAAGAT
GTTTAACACGACACAAAATATGCGGTATCGACGCGAAGTACGGAGCC
TCGCAAGCTCGTACATACGAGGCGACACTCGCTCGTTGGGCTCTGCT
GATGAGCTGATATGCT.
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[0828] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 284:
In another embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 292; SEQ ID NO: 293; and SEQ ID NO: 294 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 282.

In another embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 295; SEQ ID NO: 296; and SEQ ID NO: 297 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 283.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 290 encoding the light chain variable region of SEQ ID NO: 282; the polynucleotide SEQ ID NO: 291 encoding the heavy chain variable region of SEQ ID NO: 283; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 292; SEQ ID NO: 293; and SEQ ID NO: 294) of the light chain variable region of SEQ ID NO: 282; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 295; SEQ ID NO: 296; and SEQ ID NO: 297) of the heavy chain variable region of SEQ ID NO: 283.

The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 298:

In another embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 307; SEQ ID NO: 308; and SEQ ID NO: 310 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 298.

In another embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 308; SEQ ID NO: 309; and SEQ ID NO: 310 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 299.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 306 encoding the light chain variable region of SEQ ID NO: 289; the polynucleotide SEQ ID NO: 307 encoding the heavy chain variable region of SEQ ID NO: 290; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 308; SEQ ID NO: 309; and SEQ ID NO: 310) of the light chain variable region of SEQ ID NO: 298; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 311; SEQ ID NO: 312; and SEQ ID NO: 313) of the heavy chain variable region of SEQ ID NO: 299.

The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 314:
[0837] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 315:

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AAGAAGACTGGGCTGCGCTGGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT
CCGGTTGCTGCGCTGGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT
CCGGTTGCTGCGCTGGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT
TCTTTATGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT

[0838] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 324; SEQ ID NO: 325; and SEQ ID NO: 326 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 314.

[0839] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 327; SEQ ID NO: 328; and SEQ ID NO: 329 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 315.

[0840] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three, or more, including all of the following polynucleotide encoding antibody fragments: the polynucleotide SEQ ID NO: 322 encoding the light chain variable region of SEQ ID NO: 314; the polynucleotide SEQ ID NO: 323 encoding the heavy chain variable region of SEQ ID NO: 315; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 324; SEQ ID NO: 325; and SEQ ID NO: 326) of the light chain variable region of SEQ ID NO: 314; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 327; SEQ ID NO: 328; and SEQ ID NO: 329) of the heavy chain variable region of SEQ ID NO: 315.

[0841] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 330:

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AAGAAGACCAAGGGCCCATGCACGCTCGGCTGCCTGCTGCTGGTCTCTGAAAGTTGT
CCGGTTGCTGCGCTGGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT
CCGGTTGCTGCGCTGGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT
TCTTTATGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT

[0842] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 331:

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AAGAAGACCAAGGGCCCATGCACGCTCGGCTGCCTGCTGCTGGTCTCTGAAAGTTGT
CCGGTTGCTGCGCTGGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT
CCGGTTGCTGCGCTGGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT
TCTTTATGTCTTTCTCTGGCTGCTGGTCTCTGAAAGTTGT

[0843] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 340; SEQ ID NO: 341; and SEQ ID NO: 342 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 330.

[0844] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 343; SEQ ID NO: 344; and SEQ ID NO: 345 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 331.

[0845] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotide encoding anti-
body fragments: the polynucleotide SEQ ID NO: 338 encoding the light chain variable region of SEQ ID NO: 330; the polynucleotide SEQ ID NO: 339 encoding the heavy chain variable region of SEQ ID NO: 331; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 340; SEQ ID NO: 341; and SEQ ID NO: 342) of the light chain variable region of SEQ ID NO: 330; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 343; SEQ ID NO: 344; and SEQ ID NO: 345) of the heavy chain variable region of SEQ ID NO: 331.

[0846] The invention is further directed to polynucleotides encoding peptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 346:

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(ATGGACACAGGAGCCCACCTACACGTCGCGCTCCCTCCTCTTGCTTCTGCTTCTGCT)
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[0847] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 347:

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(ATGGACACAGGAGCCCACCTACACGTCGCGCTCCCTCCTCTTGCTTCTGCTTCTGCT
CCAGTCAGTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCT
GGAGCTGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCT
TGTCAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTG
TAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAG
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[0848] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 356; SEQ ID NO: 357; and SEQ ID NO: 358 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 346.

[0849] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 359; SEQ ID NO: 360; and SEQ ID NO: 361 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 347.

[0850] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 354 encoding the light chain variable region of SEQ ID NO: 346; the polynucleotide SEQ ID NO: 355 encoding the heavy chain variable region of SEQ ID NO: 347; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 356; SEQ ID NO: 357; and SEQ ID NO: 358) of the light chain variable region of SEQ ID NO: 346; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 359; SEQ ID NO: 360; and SEQ ID NO: 361) of the heavy chain variable region of SEQ ID NO: 347.

[0851] The invention is further directed to polynucleotides encoding peptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 362:

```
(ZHGCACAGGAGCCCACCTACACGTCGCGCTCCCTCCTCTTGCTTCTGCTTCTGCT
CCAGTCAGTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCT
GGAGCTGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCT
TGTCAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTG
TAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAG
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[0852] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 363:

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(ZHGCACAGGAGCCCACCTACACGTCGCGCTCCCTCCTCTTGCTTCTGCTTCTGCT
CCAGTCAGTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCT
GGAGCTGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCTGGCT
TGTCAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTG
TAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAGTGAG
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[0853] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of,
one or more of the polynucleotide sequences of SEQ ID NO: 372; SEQ ID NO: 373; and SEQ ID NO: 374 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 362.

[0854] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 375; SEQ ID NO: 376; and SEQ ID NO: 377 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 363.

[0855] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, or three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 370 encoding the light chain variable region of SEQ ID NO: 362; the polynucleotide SEQ ID NO: 371 encoding the heavy chain variable region of SEQ ID NO: 363; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 372; SEQ ID NO: 373; and SEQ ID NO: 374) of the light chain variable region of SEQ ID NO: 362; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 375; SEQ ID NO: 376; and SEQ ID NO: 377) of the heavy chain variable region of SEQ ID NO: 363.

[0856] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 378:

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ATGCAACAGAGGCCCACACTGACTGGGGCTTCGCTGTCTGCTG
CCCAGTTGCTGAGATGTGACTCAATTGCGACCAAGGCACTCATGCTGAG
AGCAACGCTGAGGCAAGCCACAGCTGACGCCATCGATCCAGCG
ATGCAACAGAGGCCCACACTGACTGGGGCTTCGCTGTCTGCTG
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[0857] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 379:

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ATGGGAGACCTGGGCTGCTGCTGCTTCTCGCTGCTGCTGCTG
TCACTGGTCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG
GAGATCCCTCAGCTCTACTCACAGGACCCCGCTGCCGCTGCTGCC
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ATGCAACAGAGGCCCACACTGACTGGGGCTTCGCTGTCTGCTGCTG
CCCAGTTGCTGAGATGTGACTCAATTGCGACCAAGGCACTCATGCTGAG
AGCAACGCTGAGGCAAGCCACAGCTGACGCCATCGATCCAGCG
ATGCAACAGAGGCCCACACTGACTGGGGCTTCGCTGTCTGCTGCTG
```

[0858] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 388; SEQ ID NO: 389; and SEQ ID NO: 390 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 378.

[0859] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 391; SEQ ID NO: 392; and SEQ ID NO: 393 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 379.

[0860] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, or three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 386 encoding the light chain variable region of SEQ ID NO: 378; the polynucleotide SEQ ID NO: 387 encoding the heavy chain variable region of SEQ ID NO: 379; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 388; SEQ ID NO: 389; and SEQ ID NO: 390) of the light chain variable region of SEQ ID NO: 378; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 391; SEQ ID NO: 392; and SEQ ID NO: 393) of the heavy chain variable region of SEQ ID NO: 379.

[0861] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 394:
[0862] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 395:

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GGAGGAGCTCTGCTGGAGCAGCTCACATCAAGTGCCAGGGCAGTGAG
GATATTAGACTTATCGGATTCGCGGATACAAACGGGAGGCTTCG
GACACTCTCCGATCTCAACACTGACACTTCTTCTGAGTAGCT
GGATCTCGTGCAGATGCTGCAGCTGAGCTGACGATCATCTCGAG
GACAGAGTCCCCAGTACACCAACTGGGATGCTCGAGGACAGCTG
GACAGAGTCCCCAGTACACCAACTGGGATGCTCGAGGACAGCTG
CAGAAGAGGCTCTGCTGGAGCAGCTCACATCAAGTGCCAGGGCAGTGAG
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--continued

[0863] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 404; SEQ ID NO: 405; and SEQ ID NO: 406 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 394.

[0864] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 407; SEQ ID NO: 408; and SEQ ID NO: 409 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 395.

[0865] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 402 encoding the light chain variable region of SEQ ID NO: 394; the polynucleotide SEQ ID NO: 403 encoding the heavy chain variable region of SEQ ID NO: 395; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 404; SEQ ID NO: 405; and SEQ ID NO: 406) of the light chain variable region of SEQ ID NO: 394; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 407; SEQ ID NO: 408; and SEQ ID NO: 409) of the heavy chain variable region of SEQ ID NO: 395.

[0866] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 410:

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ATGGAAGAGCTCTGCTGGAGCAGCTCACATCAAGTGCCAG
GATATTAGACTTATCGGATTCGCGGATACAAACGGGAGGCTTC
GACACTCTCCGATCTCAACACTGACACTTCTTCTGAGTAGCT
GGATCTCGTGCAGATGCTGCAGCTGAGCTGACGATCATCTCGAG
GACAGAGTCCCCAGTACACCAACTGGGATGCTCGAGGACAGCTG
GACAGAGTCCCCAGTACACCAACTGGGATGCTCGAGGACAGCTG
CAGAAGAGGCTCTGCTGGAGCAGCTCACATCAAGTGCCAGGGCAGTGAG
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--continued
The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 426:

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TCCAGGCTGGTGCACTACCTGCTCTGGTCTGGGCTCTG
GCTGGACGTCAGCTGAGGAGGACAGACCTCAGTGGCTGG
CACATGGAAACTATGACTCTGGTACAGAGAACAGGCGAC
CAGTTCCATCTCTCCATCTCAGTACTAGGAC
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[0872] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 427:

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ATCGGACACTGGGTGGGGCGCTCTGGTCTGGGCTCTG
GTCGAGGTCGCTGAGGAGGACAGACCTCAGTGGCTGG
CACATGGAAACTATGACTCTGGTACAGAGAACAGGCGAC
CAGTTCCATCTCTCCATCTCAGTACTAGGAC
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[0873] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 436; SEQ ID NO: 437; and SEQ ID NO: 438 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 426.

[0874] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 439; SEQ ID NO: 440; and SEQ ID NO: 441 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 427.

[0875] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 434 encoding the light chain variable region of SEQ ID NO: 426; the polynucleotide SEQ ID NO: 435 encoding the heavy chain variable region of SEQ ID NO: 427; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 436; SEQ ID NO: 437; and SEQ ID NO: 438) of the light chain variable region of SEQ ID NO: 426; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 439; SEQ ID NO: 440; and SEQ ID NO: 441) of the heavy chain variable region of SEQ ID NO: 427.

[0876] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 442:

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TCCAGGCTGGTGCACTACCTGCTCTGGTCTGGGCTCTG
GCTGGACGTCAGCTGAGGAGGACAGACCTCAGTGGCTGG
CACATGGAAACTATGACTCTGGTACAGAGAACAGGCGAC
CAGTTCCATCTCTCCATCTCAGTACTAGGAC
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[0877] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 443:

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ATCGGACACTGGGTGGGGCGCTCTGGTCTGGGCTCTG
GTCGAGGTCGCTGAGGAGGACAGACCTCAGTGGCTGG
CACATGGAAACTATGACTCTGGTACAGAGAACAGGCGAC
CAGTTCCATCTCTCCATCTCAGTACTAGGAC
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[0878] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 452; SEQ ID NO: 453; and SEQ ID NO: 454 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 442.

[0879] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 455; SEQ ID NO: 456; and SEQ ID NO: 457 which corre-
spond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 443.

[0880] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 450 encoding the light chain variable region of SEQ ID NO: 442; the polynucleotide SEQ ID NO: 451 encoding the heavy chain variable region of SEQ ID NO: 443; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 452; SEQ ID NO: 453; and SEQ ID NO: 454) of the light chain variable region of SEQ ID NO: 442; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 455; SEQ ID NO: 456; and SEQ ID NO: 457) of the heavy chain variable region of SEQ ID NO: 443.

[0881] The invention is further directed to polynucleotides encoding epitopes of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 458:

... (SEQ ID NO: 466)
ATGGACACGAGGGCCCCTCCTGCGGCCTCTGCTCTGCTC
TCCCGACCTGCACTTTGCCGCTGCTGACACACTCCATCCCTCCGT
GTGCAGCTGCGCTCTGGAGGCAAATCGGACTCATGCTCCATGCA
AGTGTATAATAACACTACTGCCATCTGCTGCTCAGGAGGACAGGGGC
AGCCGCTCAAGCTGCTTCTACAGGCATACCCGACTCTGGAGTGGT
CCCTCACGCTTGGGAAGCGCAGTGGATCTGACGGACGCTACTCTCAC
ATAGACGAGCTGAGTGGAGGCTGAGTGACCCTACTACTGCTGGGCGC
GTTATCTTGATAGTGTATT.

[0882] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 459:

... (SEQ ID NO: 467)
ATGGAGAAGCTGCGGCTGCGCTCTCTCCGCTCTGCTCTGCTC
TCAGCTGAGCTGAGGAGATCCTGGGCTCCCTGCTCCGAGCTGG
GACCCGCTGACACTCCAGCTGACACTCTGCAGATTCCCTTCCTAGAC
TCTACAGTCATCTGGCCACTCCGAGGAGGCCCTGCTGATGGAG
TCAGAAGCTACCTGAGTAAGTCTGACACATTCTGACGCCAATGGGAA
AGGCCGATTCACCTCGTCCAAAACTCCAGCCACAGCTGATGAAAACTC
ACAGAGCTGCAACGGGAGCAGCGCCACACTTTTCTGTCGGCGAGAGA
GTTGAAGTCAACTGATATGTGAAATTTTACATCACT.

[0883] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 468; SEQ ID NO: 469; and SEQ ID NO: 470 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 458.

[0884] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 471; SEQ ID NO: 472; and SEQ ID NO: 473 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 459.

[0885] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 466 encoding the light chain variable region of SEQ ID NO: 458; the polynucleotide SEQ ID NO: 467 encoding the heavy chain variable region of SEQ ID NO: 459; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 468; SEQ ID NO: 469; and SEQ ID NO: 470) of the light chain variable region of SEQ ID NO: 458; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 471; SEQ ID NO: 472; and SEQ ID NO: 473) of the heavy chain variable region of SEQ ID NO: 459.

[0886] The invention is further directed to polynucleotides encoding epitopes of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 474:

... (SEQ ID NO: 482)
ATGGACACGAGGGCCCCTCCTGCGGCCTCTGCTCTGCTC
TCCCGACCTGCACTTTGCCGCTGCTGACACACTCCATCCCTCCGT
GTGCAGCTGCGCTCTGGAGGCAAATCGGACTCATGCTCCATGCA
AGTGTATAATAACACTACTGCCATCTGCTGCTCAGGAGGACAGGGGC
AGCCGCTCAAGCTGCTTCTACAGGCATACCCGACTCTGGAGTGGT
CCCTCACGCTTGGGAAGCGCAGTGGATCTGACGGACGCTACTCTCAC
ATAGACGAGCTGAGTGGAGGCTGAGTGACCCTACTACTGCTGGGCGC
GTTATCTTGATAGTGTATT.

[0887] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 475:

... (SEQ ID NO: 493)
ATGGAGAAGCTGCGGCTGCGCTCTCTCCGCTCTGCTCTGCTC
TCAGCTGAGCTGAGGAGATCCTGGGCTCCCTGCTCCGAGCTGG
GACCCGCTGACACTCCAGCTGACACTCTGCAGATTCCCTTCCTAGAC
TCTACAGTCATCTGGCCACTCCGAGGAGGCCCTGCTGATGGAG
TCAGAAGCTACCTGAGTAAGTCTGACACATTCTGACGCCAATGGGAA
AGGCCGATTCACCTCGTCCAAAACTCCAGCCACAGCTGATGAAAACTC
ACAGAGCTGCAACGGGAGCAGCGCCACACTTTTCTGTCGGCGAGAGA
GTTGAAGTCAACTGATATGTGAAATTTTACATCACT.

[0888] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of,
[0888] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 484; SEQ ID NO: 485; and SEQ ID NO: 486 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 474.

[0889] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, the polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 482 encoding the light chain variable region of SEQ ID NO: 474; the polynucleotide SEQ ID NO: 483 encoding the heavy chain variable region of SEQ ID NO: 475; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 484; SEQ ID NO: 485; and SEQ ID NO: 486) of the light chain variable region of SEQ ID NO: 474; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 487; SEQ ID NO: 488; and SEQ ID NO: 489) of the heavy chain variable region of SEQ ID NO: 475.

[0890] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, the polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 482 encoding the light chain variable region of SEQ ID NO: 474; the polynucleotide SEQ ID NO: 483 encoding the heavy chain variable region of SEQ ID NO: 475; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 484; SEQ ID NO: 485; and SEQ ID NO: 486) of the light chain variable region of SEQ ID NO: 474; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 487; SEQ ID NO: 488; and SEQ ID NO: 489) of the heavy chain variable region of SEQ ID NO: 475.

[0891] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 490:

ATGGAACAGAGGGCCCTCCACTACGCTTGAGCCCTTGGGCTACTTGGAGCTTGCC
TCCAGGGTTCGAGGCAGATGGGCTCTGCTATGACTCCATTCCATCTCCCTGGTT
GTCGACGTTGCTGAGCACTGGTACACATCAGCTCAGCCATTGAGGCGATCAGG
ACCATTTATACCTTTACGGCCCTGATCAGGACCAAAACAGGGGAGGCGCTC
CCAGGTCCTCATCTTCCAGGGCCACTCGCTGCTGGGGCTGCTCATCCCTG
GCAGTTCAAGGACAGTGAGCTCAACCATCTCACCACACAGAGGCTCTG
GACTCGATGATATGATAAAATAT

[0892] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 491:

ATGGAACAGAGGGCCCTCCACTACGCTTGAGCCCTTGGGCTACTTGGAGCTTGCC
TCCAGGGTTCGAGGCAGATGGGCTCTGCTATGACTCCATTCCATCTCCCTGGTT
GTCGACGTTGCTGAGCACTGGTACACATCAGCTCAGCCATTGAGGCGATCAGG
ACCATTTATACCTTTACGGCCCTGATCAGGACCAAAACAGGGGAGGCGCTC
CCAGGTCCTCATCTTCCAGGGCCACTCGCTGCTGGGGCTGCTCATCCCTG
GCAGTTCAAGGACAGTGAGCTCAACCATCTCACCACACAGAGGCTCTG
GACTCGATGATATGATAAAATAT

[0893] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 500; SEQ ID NO: 501; and SEQ ID NO: 502 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 490.

[0894] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 503; SEQ ID NO: 504; and SEQ ID NO: 505 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 491.

[0895] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 498 encoding the light chain variable region of SEQ ID NO: 490; the polynucleotide SEQ ID NO: 499 encoding the heavy chain variable region of SEQ ID NO: 491; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 500; SEQ ID NO: 501; and SEQ ID NO: 502) of the light chain variable region of SEQ ID NO: 490; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 503; SEQ ID NO: 504; and SEQ ID NO: 505) of the heavy chain variable region of SEQ ID NO: 491.

[0896] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, the polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 506:

ATGGAACAGAGGGCCCTCCACTACGCTTGAGCCCTTGGGCTACTTGGAGCTTGCC
TCCAGGGTTCGAGGCAGATGGGCTCTGCTATGACTCCATTCCATCTCCCTGGTT
GTCGACGTTGCTGAGCACTGGTACACATCAGCTCAGCCATTGAGGCGATCAGG
ACCATTTATACCTTTACGGCCCTGATCAGGACCAAAACAGGGGAGGCGCTC
CCAGGTCCTCATCTTCCAGGGCCACTCGCTGCTGGGGCTGCTCATCCCTG
GCAGTTCAAGGACAGTGAGCTCAACCATCTCACCACACAGAGGCTCTG
GACTCGATGATATGATAAAATAT
[0897] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 507:

[0898] In a further embodiment of the invention, the polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 516; SEQ ID NO: 517; and SEQ ID NO: 518 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 506.

[0899] In another embodiment of the invention, the polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 519; SEQ ID NO: 520; and SEQ ID NO: 521 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 507.

[0900] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 514 encoding the light chain variable region of SEQ ID NO: 506; the polynucleotide SEQ ID NO: 515 encoding the heavy chain variable region of SEQ ID NO: 507; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 516; SEQ ID NO: 517; and SEQ ID NO: 518) of the light chain variable region of SEQ ID NO: 506; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 519; SEQ ID NO: 520; and SEQ ID NO: 521) of the heavy chain variable region of SEQ ID NO: 507.

[0901] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 522:

[0902] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 523:

[0903] In a further embodiment of the invention, the polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 532; SEQ ID NO: 533; and SEQ ID NO: 534 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 522.

[0904] In a further embodiment of the invention, the polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 535; SEQ ID NO: 536; and SEQ ID NO: 537 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs), or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 523.

[0905] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 514 encoding the light chain variable region of SEQ ID NO: 506; the polynucleotide SEQ ID NO: 515 encoding the heavy chain variable region of SEQ ID NO: 507; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 516; SEQ ID NO: 517; and SEQ ID NO: 518) of the light chain variable region of SEQ ID NO: 506; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 519; SEQ ID NO: 520; and SEQ ID NO: 521) of the heavy chain variable region of SEQ ID NO: 507.
body fragments: the polynucleotide SEQ ID NO: 530 encoding the light chain variable region of SEQ ID NO: 522; the polynucleotide SEQ ID NO: 531 encoding the heavy chain variable region of SEQ ID NO: 523; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 552; SEQ ID NO: 553; and SEQ ID NO: 534) of the light chain variable region of SEQ ID NO: 522; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 535; SEQ ID NO: 556; and SEQ ID NO: 557) of the heavy chain variable region of SEQ ID NO: 523.

[0906] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 538:

ATGKACACGAGGCCCGACCTACTGCGGCGCCTTCTGCTGCTGGC
TCCACAGGCGCAGTCGTCGATAGTGGCGACGAGTTCTGGTCAGAGG
GCTCTGCCATCGTCTAGATACAGCTGCGCAGAGCTGTCTGCTGGC
CCATCAGCAGCGCAGACAGTCTGCTGGTCTACTTCTGCAAGCT
ATGATATGGGCTGATTATTGAT.

[0907] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 539:

ATGKACACGAGGCCCGACCTACTGCGGCGCCTTCTGCTGCTGGC
TCCACAGGCGCAGTCGTCGATAGTGGCGACGAGTTCTGGTCAGAGG
GCTCTGCCATCGTCTAGATACAGCTGCGCAGAGCTGTCTGCTGGC
CCATCAGCAGCGCAGACAGTCTGCTGGTCTACTTCTGCAAGCT
ATGATATGGGCTGATTATTGAT.

[0908] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 548; SEQ ID NO: 549; and SEQ ID NO: 550 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 538.

[0909] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 551; SEQ ID NO: 552; and SEQ ID NO: 553 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 539.

[0910] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 546 encoding the light chain variable region of SEQ ID NO: 538; the polynucleotide SEQ ID NO: 547 encoding the heavy chain variable region of SEQ ID NO: 539; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 548; SEQ ID NO: 549; and SEQ ID NO: 550) of the light chain variable region of SEQ ID NO: 538; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 551; SEQ ID NO: 552; and SEQ ID NO: 553) of the heavy chain variable region of SEQ ID NO: 539.

[0911] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 554:

ATGKACACGAGGCCCGACCTACTGCGGCGCCTTCTGCTGCTGGC
TCCACAGGCGCAGTCGTCGATAGTGGCGACGAGTTCTGGTCAGAGG
GCTCTGCCATCGTCTAGATACAGCTGCGCAGAGCTGTCTGCTGGC
CCATCAGCAGCGCAGACAGTCTGCTGGTCTACTTCTGCAAGCT
ATGATATGGGCTGATTATTGAT.

[0912] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 555:

ATGKACACGAGGCCCGACCTACTGCGGCGCCTTCTGCTGCTGGC
TCCACAGGCGCAGTCGTCGATAGTGGCGACGAGTTCTGGTCAGAGG
GCTCTGCCATCGTCTAGATACAGCTGCGCAGAGCTGTCTGCTGGC
CCATCAGCAGCGCAGACAGTCTGCTGGTCTACTTCTGCAAGCT
ATGATATGGGCTGATTATTGAT.

[0913] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of,

In one embodiment, the invention is directed to an isolated polynucletide comprising a polynucletide encoding an anti-IL-6 V_{△} antibody amino acid sequence selected from SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 151, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 652, 656, 657, 658, 661, 664, 665, 668, 672, 676, 680, 684, 688, 691, 692, 704, or 708 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_{△} polypeptide or a conservative amino acid substitution.

In another embodiment, the invention is directed to an isolated polynucletide comprising a polynucletide sequence encoding an anti-IL-6 V_{△} antibody amino acid sequence of SEQ ID NO: 2, 20, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or 709 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_{△} polypeptide or a conservative amino acid substitution.

In yet another embodiment, the invention is directed to one or more heterologous polynucleotides comprising a sequence encoding the polypeptides contained in SEQ ID NO: 2 and SEQ ID NO: 3; SEQ ID NO: 2 and SEQ ID NO: 18; SEQ ID NO: 2 and SEQ ID NO: 19; SEQ ID NO: 20 and SEQ ID NO: 3; SEQ ID NO: 20 and SEQ ID NO: 18; SEQ ID NO: 20 and SEQ ID NO: 19; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 69 and SEQ ID NO: 70; SEQ ID NO: 85 and SEQ ID NO: 86; SEQ ID NO: 101 and SEQ ID NO: 102; SEQ ID NO: 101 and SEQ ID NO: 117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 120; SEQ ID NO: 119 and SEQ ID NO: 117; SEQ ID NO: 119 and SEQ ID NO: 118; SEQ ID NO: 122 and SEQ ID NO: 123; SEQ ID NO: 138 and SEQ ID NO: 139; SEQ ID NO: 154 and SEQ ID NO: 155; SEQ ID NO: 170 and SEQ ID NO: 171; SEQ ID NO: 186 and SEQ ID NO: 187; SEQ ID NO: 202 and SEQ ID NO: 203; SEQ ID NO: 218 and SEQ ID NO: 219; SEQ ID NO: 234 and SEQ ID NO: 235; SEQ ID NO: 250 and SEQ ID NO: 251; SEQ ID NO: 266 and SEQ ID NO: 267; SEQ ID NO: 282 and SEQ ID NO: 283; SEQ ID NO: 298 and SEQ ID NO: 299; SEQ ID NO: 314 and SEQ ID NO: 315; SEQ ID NO: 330 and SEQ ID NO: 331; SEQ ID NO: 346 and SEQ ID NO: 347; SEQ ID NO: 362 and SEQ ID NO: 363; SEQ ID NO: 378 and SEQ ID NO: 379; SEQ ID NO: 394 and SEQ ID NO: 395; SEQ ID NO: 410 and SEQ ID NO: 411; SEQ ID NO: 426 and SEQ ID NO: 427; SEQ ID NO: 442 and SEQ ID NO: 443; SEQ ID NO: 458 and SEQ ID NO: 459; SEQ ID
NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571.

[0928] In another embodiment, the invention is directed to an isolated polynucleotide that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said expressed polypeptide alone specifically binds IL-6 or specifically binds IL-6 when expressed in association with another polynucleotide sequence that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said at least one CDR is selected from those contained in the V\textsubscript{i}, or V\textsubscript{j} polypeptides contained in SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 652, 656, 657, 658, 66, 664, 665, 668, 672, 676, 680, 684, 688, 691, 692, 704, 708, 708, 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 695, 702, 706, or 709. Exemplary nucleic acid sequence encoding the VH and VL polypeptides SEQ ID NO:657 and SEQ ID NO:709 are comprised in SEQ ID NO:700 and SEQ ID NO:723 respectively.

[0929] Host cells and vectors comprising said polynucleotides are also contemplated.

[0930] In another specific embodiment the invention covers nucleic acid constructs containing any of the foregoing nucleic acid sequences and combinations thereof as well as recombinant cells containing these nucleic acid sequences and constructs containing wherein these nucleic acid sequences or constructs may be extrachromosomal or integrated into the host cell genome.

[0931] The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarily determining regions (CDRs, or hypertargetable variants) set forth herein, as well as host cells comprising said sequences. In one embodiment of the invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus *Pichia*.

[0932] In some instances, more than one exemplary polynucleotide encoding a given polypeptide sequence is provided, as summarized in Table 3.

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<tr>
<th>Polypeptide</th>
<th>Exemplary coding</th>
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[0933] In some instances, multiple sequence identifiers refer to the same polypeptide or polynucleotide sequence, as summarized in Table 4. References to these sequence identifiers are understood to be interchangeable, except where context indicates otherwise.

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[0934] Certain exemplary embodiments include polynucleotides that hybridize under moderately or highly stringent hybridization conditions to a polynucleotide having one of the exemplary coding sequences recited in Table 1, and also include polynucleotides that hybridize under moderately or highly stringent hybridization conditions to a polynucleotide encoding the same polypeptide as a polynucleotide having one of the exemplary coding sequences recited in Table 1, or polypeptide encoded by any of the foregoing polynucleotides.

[0935] The phrase “high stringency hybridization conditions” refers to conditions under which a probe will hybridize to its target sequence, typically in a complex mixture of nucleic acid, but to no other sequences. High stringency conditions are sequence dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Techniques in Biochemistry and Molecular Biology—Hybridization with Nucleic Probes, “Overview of principles of hybridization and the strategy of nucleic acid assays” (1993). Generally, high stringency conditions are selected to be about 5-10°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength p[. The Tm is the temperature (under defined ionic strength, pH, and nucleic concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at Tm, 50% of the probes are occupied at equilibrium). High stringency conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g., 10 to 50 nucleotides) and at least about 60°C for long probes (e.g., greater than 50 nucleotides). High stringency conditions may also be achieved with the addition of destabilizing agents such as formamide. For selective or specific hybridization, a positive signal is at least two times background, optionally 10 times background hybridization. Exemplary high stringency hybridization conditions can be as following: 50% formamide, 5xSSC, and 1% SDS, incubating at 42°C, or, 5xSSC, 1% SDS, incubating at 65°C, with wash in 0.2xSSC, and 0.1% SDS at 65°C. Such hybridizations and wash steps can be carried out for, e.g., 1, 2, 5, 10, 15, 30, 60; or more minutes.

[0936] Nucleic acids that do not hybridize to each other under high stringency conditions are still substantially related if the polypeptides that they encode are substantially related. This occurs, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. In such cases, the nucleic acids typically hybridize under moderate stringency hybridization conditions. Exemplary “moderate stringency hybridization conditions” include a hybridization in a buffer of 40% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 1xSSC at 45°C. Such hybridizations and wash steps can be carried out for, e.g., 1, 2, 5, 10, 15, 30, 60, or more minutes. A positive hybridization is at least twice background. Those of ordinary skill will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of similar stringency.

Exemplary Embodiments of Heavy and Light Chain Polypeptides and Polynucleotides

[0937] This section recites exemplary embodiments of heavy and light chain polypeptides, as well as exemplary polynucleotides encoding such polypeptides. These exemplary polynucleotides are suitable for expression in the disclosed Pichia expression system.

[0938] In certain embodiments, the present invention encompasses polynucleotides having at least 70%, such as at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the polynucleotides recited in this application or that encode polypeptides recited in this application, or that hybridize to said polynucleotides under conditions of low-stringency, moderate-stringency, or high-stringency conditions, preferably those that encode polypeptides (e.g. an immunoglobulin heavy and light chain, a single-chain antibody, an antibody fragment, etc.) that have at least one of the biological activities set forth herein, including without limitation thereto specific binding to an IL-6 polypeptide. In another aspect, the invention encompasses a composition comprising such a polynucleotide and/or a polypeptide encoded by such a polynucleotide. In yet another aspect, the invention encompasses a method of treatment of a disease or condition associated with IL-6 or that may be prevented, treated, or ameliorated with an IL-6 antagonist such as Abl (e.g. cachexia, cancer fatigue, arthritis, etc.) comprising administration of a composition comprising such a polynucleotide and/or polypeptide.

[0939] In certain preferred embodiments, a heavy chain polypeptide will comprise one or more of the CDR sequences
of the heavy and/or light chain polypeptides recited herein (including those contained in the heavy and light chain polypeptides recited herein) and one or more of the framework region polypeptides recited herein, including those depicted in FIGS. 2 and 34-37 or Table 1, and contained in the heavy and light chain polypeptide sequences recited herein. In certain preferred embodiments, a heavy chain polypeptide will comprise one or more Framework 4 region sequences as depicted in FIGS. 2 and 34-37 or Table 1, or as contained in a heavy or light chain polypeptide recited herein.

[0940] In certain preferred embodiments, a light chain polypeptide will comprise one or more of the CDR sequences of the heavy and/or light chain polypeptides recited herein (including those contained in the heavy and light chain polypeptides recited herein) and one or more of the framework region polypeptides recited herein, including those depicted in FIGS. 2 and 34-37 or Table 1, and contained in the heavy and light chain polypeptide sequences recited herein. In certain preferred embodiments, a light chain polypeptide will comprise one or more Framework 4 region sequences as depicted in FIGS. 2 and 34-37 or Table 1, or as contained in a heavy or light chain polypeptide recited herein.

[0941] In any of the embodiments recited herein, certain of the sequences recited may be substituted for each other, unless the context indicates otherwise. The recitation that particular sequences may be substituted for one another, where such recitations are made, are understood to be illustrative rather than limiting, and it is also understood that such substitutions are encompassed even when no illustrative examples of substitutions are recited. For example, wherever one or more of the Ab1 light chain polypeptides is recited, e.g. any of SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709, another Ab1 light chain polypeptide may be substituted unless the context indicates otherwise. Similarly, wherever one of the Ab1 heavy chain polypeptides is recited, e.g. any of SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708, another Ab1 heavy chain polypeptide may be substituted unless the context indicates otherwise. Likewise, wherever one of the Ab1 light chain polynucleotides is recited, e.g. any of SEQ ID NO: 10, 662, 698, 701, or 705, another Ab1 light chain polynucleotide may be substituted unless the context indicates otherwise. Similarly, wherever one of the Ab1 heavy chain polynucleotides is recited, e.g. any of SEQ ID NO: 11, 663, 700, 703, or 707, another Ab1 heavy chain polynucleotide may be substituted unless the context indicates otherwise. Additionally, recitation of any member of any of the following groups is understood to encompass substitution by any other member of the group, as follows: Ab2 Light chain polypeptides (SEQ ID NO: 21 and 667); Ab2 Light chain polynucleotides (SEQ ID NO: 29 and 669); Ab2 Heavy chain polypeptides (SEQ ID NO: 22 and 668); Ab2 Heavy chain polynucleotides (SEQ ID NO: 30 and 670); Ab3 Light chain polypeptides (SEQ ID NO: 37 and 671); Ab3 Light chain polynucleotides (SEQ ID NO: 45 and 673); Ab3 Heavy chain polypeptides (SEQ ID NO: 38 and 672); Ab3 Heavy chain polynucleotides (SEQ ID NO: 46 and 674); Ab4 Light chain polypeptides (SEQ ID NO: 53 and 675); Ab4 Light chain polynucleotides (SEQ ID NO: 61 and 677); Ab4 Heavy chain polypeptides (SEQ ID NO: 54 and 676); Ab4 Heavy chain polynucleotides (SEQ ID NO: 62 and 678); Ab5 Light chain polypeptides (SEQ ID NO: 69 and 679); Ab5 Light chain polynucleotides (SEQ ID NO: 77 and 681); Ab5 Heavy chain polypeptides (SEQ ID NO: 70 and 680); Ab5 Heavy chain polynucleotides (SEQ ID NO: 78 and 682); Ab6 Light chain polypeptides (SEQ ID NO: 85 and 683); Ab6 Light chain polynucleotides (SEQ ID NO: 93 and 685); Ab6 Heavy chain polypeptides (SEQ ID NO: 86 and 684); Ab6 Heavy chain polynucleotides (SEQ ID NO: 94 and 686); Ab7 Light chain polypeptides (SEQ ID NO: 101, 119, 687, 693); Ab7 Light chain polynucleotides (SEQ ID NO: 109 and 689); Ab7 Heavy chain polypeptides (SEQ ID NO: 102, 117, 118, 688, 691, and 692); Ab7 Heavy chain polynucleotides (SEQ ID NO: 110 and 690); Ab1 Light Chain CDR1 polynucleotides (SEQ ID NO: 12 and 694); Ab1 Light Chain CDR3 polynucleotides (SEQ ID NO: 14 and 695); Ab1 Heavy Chain CDR2 polynucleotides (SEQ ID NO: 16 and 696) and Ab1 Heavy Chain CDR3 polynucleotides (SEQ ID NO: 17 and 697).

Anti-IL-6 Activity

[0942] As stated previously, IL-6 is a member of a family of cytokines that promote cellular responses through a receptor complex consisting of at least one subunit of the signal-transducing glycoprotein gp130 and the IL-6 receptor (IL-6R). The IL-6R may also be present in a soluble form (sIL-6R). IL-6 binds to IL-6R, which then dimerizes the signal-transducing receptor gp130.

[0943] It is believed that the anti-IL-6 antibodies of the invention, or IL-6 binding fragments thereof, are useful by exhibiting anti-IL-6 activity. In one non-limiting embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments thereof, exhibit anti-IL-6 activity by binding to IL-6 which may be soluble IL-6 or cell surface expressed IL-6 and/or may prevent or inhibit the binding of IL-6 to IL-6R and/or activation (dimerization) of the gp130 signal-transducing glycoprotein and the formation of IL-6/gp130 multimers and the biological effects of any of the foregoing. The subject anti-IL-6 antibodies may possess different antagonistic activities based on where (i.e., epitope) the particular antibody binds IL-6 and/or how it affects the formation of the foregoing IL-6 complexes and/or multimers and the biological effects thereof. Consequently, different anti-IL-6 antibodies according to the invention e.g., may be better suited for preventing or treating conditions involving the formation and accumulation of substantial soluble IL-6 such as rheumatoid arthritis whereas other antibodies may be favored in treatments wherein the prevention of IL-6/IL-6R/gp130 or IL-6/IL-6R/gp130 multimers is a desired therapeutic outcome. This can be determined in binding and other assays.

[0944] The anti-IL-6 activity of the anti-IL-6 antibody of the present invention, and fragments thereof having binding specificity to IL-6, may also be described by their strength of binding or their affinity for IL-6. This also may affect their therapeutic properties. In one embodiment of the invention, the anti-IL-6 antibodies of the present invention, and fragments thereof having binding specificity to IL-6, bind to IL-6 with a dissociation constant (Kd) of less than or equal to 5×10^-7, 10^-7, 5×10^-8, 10^-8, 5×10^-9, 10^-9, 5×10^-10, 10^-10, 5×10^-11, 10^-11, 5×10^-12, 10^-12, 5×10^-13, 10^-13, 5×10^-14, 10^-14, 5×10^-15 or 10^-15. Preferably, the anti-IL-6 antibodies and fragments thereof bind IL-6 with a dissociation constant of less than or equal to 5×10^-10.

[0945] In another embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments thereof having binding specificity to IL-6, bind to IL-6 with an off-rate of less than or equal to 10^-4 S^-1, 5×10^-5 S^-1, S^-1, 5×10^-6 S^-1, 10^-6 S^-1, 5×10^-7 S^-1, or 10^-7.
S−. In one embodiment of the invention, the anti-IL-6 antibodies of the invention, and fragments thereof having binding specificity to IL-6, bind to a linear or conformational IL-6 epitope.

[0946] In a further embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments thereof having binding specificity to IL-6, exhibit anti-IL-6 activity by ameliorating or reducing the symptoms of, or alternatively treating, or preventing, diseases and disorders associated with IL-6. Non-limiting examples of diseases and disorders associated with IL-6 are set forth infra. As noted cancer-related fatigue, cachexia and rheumatoid arthritis are preferred indications for the subject anti-IL-6 antibodies.

[0947] In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, do not have binding specificity for IL-6R or the gp-130 signal-transducing glycoprotein.

B-Cell Screening and Isolation

[0948] In one embodiment, the present invention provides methods of isolating a clonal population of antigen-specific B cells that may be used for isolating at least one antigen-specific cell. As described and exemplified infra, these methods contain a series of culture and selection steps that can be used separately, in combination, sequentially, repetitively, or periodically. Preferably, these methods are used for isolating at least one antigen-specific cell, which can be used to produce a monoclonal antibody, which is specific to a desired antigen, or a nucleic acid sequence corresponding to such an antibody.

[0949] In one embodiment, the present invention provides a method comprising the steps of:

[0950] a. preparing a cell population comprising at least one antigen-specific B cell;

[0951] b. enriching the cell population, e.g., by chromatography, to form an enriched cell population comprising at least one antigen-specific B cell;

[0952] c. isolating a single B cell from the enriched B cell population; and

[0953] d. determining whether the single B cell produces an antibody specific to the antigen.

[0954] In another embodiment, the present invention provides an improvement to a method of isolating a single antibody-producing B cell, the improvement comprising enriching a B cell population obtained from a host that has been immunized or naturally exposed to an antigen, wherein the enriching step precedes any selection steps, comprises at least one culturing step, and results in a clonal population of B cells that produces a single monoclonal antibody specific to said antigen.

[0955] Throughout this application, a “clonal population of B cells” refers to a population of B cells that only secrete a single antibody specific to a desired antigen. That is to say that these cells produce only one type of monoclonal antibody specific to the desired antigen.

[0956] In the present application, “enriching” a cell population means increasing the frequency of desired cells, typically antigen-specific cells, contained in a mixed cell population, e.g., a B cell-containing isolate derived from a host that is immunized against a desired antigen. Thus, an enriched cell population encompasses a cell population having a higher frequency of antigen-specific cells as a result of an enrichment step, but this population of cells may contain and produce different antibodies.

[0957] The general term “cell population” encompasses pre- and post-enrichment cell populations, keeping in mind that when multiple enrichment steps are performed, a cell population can be both pre- and post-enrichment. For example, in one embodiment, the present invention provides a method:

[0958] a. harvesting a cell population from an immunized host to obtain a harvested cell population;

[0959] b. creating at least one single cell suspension from the harvested cell population;

[0960] c. enriching at least one single cell suspension to form a first enriched cell population;

[0961] d. enriching the first enriched cell population to form a second enriched cell population;

[0962] e. enriching the second enriched cell population to form a third enriched cell population; and

[0963] f. selecting an antibody produced by an antigen-specific cell of the third enriched cell population.

[0964] Each cell population may be used directly in the next step, or it can be partially or wholly frozen for long- or short-term storage or for later steps. Also, cells from a cell population can be individually suspended to yield single cell suspensions. The single cell suspension can be enriched, such that a single cell suspension serves as the pre-enrichment cell population. Then, one or more antigen-specific single cell suspensions together form the enriched cell population; the antigen-specific single cell suspensions can be grouped together, e.g., re-plated for further analysis and/or antibody production.

[0965] In one embodiment, the present invention provides a method of enriching a cell population to yield an enriched cell population having an antigen-specific cell frequency that is about 50% to about 100%, or increments therein. Preferably, the enriched cell population has an antigen-specific cell frequency greater than or equal to about 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or 100%.

[0966] In another embodiment, the present invention provides a method of enriching a cell population whereby the frequency of antigen-specific cells is increased by at least about 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or increments therein.

[0967] Throughout this application, the term “increment” is used to define a numerical value in varying degrees of precision, e.g., to the nearest 10, 1, 0.1, 0.01, etc. The increment can be rounded to any measurable degree of precision, and the increment need not be rounded to the same degree of precision on both sides of a range. For example, the range 1 to 100 or increments therein includes ranges such as 20 to 80, 5 to 50, and 0.4 to 98. When a range is open-ended, e.g., a range of less than 100, increments therein means increments between 100 and the measurable limit. For example, less than 100 or increments therein means 0 to 100 or increments therein unless the feature, e.g., temperature, is not limited by 0.

[0968] Antigen-specificity can be measured with respect to any antigen. The antigen can be any substance to which an antibody can bind including, but not limited to, peptides, proteins or fragments thereof; carbohydrates; organic and inorganic molecules; receptors produced by animal cells, bacterial cells, and viruses; enzymes; agonists and antagonists of biological pathways; hormones; and cytokines. Exemplary antigens include, but are not limited to, IL-2, IL-4,
IL-6, IL-10, IL-12, IL-13, IL-18, IFN-α, IFN-γ, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF) and Hepcidin. Preferred antigens include IL-6, IL-13, TNF-α, VEGF-α, Hepatocyte Growth Factor (HGF) and Hepcidin. In a method utilizing more than one enrichment step, the antigen used in each enrichment step can be the same as or different from one another. Multiple enrichment steps with the same antigen may yield a large and/or diverse population of antigen-specific cells; multiple enrichment steps with different antigens may yield an enriched cell population with cross-specificity to the different antigens.

[0969] Enriching a cell population can be performed by any cell-selection means known in the art for isolating antigen-specific cells. For example, a cell population can be enriched by chromatographic techniques, e.g., Millenyi bead or magnetic bead technology. The beads can be directly or indirectly attached to the antigen of interest. In a preferred embodiment, the method of enriching a cell population includes at least one chromatographic enrichment step.

[0970] A cell population can also be enriched by performed by any antigen-specificity assay technique known in the art, e.g., an ELISA assay or a halo assay. ELISA assays include, but are not limited to, selective antigen immobilization (e.g., biotinylated antigen capture by streptavidin, avidin, or neutravidin coated plate), non-specific antigen plate coating, and through an antigen build-up strategy (e.g., selective antigen capture followed by binding partner addition to generate a heteromeric protein-antigen complex). The antigen can be directly or indirectly attached to a solid matrix or support, e.g., a column. A halo assay comprises contacting the cells with antigen-loaded beads and labeled anti-host antibody specific to the host used to harvest the B cells. The label can be, e.g., a fluorophore. In one embodiment, at least one assay enrichment step is performed on at least one single cell suspension. In another embodiment, the method of enriching a cell population includes at least one chromatographic enrichment step and at least one assay enrichment step.

[0971] Methods of “enriching” a cell population by size or density are known in the art. See, e.g., U.S. Pat. No. 5,627,052. These steps can be used in the present method in addition to enriching the cell population by antigen-specificity.

[0972] The cell populations of the present invention contain at least one cell capable of recognizing an antigen. Antigen-recognizing cells include, but are not limited to, B cells, plasma cells, and progeny thereof. In one embodiment, the present invention provides a clonal cell population containing a single type of antigen-specific B-cell, i.e., the cell population produces a single monoclonal antibody specific to a desired antigen.

[0973] In such embodiment, it is believed that the clonal antigen-specific population of B cells consists predominantly of antigen-specific, antibody-secreting cells, which are obtained by the novel culture and selection protocol provided herein. Accordingly, the present invention also provides methods for obtaining an enriched cell population containing at least one antigen-specific, antibody-secreting cell. In one embodiment, the present invention provides an enriched cell population containing about 50% to about 100%, or increments therein, or greater than or equal to about 60%, 70%, 80%, 90%, or 100% of antigen-specific, antibody-secreting cells.

[0974] In one embodiment, the present invention provides a method of isolating a single B cell by enriching a cell population obtained from a host before any selection steps, e.g., selecting a particular B cell from a cell population and/or selecting an antibody produced by a particular cell. The enrichment step can be performed as one, two, three, or more steps. In one embodiment, a single B cell is isolated from an enriched cell population before confirming whether the single B cell secretes an antibody with antigen-specificity and/or a desired property.

[0975] In one embodiment, a method of enriching a cell population is used in a method for antibody production and/or selection. Thus, the present invention provides a method comprising enriching a cell population before selecting an antibody. The method can include the steps of: preparing a cell population comprising at least one antigen-specific cell, enriching the cell population by isolating at least one antigen-specific cell to form an enriched cell population, and inducing antibody production from at least one antigen-specific cell. In a preferred embodiment, the enriched cell population contains more than one antigen-specific cell. In one embodiment, each antigen-specific cell of the enriched population is cultured under conditions that yield a clonal antigen-specific B cell population before isolating an antibody producing cell therefrom and/or producing an antibody using said B cell, or a nucleic acid sequence corresponding to such an antibody. In contrast to prior techniques where antibodies are produced from a cell population with a low frequency of antigen-specific cells, the present invention allows antibody selection from among a high frequency of antigen-specific cells. Because an enrichment step is used prior to antibody selection, the majority of the cells, preferably virtually all of the cells, used for antibody production are antigen-specific. By producing antibodies from a population of cells with an increased frequency of antigen specificity, the quantity and variety of antibodies are increased.

[0976] In the antibody selection methods of the present invention, an antibody is preferably selected after an enrichment step and a culture step that results in a clonal population of antigen-specific B cells. The methods can further comprise a step of sequencing a selected antibody or portions thereof from one or more isolated, antigen-specific cells. Any method known in the art for sequencing can be employed and can include sequencing the heavy chain, light chain, variable region(s), and/or complementarity determining region(s) (CDR).

[0977] In addition to the enrichment step, the method for antibody selection can also include one or more steps of screening a cell population for antigen recognition and/or antibody functionality. For example, the desired antibodies may have specific structural features, such as binding to a particular epitope or mimicry of a particular structure; an antagonist or agonist activity; or neutralizing activity, e.g., inhibiting binding between the antigen and a ligand. In one embodiment, the antibody functionality screen is ligand-dependent. Screening for antibody functionality includes, but is not limited to, an in vitro protein-protein interaction assay that recreates the natural interaction of the antigen ligand with recombinant receptor protein; and a cell-based response that is ligand dependent and easily monitored (e.g., proliferation response). In one embodiment, the method for antibody selection includes a step of screening the cell population for antibody functionality by measuring the inhibitory concentration (IC50). In one embodiment, at least one of the isolated,
antigen-specific cells produces an antibody having an IC50 of less than about 100, 50, 30, 25, 10 μg/mL, or increments therein.

[0978] In addition to the enrichment step, the method for antibody selection can also include one or more steps of screening a cell population for antibody binding strength. Antibody binding strength can be measured by any method known in the art (e.g., BiacoreTM). In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody having a high antigen affinity, e.g., a dissociation constant (Kd) of less than about 5x10-10 M-1, preferably about 1x10-13 to 5x10-10, 1x10-12 to 1x10-10, 1x10-12 to 7.5x10-11, 1x10-11 to 2x10-11, about 1.5x10-11 or less, or increments therein. In this embodiment, the antibodies are said to be affinity mature. In a preferred embodiment, the affinity of the antibodies is comparable to or higher than the affinity of any one of Panorex® (edrecolomab), Rituxan® (rituximab), Herceptin® (trastuzumab), Mylotarg® (gentuzumab), Campath® (alemtuzumab), ZevalinTM (ibrutinomab), ErbituxTM (cetuximab), AvastinTM (bevacizumab), RaptaTM (efalizumab), Remicade® (infliximab), HumiraTM (adalimumab), and Xolair® (omalizumab). Preferably, the affinity of the antibodies is comparable to or higher than the affinity of HumiraTM. The affinity of an antibody can also be increased by known affinity maturation techniques. In one embodiment, at least one cell population is screened for at least one, preferably both, antibody functionality and antibody binding strength.

[0979] In addition to the enrichment step, the method for antibody selection can also include one or more steps of screening a cell population for antibody sequence homology, especially human homology. In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody that has a homology to a human antibody of about 50% to about 100%, or increments therein, or greater than about 60%, 70%, 80%, 85%, 90%, or 95% homologous. The antibodies can be humanized to increase the homology to a human sequence by techniques known in the art such as CDR grafting or selectivity determining residue grafting (SDR).

[0980] In another embodiment, the present invention also provides the antibodies themselves according to any of the embodiments described above in terms of IC50, Kd, and/or homology.

[0981] The B cell selection protocol disclosed herein has a number of intrinsic advantages over other methods for obtaining antibody-secreting B cells and monoclonal antibodies specific to desired target antigens. These advantages include, but are not restricted to, the following:

[0982] First, it has been found that when these selection procedures are utilized with a desired antigen such as IL-6 or TNF-α, the methods reproducibly result in antigen-specific B cells capable of generating what appears to be a substantially comprehensive complement of antibodies, i.e., antibodies that bind to the various different epitopes of the antigen. Without being bound by theory, it is hypothesized that the comprehensive complement is attributable to the antigen enrichment step that is performed prior to initial B cell recovery. Moreover, this advantage allows for the isolation and selection of antibodies with different properties as these properties may vary depending on the epitopic specificity of the particular antibody.

[0983] Second, it has been found that the B cell selection protocol reproducibly yields a clonal B cell culture containing a single B cell, or its progeny, secreting a single monoclonal antibody that generally binds to the desired antigen with a relatively high binding affinity, i.e. picomolar or better antigen binding affinities. By contrast, prior antibody selection methods tend to yield relatively few high affinity antibodies and therefore require extensive screening procedures to isolate an antibody with therapeutic potential. Without being bound by theory, it is hypothesized that the protocol results in both in vivo B cell immunization of the host (primary immunization) followed by a second in vitro B cell stimulation (secondary antigen priming step) that may enhance the ability and propensity of the recovered clonal B cells to secrete a single high affinity monoclonal antibody specific to the antigen target.

[0984] Third, it has been observed (as shown herein with IL-6 specific B cells) that the B cell selection protocol reproducibly yields enriched B cells producing IgM’s that are, on average, highly selective (antigen specific) to the desired target. Antigen-enriched B cells recovered by these methods are believed to contain B cells capable of providing the desired full complement of epitope specificities as discussed above.

[0985] Fourth, it has been observed that the B cell selection protocols, even when used with small antigens, i.e., peptides of 100 amino acids or less, e.g., 5-50 amino acids long, reproducibly give rise to a clonal B cell culture that secretes a single high affinity antibody to the small antigen, e.g., a peptide. This is highly surprising as it is generally quite difficult, labor intensive, and sometimes not even feasible to produce high affinity antibodies to small peptides. Accordingly, the invention can be used to produce therapeutic antibodies to desired peptide targets, e.g., viral, bacterial or autoantigen peptides, thereby allowing for the production of monoclonal antibodies with very discrete binding properties or even the production of a cocktail of monoclonal antibodies to different peptide targets, e.g., different viral strains. This advantage may especially be useful in the context of the production of a therapeutic or prophylactic vaccine having a desired valency, such as an HPV vaccine that induces protective immunity to different HPV strains.

[0986] Fifth, the B cell selection protocol, particularly when used with B cells derived from rabbits, tends to reproducibly yield antigen-specific antibody sequences that are very similar to endogenous human immunoglobulins (around 90% similar at the amino acid level) and that contain CDRs that possess a length very analogous to human immunoglobulins and therefore require little or no sequence modification (typically at most only a few CDR residues may be modified in the parent antibody sequence and no framework exogenous residues introduced) in order to eliminate potential immunogenicity concerns. In particular, preferably the recombinant antibody will contain only the host (rabbit) CDR1 and CDR2 residues required for antigen recognition and the entire CDR3. Thereby, the high antigen binding affinity of the recovered antibody sequences produced according to the B cell and antibody selection protocol remains intact or substantially intact even with humanization.

[0987] In sum, these methods can be used to produce antibodies exhibiting higher binding affinities to more distinct epitopes by the use of a more efficient protocol than was previously known.

[0988] In a specific embodiment, the present invention provides a method for identifying a single B cell that secretes an antibody specific to a desired antigen and that optionally
possesses at least one desired functional property such as affinity, avidity, cytolytic activity, and the like by a process including the following steps:

- a. immunizing a host against an antigen;
- b. harvesting B cells from the host;
- c. enriching the harvested B cells to increase the frequency of antigen-specific cells;
- d. creating at least one single cell suspension;
- e. culturing a sub-population from the single cell suspension under conditions that favor the survival of a single antigen-specific B cell per culture well;
- f. isolating B cells from the sub-population; and
- g. determining whether the single B cell produces an antibody specific to the antigen.

Typically, these methods will further comprise an additional step of isolating and sequencing, in whole or in part, the polypeptide and nucleic acid sequences encoding the desired antibody. These sequences or modified versions or portions thereof can be expressed in desired host cells in order to produce recombinant antibodies to a desired antigen.

As noted previously, it is believed that the clonal population of B cells predominantly comprises antibody-secreting B cells producing antibody against the desired antigen. It is also believed based on experimental results obtained with several antigens and with different B cell populations that the clonally produced B cells and the isolated antigen-specific B cells derived therefrom produced according to the invention secrete a monoclonal antibody that is typically of relatively high affinity and moreover is capable of efficiently and reproducibly producing a selection of monoclonal antibodies of greater epitopic variability as compared to other methods of deriving monoclonal antibodies from cultured antigen-specific B cells. In an exemplary embodiment the population of immune cells used in such B cell selection methods will be derived from a rabbit. However, other hosts that produce antibodies, including non-human and human hosts, can alternatively be used as a source of immune B cells. It is believed that the use of rabbits as a source of B cells may enhance the diversity of monoclonal antibodies that may be derived by the methods. Also, the antibody sequences derived from rabbits according to the invention typically possess sequences having a high degree of sequence identity to human antibody sequences making them favored for use in humans since they should possess little antigenicity. In the course of humanization, the final humanized antibody contains a much lower foreign/host residue content, usually restricted to a subset of the host CDR residues that differ dramatically due to their nature versus the human target sequence used in the grafting. This enhances the probability of complete activity recovery in the humanized antibody protein.

The methods of antibody selection using an enrichment step disclosed herein include a step of obtaining an immune cell-containing cell population from an immunized host. Methods of obtaining an immune cell-containing cell population from an immunized host are known in the art and generally include inducing an immune response in a host and harvesting cells from the host to obtain one or more cell populations. The response can be elicited by immunizing the host against a desired antigen. Alternatively, the host used a source of such immune cells can be naturally exposed to the desired antigen such as an individual who has been infected with a particular pathogen such as a bacterium or virus or alternatively has mounted a specific antibody response to a cancer that the individual is afflicted with.

Host animals are well-known in the art and include, but are not limited to, guinea pig, rabbit, mouse, rat, non-human primate, human, as well as other mammals and rodents, chicken, cow, pig, goat, and sheep. Preferably the host is a mammal, more preferably, rabbit, mouse, rat, or human. When exposed to an antigen, the host produces antibodies as part of the native immune response to the antigen. As mentioned, the immune response can occur naturally, as a result of disease, or it can be induced by immunization with the antigen. Immunization can be performed by any method known in the art, such as, by one or more injections of the antigen with or without an agent to enhance immune response, such as complete or incomplete Freund's adjuvant.

In another embodiment, the invention also contemplates intraspinal immunization. As an alternative to immunizing a host animal in vivo, the method can comprise immunizing a host cell culture in vitro.

After allowing time for the immune response (e.g., as measured by serum antibody detection), host animal cells are harvested to obtain one or more cell populations. In a preferred embodiment, a harvested cell population is screened for antibody binding strength and/or antibody functionality. A harvested cell population is preferably from at least one of the spleen, lymph nodes, bone marrow, and/or peripheral blood mononuclear cells (PBMCs). The cells can be harvested from mice, rats, or rabbits. Certain sources may be preferred for certain antigens. For example, the spleen, lymph nodes, and PBMCs are preferred for IL-6, and the lymph nodes are preferred for TNF. The cell population is harvested to about 20 to about 90 days or increments thereafter in immunization, preferably about 50 to about 60 days. A harvested cell population and/or a single cell suspension therefrom can be enriched, screened, and/or cultured for antibody selection. The frequency of antigen-specific cells within a harvested cell population is usually about 1% to about 5%, or increments therein.

In one embodiment, a single cell suspension from a harvested cell population is enriched, preferably by using Miltenyi beads. From the harvested cell population having a frequency of antigen-specific cells of about 1% to about 5%, an enriched cell population is thus derived having a frequency of antigen-specific cells approaching 100%.

The method of antibody selection using an enrichment step includes a step of producing antibodies from at least one antigen-specific cell from an enriched cell population. Methods of producing antibodies in vitro are well known in the art, and any suitable method can be employed. In one embodiment, an enriched cell population, such as an antigen-specific single cell suspension from a harvested cell population, is plated at various cell densities, such as 50, 100, 250, 500, or other increments between 1 and 1000 cells per well. Preferably, the sub-population comprises no more than about 10,000 antigen-specific, antibody-secreting cells, more preferably about 50-10,000, about 50-5,000, about 50-1,000, about 50-500, about 50-250 antigen-specific, antibody-secreting cells, or increments therein. Then, these sub-populations are cultured with suitable medium (e.g., an activated T cell conditioned medium, particularly 1-5% activated rabbit T cell conditioned medium) on a feeder layer, preferably under conditions that favor the survival of a single proliferating antibody-secreting cell per culture well. The feeder layer is generally comprised of irradiated cell matter, e.g., EL4B
cells, does not constitute part of the cell population. The cells are cultured in a suitable media for a time sufficient for antibody production, for example about 1 day to about 2 weeks, about 1 day to about 10 days, at least about 3 days, about 3 to about 5 days, about 5 days to about 7 days, at least about 7 days, or other increments therein. In one embodiment, more than one sub-population is cultured simultaneously. Preferably, a single antibody-producing cell and progeny thereof survives in each well, thereby providing a clonal population of antigen-specific B cells in each well. At this stage, the immunoglobulin G (IgG) produced by the clonal population is highly correlative with antigen specificity. In a preferred embodiment, the IgGs exhibit a correlation with antigen specificity that is greater than about 50%, more preferably greater than 70%, 85%, 90%, 95%, 99%, or increments therein. See FIG. 3, which demonstrates an exemplary correlation for IL-6. The correlations were determined by setting up B cell cultures under limiting conditions to establish single antigen-specific antibody products per well. Antigen-specific versus general IgG synthesis was compared. Three populations were observed: IgG that recognized a single format of antigen (biotinylated and direct coating), detectable IgG and antigen recognition irrespective of immobilization, and IgG production alone. IgG production was highly correlated with antigen-specificity.

A supernatant containing the antibodies is optionally collected, which can be enriched, screened, and/or cultured for antibody selection according to the steps described above. In one embodiment, the supernatant is enriched (preferably by an antigen-specificity assay, especially an ELISA assay) and/or screened for antibody functionality.

In another embodiment, the enriched, preferably clonal, antigen-specific B cell population from which a supernatant described above is optionally screened in order to detect the presence of the desired secreted monoclonal antibody is used for the isolation of a few B cells, preferably a single B cell, which is then tested in an appropriate assay in order to confirm the presence of a single antibody-producing B cell in the clonal B cell population. In one embodiment about 1 to about 20 cells are isolated from the clonal B cell population, preferably less than about 15, 12, 10, 5, or 3 cells, or increments therein, most preferably a single cell. The screen is preferably effected by an antigen-specificity assay, especially a halo assay. The halo assay can be performed with the full length protein, or a fragment thereof. The antibody-containing supernatant can also be screened for at least one of: antigen binding affinity; agonism or antagonism of antigen-ligand binding, induction or inhibition of the proliferation of a specific target cell type; induction or inhibition of lysis of a target cell, and induction or inhibition of a biological pathway involving the antigen.

The identified antigen-specific cell can be used to derive the corresponding nucleic acid sequences encoding the desired monoclonal antibody. (An Alul digest can confirm that only a single monoclonal antibody type is produced per well.) As mentioned above, these sequences can be mutated, such as by humanization, in order to render them suitable for use in human medicaments.

As mentioned, the enriched B cell population used in the process can also be further enriched, screened, and/or cultured for antibody selection according to the steps described above which can be repeated or performed in a different order. In a preferred embodiment, at least one cell of an enriched, preferably clonal, antigen-specific cell population is isolated, cultured, and used for antibody selection.

Thus, in one embodiment, the present invention provides a method comprising:

a. harvesting a cell population from an immunized host to obtain a harvested cell population;

b. creating at least one single cell suspension from a harvested cell population;

c. enriching at least one single cell suspension, preferably by chromatography, to form a first enriched cell population;

d. enriching the first enriched cell population, preferably by ELISA assay, to form a second enriched cell population which preferably is clonal, i.e., it contains only a single type of antigen-specific B cell;

e. enriching the second enriched cell population, preferably by halo assay, to form a third enriched cell population containing a single or a few number of B cells that produce an antibody specific to a desired antigen; and

f. selecting an antibody produced by an antigen-specific cell isolated from the third enriched cell population.

The method can further include one or more steps of screening the harvested cell population for antibody binding strength (affinity, avidity) and/or antibody functionality. Suitable screening steps include, but are not limited to, assay methods that detect: whether the antibody produced by the identified antigen-specific B cell produces an antibody possessing a minimal antigen binding affinity, whether the antibody agonizes or antagonizes the binding of a desired antigen to a ligand; whether the antibody induces or inhibits the proliferation of a specific cell type; whether the antibody induces or elicits a cytolytic reaction against target cells; whether the antibody binds to a specific epitope; and whether the antibody modulates (inhibits or agonizes) a specific biological pathway or pathways involving the antigen.

Similarly, the method can include one or more steps of screening the second enriched cell population for antibody binding strength and/or antibody functionality.

The method can further include a step of sequencing the polypeptide sequence or the corresponding nucleic acid sequence of the selected antibody. The method can also include a step of producing a recombinant antibody using the sequence, a fragment thereof, or a genetically modified version of the selected antibody. Methods for mutating antibody sequences in order to retain desired properties are well known to those skilled in the art and include humanization, chimerization, production of single chain antibodies; these mutation methods can yield recombinant antibodies possessing desired effector function, immunogenicity, stability, removal or addition of glycosylation, and the like. The recombinant antibody can be produced by any suitable recombinant cell, including, but not limited to mammalian cells such as CHO, COS, BHK, HEK-293, bacterial cells, yeast cells, plant cells, insect cells, and amphibian cells. In one embodiment, the antibodies are expressed in polyploid yeast cells, i.e., diploid yeast cells, particularly Pichia.

In one embodiment, the method comprises:

a. immunizing a host against an antigen to yield host antibodies;

b. screening the host antibodies for antigen specificity and neutralization;

c. harvesting B cells from the host;
d. enriching the harvested B cells to create an enriched cell population having an increased frequency of antigen-specific cells;

e. culturing one or more sub-populations from the enriched cell population under conditions that favor the survival of a single B cell to produce a clonal population in at least one culture well;

f. determining whether the clonal population produces an antibody specific to the antigen;

g. isolating a single B cell; and

h. sequencing the nucleic acid sequence of the antibody produced by the single B cell.

Methods of Humanizing Antibodies

In another embodiment of the invention, there is provided a method for humanizing antibody heavy and light chains. In this embodiment, the following method is followed for the humanization of the heavy and light chains:

Light Chain

1. Identify the amino acid that is the first one following the signal peptide sequence. This is the start of Framework 1. The signal peptide starts at the first initiation methionine and is typically, but not necessarily 22 amino acids in length for rabbit light chain protein sequences. The start of the mature polypeptide can also be determined experimentally by N-terminal protein sequencing, or can be predicted using a prediction algorithm. This is also the start of Framework 1 as classically defined by those in the field.

Example: RbVl. Amino acid residue 1 in Fig. 2, starting ‘AYDM . . .’

2. Identify the end of Framework 3. This is typically 86-90 amino acids following the start of Framework 1 and is typically a cysteine residue preceded by two tyrosine residues. This is the end of the Framework 3 as classically defined by those in the field.

Example: RbVl. amino acid residue 88 in Fig. 2, ending as ‘TYYC’

3. Use the rabbit light chain sequence of the polypeptide starting from the beginning of Framework 1 to the end of Framework 3 as defined above and perform a sequence homology search for the most similar human antibody protein sequences. This will typically be a search against human germline sequences prior to antibody maturation in order to reduce the possibility of immunogenicity, however any human sequences can be used. Typically a program like BLAST can be used to search a database of sequences for the most homologous. Databases of human antibody sequences can be found from various sources such as NCBI (National Center for Biotechnology Information).

Example: RbVl. amino acid sequence from residues numbered 1 through 88 in Fig. 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in Fig. 2 as L12A, V1 and Vx02.

4. Generally the most homologous human germline variable light chain sequence is then used as the basis for humanization. However those skilled in the art may decide to use another sequence that wasn’t the highest homology as determined by the homology algorithm, based on other factors including sequence gaps and framework similarities.

Example: In FIG. 2, L12A was the most homologous human germline variable light chain sequence and is used as the basis for the humanization of RbVl.

5. Determine the framework and CDR arrangement (FR1, FR2, FR3, CDR1 & CDR2) for the human homolog being used for the light chain humanization. This is using the traditional layout as described in the field. Align the rabbit variable light chain sequence with the human homolog, while maintaining the layout of the framework and CDR regions.

Example: In FIG. 2, the RbVl sequence is aligned with the human homologous sequence L12A, and the framework and CDR domains are indicated.

6. Replace the human homologous light chain sequence CDR1 and CDR2 regions with the CDR1 and CDR2 sequences from the rabbit sequence. If there are differences in length between the rabbit and human CDR sequences then use the entire rabbit CDR sequences and their lengths. It is possible that the specificity, affinity and/or immunogenicity of the resulting humanized antibody may be unaltered if smaller or larger sequence exchanges are performed, or if specific residue(s) are altered, however the exchanges as described have been used successfully, but do not exclude the possibility that other changes may be permitted.

Example: In FIG. 2, the CDR1 and CDR2 amino acid residues of the human homologous variable light chain L12A are replaced with the CDR1 and CDR2 amino acid sequences from the RbVl rabbit antibody light chain sequence. The human L12A frameworks 1, 2 and 3 are unaltered. The resulting humanized sequence is shown below as Vl.h from residues numbered 1 through 88. Note that the only residues that are different from the L12A human sequence are underlined, and are thus rabbit-derived amino acid residues. In this example only 8 of the 88 residues are different than the human sequence.

7. After framework 3 of the new hybrid sequence created in Step 6, attach the entire CDR3 of the rabbit light chain antibody sequence. The CDR3 sequence can be of various lengths, but is typically 9 to 15 amino acid residues in length. The CDR3 region and the beginning of the following framework 4 region are defined classically and identifiable by those skilled in the art. Typically the beginning of Framework 4, and thus after the end of CDR3 consists of the sequence ‘FGGG . . .’, however some variation may exist in these residues.

Example: In Fig. 2, the CDR3 of RbVl (amino acid residues numbered 89-100) is added after the end of framework 3 in the humanized sequence indicated as Vl.h.

8. The rabbit light chain framework 4, which is typically the final 11 amino acid residues of the variable light chain and begins as indicated in Step 7 above and typically ends with the amino acid sequence ‘ . . . VVKR’ is replaced with the nearest human light chain framework 4 homolog, usually from germline sequence. Frequently this human light chain framework 4 is of the sequence ‘TGGGTKEIKR’. It is possible that other human light chain framework 4 sequences that are not the most homologous or otherwise different may be used without affecting the specificity, affinity and/or immunogenicity of the resulting humanized antibody. This human light chain framework 4 sequence is added to the end of the variable light chain humanized sequence immediately following the CDR3 sequence from Step 7 above. This is now the end of the variable light chain humanized amino acid sequence.
Example: In FIG. 2, Framework 4 (FR4) of the RhtVH rabbit light chain sequence is shown above a homologous human FR4 sequence. The human FR4 sequence is added to the humanized variable light chain sequence (VLh) right after the end of the CD3 region added in Step 7 above.

Heavy Chain

1. Identify the amino acid that is the first one following the signal peptide sequence. This is the start of Framework 1. The signal peptide starts at the first initiation methionine and is typically 19 amino acids in length for rabbit heavy chain protein sequences. Typically, but not necessarily always, the final 3 amino acid residues of a rabbit heavy chain signal peptide are VQC, followed by the start of Framework 1. The start of the mature polypeptide can also be determined experimentally by N-terminal protein sequencing, or can be predicted using a prediction algorithm. This is also the start of Framework 1 as classically defined by those in the field.

Example: RhtVH amino acid residue 1 in FIG. 2, starting 'QEQL...

2. Identify the end of Framework 3. This is typically 95-100 amino acids following the start of Framework 1 and typically has the final sequence of 'CAR' (although the alanine can also be a value). This is the end of the Framework 3 as classically defined by those in the field.

Example: RhtVH amino acid residue 98 in FIG. 2, ending as 'FCVR'

3. Use the rabbit heavy chain sequence of the polypeptide starting from the beginning of Framework 1 to the end of Framework 3 as defined above and perform a sequence homology search for the most similar human antibody protein sequences. This will typically be against a database of human germline sequences prior to antibody maturation in order to reduce the possibility of immunogenicity, however any human sequences can be used. Typically a program like BLAST can be used to search a database of sequences for the most homologous. Databases of human antibody sequences can be found from various sources such as NCBI (National Center for Biotechnology Information).

Example: RhtVH amino acid sequence from residues numbered 1 through 98 in FIG. 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in FIGS. 2a as 3-64-04, 3-66-04, and 3-53-02.

4. Generally the most homologous human germline variable heavy chain sequence is then used as the basis for humanization. However those skilled in the art may decide to use another sequence that wasn’t the most homologous as determined by the homology algorithm, based on other factors including sequence gaps and framework similarities.

Example: 3-64-04 in FIG. 2 was the most homologous human germline variable heavy chain sequence and is used as the basis for the humanization of RhtVH.

5. Determine the framework and CDR arrangement (FR1, FR2, FR3, CDR1 & CDR2) for the human homolog being used for the heavy chain humanization. This is using the traditional layout as described in the field. Align the rabbit variable heavy chain sequence with the human homolog, while maintaining the layout of the framework and CDR regions.

Example: In FIG. 2, the RhtVH sequence is aligned with the human homologous sequence 3-64-04, and the framework and CDR domains are indicated.

6. Replace the human homologous heavy chain sequence CDR1 and CDR2 regions with the CDR1 and CDR2 sequences from the rabbit sequence. If there are differences in length between the rabbit and human CDR sequences then use the entire rabbit CDR sequences and their lengths. In addition, it may be necessary to replace the final three amino acids of the human heavy chain Framework 1 region with the final three amino acids of the rabbit heavy chain Framework 1. Typically but not always, in rabbit heavy chain Framework 1 these three residues follow a Glycine residue preceded by a Serine residue. In addition, it may be necessary replace the final amino acid of the human heavy chain Framework 2 region with the final amino acid of the rabbit heavy chain Framework 2. Typically, but not necessarily always, this is a Glycine residue preceded by an Isoleucine residue in the rabbit heavy chain Framework 2. It is possible that the specificity, affinity and/or immunogenicity of the resulting humanized antibody may be unaltered if smaller or larger sequence exchanges are performed, or if specific residue(s) are altered, however the exchanges as described have been used successfully, but do not exclude the possibility that other changes may be permitted. For example, a tryptophan amino acid residue typically occurs four residues prior to the end of the rabbit heavy chain CDR2 region, whereas in human heavy chain CDR2 this residue is typically a Serine residue. Changing this rabbit tryptophan residue to a the human Serine residue at this position has been demonstrated to have minimal to no effect on the humanized antibody’s specificity or affinity, and thus further minimizes the content of rabbit sequence-derived amino acid residues in the humanized sequence.

Example: In FIG. 2, The CDR1 and CDR2 amino acid residues of the human homologous variable heavy chain are replaced with the CDR1 and CDR2 amino acid sequences from the RhtVH rabbit antibody light chain sequence, except for the boxed residue, which is tryptophan in the rabbit sequence (position number 63) and Serine at the same position in the human sequence, and is kept as the human Serine residue. In addition to the CDR1 and CDR2 changes, the final three amino acids of Framework 1 (positions 28-30) as well as the final residue of Framework 2 (position 49) are returned as rabbit amino acid residues instead of human. The resulting humanized sequence is shown below as VHh from residues numbered 1 through 98. Note that the only residues that are different from the 3-64-04 human sequence are underlined, and are thus rabbit-derived amino acid residues. In this example only 15 of the 98 residues are different than the human sequence.

7. After framework 3 of the new hybrid sequence created in Step 6, attach the entire CDR3 of the rabbit heavy chain antibody sequence. The CDR3 sequence can be of various lengths, but is typically 5 to 19 amino acid residues in length. The CDR3 region and the beginning of the following framework 4 region are defined classically and are identifiable by those skilled in the art. Typically the beginning of framework 4, and thus after the end of CDR3 consists of the sequence WXG... (where X is usually Q or P), however some variation may exist in these residues.

Example: The CDR3 of RhtVH (amino acid residues numbered 90-110) is added after the end of framework 3 in the humanized sequence indicated as VHh.

8. The rabbit heavy chain framework 4, which is typically the final 11 amino acid residues of the variable heavy chain and begins as indicated in Step 7 above and
typically ends with the amino acid sequence ‘... TVSS’ is replaced with the nearest human heavy chain framework 4 homolog, usually from germline sequence. Frequently this human heavy chain framework 4 is of the sequence ‘WGQGTTTVTVSS’. It is possible that other human heavy chain framework 4 sequences that are not the most homologous or otherwise different may be used without affecting the specificity, affinity and/or immunogenicity of the resulting humanized antibody. This human heavy chain framework 4 sequence is added to the end of the variable heavy chain humanized sequence immediately following the CDR3 sequence from Step 7 above. This is now the end of the variable heavy chain humanized amino acid sequence.

[1058] Example: In FIG. 2, framework 4 (FR4) of the RtbVH rabbit heavy chain sequence is shown above a homologous human heavy FR4 sequence. The human FR4 sequence is added to the humanized variable heavy chain sequence (VHh) right after the end of the CD3 region added in Step 7 above.

Methods of Producing Antibodies and Fragments Thereof.

[1059] The invention is also directed to the production of the antibodies described herein or fragments thereof. Recombinant polypeptides corresponding to the antibodies described herein or fragments thereof are secreted from polyplidal, preferably diploid or tetraploid strains of mating competent yeast. In an exemplary embodiment, the invention is directed to methods for producing these recombinant polypeptides in secreted form for prolonged periods using cultures comprising polyplidal yeast, i.e., at least several days to a week, more preferably at least a month or several months, and even more preferably at least 6 months to a year or longer. These polyplidal yeast cultures will express at least 10-25 mg/liter of the polypeptide, more preferably at least 50-250 mg/liter, still more preferably at least 500-1000 mg/liter, and most preferably a gram per liter or more of the recombinant polypeptide(s).

[1060] In one embodiment of the invention a pair of genetically marked yeast haploid cells are transformed with expression vectors comprising subunits of a desired heteromultimeric protein. One haploid cell comprises a first expression vector, and a second haploid cell comprises a second expression vector. In another embodiment diploid yeast cells will be transformed with one or more expression vectors that provide for the expression and secretion of one or more of the recombinant polypeptides. In still another embodiment a single haploid cell may be transformed with one or more vectors and used to produce a polyplidal yeast by fusion or mating strategies. In yet another embodiment a diploid yeast culture may be transformed with one or more vectors providing for the expression and secretion of a desired polypeptide or polypeptides. These vectors may comprise vectors e.g., linearized plasmids or other linear DNA products that integrate into the yeast cell’s genome randomly, through homologous recombination, or using a recombinase such as Cre/Lox or FLP/Frt. Optionally, additional expression vectors may be introduced into the haploid or diploid cells; or the first or second expression vectors may comprise additional coding sequences; for the synthesis of heterotrimmers; heterodimers; etc. The expression levels of the non-identical polypeptides may be individually calibrated, and adjusted through appropriate selection, vector copy number, promoter strength and/or induction and the like. The transformed haploid cells are genetically crossed or fused. The resulting diploid or tetraploid strains are utilized to produce and secrete fully assembled and biologically functional proteins, humanized antibodies described herein or fragments thereof.

[1061] The use of diploid or tetraploid cells for protein production provides for unexpected benefits. The cells can be grown for production purposes, i.e. scaled up, and for extended periods of time, in conditions that can be deleterious to the growth of haploid cells, which conditions may include high cell density; growth in minimal media; growth at low temperatures; stable growth in the absence of selective pressure; and which may provide for maintenance of heterologous gene sequence integrity and maintenance of high level expression over time. Without wishing to be bound thereby, the inventors theorize that these benefits may arise, at least in part, from the creation of diploid strains from two distinct parental haploid strains. Such haploid strains can comprise numerous minor autotrophic mutations, which mutations are complemented in the diploid or tetraploid, enabling growth and enhanced production under highly selective conditions.

[1062] Transformed mating competent haploid yeast cells provide a genetic method that enables subunit pairing of a desired protein. Haploid yeast strains are transformed with each of two expression vectors, a first vector to direct the synthesis of one polypeptide chain and a second vector to direct the synthesis of a second, non-identical polypeptide chain. The two haploid strains are mated to provide a diploid host where optimized target protein production can be obtained.

[1063] Optionally, additional non-identical coding sequence(s) are provided. Such sequences may be present on additional expression vectors or in the first or the second expression vectors. As is known in the art, multiple coding sequences may be independently expressed from individual promoters; or may be coordinately expressed through the inclusion of an “internal ribosome entry site” or “IRES”, which is an element that promotes direct internal ribosome entry to the initiation codon, such as 4FG, of a cistron (a protein encoding region), thereby leading to the cap-independent translation of the gene. IRES elements functional in yeast are described by Thompson et al. (2001) P.N.A.S. 98:12866-12868.

[1064] In one embodiment of the invention, antibody sequences are produced in combination with a secretory J chain, which provides for enhanced stability of IgA (see U.S. Pat. Nos. 5,959,177; and 5,202,422).

[1065] In a preferred embodiment the two haploid yeast strains are each auxotrophic, and require supplementation of media for growth of the haploid cells. The pair of auxotrophs are complementary, such that the diploid product will grow in the absence of the supplements required for the haploid cells. Many such genetic markers are known in yeast, including requirements for amino acids (e.g. met, lys, his, arg, etc.), nucleosides (e.g. ura3, ade1, etc.); and the like. Amino acid markers may be preferred for the methods of the invention. Alternatively diploid cells which contain the desired vectors can be selected by other means, e.g., by use of other markers, such as green fluorescent protein, antibiotic resistance genes, various dominant selectable markers, and the like.

[1066] Two transformed haploid cells may be genetically crossed and diploid strains arising from this mating event selected by their hybrid nutritional requirements and/or antibiotic resistance spectra. Alternatively, populations of the two transformed haploid strains are spheroplasted and fused, and diploid progeny regenerated and selected. By either method,
diploid strains can be identified and selectively grown based on their ability to grow in different media than their parents. For example, the diploid cells may be grown in minimal medium that may include antibiotics. The diploid synthesis strategy has certain advantages. Diploid strains have the potential to produce enhanced levels of heterologous protein through broader complementation to underlying mutations, which may impact the production and/or secretion of recombinant protein. Furthermore, once stable strains have been obtained, any antibiotics used to select those strains do not necessarily need to be continuously present in the growth media.

[1067] As noted above, in some embodiments a haploid yeast may be transformed with a single or multiple vectors and mated or fused with a non-transformed cell to produce a diploid cell containing the vector or vectors. In other embodiments, a diploid yeast cell may be transformed with one or more vectors that provide for the expression and secretion of a desired heterologous polypeptide by the diploid yeast cell.

[1068] In one embodiment of the invention, two haploid strains are transformed with a library of polypeptides, e.g., a library of antibody heavy or light chains. Transformed haploid cells that synthesize the polypeptides are mated with the complementary haploid cells. The resulting diploid cells are screened for functional protein. The diploid cells provide a means of rapidly, conveniently and inexpensively bringing together a large number of combinations of polypeptides for functional testing. This technology is especially applicable for the generation of heterodimeric protein products, where optimized subunit synthesis levels are critical for functional protein expression and secretion.

[1069] In another embodiment of the invention, the expression level ratio of the two subunits is regulated in order to maximize product generation. Heterodimer subunit protein levels have been shown previously to impact the final product generation (Simmons L C, J Immunol Methods. 2002 May 1; 263(1-2):133-47). Regulation can be achieved prior to the mating step by selection for a marker present on the expression vector. By stably increasing the copy number of the vector, the expression level can be increased. In some cases, it may be desirable to increase the level of one chain relative to the other, so as to reach a balanced proportion between the subunits of the polypeptide. Antibiotic resistance markers are useful for this purpose, e.g., Zeocin™ (phleomycin) resistance marker, G418 resistance, etc. and provide a means of enrichment for strains that contain multiple integrated copies of an expression vector in a strain by selecting for transformants that are resistant to higher levels of Zeocin™ (phleomycin) or G418. The proper ratio, e.g., 1:1; 1:2; etc. of the subunit genes may be important for efficient protein production. Even when the same promoter is used to transcribe both subunits, many other factors contribute to the final level of protein expressed and therefore, it can be useful to increase the number of copies of one encoded gene relative to the other. Alternatively, diploid strains that produce higher levels of a polypeptide, relative to single copy vector strains, are created by mating two haploid strains, both of which have multiple copies of the expression vectors.

[1070] Host cells are transformed with the above-described expression vectors, mated to form diploid strains, and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants or amplifying the genes encoding the desired sequences. A number of minimal media suitable for the growth of yeast are known in the art. Any of these media may be supplemented as necessary with salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as phosphate, HEPES), nucleosides (such as adenosine and thymidine), antibiotics, trace elements, and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[1071] Secreted proteins are recovered from the culture medium. A protease inhibitor, such as phenyl methyl sulfonyl fluoride (PMSF) may be useful to inhibit proteolytic degradation during purification, and antibiotics may be included to prevent the growth of adventitious contaminants. The composition may be concentrated, filtered, dialyzed, etc., using methods known in the art.

[1072] The diploid cells of the invention are grown for production purposes. Such production purposes desirably include growth in minimal media, which media lacks preformed amino acids and other complex biomolecules, e.g., media comprising ammonia as a nitrogen source, and glucose as an energy and carbon source, and salts as a source of phosphate, calcium and the like. Preferably such production media lacks selective agents such as antibiotics, amino acids, purines, pyrimidines, etc. The diploid cells can be grown to high cell density, for example at about 50 g/L, more usually at least about 100 g/L; and may be at least about 300, about 400, about 500 g/L or more.

[1073] In one embodiment of the invention, the growth of the subject cells for production purposes is performed at low temperatures, which temperatures may be lowered during log phase, during stationary phase, or both. The term "low temperature" refers to temperatures of at least about 15°C, more usually about at least about 17°C, and may be about 20°C, and is usually not more than about 25°C, or more usually not more than about 22°C. In another embodiment of the invention, the low temperature is usually not more than about 28°C. Growth temperature can impact the production of full-length secreted proteins in production cultures, and decreasing the culture growth temperature can strongly enhance the intact product yield. The decreased temperature appears to assist intracellular trafficking through the folding and post-translational processing pathways used by the host to generate the target product, along with reduction of cellular protease degradation.

[1074] The methods of the invention provide for expression of secreted, active protein, preferably a mammalian protein. In one embodiment, secreted, "active antibodies", as used herein, refers to a correctly folded multimer of at least two properly paired chains, which accurately binds to its cognate antigen. Expression levels of active protein are usually at about 10-50 mg/liter culture, more usually at least about 100 mg/liter, preferably at least about 500 mg/liter, and may be 1000 mg/liter or more.

[1075] The methods of the invention can provide for increased stability of the host and heterologous coding sequences during production. The stability is evidenced, for example, by maintenance of high levels of expression of time, where the starting level of expression is decreased by more than about 20%, usually not more than 10%, and may be decreased by not more than about 5% over about 20 doublings, 50 doublings, 100 doublings, or more.
The strain stability also provides for maintenance of heterologous gene sequence integrity over time, where the sequence of the active coding sequence and requisite transcriptional regulatory elements are maintained in at least about 99% of the diploid cells, usually in at least about 99.9% of the diploid cells, and preferably in at least about 99.9% of the diploid cells over about 20 doublings, 50 doublings, 100 doublings, or more. Preferably, substantially all of the diploid cells maintain the sequence of the active coding sequence and requisite transcriptional regulatory elements.

Other methods of producing antibodies are well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (See, for example, U.S. Pat. No. 4,816,367 to Cubilly et al.; Morrison et al., P.N.A.S. USA, 81:8651-55 (1984); Neuberger, M. S. et al., Nature, 314:268-270 (1985); Boulianne, G. L. et al., Nature, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entirety).


Antibody polypeptides of the invention having IL-6 binding specificity may also be produced by constructing, using conventional techniques well known to those of ordinary skill in the art, an expression vector containing an operon and a DNA sequence encoding an antibody heavy chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

A second expression vector is produced using the same conventional means well known to those of ordinary skill in the art, said expression vector containing an operon and a DNA sequence encoding an antibody light chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

The expression vectors are transfected into a host cell by conventional techniques well known to those of ordinary skill in the art to produce a transfected host cell, said transfected host cell cultured by conventional techniques well known to those of ordinary skill in the art to produce said antibody polypeptides.

The host cell may be co-transfected with the two expression vectors described above, the first expression vector containing DNA encoding an operon and a light chain-derived polypeptide and the second vector containing DNA encoding an operon and a heavy chain-derived polypeptide. The two vectors contain different selectable markers, but preferably achieve substantially equal expression of the heavy and light chain polypeptides. Alternatively, a single vector may be used, the vector including DNA encoding both the heavy and light chain polypeptides. The coding sequences for the heavy and light chains may comprise CDNA.

The host cells used to express the antibody polypeptides may be either a bacterial cell such as E. coli or a eukaryotic cell. In a particularly preferred embodiment of the invention, a mammalian cell of a well-defined type for this purpose, such as a myeloma cell or a Chinese hamster ovary (CHO) cell line may be used.

The general methods by which the vectors may be constructed, transfection methods required to produce the host cell and culturing methods required to produce the antibody polypeptides from said host cells all include conventional techniques. Although preferably the cell line used to produce the antibody is a mammalian cell line, any other suitable cell line, such as a bacterial cell line such as an E. coli-derived bacterial strain, or a yeast cell line, may alternatively be used.

Similarly, once produced the antibody polypeptides may be purified according to standard procedures in the art, such as for example cross-flow filtration, ammonium sulphate precipitation, affinity column chromatography and the like.

The antibody polypeptides described herein may also be used for the design and synthesis of either peptide or non-peptide mimetics that would be useful for the same therapeutic applications as the antibody polypeptides of the invention. See, for example, Sargent et al, Science, 253:792-795 (1991), the contents of which are herein incorporated by reference in its entirety.

Screening Assays

The invention also includes screening assays designed to assist in the identification of diseases and disorders associated with IL-6 in patients exhibiting symptoms of an IL-6 associated disease or disorder.

In one embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments thereof, are used to detect the presence of IL-6 in a biological sample obtained from a patient exhibiting symptoms of a disease or disorder associated with IL-6. The presence of IL-6, or elevated levels thereof when compared to pre-disease levels of IL-6 in a comparable biological sample, may be beneficial in diagnosing a disease or disorder associated with IL-6.

Another embodiment of the invention provides a diagnostic or screening assay to assist in diagnosis of diseases or disorders associated with IL-6 in patients exhibiting symptoms of an IL-6 associated disease or disorder identified herein, comprising assaying the level of IL-6 expression in a biological sample from said patient using a post-translationally modified anti-IL-6 antibody or binding fragment thereof. The anti-IL-6 antibody or binding fragment thereof may be post-translationally modified to include a detectable moiety such as set forth previously in the disclosure.

The IL-6 level in the biological sample is determined using a modified anti-IL-6 antibody or binding fragment thereof as set forth herein, and comparing the level of IL-6 in the biological sample against a standard level of IL-6 (e.g., the level in normal biological samples). The skilled clinician would understand that some variability may exist between normal biological samples, and would take that into consideration when evaluating results.

The above-recited assay may also be useful in monitoring a disease or disorder, where the level of IL-6 obtained in a biological sample from a patient believed to have an IL-6
associated disease or disorder is compared with the level of IL-6 in prior biological samples from the same patient, in order to ascertain whether the IL-6 level in said patient has changed with, for example, a treatment regimen.

In another embodiment of the invention, IL-6 antagonists described herein are administered to a patient in combination with another active agent. For example, IL-6 antagonist may be co-administered with one or more chemotherapy agents, such as VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-flourouracil, gemcitabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids (e.g., vinblastine, vincristine, vinorelbin), mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGfF antagonists, TNF antagonists, IL-1 antagonists, interleukins (e.g. IL-12 or IL-12), IL-12 antagonists, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, ErbituxTM, AvastinTM, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL.625, Herceptin®, or any combination thereof.


In a preferred embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, cachexia. Diseases and disorders associated with cachexia include, but are not limited to, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia and age-related cachexia. See, for example, Barton, B E, Interleukin-6 and new strategies for the treatment of cancer, hyperproliferative

[1092] The invention is also directed to a method of in vivo imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective amount of a diagnostic composition. Said in vivo imaging is useful for the detection and imaging of IL-6 expressing tumors or metastases and IL-6 expressing inflammatory sites, for example, and can be used as part of a planning regimen for design of an effective cancer or arthritis treatment protocol. The treatment protocol may include, for example, one or more of radiation, chemotherapy, cytokine therapy, gene therapy, and antibody therapy, as well as an anti-IL-6 antibody or fragment thereof.

[1093] A skilled clinician would understand that a biological sample includes, but is not limited to, sera, plasma, urine, saliva, mucus, pleural fluid, synovial fluid and spinal fluid. Methods of Ameliorating or Reducing Symptoms of or Treating, or Preventing, Diseases and Disorders Associated with, IL-6

[1094] In an embodiment of the invention, IL-6 antagonists described herein are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with IL-6. IL-6 antagonists described herein can also be administered in a therapeutically effective amount to patients in need of treatment of diseases and disorders associated with IL-6 in the form of a pharmaceutical composition as described in greater detail below.

[1095] In another embodiment of the invention, IL-6 antagonists described herein are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with elevated C-reactive protein (CRP). Such diseases include any disease that exhibits chronic inflammation, e.g., rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, systemic lupus erythematosus, Crohn’s disease, ulcerative colitis, pemphigus, dermatomyositis, polymyositis, polymyalgia rheumatica, giant cell arteritis, vasculitis, polyarteritis nodosa, Wegener’s granulomatosis, Kawasaki disease, isolated CNS vasculitis, Churg-Strauss arteritis, microscopic polyarteritis, microscopic polyangitis, Henoch-Schönlein purpura, essential cryoglobulineemic vasculitis, rheumatoid vasculitis, cryoglobulinemia, relapsing polychondritis, Bechet’s disease, Takayasu’s arteritis, ischemic heart disease, stroke, multiple sclerosis, sepsis, vasculitis secondary to viral infection (e.g., hepatitis B, hepatitis C, HIV, cytomegalovirus, Epstein-Barr virus, Parvo B19 virus, etc.), Buenger’s Disease, cancer, advanced cancer, Osteoarthritis, systemic sclerosis, CRST syndrome, Reiter’s disease, Paget’s disease of bone, Sjogren’s syndrome, diabetes type 1, diabetes type 2, familial Mediterranean fever, autoimmune thrombocytopenia, autoimmune hemolytic anemia, autoimmune thyroid diseases, pernicious anemia, anemia, vitiligo, alopecia greata, primary biliary cirrhosis, autoimmune chronic active hepatitis, alcoholic cirrhosis, viral hepatitis including hepatitis B and C, other organ specific autoimmune diseases, burns, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, allergic asthma, other allergic conditions or any combination thereof.

[1096] In one embodiment of the invention, IL-6 antagonists described herein are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with reduced serum albumin, e.g. rheumatoid arthritis, cancer, advanced cancer, liver disease, renal disease, inflammatory bowel disease, celiac’s disease, trauma, burns, other diseases associated with reduced serum albumin, or any combination thereof.


In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful as a wakefulness aid.

Administration

In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject at a concentration of between about 0.1 and 20 mg/kg, such as about 0.4 mg/kg, about 0.8 mg/kg, about 1.6 mg/kg, or about 4 mg/kg, of body weight of recipient subject. In a preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject at a frequency of once every twenty-six weeks or less, such as once every sixteen weeks or less, once every eight weeks or less, or once every four weeks, or less. In another preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations thereof, are administered to a recipient subject with a frequency at most once per period of approximately one week, such as at most once per period of approximately two weeks, such as at most once per period of approximately four weeks, such as at most once per period of approximately eight weeks, such as at most once per period of approximately twelve weeks, such as at most once per period of approximately sixteen weeks, such as at most once per period of approximately twenty-four weeks.

It is understood that the effective dosage may depend on recipient subject attributes, such as, for example, age, gender, pregnancy status, body mass index, lean body mass, condition or conditions for which the composition is given, other health conditions of the recipient subject that may affect metabolism or tolerance of the composition, levels of IL-6 in the recipient subject, and resistance to the composition (for example, arising from the patient developing antibodies against the composition). A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A. G., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman’s the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott’s illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pharmacologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject in a pharmaceutical formulation.
A “pharmaceutical composition” refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, epicutaneous, epidermal, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intracocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transnasal. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, may be optionally administered in combination with one or more active agents. Such active agents include analgesics, antipyretics, anti-inflammatory, antibiotic, antiviral, and anticytokine agents. Active agents include agonists, antagonists, and modulators of TNF-α, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IFN-α, IFN-γ, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, including antibodies reactive against any of the foregoing, and antibodies reactive against any of their receptors. Active agents also include 2-Arylpropionic acids, Aceclofenac, Aceemetacin, Aceclofamic acid (Aspirin), Alclofenac, Alminoprofen, Amoxiprin, Ampryone, Arylalkanoic acids, Azapropazone, Benorylate, Bencaprox, Bromfenac, Carprofen, Celecoxib, Choline magnesium salicylate, Clofenoze, COX-2 inhibitors, Deribuprofen, Deriketoprofen, Diclofenac, Diflunisal, Drixiecan, Ethenza mine, Etilodac, Etoricoxib, Fasilamine, Fenamic acids, Fenbufen, Fenoprofen, Flufenamic acid, Fluoxaprofen, Flurbiprofen, Ibuprofen, Ibufropen, Indometacin, Indoprofen, Ketobaze, Ketoprofen, Ketorolac, Lornoxicam, Loxoprofen, Lumiracoxib, Magnesium salicylate, Meflofenamic acid, Mefenamic acid, Meloxicam, Metamizole, Methyl salicylate, Mofebutazone, Nabumetone, Naproxen, N-Arylamidinonic acids, Oxametacin, Oxaprozin, Oxicsam, Oxynphenbutazone, Parecoxib, Phenazone, Phenylbutazone, Phenylbutazone, Piroxicam, Pirprofen, profens, Proglumetacin, Pirozolidine derivatives, Rolfecoxib, Salicyl salicylate, Salicylamide, Salicylates, Sulfapyrazone, Sulindac, Suprofen, Tenoxicam, Tiaprofenic acid, Tolmetin acid, Tolmetin, and Valdecoxib. Antibiotics include Amikacin, Aminoglycosides, Amoxicillin, Ampicillin, Ampansycin, Arsenophame, Azithromycin, Azlocillin, Aztreonam, Bacitracin, Carbacephem, Carbapenem, Carbencillin, Cefaclor, Cefadroxil, Cefalexin, Cefalothin, Cefadolin, Cefadomandole, Cefazolin, Cefamandole, Cefli toren, Cefepime, Cefixime, Cefoperazone, Cefotaxime, Cefoxitin, Cefpodoxime, Cefprozil, Cefotizidime, Cefibuten, Cefitoxime, Cefiboprole, Ceftriadone, Cefuroxime, Cephalosporins, Chloramphenicol, Cloxacillin, Ciprofloxacin, Clarithromycin, Clindamycin, Cloxacillin, Colistin, Co-trimoxazole, Dalprofistin, Demeclocycline, Dicloxacinil, Dirithromycin, Doripenem, Doxycycline, Enoxacin, Erapt enem, Erythromycin, Ethambutol, Fluoxaloxacin, Fosfomy cin, Furazolidone, Fusidic acid, Gatifloxacin, Geldamycin, Gentamicin, Glycopeptides, Herbimycin, Imipenem, Iso novad, Kanamycin, Levofloxacinn, Lincomycin, Linezolid, Lomefloxacin, Lorcarbem, Macrolides, Mafenide, Meropenem, Meteclinil, Metronidazole, Mozlocillin, Minocycline, Monobactams, Moxifloxacin, Mupirocin, NaCcillin, Neomycin, Netilmicin, Nitrofurantoin, Norfloxaclin, Oxacillin, Oxetetracycline, Paromomycin, Penicillin, Pencillin, Peracillin, Piperacillin, Plratomycin, Polymyxin B, Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinupristin, Rifampicin, Rifampin, Roxithromycin, Spectinomycin, Streptomycin, Sulactamid, Sulinflumidine, Sulfasalazine, Sulfoxazone, Sulphonamides, Teicoplanin, Telithromycin, Tetracyclines, Ticarcillin, Timi dazole, Tobramycin, Trimethoprim, Trismethoprim-Sul famethoxazole, Troleandomycin, Trovafloxacin, and Vancomycin. Active agents also include Aldosterone, Becloamethasone, Betamethasone, Corticosteroids, Cortisol, Cortisone acetate, Decoxytocriocetate acetate, Dexamethasone, Fluorocortisone acetate, Glucocorticoids, Hydrocortisone, Methylprednisolone, Prednisone, Predni solone, Steroids, and Triamcinolone. Antiviral agents include abacavir, aciclovir, acyclovir, adefovir, amantadine, ampravir, an anti retroviral fixed dose combination, an antiretroviral synergistic enhancer, arbidol, atazanavir, atipra, brivudin, cidofovir, comivir, darunavir, delavirdine, didanosine, docusan, edoxidone, efavirenz, emtricitabine, enfuvirtide, entecavir, entry inhibitors, famciclovir, fomiviren, fosampravir, foscarnet, fosfomycin, fusion inhibitor, ganciclovir, gardsil, ibacitabine, idoxuridine, imiquimod, immunovir, indinovir, inosine, integrase inhibitor, interferon, interferon type I, interferon type II, interferon type III, lamivudine, lopinavir, loviride, maraviroc, MK-0518, moroxyidine, nelfinavir, nevirapine, nexavir, nucleoside analogues, oseltamivir, penciclovir, peramivir, pleconaril, podophyllotoxine, protease disoprol, tipranavir, trifluridine, trizivir, tramontadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, and zidovudine. Any suitable combination of these active agents is also contemplated.

A “pharmaceutical excipient” or a “pharmaceutically acceptable excipient” is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington’s Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

As used herein “pharmacologically acceptable carrier” or “excipient” includes any and all solvents, dispersion media, coatings, antibacterial and anti fungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmacologically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmacologically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

In one embodiment of the invention that may be used to intravenously administer antibodies of the invention,
including Ab1, for cancer indications, the administration formulation comprises, or alternatively consists of, about 10.5 mg/mL of antibody, 25 mM Histidine base, Phosphoric acid q.s. to pH 6, and 250 mM sorbitol.

[1114] In another embodiment of the invention that may be used to intravenously administer antibodies of the invention, including Ab1, for cancer indications, the administration formulation comprises, or alternatively consists of, about 10.5 mg/mL of antibody, 12.5 mM Histidine base, 12.5 mM Histidine HCl (or 25 mM Histidine base and Hydrochloric acid q.s. to pH 6), 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80.

[1115] In one embodiment of the invention that may be used to subcutaneously administer antibodies of the invention, including Ab1, for rheumatoid arthritis indications, the administration formulation comprises, or alternatively consists of, about 50 or 100 mg/mL of antibody, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80.

[1116] In another embodiment of the invention that may be used to subcutaneously administer antibodies of the invention, including Ab1, for rheumatoid arthritis indications, the administration formulation comprises, or alternatively consists of, about 20 or 100 mg/mL of antibody, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 to 280 mM sorbitol (or sorbitol in combination with sucrose), and 0.015% (w/w) Polysorbate 80, said formulation having a nitrogen headspace in the shipping vials.

[1117] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition.

[1118] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[1119] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, micro-

particles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[1120] The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

[1121] These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

[1122] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[1123] Certain teachings related to methods for obtaining a clonal population of antigen-specific B cells were disclosed in U.S. Provisional patent application No. 60/801,412, filed May 19, 2006, the disclosure of which is herein incorporated by reference in its entirety.

[1124] Certain teachings related to humanization of rabbit-derived monoclonal antibodies and preferred sequence modifications to maintain antigen binding affinity were disclosed in International application Ser. No. 12/124,723, corresponding to Attorney Docket No. 67858.704001, entitled “Novel Rabbit Antibody Humanization Method and Humanized Rabbit Antibodies”, filed May 21, 2008, the disclosure of which is herein incorporated by reference in its entirety.


[1126] Certain teachings related to anti-IL-6 antibodies, methods of producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. provisional patent application No. 60/924,550, filed May 21, 2007, the disclosure of which is herein incorporated by reference in its entirety.

[1127] Certain teachings related to anti-IL-6 antibodies and methods of using those antibodies or fragments thereof to raise albumin levels or lower CRP levels were disclosed in U.S. provisional patent application No. 61/177,811, filed Nov. 25, 2008, the disclosure of which is herein incorporated by reference in its entirety.

[1128] Certain anti-IL-6 antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

[1129] The entire disclosure of each document cited (including patents, patent applications, journal articles,
abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entirety.

[1130] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (e.g., amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

EXAMPLES

Example 1
Production of Enriched Antigen-Specific B Cell Antigen Culture

[1131] Panels of antibodies are derived by immunizing traditional antibody host animals to exploit the native immune response to a target antigen of interest. Typically, the host used for immunization is a rabbit or other host that produces antibodies using a similar maturation process and provides for a population of antigen-specific B cells producing antibodies of comparable diversity, e.g., epitopic diversity. The initial antigen immunization can be conducted using complete Freund’s adjuvant (CFA), and the subsequent boosts effected with incomplete adjuvant. At about 50–60 days after immunization, preferably at day 55, antibody titers are tested, and the Antibody Selection (ABS) process is initiated if appropriate titers are established. The two key criteria for ABS initiation are potent antigen recognition and function-modifying activity in the polyclonal sera.

[1132] At the time positive antibody titers are established, animals are sacrificed and B cell sources isolated. These sources include: the spleen, lymph nodes, bone marrow, and peripheral blood mononuclear cells (PBMCs). Single cell suspensions are generated, and the cell suspensions are washed to make them compatible for low temperature long term storage. The cells are then typically frozen.

[1133] To initiate the antibody identification process, a small fraction of the frozen cell suspensions are thawed, washed, and placed in tissue culture media. These suspensions are then mixed with a biotinylated form of the antigen that was used to generate the antigen immune response, and antigen-specific cells are recovered using the Miltenyi magnetic bead cell selection methodology. Specific enrichment is conducted using streptavidin beads. The enriched population is recovered and progressed in the next phase of specific B cell isolation.

Example 2
Production of Clonal, Antigen-Specific B Cell-Containing Culture

[1134] Enriched B cells produced according to Example 1 are then plated at varying cell densities per well in a 96 well microtiter plate. Generally, this is at 50, 100, 250, or 500 cells per well with 10 plates per group. The media is supplemented with 4% activated rabbit T cell conditioned media along with 50K frozen irradiated IL-45 feeder cells. These cultures are left undisturbed for 5–7 days at which time supernatant containing secreted antibody is collected and evaluated for target properties in a separate assay setting. The remaining supernatant is left intact, and the plate is frozen at ~70°C. Under these conditions, the culture process typically results in wells containing a mixed cell population that comprises a clonal population of antigen-specific B cells, i.e., a single well will only contain a single monoclonal antibody specific to the desired antigen.

Example 3
Screening of Antibody Supernatants for Monoclonal Antibody of Desired Specificity and/or Functional Properties

[1135] Antibody-containing supernatants derived from the well containing a clonal antigen-specific B cell population produced according to Example 2 are initially screened for antigen recognition using ELISA methods. This includes selective antigen immobilization (e.g., biotinylated antigen capture by streptavidin coated plate), non-specific antigen plate coating, or alternatively, through an antigen build-up strategy (e.g., selective antigen capture followed by binding partner addition to generate a heteromeric protein-antigen complex). Antigen-positive well supernatants are then optionally tested in a function-modifying assay that is strictly dependent on the ligand. One such example is an in vitro protein-protein interaction assay that recreates the natural interaction of the antigen ligand with recombinant receptor protein. Alternatively, a cell-based response that is ligand dependent and easily monitored (e.g., proliferation response) is utilized. Supernatant that displays significant antigen recognition and potency is deemed a positive well. Cells derived from the original positive well are then transitioned to the antibody recovery phase.

Example 4
Recovery of Single, Antibody-Producing B Cell of Desired Antigen Specificity

[1136] Cells are isolated from a well that contains a clonal population of antigen-specific B cells (produced according to Example 2 or 3), which secrete a single antibody sequence. The isolated cells are then assayed to isolate a single, antibody-secreting cell. Dynal streptavidin beads are coated with biotinylated target antigen under buffered medium to prepare antigen-containing microbeads compatible with cell viability. Next antigen-loaded beads, antibody-producing cells from the positive well, and a fluorescein isothiocyanate (FITC)-labeled anti-host IgG antibody (as noted, the host can be any mammalian host, e.g., rabbit, mouse, rat, etc.) are incubated together at 37°C. This mixture is then re-pippeted in aliquots onto a glass slide such that each aliquot has an average single, antibody-producing B-cell. The antigen-specific, antibody-secreting cells are then detected through fluorescence microscopy. Secreted antibody is locally concentrated onto the adjacent beads due to the bound antigen and provides localization information based on the strong fluorescent signal. Antibody-secreting cells are identified via FITC detection of antibody-antigen complexes formed adjacent to the secreting cell. The single cell found in the center of this complex is then recovered using a micro-
The cell is snap-frozen in an eppendorf PCR tube for storage at -80° C. until antibody sequence recovery is initiated.

**Example 5**

**Isolation of Antibody Sequences From Antigen-Specific B Cell**

Antibody sequences are recovered using a combined RT-PCR based method from a single isolated B-cell produced according to Example 4 or an antigenic specific B cell isolated from the clonal B cell population obtained according to Example 2. Primers are designed to anneal in conserved and constant regions of the target immunoglobulin genes (heavy and light), such as rabbit immunoglobulin sequences, and a two-step nested PCR recovery step is used to obtain the antibody sequence. Amplicons from each well are analyzed for recovery and size integrity. The resulting fragments are then digested with Alul to fingerprint the sequence clonality. Identical sequences display a common fragmentation pattern in their electrophoretic analysis. Significantly, this common fragmentation pattern which proves cell clonality is generally observed even in the wells originally plated up to 1000 cells/well. The original heavy and light chain amplicon fragments are then restriction enzyme digested with HindIII and XhoI or HindIII and HsiWI to prepare the respective pieces of DNA for cloning. The resulting digests are then ligated into an expression vector and transformed into bacteria for plasmid propagation and production. Colonies are selected for sequence characterization.

**Example 6**

**Recombinant Production of Monoclonal Antibody of Desired Antigen Specificity and/or Functional Properties**

Correct full-length antibody sequences for each well containing a single monoclonal antibody is established and miniprep DNA is prepared using Qiagen solid-phase methodology. This DNA is then used to transfect mammalian cells to produce recombinant full-length antibody. Crude antibody product is tested for antigen recognition and functional properties to confirm the original characteristics are found in the recombinant antibody protein. Where appropriate, large-scale transient mammalian transfections are completed, and antibody is purified through Protein A affinity chromatography. Kd is assessed using standard methods (e.g., Biacore™) as well as IC50 in a potency assay.

**Example 7**

**Preparation of Antibodies that Bind Human IL-6**

By using the antibody selection protocol described herein, one can generate an extensive panel of antibodies. The antibodies have high affinity towards IL-6 (single to double digit pM Kd) and demonstrate potent antagonism of IL-6 in multiple cell-based screening systems (T1165 and HepG2). Furthermore, the collection of antibodies display distinct modes of antagonism toward IL-6-driven processes.

**Immunization Strategy**

Rabbits were immunized with huIL-6 (R&R). Immunization consisted of a first subcutaneous (sc) injection of 100 µg in complete Freund's adjuvant (CFA) (Sigma) followed by two boosts, two weeks apart, of 50 µg each in incomplete Freund's adjuvant (IFA) (Sigma). Animals were bled on day 55, and serum titers were determined by ELISA (antigen recognition) and by non-radioactive proliferation assay (Promega) using the T1165 cell line.

**Antibody Selection Titer Assessment**

Antigen recognition was determined by coating Immulon 4 plates (Thermo) with 1 µg/mL of huIL-6 (50 µL/well) in phosphate buffered saline (PBS, Hyclone) overnight at 4°C. On the day of the assay, plates were washed 3 times with PBS/Tween 20 (PBST tablets, Calbiochem). Plates were then blocked with 200 µL/well of 0.5% fish skin gelatin (FSG, Sigma) in PBS for 30 minutes at 37°C. Blocking solution was removed, and plates were blotted. Serum samples were made (bleeds and pre-bleeds) at a starting dilution of 1:100 (all dilutions were made in FSG 50 µL/well) followed by 1:10 dilutions across the plate (column 12 was left blank for background control). Plates were incubated for 3 minutes at 37°C. Plates were washed 3 times with PBS/Tween 20. Goat anti-rabbit FC-HRP (Pierce) diluted 1:5000 was added to all wells (50 µL/well), and plates were incubated for 30 minutes at 37°C. Plates were washed as described above. 50 µL/well of MB-Stable stop (Fitzgerald Industries) was added to plates, and color was allowed to develop, generally for 3 to 5 minutes. The development reaction was stopped with 50 µL/well 0.5 M HCl. Plates were read at 450 nm. Optical density (OD) versus dilution was plotted using Graph Pad Prizm software, and titers were determined.

**Functional Titer Assessment**

The functional activity of the samples was determined by a T1165 proliferation assay. T1165 cells were routinely maintained in modified RPMI medium (Hyclone) supplemented with Hepes, sodium pyruvate, sodium bicarbonate, L-glutamine, high glucose, penicillin/streptomycin, 10% heat inactivated fetal bovine serum (FBS) (all supplements from Hyclone), 2-mercaptoethanol (Sigma), and 10 ng/mL of huIL-6 (R&D). On the day of the assay, cell viability was determined by trypan blue (Invitrogen), and cells were seeded at a fixed density of 20,000 cells/well. Prior to seeding, cells were was twice in the medium described above without human-IL-6 (by centrifuging at 13,000 rpm for 5 minutes and discarding the supernatant). After the last wash, cells were resuspended in the same medium used for washing in a volume equivalent to 50 µL/well. Cells were set aside at room temperature.

In a round-bottom, 96-well plate (Costar), serum samples were added starting at 1:100, followed by a 1:10 dilution across the plate (columns 2 to 10) at 30 µL/well in replicates of 5 (rows B to F; dilution made in the medium described above with no huIL-6). Column 11 was medium only for IL-6 control. 30 µL/well of huIL-6 at 4x concentration of the final EC50 (concentration previously determined) were added to all wells (huIL-6 was diluted in the medium described above). Wells were incubated for 1 hour at 37°C to allow antibody binding to occur. After 1 hour, 50 µL/well of antibody-antigen (Ab-Ag) complex were transferred to a flat-bottom, 96-well plate (Costar) following the plate map format laid out in the round-bottom plate. On Row G, 50 µL/well of medium were added to all wells (columns 2 to 11) for background control. 50 µL/well of the cell suspension set aside were added to all wells (columns 2 to 11, rows B to G).
Columns 1 and 12 and on rows A and H, 200 µl/well of medium was added to prevent evaporation of test wells and to minimize edge effect. Plates were incubated for 72 h at 37°C in 4% CO₂. At 72 h, 20 µl/well of CellTiter96 (Promega) reagents was added to all test wells per manufacturer protocol, and plates were incubated for 2 h at 37°C. At 2 h, plates were gently mixed on an orbital shaker to disperse cells and to allow homogeneity in the test wells. Plates were read at 490 nm wavelength. Optical density (OD) versus dilution was plotted using GraphPad Prism software, and functional unit B was determined. A positive assay control plate was conducted as described above using MAB2061 (R&D Systems) at a starting concentration of 1 µg/ml (final concentration) followed by 1:3 dilutions across the plate.

Tissue Harvesting

Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows: Spleen and lymph nodes were processed into a single cell suspension by dissociating the tissue and pushing through sterile wire mesh at 70µm (Fisher) with a plunger of a 20 cc syringe. Cells were collected in the modified RPMI medium described above without huIL-6, but with low glucose. Cells were washed twice by centrifugation. After the last wash, cell density was determined by trypan blue. Cells were centrifuged at 1500 rpm for 10 minutes; the supernatant was discarded. Cells were resuspended in the appropriate volume of 10% dimethyl sulfoxide (DMSO, Sigma) in FBS (Hyclone) and dispensed at 1 ml/vial. Vials were then stored at -70°C for 24 h prior to being placed in a liquid nitrogen (LN2) tank for long-term storage.

Peripheral blood mononuclear cells (PBMCs) were isolated by mixing whole blood with equal parts of the low glucose medium described above without FBS. 35 ml of the whole blood mixture was carefully layered onto 8 ml of Lympholyte Rabbit (Cedarlane) into a 45 ml conical tube (Corning) and centrifuged 30 minutes at 2500 rpm at room temperature without brakes. After centrifugation, the PBMC layers were carefully removed using a glass Pasteur pipette (VWR), combined, and placed into a clean 50 ml vial. Cells were washed twice with the modified medium described above by centrifugation at 1500 rpm for 10 minutes at room temperature, and cell density was determined by trypan blue staining. After the last wash, cells were resuspended in an appropriate volume of 10% DMSO/FBS medium and frozen as described above.

B Cell Culture

On the day of setting up B cell culture, PBMC, splenocyte, or lymph node vials were thawed for use. Vials were removed from LN2 tank and placed in a 37°C water bath until thawed. Contents of vials were transferred into 15 ml conical centrifuge tube (Corning) and 10 ml of modified RPMI described above was slowly added to the tube. Cells were centrifuged for 5 minutes at 1.5K rpm, and the supernatant was discarded. Cells were resuspended in 10 ml of fresh media. Cell density and viability was determined by trypan blue. Cells were washed again and resuspended at 1 x 10⁶ cells/80 μl medium. Biotinylated huIL-6 (B huIL-6) was added to the cell suspension at the final concentration of 3 µg/ml and incubated for 30 minutes at 4°C. Unbound B huIL-6 was removed with two 10 ml washes of phosphate-buffered (PB):Ca/Mg free PBS (Hyclone), 2 mM ethylenediamine tetraacetic acid (EDTA), 0.5% bovine serum albumin (BSA) (Sigma-herion free). After the second wash, cells were resuspended at 1 x 10⁶ cells/80 µl PB: 20 µl of MACS® streptavidin beads (Miltenyi) 1/10E7 cells were added to the cell suspension. Cells were incubated at 4°C for 15 minutes. Cells were washed once with 2 ml of PB:1/10E7 cells. After washing, the cells were resuspended at 1 x 10⁶ cells/500 µl of PB and set aside. A MACS® MS column (Miltenyi) was pre-rinsed with 500 ml of PBF on a magnetic stand (Miltenyi). Cell suspension was applied to the column through a pre-filter, and unbound fraction was collected. The column was washed with 1.5 ml of PBF buffer. The column was removed from the magnet stand and placed onto a clean, sterile 5 ml Polystyrene Falcon tube. 1 ml of PBF buffer was added to the top of the column, and positive selected cells were collected. The yield and viability of positive and negative cell fraction was determined by trypan blue staining. Positive selection yielded an average of 1% of the starting cell concentration.

A pilot cell screen was established to provide information on seeding levels for the culture. Three 10-cell groups (a total of 30 plates) were seeded at 50, 100, and 200 enriched B cells/well. In addition, each well contained 50K cells/well of irradiated EL-4.B5 cells (5,000 Rads) and an appropriate level of T cell supernatant (ranging from 1-5% depending on preparation) in high glucose modified RPMI medium at a final volume of 250 µl/well. Cultures were incubated for 5 to 7 days at 37°C in 4% CO₂.

Identification of Selective Antibody Secreting B Cells

Cultures were tested for antigen recognition and functional activity between days 5 and 7.

Antigen Recognition Screening

The ELISA format used is as described above except 50 µl of supernatant from the B cell cultures (BCC) wells (all 30 plates) was used as the source of the antibody. The conditioned medium was transferred to antigen-coated plates. After positive wells were identified, the supernatant was removed and transferred to a 96-well master plate(s). The original culture plates were then frozen by removing all the supernatant except 40 µl/well and adding 60 µl/well of 16% DMSO in FBS. Plates were wrapped in paper towels to slow freezing and placed at -70°C.

Functional Activity Screening

Master plates were then screened for functional activity in the T1165 proliferation assay as described before, except row B was media only for background control, row C was media+LT-6 for positive proliferation control, and rows D-G and columns 2-11 were the wells from the BCC (50 µl/well, single points). 40 µl of IL-6 was added to all wells except the media row at 2.5 times the EC50 concentration determined for the assay. After 1 h incubation, the Ab/Ag complex was transferred to a tissue culture (TC) treated, 96-well, flat-bottom plate. 20 µl of cell suspension in modified RPMI medium without huIL-6 (T1165 at 20,000 cells/well) was added to all wells (100 µl final volume per well). Background was subtracted, and observed OD values were transformed into % of inhibition.

B Cell Recovery

Plates containing wells of interest were recovered from -70°C, and the cells from each well were recovered...
with 5-200 μl washes of medium/well. The washes were pooled in a 1.5 ml sterile centrifuge tube, and cells were pelleted for 2 minutes at 1500 rpm.

[1153] The tube was inverted, the spin repeated, and the supernatant carefully removed. Cells were resuspended in 100 μl of medium. 100 μl of biotinylated IL-6 coated streptavidin M280 dynabeads (Invitrogen) and 16 μl of goat anti-rabbit H&L IgG-FITC diluted 1:100 in medium was added to the cell suspension.

[1154] 20 μ1 of cell/beads/FITC suspension was removed, and 5 μl droplets were prepared on a glass slide (Corning) previously treated with Sigmacon (Sigma), 35 to 40 droplets/slide. An impermeable barrier of paraffin oil (JT Baker) was added to submerge the droplets, and the slide was incubated for 90 minutes at 37° C., 4% CO₂ in the dark.

[1155] Specific B cells that produce antibody can be identified by the fluorescent ring around them due to antibody secretion, recognition of the bead-associated biotinylated antigen, and subsequent detection by the fluorescent-IgG detection reagent. Once a cell of interest was identified, the cell in the center of the fluorescent ring was recovered via a micromanipulator (Eppendorf). The single cell synthesizes and exporting the antibody was transferred into a 250 μl microcentrifuge tube and placed in dry ice. After recovering all cells of interest, these were transferred to ~70° C. for long-term storage.

Example 8

Yeast Cell Expression

[1156] Antibody genes: Genes were cloned and constructed that directed the synthesis of a chimeric humanized rabbit monoclonal antibody.

[1157] Expression vector: The vector contains the following functional components:

[1158] 1) a mutant CoE1 origin of replication, which facilitates the replication of the plasmid vector in cells of the bacterium Escherichia coli; 2) a bacterial Sh ble gene, which confers resistance to the antibiotic Zeocin™ (phleomycin) and serves as the selectable marker for transformations of both E. coli and P. pastoris; 3) an expression cassette composed of the glyceraldehyde dehydrogenase gene (GAP gene) promoter, fused to sequences encoding the Saccharomyces cerevisiae alpha mating factor pro pro secretion leader sequence, followed by sequences encoding a P. pastoris transcriptional termination signal from the P. pastoris alcohol oxidase I gene (AOX1). The Zeocin™ (phleomycin) resistance marker gene provides a means of enrichment for strains that contain multiple integrated copies of an expression vector in a strain by selecting for transformants that are resistant to higher levels of Zeocin™ (phleomycin).

[1159] P. pastoris strains: P. pastoris strains met1, lys3, ura3 and ade1 may be used. Although any two complementing sets of auxotrophic strains could be used for the construction and maintenance of diploid strains, these two strains are especially suited for this method for two reasons. First, they grow more slowly than diploid strains that are the result of their mating or fusion. Thus, if a small number of haploid ade1 or ura3 cells remain present in a culture or arise through meiosis or other mechanism, the diploid strain should outgrow them in culture.

[1160] The second is that it is easy to monitor the sexual state of these strains since diploid Ade+ colonies arising from their mating are a normal white or cream color, whereas cells of any strains that are haploid ade1 mutants will form a colony with a distinct pink color. In addition, any strains that are haploid ura3 mutants are resistant to the drug 5-fluoro-orotic acid (FOA) and can be sensitively identified by plated samples of a culture on minimal medium-ura1 plates with FOA. On these plates, only ura1-requiring ura3 mutant (presumably haploid) strains can grow and form colonies. Thus, with haploid parent strains marked with ade1 and ura3, one can readily monitor the sexual state of the resulting antibody-producing diploid strains (haploid versus diploid).

Methods

[1161] Construction of pGAPZ-alpha expression vectors for transcription of light and heavy chain antibody genes. The humanized light and heavy chain fragments were cloned into the pGAPZ expression vectors through a PCR directed process. The recovered humanized constructs were subjected to amplification under standard KOD polymerase (Novagen) kit conditions ((1) 94° C., 2 minutes; (2) 94° C., 30 seconds (3) 55° C., 30 seconds; (4) 72° C., 30 seconds-cycling through steps 2-4 for 35 times; (5) 72° C. 2 minutes) employing the following primers (1) light chain forward AGGCCGTTATCCGCTATCCAGATGACCCAGTC-the Aefl site is single underlined. The end of the HSA signal sequence is double underlined, followed by the sequence for the mature variable light chain (not underlined); the reverse CTTAGCTTTGAGATCCACCTGTG.

[1162] Variable light chain reverse primer. BsiWI site is underlined, followed by the reverse complement for the 3' end of the variable light chain. Upon restriction enzyme digest with Aefl and BsiWI this enable insertion in-frame with the pGAPZ vector using the human HSA leader sequence in frame with the human kappa light chain constant region for export. (2) A similar strategy is performed for the heavy chain. The forward primer employed is AGGCCGTATCCGAGGTTGACCTGACGGAGTGTC. The XhoI site is underlined, followed by the reverse complement for the 3' end of the variable heavy chain. This enables cloning of the heavy chain in-frame with IgG-γ1 CH1-CH2-CH3 region previously inserted within pGAPZ using a compatible directional cloning strategy.


[1164] Prior to transformation, each expression vector is linearized within the GAP promoter sequences with AvrII to direct the integration of the vectors into the GAP promoter locus of the P. pastoris genome. Samples of each vector are then individually transformed into electrocompetent cultures of the ade1, met1, and lys3 strains by electroporation and successful transformants are selected on YPD Zeocin™ (phleomycin) plates by their resistance to this antibiotic. Resulting colonies are selected, streaked for single colonies on YPD Zeocin™ (phleomycin) plates and then examined for the presence of the antibody gene insert in a PCR assay on genomic DNA extracted from each strain for the proper anti-
body gene insert and/or by the ability of each strain to synthesize an antibody chain by a colony lift/immunoblot method (Wung et al. Biotechniques 21 808-812 (1996). Haploid ade1, met1 and lys3 strains expressing one of the three heavy chain constructs are collected for diploid constructions along with haploid ura3 strain expressing light chain gene. The haploid expressing heavy chain genes are mated with the appropriate light chain haploid ura3 to generate diploid secreting protein.

[1165] Mating of haploid strains synthesizing a single antibody chain and selection of diploid derivatives synthesizing tetrameric functional antibodies. To mate P. pastoris haploid strains, each ade1 (or met1 or lys3) heavy chain producing strain to be crossed is streaked across a rich YPD plate and the ura3 light chain producing strain is streaked across a second YPD plate (~10 streaks per plate). After one or two days incubation at 30° C., cells from one plate containing heavy chain strains and one plate containing ura3 light chain strains are transferred to a sterile velvet cloth on a replica-plating block in a cross hatched pattern so that each heavy chain strain contain a patch of cells mixed with each light chain strain. The cross-streaked replica plates cells are then transferred to a mating plate and incubated at 25° C. to stimulate the initiation of mating between strains. After two days, the cells on the mating plates are transferred again to a sterile velvet on a replica-plating block and then transferred to minimal medium plates. These plates are incubated at 30° C. for three days to allow for the selective growth of colonies of prototrophic diploid strains. Colonies that arise are picked and streaked onto a second minimal medium plate to single colony isolate and purify each diploid strain. The resulting diploid cell lines are then examined for antibody production.

[1166] Putative diploid strains are tested to demonstrate that they are diploid and contain both expression vectors for antibody production. For diploidy, samples of a strain are spread on mating plates to stimulate them to go through meiosis and form spores. Haploid spore products are collected and tested for phenotype. If a significant percentage of the resulting spore products are single or double auxotrophs it may be concluded that the original strain must have been diploid. Diploid strains are examined for the presence of both antibody genes by extracting genomic DNA from each and utilizing this DNA in PCR reactions specific for each gene.

[1167] Fusion of haploid strains synthesizing a single antibody chain and selection of diploid derivatives synthesizing tetrameric functional antibodies. As an alternative to the mating procedure described above, individual cultures of single-chain antibody producing haploid ade1 and ura3 strains are spheroplasted and their resulting spheroplasts fused using polyethylene glycol/CaCl2. The fused haploid strains are then embedded in agar containing 1 M sorbitol and minimal medium to allow diploid strains to regenerate their wall and grow into visible colonies. Resulting colonies are picked from the agar, streaked onto a minimal medium plate, and the plates are incubated for two days at 30° C. to generate colonies from single cells of diploid cell lines. The resulting putative diploid cell lines are then examined for diploidy and antibody production as described above.

[1168] Purification and analysis of antibodies. A diploid strain for the production of full length antibody is derived through the mating of met1 light chain and lys3 heavy chain using the methods described above. Culture media from shake flask or fermenter cultures of diploid P. pastoris, expression strains are collected and examined for the presence of antibody protein via SDS-PAGE and immunoblotting using antibodies directed against heavy and light chains of human IgG, or specifically against the heavy chain of IgG.

[1169] To purify the yeast secreted antibodies, clarified media from antibody producing cultures are passed through a protein A column and after washing with 20 mM sodium phosphate, pH 7.0, binding buffer, protein A bound protein is eluted using 0.1 M glycine HCl buffer, pH 3.0. Fractions containing the most total protein are examined by Coomassie blue stained SDS-PAGE and immunoblotting for antibody protein. Antibody is characterized using the ELISA described above for IL-6 recognition.

[1170] Assay for antibody activity. The recombinant yeast-derived humanized antibody is evaluated for functional activity through the IL-6 driven T1165 cell proliferation assay and IL-6 stimulated HepG2 haptoglobin assay described above.

Example 9

Acute Phase Response Neutralization by Intravenous Administration of Anti-IL-6 Antibody Ab1

[1171] Human IL-6 can provoke an acute phase response in rats, and one of the major acute phase proteins that is stimulated in the rat is α-2 macroglobulin (A2M). A study was designed to assess the dose of antibody Ab1 required to ablate the A2M response to a single s.c. injection of 100 μg of human IL-6 given one hour after different doses (0.03, 0.1, 0.3, 1, and 3 mg/kg) of antibody Ab1 administered intravenously (n=10 rats/dose level) or polyclonal human IgG1 as the control (n=10 rats). Plasma was recovered and the A2M was quantitated via a commercial sandwich ELISA kit (ICL Inc., Newberg, Ore., cat. no.—E-25AZM). The endpoint was the difference in the plasma concentration of A2M at the 24 hour time point (post-Ab1). The results are presented in FIG. 4.

[1172] The ID50 for antibody Ab1 was 0.1 mg/kg with complete suppression of the A2M response at the 0.3 mg/kg. This firmly establishes in vivo neutralization of human IL-6 can be accomplished by antibody Ab1.

Example 10

RXF393 Cachexia Model Study 1

Introduction

[1173] The human renal cell cancer cell line, RXF393 produces profound weight loss when transplanted into athymic nude mice. Weight loss begins around day 15 after transplantation with 80% of all animals losing at least 30% of their total body weight by day 18-20 after transplantation. RXF393 secretes human IL-6 and the plasma concentration of human IL-6 in these animals is very high at around 10 ng/ml. Human IL-6 can bind murine soluble IL-6 receptor and activate IL-6 responses in the mouse. Human IL-6 is approximately 10 times less potent than murine IL-6 at activating IL-6 responses in the mouse. The objectives of this study were to determine the effect of antibody Ab1, on survival, body weight, serum amyloid A protein, hematology parameters, and tumor growth in athymic nude mice transplanted with the human renal cell cancer cell line, RXF393.

Methods

[1174] Eighty, 6 week old, male athymic nude mice were implanted with RXF393 tumor fragments (30-40 mg) subcutaneously in the right flank. Animals were then divided into
eight groups of ten mice. Three groups were given either antibody Ab1 at 3 mg/kg, 10 mg/kg, or 30 mg/kg intravenously weekly on day 1, day 8, day 15 and day 22 after transplantation (progression groups). Another three groups were given either antibody Ab1 at 3 mg/kg, or 10 mg/kg, or 30 mg/kg intravenously weekly on day 8, day 15 and day 22 after transplantation (regression groups). Finally, one control group was given polyclonal human IgG 30 mg/kg and a second control group was given phosphate buffered saline intravenously weekly on day 1, day 8, day 15 and day 22 after transplantation.

[1175] Animals were euthanized at either day 28, when the tumor reached 4,000 mm³ or if they became debilitated (>30% loss of body weight). Animals were weighed on days 1, 6 and then daily from days 9 to 28 after transplantation. Mean Percent Body Weight (MPBW) was used as the primary parameter to monitor weight loss during the study. It was calculated as follows: (Body Weight—Tumor Weight)/Baseline Body Weight×100. Tumor weight was measured on days 1, 6, 9, 12, 15, 18, 22, 25 and 28 after transplantation. Blood was taken under anesthesia from five mice in each group on days 3 and 10 for each group when euthanized (day 28 in most cases). Blood was analyzed for hematology and serum amyloid A protein (SAA) concentration. An additional group of 10 non-tumor bearing 6 week old, athymic nude male mice had blood samples taken for hematology and SAA concentration estimation to act as a baseline set of values.

Results—Survival

[1176] No animals were euthanized or died in any of the antibody Ab1 groups prior to the study termination date of day 28. In the two control groups, 15 animals (% in the polyclonal human IgG group and º in the phosphate buffered saline group) were found dead or were euthanized because they were very debilitated (>30% loss of body weight). Median survival time in both control groups was 20 days.

[1177] The survival curves for the two control groups and the antibody Ab1 progression (dosed from day 1 of the study) groups are presented in FIG. 5.

[1178] The survival curves for the two control groups and the antibody Ab1 regression (dosed from day 8 of the study) groups are presented in FIG. 6.

[1179] There was a statistically significant difference between the survival curves for the polyclonal human IgG (p=0.0038) and phosphate buffered saline (p=0.0003) control groups and the survival curve for the six antibody Ab1 groups. There was no statistically significant difference between the two control groups (p=0.97).

Results—Tumor Size

[1180] Tumor size in surviving mice was estimated by palpation. For the first 15 days of the study, none of the mice in any group were found dead or were euthanized, and so comparison of tumor sizes between groups on these days was free from sampling bias. No difference in tumor size was observed between the antibody Ab1 progression or regression groups and the control groups through day 15. Comparison of the tumor size between surviving mice in the control and treatment groups subsequent to the onset of mortality in the controls (on day 15) was not undertaken because tumor size the surviving control mice was presumed to be biased and accordingly the results of such comparison would not be meaningful.

[1181] As administration of antibody Ab1 promoted survival without any apparent reduction in tumor size, elevated serum IL-6 may contribute to mortality through mechanisms independent of tumor growth. These observations suggest the hypothesis that antibody Ab1 can promote cancer patient survival without directly affecting tumor growth, possibly by enhancing general patient well-being.

Results—Weight Loss

[1182] Mean Percent Body Weight (MPBW) (±SEM) versus time is shown in FIG. 27. Compared to controls, mice dosed with Ab1 were protected from weight loss. On day 18, MPBW in control mice was 75%, corresponding to an average weight loss of 25%. In contrast, on the same day, MPBW in Ab1 treated groups was minimally changed (between 97% and 103%). There was a statistically significant difference between the MPBW curves for the controls (receiving polyclonal human IgG or PBS) and the 10 mg/kg dosage group (p<0.0001) or 3 mg/kg and 30 mg/kg dosage groups (p<0.0005). There was no statistically significant difference between the two control groups.

[1183] Representative photographs of control and Ab1-treated mice (FIG. 28) illustrate the emaciated condition of the control mice, compared to the normal appearance of the Ab1-treated mouse, at the end of the study (note externally visible tumor sites in right flank).

[1184] These results suggest that Ab1 may be useful to prevent or treat cachexia caused by elevated IL-6 in humans.

Results—Plasma Serum Amyloid A

[1185] The mean (±SEM) plasma serum amyloid A concentration versus time for the two control groups and the antibody Ab1 progression (dosed from day 1 of the study) and regression (dosed from day 8 of the study) groups are presented in Table 5 and graphically in FIG. 32.

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Mean Plasma SAA - antibody Ab1, all groups versus control groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Plasma</td>
<td>SAA ± SEM</td>
</tr>
<tr>
<td>Day 5 (µg/ml)</td>
<td></td>
</tr>
<tr>
<td>Polyclonal IgG iv</td>
<td>675 ± 240</td>
</tr>
<tr>
<td>weekly from day 1</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>PBS iv weekly</td>
<td>335 ± 207</td>
</tr>
<tr>
<td></td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 30 mg/kg iv</td>
<td>246 ± 100</td>
</tr>
<tr>
<td>weekly from day 1</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 10 mg/kg iv</td>
<td>3629 ± 624</td>
</tr>
<tr>
<td>weekly from day 1</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 3 mg/kg iv</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>weekly from day 1</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 30 mg/kg iv</td>
<td>375 ± 177</td>
</tr>
<tr>
<td>weekly from day 8</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 10 mg/kg iv</td>
<td>487 ± 170</td>
</tr>
<tr>
<td>weekly from day 8</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 3 mg/kg iv</td>
<td>1255 ± 516</td>
</tr>
<tr>
<td>weekly from day 8</td>
<td>(n = 5)</td>
</tr>
</tbody>
</table>

[1186] SAA is up-regulated via the stimulation of hIL-6 and this response is directly correlated with circulating levels of hIL-6 derived from the implanted tumor. The surrogate
marker provides an indirect readout for active hIL-6. Thus in
the two treatment groups described above there are signifi-
cantly decreased levels of SAA due to the neutralization of
tumor-derived hIL-6. This further supports the contention
that antibody Ab1 displays in vivo efficacy.

Example 11
RXF393 cachexia Model Study 2

Introduction

A second study was performed in the RXF-393 cachexia model
where treatment with antibody Ab1 was started at a later stage (days 10 and 13 post-transplantation)
and with a more prolonged treatment phase (out to 49 days
post transplantation). The dosing interval with antibody Ab1
was shortened to 3 days from 7 and also daily food consump-
tion was measured. There was also an attempt to standardize
the tumor sizes at the time of initiating dosing with antibody
Ab1.

Methods

Eighty, 6 week old, male athymic nude mice were
implanted with RXF393 tumor fragments (30-40 mg) subcuta-
nenously in the right flank. 20 mice were selected whose
mice had reached 270-320 mg in size and divided into
two groups. One group received antibody Ab1 at 10
mg/kg i.v. every three days and the other group received
polycional human IgG10 mg/kg every 3 days from that time-
point (day 10 after transplantation). Another 20 mice were
selected when their tumor size had reached 400-527 mg in
size and divided into two groups. One group received anti-
body Ab1 at 10 mg/kg i.v. every three days and the other
polycional human IgG10 mg/kg every 3 days from that time-
point (day 13 after transplantation). The remaining 40 mice
took no further part in the study and were euthanized at either day 49, when the tumor reached 4,000
mm3 or if they became very debilitated (>30% loss of body
weight).

Animals were weighed every 3-4 days from day 1 to
day 49 after transplantation. Mean Percent Body Weight
(MPBW) was used as the primary parameter to monitor weight loss during the study. It was calculated as follows:
((Body Weight—Tumor Weight)/Baseline Body Weight)×100.
Tumor weight was measured every 3-4 days from day 5
to day 49 after transplantation. Food consumption was mea-
sured (amount consumed in 24 hours by weight (g) by each
treatment group) every day from day 10 for the 270-320 mg
tumor groups and day 13 for the 400-527 mg tumor groups.

Results—Survival

The survival curves for antibody Ab1 at 10 mg/kg
i.v. every three days (270-320 mg tumor size) and for the
polycional human IgG10 mg/kg i.v. every three days (270-
320 mg tumor size) are presented in FIG. 7.

Median survival for the antibody Ab1 at 10 mg/kg
i.v. every three days (270-320 mg tumor size) was 46 days
and for the polycional human IgG at 10 mg/kg i.v. every three
days (270-320 mg tumor size) was 32.5 days (p=0.001).

The survival curves for the antibody Ab1 at 10
mg/kg i.v. every three days (400-527 mg tumor size) and for
the polycional human IgG at 10 mg/kg i.v. every three
days (400-527 mg tumor size) are presented in FIG. 8.

Example 12
Multi-Dose Pharmacokinetic Evaluation of Antibody
Ab1 in Non-human Primates

Antibody Ab1 was dosed in a single bolus infusion
to a single male and single female cynomolgus monkey in
phosphate buffered saline. Plasma samples were removed at
fixed time intervals and the level of antibody Ab1 was quan-
titated through the use of an antigen capture ELISA assay.
Biotinylated IL-6 (50 µl of 3 mg/ml) was captured on Strepa-
vidin coated 96 well microtiter plates. The plates were
washed and blocked with 0.5% Fish skin gelatin. Appropria-
tely diluted plasma samples were added and incubated for 1
hour at room temperature. The supernatants removed and an
anti-hFc-HRP conjugated secondary antibody applied and
left at room temperature.

The plates were then aspirated and TMB added to
visualize the amount of antibody. The specific levels were
then determined through the use of a standard curve. A second
dose of antibody Ab1 was administered at day 35 to the same
two cynomolgus monkeys and the experiment replicated
using an identical sampling plan. The resulting concentra-
tions are then plot vs. time as show in FIG. 9.

This humanized full length aglycosylated antibody
depressed and purified Pichia pastoris displays comparable
characteristics to mammalian expressed protein. In addition,
multiple doses of this product display reproducible half-lives
inferring that this production platform does not generate
products that display enhanced immunogenicity.

Example 13
Octet Mechanistic Characterization of Antibody Pro-
teins

IL-6 signaling is dependent upon interactions
between IL-6 and two receptors, IL-6R1 (CD126) and gp130
(IL-6 signal transducer). To determine the antibody
mechanism of action, mechanistic studies were performed using
bio-layer interferometry with an Octet QK instrument (Fortec-
Bio; Menlo Park, Calif.). Studies were performed in two
different configurations. In the first orientation, biotinylated
IL-6 (R&D systems part number 206-IL-001MG/CF); bioti-

yalted using Pierce EZ-link sulfo-NHS-LC-biotin product
number 21338 according to manufacturer’s protocols) was
initially bound to a streptavidin coated biosensor (Fortec-
Bio part number 18-5006). Binding is monitored as an
increase in signal.

The IL-6 bound to the sensor was then incubated either
with the antibody in question or diluent solution alone.
The sensor was then incubated with soluble IL-6R1 (R&D
systems product number 227-SR-025/CF) molecule. If the
IL-6R1 molecule failed to bind, the antibody was deemed to
block IL-6/IL-6R1 interactions. These complexes were incu-

bated with gp130 (R&D systems 228-GP-010/CF) in the
presence of IL-6R1 for stability purposes. If gp130 did not
bind, it was concluded that the antibody blocked gp130 inter-
actions with IL-6.

In the second orientation, the antibody was bound to
a biosensor coated with an anti-human IgG1 Fc-specific
reagent (FortecBio part number 18-5001). The IL-6 was bound
to the immobilized antibody and the sensor was incubated with IL-6R1. If the IL-6R1 did not interact with the IL-6, then it was concluded that the IL-6 binding antibody blocked IL-6/IL-6R1 interactions. In those situations where antibody/IL-6/IL-6R1 was observed, the complex was incubated with gp130 in the presence of IL-6R1. If gp130 did not interact, then it was concluded that the antibody blocked IL-6/gp130 interactions. All studies were performed in a 200 μl final volume, at 50 C and 1000 rpsms. For these studies, all proteins were diluted using ForteBio’s sample diluent buffer (part number 18-5028).

Results are presented in FIGS. 10 (A-E) and FIG. 11.

Example 14

Peptide Mapping

In order to determine the epitope recognized by Ab1 on human IL-6, the antibody was employed in a western-blot assay. The form of human IL-6 utilized in this example had a sequence of 183 amino acids in length (shown below). A 57-member library of overlapping 15 amino acid peptides encompassing this sequence was commercially synthesized and covalently bound to a PepSpots nitrocellulose membrane (PepTide technologies, Berlin, Germany). The sequences of the overlapping 15 amino acid peptides is shown in FIG. 12. Blots were prepared and probed according to the manufacturer’s recommendations.

Briefly, blots were pre-wet in methanol, rinsed in PBS, and blocked for over 2 hours in 10% non-fat milk in PBS/0.05% Tween (Blocking Solution). The Ab1 antibody was used at 1 mg/ml final dilution, and the HRP-conjugated Mouse Anti-Human-Kappa secondary antibody (Southern BioTech #9220-05) was used at a 1:5000 dilution. Antibody dilutions/incubations were performed in blocking solution. Blots were developed using Amersham ECL advanced reagents (GE RPN2135) and chemiluminescent signal documented using a CCD camera (AlphaImager). The results of the blots is shown in FIG. 13 and FIG. 14.

The sequence of the form of human IL-6 utilized to generate peptide library is set forth:

SEQ ID NO: 1
YPPGQDSKIVAAPHRQPULTSEREDQYRILGDISALRKEKHIMS
EESKEALENMLPKMAEEDGCPQCQGPHETCJVKITGLLSEFYVL
YLQNPBESREQRAVQMKSTVLQGQFOKAKNLDAITPPDPTTNSLL
TELQAOQNWQDQMTTHLRLSFKELQSSLRALRQN.

Example 15

Ab1 has High Affinity for IL-6

Surface plasmon resonance was used to measure association rate (K_a) dissociation rate (K_d) and dissociation constant (K_D) for Ab1 to IL-6 from rat, mouse, dog, human, and cynomolgus monkey at 25°C. (FIG. 15A). The dissociation constant for human IL-6 was 4 μM, indicating very high affinity. As expected, affinity generally decreased with phylogenetic distance from human. The dissociation constants of Ab1 for IL-6 of cynomolgus monkey, rat, and mouse were 31 pM, 1.4 nM, and 0.4 nM, respectively. Ab1 affinity for dog IL-6 below the limit of quantitation of the experiment.

The high affinity of Ab1 for mouse, rat, and cynomolgus monkey IL-6 suggest that Ab1 may be used to inhibit IL-6 of these species. This hypothesis was tested using a cell proliferation assay. In brief, each species’ IL-6 was used to stimulate proliferation of T1165 cells, and the concentration at which Ab1 could inhibit 50% of proliferation (IC50) was measured. Inhibition was consistent with the measured dissociation constants (FIG. 15B). These results demonstrate that Ab1 can inhibit the native IL-6 of these species, and suggest the use of these organisms for in vitro or in vivo modeling of IL-6 inhibition by Ab1.

Example 16

Multi-Dose Pharmacokinetic Evaluation of Antibody Ab1 in Healthy Human Volunteers

Antibody Ab1 was dosed in a single bolus infusion in histidine and sorbitol to healthy human volunteers. Doses of 1 mg, 3 mg, 10 mg, 30 mg, or 100 mg were administered to each individual in dosage groups containing five to six individuals. Plasma samples were removed at fixed time intervals for up to twelve weeks. Human plasma was collected via venipuncture into a vacuum collection tube containing EDTA. Plasma was separated and used to assess the circulating levels of Ab1 using a monoclonal antibody specific for Ab1, as follows. A 96 well microtiter plate was coated overnight with the monoclonal antibody specific for Ab1 in 1 x PBS overnight at 4°C. The remaining steps were conducted at room temperature. The wells were aspirated and subsequently blocked using 0.5% Fish Skin Gelatin (Sigma) in 1 x PBS for 60 minutes. Human plasma samples were then added and incubated for 60 minutes, then aspirated, then 50 μl of 1 mg/ml biotinylated IL-6 was then added to each well and incubated for 60 minutes. The wells were aspirated, and 50 μL streptavidin-HRP (Pharmingen), diluted 1:5,000 in 0.5% FSG/PBS, was added and incubated for 45 minutes. Development was conducted using standard methods employing TMB for detection. Levels were then determined via comparison to a standard curve prepared in a comparable format.

Average plasma concentration of Ab1 for each dosage group versus time is shown in FIG. 16. Mean AUC and C_max increased linearly with dosage (FIG. 17 and FIG. 18, respectively). For dosages of 30 mg and above, the average Ab1 half-life in each dosage group was between approximately 25 and 30 days (FIG. 19).

Example 17

Pharmacokinetics of Ab1 in Patients with Advanced Cancer

Antibody Ab1 was dosed in a single bolus infusion in phosphate buffered saline to five individuals with advanced cancer. Each individual received a dosage of 80 mg (n=2) or 160 mg (n=3) of Ab1. Plasma samples were drawn weekly, and the level of antibody Ab1 was quantitated as in Example 16.

Average plasma concentration of Ab1 in these individuals as a function of time is shown in FIG. 20. The average Ab1 half-life was approximately 31 days.

Example 18

Unprecedented Half-Life of Ab1

Overall, the average half-life of Ab1 was approximately 31 days in humans (for dosages of 10 mg and above),
and approximately 15-21 days in cynomolgus monkey. The Ab1 half-life in humans and cynomolgus monkeys are unprecedented when compared with the half-lives of other anti-IL-6 antibodies (FIG. 21). As described above, Ab1 was derived from humanization of a rabbit antibody, and is produced from *Pichia pastoris* in an aglycosylated form. These characteristics result in an antibody with very low immunogenicity in humans. Moreover, the lack of glycosylation prevents Ab1 from interacting with the Fc receptor or complement. Without intact Fc domain, it is believed that the unprecedented half-life of Ab1 is at least partially attributable to the humanization and/or lack of glycosylation. The particular sequence and/or structure of the antigen binding surfaces may also contribute to Ab1's half-life.

Example 19

Ab1 Effect on Hemoglobin Concentration, Plasma Lipid Concentration, and Neutrophil Counts in Patients with Advanced Cancer

[1210] Antibody Ab1 was dosed in a single bolus infusion in phosphate buffered saline to eight individuals with advanced cancer (NSCLC, colorectal cancer, cholangiocarcinoma, or mesothelioma). Each individual received a dosage of 80 mg, 160 mg, or 320 mg of Ab1. Blood samples were removed just prior to infusion and at fixed time intervals for six weeks, and the hemoglobin concentration, plasma lipid concentration, and neutrophil counts were determined. Average hemoglobin concentration rose slightly (FIG. 22), as did total cholesterol and triglycerides (FIG. 23), while mean neutrophil counts fell slightly (FIG. 24).

[1211] These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration in these individuals. Similarly, as IL-6 is centrally important in increasing neutrophil counts in inflammation, the observed slight reduction in neutrophil counts further confirms that Ab1 inhibits IL-6. Finally, IL-6 causes anorexia as well as cachexia in these patients; neutralization of IL-6 by Ab1 results in the return of appetite and reversal of cachexia. The increase in plasma lipid concentrations reflect the improved nutritional status of the patients. Taken together, these results further demonstrate that Ab1 effectively reverses these adverse consequences of IL-6 in these patients.

Example 20

Ab1 Suppresses Serum CRP in Healthy Volunteers and in Patients with Advanced Cancer

Introduction

[1212] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto et al. performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence (Hashimoto, K., et al., Cancer, 103(9):1856-1864 (2005)). Patients were classified into two groups, those with serum CRP levels >1.0 mg/dL ("the CRP positive group") and those with serum CRP levels <1.0 mg/dL ("the CRP negative group"). The authors identified "a significant correlation between preoperative serum CRP level and tumor size." Id. Furthermore, the authors found that "[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group." Id. The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator or poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[1213] Similar correlations have been identified by other investigators. For example, Karakiewicz et al. determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality (Karakiewicz, P. I. et al., Cancer, 110(6):1241-1247 (2007)). Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

[1214] Healthy volunteers received a single 1-hour intravenous (IV) infusion of either 100 mg (5 patients), 30 mg (5 patients), 10 mg (6 patients), 3 mg (6 patients) or 1 mg (6 patients) of the Ab1 monoclonal antibody, while another 14 healthy volunteers received intravenous placebo. Comparatively, 2 patients with advanced forms of colorectal cancer received a single 1-hour intravenous (IV) infusion of 80 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[1215] Patients were evaluated prior to administration of the dosage, and thereafter on a weekly basis for at least 5 weeks post dose. At the time of each evaluation, patients were screened for serum CRP concentration.

Results

Healthy Volunteers

[1216] As noted above, serum CRP levels are a marker of inflammation; accordingly, baseline CRP levels are typically low in healthy individuals. The low baseline CRP levels can make a further reduction in CRP levels difficult to detect. Nonetheless, a substantial reduction in serum CRP concentrations was detectable in healthy volunteers receiving all concentrations of the Ab1 monoclonal antibody, compared to controls (FIG. 25). The reduction in serum CRP levels was rapid, occurring within one week of antibody administration, and prolonged, continuing at least through the final measurement was taken (8 or 12 weeks from antibody administration).

Cancer Patients

[1217] Five advanced cancer patients (colorectal cancer, cholangiocarcinoma, or NSCLC) having elevated serum CRP levels were dosed with 80 mg or 160 mg of Ab1. Serum CRP levels were greatly reduced in these patients (FIG. 26A). The reduction in serum CRP levels was rapid, with 90% of the decrease occurring within one week of Ab1 administration, and prolonged, continuing at least until the final measurement was taken (up to twelve weeks). The CRP levels of two representative individuals are shown in FIG. 26B. In those individuals, the CRP levels were lowered to below the normal reference range (less than 5-6 mg/L) within one week. Thus,
administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 21
Ab1 Improved Muscular Strength, Improved Weight, and Reduced Fatigue in Patients with Advanced Cancer

Introduction

Weight loss and fatigue (and accompanying muscular weakness) are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue, weight loss and muscular weakness can have significant negative effects on the recovery of patients with advanced forms of cancer, for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue, weight loss and muscular weakness include regular routines of fitness and exercise, methods of conserving the patient’s energy, and treatments that address anemia-induced fatigue and muscular weakness. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue, weight loss and muscular weakness in cancer patients.

Methods

Four patients with advanced forms of cancer (colorectal cancer (2), NSCLC (1), cholangiocarcinoma (1)) each received a single I-hour intravenous (IV) infusion of either 80 mg or 160 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

Patients were evaluated prior to administration of the dosage, and thereafter for at least 6 weeks post dose. At the time of each evaluation, patients were screened for the following: a) any change in weight; b) fatigue as measured using the Facit-F Fatigue Subscale questionnaire a medically recognized test for evaluating fatigue (see, e.g., Cella, D., Lai, J. S., Chang, C. H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general population. Cancer, 94(2), 528-538; Cella, D., Eton, D. T., Lai, J.-S., Peterman, A. H & Merkel, D. E. (2002). Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy anemia and fatigue scales. Journal of Pain & Symptom Management, 24 (6) 547-561; and hand-grip strength (a medically recognized test for evaluating muscle strength, typically employing a handgrip dynamometer).

Results

Weight Change

The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase of about 2 kilograms of weight per patient over the period of 6 weeks (FIG. 29).

Fatigue

The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase in the mean Facit-F FS subscale score of at least about 10 points in the patient population over the period of 6 weeks (FIG. 30).

Hand-Grip Strength

The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase in the mean hand-grip strength of at least about 10 percent in the patient population over the period of 6 weeks (FIG. 31).

Example 22
Ab1 for Prevention of Thrombosis

Prior studies have shown that administration of an anti-IL-6 antibody can cause decreased platelet counts. Emile, D. et al., Blood, 84(8):2472-9 (1994); Blay et al., Int J Cancer, 72(3):424-30 (1997). These results have apparently been viewed as an indicator of potential danger, because further increases in platelet counts could cause complications such as bleeding. However, Applicants have now discerned that inhibiting IL-6 restores a normal coagulation profile, which Applicants predict will prevent thrombosis. Decreased platelet counts resulting from inhibition of IL-6 is not a sign of potential danger but rather reflects the beneficial restoration of normal coagulation.

The mechanism by which normal coagulation is restored is believed to result from the interplay between IL-6 and the acute phase reaction. In response to elevated IL-6 levels, as for example in a cancer patient, the liver produces acute phase proteins. These acute phase proteins include coagulation factors, such as Factor II, Factor V, Factor VIII, Factor IX, Factor XI, Factor XII, fibrinogen, fibrin, prothrombin, and von Willebrand factor. This increase in coagulation factors may be measured directly, or may be inferred from functional measurements of clotting ability. Antagonists of IL-6, such as Ab1, suppresses acute phase proteins, e.g., Serum Amyloid A (see FIG. 32 and Example 10). Applicants now predict that this suppression of acute phase proteins will restore the normal coagulation profile, and thereby prevent thrombosis. The restoration of normal coagulation may cause a slight drop in platelet counts, but the patient will nonetheless retain normal coagulation ability and thus will not have an increased risk of bleeding. Such a treatment will represent a vast improvement over the available anticoagulation therapies whose usefulness is limited by the risk of adverse side-effects, such as major bleeding.

Applicants contemplate that the same beneficial effects of inhibiting IL-6 will be obtained regardless of the method of inhibition. Suitable methods of inhibiting IL-6 include administration of anti-IL-6 antibodies, antisense therapy, soluble IL-6 receptor, etc. either individually or in combinations.

Example 23
Ab1 Increases Plasma Albumin Concentration in Patients with Advanced Cancer

Introduction

Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbuminemia correlates strongly with
poor patient performance in numerous forms of cancer. For example, in one study no patients undergoing systemic chemotherapy for metastatic pancreatic adenocarcinoma and having serum albumin levels less than 3.5 g/dL successfully responded to systemic chemotherapy (Fujishiro, M., et al., Hepatogastroenterology, 47(36):1744-4 (2000)). The authors conclude that “[p]atients with . . . hypoalbuminemia . . . might be inappropriate candidates for systemic chemotherapy and might be treated with other experimental approaches or supportive care.”

[1228] Similarly, Senior and Maroni state that “[t]he recent appreciation that hypoalbuminemia is the most powerful predictor of mortality in end-stage renal disease highlights the critical importance of ensuring adequate protein intake in this patient population.” (J. R. Senior and B. J. Maroni, Am. Soc. Nutr. Sci., 129:313 S-314S (1999)).

[1229] In at least one study, attempts to rectify hypoalbuminemia in 27 patients with metastatic cancer by daily intravenous albumin infusion of 20 g until normal serum albumin levels (>3.5 g/dL) were achieved had little success. The authors note that “[a]lbumin infusions for the advanced stage cancer patients have limited value in clinical practice. Patients with PS 4 and hypoalbuminemia have poorer prognosis.” (Demirkoz, A., et al., Proc. Am. Soc. Clin. Oncol., 21:Abstr 2892 (2002)).

[1230] Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

Methods

[1231] Four patients with advanced forms of cancer (colorectal cancer (2), NSCLC (1), cholangiocarcinoma (1) received a single 1-hour intravenous (IV) infusion of either 80 mg or 160 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[1232] Patients were evaluated prior to administration of the dosage, and thereafter for at least 6 weeks post dose. At the time of each evaluation, patients were screened for plasma albumin concentration.

Results

[1233] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase of about 5 g/L of plasma albumin concentration per patient over the period of 6 weeks (FIG. 33).

Example 24

Ab1 Suppresses Serum CRP in Patients with Advanced Cancer

Introduction

[1234] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto et al. performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence (Hashimoto, K., et al., Cancer, 103(9):1856-1864 (2005)). Patients were classified into two groups, those with serum CRP levels<1.0 mg/dL (“the CRP negative group”) and those with serum CRP levels>1.0 mg/dL (“the CRP positive group”). The authors identified “a significant correlation between preoperative serum CRP level and tumor size.” Id. Furthermore, the authors found that “[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group.” Id. The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator of poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[1235] Similar correlations have been identified by other investigators. For example, Karkiewicz et al. determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality (Karkiewicz, P I, et al., Cancer, 110(6):1241-1247 (2007)). Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

[1236] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (i.e. Roche CRP Tiasquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer.

[1237] Patients were evaluated prior to administration of the dosage, and thereafter at weeks 2, 4, 8, and 12. At the time of each evaluation, patients were screened for serum CRP concentration.

Results

[1238] The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody are plotted in FIG. 38. All dosage levels of Ab1 antibody demonstrated an immediate drop in CRP concentrations relative to placebo over the period of 12 weeks. CRP levels displayed breakthrough at 8 weeks post dosing. The CRP levels fell below 5 mg/L by week 12. Median values of CRP demonstrated rapid and sustained decreases for all dosage concentrations relative to placebo (FIG. 39). Thus, administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 25

Ab1 Suppresses Serum CRP in Patients with Advanced Cancers

Introduction

[1239] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of
cancer. For example, Hashimoto et al. performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence (Hashimoto, K., et al., Cancer, 103(9):1856-1864 (2005)). Patients were classified into two groups, those with serum CRP levels >1.0 mg/dL (“the CRP positive group”) and those with serum CRP levels <1.0 mg/dL (“the CRP negative group”). The authors identified a “significant correlation between preoperative serum CRP level and tumor size.” Id. Furthermore, the authors found that “[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group.” Id. The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator of poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[1240] Similar correlations have been identified by other investigators. For example, Karaskiewicz et al. determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality (Karaskiewicz, P. L., et al., Cancer, 110(6):1241-1247 (2007)). Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

[1241] Eight patients with various forms of advanced cancer (colorectal (3), NSCLC (1), cholangio (1), and mesothelioma (2)) received a single 1-hour intravenous infusion of either 80 mg (2 patients), 160 mg (3 patients) or 320 mg (3 patients) of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[1242] Patients were evaluated prior to administration of the dosage and thereafter on a weekly basis for at least 8 weeks post dose. At the time of each evaluation, patients were screened for serum CRP concentration. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (i.e. Roche CRP Tinquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer.

Results

[1243] Serum CRP levels were greatly reduced in all patients studied (FIG. 40). The reduction in serum CRP levels was rapid, with approximately 90% of the decrease occurring within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to twelve weeks). In all cases except one patient with colorectal cancer, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. The colorectal cancer patient achieved similar normal levels by week 4 of the study. Thus, administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 26

Ab1 Suppresses Serum CRP in Patients with Rheumatoid Arthritis

Introduction

[1244] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with rheumatoid arthritis. Patients suffering from rheumatoid arthritis with high levels of CRP demonstrated almost universal deterioration. Anos et al., 1 Br. Med. J. 195-97 (1977). Conversely, patients with low CRP levels showed no disease progression, suggesting that sustaining low levels of CRP is necessary for effectively treating rheumatoid arthritis. Id. Tracking of CRP during rheumatoid arthritis treatment regimes of gold, D-penicillamine, chloroquine, or dapsone indicated that radiological deterioration was impeded after the first 6 months of treatment when CRP levels were consistently controlled. Dawes et al., 25 Rheumatology 44-49 (1986). A highly significant correlation between CRP production and radiological progression was identified. van Leeuwen et al., 32 (Supp. 3) Rheumatology 9-13 (1997). Another study revealed that for patients with active rheumatoid arthritis, suppression of abnormally elevated CRP led to improvement in functional testing metrics, whereas sustained CRP elevation associated with deterioration in the same metrics. Devlin et al., 24 J. Rheumatol. 9-13 (1997). No further deterioration was observed without CRP re-elevation, indicating CRP suppression as a viable candidate for rheumatoid arthritis treatment. Id. Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in rheumatoid arthritis patients.

Methods

[1245] One-hundred twenty-seven patients with active rheumatoid arthritis and CRP ≥10 mg/L were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=35), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Ab1 monoclonal antibody, once at the start of the 16 week trial and again at week 8. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (i.e. Roche CRP Tinquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer. Data on CRP concentration was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16.

Results

[1246] Serum CRP levels were greatly reduced in all patients studied (FIG. 41). The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Ab1 administration, and pro-
longed diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Ab1 to rheumatoid arthritis patients can cause a rapid and sustained suppression of serum CRP levels and presents an effective treatment regime.

Example 27
Ab1 Increases Hemoglobin in Patients with Advanced Cancer

[1247] Antibody Ab1 was dosed at 80 mg, 160 mg, or 320 mg of Ab1 in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. The placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the hemoglobin concentration was determined. Mean hemoglobin concentration rose for those receiving antibody Ab1, while mean hemoglobin concentration of those receiving placebo did not rise after twelve weeks when compared to the concentration just prior to dosing (zero week) (FIGS. 42 and 43).

[1248] A subset of the study population began the study with low levels of hemoglobin, defined as a baseline hemoglobin concentration below 11 g/l. Mean hemoglobin concentration rose above 11 g/l after eight weeks for those receiving antibody Ab1 at dosages of 160 mg and 320 mg, while mean hemoglobin concentration of those receiving antibody Ab1 at dosages of 80 mg or placebo did not rise above 11 g/l after eight weeks (FIG. 44).

[1249] These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration in these individuals.

Example 28
Ab1 Increases Hemoglobin in Patients with Rheumatoid Arthritis

[1250] Hemoglobin levels were analyzed in patients with rheumatoid arthritis during treatment with Ab1 antibody. Ab1 antibody was dosed at 80 mg, 160 mg, or 320 mg in phosphate buffered saline to 94 individuals with rheumatoid arthritis. The placebo group of 33 individuals with rheumatoid arthritis was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at one, two, three, four, six, eight, ten, twelve, and sixteen weeks, and the hemoglobin concentration was determined. Mean hemoglobin concentration rose for those receiving antibody Ab1, while mean hemoglobin concentration of those receiving placebo did not appreciably rise after sixteen weeks when compared to the concentration just prior to dosing (zero week) (FIG. 45).

[1251] These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration.

Example 29
Ab1 Increases Albumin in Patients with Advanced Cancer

Introduction

[1252] Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbuminemia correlates strongly with poor patient performance in numerous forms of cancer. For example, in one study to patients undergoing systemic chemotherapy for metastatic pancreatic adenocarcinoma and having serum albumin levels less than 3.5 g/dL successfully responded to systemic chemotherapy (Fujishiro, M., et al., Hepatogastroenterology, 47(36):1744-46 (2000)). The authors conclude that "[p]atients with hypoalbuminemia . . . might be inappropriate candidates for systemic chemotherapy and might be treated with other experimental approaches or supportive care.” Id.

[1253] Similarly, Senior and Maroni state that “[t]he recent appreciation that hypoalbuminemia is the most powerful predictor of mortality in end-stage renal disease highlights the critical importance of ensuring adequate protein intake in this patient population.” (J. R. Senior and B. J. Maroni, Am. Soc. Nutr. Sci., 129:313 S-314S (1999)).

[1254] In at least one study, attempts to rectify hypoalbuminemia in 27 patients with metastatic cancer by daily intravenous albumin infusion of 20 g until normal serum albumin levels (≥3.5 g/dL) were achieved had little success. The authors note that “albumin infusion for the advanced stage cancer patients has limited value in clinical practice. Patients with PS 4 and hypoalbuminemia have poorer prognosis.” (Demirkazik, A., et al., Proc. Am. Soc. Clin. Oncol., 21: Abstr 2892 (2002)).

[1255] Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

Methods

[1256] Antibody Ab1 was dosed at 80 mg, 160 mg, or 320 mg of Ab1 in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. Each individual received a dosage of. The placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the albumin concentration was determined.

Results

[1257] Mean albumin concentration rose for those receiving antibody Ab1, while mean albumin concentration of those receiving placebo did not rise after twelve weeks when compared to the concentration just prior to dosing (zero week) (FIG. 46). The change from baseline albumin values for all dosage concentration groups is plotted in FIG. 47.

[1258] A subset of the study population began the study with low levels of albumin, defined as a baseline albumin concentration less than or equal to 35 g/L. Mean albumin
concentration initially rose with all dosages of antibody Ab1 over placebo, but only patients receiving 160 mg or 320 mg demonstrated sustained albumin levels above 35 g/L over 8 weeks of the study (FIG. 48). The 80 mg dosage group demonstrated an initial increase, but gradually declined after week 2 and never rose above 35 g/L during the 8 weeks where data was available (id.).

Example 30
Ab1 Improved Weight and Reduced Fatigue in Patients with Advanced Cancer

Introduction
[1259] Weight loss and fatigue are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue and weight loss can have significant negative effects on the recovery of patients with advanced forms of cancer, for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue and weight loss include regular routines of fitness and exercise, methods of conserving the patient’s energy, and treatments that address anemia-induced fatigue. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue and weight loss in cancer patients.

Methods
[1260] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses. [1261] Patients were evaluated prior to administration of the dosage, and thereafter for at least 12 weeks post dose. At the time of each evaluation, patients were screened for the following: a) any change in weight; and b) fatigue as measured using the Fatigue-F Subscale questionnaire a medically recognized test for evaluating fatigue (See, e.g., Celli, D., Lai, J. S., Chang, C. H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general population. Cancer, 94(2), 528-538; Cella, D., Ylon, D. T., Lai, F. J.-S., Peterman, A. H & Merkel, D. E. (2002). Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy Anemia and fatigue scales. Journal of Pain & Symptom Management, 24 (6) 547-561).

Results

Weight Change
[1262] The averaged weight change data from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody over 12 weeks is plotted in FIG. 49. The average percent change in body weight from each dosage concentration is plotted in FIG. 50. The averaged lean body mass data for the dosage concentration groups is plotted in FIG. 51.

Fatigue
[1263] The averaged fatigue from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody demonstrated increases in the mean Facit-F FS subscale score for some of the dosage concentration groups in the patient population over the period of 8 weeks (FIG. 52). The change from baseline Facit-F subscale score is plotted in FIG. 53.

Example 31
Ab1 Decreases D-Dimer Levels in Patients with Advanced Cancer

Introduction
[1264] D-dimer concentrations are recognized as useful diagnostic tools in predicting risks of thrombotic events in patients. (Adam et al., 113 Blood 2878-87 (2009).) Patients that are negative for D-dimer have a low probability for thrombosis. For example, D-dimer analysis can rule out suspected lower-extremity deep-vein thrombosis in patients. (Wells et al., 349 N. Engl. J. Med. 1227-35 (2003).) Clinical evaluation in combination with negative D-dimer test can effectively lower the instance of pulmonary embolism to 0.5%. (Van Belle et al., 295 JAMA 172-79 (2006); Krup et al., 162 Arch. Intern. Med. 1631-35 (2002); Wells et al., 135 Ann. Intern. Med. 98:107 (2001)).

[1265] D-dimer analysis may have utility in tracking the progress of treating coagulation disorders. One study indicated that anticoagulation treatment for acute venous thromboembolism resulted in a gradual decline in D-dimer concentrations. (Adam et al., 113 Blood 2878-87 (2009); Schutgens et al., 144 J. Lab. Clin. Med. 100-07 (2004).) This discovery led to the conclusion that D-dimer levels monitoring could be used to assess treatment responsiveness. (Adam et al., 113 Blood at 2883)

[1266] For patients with cancer, D-dimer analysis may have additional significance, as cancer increases the prevalence of thrombosis. (Adam et al., 113 Blood 2878-87 (2009).) One study with oncotherapy patients indicated that D-dimer concentrations have a high negative predictive value and high sensitivity in diagnosing pulmonary embolism. (King et al., 247 Radiology 854-61 (2008).) Deep-vein thrombosis can similarly be excluded for cancer patients with low probability of developing deep-vein thrombosis and a negative test for D-dimer, although such a combination is less likely for oncology patients. (Lee et al., 123 Thromb. Res. 177-83 (2008).) A higher threshold for a negative D-dimer result may be necessary in cancer patients. (Richini et al., 95 Haemost. 715-19 (2006)).

[1267] Accordingly, there remains a need in the art for methods and/or treatments of thrombosis that improve D-dimer concentrations in cancer patients and address elevated D-dimer states in cancer patients, particularly those with advanced cancers.

Methods
[1268] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses. Data on D-dimer concentration was collected for the first 8 weeks of treatment. D-dimer data concentration was quantitated by a D-dimer immunoturbidimetric assay. Briefly, the assay is based on the change in turbidity of a microparticle
suspension that is measured by photometry. About 1.5 mL of 
patient sample sodium citrate plasma was collected and 
stored in a plastic collection tube. A suspension of latex 
microparticles, coated by covalent bonding with monoclonal 
antibodies specific for D-dimer, was mixed with the test 
plasma whose D-dimer level was to be assayed. Antigen- 
antibody reactions leading to an agglutination of the latex 
microparticles induced an increase in turbidity of the reaction 
medium. This increase in turbidity was reflected by an 
increase in absorbance, the latter being measured photomet-
rially using a STAGO STA analyzer. The increase in absorb-
ance was a function of the D-dimer level present in the test 
sample.

Results

[1269] The averaged data for each dosage concentrations 
(placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal 
antibody are plotted in Fig. 54. Error bars were omitted from 
the graph for clarity purposes. The percent change from base-
line in D-dimer concentration is plotted in Fig. 55. All dosage 
levels of Ab1 antibody demonstrated a drop in D-dimer levels 
over placebo over the period of 8 weeks.

Example 32

Ab1 Efficacy and Safety in Patients with Advanced 
NSCLC

[1270] The primary objective of this study was to determine 
the efficacy and safety of ALD518 or humanized Ab1 in 
patients with advanced NSCLC.

[1271] Methods:

[1272] 124 patients (pts) with NSCLC, ECOG 0-3, weight 
loss in the preceding 3 months of >5% body weight, hemog-
ine (Hb)>7 g/dL, and C-reactive protein (CRP)>10 mg/L were 
dosed. Pts were randomized to 1 of 4 groups (n=30/
group). Placebo or ALD518 80 mg, 160 mg, or 320 mg was 
administered intravenously every 8 weeks. Pts were followed 
up for 24 weeks. Data included hematology, clinical chemis-
try, CRP and adverse events (AEs).

[1273] Results:

[1274] 29 pts completed the study treatments and evalua-
tions, 38 failed to complete every visit, 52 died of progressive 
disease, and 5 withdrew because of adverse events. There 
were no dose limiting toxicities (DLTs) or infusion reactions. 
84 pts had serious AEs of which 1 was deemed to be possibly 
related to administration of ALD518 (rectal hemorrhage). The 
mean ±SD values for Hb, hematocrit (Hct), mean cor-
puscular Hb (MCH), and albumin are below:

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Hb (g/dL)</th>
<th>Hct (%)</th>
<th>MCH (pg)</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD518</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dose</td>
<td>93</td>
<td>11.5±(±2.1)</td>
<td>37.9±(±6.2)</td>
<td>28.4±(±2.8)</td>
<td>37.3±(±5.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dose</td>
<td>31</td>
<td>12.2±(±1.8)</td>
<td>39.0±(±5.9)</td>
<td>29.0±(±2.8)</td>
<td>37.5±(±5.7)</td>
</tr>
</tbody>
</table>

*p = 0.0001

**Conclusion:**

[1275] ALD518 increased Hb, Hct, MCH and albumin in 
NSCLC pts and raised Hb to ≥12 g/dL in 58% of pts with a 
Hb≥11 g/dL at baseline. This further indicates that ALD518 
can be administered as a non-erythropoietic stimulating agent 
for treating cancer-related anemia.

Example 33

Ab1 Achieved ACR 20/50/70 in Patients with Rheu-
matoid Arthritis

Introduction

[1277] Rheumatoid arthritis is a chronic, systemic inflam-
matory disorder that principally attack synovium of joints. 
The disease causes painful and potentially disabling inflam-
mation, with onset typically occurring between 40 and 50 
years of age. Interpretation of drug treatment efficacy in rheu-
matoid arthritis is made difficult by the myriad of subjective 
and objective assessment tools made available over the years. 
The American College of Rheumatology (“ACR”) released a 
standardized set of rheumatoid arthritis measures to facilitate 
evaluation of improvement of the disease in clinical trials. 

Methods

[1278] One-hundred twenty-seven patients with active 
rheumatoid arthritis and CRP ≥10 mg/L were divided into 4 
treatment groups. Patients in one group received one 1-hour 
intravenous (IV) infusion of either placebo (n=33), 80 mg 
(n=32), 160 mg (n=34), or 320 mg (n=28) of the Ab1 mono-
clonal antibody, once at the start of the 16 week trial and again 
at week 8. Data on CRP concentration was collected every 
week for the first 4 weeks, every two weeks between weeks 4 
and 12, and at the conclusion of the test at week 16.

Assessment under the standardized protocols from 
the American College of Rheumatology were employed in 
determining the percentage of improvement of patients dur-
ing the clinical trial and conducted by a person trained in the 
orinary art of evaluating rheumatoid arthritis. The evalua-
tion was based upon activity measures, including tender joint 
count, swollen joint count, the patient’s assessment of pain, 
the patient’s and physician’s global assessments of disease 
activity, and laboratory evaluation of either erythrocyte sedi-
mentation rate or CRP level. Id. The patient’s assessment of 
pain was based upon the Stanford Health Assessment Ques-
tionnaire Disability Index (HAQ DI). Patients that achieve a 
20% increase in activity measures for rheumatoid arthritis.
during a clinical trial are categorized as achieving ACR 20. Similarly, patients achieving 50% and 70% improvements are categorized as ACR 50 and ACR 70, respectively.

Results

A significant portion of patients suffering from rheumatoid arthritis achieved ACR 20 or greater during the course of the study (FIG. 56). Patients observed rapid improvement in systems within the first 4 weeks of the study, as well as continued, steady improvement throughout the course of the 16 week evaluation (FIGS. 57, 58, and 59). The greatest results were exhibited by patients receiving the 320 mg dosage level, with 43% achieving ACR 70 status during the study (FIG. 59).

Analysis of the individual components of the ACR evaluation demonstrated gains in every component (FIG. 60). HAQ-DI scores demonstrated clinically meaningful change over placebo during the course of the evaluation (FIG. 61). Serum CRP levels were greatly reduced in all patients studied (FIG. 41). The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to or below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Ab1 can cause a rapid and sustained improvement rheumatoid arthritis patients, as evidenced by the significant improvement in ACR scores during clinical evaluation, and presents an effective treatment regime.

Example 34

Ab1 Achieved Improved DAS28 and EULAR Scores in Patients with Rheumatoid Arthritis

Introduction

Rheumatoid arthritis is a chronic, systemic inflammatory disorder that principally attack synovium of joints. The disease causes painful and potentially disabling inflammation, with onset typically occurring between 40 and 50 years of age. Interpretation of drug treatment efficacy in rheumatoid arthritis is made difficult by the myriad of subjective and objective assessment tools made available over the years. The American College of Rheumatology (“ACR”) released a standardized set of rheumatoid arthritis measures to facilitate evaluation of improvement in the disease in clinical trials. Felson et al., 36 Arthritis & Rheumatism 729-40 (1993).

Inflammatory activity associated with rheumatoid arthritis is measured using numerous variables through validated response criteria such as Disease Activity Score (DAS), DAS28 and EULAR. The DAS is a clinical index of rheumatoid arthritis disease activity that combines information from swollen joints, tender joints, the acute phase response, and general health. Fransen, J., et al., Clin. Exp. Rheumatol., 23 (Suppl. 39): S93-S99 (2005). The DAS 28 is an index similar to the original DAS, but utilizes a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR (erythrocyte sedimentation rate), and an optional general health assessment on a visual analogue scale (range 0-100).Id. The European League against Rheumatism (EULAR) response criteria classify patients using the individual amount of change in the DAS and the DAS value (low, moderate, high) reached into one of the following classifications: Good; Moderate; or Non-Responders. Id. Methods

One-hundred twenty-seven patients with active rheumatoid arthritis were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Ab1 monoclonal antibody, once at the start of the 16 week trial and again at week 8. Data on the DAS28 and EULAR scores was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16. Assessment under the standardized DAS28 and EULAR protocols were employed in determining the respective scores of patients during the clinical trial and conducted by a person trained in the ordinary art of evaluating rheumatoid arthritis.

Results

Patients receiving 80 mg, 160 mg or 320 mg of Ab1 demonstrated improved DAS28 scores relative to those patients receiving placebo over the course of 16 weeks, as presented in FIG. 62 as a mean change from the baseline DAS28 score. Furthermore, a significant percentage of patients receiving 80 mg, 160 mg or 320 mg of Ab1 achieved “Good” or “Moderate” classifications relative to those patients receiving placebo over the course of 16 weeks. (FIG. 63).

Thus, administration of Ab1 can result in improved DAS28 and EULAR scores in rheumatoid arthritis when compared to those patients receiving placebo.

Example 35

Safety, Pharmacokinetics (PK), and Pharmacodynamics ((PD) of Ab1 in Human Subjects

Background:

A humanized antibody derived from Ab1 (humanized Ab1 or AL0518) containing the variable heavy and light sequences in SEQ ID NO:19 and 20 was administered to rheumatoid arthritis patients. This antibody is a humanized, isolated, IgG1 monoclonal antibody against IL-6 which has been shown to have a half-life (VA) of approximately 30 days in humans. In studies in patients with RA, intravenous (IV) with this antibody (humanized Ab1) has demonstrated: efficacy over 16 weeks with rapid American College of Rheumatology (ACR) responses; Complete and durable suppression of C-reactive protein (CRP); Good tolerability, and a safety profile consistent with the biology of IL-6 blockade. This humanized antibody binds to IL-6 with high affinity, preventing interaction and signalling mediated via IL-6R. Rapid and significant treatment responses have been demonstrated with intravenous (IV) administration of humanized Ab1 in patients with RA. In this example we study the safety, pharmacokinetics and pharmacodynamics of subcutaneous (SC) administration of humanized Ab1 in healthy subjects.

The objective of this study was to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of a single SC injection of this humanized antibody in healthy male subjects.

Methods:

In this Phase I, double-blind, placebo-controlled study, 27 subjects were randomized 2:1 to receive a single dose of humanized Ab1 or placebo in the following groups:
humanized Ab1 50 mg SC, humanized Ab1 100 mg SC or humanized Ab1 100 mg IV (n=6 active and n=3 placebo per group). The primary objective was to assess safety of SC humanized Ab1 versus placebo over 12 weeks. Plasma concentrations of humanized Ab1 and serum concentrations of C-reactive protein (CRP) were assessed as secondary objectives. Assessments were performed daily in Week 1 and then on Day 10, Weeks 2, 4, 6 and 8, and then monthly to Week 12. The study was unblinded at Week 12, and humanized Ab1 subjects were monitored to Week 24.

Study Design and Population

The study included 27 healthy male subjects (aged 18-65 years). Subjects were dosed in three treatment groups of nine subjects each, randomized 2:1 to receive a single dose of humanized Ab1 or placebo on Day 1 (FIG. 64). Humanized Ab1 treatments per group were:

- [1291] humanized Ab1 IV 100 mg infusion over 60 minutes
- [1292] humanized Ab1 SC 50 mg injection (1 mL)
- [1293] humanized Ab1 100 mg injection (1 mL)

The study was unblinded at Week 12, after which placebo subjects discontinued the trial and BMS-045429 subjects were monitored to Week 24 (FIG. 64).

Safety and Immunogenicity Assessments

The primary objective of the study was to assess the safety of SC humanized Ab1 compared with placebo over 12 weeks. Safety was monitored over 12 weeks for all subjects. The study was unblinded at Week 12, and Humanized Ab1 subjects were monitored to Week 24.

Laboratory safety tests were performed pre-dose at screening and Day -1, and post dose on Days 2 and 7, Weeks 2, 4, 6, 8 and 12 for all subjects, and Weeks 16, 20 and 24 post-dose for those randomized to Humanized Ab1. Anti-Humanized Ab1 antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Blood samples were collected at Day 1 (pre-dose) and Week 12 post-dose for all subjects, and Week 24 post-dose for those randomized to Humanized Ab1.

Pharmacokinetic and Pharmacodynamic Assessments

Plasma Humanized Ab1 and serum CRP concentrations were assessed by ELISA. For all subjects, samples were collected at screening, pre-dose on Day 1, and post-dose on Days 2 and 7 and Weeks 2, 4, 6, 8 and 12. For subjects randomized to Humanized Ab1, further samples were collected at Weeks 16, 20 and 24 post-dose.

Statistical Analysis

All subjects who received a dose of Humanized Ab1 or placebo were included in the safety analysis. All subjects who received a dose of Humanized Ab1 or placebo were included in PD and immunogenicity analyses. All subjects who received a dose of Humanized Ab1 were included in PK analyses (n=18). All PK samples for placebo subjects were confirmed below quantification.

Descriptive statistics were generated for baseline demographics, safety data, plasma Humanized Ab1 parameters and serum CRP concentrations. Wilcoxon Rank Sum test was used to compare CRP concentrations for Humanized Ab1 treatments versus placebo.

Results:

Summary

Over 24 weeks, there were no deaths or serious AEs, and no withdrawals due to AEs. Nearly all subjects (89%) experienced AEs, which were mild or moderate except one event of severe gastroenteritis in the Humanized Ab1 SC 50 mg group. Injection site reactions occurred in ½ Humanized Ab1 SC subjects, ⅔ placebo SC subjects and ½ placebo IV subjects (none were reported in Humanized Ab1 IV subjects). These were mild except one case of moderate erythema and pruritus in the Humanized Ab1 100 mg SC group. Increases in direct bilirubin and neutrophil counts below the limit of normal were more common in subjects receiving Humanized Ab1 than placebo; all were CTC Grade 1 or 2. The half-life of Humanized Ab1 was similar across all groups (mean range: 30.7-33.6 days). The median T_max of Humanized Ab1 was longer after SC (~1 week) than after IV administration (~end of infusion). The PK of SC Humanized Ab1 was dose-proportional in terms of AUC and C_max at doses of 50 mg and 100 mg. Based on AUC_0-28 day*(mg/mL) of 237, 452 and 764 for the Humanized Ab1 50 mg SC, 100 mg SC and 100 mg IV groups, respectively, the bioavailability of Humanized Ab1 was ~60% for the versus IV groups. Subjects receiving Humanized Ab1 experienced rapid and sustained reductions in serum CRP (FIG. 66).

Subject Disposition and Baseline Demographics

A total of 27 subjects were enrolled and completed the study (n=18 Humanized Ab1 and n=9 placebo). No subjects were withdrawn for any reason.

All subjects were male; 23/27 subjects were Caucasian and 4/27 were Asian. Mean age was 29 (range 20-59) and was similar across the groups. Mean height and weight were also generally comparable across groups, although the IV placebo group were slightly lighter.

Safety and immunogenicity to Week 12 for Humanized Ab1 and placebo

A summary of safety is presented in FIG. 67. For the SC Humanized Ab1 groups, a total of 11/28 (91%) patients experienced an adverse event (AE) compared with:

- [1306] ½ (100%) for the IV Humanized Ab1 group;
- [1307] ½ (66.6%) for the SC placebo group; and
- [1308] ½ (100%) for the IV placebo group.

Across groups:

No deaths or serious AEs were reported and there were no withdrawals due to AEs.

Most AEs were mild or moderate in intensity.

One case of gastroenteritis in a SC Humanized Ab1 50 mg subject was considered severe, but not serious, and not related to study medication.

No anti-Humanized Ab1 antibodies were detected in any subject during this period.

Injection Site Reactions

Injection site reactions were reported in 26% (7/27) of subjects, and all occurred prior to Week 12 (FIG. 68). Injection site reactions occurred in ½ SC Humanized Ab1 subjects and ½ SC placebo subjects. In the IV groups, 0/6 Humanized Ab1 subjects and ½ placebo subjects experienced injection site reactions. All injection site reactions were mild except in one SC Humanized Ab1 100 mg subject with moderate injection site erythema and pruritus. No injection
site reactions occurred after Week 12 in any of the Humanized AB1 groups. Infusion site reactions were reported in 0/6 subjects receiving IV Humanized AB1 and 1/3 IV placebo subjects (infusion site pruritus).

Clinical Laboratory Evaluations

[1315] FIG. 69 shows incidences of increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and bilirubin levels across the Humanized AB1 and placebo groups. All ALT and AST levels were Grade 1 by the Common Terminology Criteria for Adverse Events (CTCAE), and no levels were ≥3 times the upper limit of normal (ULN). All increases in total and direct bilirubin were CTCAE Grade 1 or 2 and no subject met criteria for drug-induced liver damage. Only one subject (SC Humanized AB1 100 mg group) had total bilirubin out of range (26 μmol/L, range: 0-24 μmol/L), at Week 24.

[1316] Sporadic decreases in neutrophil and platelet counts were also observed in the Humanized AB1 and placebo groups (FIG. 69). Neutrophil counts below the limit of normal were more common in subjects receiving Humanized AB1 than placebo but all decreases were CTCAE Grade 1 or 2. Only one subject (SC Humanized AB1 50 mg group) had a consistent mild neutropenia to Week 24 (1.6×10⁹/L at Week 24). Reductions in platelet counts were all CTCAE Grade 1 (lowest level 134×10⁹/L) and no subject had a low platelet count past Week 8.

Pharmacokinetics

[1317] Bioavailability of Humanized AB1 was 60% for SC Humanized AB1 50 and 100 mg versus IV Humanized AB1 100 mg based on the mean AUC₀₋∞ (FIG. 70). The half-life of Humanized AB1 was similar across all groups (mean range: 30.7-33.6 days) (FIG. 70). Peak plasma concentration (Cₚₑₚ) of SC Humanized AB1 was reduced as compared to IV (FIG. 65). Median time to maximum plasma concentration (Tₚₑₚ) of Humanized AB1 was longer after SC Humanized AB1 (at approximately one week) than after IV Humanized AB1 administration (at approximately the end of infusion).

Pharmacodynamics

[1318] CRP levels were reduced in all subjects who received Humanized AB1 irrespective of dose or administration route. From Weeks 4 to 12, CRP levels were significantly lower in subjects who received Humanized AB1 compared with placebo (unadjusted p-value <0.05; FIG. 3). In FIG. 66, the data line for the SC Placebo group is labelled to ensure that it can be distinguished from the SC BMC-945429 50 mg group in a black and white reproduction).

[1319] In Humanized AB1 subjects, CRP levels were lowered to <20% of pre-dose levels in:

- 72% (7/10) of subjects at Week 1;
- 73% (7/10) of subjects at Week 12; and
- 56% (7/12) of subjects at Week 24.

Conclusions:

[1323] In this Phase I study, the anti-IL-6 antibody Humanized AB1 was generally well tolerated when administered in a single SC dose in healthy male subjects. Injection site reactions were generally mild. No anti-Humanized AB1 antibodies were detected. Changes in liver enzymes, neutrophil and platelet counts were reversible. The bioavailability of SC Humanized AB1 was approximately 60% of that observed with IV Humanized AB1. The half-life of Humanized AB1 was approximately 30 days, irrespective of route of administration. These data concur with previous data using IV Humanized AB12. Subcutaneous Humanized AB1 led to rapid and large reductions in serum CRP. Reductions in CRP observed during the first 12 weeks of the study were sustained over 24 weeks of assessment. These preliminary data support the continued development and evaluation of SC Humanized AB1 for the treatment of patients with RA.

[1324] In summary, in this Phase I study, the anti-IL-6 antibody Humanized Ab1 was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC Humanized AB1 was ~60% of IV Humanized Ab1, and the half life was ~30 days. Rapid and significant reductions in CRP were observed, which were sustained over 24 weeks of assessment.

Example 36

Effect of Ab1 on DAS28-Assessed Disease Activity

[1325] As discussed above, ALD518® is an asialylated, humanized anti-IL-6 monoclonal antibody with a half-life of ~30 days containing the humanized variable heavy and light sequences contained in SEQ ID NO: 19 and 20. These humanized heavy and light sequences are derived from a parent rabbit antibody that specifically binds human IL-6 which antibody is referred to in said incorporated application as Ab1. ALD518 binds to IL-6 with high affinity, preventing interaction and signalling mediated via soluble and membrane-bound IL-6R. Rapid and significant ACR responses have been demonstrated with ALD518® in patients with RA.

In this example we report the impact of ALD518 on DAS28-assessed disease activity over 16 weeks.

[1326] Methods:

[1327] Patients with active RA and an inadequate response to MTX were randomized 1:1:1:1 to intravenous ALD518® 80, 160 or 320 mg or placebo during this 16-week, double-blind, placebo-controlled Phase II study. Patients received two IV infusions of ALD518 (Day 1 and Week 8), while continuing on stable doses of MTX. The primary efficacy endpoint was the proportion of patients achieving ACR20 at Week 12; disease activity was assessed via Disease Activity Score (DAS28) based on C-reactive protein (CRP) as a secondary endpoint. The proportion of patients achieving DAS28-defined remission (score <2.6), low disease activity state (LDAS; score ≤3.2) and good EULAR responses (current DAS28 ≤3.2 and improvement from baseline >1.2) were assessed for the modified intention-to-treat population, and are presented for patients with available data (as observed). P-values are based on Chi-square tests.

[1328] Results:

[1329] Of 127 randomized and treated patients, 116 completed the trial. At baseline, mean age was 52.3 years and RA duration was 6.8 years. At Weeks 4, 12 and 16, the proportion of patients achieving LDAS and remission was greater than placebo for all ALD518® doses; differences were significant versus placebo (p<0.05) for all assessments except ALD518® 80 mg at Week 4 (p=0.056). Similarly, EULAR responses were significantly better for all ALD518® doses versus placebo (p<0.01) at Weeks 4, 12 and 16. There was a trend toward greater responses with higher ALD518® doses.
Proportion of patients achieving DAS28-defined remission, LDAS and good EULAR responses

<table>
<thead>
<tr>
<th></th>
<th>ALD518*</th>
<th>ALD518*</th>
<th>ALD518*</th>
<th>Placebo -</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 mg</td>
<td>160 mg</td>
<td>320 mg</td>
<td>(N = 32)</td>
</tr>
<tr>
<td></td>
<td>(N = 34)</td>
<td>(N = 28)</td>
<td>(N = 33)</td>
<td></td>
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<tr>
<td>DAS28-defined remission</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Week 4</td>
<td>10.0</td>
<td>8.8</td>
<td>17.9</td>
<td>0</td>
</tr>
<tr>
<td>Week 12</td>
<td>17.2</td>
<td>21.2</td>
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</tr>
<tr>
<td>Week 16</td>
<td>13.8</td>
<td>28.1</td>
<td>44.0</td>
<td>0</td>
</tr>
<tr>
<td>LDAS</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Week 4</td>
<td>10.0</td>
<td>23.5</td>
<td>28.6</td>
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<td>Week 12</td>
<td>20.6</td>
<td>33.3</td>
<td>46.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Week 16</td>
<td>20.7</td>
<td>50.0</td>
<td>52.0</td>
<td>3.4</td>
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<tr>
<td>Good EULAR response</td>
<td></td>
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<tr>
<td>Week 4</td>
<td>10.0</td>
<td>23.5</td>
<td>28.6</td>
<td>0</td>
</tr>
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<td>Week 12</td>
<td>20.7</td>
<td>50.0</td>
<td>52.0</td>
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</table>

DAS28 = Disease Activity Score 28; LDAS = low disease activity state.

<table>
<thead>
<tr>
<th></th>
<th>80 mg</th>
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<th>320 mg</th>
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<td></td>
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<td>(n = 34)</td>
<td>(n = 28)</td>
<td>(n = 33)</td>
</tr>
<tr>
<td>ACR20</td>
<td>50% (16)*</td>
<td>56% (19)*</td>
<td>71% (20)*</td>
<td>32% (8)*</td>
</tr>
<tr>
<td>ACR50</td>
<td>9% (3)</td>
<td>15% (5)</td>
<td>29% (8)*</td>
<td>3% (1)</td>
</tr>
<tr>
<td>ACR70</td>
<td>6% (2)</td>
<td>0% (0)</td>
<td>11% (3)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Mean Δ DAS28</td>
<td>-1.8</td>
<td>-2.1</td>
<td>-2</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

*p<0.04; "fp = 0.009

[1330] SAEs were reported in two ALD518 patients (both had significant increases in liver enzymes, and discontinued treatment). Elevations in liver enzymes >2×ULN occurred in 17% of ALD518—versus 0% placebo-treated patients; the frequency was highest in the 320 mg dose group. Modest increases in total cholesterol were observed (mean increase by Week 16:1.1 mmol/L for ALD518 versus 0.2 mmol/L for placebo). Nine ALD518 patients had transient Grade H and two had transient Grade III neutropenias. There were no serious infections or infusion reactions in any treatment group, and no evident immunogenicity.

[1331] Conclusions:

[1332] In this Phase II study, the novel IL-6 inhibitor ALD518 resulted in rapid and significant improvements in disease activity sustained over 16 weeks of assessment in patients with RA and an inadequate response to MTX. ALD518 was well tolerated, with a safety profile consistent with the biology of IL-6 blockade.

Example 37

Ab1 Administration

[1333] Methods: Patients with active RA were randomized into a 16 week, double-blind, placebo-controlled trial comparing multiple iv infusions of ALD518 (80, 160 or 320 mg). Patients received an infusion every 8 weeks and were maintained on a stable dose of MTX throughout the trial. Assessments included ACR 20/50/70 responses and DAS28. All patients were evaluated for safety. For early withdrawals, LOCF analysis was used for continuous variables and non-responder imputation for categorical variables.

[1334] Results:

[1335] 132 patients were randomized; 127 were dosed. Mean disease duration was 6.6 years; mean DAS28 score was 6.2 and mean HAQ-DI was 1.72. 11 patients did not complete the 16-week trial: 320 mg-3, 160 mg-1, 80 mg-3, placebo-4; 4 discontinued due to adverse events (80 mg-2, 320 mg-2), with 2 SAEs (80 mg-1, 320 mg-1). Elevations in liver enzymes (LFTs)>2×ULN were observed in 17% ALD518 versus 0% placebo. There were modest increases in total cholesterol (mean increase by week 16:1.1 mmol/L ALD518 versus 0.2 mmol/L placebo). 9 patients on ALD518 had transient grade 2 neutropenias; 2 pts transient grade 3 neutropenias. There were no serious infections reported in any treatment group. Infusions of ALD518 were well tolerated without infusion reactions or evident immunogenicity. At weeks 4 and 16, ACR responses (non responder imputation analysis) and improvements in DAS28 scores were:

<table>
<thead>
<tr>
<th></th>
<th>80 mg</th>
<th>160 mg</th>
<th>320 mg</th>
<th>PBO + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 32)</td>
<td>(n = 34)</td>
<td>(n = 28)</td>
<td>(n = 33)</td>
</tr>
<tr>
<td>ACR20</td>
<td>75% (24)*</td>
<td>65% (22)*</td>
<td>82% (23)*</td>
<td>76% (12)*</td>
</tr>
<tr>
<td>ACR50</td>
<td>41% (13)*</td>
<td>41% (14)*</td>
<td>50% (14)*</td>
<td>15% (5)</td>
</tr>
<tr>
<td>ACR70</td>
<td>22% (7)*</td>
<td>18% (6)*</td>
<td>45% (12)*</td>
<td>6% (2)</td>
</tr>
<tr>
<td>Mean Δ DAS28</td>
<td>-2.7</td>
<td>-2.7</td>
<td>-3.2</td>
<td>-1.1</td>
</tr>
</tbody>
</table>

*p<0.03; "fp = 0.08 "fp = 0.26

[1336] Conclusion:

[1337] ALD518 is the first mAb to IL-6, as opposed to an anti-IL-6 receptor mAb, to show a significant, rapid and sustained improvement in disease activity in RA. ALD518 in doses ranging from 80 to 320 mg given as 2 IV infusions to pts with active RA was well tolerated with increases in LFTs and total cholesterol and transient neutropenia observed in some patients. There were no infusion reactions associated with administration of ALD518 and no detectable immunogenicity.

Example 19

Ab1 Effect on Hemoglobin Concentration, Plasma Lipid

[1338] Concentration, and Neutrophil Counts in Patients with Advanced Cancer

[1339] Antibody Ab1 was dosed in a single bolus infusion in phosphate buffered saline to eight individuals with advanced cancer (NSCLC, colorectal cancer, cholangiocarcinoma, or mesothelioma). Each individual received a dosage of 80 mg, 160 mg, or 320 mg of Ab1. Blood samples were removed just prior to infusion and at fixed time intervals for six weeks, and the hemoglobin concentration, plasma lipid concentration, and neutrophil counts were determined. Average hemoglobin concentration rose slightly (FIG. 22), as did total cholesterol and triglycerides (FIG. 23), while mean neutrophil counts fell slightly (FIG. 24).
These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration in these individuals. Similarly, as IL-6 is centrally important in increasing neutrophil counts in inflammation, the observed slight reduction in neutrophil counts further confirms that Ab1 inhibits IL-6. Finally, IL-6 causes anorexia as well as cachexia in these patients; neutralization of IL-6 by Ab1 results in the return of appetite and reversal of cachexia. The increase in plasma lipid concentrations reflect the improved nutritional status of the patients. Taken together, these results further demonstrate that Ab1 effectively reverses these adverse consequences of IL-6 in these patients.

Example 20
Ab1 Suppresses Serum CRP in Healthy Volunteers and in Patients with Advanced Cancer

Introduction

Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto et al. performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence (Hashimoto, K., et al., Cancer, 103(9):1856-1864 (2005)). Patients were classified into two groups, those with serum CRP levels<1.0 mg/dL (“the CRP positive group”) and those with serum CRP levels<1.0 mg/dL (“the CRP negative group”). The authors identified “a significant correlation between preoperative serum CRP level and tumor size” Id. Furthermore, the authors found that “[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group.” Id. The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator or poor prognosis and early recurrence in patients with hepatocellular carcinoma.

Similar correlations have been identified by other investigators. For example, Karakiewicz et al. determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality (Karakiewicz, P. I., et al., Cancer, 110(6):1241-1247 (2007)). Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

Healthy volunteers received a single 1-hour intravenous (IV) infusion of either 100 mg (5 patients), 30 mg (5 patients), 10 mg (6 patients), 3 mg (6 patients) or 1 mg (6 patients) of the Ab1 monoclonal antibody, while another 14 healthy volunteers received intravenous placebo. Comparatively, 2 patients with advanced forms of colorectal cancer received a single 1-hour intravenous (IV) infusion of 80 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

Patients were evaluated prior to administration of the dosage, and thereafter on a weekly basis for at least 5 weeks post dose. At the time of each evaluation, patients were screened for serum CRP concentration.

Results

Healthy Volunteers

As noted above, serum CRP levels are a marker of inflammation; accordingly, baseline CRP levels are typically low in healthy individuals. The low baseline CRP levels can make a further reduction in CRP levels difficult to detect. Nonetheless, a substantial reduction in serum CRP concentrations was detectable in healthy volunteers receiving all concentrations of the Ab1 monoclonal antibody, compared to controls (FIG. 25). The reduction in serum CRP levels was rapid, occurring within one week of antibody administration, and prolonged, continuing at least through the final measurement was taken (8 or 12 weeks from antibody administration).

Cancer Patients

Five advanced cancer patients (colorectal cancer, cholangiocarcinoma, or NSCLC) having elevated serum CRP levels were dosed with 80 mg or 160 mg of Ab1. Serum CRP levels were greatly reduced in these patients (FIG. 26A). The reduction in serum CRP levels was rapid, with 90% of the decrease occurring within one week of Ab1 administration, and prolonged, continuing at least until the final measurement was taken (up to twelve weeks). The CRP levels of two representative individuals are shown in FIG. 26B. In those individuals, the CRP levels were lowered to below the normal reference range (less than 5.6 mg/l) within one week. Thus, administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 21
Ab1 Improved Muscular Strength, Improved Weight, and Reduced Fatigue in Patients with Advanced Cancer

Introduction

Weight loss and fatigue (and accompanying muscular weakness) are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue, weight loss and muscular weakness can have significant negative effects on the recovery of patients with advanced forms of cancer, for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue, weight loss and muscular weakness include regular routines of fitness and exercise, methods of conserving the patient’s energy, and treatments that address anemia-induced fatigue and muscular weakness. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue, weight loss and muscular weakness in cancer patients.

Methods

Four patients with advanced forms of cancer (colorectal cancer (2), NSCLC (1), cholangiocarcinoma (1) received a single 1-hour intravenous (IV) infusion of either 80 mg or 160 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population. Patients were evaluated prior to admini-
istration of the dosage, and thereafter for at least 6 weeks post dose. At the time of each evaluation, patients were screened for the following: a) any change in weight; b) fatigue as measured using the Facit-F Fatigue Subscale questionnaire a medically recognized test for evaluating fatigue (See, e.g., Cella, D., Lai, J. S., Chang, C. H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general population. Cancer, 94(2), 528-538; Cella, D., Eton, D. T., Lai, F. J-S., Peterman, A. H & Merkel, D. E. (2002). Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy anemia and fatigue scales. Journal of Pain & Symptom Management, 24 (6) 547-561); and hand-grip strength (a medically recognized test for evaluating muscle strength, typically employing a handgrip dynamometer).

Results

Weight Change

[1349] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase of about 2 kilograms of weight per patient over the period of 6 weeks (FIG. 29).

Fatigue

[1350] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase in the mean Facit-F PS subscale score of at least about 10 points in the patient population over the period of 6 weeks (FIG. 30).

Hand-Grip Strength

[1351] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase in the mean hand-grip strength of at least about 10 percent in the patient population over the period of 6 weeks (FIG. 31).

Example 22

Ab1 for Prevention of Thrombosis

[1352] Prior studies have shown that administration of an anti-IL-6 antibody can cause decreased platelet counts. Emiliie, D. et al., Blood, 84(8):2472-9 (1994); Blay et al., Int J Cancer, 72(3):424-30 (1997). These results have apparently been viewed as an indicator of potential danger, because further decreases in platelet counts could cause complications such as bleeding. However, Applicants have now discerned that inhibiting IL-6 restores a normal coagulation profile, which Applicants predict will prevent thrombosis. Decreased platelet counts resulting from inhibition of IL-6 is not a sign of potential danger but rather reflects the beneficial restoration of normal coagulation.

[1353] The mechanism by which normal coagulation is restored is believed to result from the interplay between IL-6 and the acute phase reaction. In response to elevated IL-6 levels, as for example in a cancer patient, the liver produces acute phase proteins. These acute phase proteins include coagulation factors, such as Factor II, Factor V, Factor VIII, Factor IX, Factor XI, Factor XII, Fibronectin degradation products, thrombin-antithrombin III complex, fibrinogen, plasminogen, prothrombin, and von Willebrand factor. This increase in coagulation factors may be measured directly, or may be inferred from functional measurements of clotting ability. Antagonists of IL-6, such as Ab1, suppresses acute phase proteins, e.g., Serum Amyloid A (see FIG. 32 and Example 10). Applicants now predict that this suppression of acute phase proteins will restore the normal coagulation profile, and thereby prevent thrombosis. The restoration of normal coagulation may cause a slight drop in platelet counts, but the patient will nonetheless retain normal coagulation ability and thus will not have an increased risk of bleeding. Such a treatment will represent a vast improvement over the available anticoagulation therapies whose usefulness is limited by the risk of adverse side-effects, such as major bleeding.

[1354] Applicants contemplate that the same beneficial effects of inhibiting IL-6 will be obtained regardless of the method of inhibition. Suitable methods of inhibiting IL-6 include administration of anti-IL-6 antibodies, antisense therapy, soluble IL-6 receptor, etc. either individually or in combinations.

Example 23

Ab1 Increases Plasma Albumin Concentration in Patients with Advanced Cancer

Introduction

[1355] Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbuminemia correlates strongly with poor patient performance in numerous forms of cancer. For example, in one study to patients undergoing systemic chemotherapy for metastatic pancreatic adenocarcinoma and having serum albumin levels less than 3.5 g/dL successfully responded to systemic chemotherapy (Fujishiro, M., et al., Hepatogastroenterology, 47(36):1744-46 (2000)). The authors conclude that “[p]atients with . . . hypoalbuminemia . . . might be inappropriate candidates for systemic chemotherapy and might be treated with other experimental approaches or supportive care.” Id.

[1356] Similarly, Senior and Maroni state that “[t]he recent appreciation that hypoalbuminemia is the most powerful predictor of mortality in end-stage renal disease highlights the critical importance of ensuring adequate protein intake in this patient population.” (J. R. Senior and B. J. Maroni, Am. Soc. Nutr. Sci., 129:313 S-314S (1999)).

[1357] In at least one study, attempts to rectify hypoalbuminemia in 27 patients with metastatic cancer by daily intravenous albumin infusion of 20 g until normal serum albumin levels (>3.5 g/dL) were achieved had little success. The authors note that “[a]lbumin infusion for the advanced stage cancer patients has limited value in clinical practice. Patients with PS 4 and hypoalbuminemia have poorer prognosis.” (Demirkazik, A., et al., Proc. Am. Soc. Clin. Oncol., 21:Abstr 2892 (2002)).

[1358] Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

Methods

[1359] Four patients with advanced forms of cancer (colorectal cancer (2), NSCLC (1), cholangiocarcinoma (1) received a single 1-hour intravenous (IV) infusion of either 80
mg or 160 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[1360] Patients were evaluated prior to administration of the dosage, and thereafter for at least 6 weeks post dose. At the time of each evaluation, patients were screened for plasma albumin concentration.

Results

[1361] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase of about 5 g/L of plasma albumin concentration per patient over the period of 6 weeks (FIG. 33).

Example 24
Ab1 Suppresses Serum CRP in Patients with Advanced Cancer

Introduction

[1362] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto et al. performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence (Hashimoto, K., et al., Cancer, 103(9):1856-1864 (2005)). Patients were classified into two groups, those with serum CRP levels=1.0 mg/dL (“the CRP positive group”) and those with serum CRP levels<1.0 mg/dL (“the CRP negative group”). The authors identified “a significant correlation between preoperative serum CRP level and tumor size.” Id. Furthermore, the authors found that “[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group.” Id. The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator of poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[1363] Similar correlations have been identified by other investigators. For example, Karakiewicz et al. determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality (Karakiewicz, P. L., et al., Cancer, 110(6):1241-1247 (2007)). Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

[1364] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (i.e. Roche CRP Tinaquant®). Briefly, about 1.0 mL of patient sample was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer.

[1365] Patients were evaluated prior to administration of the dosage, and thereafter at weeks 2, 4, 8, and 12. At the time of each evaluation, patients were screened for serum CRP concentration.

Results

[1366] The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody are plotted in FIG. 38. All dosage levels of Ab1 antibody demonstrated an immediate drop in CRP concentrations relative to placebo over the period of 12 weeks. CRP levels displayed breakthrough at 8 weeks post-dosing. The CRP levels fell below 5 mg/L by week 12. Median values of CRP demonstrated rapid and sustained decreases for all dosage concentrations relative to placebo (FIG. 39). Thus, administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 25
Ab1 Suppresses Serum CRP in Patients with Advanced Cancers

Introduction

[1367] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto et al. performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence (Hashimoto, K., et al., Cancer, 103(9):1856-1864 (2005)). Patients were classified into two groups, those with serum CRP levels=1.0 mg/dL (“the CRP positive group”) and those with serum CRP levels<1.0 mg/dL (“the CRP negative group”). The authors identified “a significant correlation between preoperative serum CRP level and tumor size.” Id. Furthermore, the authors found that “[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group.” Id. The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator of poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[1368] Similar correlations have been identified by other investigators. For example, Karakiewicz et al. determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality (Karakiewicz, P. L., et al., Cancer, 110(6):1241-1247 (2007)). Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

[1369] Eight patients with various forms of advanced cancer (colorectal (3), NSCLC (1), cholangio (1), and mesothelioma (2)) received a single 1-hour intravenous infusion of either 80 mg (2 patients), 160 mg (3 patients) or 320 mg (3
patients) of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[1370] Patients were evaluated prior to administration of the dosage and thereafter on a weekly basis for at least 8 weeks post dose. At the time of each evaluation, patients were screened for serum CRP concentration. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (i.e. Roche CRP Tiaquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer.

Results

[1371] Serum CRP levels were greatly reduced in all patients studied (FIG. 40). The reduction in serum CRP levels was rapid, with approximately 90% of the decrease occurring within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to twelve weeks). In all cases except one patient with colorectal cancer, CRP levels fell to or below the normal reference range (less than 5-6 mg/L) within one week. The colorectal cancer patient achieved similar normal levels by week 4 of the study. Thus, administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 26

Ab1 Suppresses Serum CRP in Patients with Rheumatoid Arthritis

Introduction

[1372] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with rheumatoid arthritis. Patients suffering from rheumatoid arthritis with high levels of CRP demonstrated almost universal deterioration. Amos et al., 1 Br. Med. J. 195-97 (1977). Conversely, patients with low CRP levels showed no disease progression, suggesting that sustaining low levels of CRP is necessary for effectively treating rheumatoid arthritis. Id. Tracking of CRP during rheumatoid arthritis treatment regimes of gold, D-penicillamine, chloroquine, or dapsone indicated that radiological deterioration was impeded after the first 6 months of treatment when CRP levels were consistently controlled. Dawes et al., 25 Rheumatology 44-49 (1986). A highly significant correlation between CRP production and radiological progression was identified. van Leeuwen et al., 32 (Supp. 3) Rheumatology 9-13 (1997). Another study revealed that for patients with active rheumatoid arthritis, suppression of abnormally elevated CRP led to improvement in functional testing metrics, whereas sustained CRP elevation associated with deterioration in the same metrics. Devlin et al., 24 J. Rheumatol. 9-13 (1997). No further deterioration was observed without CRP re-elevation, indicating CRP suppression as a viable candidate for rheumatoid arthritis treatment. Id. Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in rheumatoid arthritis patients.

Methods

[1373] One-hundred twenty-seven patients with active rheumatoid arthritis and CRP ≥ 10 mg/L were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n = 33), 80 mg (n = 32), 160 mg (n = 34), or 320 mg (n = 28) of the Ab1 monoclonal antibody, once at the start of the 16 week trial and again at week 8. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (i.e. Roche CRP Tiaquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer. Data on CRP concentration was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16.

Results

[1374] Serum CRP levels were greatly reduced in all patients studied (FIG. 41). The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to or below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Ab1 to rheumatoid arthritis patients can cause a rapid and sustained suppression of serum CRP levels and presents an effective treatment regime.

Example 27

Ab1 Increases Hemoglobin in Patients with Advanced Cancer

[1375] Antibody Ab1 was dosed at 80 mg, 160 mg, or 320 mg of Ab1 in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. The placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the hemoglobin concentration was determined. Mean hemoglobin concentration rose for those receiving antibody Ab1, while mean hemoglobin concentration of those receiving placebo did not rise after twelve weeks when compared to the concentration just prior to dosing (zero week) (FIGS. 42 and 43).

[1376] A subset of the study population began the study with low levels of hemoglobin, defined as a baseline hemoglobin concentration below 11 g/l. Mean hemoglobin concentration rose above 11 g/l after eight weeks for those receiving antibody Ab1 at dosages of 160 mg and 320 mg, while mean hemoglobin concentration of those receiving antibody Ab1 at dosages of 80 mg or placebo did not rise above 11 g/l after eight weeks (FIG. 44).
These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration in these individuals.

Example 28
Ab1 Increases Hemoglobin in Patients with Rheumatoid Arthritis

Hemoglobin levels were analyzed in patients with rheumatoid arthritis during treatment with Ab1 antibody. Ab1 antibody was dosed at 80 mg, 160 mg, or 320 mg in phosphate buffered saline to 94 individuals with rheumatoid arthritis. The placebo group of 33 individuals with rheumatoid arthritis was dosed with phosphate buffered saline only. Blood samples were removed prior to dosing (zero week), and at one, two, three, four, six, eight, ten, twelve, and sixteen weeks, and the hemoglobin concentration was determined. Mean hemoglobin concentration rose for those receiving antibody Ab1, while mean hemoglobin concentration of those receiving placebo did not appreciably rise after sixteen weeks when compared to the concentration just prior to dosing (zero week) (FIG. 45).

These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration.

Example 29
Ab1 Increases Albumin in Patients with Advanced Cancer

Introduction

Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbuminemia correlates strongly with poor patient performance in numerous forms of cancer. For example, in one study no patients undergoing systemic chemotherapy for metastatic pancreatic adenocarcinoma and having serum albumin levels less than 3.5 g/dL successfully responded to systemic chemotherapy (Fujishiro, M., et al., Hepatogastroenterology, 47(36):1744-46 (2000)). The authors conclude that “[p]atients with . . . hypoalbuminemia . . . might be inappropriate candidates for systemic chemotherapy and might be treated with other experimental approaches or supportive care.” Id.

Similarly, Senior and Maroni state that “[t]he recent appreciation that hypoalbuminemia is the most powerful predictor of mortality in end-stage renal disease highlights the critical importance of ensuring adequate protein intake in this patient population.” (J. R. Senior and B. J. Maroni, Am. Soc. Nutr. Sci., 129:313 S-314 S (1999)).

In at least one study, attempts to rectify hypoalbuminemia in 27 patients with metastatic cancer by daily intravenous albumin infusion of 20 g until normal serum albumin levels (>3.5 g/dL) were achieved had little success. The authors note that “[a]lbumin infusion for the advanced stage cancer patients has limited value in clinical practice. Patients with PS 4 and hypoalbuminemia have poorer prognosis.” (Demirkazik, A., et al., Proc. Am. Soc. Clin. Oncol., 21:Abstr 2892 (2002)).

Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

Methods

Antibody Ab1 was dosed at 80 mg, 160 mg, or 320 mg of Ab1 in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. Each individual received a dosage of the placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the albumin concentration was determined.

Results

Mean albumin concentration rose for those receiving antibody Ab1, while mean albumin concentration of those receiving placebo did not rise after twelve weeks when compared to the concentration just prior to dosing (zero week) (FIG. 46). The change from baseline albumin values for all dosage concentration groups is plotted in FIG. 47.

A subset of the study population began the study with low levels of albumin, defined as a baseline albumin concentration less than or equal to 35 g/L. Mean albumin concentration initially rose with all dosages of antibody Ab1 over placebo, but only patients receiving 160 mg or 320 mg demonstrated sustained albumin levels above 35 g/L over 8 weeks of the study (FIG. 48). The 80 mg dosage group demonstrated an initial increase, but gradually declined after week 2 and never rose above 35 g/L during the 8 weeks where data was available (Id.).

Introduction

Weight loss and fatigue are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue and weight loss can have significant negative effects on the recovery of patients with advanced forms of cancer, for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue and weight loss include regular routines of fitness and exercise, methods of conserving the patient’s energy, and treatments that address anemia-induced fatigue. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue and weight loss in cancer patients.

Methods

One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses.
[1390] Patients were evaluated prior to administration of the dosage, and thereafter for at least 12 weeks post dose. At the time of each evaluation, patients were screened for the following: a) any change in weight; and b) fatigue as measured using the Facit-F Fatigue Subscale Questionnaire a medically recognized test for evaluating fatigue (See, e.g., Cella, D., Lai, J.S., Chang, C.H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general population. Cancer, 94(2), 528-538; Cella, D., Fion, D.T., Lai, F.J.S., Peterman, A., H & Merkel, D. E. (2002). Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy anemia and fatigue scales. Journal of Pain & Symptom Management, 24 (6) 547-561).

Results

Weight Change

[1390] The averaged weight change data from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody over 12 weeks is plotted in FIG. 49. The average percent change in body weight from each dosage concentration is plotted in FIG. 50. The averaged lean body mass data for the dosage concentration groups is plotted in FIG. 51.

Fatigue

[1391] The averaged fatigue from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody demonstrated increases in the mean Facit-F FS subscale score for some of the dosage concentration groups in the patient population over the period of 8 weeks (FIG. 52). The change from baseline Facit-F subscale score is plotted in FIG. 53.

Example 31

Ab1 Decreases D-dimer Levels in Patients with Advanced Cancer

Introduction

[1392] D-dimer concentrations are recognized as useful diagnostic tools in predicting risks of thrombotic events in patients. (Adam et al., 113 Blood 2878-87 (2009)) Patients that are negative for D-dimer have a low probability for thrombosis. For example, D-dimer analysis can rule out suspected lower-extremity deep-vein thrombosis in patients. (Wells et al., 349 N. Engl. J. Med. 1227-35 (2003)). Clinical evaluation in combination with negative D-dimer test can effectively lower the instance of pulmonary embolism to 0.5%. (Van Belle et al., 295 JAMA 172-79 (2006); Knip et al., 162 Arch. Intern. Med. 1651-35 (2002); Wells et al., 135 Ann. Intern. Med. 98-107 (2001))

[1393] D-dimer analysis may have utility in tracking the progress of treating coagulation disorders. One study indicated that anticoagulation treatment for acute venous thromboembolism resulted in a gradual decline in D-dimer concentrations. (Adam et al., 113 Blood 2878-87 (2009); Schoutgens et al., 144 J. Lab. Clin. Med. 100-07 (2004)) This discovery led to the conclusion that D-dimer levels monitoring could be used to assess treatment responsiveness. (Adam et al., 113 Blood at 2883)

[1394] For patients with cancer, D-dimer analysis may have additional significance, as cancer increases the prevalence of thrombosis. (Adam et al., 113 Blood 2878-87 (2009)) One study with oncology patients indicated that D-dimer concentrations have a high negative predictive value and high sensitivity in diagnosing pulmonary embolism. (King et al., 247 Radiology 854-61 (2008)) Deep-vein thrombosis can similarly be excluded for cancer patients with low probability of developing deep-vein thrombosis and a negative test for D-dimer, although such a combination is less likely for oncology patients. (Lee et al., 123 Thromb. Res. 177-83 (2008)) A higher threshold for a negative D-dimer result may be necessary in cancer patients. (Righini et al., 95 Haemost. 715-19 (2006))

[1395] Accordingly, there remains a need in the art for methods and/or treatments of thrombosis that improve D-dimer concentrations in cancer patients and address elevated D-dimer states in cancer patients, particularly those with advanced cancers.

Methods

[1396] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses. Data on D-dimer concentration was collected for the first 8 weeks of treatment. D-dimer data concentration was quantitated by a D-dimer immunoturbidimetric assay. Briefly, the assay is based on the change in turbidity of a microparticle suspension that is measured by photometry. About 1.5 mL of patient sample sodium citrate plasma was collected and stored in a plastic collection tube. A suspension of latex microparticles, coated by covalent bonding with monoclonal antibodies specific for D-dimer, was mixed with the test plasma whose D-dimer level was to be assayed. Antibody-antigen reactions leading to an agglutination of the latex microparticles induced an increase in turbidity of the reaction medium. This increase in turbidity was reflected by an increase in absorbance, the latter being measured photometrically using a STAGO STA analyzer. The increase in absorbance was a function of the D-dimer level present in the test sample.

Results

[1397] The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody are plotted in FIG. 54. Error bars were omitted from the graph for clarity purposes. The percent change from baseline in D-dimer concentration is plotted in FIG. 55. All dosage levels of Ab1 antibody demonstrated a drop in D-dimer levels over placebo over the period of 8 weeks.

Example 32

Ab1 Efficacy and Safety in Patients with Advanced NSCLC

[1398] The primary objective of this study was to determine the efficacy and safety of ALD518 or humanized Ab1 in patients with advanced NSCLC.
Methods:

124 patients (pts) with NSCLC, ECOG 0-3, weight loss in the preceding 3 months of >5% body weight, hemoglobin (Hb) >7 g/dL, and C-reactive protein (CRP) >10 mg/L were dosed. Pts were randomized to 1 of 4 groups (n=30/group). Placebo or ALD518 80 mg, 160 mg, or 320 mg was administered intravenously every 8 weeks. Pts were followed up for 24 weeks. Data included hematology, clinical chemistry, CRP and adverse events (AEs).

Results:

29 pts completed the study treatments and evaluations, 38 failed to complete every visit, 52 died of progressive disease, and 5 withdrew because of adverse events. There were no dose limiting toxicities (DLTs) or infusion reactions. 84 pts had serious AEs of which 1 was deemed to be possibly related to administration of ALD518 (rectal hemorrhage). The mean (±SD) values for Hb, hematocrit (Hct), mean corpuscular Hb (MCH), and albumin are below:

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Hb (g/dL)</th>
<th>Hct (%)</th>
<th>MCH (pg)</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD518</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dose</td>
<td>31</td>
<td>12.2 ±0.8</td>
<td>39.0 ±5.9</td>
<td>29.0 ±2.8</td>
<td>37.5 ±5.7</td>
</tr>
<tr>
<td>(pooled) Week 4</td>
<td>69</td>
<td>13.1 ±1.6*</td>
<td>42.5 ±5.0*</td>
<td>29.2 ±2.5*</td>
<td>43.6 ±4.7*</td>
</tr>
<tr>
<td>Week 12</td>
<td>39</td>
<td>13.4 ±1.6*</td>
<td>42.5 ±4.7*</td>
<td>29.8 ±2.8*</td>
<td>45.2 ±4.5*</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dose</td>
<td>27</td>
<td>11.8 ±2.0</td>
<td>39.5 ±6.4</td>
<td>28.0 ±2.8*</td>
<td>37.3 ±6.8</td>
</tr>
<tr>
<td>(pooled) Week 4</td>
<td>29</td>
<td>11.8 ±2.0</td>
<td>39.5 ±6.4</td>
<td>28.0 ±2.8*</td>
<td>37.3 ±6.8</td>
</tr>
<tr>
<td>Week 12</td>
<td>21</td>
<td>12.0 ±2.5</td>
<td>39.6 ±7.4</td>
<td>27.8 ±3.0*</td>
<td>37.0 ±7.5</td>
</tr>
</tbody>
</table>

*p = 0.001
*p < 0.001 (paired t-test compared to pre-dose)

38/92 pts treated ALD518 and 10/31 given placebo had a pre-dose Hb ≤11 g/dL. 24 of those pts on ALD518 and 7 of those on placebo remained in the study at week 4. 14/24 pts on ALD518 and 0/7 on placebo had raised Hb from ≤11 g/dL to >12 g/dL.

Conclusion:

ALD518 increased Hb, Hct, MCH and albumin in NSCLC pts and raised Hb to >12 g/dL in 58% of pts with a Hb≤11 g/dL at baseline. This further indicates that ALD518 can be administered as a non-erythropoietic stimulating agent for treating cancer-related anemia.

Example 33

Ab1 Achieved ACR 20/50/70 in Patients with Rheumatoid Arthritis

Introduction

Rheumatoid arthritis is a chronic, systemic inflammatory disorder that principally attack synovium of joints. The disease causes painful and potentially disabling inflammation, with onset typically occurring between 40 and 50 years of age. Interpretation of drug treatment efficacy in rheumatoid arthritis is made difficult by the myriad of subjective and objective assessment tools made available over the years. The American College of Rheumatology ("ACR") released a standardized set of rheumatoid arthritis measures to facilitate evaluation of improvement of the disease in clinical trials. Felson et al., Arthritis & Rheumatism 729-40 (1993).

Methods

One-hundred twenty-seven patients with active rheumatoid arthritis and CRP ≥10 mg/L were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg during a clinical trial were categorized as achieving ACR 20. Similarly, patients achieving 50% or 70% improvements were categorized as ACR 50 and ACR 70, respectively.

Results

A significant portion of patients suffering from rheumatoid arthritis achieved ACR 20 or greater during the course of the study (FIG. 56). Patients observed rapid improvement in systems within the first 4 weeks of the study, as well as continued, steady improvement throughout the course of the 16 week evaluation (FIGS. 57, 58, and 59). The greatest results where exhibited by patients receiving the 320 mg dosage level, with 43% achieving ACR 70 status during the study (FIG. 59).

Analysis of the individual components of the ACR evaluation demonstrated gains in every component (FIG. 60). HAQ DI scores demonstrated clinically meaningful change over placebo during the course of the evaluation (FIG. 61). Serum CRP levels were greatly reduced in all patients studied (FIG. 41). The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Ab1 can cause a rapid and sustained improvement in rheumatoid arthritis patients, as evidenced by the significant improvement in ACR scores during clinical evaluation, and presents an effective treatment regime.
Example 34
Ab1 Achieved Improved DAS28 and EULAR Scores in Patients with Rheumatoid Arthritis

Introduction
Rheumatoid arthritis is a chronic, systemic inflammatory disorder that principally attack synovium of joints. The disease causes painful and potentially disabling inflammation, with onset typically occurring between 40 and 50 years of age. Interpretation of drug treatment efficacy in rheumatoid arthritis is made difficult by the myriad of subjective and objective assessment tools made available over the years. The American College of Rheumatology (“ACR”) released a standardized set of rheumatoid arthritis measures to facilitate evaluation of improvement of the disease in clinical trials. Felson et al., 36 Arthritis & Rheumatism 729-40 (1993).

Inflammatory activity associated with rheumatoid arthritis is measured using numerous variables through validated response criteria such as Disease Activity Score (DAS), DAS28 and EULAR. The DAS is a clinical index of rheumatoid arthritis disease activity that combines information from swollen joints, tender joints, the acute phase response, and general health. Fransen, J., et al., Clin. Exp. Rheumatol., 23 (Suppl. 39); S93-S99 (2005). The DAS 28 is an index similar to the original DAS, but uses a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR (erythrocyte sedimentation rate), and an optional general health assessment on a visual analogue scale (range 0-100). Id. The European League against Rheumatism (EULAR) response criteria classify patients using the individual amount of change in the DAS and the DAS value (low, moderate, high) reached into one of the following classifications: Good, Moderate, or Non-Responders. Id. Methods

One-hundred twenty-seven patients with active rheumatoid arthritis were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Ab1 monoclonal antibody, once at the start of the 16 week trial and again at week 8. Data on the DAS28 and EULAR scores was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16. Assessment under the standardized DAS28 and EULAR protocols were employed in determining the respective scores of patients during the clinical trial and conducted by a person trained in the ordinary art of evaluating rheumatoid arthritis.

Results
Patients receiving 80 mg, 160 mg or 320 mg of Ab1 demonstrated improved DAS28 scores relative to those patients receiving placebo over the course of 16 weeks, as presented in FIG. 62 as a mean change from the baseline DAS28 score. Furthermore, a significant percentage of patients receiving 80 mg, 160 mg or 320 mg of Ab1 achieved “Good” or “Moderate” classifications relative to those patients receiving placebo over the course of 16 weeks. (FIG. 63).

Thus, administration of Ab1 can result in improved DAS28 and EULAR scores in rheumatoid arthritis when compared to those patients receiving placebo.

Example 35
Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Ab1 in Human Subjects

Background:
A humanized antibody derived from Ab1 (humanized Ab1 or ALD518) containing the variable heavy and light sequences in SEQ ID NO:19 and 20 was administered to rheumatoid arthritis patients. This antibody is a humanized, asiallated, IgG1 monoclonal antibody against IL-6 which has been shown to have a half-life (1/2) of approximately 30 days in humans. In studies in patients with RA, intravenous (IV) with this antibody (humanized Ab1) has demonstrated efficacy over 16 weeks with rapid American College of Rheumatology (ACR) responses; Complete and durable suppression of C-reactive protein (CRP); Good tolerability, and a safety profile consistent with the biology of IL-6 blockade. This humanized antibody binds to IL-6 with high affinity, preventing interaction and signalling mediated via IL-6R. Rapid and significant treatment responses have been demonstrated with intravenous (IV) administration of humanized Ab1 in patients with RA. In this example we study the safety, pharmacokinetics and pharmacodynamics of subcutaneous (SC) administration of humanized Ab1 in healthy subjects.

The objective of this study was to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of a single SC injection of this humanized antibody in healthy male subjects.

Methods:
In this Phase I, double-blind, placebo-controlled study, 27 subjects were randomized 2:1 to receive a single dose of humanized Ab1 or placebo in the following groups: humanized Ab1 50 mg SC, humanized Ab1 100 mg SC or humanized Ab1 100 mg IV (n=6 active and n=3 placebo per group). The primary objective was to assess safety of SC humanized Ab1 versus placebo over 12 weeks. Plasma concentrations of humanized Ab1 and serum concentrations of C-reactive protein (CRP) were assessed as secondary objectives. Assessments were performed daily in Week 1 and then on Day 10, Weeks 2, 4, 6 and 8, and then monthly to Week 12. The study was unblinded at Week 12, and humanized Ab1 subjects were monitored to Week 24.

Study Design and Population
The study included 27 healthy male subjects (aged 18-65 years). Subjects were dosed in three treatment groups of nine subjects each, randomized 2:1 to receive a single dose of humanized Ab1 or placebo on Day 1 (FIG. 64). Humanized Ab1 treatments per group were:

- Humanized Ab1 IV 100 mg infusion over 60 minutes
- Humanized Ab1 SC 50 mg injection (1 mL)
- Humanized Ab1 SC 100 mg injection (1 mL)

The study was unblinded at Week 12, after which placebo subjects discontinued the trial and BMS-945429 subjects were monitored to Week 24 (FIG. 64).

Safety and Immunogenicity Assessments
The primary objective of the study was to assess the safety of SC humanized Ab1 compared with placebo over 12 weeks. Safety was monitored over 12 weeks for all subjects. The study was unblinded at Week 12, and Humanized AB1 subjects were monitored to Week 24.

Laboratory safety tests were performed pre-dose at screening and Day -1, and post dose on Days 2 and 7, Weeks 2, 4, 6, 8 and 12 for all subjects, and Weeks 16, 20 and 24 post-dose for those randomized to Humanized Ab1. Anti-Humanized Ab1 antibodies were measured by enzyme-
linked immunoassorbent assay (ELISA). Blood samples were collected at Day 1 (pre-dose) and Week 12 post-dose for all subjects, and Week 24 post-dose for those randomized to Humanized Ab1.

Pharmacokinetic and Pharmacodynamic Assessments

[1425] Plasma Humanized Ab1 and serum CRP concentrations were assessed by ELISA. For all subjects, samples were collected at screening, pre-dose on Day 1, and post-dose on Days 2 and 7 and Weeks 2, 4, 6, 8 and 12. For subjects randomized to Humanized Ab1, further samples were collected at Weeks 16, 20 and 24 post-dose.

Statistical Analysis

[1426] All subjects who received a dose of Humanized Ab1 or placebo were included in the safety analysis. All subjects who received a dose of Humanized Ab1 or placebo were included in PD and immunogenicity analyses. All subjects who received a dose of Humanized Ab1 were included in PK analyses (n=16). All PK samples for placebo subjects were confirmed as below quantitation.

[1427] Descriptive statistics were generated for baseline demographics, safety data, plasma Humanized Ab1 parameters and serum CRP concentrations. Wilcoxon Rank Sum test was used to compare CRP concentrations for Humanized Ab1 treatments versus placebo.

Results:

Summary

[1428] Over 24 weeks, there were no deaths or serious AEs, and no withdrawals due to AEs. Nearly all subjects (89%) experienced AEs, which were mild or moderate except one event of severe gastroenteritis in the Humanized Ab1 SC 50 mg group. Injection site reactions occurred in ½ Humanized Ab1 SC subjects, ½ placebo SC subjects and ½ placebo IV subjects (none were reported in Humanized Ab1 IV subjects). These were mild except one case of moderate erythema and pruritis in the Humanized Ab1 100 mg SC group. Increases in direct bilirubin and neutrophil counts below the limit of normal were more common in subjects receiving Humanized Ab1 than placebo; all were CTC Grade 1 or 2. The half-life of Humanized Ab1 was similar across all groups (mean range: 30.7-33.6 days). The median T_{max} of Humanized Ab1 was longer after SC (~1 week) than after IV administration (~end of infusion). The PK of SC Humanized Ab1 was dose-proportional in terms of AUC and C_{max} at doses of 50 mg and 100 mg. Based on AUC_{0-14} (day*mg/mL) of 237, 452 and 764 for the Humanized Ab1 50 mg SC, 100 mg SC and 100 mg IV groups, respectively, the bioavailability of Humanized Ab1 was ~60% for the versus IV groups. Subjects receiving Humanized Ab1 experienced rapid and sustained reductions in serum CRP (FIG. 66).

Subject Disposition and Baseline Demographics

[1429] A total of 27 subjects were enrolled and completed the study (n=18 Humanized Ab1 and n=9 placebo). No subjects were withdrawn for any reason.

[1430] All subjects were male; 2/27 subjects were Caucasian and 2/27 were Asian. Mean age was 29 (range 20-59) and was similar across the groups. Mean height and weight were also generally comparable across groups, although the IV placebo group were slightly lighter.

Safety and immunogenicity to Week 12 for Humanized Ab1 and Placebo

[1431] A summary of safety is presented in FIG. 67. For the SC Humanized Ab1 groups, a total of 1½ (91%) patients experienced an adverse event (AE) compared with:

[1432] 6/6 (100%) for the IV Humanized Ab1 group;

[1433] 1/6 (66.6%) for the SC placebo group; and

[1434] 0/6 (0%) for the IV placebo group.

[1435] Across groups:

[1436] No deaths or serious AE were reported and there were no withdrawals due to AEs.

[1437] Most AEs were mild or moderate in intensity.

[1438] One case of gastroenteritis in a SC Humanized Ab1 50 mg subject was considered severe, but not serious, and not related to study medication.

[1439] No anti-Humanized Ab1 antibodies were detected in any subject during this period.

Injection Site Reactions

[1440] Injection site reactions were reported in 26% (2/7) of subjects, and all occurred prior to Week 12 (FIG. 68). Injection site reactions occurred in ½ SC Humanized Ab1 subjects and ½ placebo subjects. In the IV groups, % Humanized Ab1 subjects and ½ placebo subjects experienced injection site reactions. All injection site reactions were mild except in one SC Humanized Ab1 100 mg subject with moderate injection site erythema and pruritis. No injection site reactions occurred after Week 12 in any of the Humanized Ab1 groups. Infusion site reactions were reported in ½ subjects receiving IV Humanized Ab1 and ½ IV placebo subjects (infusion site pruritis).

Clinical Laboratory Evaluations

[1441] FIG. 69 shows incidences of increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and bilirubin levels across the Humanized Ab1 and placebo groups. All ALT and AST levels were Grade 1 by the Common Terminology Criteria for Adverse Events (CTCAE), and no levels were ≥3 times the upper limit of normal (ULN). All increases in total and direct bilirubin were CTCAE Grade 1 or 2 and no subject met criteria for drug-induced liver damage. Only one subject (SC Humanized Ab1 100 mg group) had total bilirubin out of range (26 µmol/L, range 0-24 µmol/L), at Week 24.

[1442] Sporadic decreases in neutrophil and platelet counts were also observed in the Humanized Ab1 and placebo groups (FIG. 69). Neutrophil counts below the lower limit of normal were more common in subjects receiving Humanized Ab1 than placebo but all decreases were CTCAE Grade 1 or 2. Only one subject (SC Humanized Ab1 50 mg group) had consistent mild neutropenia to Week 24 (1.5x10^9/L, at Week 24). Reductions in platelet counts were all CTCAE Grade 1 (lowest level 134x10^9/L and no subject had a low platelet count past Week 8.

Pharmacokinetics

[1443] Bioavailability of Humanized Ab1 was 60% for SC Humanized Ab1 50 and 100 mg versus IV Humanized Ab1 100 mg groups based on the mean AUC_{0-14} (FIG. 70). The half-life of Humanized Ab1 was similar across all groups (mean range: 30.7-33.6 days) (FIG. 70). Peak plasma concentration (C_{max}) of SC Humanized Ab1 was reduced as compared to IV (FIG. 65). Median time to maximum plasma
concentration (T_max) of Humanized Ab1 was longer after SC Humanized Ab1 (at approximately one week) than after IV Humanized Ab1 administration (at approximately the end of infusion).

Pharmacodynamics

[1444] CRP levels were reduced in all subjects who received Humanized Ab1 irrespective of dose or administration route. From Weeks 4 to 12, CRP levels were significantly lower in subjects who received Humanized Ab1 compared with placebo (unadjusted p-value <0.05; FIG. 3). In FIG. 66, the data line for the SC Placebo group is labelled to ensure that it can be distinguished from the SC BMC-945429 50 mg group in a black and white reproduction.

[1445] In Humanized Ab1 subjects, CRP levels were lowered to <20% of pre-dose levels in:
- 72% (1/31) of subjects at Week 1;
- 73% (1/31) of subjects at Week 12; and
- 56% (1/31) of subjects at Week 24.

Conclusions:

[1449] In this Phase I study, the anti-II-6 antibody Humanized Ab1 was generally well tolerated when administered in a single SC dose in healthy male subjects. Injection site reactions were generally mild. No anti-Humanized Ab1 antibodies were detected. Changes in liver enzymes, neutrophil and platelet counts were reversible. The bioavailability of SC Humanized Ab1 was approximately 60% of that observed with IV Humanized Ab1. The half-life of Humanized Ab1 was approximately 30 days, irrespective of route of administration. These data concur with previous data using IV Humanized Ab12. Subcutaneous Humanized Ab1 led to rapid and large reductions in serum CRP. Reductions in CRP observed during the first 12 weeks of the study were sustained over 24 weeks of assessment. These preliminary data support the continued development and evaluation of SC Humanized Ab1 for the treatment of patients with RA.

[1450] In summary, in this Phase I study, the anti-II-6 antibody Humanized Ab1 was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC Humanized Ab1 was ~60% of IV Humanized Ab1, and the half-life was ~30 days. Rapid and significant reductions in CRP were observed, which were sustained over 24 weeks of assessment.

Example 36

Effect of Ab1 on DAS28-Assessed Disease Activity

[1451] As discussed above, ALD518* is an asiallated, humanized anti-II-6 monoclonal antibody with a half-life of ~30 days containing the humanized variable heavy and light sequences contained in SEQ ID NO:19 and 20. These humanized heavy and light sequences are derived from a parent rabbit antibody that specifically binds human II-6 which antibody is referred to in said incorporated application as Ab1. ALD518 binds to II-6 with high affinity, preventing interaction and signalling mediated via soluble and membrane-bound II-6R. Rapid and significant ACR responses have been demonstrated with ALD518* in patients with R.A. In this example we report the impact of ALD518 on DAS28-assessed disease activity over 16 weeks.

[1452] Methods:

[1453] Patients with active RA and an inadequate response to MTX were randomized 1:1:1:1 to intravenous ALD518* 80, 160 or 320 mg or placebo during this 16-week, double-blind, placebo-controlled Phase II study. Patients received two IV infusions of ALD518* (Day 1 and Week 8), while continuing on stable doses of MTX. The primary efficacy endpoint was the proportion of patients achieving ACR20 at Week 12; disease activity was assessed via Disease Activity Score (DAS28) based on C-reactive protein (CRP) as a secondary endpoint. The proportion of patients achieving DAS28-defined remission (score <2.6), low disease activity state (LDAS; score ≤3.2) and good EULAR responses (current DAS28 ≤3.2 and improvement from baseline >1.2) were assessed for the modified intent-to-treat population, and are presented for patients with available data (as observed). P-values are based on Chi-square tests.

[1454] Results:

[1455] Of 127 randomized and treated patients, 116 completed the trial. At baseline, mean age was 52.3 years and RA duration was 6.8 years. At Weeks 4, 12 and 16, the proportion of patients achieving LDAS and remission was greater than placebo for all ALD518* doses; differences were significant versus placebo (p<0.05) for all assessments except ALD518* 80 mg at Week 4 (p=0.056). Similarly, EULAR responses were significantly better for all ALD518* doses versus placebo (p<0.01) at Weeks 4, 12 and 16. There was a trend toward greater responses with higher ALD518* doses.

| Proportion of patients achieving DAS28-defined remission, LDAS and good EULAR responses |
|----------------------------------|----------------|----------------|----------------|----------------|
| DAS28-defined remission          | ALD518* 80 mg  | ALD518* 160 mg | ALD518* 320 mg | Placebo -     |
| (N = 32)                         | (N = 34)      | (N = 28)      | (N = 33)       |               |
| Week 4                           | 10.0          | 8.8           | 17.9           | 0             |
| Week 12                          | 17.2          | 21.2          | 34.6           | 3.3           |
| Week 16                          | 13.8          | 28.1          | 44.0           | 0             |
| LDAS                             | 12.5          | 31.3          | 46.1           | 6.6           |
| Week 4                           | 10.0          | 23.5          | 28.6           | 0             |
| Week 12                          | 20.6          | 33.3          | 46.1           | 6.6           |
| Week 16                          | 20.7          | 50.0          | 52.0           | 3.4           |
| Good EULAR response              | 10.0          | 23.5          | 28.6           | 0             |
| Week 12                          | 20.7          | 33.3          | 46.2           | 6.7           |
| Week 16                          | 20.7          | 50.0          | 52.0           | 3.4           |

DAS28 = Disease Activity Score 28; LDAS = low disease activity state

[1456] SAEs were reported in two ALD518 patients (both had significant increases in liver enzymes, and discontinued treatment). Overall, elevations in liver enzymes >2xULN occurred in 17% of ALD518* -- versus 0% placebo-treated patients; the frequency was highest in the 320 mg dose group. Modest increases in total cholesterol were observed (mean increase by Week 16=1.1 mmol/L for ALD518* versus 0.2 mmol/L for placebo). Nine ALD518 patients had transient Grade II and two had transient Grade III neutropenias. There were no serious infections or infusion reactions in any treatment group, and no evident immunogenicity.

[1457] Conclusions:

[1458] In this Phase II study, the novel II-6 inhibitor ALD518 resulted in rapid and significant improvements in
disease activity sustained over 16 weeks of assessment in patients with RA and an inadequate response to MTX. ALD518 was well tolerated, with a safety profile consistent with the biology of IL-6 blockade.

Example 37

Ab1 Administration

Methods: Patients with active RA were randomized into a 16 week, double-blind, placebo-controlled trial comparing multiple iv infusions of ALD518 (80, 160 or 320 mg). Patients received an infusion every 8 weeks and were maintained on a stable dose of MTX throughout the trial. Assessments included ACR 20/50/70 responses and DAS28. All patients were evaluated for safety. For early withdrawals, LOCF analysis was used for continuous variables and non-responder imputation for categorical variables.

Results:

132 patients were randomized; 127 were dosed. Mean disease duration was 6.6 years; mean DAS28 score was 6.2 and mean HAQ-DI was 1.72. 11 patients did not complete the 16-week trial: 320 mg-3, 160 mg-1, 80 mg-3, placebo-4. 4 discontinued due to adverse events (80 mg-2, 320 mg-2), with 2 SAEs (80 mg-1, 320 mg-1). Elevations in liver enzymes (LFTs)>2xULN were observed in 17% ALD518 versus 0% placebo. There were modest increases in total cholesterol (mean increase by week 16–1.1 mmol/L ALD518 versus 0.2 mmol/L placebo). 9 patients on ALD518 had transient grade 2 neutropenias; 2 pts transient grade 3 neutropenias. There were no serious infections reported in any treatment group. Infusions of ALD518 were well tolerated without infusion reactions or evident immunogenicity. At weeks 4 and 16, ACR responses (non responder imputation analysis) and improvements in DAS28 scores were:

<table>
<thead>
<tr>
<th>Week 4</th>
<th>80 mg (n = 32)</th>
<th>160 mg (n = 54)</th>
<th>320 mg (n = 28)</th>
<th>PBO + MTX (n = 33)</th>
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<tbody>
<tr>
<td>ACR20</td>
<td>50% (16)*</td>
<td>56% (19)*</td>
<td>71% (20)*</td>
<td>23% (8)</td>
</tr>
<tr>
<td>ACR50</td>
<td>9% (3)</td>
<td>15% (5)</td>
<td>29% (8)*</td>
<td>3% (1)</td>
</tr>
<tr>
<td>ACR70</td>
<td>6% (2)</td>
<td>0% (0)</td>
<td>11% (3)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Mean Δ DAS28</td>
<td>-1.8</td>
<td>-2.1</td>
<td>-2</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

*p=0.04;  
fp = 0.009

<table>
<thead>
<tr>
<th>Week 16</th>
<th>80 mg (n = 32)</th>
<th>160 mg (n = 34)</th>
<th>320 mg (n = 28)</th>
<th>PBO + MTX (n = 33)</th>
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<td>75% (24)*</td>
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<td>41% (13)*</td>
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<td>22% (7)†</td>
<td>18% (6)†</td>
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*p=0.03  
fp = 0.08  
fp = 0.26

Conclusion: ALD518 is the first mAb to IL-6, as opposed to an anti-IL-6 receptor mAb, to show a significant, rapid and sustained improvement in disease activity in RA. ALD518 in doses ranging from 80 to 320 mg given as 2 IV infusions to pts with active RA was well tolerated with increases in LFTs and total cholesterol and transient neutropenia observed in some patients. There were no infusion reactions associated with administration of ALD518 and no detectable immunogenicity.

SEQUENCE LISTING

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Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met 35 40 45
Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro 50 55 60
Lys Met Ala Glu Lys Asp Gly Cys Phe Glu Ser Gly Phe Asn Glu 65 70 75 80
Thr Cys Leu Val Lys Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr 85 90 95
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115 120 125
Ala Lys Asn Leu Asp Ala Ile Thr Pro Asp Pro Thr Thr Asn Ala
130 135 140
Ser Leu Leu Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp Met
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Leu Arg Ala Leu Arg Gln Met
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Val Ser Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35  40  45
Gln Ser Ile Asn Asn Glu Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
50  55  60
Arg Pro Lys Leu Leu Ile Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val
65  70  75  80
Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85  90  95
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110
Gly Tyr Ser Leu Arg Asn Ile Asp Asn Ala Phe Gly Gly Gly Thr Glu
115 120 125
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Leu Asn Asn

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Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20  25  30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35  40  45
Asn Tyr Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50  55  60
Trp Ile Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Trp
-continued

65  70  75  80
Ala Ile Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
  95  90  95
Lys Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe Cys Ala
  100 105 110
Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gln
  115 120 125
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
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Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
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Leu Gly Cys Leu Val Val Lys
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<213> ORGANISM: Oryctolagus cuniculus

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gtccacctca agtgcctgcc cagctcgagc attaaccatg aattatcctgt gttcagcagc 180
aaaccagggc agcgcctcca aactcctggtt tatagggcat ccacctctggc atctgaggggtc 240
tcagctctgt tcaaaagcag tggagcctgg acagtgctca ctctccacact cagcagccct 300
gagtttgct gcaggggacc gggctgtggtg gtcgaagctta cgcggagcccg cccatctgtc 360
aatgcctgct gcaggggagg gggctgtggtg gtcgaagctta cgcggagcccg cccatctgtc 420
tccatctgct gcaggggagg gggctgtggtg gtcgaagctta cgcggagcccg cccatctgtc 480
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aaggggctcg ggtgcctggtg acatcatctgc gcagtcagctt gcagctgccg gtcgcctgccg 240
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Glu  Val  Gln  Leu  Val  Glu  Ser  Gly  Gly  Leu  Val  Gln  Pro  Gly  Gly  1  5  10  15
Ser  Leu  Arg  Leu  Ser  Cys  Ala  Ala  Ser  Gly  Phe  Ser  Leu  Ser  Asn  Tyr  20  25  30
Tyr  Val  Thr  Trp  Val  Arg  Gln  Ala  Pro  Gly  Lys  Gly  Leu  Glu  Trp  Val  35  40  45
Gly  Ile  Ile  Tyr  Gly  Ser  Asp  Glu  Thr  Ala  Tyr  Ala  Thr  Trp  Ala  50  55  60
Gly  Arg  Phe  Thr  Ile  Ser  Arg  Asp  Ser  Arg  Ser  Lys  Asn  Thr  Tyr  Leu  65  70  75  80
Gln  Met  Asn  Ser  Leu  Arg  Ala  Glu  Thr  Ala  Val  Tyr  Tyr  Cys  Ala  85  90  95
Arg  Asp  Asp  Ser  Ser  Asp  Trp  Ala  Lys  Phe  Asn  Leu  100  105
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Glu Val Gln Leu Val Glu Ser Gly Gly dly Leu Val Gln Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20      25      30

Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35      40      45

Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile
50      55      60

Gly Arg Phe Thr Ile Ser Arg Asp Ser Asn Ser Lys Asn Thr Leu Tyr Leu
65      70      75      80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Cys Ala
85      90      95

Arg Asp Asp Ser Ser Asp Trp Ala Lys Phe Asn Leu
100     105

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Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Asn Asn Glu Leu
20      25      30

Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile Tyr
35      40      45

Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50      55      60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65      70      75      80

Asp Phe Ala Thr Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn Ile
85      90      95

Asp Asn Ala

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Val Gln Val Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35      40      45

Glu Thr Ile Tyr Ser Trp Leu Ser Ser Trp Tyr Gln Gln Lys Pro Gly Gln
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<210> SEQ ID NO 35
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Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20    25    30
Val Ser Ala Ala Val Gly Thr Val Ser Ile Ser Cys Gln Ala Ser
35    40    45
Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ser Trp Phe Gln Gln Lys Pro
50    55    60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Leu Ala Ser
65    70    75    80
Gly Val Pro Ser Arg Phe Val Gly Ser Gly Ser Gly Thr Gln Phe Thr
85    90    95
Leu Thr Ile Thr Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100   105   110
Ala Gly Val Tyr Asp Asp Ser Asp Asn Ala Phe Gly Gly Gly Thr
115   120   125
Glu Val Val Val Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
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Leu Leu Asn Asn Phe
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<213> ORGANISM: Oryctolagus cuniculus

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20    25    30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35    40    45
Val Tyr Tyr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50    55    60
Trp Ile Gly Phe Ile Thr Met Ser Asp Asn Ile Asn Tyr Ala Ser Trp
65    70    75    80
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

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Val Ser Ala Pro Val Gly Thr Val Ser Ile Ser Cys Gly Ala Ser
35 40 45

Gln Ser Val Tyr Glu Asn Asn Tyr Leu Ser Trp Phe Gln Gln Lys Pro
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Leu Asp Ser
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Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
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<211> LENGTH: 21
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<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 64
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<210> SEQ ID NO 65
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 65
gcaggggttt atgatgatga tagttagat ggc 33

<210> SEQ ID NO 66
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 66
gctactaca tgaac 15

<210> SEQ ID NO 67
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 67
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<210> SEQ ID NO 68
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 68
agtcggtgct gggtgcaat gggctggttg gatctc 36
<210> SEQ ID NO: 69
<211> LENGTH: 164
<212> TYPE: PRT
<213> ORGANISM: Orictolagus cuniculus

<400> SEQUENCE: 69

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ser Pro
20   25   30
Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35   40   45
Gln Ser Val Gln Asp Asn Asn Trp Leu Gly Trp Tyr Gln Gln Lys Arg
50   55   60
Gly Gln Pro Pro Lys Tyr Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser
65   70   75   80
Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
85   90   95
Leu Thr Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100  105  110
Ala Gly Gln Phe Ser Gly Asn Ile Phe Ala Phe Gly Gly Gly Thr Glu
115  120  125
Val Val Val Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
130  135  140
Ser Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145  150  155  160
Leu Asn Asn Phe

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<211> LENGTH: 164
<212> TYPE: PRT
<213> ORGANISM: Orictolagus cuniculus

<400> SEQUENCE: 70

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Val Gln Cys Gln Ser Val Glu Ser Gly Gly Arg Leu Val Thr Pro
20   25   30
Gly Thr Pro Leu Thr Leu Tyr Thr Val Ser Gly Phe Ser Leu Ser
35   40   45
Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50   55   60
Trp Ile Gly Ile Ile Gly Phe Gly Thr Thr Tyr Tyr Ala Thr Trp
65   70   75   80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85   90   95
Arg Ile Thr Ser Pro Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100  105  110
Arg Gly Gly Pro Gly Asn Gly Gly Asp Ile Trp Gly Gin Gly Thr Leu
115  120  125
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
130  135  140
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
145  150  155  160
Leu Val Lys Asp

<210> SEQ ID NO 71
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 71

Gln Ala Ser Gin Ser Val Asp Asp Asn Trp Leu Gly
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<210> SEQ ID NO 72
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 72

Ser Ala Ser Thr Leu Ala Ser
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<210> SEQ ID NO 73
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 73

Ala Gly Gly Phe Ser Gly Asn Ile Phe Ala
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<210> SEQ ID NO 74
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<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 74

Ser Tyr Ala Met Ser
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<210> SEQ ID NO 75
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 75

Ile Ile Gly Gly Phe Gly Thr Thr Tyr Ala Thr Trp Ala Lys Gly
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<210> SEQ ID NO 76
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<212> TYPE: PRT
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<210> SEQ ID NO 77
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gtacaatatc actgcagcag cagtcagagt gttgatgata acaacttggtt aggggtgtat 180
cacgcaagac gggagcagcc tcccaagtac cttgatatt ttcgatccac cttgcccctt 240
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ttttggtttag gcaggagcag ccagtaactgc gttcagcagtc cccacaggttc cccacactgc 420
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cgatattatctc ttc 493

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cgatattatctc ttc 493

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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 80
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<210> SEQ ID NO: 81
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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<210> SEQ ID NO 82
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 82

agctatgca atggc 15

<210> SEQ ID NO 83
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 83

atcatgtgt gtttgggac cacactac gogactggg cgaaggg 48

<210> SEQ ID NO 84
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 84

ggtgtcctg gtaatgtggc tgcac 27

<210> SEQ ID NO 85
<211> LENGTH: 164
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 85

Met  Asp  Thr  Arg  Ala  Pro  Thr  Gln  Leu  Leu  Gly  Leu  Leu  Leu  Leu  Leu  Trp
1     5     10    15
     Leu  Pro  Gly  Ala  Thr  Phe  Ala  Ala  Val  Leu  Thr  Gln  Thr  Pro  Ser  Pro
20    25    30
     Val  Ser  Val  Pro  Val  Gly  Gly  Thr  Val  Thr  Ile  Lys  Cys  Gln  Ser  Ser
35    40    45
     Gln  Ser  Val  Tyr  Asn  Asn  Phe  Leu  Ser  Trp  Tyr  Gln  Gln  Lys  Pro  Gly
50    55    60
     Gln  Pro  Pro  Lys  Leu  Leu  Ile  Tyr  Gln  Ala  Ser  Lys  Leu  Ala  Ser  Gly
65    70    75    80
     Val  Pro  Asp  Arg  Phe  Ser  Gly  Ser  Gly  Ser  Gly  Ser  Gln  Phe  Thr  Leu
85    90    95
     Thr  Ile  Ser  Gly  Val  Gln  Cys  Asp  Asp  Ala  Ala  Thr  Tyr  Cys  Leu
100   105   110
     Gly  Gly  Tyr  Asp  Asp  Asp  Ala  Asp  Ala  Phe  Gly  Gly  Gly  Gly  Thr  Glu
115   120   125
     Val  Val  Val  Lys  Arg  Thr  Val  Ala  Ala  Pro  Ser  Val  Phe  Ile  Phe  Pro
130   135   140
     Pro  Ser  Asp  Glu  Gln  Leu  Lys  Ser  Gly  Thr  Ala  Ser  Val  Val  Cys  Leu
145   150   155   160
     Leu  Asn  Asn  Phe

<210> SEQ ID NO 86
<211> LENGTH: 170
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 86
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Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
   20   25    30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
   35   40    45
Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
   50   55    60
Trp Ile Gly Ile Ile Tyr Ala Gly Ser Gly Ser Thr Trp Tyr Ala Ser
   65   70    75    80
Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Val Asp
   85   90    95
Leu Lys Ile Thr Ser Pro Thr Glu Asp Thr Ala Thr Tyr Phe Cys
  100  105   110
Ala Arg Asp Gly Tyr Asp Asp Tyr Gly Asp Phe Asp Arg Leu Asp Leu
  115  120   125
Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ala Ser Thr Lys Gly
  130  135   140
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Lys
  145  150   155   160
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
  165

<210> SEQ ID NO 87
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 87
Gln Ser Ser Gln Ser Val Tyr Asn Asn Phe Leu Ser
   1    5    10

<210> SEQ ID NO 88
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 88
Gln Ala Ser Lys Leu Ala Ser
   1    5

<210> SEQ ID NO 89
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 89
Leu Gly Gly Tyr Asp Asp Ala Asp Asn Ala
   1    5    10

<210> SEQ ID NO 90
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 90
Asp Tyr Ala Met Ser
<210> SEQ ID NO 91
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 91

Ile Ile Tyr Ala Gly Ser Gly Ser Thr Trp Tyr Ala Ser Trp Ala Lys

Gly

<210> SEQ ID NO 92
<211> LENGTH: 14
<212> TYPE: PRT
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<400> SEQUENCE: 92

Amp Gly Tyr Amp Tyr Gly Amp Phe Amp Arg Leu Amp Arg Leu

<210> SEQ ID NO 93
<211> LENGTH: 492
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 93

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cctgataact tc 492

<210> SEQ ID NO 94
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 94

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<210> SEQ ID NO: 95
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 95

cagtcagtc agagtgttta tastaatttc ttatcg

<210> SEQ ID NO: 96
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 96

caggtcatca aactggtcatc t

<210> SEQ ID NO: 97
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 97

caggggytt atgatgatga tgctgataat gct

<210> SEQ ID NO: 98
<211> LENGTH: 15
<212> TYPE: DNA
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<400> SEQUENCE: 98

gactatgca tgcgc

<210> SEQ ID NO: 99
<211> LENGTH: 51
<212> TYPE: DNA
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<400> SEQUENCE: 99

atcattttag tggtagtgg tagcacatgg taagcgagct gggcgaaggg c

<210> SEQ ID NO: 100
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
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<210> SEQ ID NO: 101
<211> LENGTH: 164
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 101

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50   55   60
Gly Arg Phe Thr Ile Ser Arg Asp Ser Asp Gly Leu Ala Tyr Leu Tyr
65   70   75   80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Cys Ala
85   90   95
Arg Asp Asp Ser Ser Asp Thr Val Ala Lys Phe Asn Leu
100  105
<210> SEQ ID NO 119
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 119

Amp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1    5    10    15
Amp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Asn Asn Glu
20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35   40   45
Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50   55   60
Ser Gly Ser G1y Thr G1y Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Amp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn
85   90   95
Ile Asp Asn Ala
100

<210> SEQ ID NO 120
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 120

Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile Gly
1    5    10    15

<210> SEQ ID NO 121
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 121

Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Ser Ala Ile Gly
1    5    10    15

<210> SEQ ID NO 122
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 122

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1    5    10    15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20   25   30
Val Ser Ala Ala Val Gly Thr Val Thr Ile Ser Cys Gln Ser Ser
35   40   45
Gln Ser Val Gly Asn Ala Gln Asp Leu Ser Thr Phe Gln Gln Arg Pro
50   55   60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr G1y Ile Ser Lys Leu Glu Ser
65   70   75   80
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr His Phe Thr
85   90   95
Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
1 100 105 110

Leu Gly Gly Tyr Asp Asp Ala Asp Asn Ala
115 120

<210> SEQ ID NO 123
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Orzyctolagus cuniculus

<400> SEQUENCE: 123

Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys His Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45

Ser Arg Thr Met Ser Thr Val Arg Gly Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Tyr Ile Thr Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp
65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Leu Gly Asp Thr Gly Gly His Ala Tyr Ala Thr Arg Leu Asn Leu
115 120 125

<210> SEQ ID NO 124
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Orzyctolagus cuniculus

<400> SEQUENCE: 124

Gln Ser Ser Gln Ser Val Gly Asn Asn Gln Asp Leu Ser
1 5 10

<210> SEQ ID NO 125
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Orzyctolagus cuniculus

<400> SEQUENCE: 125

Glu Ile Ser Lys Leu Glu Ser
1 5

<210> SEQ ID NO 126
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Orzyctolagus cuniculus

<400> SEQUENCE: 126

Leu Gly Gly Tyr Asp Asp Ala Asp Asn Ala
1 5 10

<210> SEQ ID NO 127
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Orzyctolagus cuniculus
<400> SEQUENCE: 127
Ser Arg Thr Met Ser
1  5

<210> SEQ ID NO 128
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 128
Tyr Ile Trp Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1    5  10  15

<210> SEQ ID NO 129
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 129
Leu Gly Asp Thr Gly Lys His Ala Tyr Ala Thr Arg Leu Asn Leu
1    5  10  15

<210> SEQ ID NO 130
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 130
atggacacg gggcccccac tcagctgtcg gggctctgct gcctctgct cccacgtgcc  60
acatttgcc cgtgtgtcag ccagacacca tccaccgtgt ctgcagctgt gggacgacga 120
gtccacatca gtgcacagtct gttcggtctata accacagctt atctggtgttt 180
cagccagac cgggccggcc tccccagctt ccagttctac agaatcactaa actgtactct 240
gggtcccat cggccggtcag ccgagctgga tctggacac acctcactct caccatcacg 300
gggtcagcg tgcagcctgc tgtcacttac atcagttcct ggcggatatga tgcagctgt 360
gataagct 369

<210> SEQ ID NO 131
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 131
atgggaagctg ggtgcaagctg gtcttcctctg gcctgtgtgc tccaaagtgt gcagtggtcag  60
tcggtggagc atgctgggtg cgtgcgtggtgc aaccggtgga ccacactgac actcactggc 120
acagcctctgt gttctggtcg cagcgtggtgc aacaagctggt ggggtgcggga ggtga caggg 180
aacgctggac atgctgggtgc atcagttggat ggtggtggtct gcacactcact cagcagctgc 240
ggctaacggg gatgcagcact ctccaaacct cggcagcggc tggcagcgc aaccggtact 300
cggcaacag cggcagcggc cacacttttc gtagcagat tggcgggta cggcttgcag 360
gcgttgatctgcggttaaact cttc 384

<210> SEQ ID NO 132
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 132

caagtccagtc agastgttgg taataaccag gaacctc 39
c

<210> SEQ ID NO 133
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 133
gaaatatcca aactggaatct 21
g

<210> SEQ ID NO 134
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 134
cctaggggtt atgtagttag tgcgtgtaat gct 33
g

<210> SEQ ID NO 135
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 135
agctgtaac a tgtcc 15
g

<210> SEQ ID NO 136
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 136	
tacatttgggtgtgtag cacatacatcgacacctgg ccgaaagg 48
g

<210> SEQ ID NO 137
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 137			ttggtagcata cgttgtgtaaat cactgtttaac ata 45
g

<210> SEQ ID NO 138
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 138

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Leu Trp 1 5 10 15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Ser 20 25 30
Val Ser Ala Ala Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ser Ser 35 40 45
Gln Ser Val Tyr Ser Asn Lys Tyr Leu Ala Trp Tyr Gln Gln Lys Pro 50 55 60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Thr Ser Lys Leu Ala Ser
65 70 75 80

Gly Ala Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr
95 90 95

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Leu Gly Ala Tyr Asp Asp Ala Asp Asn Ala
115 120

<210> SEQ ID NO 139
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Orectolagus cuniculus

<400> SEQUENCE: 139

Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gin Ser Val Glu Ser Gly Gly Arg Leu Val Lys Pro
20 25 30

Asp Glu Thr Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Glu
35 40 45

Gly Gly Tyr Met Thr Trp Val Arg Gin Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Ile Ser Tyr Asp Ser Gly Ser Thr Tyr Ala Ser Thr
65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp
95 100 105 110

Leu Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110

Val Arg Ser Leu Lys Tyr Pro Trp Val Thr Ser Asp Asp Ala
115 120 125

<210> SEQ ID NO 140
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Orectolagus cuniculus

<400> SEQUENCE: 140

Gln Ser Ser Gin Ser Val Tyr Ser Asn Lys Tyr Leu Ala
1 5 10

<210> SEQ ID NO 141
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Orectolagus cuniculus

<400> SEQUENCE: 141

Trp Thr Ser Lys Leu Ala Ser
1 5

<210> SEQ ID NO 142
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Orectolagus cuniculus

<400> SEQUENCE: 142

Leu Gly Ala Tyr Asp Asp Ala Asp Asn Ala
1 5 10
<210> SEQ ID NO 143
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 143

Gly Gly Tyr Met Thr
1  5

<210> SEQ ID NO 144
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 144

Ile Ser Tyr Asp Ser Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 145
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 145

Ser Leu Lys Tyr Pro Thr Val Thr Ser Asp Asp Leu
1  5  10

<210> SEQ ID NO 146
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 146

atggaacacga gggccccac tcagctgctg gggctctgcg tgcctctgtc cccaggtgcc 60
ccatattgac acctctgtagc ccacacacca tcgctgctgt cttcgactcgt gggaggca 120
ttcggagatac cgacgagtctcg gggttatactg tattatga ataagttacct aggatggtat 180
gagcagagcg gggcggcccc gcggccccctcg ctatctctcg gggcatcctaa actggccatct 240
aggggcccct qctctgctgc aggagttgag tgggttgaattgcaccct gacccattgagagcac 300
tgctgctagtg gttggttagc ttcctctctctgtctctgct tgcctctctgc 360
gataatgtctg 369

<210> SEQ ID NO 147
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 147

atggaactg ggcgtgctgtg gctttccttg tgcgctgtgc tccaaaggtgc ccaagtgctg 60
ttcggagagc gggagggggttcgctggtgc aacccctgtgc ggggtgggctt ggcggccggg 120
ttggtgtctgg tggaggtttgcc cagtgccgag cttgacccct ggcggggggg 180
tggaggggtgg ctcgttactg atacggatgaa cagcattgatt gccacagacgt ccggctctg 240
gcgaggtgtct gggtgtgagc ttcctgcttg ttgccgtgtgc gcgtggactgc ggggttgtgt 300
agtctgacaa ccagagccac ggccccctcg ccagatgttg tttcctgctg gacactaata atagctact 360
gttaaccttg atgacttg

<210> SEQ ID NO 148
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 148
cagtcaacgc aggtagttta tagtaataag tacctagcc

<210> SEQ ID NO 149
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 149
tggatcatca aactggcatc t

<210> SEQ ID NO 150
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 150
catggcgctt atgatgatga tgtgataat gct

<210> SEQ ID NO 151
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 151
ggaggtcaco tggccc

<210> SEQ ID NO 152
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 152
atcagtttag atagtgtag cacatactac gcagctgggg c8aagggc

<210> SEQ ID NO 153
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 153
tcaactaaat atocactctgcc ttcttgat gacttg

<210> SEQ ID NO 154
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 154
Met Asp Thr Arg Ala Pro Thr Glu Leu Leu Gly Leu Leu Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Glu Thr Pro Ser Pro
20 25 30
Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Ser Cys Gln Ser Ser
35 36 40 45
Gln Ser Val Tyr Asn Asn Asn Leu Ala Trp Tyr Gln Gln Lys Pro
90 95 100 105 110
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ser Thr Leu Ala Ser
45 70 75 80
Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95
Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Ala Tyr Tyr Cys
100 105 110
Leu Gly Gly Tyr Asp Asp Ala Asp Asn Ala
115 120

<210> SEQ ID NO 155
<211> LENGTH: 129
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 155

Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Gln Ser Val Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Leu Ser Leu Ser
35 40 45
Ser Asn Thr Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Ile Gly Tyr Ile Trp Ser Gly Ser Thr Tyr Ala Ser Trp
65 70 75 80
Val Asn Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
95 100 105 110
Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
120
Arg Gly Gly Tyr Ala Ser Gly Gly Tyr Pro Tyr Ala Thr Arg Leu Asp
115 120 125
Leu

<210> SEQ ID NO 156
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 156

Gln Ser Ser Gln Ser Val Tyr Asn Asn Asp Leu Ala
1 5 10

<210> SEQ ID NO 157
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 157

Tyr Ala Ser Thr Leu Ala Ser
1 5

<210> SEQ ID NO 158
Leu Gly Gly Tyr Aep Aep Ala Aep Aem Ala
1 5 10

Ser Asn Thr Ile Aem
1 5

Tyr Ile Trp Ser Gly Gly Ser Thr Tyr Ala Ser Trp Val Asn Gly
1 5 10 15

Gly Gly Tyr Ala Ser Gly Gly Tyr Pro Tyr Ala Thr Arg Leu Aep Leu
1 5 10 15

atggaacagcg gggcccccaca tcaagtgtcg gggctcctgc tgcctctgct ccaggtgccc
60
acatiggcg cgggctgtgac ccagacacca tccactcggtct gcaggtgtgct gggaggcaca
120
gtcaacatca gttccagctg cactcagagttggtttataaatat saacactttt agctgtgtat
180
cacggcaacac ggcggcagcc tcttttaactctgcatctattt atggcatccac tctggcactct
240
gggctcctca ggcggcttgggagccactggtgtctctgt caccattcagcagagagagac
300
gggctcctca gggctcctca gggctcctca gggctcctca gggctcctca gggctcctca
360
gataatgct
369

gggctcctca gggctcctca gggctcctca gggctcctca gggctcctca gggctcctca
360
gataatgct
369
acagtatctgc gattatccct cagttgacaat acataaaact gggtccgcca ggctccaggg
180
aaaggggttgg cagcagctgg atacatttgg agtgggtgta gtcatacta cgccagcttg
240
gtgaaatgtc gattcaccat ctcccaaaacc tgcacccagg tggatctgaa aatccaccgt
300
cggacaacgc agsgaaccgc cacacttttc tgtgccagasag ggggttaagc tgggtggtt
360
tacctttatg cacctggttt ggtatccc
387

<210> SEQ ID NO: 164
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 164
cagttcagtc agaggttatta taataataac gacctagcc
39

<210> SEQ ID NO: 165
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 165
tatgccatca ctctggcatc t
21

<210> SEQ ID NO: 166
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 166
cagcgggttt atgatgatga tgtgtgataat gct
33

<210> SEQ ID NO: 167
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 167
agccatcaca taasc
15

<210> SEQ ID NO: 168
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 168
tcatttggga tgggtsgtag tacata tactc gcgagctggg tggatggtt
48

<210> SEQ ID NO: 169
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 169
sggggttaag ctagtggctgt tatctct taticctggt tggatcctc
48

<210> SEQ ID NO: 170
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 170

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Leu Leu 1 5 10 15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Ser 20 25 30
Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser 35 40 45
Gln Ser Val Tyr Asn Asn Asp Tyr Leu Ser Trp Tyr Gln Gln Arg Pro 50 55 60
Gly Gln Arg Pro Lys Leu Leu Ile Tyr Gly Ala Ser Lys Leu Ala Ser 65 70 75 80
Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Lys Gln Phe Thr 95 90 95
Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys 100 105 110
Leu Gly Asp Tyr Asp Asp Ala Asp Asp Asn Thr 115 120

<210> SEQ ID NO 171
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 171

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Leu Gln 1 5 10 15
Val Gln Cys Gln Ser Leu Glu Ser Gly Gly Arg Leu Val Thr Pro 20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Leu Ser 35 40 45
Thr Asn Tyr Tyr Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu 50 55 60
Glu Thr Ile Gly Ile Ile Tyr Pro Ser Gly Asn Thr Tyr Cys Ala Lys 65 70 75 80
Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val 95 90 95
Asp Leu Lys Met Thr Ser Pro Thr Thr Gly Asp Thr Ala Thr Tyr Phe 100 105 110
Cys Ala Arg Asn Tyr Gly Gly Asp Glu Ser Leu 115 120

<210> SEQ ID NO 172
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 172

Gln Ser Ser Gln Ser Val Tyr Asn Asp Tyr Leu Ser 1 5 10

<210> SEQ ID NO 173
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 173
Gly Ala Ser Lys Leu Ala Ser  
1  5

<210> SEQ ID NO 174
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 174

Leu Gly Asp Tyr Asp Asp Ala Asp Asn Thr  
1  5  10

<210> SEQ ID NO 175
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 175

Thr Asn Tyr Tyr Leu Ser  
1  5

<210> SEQ ID NO 176
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 176

Ile Ile Tyr Pro Ser Gly Asn Thr Tyr Cys Ala Lys Trp Ala Lys Gly  
1  5  10  15

<210> SEQ ID NO 177
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 177

Asn Tyr Gly Gly Asp Glu Ser Leu  
1  5

<210> SEQ ID NO 178
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 179

atggacagag ggccccccac tcagctgtcg gggctccctcg tgcctctggt ccagctgcgc  60
acctttgag cctgtgtgac cccagcaca ccctccctgt ctgcagctgt gggagcacca  120
gtcaacctca atttgcaagt ctgctcaact gttttataa acgactacct attccttgtat  180
caccaaggg ccagcacaag gtctcaacgc aatacatctg gttgtcaccat actgctactt  240
ggggtccgct caggagtaga tctggaagac agtctactct cacatcagc  300
ggggtgccagtg gagaagtgcg tyccccctac tctgctcgag gcgtattatag tgggtatgct  360

gataatacct  369
<400> SEQUENCE: 179
atggagactg ggtgctgtg cttttocctg gtgcatgtg gcaaaagtgt ccaggttcag
60
tgcggagag agtctcggg cttccttgac acgcgggag cacccttgac acacacttgc
120
agacatctgg gattcaccct cagtaacacct tactacctgag tgtggctcag ccaggttcca
180
gggaaggggg tagaatggtg caagaacatt tatccatagt gtaaacata ttgccgcaag
240
tggggcaag ggcgatcacc catcttccaa acctcgtcga ccacggttga cttgaaaatg
300
acacgtcga caccggagga cacagcaacg tattcctgtg ccagaatga tgggtgtgtgat
360
gaagaattg
369

<210> SEQ ID NO 180
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 180
cagttccagtc aatggttta taattacgc tattatatc
39

<210> SEQ ID NO 181
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 181
gtgcttcca acctggtac t
21

<210> SEQ ID NO 182
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 182
cggggcatt atgatgatga tggataaat act
33

<210> SEQ ID NO 183
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 183
accactact acctgagc
18

<210> SEQ ID NO 184
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 184
tatcatttac ctagtgtgaa cacatattg gcgaagctgg gcgaaggc
48

<210> SEQ ID NO 185
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 185
aatatatggtg ggtgatgaag tttg
24
<210> SEQ ID NO 186
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 186

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1      5     10    15

Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20   25     30

Val Glu Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35   40     45

Glu Thr Ile Gly Aam Ala Leu Ala Trp Tyr Gln Gin Lys Ser Gly Gin
50   55    60

Pro Pro Lys Leu Leu Ile Tyr Lys Ala Ser Lys Leu Ala Ser Gly Val
65   70    75    80

Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr
85   90    95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gin Trp
100  105   110

Cys Tyr Phe Gly Asp Ser Val
115

<210> SEQ ID NO 187
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 187

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Thr Val Leu Lys Gly
1     5      10   15

Val Gin Cys Gin Glu Gin Leu Val Glu Ser Gly Gly Gly Leu Gin Val
20   25     30

Pro Glu Gly Ser Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Asp Phe
35   40    45

Ser Ser Gly Tyr Tyr Met Cys Trp Val Arg Gin Ala Pro Gly Lys Gly
50   55    60

Leu Glu Trp Ile Ala Cys Ile Phe Thr Ile Thr Thr Asn Thr Tyr Tyr
65   70    75    80

 Ala Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr
85   90    95

Thr Val Thr Leu Gin Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr
100  105   110

Tyr Leu Cys Ala Arg Gly Ile Tyr Ser Asp Asn Asn Tyr Tyr Ala Leu
115  120   125

<210> SEQ ID NO 188
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 188

Gln Ala Ser Glu Thr Ile Gly Asn Ala Leu Ala
1     5      10
Lys Ala Ser Lys Leu Ala Ser
1 5

Gln Trp Cys Tyr Phe Gly Asp Ser Val
1 5

Ser Gly Tyr Tyr Met Cys
1 5

Cys Ile Phe Thr Ile Thr Thr Asn Thr Tyr Tyr Ala Ser Trp Ala Lys
1 5 10 15

Gly

Gly Ile Tyr Ser Asp Asn Asn Tyr Tyr Ala Leu
1 5 10

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**SEQ ID NO 189**
LENGTH: 7
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

**SEQUENCE: 189**
Lys Ala Ser Lys Leu Ala Ser 1 5

**SEQ ID NO 190**
LENGTH: 9
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

**SEQUENCE: 190**
Gln Trp Cys Tyr Phe Gly Asp Ser Val 1 5

**SEQ ID NO 191**
LENGTH: 6
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

**SEQUENCE: 191**
Ser Gly Tyr Tyr Met Cys 1 5

**SEQ ID NO 192**
LENGTH: 17
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

**SEQUENCE: 192**
Cys Ile Phe Thr Ile Thr Thr Asn Thr Tyr Tyr Ala Ser Trp Ala Lys 1 5 10 15

Gly

**SEQ ID NO 193**
LENGTH: 11
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

**SEQUENCE: 193**
Gly Ile Tyr Ser Asp Asn Asn Tyr Tyr Ala Leu 1 5 10

**SEQ ID NO 194**
LENGTH: 357
TYPE: DNA
ORGANISM: Oryctolagus cuniculus

**SEQUENCE: 194**
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agatgtgatg ttgtgatgac ccagactcca gcctcgctgg aggccagcttg gggaggcaca 120
gtcaacctac agtgccaggg cagtgagacc attggaastg cattagcttg gttcagcgag 180
aactcaggg cgctcccaac gcctcggtac tacaagccat ccaacctggc atctggggtc 240
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gagtggtccg atgctgcocac ttactacctg cattgcggtt atttgggtga tagttg 357
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60
gagcgacttg tggagtcctgc ggagagcctg gtccagcttg agggatcctc gacaatcacc
120
tgcaacgct ctggattcga ctteactagc ggatactaca tggtaggtggt cggcaggtg
180
cgaagggaggg ggttagctgt gatgggtgtg atttcacta ttactactaa cacttactac
240
gcgagcgtgg cgaagggcgg attccacct tocagacct ctgctgaccac ggtgcacttg
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caaatgcacg gtctgacacg cgccgacag ggcacactct tcgtgctgag aggattattat
360
tcctgataata atttattatgc ttg
384

<210> SEQ ID NO 196
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 196
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<210> SEQ ID NO 197
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 197
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21

<210> SEQ ID NO 198
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 198
caaagctggtt atttggtgag tattggtt
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<210> SEQ ID NO 199
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 199
agcgctact acatgtgc
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<210> SEQ ID NO 200
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 200
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51
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 201

gggtttatt ctgataataa ttattagct ttg

SEQ ID NO: 202
LENGTH: 119
TYPE: PRT

ORGANISM: Oryctolagus cuniculus

SEQUENCE: 202

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1  5  10  15
Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20 25 30
Val Glu Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45
Glu Ser Ile Gly Asn Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60
Pro Pro Lys Leu Leu Ile Tyr Lys Ala Ser Thr Leu Ala Ser Gly Val
65 70 75 80
Pro Ser Arg Phe Ser Gly Ser Gly Ser Thr Glu Phe Thr Leu Thr
85 90 95
Ile Ser Gly Val Gln Cys Ala Asp Ala Ala Ala Tyr Tyr Cys Gln Trp
100 105 110

Cys Tyr Phe Gly Asp Ser Val
115

SEQ ID NO: 203
LENGTH: 128
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 203

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1  5  10  15
Val Gln Cys Gln Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30
Pro Gly Ala Ser Leu Thr Leu Thr Cys Lys Ala Ser Gly Phe Ser Phe
35 40 46
Ser Ser Gly Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly
50 55 60
Leu Glu Ser Ile Ala Cys Ile Phe Thr Ile Thr Asp Asn Thr Tyr Tyr
65 70 75 80
Ala Asn Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Pro Ser Ser Pro
85 90 95
Thr Val Thr Leu Gln Met Thr Ser Leu Thr Ala Asp Thr Ala Thr
100 105 110
Tyr Phe Cys Ala Arg Gly Ile Tyr Ser Thr Asp Asn Tyr Tyr Ala Leu
115 120 125
<400> SEQUENCE: 204

Gln Ala Ser Glu Ser Ile Gly Asn Ala Leu Ala
1    5    10

<210> SEQ ID NO 205
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 205

Lys Ala Ser Thr Leu Ala Ser
1    5

<210> SEQ ID NO 206
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 206

Gln Trp Cys Tyr Phe Gly Asp Ser Val
1    5

<210> SEQ ID NO 207
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 207

Ser Gly Tyr Tyr Met Cys
1    5

<210> SEQ ID NO 208
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 208

Cys Ile Phe Thr Ile Thr Asp Asn Thr Tyr Tyr Ala Asn Trp Ala Lys
1    5    10    15

Gly

<210> SEQ ID NO 209
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 209

Gly Ile Tyr Ser Thr Asp Asn Tyr Tyr Ala Leu
1    5    10

<210> SEQ ID NO 210
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 210

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agatgtagtg tgtgtagagc ccaagactcca gctcctggag gggcagctgtg gggagggcaca 120
gtccacatcca agagcgagc gatggcagag cattggccttg gatcagcag 180
<210> SEQ ID NO 211
<211> LENGTH: 364
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 211
atggagactg ggtgcgtcgtg gccttccttg gtgcgtgtgc tcaaaaggtgt ccaagtctcag 60
cagcgacttg tggactgcgg ggagggcttg gtcaagcgcg gggcatccct gacaactcacc 120
tgsaagct ctgtatctc cttcgagtac gcgtactaca tggcgtgggt cgccgacgct 180
cagggaggg ggacgcgtgct gatgctactg ctattttacta ttactgtgata caacctactac 240
gcagaacgct cgsagggctg attcaccact tcaagccct cgtgcggcacc ggtgacgctt 300
caatgacca gtcgacagcg cgccgacgcgt ggcacctatt tgtggtcgag ggcttttat 360
tctactgata attattatgc cttg 384

<210> SEQ ID NO 212
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 212
caggctgagt agagcatcttg ctaagcatta gcc 33

<210> SEQ ID NO 213
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 213
aagggcatcca ctctggcata t 21

<210> SEQ ID NO 214
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 214
caatgggttgt attttgtgta tagtgtt 27

<210> SEQ ID NO 215
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 215
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<210> SEQ ID NO 216
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 216
tgcatatatga ttaactttaac tacgcaagcttac ggggcaaggg c

<210> SEQ ID NO 217
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 217

ggatttatt ctaattgtaaa tttatgcct ttg

<210> SEQ ID NO 218
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 218

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Arg Cys Val Val Met Thr Gln Thr Pro Ala Ser
20  25  30
Val Glu Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gin Ala Ser
35  40  45
Gln Ser Val Ser Ser Tyr Leu Asn Trp Tyr Gln Gin Lys Pro Gly Gln
50  55  60
Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Thr Leu Glu Ser Gly Val
65  70  75  80
Pro Ser Arg Phe Lys Gin Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
95  100  105  110
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gin Cys
115 120
Thr Tyr Gly Thr Ser Ser Ser Tyr Gly Ala Ala

<210> SEQ ID NO 219
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 219

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1  5  10  15
Val Gln Cys Gin Ser Val Glu Ser Gly Arg Leu Val Thr Pro
20  25  30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Ser Leu Ser
35  40  45
Ser Asn Ala Ile Ser Trp Val Arg Gin Ala Pro Gly Lys Gin Leu Glu
50  55  60
Trp Ile Gly Ile Ile Ser Tyr Ser Gly Thr Thr Tyr Thr Tyr Ala Ser Trp
65  70  75  80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp
85  90  95
Leu Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110
Ala Arg Asp Asp Pro Thr Thr Val Met Val Met Leu Ile Pro Phe Gly
115 120 125
-continued

Ala Gly Met Asp Leu

130

<210> SEQ ID NO 220
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 220

Gln Ala Ser Gin Ser Val Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 221
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 221

Arg Ala Ser Thr Leu Glu Ser
1 5

<210> SEQ ID NO 222
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 222

Gln Cys Thr Tyr Gly Thr Ser Ser Ser Tyr Gly Ala Ala
1 5 10

<210> SEQ ID NO 223
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 223

Ser Asn Ala Ile Ser
1 5

<210> SEQ ID NO 224
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 224

Ile Ile Ser Tyr Ser Gly Thr Thr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> SEQ ID NO 225
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 225

Asp Asp Pro Thr Thr Val Met Val Met Leu Ile Pro Phe Gly Ala Gly
1 5 10 15

Met Asp Leu

<210> SEQ ID NO 226
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
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agatgtgtag tgtgtgtagc cccacactca goctgctttg aggacgctgt gggaggccca 120
gtcacacta agtggcagcc gagtacagcc gttagctgc acttaaactt gtatccagcag 180
aaccagggcg agcttcocca aacagctgatc tacagggcat caactctgga atctggggtc 240
cacgctgtgg tcgaagggca atgtgctgcgg gcagagtcct cacccacoctc cagacagctg 300
gagtgcttcg atgtgctgcac taactctgt caatgtaatc atggtactag tagtattgatt 360
ggtgtgctg 369

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<211> LENGTH: 399
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 227
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tcgggtggagg atgcaggggag tcggctctgcag caaaccagctg cactgtcag 120
acgcctcctg gtactcctcc gactagcacat gactaagctg ggtgctccgc gctgcttcag 180
aaggggtgag atgggtggag gatcattctg tataagtgata caacactacta cggagctgg 240
gcgaagggcg gtcacctat cacccacoctc ttcgggcacc ggtgtgatat gaaatctact 300
gacgacacag cagacacact actctgtgctgc gagatgaccc taccacagtt 360
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<210> SEQ ID NO: 228
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 228
cacgacagtc agacggttagc tagctactta aac 33

<210> SEQ ID NO: 229
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 229
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<210> SEQ ID NO: 230
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 230
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<210> SEQ ID NO: 231
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe
100 105 110
Cys Ala Lys Ala Tyr Asp Leu
115

<210> SEQ ID NO 236
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 236

Gln Ala Ser Gin Ser Val Tyr Lys Asn Asn Tyr Leu Ser
5  10

<210> SEQ ID NO 237
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 237

Ser Ala Ser Thr Leu Asp Ser
5  1

<210> SEQ ID NO 238
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 238

Leu Gly Ser Tyr Asp Cys Ser Ser Gly Asp Cys Tyr Ala
5  10

<210> SEQ ID NO 239
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 239

Ser Tyr Trp Met Cys
5  1

<210> SEQ ID NO 240
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 240

Cys Ile Val Thr Gly Asn Gly Asn Thr Tyr Tyr Ala Asn Trp Ala Lys
5  10  15

Gly

<210> SEQ ID NO 241
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 241
Ala Tyr Asp Leu

<210> SEQ ID NO 242
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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120
gtccacacta aagcgcagcc cagcagaggt gtatataaga acaactacct atcagtgatg
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cagcagaaac cagcgccagc tcctaaaggc ctgatctatt ctgcctgcaac tctagatctt
240
gggggtcccat tgcggctcag aggctagagg tctgggacac agtttacactt cccatcago
c300
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360
ggtgattgtg atgt
375

<210> SEQ ID NO 243
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 243
atggagactg ggcgtcgctgt cttttccttg gtgcgtgtgc tcacaagtgtg ccaattgtcag
60
tcgttggag aagctccgggg gaaaggtgtgc aagctctggg gatccotgcac actcactgctg
120
acagcctctc gcccttctct cagagactac caggtggtgc ggggtcgcga gggccagggg
180
aagggggtgg aagctctagag aagtcgttctg aatgcgtagt gtagcatctg ataacactgcctcagac
240
tgctggcgcag ggcagccgac acttcctcaaa aacctgctga ccaaggtggc tctgcaatgt
300
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367

<210> SEQ ID NO 244
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 244
cagggcagtc agagttttta taagaacaaac tacattac
39

<210> SEQ ID NO 245
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 245
tctgcacgca cttcaagatc t
21

<210> SEQ ID NO 246
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 246
taggtcagtt atgatttgtag tagtggtgat tgttatgtc
39
<210> SEQ ID NO 247
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 247

agctactgga tytgsc 15

<210> SEQ ID NO 248
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 248
tgcatgttga tggtagat gg aacgta ctg gctgag c 51

<210> SEQ ID NO 249
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 249
gcctatgact tg 12

<210> SEQ ID NO 250
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 250
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp 1 5 10 15
Leu Pro Gly Ser Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro 20 25 30
Val Ser Ala Ala Val Gly Thr Val Ser Ile Ser Cys Gln Ala Ser 35 40 45
Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ser Thr Trp Tyr Gln Gln Lys Pro 50 55 60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Leu Ala Ser 65 70 75 80
Gly Val Pro Ser Arg Phe Lys Gly Thr Gly Ser Gly Thr Gln Phe Thr 85 90 95
Leu Thr Ile Thr Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys 100 105 110
Ala Gly Val Phe Asn Asp Ser Asp Asp Ala 115 120

<210> SEQ ID NO 251
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 251
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Pro Lys Gly 1 5 10 15
Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gln Arg Leu Val Thr Pro 20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Leu Ser Gly Phe Ser Leu Ser
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 252

Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ser
1   5   10

<210> SEQ ID NO 253
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 253

Gly Ala Ser Thr Leu Ala Ser
1   5

<210> SEQ ID NO 254
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 254

Ala Gly Val Phe Asn Asp Ser Asp Asp Ala
1   5   10

<210> SEQ ID NO 255
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 255

Ala Tyr Tyr Met Ser
1   5

<210> SEQ ID NO 256
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 256

Phe Ile Thr Leu Ser Asp His Ile Ser Tyr Ala Arg Trp Ala Lys Gly
1   5   10   15

<210> SEQ ID NO 257
<211> LENGTH: 12
<212> TYPE: PRT
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 257

Ser Arg Gly Trp Gly Ala Met Gly Leu Asp Leu
1
5

SEQ ID NO 258
LENGTH: 369
TYPE: DNA
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 258

atggacacga ggcgcctcac tgcgctgtgc gggctctgcg tgcctctgct cccaggttcg 60
acatgtcggc cggctctgac ccagacataa ttcctccctt ctgcagctgt gggaggcaca 120
gtcagcatca gttggcaggc cagtcagagt gttatgaca acaactatatt atctcggtat 180
cagcagaaac cagcagacag ttcocacgtct cgtatctagt gttgatccac tctgtagact 240
ggggtcgcct ccggtctcga aaggcaaggg tagctgagcc agtctactct caccctcaca 300
gagcgtgtag tgcacgtgat tcgcactttc tatttgctg cggctcttttta tggatgatg 360
gatgatgctcc 369

SEQ ID NO 259
LENGTH: 375
TYPE: DNA
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 259

atggagatgt ggtgcgcctg gctttctctg gtgcctgtgc ccaaggtgtg ccagttgc 60
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acacctctcg gatctctcct cagtcataac tataagctgt ggggtcgcctt ggtcctggc 180
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gcagaaagcc cattcaaac tctcgtcttg cggcagcgtt cctatgacag aattgacactg 300
cgcacaacgc aggagcggc cactctttt tcggcaggc gttgtgcgttg gggtgcactg 360

ggtcctggcttg atctctct 375

SEQ ID NO 260
LENGTH: 39
TYPE: DNA
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 260

ccaggtcgcagtc agatgtgtttta tgcacacata tatttatctc 39

SEQ ID NO 261
LENGTH: 21
TYPE: DNA
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 261
ggtcgatccag cttggcgatc t 21

SEQ ID NO 262
LENGTH: 33
TYPE: DNA
ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 262
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<210> SEQ ID NO 263
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 263
gcatactata tgcagc

<210> SEQ ID NO 264
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 264
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<210> SEQ ID NO 265
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 265
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<210> SEQ ID NO 266
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 266
Met Asp Thr Arg Ala Pro Thr Gin Leu Leu Gly Leu Leu Leu Leu Leu Trp 1 5 10 15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gin Thr Pro Ser Pro 20 25 30
Val Ser Ala Ala Val Gly Thr Val Thr Ile Ser Cys Gin Ala Ser 35 40 45
Gln Ser Val Tyr Asn Asn Lys Asn Leu Ala Trp Tyr Gin Gin Lys Ser 50 55 60
Gly Gin Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Leu Ala Ser 65 70 75 80
Gly Val Ser Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gin Phe Thr 85 90 95
Leu Thr Val Ser Gly Val Gin Cys Asp Asp Ala Ala Thr Tyr Tyr Cys 100 105 110
Leu Gly Val Phe Asp Asp Ala Asp Asp Asn Ala 115 120

<210> SEQ ID NO 267
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 267
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
Val Cln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35 40 45
Ser Tyr Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Tyr Ile Gly Val Ile Gly Thr Ser Gly Ser Thr Tyr Tyr Ala Thr Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Ala Leu
85 90 95
Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Val
100 105 110
Arg Ser Leu Ser Ser Ile Thr Phe Leu
115 120

<210> SEQ ID NO 268
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 268
Gln Ala Ser Gln Ser Val Tyr Asn Asn Lys Asn Leu Ala
1  5  10

<210> SEQ ID NO 269
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 269
Trp Ala Ser Thr Leu Ala Ser
1  5

<210> SEQ ID NO 270
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 270
Leu Gly Val Phe Asp Asp Asp Ala Asp Asn Ala
1  5  10

<210> SEQ ID NO 271
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 271
Ser Tyr Ser Met Thr
1  5

<210> SEQ ID NO 272
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 272
Val Ile Gly Thr Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
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1 5 10 15

<210> SEQ ID NO 273
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 273

Ser Leu Ser Ser Ile Thr Phe Leu
1 5

<210> SEQ ID NO 274
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 274

atgagacaag gggcccccac tcagtcgctg ggcacctcgtg tcgcctcgct cccaggtgcc 60
acatcgcag cctgctgtaa ccagcaggca tcgcccgtgt ctggcggctg tggaggcaca 120
gtcacataca gttgccaggc cagctcagag gtttatccaa cccaaaattt acgctggtat 180
cagcagaat cagggcagcc tcccaagctc ctgctctact gggcatcaca ttcgctcatt 240
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gataatgct 369

<210> SEQ ID NO 275
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 275

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tcggtgaggc agttcggcggg tcgcgctgct cggctggtctg aacgctggga caccccctgac aactcaacgc 120
aacagctggc gttctcctct cagtagctac tcatagacct ggttcgctgga ggttcggcgg 180
aagggctgtg agtcattgtt actagtgta cgcataactc cgctgacggcctg 240
gagggagggc ggtaccaagc ttcggaagcc tgcacacggc tcgctctcag aattaccagt 300
cggcagcacc aggacagccg cacacatcct tctgctcagga gctttttcttttattacttctc 360
ttg 363

<210> SEQ ID NO 276
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 276
cagggcagtc agaagttttta taacacaaa aatattagcc 39

<210> SEQ ID NO 277
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 277
tgagcactcc caactgccatc t 21
<210> SEQ ID NO 278
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 278
cagggcttt ttgatgatga tgcgtgtaat gct

33

<210> SEQ ID NO 279
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 279
agctacctca tgacc

15

<210> SEQ ID NO 280
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 280
gtcattgctg tgaagctgtag cacatactac gcgagctggg cgaaagggc

48

<210> SEQ ID NO 281
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 281
agctctctct ctattaacttt ctg

24

<210> SEQ ID NO 282
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 282
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
Leu Pro Gly Ala Arg Cys Ala Phe Glu Leu Thr Gln Thr Pro Ala Ser
Leu Glu Ala Ala Val Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
Gln Asn Ile Tyr Arg Tyr Leu Ala Trp Tyr Gln Gly Lys Pro Gly Gln
Pro Pro Lys Phe Leu Ile Tyr Leu Ala Ser Thr Leu Ala Ser Gly Val
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Cys Gln Ser
Tyr Tyr Ser Ser Asn Ser Val Ala

<210> SEQ ID NO 283
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 283

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1    5    10    15
Val Gln Cys Gin Glu Gin Leu Val Glu Ser Gly Gly Asp Leu Val Gin
20   25   30
Pro Glu Gly Ser Leu Thr Leu Thr Cyu Thr Ala Ser Gin Leu Asp Phe
35   40   45
Ser Ser Gly Tyr Trp Ile Cys Trp Val Arg Gin Val Pro Gly Lys Gly
50   55   60
Leu Glu Trp Ile Gly Cys Ile Tyr Thr Gly Ser Gly Ser Ser Thr Phe
65   70   75   80
Tyr Ala Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser
90   95
Thr Thr Val Thr Leu Gin Met Thr Ser Leu Thr Ala Ala Gin Thr Ala
100  105  110
Thr Tyr Phe Cys Ala Arg Gly Tyr Ser Gly Phe Gly Tyr Phe Lys Leu
115  120  125

<210> SEQ ID NO 284
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 284

Gln Ala Ser Gin Asn Ile Tyr Arg Tyr Leu Ala
1    5    10

<210> SEQ ID NO 285
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 285

Leu Ala Ser Thr Leu Ala Ser
1    5

<210> SEQ ID NO 286
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 286

Gln Ser Tyr Tyr Ser Ser Asn Ser Val Ala
1    5    10

<210> SEQ ID NO 287
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 287

Ser Gly Tyr Trp Ile Cys
1    5

<210> SEQ ID NO 288
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 288

Cys Ile Tyr Thr Gly Ser Ser Gly Ser Thr Phe Tyr Ala Ser Trp Ala
1    5    10    15
Lys Gly

<210> SEQ ID NO 289
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 289

Gly Tyr Ser Gly Phe Gly Tyr Phe Lys Leu
1    5    10

<210> SEQ ID NO 290
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 290

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agagtgctg tcgaaatgac ccagactca gctcctgtgg aggccagctg gggaggaca 120
gtaccatac atggccaggg cagtcgaaac atatatagat acctagcctg gtaatcagcag 180
aaaacagggc agcctccca gttctgtaatctgttgttt catctctgcgatctggtgcc 240
cctagcgct ttaaagcggct tgtatctggg acagagttaca ccttcacact cagccgccctg 300
gaggtgtccgg atgtgctgcc ttaatctgttt caaaagttat ataggtgtaa ttagtgcctg 360

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<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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gagccagctg tggagctcgg ggccacgcct gtcacgcttg aggatccct gacactaccc 120
tgcaagcgtg ctgagactaga ctgcagttgc ggactctggag tgcctgctcg cgcagctg 180
ccaggaaggg gggcggaggt gatgcgattgc atttataactg tggtagtgg tagcacttttt 240
tacgtggagtgg ggcgacctgg ccgctctcaac acctcccaaa otctgtgcag cagctgtcact 300
cctgcaaatgca ccaatgtcag agcctggagac aggccacact atttctgtgc gagaggttat 360
agttgcttg tttatcttac attg 384

<210> SEQ ID NO 292
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 292
caggccagtgc agaacatatta tagatactta gcc 33

<210> SEQ ID NO 293
<211> LENGTH: 21
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 293

cggcatct a ctcggcatc t
21

<210> SEQ ID NO: 294
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 294

casgattatt tagtagtaaa tagtgctgc t
30

<210> SEQ ID NO: 295
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 295

aggggtcact g gatatgc
18

<210> SEQ ID NO: 296
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 296

tggctattata ctggtagtag tggtagcact tttaagcga gttggggcagaa aggc tgcatttata ctggtagtag tggtagcact tttaagcga gttggggcagaa aggc
54

<210> SEQ ID NO: 297
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 297

ggttatagt g gtttggtta ctttaagttg
30

<210> SEQ ID NO: 298
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 298

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30
Val Glu Val Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45
Glu Asp Ile Tyr Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60
Pro Pro Lys Leu Leu Ile Tyr Asp Ser Ser Asp Leu Ala Ser Gly Val
65 70 75 80
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Ala
85 90 95
Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110
 Ala Trp Ser Tyr Ser Asp Ile Asp Asn Ala
 115 120

<210> SEQ ID NO 299
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<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 299

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Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35 40
Ser Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Ile Gly Ile Ile Thr Thr Ser Gly Asn Thr Phe Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Leu Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu
85 90 95
Lys Ile Thr Ser Pro Thr Thr Glu Thr Ala Tyr Thr Phe Cys Ala
100 105 110
Arg Thr Ser Asp Ile Phe Tyr Tyr Arg Asn Leu
115 120

<210> SEQ ID NO 300
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 300

Gln Ala Ser Glu Asp Ile Tyr Leu Leu Ala
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<210> SEQ ID NO 301
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 301

Asp Ser Ser Asp Leu Ala Ser
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<210> SEQ ID NO 302
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 302

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<210> SEQ ID NO 303
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<212> TYPE: PRT
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<400> SEQUENCE: 303
Ser Tyr Tyr Met Ser
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<210> SEQ ID NO 304
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 304

Ile Ile Thr Thr Ser Gly Asn Thr Phe Tyr Ala Ser Trp Ala Lys Gly
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<210> SEQ ID NO 305
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<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 305

Thr Ser Asp Ile Phe Tyr Tyr Arg Asn Leu
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<210> SEQ ID NO 306
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<212> TYPE: DNA
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aaccgggg agctccoca gctccgtgac tattgctctg ccgatctgga atctggggttc 240
cctcggcgt tcaagacgcc tgggtctgac acagagctica cctctgcctg caggtggctg 300
cagtttgacg tctgctgacag ttaagacctg caacagcctt ggagtaaatg tggatggtat
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aattgt
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<210> SEQ ID NO 307
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 307

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120
acagccgctc gcttcctccct cagtagactivity ggtcggccaa ggtgcccaggg
180
aagggcgtgtg aatggatgctg atcccactctg actagtgtact atacattttact cgccgagctg
240
ggcaagcgc ggtcggactc tctcagactc tggatactgaa aatacagctc
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cgtacacctg
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<210> SEQ ID NO 308
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 308
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33

<210> SEQ ID NO 309
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 309
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<210> SEQ ID NO 310
<211> LENGTH: 36
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<400> SEQUENCE: 310
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<210> SEQ ID NO 311
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<400> SEQUENCE: 311
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<210> SEQ ID NO 312
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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<210> SEQ ID NO 313
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 313
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Val Ser Ala Ala Val Gly Ala Thr Val Thr Ile Asn Cys Gln Ser Ser 30 35 40 45
Gln Ser Val Tyr Asp Met Asp Leu Ala Trp Phe Gln Gln Lys Pro 50 55 60
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser 65 70 75 80
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
85 90 95

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
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Leu Gly Ala Phe Asp Asp Ala Asp Asn Thr
115 120

<210> SEQ ID NO 315
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<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 315

Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
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Val Gln Cys Gln Ser Val Glu Ser Gly Ser Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr
35 40 45

Arg His Ala Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Cys Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp
65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95

Arg Ile THR Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Val Ile Gly Asp Thr Ala Gly Tyr Ala Tyr Phe Thr Gly Leu Asp
115 120 125

Leu

<210> SEQ ID NO 316
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<400> SEQUENCE: 316

Gln Ser Ser Gln Ser Val Tyr Asn Asp Met Asp Leu Ala
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<210> SEQ ID NO 317
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 317

Ser Ala Ser Thr Leu Ala Ser
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<210> SEQ ID NO 318
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 318

Leu Gly Ala Phe Asp Asp Ala Asp Asn Thr
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Arg His Ala Ile Thr
1  5

Cys Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1  5  10  15

Val Ile Gly Asp Thr Ala Gly Tyr Ala Tyr Phe Thr Gly Leu Asp Leu
1  5  10  15

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aegttgacag aagttgacag cccagctgcc tacccctgct gtttctctgt ccagcctgcc
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tctgtcacc cgcctgcgtg ctgtgttggt gccttttgtg taattgtgtc
360
gtttataacta 369

atggagagtgc ggtctgctgt gttttctctg gttctgtggt tcaagaggtgt ccaaggtgca
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180
aaggggtcttg atgataggtgt atgactttgg aagttggtagta gctactaatc cggacagtgg
240
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<210> SEQ ID NO 324
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 324

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<210> SEQ ID NO 325
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 325
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<210> SEQ ID NO 326
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 326
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<210> SEQ ID NO 327
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 327
aggcatgca taacc 15

<210> SEQ ID NO 328
<211> LENGTH: 48
<212> TYPE: DNA
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<213> ORGANISM: Oryctolagus cuniculus

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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20  25   30

Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
Gln Ser Val Tyr Asn Trp Leu Ser Trp Tyr Gin Gin Lys Pro Gly Gin 95
  55  60
Pro Pro Lys Leu Leu Ile Tyr Thr Ala Ser Ser Leu Ala Ser Gly Val 65
  70  75  95
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gin Phe Thr Leu Thr 95
  90  95
Ile Ser Gly Val Glu Cys Ala Asp Ala Ala Thr Tyr Cys Gin Gin 100
  105 110
Gly Tyr Thr Ser Asp Val Asp Asn Val 115
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Val Gin Cys Gin Ser Leu Glu Ala Gly Gly Arg Leu Val Thr Pro 20
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Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser 35
  40 45
Ser Tyr Ala Met Gly Thr Val Arg Gin Ala Pro Gly Lys Gin Gly Glu 50
  55 60
Tyr Ile Gly Ile Ile Ser Ser Ser Gly Ser Thr Tyr Thr Ala Thr Trp 65
  70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Gin Ala Ser Ser Thr Thr Val Asp 85
  90 95
Leu Lys Ile Thr Ser Pro Thr Thr Glu Asp Ser Ala Thr Tyr Phe Cys 100
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Ala Arg Gly Gly Ala Gly Ser Gly Gly Val Trp Leu Leu Asp Gly Phe 115
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Asp Pro 130

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<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 332
Gln Ala Ser Gin Ser Tyr Asn Trp Leu Ser 1
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<210> SEQ ID NO 333
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 333
Thr Ala Ser Ser Leu Ala Ser 1
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<210> SEQ ID NO 334
<211> LENGTH: 11
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<213> ORGANISM: Oryctolagus cuniculus

<400>_SEQUENCE: 334

Gln Gln Gly Tyr Thr Ser Asp Val Asp Asn Val
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<210> SEQ ID NO 335
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400>_SEQUENCE: 335

Ser Tyr Ala Met Gly
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<210> SEQ ID NO 336
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400>_SEQUENCE: 336

Ile Ile Ser Ser Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> SEQ ID NO 337
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400>_SEQUENCE: 337

Gly Gly Ala Gly Ser Gly Gly Val Trp Leu Leu Asp Gly Phe Asp Pro
1 5 10 15

<210> SEQ ID NO 338
<211> LENGTH: 363
<212> TYPE: DNA
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cctcgcgtgc tcgcgtgcag ttgtactctg gcgtataag ggcagtttca ctctcaccct cagcgggtgtg 300
gagtggtccag atccggtcagc ttaactagtct cacccccctgatatagtga tgggtgtact 360
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<210> SEQ ID NO 339
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400>_SEQUENCE: 339

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acagtctctg gaaactgacct cagtagctat gcataatggtc gggctccgcca ggtccagagg 180
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gcgaagccg gattccacat ctcacaagcc tcgctggaac cggctgatct gaaattacc 300
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<211> LENGTH: 39
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<211> LENGTH: 21
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<212> TYPE: DNA
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| Ala  | Pro  |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
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| Glu  | Ala  | Ser  | Glu  | Asn  | Ile  | Tyr  | Asn  | Trp  | Leu  | Ala  |      |      |      |      |      |
|------|------|------|------|------|------|------|------|------|------|      |      |      |      |      |      |
| 1    | 5    | 10   |      |      |      |      |      |      |      |      |      |      |      |      |      |

-continued
Thr Val Gly Asp Leu Ala Ser
1 5

Gln Gln Gly Tyr Ser Ser Ser Tyr Val Asp Asn Val
1 5 10

Asp Tyr Ala Val Gly
1 5

Tyr Ile Arg Ser Ser Gly Thr Thr Ala Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

Gly Gly Ala Gly Ser Ser Gly Val Trp Ile Leu Asp Gly Phe Ala Pro
1 5 10 15

atgacacca gggccccac tcaagtgcctg ggcctctgcg tgcgtctggt cccaggtgcc 60
aagtggcgg atgtggtgat gacccagact ccagcctccg tgtcgtcagc tgtgggaggc 120
acagtcacca tcaattgcca ggcagtgag aacctttata atgggttacgc ctgtatcag 180
cacaaacagc ggcagctcgc caagctcctg acctatactg taggcatgct ggcatctggg 240
gtctctcagc ggttcaaaagc cagttgatat gcggcagagt tcacctctcag cacagcgcag 300
cctggtttgct cgcagtcgc ccaattccat tgtcaacagc gtttatactg tagggtatgtt 360
gataatgct 369

Gly Gly Ala Gly Ser Ser Gly Val Trp Ile Leu Asp Gly Phe Ala Pro
1 5 10 15

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aagtggcgg atgtggtgat gacccagact ccagcctccg tgtcgtcagc tgtgggaggc 120
acagtcacca tcaattgcca ggcagtgag aacctttata atgggttacgc ctgtatcag 180
cacaaacagc ggcagctcgc caagctcctg acctatactg taggcatgct ggcatctggg 240
gtctctcagc ggttcaaaagc cagttgatat gcggcagagt tcacctctcag cacagcgcag 300
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gataatgct 369
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<210> SEQ ID NO 357
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 357
actgtaggg atctgggcac t 21

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<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
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cacaggttt ataagtgtag tttatgtgt aatgtt 36

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<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 359
gactatgcag tgggc 15

<210> SEQ ID NO 360
<211> LENGTH: 48
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<213> ORGANISM: Oryctolagus cuniculus
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tacattcga gtatgtgtac cacacttcag cgcacctgag cgaagggc 48

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<212> TYPE: DNA
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<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 362

Met Asp Thr Arg Ala Pro Thr Gin Leu Leu Gly Leu Leu Leu Leu Leu Trp
1  5   10  15
Leu Pro Gly Ala Thr Phe Ala Gin Val Leu Thr Gin Thr Pro Ser Ser
20  25  30
Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gin Ala Ser
35  40  45
Gln Ser Val Tyr Gin Asn Asn Tyr Leu Ser Trp Phe Gin Gin Lys Pro
50  55  60
Gly Gin Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ala Thr Leu Ala Ser
65  70  75  80
Gly Val Pro Ser Arg Phe Lys Gin Gin Ser Gly Ser Gly Thr Gin Phe Thr
85  90  95
Leu Thr Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110
Ala Gly Ala Tyr Arg Asp Val Asp Ser
115 120

<210> SEQ ID NO 363
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 363

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1  5   10  15
Val Gin Cys Gin Ser Leu Leu Glu Ser Gly Gly Asp Leu Val Lys Pro
20  25  30
Gly Ala Ser Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Phe Thr
35  40  45
Ser Thr Tyr Tyr Ile Tyr Trp Val Arg Gin Ala Ala Pro Gly Lys Gly Leu
50  55  60
Glu Trp Ile Ala Cys Ile Asp Ala Gly Ser Ser Gly Ser Thr Tyr Tyr
65  70  75  80
Ala Thr Trp Val Asn Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr
85  90  95
Thr Val Thr Leu Gin Met Thr Ser Leu Thr Ala Asp Thr Ala Thr
100 105 110 115
Tyr Phe Cys Ala Lys Trp Asp Tyr Gly Gin Asn Val Gly Gly Trp Gly Tyr
120 125
Asp Leu
130

<210> SEQ ID NO 364
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 364
Gln Ala Ser Gln Ser Val Tyr Gln Asn Asn Tyr Leu Ser
1  5 10

<210> SEQ ID NO: 365
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 365
Gly Ala Ala Thr Leu Ala Ser
1  5

<210> SEQ ID NO: 366
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 366
Ala Gly Ala Tyr Arg Asp Val Asp Ser
1  5

<210> SEQ ID NO: 367
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 367
Ser Thr Tyr Tyr Ile Tyr
1  5

<210> SEQ ID NO: 368
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 368
Cys Ile Asp Ala Gly Ser Ser Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Val
1  5 10 15

Asn Gly

<210> SEQ ID NO: 369
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 369
Trp Asp Tyr Gly Asn Val Gly Trp Gly Tyr Asp Leu
1  5 10

<210> SEQ ID NO: 370
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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acattttgc acagtgcg acagactcga tcgctgctgct ctgcagctgct ggggaccaca 120
gtcaccatca atgcgccagc cgacgaggt gtgtatcaga acaactcttt acctgtggtt 180
cagccgaaacc cagggccacgc tcccaagtct ctagctctag gtcgggccac ctcgcatct
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gggtgccat cggctgtaaa aggcagtgga tctgggccac gatctcaacct caccacacgc
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gccttggagt gtgagcacag tcgtcactac tctgtgctag gctcctatag ggatggtgat
tct
  360
<210> SEQ ID NO: 371
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
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tgctgtggag aagcctgggg ggagctgggtc aagcgctgtggg cactctggac actcactggc
  120
acacccctcg gattcctcct tactagtaact tactacatct actctgggctcg cagagcttca
  180
gggagggcgg tggctgggtg cgcctgtatt gatgctggta gtagggtgtag cactctctac
  240
gggaggggg gttgagctcg gttgctgcg gctcggacttc gtcggccacgc ggtagcttggc
  300
cctggtggcag ccagkgcagc ggggaggttg ctcgggctgaa atgggattgttggtgcctg
  360
<210> SEQ ID NO: 372
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 372
cagggccagtc aagaggtttta tcagaacaac tatttacct
  39
<210> SEQ ID NO: 373
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 373
ggtgcggcgc ccacggcatct t
  21
<210> SEQ ID NO: 374
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 374
gcagggcttt atagggctgt ggattct
  27
<210> SEQ ID NO: 375
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 375
agtaacctct acactctac
  18
<210> SEQ ID NO: 376
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 376

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tgattgtag cgtagtagtg tgtagcaact tacatacoga cgtagtggaa tggc
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<210> SEQ ID NO 377
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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tggtatagcgctgtggaagtttgacttg
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<210> SEQ ID NO 378
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1      5      10      15
Leu Pro Gly Ala Arg Cys Ala Phe Glu Leu Thr Gln Thr Pro Ser Ser
20     25     30
Val Gln Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35     40     45
Gln Ser Ile Ser Ser Tyr Leu Ala Ala Tyr Gln Gln Lys Pro Gly Gln
50     55     60
Pro Pro Lys Phe Leu Ile Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val
65     70     75     80
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85     90     95
Ile Ser Asp Ala Glu Cys Ala Asp Ala Thr Tyr Tyr Cys Gln Ser
100    105    110
Tyr Tyr Asp Ser Val Ser Asn Pro
115    120
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<210> SEQ ID NO 379
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1      5      10      15
Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Asp Leu Val Lys Pro
20     25     30
Glu Gly Ser Leu Thr Leu Thr Cys Lys Ala Ser Gly Leu Asp Leu Gly
35     40     45
Thr Tyr Trp Phe Met Cys Trp Val Arg Gin Ala Pro Gly Lys Gly Leu
50     55     60
Glu Trp Ile Ala Cys Ile Tyr Thr Gly Ser Gly Ser Thr Phe Tyr
65     70     75     80
Ala Ser Trp Val Asn Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr
85     90     95
Thr Val Thr Leu Gin Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr
100    105    110
Tyr Phe Cys Ala Arg Gly Tyr Ser Gly Tyr Gly Tyr Phe Lys Leu
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<210> SEQ ID NO 380
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 380

Gln Ala Ser Gln Ser Ile Ser Ser Tyr Leu Ala
1  5   10

<210> SEQ ID NO 381
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 381

Arg Ala Ser Thr Leu Ala Ser
1  5

<210> SEQ ID NO 382
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 382

Gln Ser Tyr Tyr Asp Ser Val Ser Asn Pro
1  5   10

<210> SEQ ID NO 383
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 383

Thr Tyr Trp Phe Met Cys
1  5

<210> SEQ ID NO 384
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 384

Cys Ile Tyr Thr Gly Ser Ser Gly Ser Thr Phe Tyr Ala Ser Trp Val
1  5   10   15

Asn Gly

<210> SEQ ID NO 385
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 385

Gly Tyr Ser Gly Tyr Gly Tyr Phe Lys Leu
1  5   10

<210> SEQ ID NO 386
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
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agatgtcctc togaattgac ccagactcct caacttcctgg agggagctgtg gggagggccaa 120
gtcaacatca agtgccgggc cagtcacgcc attgataggt aatgccgctg gttacacgcag 190
aaaccagggc agctctcaca gttcctggtc tacaagggct ccaaccttcgc atctgggggctc 240
catcgcgtat ccaaaggcctg tcgaatactgg acagagttca cttacaccat cagcagcctg 300
gagtgtgcgcg attggacccct ctaactactgta caaagctatt atgataggtg ttcaattcct 360

<210> SEQ ID NO 387
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 387
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tgttggaggg agtgcagggg aagcctgtgct aagctgtgac gcacccctgc acaactcctgc 120
aaagcctctcg gactcgaacct ccgtactctac tcggtgcattg gtctgggtcc ccaggtctcg 180
gggagggggc tggagtggat cgctgttatt tatactctgtta gtatgtggttc caacttctac 240
gagcaagcctgg tgaattgcgcg atctacacct tcctaaacct cggcccacac gggactctg 300
caaagccac ggtggtgacgc ccgccagcgc gcacactttatt tttgtggtgag aagttatagt 360
ggtatgtgt attttatatgt g 381

<210> SEQ ID NO 388
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 389
cagggcagtc agagcattag tagttactta gcc 33

<210> SEQ ID NO 389
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 389
aggggtccaa ctctggccatc t 21

<210> SEQ ID NO 390
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 390
cagaagcgatt atgataggtg ttcaattcct 30

<210> SEQ ID NO 391
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 391
acctactgtg tcatgtggc 18
<210> SEQ ID NO 392
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 392

tgtattata ctgtaagtag tgattcact ttctacgca gctgggtgaa ttgct

<210> SEQ ID NO 393
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 393

gttatatg gttatgtta ttttagtgg

<210> SEQ ID NO 394
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 394

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1  5  10  15

Leu Pro Gly Val Thr Phe Ala Ile Glu Met Thr Gln Ser Pro Phe Ser
20  25  30

Val Ser Ala Ala Val Gly Thr Val Ser Ile Ser Cys Gln Ala Ser
35  40  45

Gln Ser Val Tyr Lys Asn Asn Gln Leu Ser Trp Tyr Gln Gln Lys Ser
50  55  60

Gly Gln Pro Pro Gly Leu Leu Ile Tyr Gly Ala Ser Ala Leu Ala Ser
65  70  75  80

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr
85  90  95

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Ala Gly Ala Ile Thr Gly Ser Ile Asp Thr Asp Gly
115 120

<210> SEQ ID NO 395
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 395

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1  5  10  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Asp Leu Val Lys Pro
20  25  30

Gly Ala Ser Leu Thr Leu Thr Cys Thr Thr Ser Gly Phe Ser Phe Ser
35  40  45

Ser Ser Tyr Phe Ile Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50  55  60

Glu Trp Ile Ala Cys Ile Tyr Gly Gly Asp Gly Ser Thr Tyr Tyr Ala
65  70  75  80

Ser Thr Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr
Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr
Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr
100 105 110

Phe Cys Ala Arg Glu Trp Ala Tyr Ser Gin Gly Tyr Phe Gly Ala Phe
Phe Cys Ala Arg Glu Trp Ala Tyr Ser Gin Gly Tyr Phe Gly Ala Phe
115 120 125

Asp Leu
Asp Leu
130

<210> SEQ ID NO 396
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 396
Gln Ala Ser Gin Ser Val Tyr Lys Asn Asn Gin Leu Ser
1 5 10

<210> SEQ ID NO 397
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 397
Gly Ala Ser Ala Leu Ala Ser
1 5

<210> SEQ ID NO 398
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 398
Ala Gly Ala Ile Thr Gly Ser Ile Asp Thr Asp Gly
1 5 10

<210> SEQ ID NO 399
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 399
Ser Ser Tyr Phe Ile Cys
1 5

<210> SEQ ID NO 400
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 400
Cys Ile Tyr Gly Gly Asp Gly Ser Thr Tyr Tyr Ala Ser Thr Ala Lys
1 5 10 15

Gly

<210> SEQ ID NO 401
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 401
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Glu Trp Ala Tyr Ser Gln Gly Tyr Phe Gly Ala Phe Asp Leu
1 5 10

<210> SEQ ID NO: 402
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 402

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acattgcca tcgaataagc ccagagtcga tttctctgtg tgtcagctgt gggagggaca  120
gtcagcatac gttgccaggg cagtcagagt gtttataaga acaaccacatt atctctgtat  180
cagcagaat cagggcgacgc ttcgagaagtc tgtactcatt tgtgcttcggc tgtggcatct  240
ggggtcccat ccggccagaag agggattggag atctctctct ccccatcaggtgacg  300
gacgctgagt gttgacagtc tgcagcattac tgcctgtcag gggctattac tgtgtgtatt  360
gatacgggtg gttggggagg 372

<210> SEQ ID NO: 403
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 403

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tgctggagg agtcgggagg agaacggtgct aagcctgagg cattcaagtgc accaacctgc  120
acacttctct gcctctttct cagtcgcagc tacctctatt gctgggtccgg ccaggtccta  180
gggagggggc tgagtggtgt cgcacgtatt tgtgtctgttg atggccagac atacacgccg  240
gagctcgggca aagggagcgta cccatcttcc aacaaccttt gcagacggtc gcagccgctaa  300
atgacacgct tcagacagcg ggaacagggc accatattct tgtgagagaga atgggacat  360
agtcagagtt atttggtgct ttttatcctg  390

<210> SEQ ID NO: 404
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 404

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<210> SEQ ID NO: 405
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 405

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<210> SEQ ID NO: 406
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 406

gcaggcgctc ttactgttag tatgtacag gatgtg  36
<210> SEQ ID NO 407
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<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 407

agcagcactcctttgca

<210> SEQ ID NO 408
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 408

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<210> SEQ ID NO 409
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 409
gaatgcggcatgtatgcaagtttttggacttttgatctc

<210> SEQ ID NO 410
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 410

Met Asp Thr Arg Ala Pro Thr Gin Leu Leu Gly Leu Leu Leu Leu Trp
1      5           10  15
Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gin Thr Pro Ala Ser
20     25          30
Val Glu Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gin Ala Ser
35     40          45
Glu Asp Ile Ser Ser Tyr Leu Ala Trp Tyr Gin Gin Lys Pro Gly Gin
50     55          60
Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val
65     70          75  80
Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr
85     90          95
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gin Cys
100    105         110
Thr Tyr Gly Thr Ile Ser Ile Ser Asp Gly Asn Ala
115

<210> SEQ ID NO 411
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 411

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1      5           10  15
Val Gln Cys Gin Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20     25          30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35  40  45
Ser Tyr Phe Met Thr Trp Val Arg Glu Ala Pro Gly Gly Leu Glu
50  55  60
Tyr Ile Gly Phe Ile Asn Pro Gly Gly Ser Ala Tyr Ala Ser Trp
65  70  75  80
Val Lys Gly Arg Phe Thr Ile Ser Lys Ser Ser Thr Thr Val Asp Leu
85  90  95
Lys Ile Thr Ser Pro Thr Thr Gly Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110 115
Arg Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
120

<210> SEQ ID NO 412
<211> LENGTH: 11
<212> TYPE: PRF
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 412
Gln Ala Ser Glu Asp Ile Ser Ser Tyr Leu Ala
1  5
10

<210> SEQ ID NO 413
<211> LENGTH: 7
<212> TYPE: PRF
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 413
Ala Ala Ser Asn Leu Glu Ser
1  5

<210> SEQ ID NO 414
<211> LENGTH: 14
<212> TYPE: PRF
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 414
Gln Cys Thr Tyr Gly Thr Ile Ser Ile Ser Asp Gly Asn Ala
1  5
10

<210> SEQ ID NO 415
<211> LENGTH: 5
<212> TYPE: PRF
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 415
Ser Tyr Phe Met Thr
1  5

<210> SEQ ID NO 416
<211> LENGTH: 16
<212> TYPE: PRF
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 416
Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp Val Lys Gly
1  5
10
15

<210> SEQ ID NO 417
Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile

Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile

Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile

Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile

Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 422

caatgtacct atgtaactat ttctattagt gatggtactg ct

<210> SEQ ID NO 423
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 423

agctacctca tgcgc

<210> SEQ ID NO 424
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 424

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<210> SEQ ID NO 425
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 425

gtcgtacttg tttcattagg aaccttaacc atc

<210> SEQ ID NO 426
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 426

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1  5 10 15

Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Ser Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Glu Asp Ile Glu Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asp Leu Glu Ser Gly Val
65 70 75 80

Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
95 90 95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Cys
100 105 110

Thr Tyr Gly Ile Ile Ser Ile Ser Asp Gly Asn Ala
115 120

<210> SEQ ID NO 427
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 427
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1  5  10  15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20  25  30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35  40  45
Ser Tyr Phe Met Thr Thr Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
50  55  60
Tyr Ile Gly Phe Met Asn Thr Gly Asp Asn Ala Tyr Tyr Ala Ser Trp
65  70  75  80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85  90  95
Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Val Leu Val Val Ala Tyr Gly Ala Phe Asn Ile
115 120

<210> SEQ ID NO 428
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 428
Gln Ala Ser Glu Asp Ile Glu Ser Tyr Leu Ala
1  5  10

<210> SEQ ID NO 429
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 429
Gly Ala Ser Asn Leu Glu Ser
1  5

<210> SEQ ID NO 430
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 430
Gln Cys Thr Tyr Gly Ile Ile Ser Ile Ser Asp Gly Asn Ala
1  5  10

<210> SEQ ID NO 431
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 431
Ser Tyr Phe Met Thr
1  5

<210> SEQ ID NO 432
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 432
<210> SEQ ID NO 433
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 433

Val Leu Val Val Ala Tyr Gly Ala Phe Arg Ile
1   5   10

<210> SEQ ID NO 434
<211> LENGTH: 722
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 434

atggaacagc ggcccccac tcagctgtct gggactctgc tgcctctgct cccaggtgcc

agatgtgtat tttgctatgc ccagactcca ggctctgctgt tgcaggtctg tgtgggacca

gtcaccatca agtgccaggc cagtggagac attgagactg agtctagctg gtacacgcag

aacacaggcg agccctccaa gcctctgact tattgtggat ccaatgctgg aattgggggc

tcactggct ctaaaagggg caggtctgct tgtgggagtt cagagatcca ctctcaactt cagacgacctg
gggtgtgccc atgggtgacat tcactattgt gattgcctt ctattgatg tagtattag

gattgtaatg ct

<210> SEQ ID NO 435
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 435

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tgatggagag tgtggggcag tcagctgtgc acgcagctgg aacccctgac atcgagctgc

acagctgtcg gatttctctt cagtagctac ttcagcctt ggtgctccagc ggtgtccagg

aggggctgag aatacatacg attcagtaa actgtgcata acgcctataa cgcagagctg

gcagaagcgc gattccacat ctctcataac tctgacccagtg tggatcgtga aatcaccagt

cggacaacgc aggacagcgg ccccttatttc tgtggccagg tgtggtggtg tggcttattg

gctttaaca tc

<210> SEQ ID NO 436
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 436
cagagcaggtg aggacatatga aacagtatcata gcc

<210> SEQ ID NO 437
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 437

cagagcaggtg aggacatatga aacagtatcata gcc
<210> SEQ ID NO 438
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 438

ggtgccatca atctggaaca t 21
<210> SEQ ID NO 439
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 439

cagtgcactt atgttattc tagtattagt gatggtaatg ct 42

<210> SEQ ID NO 440
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 440

agctacctac tgaacc 15
<210> SEQ ID NO 441
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 441

ttcatgata ctgggtgata cgcatacact gcgagctggg cgsaaggc 48

<210> SEQ ID NO 442
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 442

Met Asp Thr Arg Ala Pro Thr Gin Leu Leu Gly Leu Leu Leu Leu Trp 1 5 10 15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gin Thr Pro Ser Pro 20 25 30
Val Ser Glu Pro Val Gly Thr Val Ser Ile Ser Cys Gin Ser Ser 35 40 45
Lys Ser Val Met Asn Asn Asn Tyr Leu Ala Trp Tyr Gin Gin Lys Pro 50 55 60
Gly Gin Pro Pro Lys Leu Leu Ile Tyr Gin Ala Ser Aen Leu Ala Ser 65 70 75 80
Gly Val Pro Ser Arg Phe Ser Gin Ser Gin Ser Gin Ser Gly Thr Gin Phe Thr 95 90 95
Leu Thr Ile Ser Asp Val Gin Cys Asp Asp Ala Ala Thr Tyr Tyr Cys 100 105 110
Gln Gly Gly Tyr Thr Gly Tyr Ser Asp His Gly Thr 115 120
Merc Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Lys Pro
20 25 30
Asp Glu Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
35 40 45
Ser Tyr Pro Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Ile Gly Phe Ile Asn Thr Gly Thr Ile Val Tyr Ala Ser Trp
65 70 75 80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95
Lys Met Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Gly Ser Tyr Val Ser Ser Gly Tyr Ala Tyr Tyr Phe Asn Val
115 120 125
<210> SEQ ID NO 448
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 448

Phe Ile Ala Thr Gly Gly Thr Ile Tyr Ala Ser Trp Ala Lys Gly
1     5     10     15

<210> SEQ ID NO 449
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 449

Gly Ser Tyr Val Ser Ser Gly Tyr Ala Tyr Phe Ala Val
1     5     10

<210> SEQ ID NO 450
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 450

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gcagcatca gttgcccagt cagtaagaggt gtatgatata acaactacct agctgggtat 180
cagcagacac cagggccagcc tccaatagct tgactctatg tgccttccaa ttcggctact 240
gggctccac ccaggtgtca cccctggttga tctgggtccac agttcactctc accacacgc 300
gcagctgcat ggtcagctgc tgccacttac tacgtgcag ggccttacag tggcttacgt 360
gcagcgtggt gccatgtgga ctc
372

<210> SEQ ID NO 451
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 451

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tcggtggagg agtgccgggg tcggctgtgc caagctacgc aaccctgtgc actaactgct 120
acagttctctg gatcgacact cagtagctct ccatacgacg ggtctgcacc caagctcagg 180
aaggggctgc aagtcacgct ataccaaat actggtggtca ccatacgtctg cgccagctgg 240
gccaaagggcc gattcaccatt ctctaaacc ctagaaccgg tggtactgtaa aataggcact 300
cctacaaccg aggaaaccgc caccatattc ttgtgccagag gcagttataag ttcattctgtt 360
tatgtcatct atttaaattg c
381

<210> SEQ ID NO 452
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 452

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115 120

<210> SEQ ID NO 459  
<211> LENGTH: 126  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 459  
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly  
1  5 10 15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Arg Leu Val Thr Pro  
20 25 30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser  
35 40 45
Thr Tyr Ser Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu  
50 55 60
Trp Ile Gly Ile Ile Ala Asn Ser Gly Thr Thr Phe Tyr Ala Asn Trp  
65 70 75 80
Ala Lys Gly Arg Phe Thr Val Ser Lys Thr Ser Thr Thr Val Asp Leu  
85 90 95
Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala  
100 105 110
Arg Glu Ser Gly Met Tyr Asn Glu Tyr Gly Lys Phe Asn Ile  
115 120 125

<210> SEQ ID NO 460  
<211> LENGTH: 13  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 460  
Gln Ser Ser Gln Ser Val Tyr Asn Asn Trp Leu Ser  
1  5 10

<210> SEQ ID NO 461  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 461  
Lys Ala Ser Thr Leu Ala Ser  
1  5

<210> SEQ ID NO 462  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 462  
Ala Gly Gly Tyr Leu Asp Ser Val Ile  
1  5

<210> SEQ ID NO 463  
<211> LENGTH: 5  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 463

Thr Tyr Ser Ile Asn
1 5

<210> SEQ ID NO 464
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 464

Ile Ile Ala Asn Ser Gly Thr Thr Phe Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> SEQ ID NO 465
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 465

Glu Ser Gly Met Tyr Asn Glu Tyr Gly Lys Phe Asn Ile
1 5 10

<210> SEQ ID NO 466
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 466

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60
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120
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cacgctttgtc gttgttctttt gtcacttcat tcaataaact ggtgtgcgcca agggtcgagg
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gcggaaagcc cttgacgtgt tcggacaaacc tccggccaggg tgtgtgattg ggttcaacatg
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<400> SEQUENCE: 468

cagtcagtc aagtagttta tastaacaac tggttatcc  
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<400> SEQUENCE: 470
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<210> SEQ ID NO 471
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<400> SEQUENCE: 471

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<212> TYPE: DNA
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<400> SEQUENCE: 472

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Glu Asn Ile Tyr Ser Phe Leu Ala Ala Trp Tyr Gin Gin Lys Pro Gly Gin 50 55 60
Pro Pro Lys Leu Leu Ile Phe Lys Ala Ser Thr Leu Ala Ser Gly Val
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65  70  75  80
Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Thr Leu Thr
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Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Glu Glu
100    105          110
Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
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20       25   30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
35       40   45
Ala Tyr Ala Met Ile Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
50       55   60
Trp Ile Thr Ile Ile Tyr Pro Asn Gly Ile Thr Tyr Tyr Ala Asn Trp
65       70   75   80
Ala Lys Gly Arg Phe Thr Val Ser Lys Thr Ser Thr Ala Met Asp Leu
85       90   95
Lys Ile Thr Ser Pro Thr Glu Asp Thr Ala Tyr Phe Cys Ala
100      105  110
Arg Asp Ala Glu Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val
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Lys Ala Ser Thr Leu Ala Ser
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<210> SEQ ID NO 478
<211> LENGTH: 12
<212> TYPE: PRT
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Gln Gln Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 479

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<210> SEQ ID NO 480
<211> LENGTH: 16
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<210> SEQ ID NO 481
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 481

Asp Ala Glu Ser Ser Asp Ala Tyr Trp Gly Tyr Phe Asn Val
1  5 10 15

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gtcacatca atggccagcg cagttgagaac atttatagct ttttgccctg gttacagcag
180
aaacagggc agcgcacca tctcctgtat ctcacgggtt ccacccctgc atctgggggc
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aataat
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<212> TYPE: DNA
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<210> SEQ ID NO 488
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<400> SEQUENCE: 489
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Leu Pro Gly Ala Arg Cys Ala Ser Asp Met Thr Gln Thr Pro Ser Ser 20 25 30
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 491

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Ala | Tyr | Ala | Met | Ile | Trp | Val | Arg | Gln | Ala | Pro | Gly | Glu | Gly | Leu | Glu |
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Arg | Asp | Ala | Glu | Ser | Ser | Lys | Asn | Ala | Tyr | Trp | Gly | Tyr | Phe | Asn | Val |
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Gln | Ala | Ser | Glu | Asn | Ile | Tyr | Ser | Phe | Leu | Ala |
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Arg | Ala | Ser | Thr | Leu | Ala | Ser |
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Ala Tyr Ala Met Ile
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gtccacata atgccaggg cagtgaaac attatctgt ttgtggcttg gtatcagcag  180
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gaggggctgg atgaggacaa aacatctttat cctaatgtgta tcacatcata ccagcaactgg  240
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Glu Ser Val Phe Asn Asn Met Leu Ser Trp Tyr Glu Glu Lys Pro Gly
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His Ser Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly
   65     70     75     80

Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
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Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Asn
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Arg Asn Ser Ile Thr Trp Val Arg Glu Ala Pro Gly Glu Gly Leu Glu
  50    55     60

Trp Ile Gly Ile Ile Thr Gly Ser Gly Arg Thr Tyr Ala Asn Trp
  65    70     75     80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
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| Gln | Ser | Ser | Val | Tyr | Asn | Asn | Tyr | Leu | Ser |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|     | 1   |     |     |     |     |     |     |     |     |
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 525

Thr Ala Ser Ser Leu Ala Ser
1 5

<210> SEQ ID NO 526
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 526

Gln Gly Tyr Tyr Ser Gly Pro Ile Ile Thr
1 5 10

<210> SEQ ID NO 527
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 527

Asn Tyr Tyr Ile Gln
1 5

<210> SEQ ID NO 528
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 528

Ile Ile Tyr Ala Gly Gly Ser Ala Tyr Ala Thr Trp Ala Asn Gly
1 5 10 15

<210> SEQ ID NO 529
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 529

Gly Thr Phe Asp Gly Tyr Glu Leu
1 5

<210> SEQ ID NO 530
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 530

atgacacaga gggccccccac tcagtcgtct gggctcctcg ccagctgccc 60
acattgcgc aagtttggtgcc caggactgca tgcctcgtgt agttggtgg 120
gtcacatca atgctcagct gtttataata actacttatc ctgtatcg 180
cagaaacgag ggcgcctccc cagctcctcg atctataactg cagcagcttg 240
gttccctcgc ggttccaaag gctggtatct gggacacagt tccctctcac cactcagcag 300
gttcagtgg agttagtcgc caattacagct tgctcaggg attatatggt toctataatt 360
act 363

<210> SEQ ID NO 531
<211> LENGTH: 366
-continued

<210> SEQ ID NO 532
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 532

cagtccagtc agagtgttta tastaactac ttatcc

<210> SEQ ID NO 533
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 533

actgcatca gcgtggtac t

<210> SEQ ID NO 534
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 534

caatgccatta ttagtggtcc tataacta
c

<210> SEQ ID NO 535
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 535

aactactaca taca

<210> SEQ ID NO 536
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 536

atcattttag ctagtggtag cgcatactac gcgacctgag csaacgagc
c

<210> SEQ ID NO 537
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 537

agtgtgggag ctggcagcgg cgacgcgtcc gcgtccttct

gggacattg argttatga gtgt

<210> SEQ ID NO 538
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 539
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1   5   10   15
Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ser Pro
20  25  30
Val Ser Val Pro Val Gly Asp Thr Val Thr Ile Ser Cys Gln Ser Ser
35  40  45
Glu Ser Val Tyr Ser Asn Asn Leu Ser Ser Thr Tyr Gln Gln Lys Pro
50  55  60
Gly Gln Pro Pro Lys Leu Leu Leu Ile Tyr Arg Ala Ser Asn Leu Ala Ser
65  70  75  80
Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
85  90  95
Leu Thr Ile Ser Gly Ala Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110
Gln Gly Tyr Tyr Ser Gly Val Ile Asn Ser
115 120

<210> SEQ ID NO 539
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 539
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1   5   10  15
Val Gln Cys Gln Ser Val Gln Ser Gly Gly Arg Leu Val Thr Pro
20  25  30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35  40  45
Ser Tyr Phe Met Ser Trp Val Arg Gln Ala Pro Gly Gly Leu Gly  Glu
50  55  60
Tyr Ile Gly Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp
65  70  75  80
Ala Ser Gly Arg Leu Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85  90  95
Lys Ile Thr Ser Pro Thr Gln Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Ile Leu Ile Val Ser Tyr Ser Gly Ala Phe Thr Ile
115 120

<210> SEQ ID NO 540
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 540
Gln Ser Ser Gln Ser Val Tyr Ser Asn Asn Leu Leu Ser
Arg Ala Ser Asn Leu Ala Ser  
1  5

Gln Gly Tyr Tyr Ser Gly Val Ile Asn Ser  
1  5  10

Ser Tyr Phe Met Ser  
1  5

Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp Ala Ser Gly  
1  5  10  15

Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile  
1  5  10

atggcacacg gggccccac tcagctgtgc ggcctocgtgc tgctctgtgc cccaggtgcc  60  
acattgccc asgtctgac cccactcca tccccctgtc ctgctcccctg gggagacaca  120  
gtacacacga tgtcagcgtc cagtgagcgc gtttatagta ataacctcct atctggtat  180  
cagcagaaac ccggsgagcc tcccaagctc cgtgctctaca gggcactccaa tctggcactct  240  
ggtgctccat cgcgcgtcgc aggcagtcga tctgggcacac agttcaacct caccacctgc  300  
ggcgcaagt tgtcagctgc tgccacattac tactgtcaag gctatttaga tggcttcatt  360
aatagtaa

<210> SEQ ID NO: 547
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 547

atgagagctg ggctgctgtg gctttctctg tctgtgtgc tcuaaggtgt ccagtgccag
60
tgcgtggag agtcccggtgg tctgctgtgc aaccgctggga caacccctgac actcaacctc
120
acagtcctct gccatctctc cagtagctac ttcatgatct ggtcgcgcca ggtctccagg
180
gaggggcttg aatcatacgg atcataat attcggtgtgta gctgctgta ctgctgctgta
cgctggtgc
gcagtcctct ctctcccccc ctgacacccg tagatctgaa aatcaccagt
gcagtcctct ccctcccccc ctgacacccg tagatctgaa aatcaccagt
gctttataa
360
ggccttccac t
372

<210> SEQ ID NO: 548
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 548
cagtcagctg agagcgttta tagtaataac cctttatcc
39

<210> SEQ ID NO: 549
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 549

agggcacaatc atctggtcatct
21

<210> SEQ ID NO: 550
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 550

ciaaggtatt ataggtgtgtg cattatagta
30

<210> SEQ ID NO: 551
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 551

agcttttcc tgaec
15

<210> SEQ ID NO: 552
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 552

ttcatttaac cttgtgtag cgcatactac gcagcgctgg gcagtgccc
48
-continued

SEQ ID NO 553
LENGTH: 33
TYPE: DNA
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 553

atctctatg tttcttatag agcttttacc atc

SEQ ID NO 554
LENGTH: 122
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 554

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1   5   10   15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20  25   30
Val Glu Val Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Thr
35  40   45
Glu Ser Ile Gly Asn Glu Leu Ser Trp Tyr Gln Glu Lys Pro Gly Gln
50  55   60
Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val
65  70   75   80
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
85  90   95
Ile Thr Gly Val Glu Cys Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105  110
Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
115  120

SEQ ID NO 555
LENGTH: 128
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

SEQUENCE: 555

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1   5   10   15
Val Glu Cys Gln Ser Leu Glu Glu Ser Gly Arg Leu Val Thr Pro
20  25   30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35  40   45
Lys Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Lys
50  55   60
Tyr Ile Gly Tyr Ile Asp Ser Thr Thr Val Asn Thr Tyr Tyr Ala Thr
65  70   75   80
Trp Ala Arg Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp
85  90   95
Leu Lys Ile Thr Ser Pro Thr Ser Gly Asp Thr Ala Thr Tyr Phe Cys
100 105  110
Ala Arg Gly Ser Thr Tyr Phe Thr Asp Gly Gly His Arg Leu Asp Leu
115  120  125

SEQ ID NO 556
LENGTH: 11
-continued

<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 556

Gln Ala Thr Glu Ser Ile Gly Asn Glu Leu Ser
1  5 10

<210> SEQ ID NO 557
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 557

Ser Ala Ser Thr Leu Ala Ser
1  5

<210> SEQ ID NO 558
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 558

Gln Gln Gly Tyr Ser Ser Ala Asp Asn Ala
1  5 10

<210> SEQ ID NO 559
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 559

Lys Tyr Tyr Met Ser
1  5

<210> SEQ ID NO 560
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 560

Tyr Ile Asp Ser Thr Thr Val Asn Thr Tyr Ala Thr Trp Ala Arg
1  5 10  15

Gly

<210> SEQ ID NO 561
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 561

Gly Ser Thr Tyr Phe Thr Asp Gly Gly His Arg Leu Asp Leu
1  5 10

<210> SEQ ID NO 562
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 562

atggcacagc ggcccctcag tcaagtgcgt gggctctgcg tgcctctgct cccaggtgcc
agatgtgcct atgatgacg ccgactcaca gctctgtgg agtagctgt ggaggcaca
gtcacacatca agtgcagagc caagtgaagc atgtgcaagt agttatatctg gtatacgacag 180
aaacagggc aagctcccaaa gcttctgtct taattctctac ccatcctttggtc atctgggggtc 240
cctatgcttg tcaaaagggag tgatctgtgc agacacacatca cctcactacat cacaggcgtg 300
gagtgtgatg atgtgcttggct ttaactctgt ccaaggggctt ataggtgcgct taatattcgt 360
aattgot 366

<210> SEQ ID NO 563
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 563
atgggagcttg ggctgaggctg gcttcctcttg gtcgctgtgct tcgaaggtgtg ccaggtgctcag 60
tcgctgaggg agtgcagagg tccgctgtgct acgcctggga caaaccctgac actaacctgc 120
acccgtctcttg gattctcctc cagtaaatgc tcatgagctg gggctccggca ggttccagag 180
aaggggctga aatcactcgg atacactctg agcactacctg ttatacata ctgcgggacc 240
tgggctgagactcgat cctctccaa aacctgaccc cggctgattct gaagactcacc 300
agttccgcag cagggagac aggcacattc ttctgtgcga gggagactac ttaattttact 360
gagatggagc aatcgcgtggaa tcte 384

<210> SEQ ID NO 564
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 564
caggccatcg agagcattgga caatgagttt ccc 33

<210> SEQ ID NO 565
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 565
ttggatcaca ctgtgatactc t 21

<210> SEQ ID NO 566
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 566
cacaggggtt atagagtgcgct taatattgat aatggt 36

<210> SEQ ID NO 567
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 567
aagtcctaca tgaagc 15

<210> SEQ ID NO 568
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 568

```
tacattgata gtaactactgta taacagactc gggcgagagc g 51
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<210> SEQ ID NO: 569
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 569

```
ggagctacctt aatgtgtgta tggagccat cggatgcaga tc 42
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<210> SEQ ID NO: 570
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 570

```
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1   5   10   15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20  25  30
Val Glu Val Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Thr
35  40  45
Glu Ser Ile Gly Asn Glu Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
50  55  60
Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val
65  70  75  80
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
85  90  95
Ile Thr Gly Val Glu Cys Asp Ala Ala Thr Tyr Cys Gln Gln
100 105 110
Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
115 120
```

<210> SEQ ID NO: 571
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 571

```
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1   5   10   15
Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20  25  30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35  40  45
Thr Tyr Asn Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50  55  60
Trp Ile Gly Ser Ile Thr Ile Asp Gly Arg Thr Tyr Tyr Ala Ser Trp
65  70  75  80
Ala Lys Gly Arg Phe Thr Val Ser Lys Ser Ser Thr Thr Val Asp Leu
85  90  95
Lys Met Thr Ser Leu Thr Gly Asp Thr Ala Thr Tyr Phe Cys Ala
```
Arg Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile

110

<210> SEQ ID NO 572
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 572

Gln Ala Thr Glu Ser Ile Gly Asn Glu Leu Ser

1510

<210> SEQ ID NO 573
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 573

Ser Ala Ser Thr Leu Ala Ser

15

<210> SEQ ID NO 574
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 574

Gln Gln Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala

1510

<210> SEQ ID NO 575
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 575

Thr Tyr Asn Met Gly

15

<210> SEQ ID NO 576
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 576

Ser Ile Thr Ile Asp Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys Gly

151015

<210> SEQ ID NO 577
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 577

Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile

15

<210> SEQ ID NO 578
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 578
atggacacga ggcccccaca tcaagctgtgc ggtcctctgc tgctctgtgc cccaggtgcc 60
agatgtgctc atgtatagca ccagactcaca gctcttgcga aggtagctgtg ggaggccaca 120
gtccacatca agtggcaggc cactgagacg attggcaagt gttatccctg gtatccagcag 180
aaacagggcg aggtctccac gctcctgac tatttctgat ccactctggcc atctgggggtc 240
catcgcggt tcacaagggcag tggatctggg acacagttca ctctaacact cacgcgcttg 300
gagtgtgtac atgctgcac ccactacttg ccaaggggtt atagtagtgc tataattgag 360
aaggtcgtgctggt ctgtcatcag tctttatcgtt ttctttatcgc tctctaggg 366

<210> SEQ ID NO 579
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 579
atggagactc ggctgcgtgct gctcttccttg gtcgctgtgc tcaaggggtg cccaggtgcc 60
tcgcgagaagg atgcctggggg tcgcgctgtga aacgccggga cacccctgcac actccctgcc 120
acaacgcctct gattcccctc cgactacact aacatcggtct gggtcggcga ggcgtcaggg 180
aaggggctgg atagagccgg aagattattct attgatggct gcacatacta cgccagcctgg 240
gccaaaggcct gtcaccacgt cttcctagct tcctctagctg cgcagcggcg atcttgcttgg aaggtcgtgctggt ctgtcatcag tctttatcgtt ttctttatcgc tctctaggg 360
<410> SEQUENCE: 580
cgggcaacgc agagcagcctg caagttttac tcc
<210> SEQ ID NO 581
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 581
tcgcgatcca ctctggccatc t
<210> SEQ ID NO 582
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 582
cacccaggggt atagtagtgc tataattgag aaggtcgtgctggt ctgtcatcag tctttatcgtt ttctttatcgc tctctaggg 366
<410> SEQUENCE: 583
cgggcaacgc agagcagcctg caagttttac tcc
<210> SEQ ID NO 583
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 583
ACTACACAG TGGGC 15

<210> SEQ ID NO 584
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 584
AGTTATCTA TTTAGTGTCG CACATACTAC GCGAGCTGGG CGAAGGGG 48

<210> SEQ ID NO 585
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 585
ATCTTATGT TTTTCATGG GCCTTATCCC ATC 33

<210> SEQ ID NO 586
<211> LENGTH: 105
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE: OTHER INFORMATION: Kappa constant domain
<400> SEQUENCE: 586

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu 1 5 10 15
Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Aen Aen Phe Tyr Pro 20 25 30
Arg Glu Ala Lys Val Glu Trp Lys Val Asp Aen Ala Leu Gln Ser Gly 35 40 45
Aen Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr 50 55 60
Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His 65 70 75 80
Lys Val Tyr Ala Cys Glu Val Val Thr His Gln Gly Leu Ser Ser Pro Val 85 90 95
Thr Lys Ser Phe Aen Arg Gly Glu Cys 100 105

<210> SEQ ID NO 587
<211> LENGTH: 315
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: OTHER INFORMATION: Kappa constant domain
<400> SEQUENCE: 587
GTGGCCTGGC CATCTGTCCT CATTCCTCCG CCATCTGATG AGCAGTGAA ATCTGGAACT 60
gcctctgcag tgtgcctgcgt gtaaaccttc tatcccaagag aagcccaagt acagtggaag 120
gtggataaeg ccgctcaagtg caggagaggt tcacagagca ggcagcaag 180
gcagcagctt acagcagcttg cagcagcgtc aagctcagca aagcagacta caggaacac 240
aagatcacoctgcagtaagcag tcgctgagct cgccggctc ccagagcctt 300
aaccaggggac aagtc 315
 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1      5      10     15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20     25     30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35     40     45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Gly Leu Tyr Ser
 50     55     60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65     70     75     80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85     90     95
 Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100   105    110
 Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro
115   120    125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130   135    140
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145   150    155    160
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165   170    175
 Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Leu Thr Val Leu
180   185    190
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195   200    205
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210   215    220
 Gln Pro Arg Glu Pro Glu Val Tyr Thr Leu Pro Ser Arg Glu Glu
225   230    235    240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245   250    255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Ann
260   265    270
 Asn Tyr Lys Thr Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275   280    285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Glu Gln Gly Ann
290   295    300
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305   310    315    320
 Glu Lys Ser Leu Ser Leu Ser Pro Gly Lys
325   330

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Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr Ser Ser
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Pro His Arg Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln
  1  5  10  15

Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr
  1  5  10  15

Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp
  1  5  10  15

Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile Ser
  1  5  10  15

Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile Ser Ala Leu Arg
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Ile Arg Tyr Ile Leu Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr
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Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met
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Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser
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Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser Ser Lys Glu
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Cys Asn Lys Ser Asn Met Cys Glu Ser Ser Lys Glu Ala Leu Ala
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Ser Asn Met Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn
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Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Leu
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Gly Phe Asn Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu
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Gly Thr Val Thr Ile Lys Cys Gln Ala Ser Gln Ser Ile Asn Asn Glu
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Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Arg Pro Lys Leu Leu Ile
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Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Lys Gly
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Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Asp Leu Glu Cys
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Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Gln Gln Gln Tyr Ser Leu Arg Asn
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Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys
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<210> SEQ ID NO 649
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 649
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Val Ala Thr Tyr Tyr Cys
85

<210> SEQ ID NO 650
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 650
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Ser Ile Ser Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Lys Ala Ser Ser Lys Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys
85

<210> SEQ ID NO 651
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanised antibody

<400> SEQUENCE: 651
Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1  5 10 15
Asp Arg Val Thr Ile Thr Cys Gin Ala Ser Gin Ser Ile Asn Asn Glu
20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin Gly Tyr Ser Leu Arg Asn
85 90 95
Ile Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

<210> SEQ ID NO 652
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 652
Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1  5 10 15
Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser Asn Tyr Tyr
20 25 30
Val Thr Trp Val Arg Gin Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45
Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Trp Ala Ile Gly
50 55 60
Arg Phe Thr Ile Ser Lys Thr Ser Thr Val Asp Leu Lys Met Thr
65 70 75 80
Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe Cys Ala Arg Asp Asp
85 90 95
Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gin Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
<210> SEQ ID NO 653
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 653

Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn 20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys 50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr Leu 65 70 75 80
Gln Met Asn Ser Leu Arg Ala Asp Thr Ala Val Tyr Tyr Cys Ala 85 90 95

Arg

<210> SEQ ID NO 654
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 654

Glu Val Gln Leu Val Glu Ser Gly Gly Leu Leu Ile Gln Pro Gly Gly 1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn 20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys 50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr Leu 65 70 75 80
Gln Met Asn Ser Leu Arg Ala Asp Thr Ala Val Tyr Tyr Cys Ala 85 90 95

Arg

<210> SEQ ID NO 655
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 655

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45
Ser Val Ile Tyr Ser Gly Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
95 90 95
Ala Lys

<210> SEQ ID NO 656
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized antibody

<400> SEQUENCE: 656
Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Trp Ala Ile
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
95 90 95
Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 657
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized antibody

<400> SEQUENCE: 657
Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30
Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
95 90 95
Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
<210> SEQ ID NO 658
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 658

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1      5     10    15
Val Glu Cys Gln Ser Leu Glu Ser Gly Gly Leu Val Thr Pro
20     25    30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35    40    45
Asn Tyr Tyr Val Thr Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu
50    55    60
Trp Ile Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser
65    70    75    80
Ala Ile Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85    90    95
Lys Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe Cys Ala
100   105   110
Arg Asp Ser Ser Ser Asp Trp Ala Lys Phe Asn Leu Trp Gly Gln
115   120   125
Gly Thr Leu Val Thr Val Ser Ala Ser Ala Thr Lys Gly Pro Ser Val
130   135   140
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
145   150   155   160
Leu Gly Cys Leu Val Lys
165

<210> SEQ ID NO 659
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 659

Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile Gly
1      5     10    15

<210> SEQ ID NO 660
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 660

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1      5     10    15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20     25    30
Val Ser Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35    40    45
Gln Ser Ile Asn Asp Glu Leu Ser Ser Tyr Gln Gln Lys Pro Gly Gln
50    55    60
Arg Pro Lys Leu Leu Ile Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val
65    70    75    80
Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85  90  95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Gly Tyr Ser Leu Arg Asn Ile Asp Asn Ala
115 120

<210> SEQ ID NO 661
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 661

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1   5   10  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Arg Leu Val Thr Pro
20  25  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35  40  45

Asn Tyr Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50  55  60

Trp Ile Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Trp
65  70  75  80

Ala Ile Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Val Asp Leu
85  90  95

Lys Met Thr Ser Leu Thr Ala Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
115 120 125

<210> SEQ ID NO 662
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 662

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agatgtacct atgtatagac ccaagactcgc gctcggttct ctcagctgct gggggcaaca 120
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tctcgcgtct tcaagagcgcc tggacctgct cagcagctgc cagcagcagctg 300
gcgatcgtgcg atctgcggcag ttcacagtctc gatagttg attactgttga 360
aatgctgct

366

<210> SEQ ID NO 663
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 663

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<210> SEQ ID NO 664
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

400> SEQUENCE: 664

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1  5  10  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Aen Tyr
20 25  30
Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40  45
Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Trp Ala Ile
50  55  60
Gly Arg Phe Thr Ile Ser Arg Asp Ser Lys Aen Thr Leu Tyr Leu
65  70  75  80
Gln Met Aen Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Cys Ala
85  90  95
Arg Asp Asp Ser Ser Asp Trp Ala Lys Phe Aen Leu Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ala Ser Ser Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Aen Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Thr Val Pro
180 185 190
Ser Ser Ser Gly Leu Thr Gln Thr Tyr Ile Cys Aen Val Aen His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Arg Val Glu Pro Lys Ser Cys Asp
210 215 220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Gly Leu Gly
225 230 235 240
Pro Ser Val Phe Leu Phe Pro Pro Lys Asp Thr Leu Met Ile
245 250 255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270
Asp Pro Glu Val Lys Phe Aen Thr Tyr Val Asp Gly Val Glu Val His
275 280 285
Aen Ala Lys Thr Lys Pro Arg Glu Gln Tyr Ala Ser Thr Tyr Arg
290 295 300
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**<210> SEQ ID NO 665**

**<211> LENGTH: 450**

**<212> TYPE: PRT**

**<213> ORGANISM: Oryctolagus cuniculus**

**<400> SEQUENCE: 665**

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Asn Ala Lys Thr Lys Pro Arg Glu Glu Gin Tyr Ala Ser Thr Tyr Arg 290 295 300
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Glu Tyr Lys Cys Lys Val Ser Lys Ala Leu Pro Ala Pro Ile Glu 325 330 335
Lys Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Glu Pro Gin Val Tyr 340 345 350
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Thr Cys Leu Val Lys Gly Phe Tyr Ser Asp Ile Ala Val Glu Trp 370 375 380
Glu Ser Asn Gly Gin Pro Glu Asn Tyr Lys Thr Thr Pro Pro Val 385 390 395 400
Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val Asp 405 410 415
Lys Ser Arg Trp Gin Gin Gly Asn Val Phe Ser Cys Ser Val Met His 420 425 430
Glu Ala Leu His Asn His Tyr Thr Gin Lys Ser Leu Ser Leu Ser Pro 435 440 445
Gly Lys 450

<210> SEQ ID NO: 666
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Gryctolagus cuniculus
<400> SEQUENCE: 666

Ile Glu Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp 1 5 10 15
Arg Val Thr Ile Thr Cys Gin Ala Ser Gin Ser Ile Asn Gin Glu Leu 20 25 30
Ser Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr 35 40 45
Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser 50 55 60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro Asp 65 70 75 80
Asp Phe Ala Thr Tyr Cys Gin Gin Gly Tyr Ser Leu Arg Asn Ile 85 90 95
Asp Asn Ala Phe Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val 100 105 110
Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
115 120 125
Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Phe Tyr Pro Arg
130 135 140
Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145 150 155 160
Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
165 170 175
Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
180 185 190
Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205
Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 667
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Grycotalagus cuniculus

<400> SEQUENCE: 667
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25
Val Glu Val Ala Val Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40
Glut Thr Ile Tyr Ser Trp Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60
Pro Pro Lys Leu Leu Ile Tyr Gln Ala Ser Asp Leu Ala Ser Gly Val
65 70 75 80
Pro Ser Arg Phe Ser Gly Ser Gly Ala Gly Thr Glu Tyr Thr Leu Thr
85 90 95
Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Cys Gln Gln
100 105 110
Gly Tyr Ser Gly Ser Asn Val Asp Asn Val
115 120

<210> SEQ ID NO 668
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Grycotalagus cuniculus

<400> SEQUENCE: 668
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Gln Gln Leu Gly Ser Gly Gln Arg Leu Val Thr
20 25 30
Pro Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu
35 40 45
Asn Asp His Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Tyr Ile Gly Phe Ile Asn Ser Gly Ser Ala Arg Tyr Ala Ser
65 70 75 80
-continued

Trp Ala Glu Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp  
95 90 95

Leu Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys  
100 105 110

Val Arg Gly Gly Ala Val Trp Ser Ile His Ser Phe Asp Pro  
115 120 125

<210> SEQ ID NO 669  
<211> LENGTH: 366  
<212> TYPE: DNA  
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 669

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60

agatgtgcc atgatagac ccagactcca gctctgtggg agtgtacgtg ggaggaccac  
120

gtcacactca atggaccagc cagatgacc attacagtt ggttatctcg gtagacacag  
180

agccagggc agcctccca aacctgctgtc taccagccat cgcattgccc atctgggtgc  
240

ccatctgcat tccagggctg tggggctgac agaagatcaca cctccacat cagggccctg  
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cagtctgacag atgcggccac ttaactctgt caacagggtt atagggtag taatgttagt  
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aattggt  
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<210> SEQ ID NO 670  
<211> LENGTH: 378  
<212> TYPE: DNA  
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 670

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60

gagcagctcg aggctcgccg gcgtggtctgg gcacacctcc gacacattcc  
120

tgcacagcttg atggattcct ccctaatttg ctagaatgcg ttgctgctgg ccagtcctca  
180

gggagggggc tgggatatgt cggatcatt aataggtggttg gtagggcagc ctagggcagc  
240

tggggcagag gcggatctac cctctccgca ccctgaccct cgggtgtgtct cggaaattgacc  
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agctctgaca ccagggacac gcggacatt tttctgtcga gagggtgtggc tgtttgagtt  
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attcagtt gtacatcc  
378

<210> SEQ ID NO 671  
<211> LENGTH: 123  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 671

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp  
1  5  10  15

Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro  
20  25  30

Val Ser Ala Ala Val Gly Thr Val Ser Ile Ser Cys Gln Ala Ser  
35  40  45

Gln Ser Val Tyr Asp Asn Tyr Leu Ser Trp Phe Gln Gln Lys Pro  
50  55  60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Leu Ala Ser  
65  70  75  80
ACAGCCTCTG GATTCCTCCT CAGTGCTCAC TACATGGAAT GGGTCCGCAA GGGTCCAGGG
AAGGCGGGTC AATGGACCG AATGATTACA ATAGTGATAT ATATAATTA CGGTAAGCTT
GGCGAAGGC CGTATCCAC TCTCGACAAC TCACCCACAG GGTGACGGAA AATGACCAAT
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GTCGGTGGT ATCTC

<210> SEQ ID NO: 675
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 675

Metc Asp Thr Arg Ala Pro Thr Glu Leu Gly Leu Leu Leu Leu Leu Trp
1     5     10    15
Leu Pro Gly Ala Ile Cys Asp Pro Val Leu Thr Glu Thr Pro Ser Pro
20    25    30
Val Ser Ala Pro Val Gly Thr Val Ser Ile Ser Cys Gin Ala Ser
35    40    45
Gln Ser Val Tyr Glu Asn Asn Tyr Leu Ser Thr Pro Phe Gin Gin Lys Pro
50    55    60
Gly Gin Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Leu Asp Ser
65    70    75    80
Gly Val Pro Ser Arg Phe Lys Gin Ser Gly Ser Gly Thr Gin Phe Thr
85    90    95
Leu Thr Ile Thr Asp Val Gin Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100   105   110
Ala Gly Val Tyr Asp Asp Asp Ser Asp Asp Ala
115   120

<210> SEQ ID NO: 676
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 676

Metc Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1     5     10    15
Val Gin Cys Gin Glu Gin Leu Lys Gin Ser Gly Gly Leu Val Thr
20    25    30
Pro Gly Gly Thr Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu
35    40    45
Asn Ala Tyr Tyr Met Asn Trp Val Arg Gin Ala Pro Gly Lys Gly Leu
50    55    60
Glu Trp Ile Gly Phe Ile Thr Leu Asn Asn Asn Val Ala Tyr Ala Asn
65    70    75    80
Trp Ala Lys Gly Arg Phe Thr Phe Ser Lys Thr Ser Thr Thr Val Asp
85    90    95
Leu Lys Met Thr Ser Pro Thr Pro Glu Asp Thr Ala Thr Tyr Phe Cys
100   105   110
Ala Arg Ser Arg Gly Trp Gly Ala Met Gly Arg Leu Asp Leu
115   120   125

<210> SEQ ID NO: 677
<210> SEQ ID NO 670
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 678

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tgacacagct cggatctccc aatctgccga acgcaggtct cagagcag 180
ggagggtcct ggtggtggtgt ctgctggttactgtgtggtggtgtc 240
tggtgccagc gcaggtggtgt gttggtggtggt gttggtggtggtggt 300
gtgttggtgt tgttggtggtggt gttggtggtggtggtggtggtggt 360
gagtctctcc 378

<210> SEQ ID NO 679
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 679

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp 1    5    10    15
Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ser Pro 20   25   30
Val Ser Ala Ala Val Gly Thr Val Thr Ile Asn Cys Gln Ala Ser 35   40   45
Gln Ser Val Asp Asp Asn Trp Leu Gly Trp Tyr Gln Gln Lys Arg 50   55   60
Gly Gln Pro Pro Lys Tyr Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser 65   70   75   80
Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gln Thr Gln Phe Thr 85   90   95
Leu Thr Ile Ser Asp Leu Glu Cys Asp Asp Ala Thr Tyr Cys 100  105  110
Ala Gly Gly Phe Ser Gly Asn Ile Phe Ala 115 120

<210> SEQ ID NO 680
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 680

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1      5     10     15
Val Gln Cys Glu Ser Gly Arg Gly Val Gln Arg Ser Gly Arg Leu Val Thr Pro
20     25     30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35     40     45
Ser Tyr Ala Met Ser Trp Val Arg Gly Ala Pro Gly Lys Gly Leu Glu
50     55     60
Trp Ile Gly Ile Gly Gly Phe Gly Thr Thr Tyr Ala Thr Trp
65     70     75     80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Val Asp Leu
85     90     95
Arg Ile Thr Ser Pro Thr Gly Asp Thr Ala Thr Tyr Phe Cys Ala
100    105    110
Arg Gly Gly Pro Gly Asn Gly Gly Asp Ile
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<210> SEQ ID NO 681
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 681

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acatggcc gggtgtgtgc ccaagctccac tcagctgtcg tgcctctgtc gggagccca
120
gttgatccaa acgctgagcg cagctcaggt gttgatcaga caaagctcgtg aggctggtat
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cagcgaaac gaggccacctccccagcacttactt cgtccgacac tgcgctgctatc
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gggatccagttgacccat gagctgatga tttgggagag aagctctctt caccacagc
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tttgc
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<210> SEQ ID NO 682
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 682

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tcgagagactg ggtcgtcttc tgtgcgctgc cccctctctg gccgtggctg ccaagcttcg
120
cagccgctct gcagcagcgt gcagcagcgc ctcctctctc gcagcagcgc ctcctctctc
180
gggctccagttgacccat gagctgatga tttgggagag aagctctctt caccacagc
240
gacctgagttgacccat gagctcctc ttgcccttcgt cggcttgtgct gccgtgtttag tggtaatc
300
gacatc
366

<210> SEQ ID NO 683
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 683

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
   1      5      10     15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
   20     25     30
Val Ser Val Pro Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ser Ser
   35     40     45
Gln Ser Val Tyr Asn Asn Phe Leu Ser Trp Tyr Gln Gln Lys Pro Gly
   50     55     60
Gln Pro Pro Lys Leu Leu Ile Tyr Gln Ala Ser Lys Leu Ala Ser Gly
   65     70     75     80
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu
   85     90     95
Thr Ile Ser Gly Val Gln Cys Asp Ala Ala Thr Tyr Cys Leu
 100    105    110
Gly Gly Tyr Asp Asp Ala Asp Asn Ala
 115    120

<210> SEQ ID NO 684
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 684

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
   1      5      10     15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
   20     25     30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
   35     40     45
Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
   50     55     60
Trp Ile Gly Ile Ile Tyr Ala Gly Ser Gly Ser Thr Trp Tyr Ala Ser
   65     70     75     80
Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp
   95     90    105     110
Leu Lys Ile Thr Ser Pro Thr Glu Asp Ala Thr Tyr Phe Cys
 100    105    110
Ala Arg Asp Gly Tyr Asp Asp Tyr Gly Asp Phe Arg Leu Asp Leu
 115    120    125

<210> SEQ ID NO 685
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 685

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acatttgcag cgggtgcac ccagacacca tcgcccctgt ctgtacctgt gggagggcaca
   61     120
gtccacatca agtggccagtc cagtcagagt gttaataa atttccttac gtgtattcag
   121    180
cagaaaccag gcgcagctcc caagctcctg atctaccagg catcacaact gcacatctggg
240
gtccagattg ggttacaagg caagtggatct gggacacagt tcaccttcac ctaoagggc
300
gtgcacagttg acagatgtgc caacctactc tgtctagggc gttatgatga tgatgtcgtat
360
aatgct
366

<210> SEQ ID NO 686
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 686
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tcggtggag agttccgggctgtggctgc agccttggaga cacccctgac gctacactgc
120
acagttctcg gaacctcaotc catgactat gccttagct gcggcagcaca ggcgtcaggg
180
aagggggtcg aaatgatacg aatcttttat gctggatctg gtgcacatg tgctgcaagc
240
tggcggcag acgcgtcctc atctcctaaa acctgacaca ctgggtgatct gaaacactc
300
agctcggcaca cgagggacgc gcgcacgcgt ttcgtgctga gataggtgata ctagtacact
360
ggcagtctgg atgtatttgg tccc
384

<210> SEQ ID NO 687
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 687
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30
Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45
Gln Ser Ile Asn Asn Glu Leu Ser Ser Trp Tyr Gln Gln Lys Ser Gly Gln
50 55 60
Arg Pro Lys Leu Leu Ile Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val
65 70 75 80
Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Cys Gln Gln
100 105 110
Gly Tyr Ser Leu Arg Asn Ile Asp Asn Ala
115 120

<210> SEQ ID NO 688
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 688
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Ser Gly
1 5 10 15
Val Gln Cys Gln Ser Leu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30
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<210> SEQ ID NO: 689
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 689
atggacacga ggccccccac tcagctgcgt ggcctctgct cgcttgtgc ctccaggtgcc 60
agagtgctct atgtagatgc ccagactcct gcgctggagt tcggagctgc gggagagcaca 120
gtccatcct aaggcagggc cagcagaggc attataacag aattatctcg gtatcagcag 180
aaatcagggc agctcgccaa cgccctgtac tctagggc ctactctggtg atctggggtc 240
tctgctggt tcaasagccag tggatctggtg acagagttca cttcagacat cagcagcctg 300
gatgtgccc atgtgccccg ttactactgt ccaaggggtt atagtcttag gaattattgat 360
aatgcg 366

<210> SEQ ID NO: 690
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 690
atggaacgtc gcgcgctgcag tctttctctg gtcggctgtgc ttctaggtgt ccaggtgctcag 60
tcgccgggag cgctcggggg agctcgaggg gatcaggtgga aaccagctgg actaacctgc 120
acagcctgct gcacagactc gctagactc gcgctggcag gcgcctggg agctgggagagc 180
agagggtggc aaggtgctgg agatgatta gatagattag aacacgctta cgccaaccttg 240
ggcagatggc gatcagggct ctcctaaaaacc tgagacggg aataagagacgt 300
tcggcagcct cggagagcgg ccccttttc ttcggccggag atgtactagg tgcagttggat 360
gccaaatttca actcg 375

<210> SEQ ID NO: 691
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 691

1    5     10     15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser Asn Tyr
20    25     30
-continued

Tyr Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Glu Trp Val 35 40 45
Gly Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Trp Ala Ile 50 95 60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Tyr Leu 65 70 75 80
Gln Met Asn Ser Leu Arg Ala Glu Thr Ala Val Tyr Tyr Cys Ala 85 90 95
Arg Asp Asp Ser Ser Asp Trp Ala Lys Phe Asn Leu Trp Gly Gln 100 105 110
Gly Thr Leu Val Thr Val Ser Ala Ser Thr Lys Gly Pro Ser Val 115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Gly Gly Thr Ala Ala 130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser 145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val 165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro 180 185 190
Ser Ser Ser Gln Ser Gln Thr Tyr Ile Cys Asn Val Asn His Lys 195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp 210 215 220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly 225 230 235 240
Pro Ser Ile Phe Leu Phe Pro Pro Lys Asp Thr Leu Met Ile 245 250 255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu 260 265 270 275
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His 280 285 290
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gin Tyr Ala Ser Thr Tyr Arg 290 295 300
Val Val Ser Val Leu Val Leu His Gin Asp Trp Leu Asn Gly Lys 305 310 315 320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu 325 330 335
Lys Thr Ile Ser Lys Ala Leu Gly Gin Pro Arg Glu Pro Gin Val Tyr 340 345 350
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gin Val Ser Leu 355 360 365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp 370 375 380
Glu Ser Asn Gly Gin Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val 385 390 395 400
Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val Asp 405 410 415
Lys Ser Arg Trp Gin Gin Gly Asn Val Phe Ser Cys Ser Val Met His 420 425 430
Glu Ala Leu His Asn His Tyr Thr Gin Lys Ser Leu Ser Leu Ser Pro
Gly Lys
450

<210> SEQ ID NO 692
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 692

Glu Val Gln Leu Val Glu Val Gly Gly Gly Leu Val Gln Pro Gly Gly
1         5           10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20         25          30
Tyr Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35         40          45
Gly Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Ser Ala Ile
50         55          60
Gly Arg Phe Thr Ile Ser Arg Asp Ser Asn Ser Lys Asn Thr Leu Tyr Leu
65         70          75          80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Cys Ala
85         90          95
Arg Asp Asp Ser Ser Asp Trp Ala Lys Phe Asn Leu Trp Gly Gln
100       105         110
Gly Thr Leu Val Thr Val Ser Ala Ser Thr Lys Gly Pro Ser Val
115       120         125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Gly Gly Thr Ala Ala
130       135         140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145       150         155          160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165       170          175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Thr Val Pro
180       185          190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195       200          205
Pro Ser Asn Thr Lys Val Asp Arg Val Glu Pro Lys Ser Cys Asp
210       215          220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225       230          235          240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245       250          255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260       265          270
Asp Pro Glu Val Lys Phe Asn Thr Tyr Val Asp Gly Val Glu Val His
275       280          285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg
290       295          300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Thr Leu Asn Gly Lys
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Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
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<400> SEQUENCE: 693

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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 695

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<210> SEQ ID NO 696
<211> LENGTH: 48
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<210> SEQ ID NO 697
<211> LENGTH: 36
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 697

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<210> SEQ ID NO 698
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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ggggagaaggcc ataagctctc gattatatgc gagtcactcgt tggactctgg ggtgtcacc

aggtctcgag ccagctggtct ctggagcagc tttactctctc acatccagcag cctgctgct

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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 699

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Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Aen Aen Glu

20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Ser Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn
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Ile Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Gln Ile Lys Arg Thr
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cacgggaaag ggtcggagtg ggtcggattc atctatggta ggtatgaacac cgcctcaggt 180
acctcggta taggccgatg cccacattccc agcgacatatt ccaagacac ccctgtacttc 240
caaatgacact ggtgctacta ctgctgtatt acctgtgctag agactatagt 300
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gggagaaagcc ctaagctgcc gagatctttct ggtatgtgctt cggccgattgt tggccgaatact 180
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<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

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Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Leu Gln Pro  
65 70 75 60
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gin Gly Tyr Ser Leu Arg Asn  
95 90 95
Ile Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr  
100 105 110
Val Ala Ala Pro Ser Val Phe Pro Pro Pro Ser Asp Glu Gin Leu  
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Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro  
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Arg Glu Ala Lys Val Gin Trp Lys Val Asp Asn Ala Leu Gin Ser Gly  
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Asn Ser Gin Glu Ser Val Thr Glu Gin Asp Ser Lys Asp Ser Thr Tyr  
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<213> ORGANISM: Oryctolagus cuniculus
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<213> ORGANISM: Oryctolagus cuniculus

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36   40
Gly Ile Ile Tyr Gly Ser Asp Ser LEU Gln Ser Ser Ala Ile
46   50
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Thr Leu Tyr Leu
65   70
Gln Met Asn Ser Leu Arg Ala Gln Ser Thr Ala Val Tyr Cys Ala
75   80
Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gln
100  105
Gly Thr Leu Val Thr Val Ser Ala Ser Thr Lys Gly Pro Ser Val
115  120
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Gly Leu Thr Ala Ala
130  135
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Glu Pro Val Thr Val
145  150
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
160  170
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
185  190
Ser Ser Ser Ser Leu Gly Thr Glu thr Tyr Ile Cys Asn Val Asn His Lys
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Pro Ser Asn Thr Lys Val Asp Arg Val Glu Pro Lys Ser Cys Asp
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Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Lys
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Pro Ser Val Phe Leu Phe Pro Pro Lys Asp Thr Leu Met Ile
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Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ser His Glu
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Asp Pro Glu Val Lys Phe Asn Thr Tyr Val Asp Gly Glu Val His
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Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Glu Val Tyr
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val Asp
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<212> TYPE: DNA
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aggggctagt gatctgtgggc aagctctcaact ttcacatctca gcagcctgca gcctgtgtat
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Val Gly Asp Arg Val Thr Ile Thr Cys Gin Ala Ser Gin Ser Ile Asn
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Asn Glu Leu Ser Trp Tyr Gin Gin Lys Pro Gin Lys Ala Pro Lys Leu
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Leu Ile Tyr Arg Ala Ser Thr Leu Ala Ser Gin Val Pro Ser Arg Phe
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Ser Gin Ser Gly Ser Gin Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
80
Gln Pro Asp Gin Phe Ala Thr Tyr Cys Gin Gin Gly Tyr Ser Leu
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Arg Asn Ile Gin Ala Phe Gly Gly Thr Gin Val Gin Ille Leu
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Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Gin Glu
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Gln Thr Gin Gin Thr Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin
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Ser Gin Gin Ser Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin
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Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser
35 40 45
Asn Tyr Tyr Val Thr Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Val Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser
65 70 75 80
Ala Ile Gly Arg Phe Thr Ile Ser Arg Asp Ser Asp Ser Lys Asn Thr Leu
85 90 95
Tyr Leu Glu Met Asn Ser Leu Arg Ala Glu Aep Thr Ala Val Tyr Tyr
100 105 110
Cys Ala Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp
115 120 125
Gly Glu Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
130 135 140
Ser Val Pro Leu Arg Pro Ser Ser Lys Ser Thr Ser Gly Lys Thr
145 150 155 160
Ala Ala Leu Gly Cys Leu Val Arg Tyr Phe Pro Glu Pro Val Thr
165 170 175
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
180 185 190
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Thr
195 200 205
Val Pro Ser Ser Ser Leu Gly Thr Glu Thr Tyr Ile Cys Asn Val Asn
210 215 220
His Lys Pro Ser Arg Thr Lys Val Arg Lys Arg Val Glu Pro Lys Ser
225 230 235 240
Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
245 250 255
-continued-

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275 280 285
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Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
305 310 315 320
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
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355 360 365
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370 375 380
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Glu Trp Glu Ser Asn Gin Pro Gin Glu Asn Asn Tyr Lys Thr Thr Pro
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Val Asp Lys Ser Arg Trp Gin Gin Gly Asn Val Phe Ser Cys Ser Val
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Leu Ser Trp Tyr Gin Gin Gin Pro Gin Lys Ala Pro Lys Leu Leu Ile
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Tyr Arg Ala Ser Thr Leu Ala Ser Gin Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
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**Sequence:** 717

**Organism:** Homo sapiens

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**Sequence:** 719

**Organism:** Artificial Sequence

**Feature:** Other Information: Gamma-1 constant domain

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260 265 270
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275 280 285
Leu Tyr Ser Lys Thr Val Lys Thr Arg Trp Gln Gln Gly Asn
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gggtcacaact ccacatcttt tttactcttg gacggctatt cgtgtgtcttg ggtcctcttg 180
cggctcggg gccagtgtcg tgggagccag ctctctcatca ccaaccagctt cctcggtggt 240
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gattttgctca cttattacgct ccacaggtgg tatagttgca ggacattgta taatgtct 300
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ctgagcgtga gcagaagcaga ctaagagaa cacaaggtct aagcctctga agtcaccat 600
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Phe Gly Gln Thr Asp Met Ser Arg Lys Ala Phe Val Phe Pro Lys Glu
20    25    30
Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys Pro Leu
35    40    45
Lys Ala Phe Thr Val Cys Leu His Phe Tyr Thr Glu Leu Ser Ser Thr
50    55    60
Arg Gly Tyr Ser Ile Phe Ser Tyr Ala Thr Lys Arg Glu Asp Glu Glu
65    70    75    80
Ile Leu Ile Phe Trp Ser Lys Asp Ile Gly Tyr Ser Phe Thr Val Gly
85    90    95
Gly Ser Glu Ile Leu Phe Glu Val Pro Glu Val Thr Val Ala Pro Val
100   105   110
His Ile Cys Thr Ser Trp Glu Ser Ala Ser Gly Ile Val Glu Phe Trp
115   120   125
Val Asp Gly Lys Pro Arg Val Arg Lys Ser Leu Lys Gly Tyr Thr
130   135   140
Val Gly Ala Glu Ala Ser Ile Ile Leu Gly Gin Glu Gin Asp Ser Phe
145   150   155   160
Gly Gly Asn Phe Gly Gin Ser Gin Ser Leu Val Gly Asp Ile Gly Asn
165   170   175
Val Asn Met Trp Asp Phe Val Leu Ser Pro Asp Glu Ile Asn Thr Ile
180   185   190
Tyr Leu Gly Gly Pro Phe Ser Pro Asn Val Leu Asn Trp Arg Ala Leu
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Lys Tyr Glu Val Gin Gly Glu Val Phe Thr Lys Pro Glu Leu Trp Pro
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Gly Val Leu Thr Ser Leu Pro Gly Asp Ser Val Thr Leu Thr Cys Pro
35    40    45
Gly Val Glu Pro Glu Asp Asn Ala Thr Val His Trp Val Leu Arg Lys
50    55    60
Pro Ala Ala Gly Ser His Pro Ser Arg Trp Ala Gly Met Gly Arg Arg
65    70    75    80
Leu Leu Arg Ser Val Gin Leu His Asp Ser Gly Asn Tyr Ser Cys
85    90    95
Tyr Arg Ala Gly Arg Pro Ala Gly Thr Val His Leu Leu Val Asp Val
100   105   110
Pro Pro Glu Glu Pro Gin Leu Ser Cys Phe Arg Lys Ser Pro Leu Ser
115   120   125
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AAs Val Val Cys Glu Trp Gly Pro Arg Ser Thr Pro Ser Leu Thr Thr
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Lys Ala Val Leu Leu Val Arg Phe Gin Asn Ser Pro Ala Glu Asp
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Phe Gin Glu Pro Cys Gin Tyr Ser Gin Glu Ser Gin Lys Phe Ser Cys
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Gln Leu Ala Val Pro Glu Gly Asp Ser Ser Phe Tyr Ile Val Ser Met
180 185 190
Cys Val Ala Ser Ser Val Gly Ser Lys Phe Ser Lys Thr Gin Thr Phe
195 200 205
Gln Gly Cys Gly Ile Leu Gin Pro Asp Pro Pro Ala Asn Ile Thr Val
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Thr Ala Val Ala Arg Asn Pro Arg Thr Leu Ser Val Thr Trp Gin Asp
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Pro His Ser Trp Asn Ser Ser Phe Tyr Arg Leu Arg Phe Glu Leu Arg
245 250 255
Tyr Arg Ala Glu Arg Ser Lys Thr Phe Thr Thr Trp Met Val Lys Asp
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Val Val Gin Leu Arg Ala Gin Glu Glu Phe Gly Gin Gly Glu Thr Ser
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Pro Pro Ala Glu Asn Glu Val Ser Thr Pro Met Gin Ala Leu Thr Thr
325 330 335
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340 345 350
Ser Leu Pro Val Gin Asp Ser Ser Ser Val Pro Leu Pro Thr Phe Leu
355 360 365
Val Ala Gly Gin Ser Leu Ala Phe Gly Thr Leu Leu Cys Ile Ala Ile
370 375 380
Val Leu Arg Phe Lys Thr Trp Lys Leu Arg Ala Leu Lys Glu Gly
385 390 395 400
Lys Thr Ser Met His Pro Pro Tyr Ser Leu Gly Gln Val Leu Pro Gin
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1-112. (canceled)

113. A method of improving survivability or quality of life of a patient in need thereof, by increasing the patient's serum albumin level, and decreasing the patient's serum C reactive protein ("CRP") level, comprising administering to the patient an effective amount of an anti-IL-6 antagonist that blocks the binding of human IL-6 to IL-6Rα and gp130, whereby the patient's serum albumin level is reduced, and the patient's serum C reactive protein ("CRP") level is reduced.

114. The method of claim 113, wherein the IL-6 antagonist is an anti-human IL-6 antibody or antibody fragment.

115. The method of claim 114, wherein the anti-human IL-6 antibody or antibody fragment competes with and/or binds the same epitope as an anti-human IL-6 antibody comprising the variable heavy and light sequences respectively in SEQ ID NO:2 and 3.

116. The method of claim 113, which further includes monitoring the patient to assess the reduction in the patient's serum CRP level.

117. The method of claim 113, which further includes monitoring the patient to assess the increase in the patient's serum albumin level.

118. The method of claim 113, wherein said patient has an elevated serum CRP level prior to treatment and/or a reduced serum albumin level prior to treatment.

119. The method of claim 113, whereby the patient's Glasgow Prognostic Score (GPS) is improved.

120. The method of claim 113, wherein the IL-6 antagonist comprises an anti-IL-6, anti-gp130, anti-p38 MAP kinase, anti-JAK1, anti-JAK2, anti-JAK3, or anti-SYK antibody or antibody fragment or comprises a small molecule comprising thalidomide, lenalidomide, or any combination thereof.

121. The method of claim 113, wherein the anti-IL-6 antibody or fragment comprises the variable heavy chain in SEQ ID NO: 657 and the variable light chain in SEQ ID NO: 709 respectively or a antibody comprising variable heavy and/or light chain sequences comprising the same CDRs as the variable sequences in SEQ ID NO:657 and 709.

122. The method of claim 121, wherein the anti-IL-6 antibody or fragment comprises the heavy chain and light chain constant regions comprised in SEQ ID NO:588 and SEQ ID NO:586 respectively.

123. The method of claim 114, wherein the anti-IL-6 antibody or antibody fragment specifically binds to the same epitope on an intact IL-6 polypeptide or fragment thereof that is specifically bound by an antibody containing the variable heavy and light sequences in SEQ ID NO:3 and 2 respectively, and wherein said epitope(s) when ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide includes one or more residues comprised in each of the IL-6 fragments selected from those respectively consisting of amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72 of SEQ ID NO:1.

124. The method of claim 114, wherein the anti-IL-6 antibody or antibody fragment is glycosylated and/or contains an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation.

125. The method of claim 114, wherein the anti-IL-6 antibody or antibody fragment is a human, humanized, single chain or chimeric antibody.

126. The method of claim 114, wherein the anti-IL-6 antibody or antibody fragment is administered to the patient with a frequency of about every four weeks or eight weeks.

127. The method of claim 114, wherein said antibody comprises a human Fc derived from IgG1, IgG2, IgG3, or IgG4.

128. The method of claim 114, wherein the anti-IL-6 antibody or antibody fragment has an elimination half-life of at least about 22 days, at least about 25 days or at least about 30 days.

129. The method of claim 113, wherein the IL-6 antagonist is coadministered with a chemotherapy.

130. The method of claim 114, wherein the anti-IL-6 antibody or antibody fragment which is directly or indirectly attached to a detectable label or therapeutic agent.

131. The method of claim 113, wherein the IL-6 antagonist is coupled to a half-life increasing moiety.

132. The method of claim 113, wherein 42, 49 or 56 days after IL-6 antagonist administration the patient's serum albumin level remains above 35 g/L.

133. The method of claim 113, wherein the patient has been diagnosed with an autoimmune disorder or cancer.

134. The method of claim 114, wherein the antibody or fragment has variable heavy and light sequences contained at
least 98% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

135. A method of increasing survivability or quality of life of a patient in need thereof, comprising administering to the patient an IL-6 antagonist, whereby the patient's serum CRP level is reduced and/or the patient's serum albumin level is increased, and monitoring the patient to assess the reduction in the patient's serum CRP level and the increase in the patient's serum albumin level comprising intravenously or subcutaneously administering an anti-IL-6 antibody or antibody fragment having the same epitopic specificity as an antibody containing the variable light and heavy sequences in SEQ ID NO:2 and 3 respectively by intravenously administering a dosage of about (+1-20%) 80, 160 or 320 mg of said antibody to a patient in need thereof.

136. The method of claim 135, wherein the patient is administered said dosage every 8 weeks or 2 months.

137. The method of claim 135, wherein said dosage is administered at least twice.

138. The method of claim 135, wherein the first dosage is on day one and the second dosage during week 8 (8th week after day 0).

139. The method of any one of claim 135, wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 95% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

140. The method of claim 139, wherein said anti-IL-6 antibody or antibody fragment contains the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

141. The method of claim 113, wherein said anti-IL-6 antibody is comprised in a composition formulated for subcutaneous or intravenous injection.

142. The method of claim 135, wherein said anti-IL-6 antibody is comprised in a composition formulated for subcutaneous or intravenous injection.

* * * * *