

IL-11 Antibodies

This application claims priority from GB1809699.0 filed 13 June 2018, the contents and elements of which are herein incorporated by reference for all purposes.

5 Field of the Invention

The present invention relates to the fields of molecular biology, more specifically antibody technology. The present invention also relates to methods of medical treatment and prophylaxis. In particular, antigen-binding molecules capable of binding to IL-11 are provided.

10 Background to the Invention

IL-11-mediated signalling has been shown to stimulate haematopoiesis, stimulate osteoclast activity, stimulate neurogenesis, inhibit adipogenesis, reduce pro inflammatory cytokine expression, modulate extracellular matrix (ECM) metabolism, and mediate normal growth control of gastrointestinal epithelial cells. The physiological role of Interleukin 11 (IL-11) remains unclear. IL-11 has been most strongly linked with
15 activation of haematopoietic cells and with platelet production, but has also been suggested to be pro-inflammatory as well as anti-inflammatory, pro-angiogenic and important for neoplasia.

Summary of the Invention

In a first aspect the present invention provides an antigen-binding molecule, optionally isolated, which is
20 capable of binding to IL-11, wherein the antigen-binding molecule comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36 or 37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39 or 40; and

25 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:41, 42 or 43

LC-CDR2 having the amino acid sequence of SEQ ID NO:44, 45 or 46

LC-CDR3 having the amino acid sequence of SEQ ID NO:80 or 81.

30 In some embodiments the antigen-binding molecule comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and

35 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:80.

40 In some embodiments the antigen-binding molecule comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

- HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:42
5 LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:81.

In some embodiments the antigen-binding molecule comprises:

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
10 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:43
15 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:80.

In some embodiments the antigen-binding molecule comprises:

- (a)
20 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:36
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
25 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:48;

- (b)
30 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:36
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:41
35 LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:49;

- (c)
40 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:36
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:50;

(d)

5 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

10 LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:51;

(e)

15 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

20 LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:52;

(f)

25 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

30 LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:53;

(g)

35 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:54; or

40 (h)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

- HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:41
5 LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:55.

In some embodiments the antigen-binding molecule comprises:

- (a)
10 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
15 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:57;
- (b)
20 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
25 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:58;
- (c)
30 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
35 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:59;
- (d)
40 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:42

LC-CDR2 having the amino acid sequence of SEQ ID NO:45

LC-CDR3 having the amino acid sequence of SEQ ID NO:60;

(e)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

5 HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

10 LC-CDR1 having the amino acid sequence of SEQ ID NO:42

LC-CDR2 having the amino acid sequence of SEQ ID NO:45

LC-CDR3 having the amino acid sequence of SEQ ID NO:61;

(f)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

15 HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:42

LC-CDR2 having the amino acid sequence of SEQ ID NO:45

20 LC-CDR3 having the amino acid sequence of SEQ ID NO:62;

(g)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

25 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:42

LC-CDR2 having the amino acid sequence of SEQ ID NO:45

LC-CDR3 having the amino acid sequence of SEQ ID NO:63; or

30 (h)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

35 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:42

LC-CDR2 having the amino acid sequence of SEQ ID NO:45

LC-CDR3 having the amino acid sequence of SEQ ID NO:64.

40 In some embodiments the antigen-binding molecule comprises:

(a)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:48;

(b)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:49;

(c)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:50;

(d)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:51;

(e)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46

LC-CDR3 having the amino acid sequence of SEQ ID NO:52;

(f)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

5 HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:43

LC-CDR2 having the amino acid sequence of SEQ ID NO:46

10 LC-CDR3 having the amino acid sequence of SEQ ID NO:53;

(g)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

15 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:43

LC-CDR2 having the amino acid sequence of SEQ ID NO:46

LC-CDR3 having the amino acid sequence of SEQ ID NO:54; or

20 (h)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

25 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:43

LC-CDR2 having the amino acid sequence of SEQ ID NO:46

LC-CDR3 having the amino acid sequence of SEQ ID NO:55.

30 In some embodiments the antigen-binding molecule comprises:

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6, 8 or 10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:82, 83 or 84.

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In some embodiments the antigen-binding molecule comprises:

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:82.

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In some embodiments the antigen-binding molecule comprises:

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:83.

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In some embodiments the antigen-binding molecule comprises:

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

10 a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:84.

In some embodiments the antigen-binding molecule comprises:

(a)

15 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:12;

(b)

20 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:13;

(c)

25 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:14;

(d)

30 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:15;

(e)

35 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:16;

(f)

40 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:17;

(g)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:18; or

(h)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:19.

In some embodiments the antigen-binding molecule comprises:

(a)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:20;

(b)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:21;

(c)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:22;

(d)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:23;

(e)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:24;

(f)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:25;

(g)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:26; or

(h)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:27.

In some embodiments the antigen-binding molecule comprises:

(a)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:28;

(b)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:29;

(c)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:30;

(d)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:31;

(e)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:32;

(f)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:33;

(g)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:34; or

(h)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:35.

The present invention also provides an antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:95

HC-CDR2 having the amino acid sequence of SEQ ID NO:96

HC-CDR3 having the amino acid sequence of SEQ ID NO:97; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:98 or 101

LC-CDR2 having the amino acid sequence of SEQ ID NO:99 or 102

LC-CDR3 having the amino acid sequence of SEQ ID NO:100 or 103.

In some embodiments the antigen-binding molecule comprises:

(a)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:95

HC-CDR2 having the amino acid sequence of SEQ ID NO:96

HC-CDR3 having the amino acid sequence of SEQ ID NO:97; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:98

LC-CDR2 having the amino acid sequence of SEQ ID NO:99

LC-CDR3 having the amino acid sequence of SEQ ID NO:100; or

(b)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:95

HC-CDR2 having the amino acid sequence of SEQ ID NO:96

HC-CDR3 having the amino acid sequence of SEQ ID NO:97; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:101

LC-CDR2 having the amino acid sequence of SEQ ID NO:102

LC-CDR3 having the amino acid sequence of SEQ ID NO:103.

In some embodiments the antigen-binding molecule comprises:

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:91, 92, 116, 117, 118, 119 or 120; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:93, 94, 121, 122, 123, 124, 125, 126, 127 or 128.

In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID

NO:220. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:223. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:224. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of one of SEQ ID NO:236 to 240. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:220 or 223, and a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of one of SEQ ID NO:224, 236, 237, 238, 239, or 240.

In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID

NO:225. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:228. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:229. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:230. In some embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:225 or 228, and a polypeptide comprising or

consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:229 or 230.

5 In accordance with various aspects of the present invention, in some embodiments the antigen-binding molecule is capable of inhibiting IL-11 mediated signalling.

The present invention also provides an antigen-binding molecule, optionally isolated, comprising (i) an antigen-binding molecule described herein, and (ii) an antigen-binding molecule capable of binding to an
10 antigen other than IL-11.

In accordance with various aspects of the present invention, in some embodiments the antigen-binding molecule is capable of inhibiting interaction between IL-11 or a complex comprising IL-11 and an IL-11
15 receptor.

The present invention also provides a chimeric antigen receptor (CAR) comprising an antigen-binding molecule described herein.

The present invention also provides a nucleic acid, or a plurality of nucleic acids, optionally isolated,
20 encoding an antigen-binding molecule described herein or a CAR described herein.

The present invention also provides an expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids described herein.

25 The present invention also provides a cell comprising an antigen-binding molecule, a CAR, a nucleic acid or a plurality of nucleic acids, or an expression vector or a plurality of expression vectors described herein.

The present invention also provides a method comprising culturing a cell comprising a nucleic acid or a plurality of nucleic acids according or an expression vector or a plurality of expression vectors described
30 herein, under conditions suitable for expression of the antigen-binding molecule or CAR from the nucleic acid(s) or expression vector(s).

The present invention also provides a composition comprising an antigen-binding molecule, a CAR, a nucleic acid or a plurality of nucleic acids, an expression vector or a plurality of expression vectors, and/or a cell as
35 provided herein.

The present invention also provides an antigen-binding molecule, a CAR, a nucleic acid or a plurality of nucleic acids, an expression vector or a plurality of expression vectors, a cell, or a composition described
40 herein for use in a method of medical treatment or prophylaxis.

The present invention also provides an antigen-binding molecule, a CAR, a nucleic acid or a plurality of nucleic acids, an expression vector or a plurality of expression vectors, a cell, or a composition described

herein, for use in a method of treatment or prevention of fibrosis, a disease characterised by fibrosis, a cancer, inflammation, or a disease characterised by inflammation.

- 5 The present invention also provides the use of an antigen-binding molecule, a CAR, a nucleic acid or a plurality of nucleic acids, an expression vector or a plurality of expression vectors, a cell, or a composition described herein, in the manufacture of a medicament for use in a method of treatment or prevention of fibrosis, a disease characterised by fibrosis, a cancer, inflammation, or a disease characterised by inflammation.
- 10 The present invention also provides a method of treating or preventing fibrosis, a disease characterised by fibrosis, a cancer, inflammation, or a disease characterised by inflammation, comprising administering to a subject a therapeutically or prophylactically effective amount of an antigen-binding molecule, a CAR, a nucleic acid or a plurality of nucleic acids, an expression vector or a plurality of expression vectors, a cell, or a composition described herein.
- 15 The present invention also provides a method of inhibiting IL-11 mediated signalling, comprising contacting IL-11-expressing cells with an antigen-binding molecule described herein. The method may be performed *in vitro*, *in vivo*, *in situ* or *ex vivo*.
- 20 The present invention also provides an *in vitro* complex, optionally isolated, comprising an antigen-binding molecule described herein bound to IL-11 or a complex comprising IL-11.
- 25 The present invention also provides a method comprising contacting a sample containing, or suspected to contain, IL-11 or a complex comprising IL-11 with an antigen-binding molecule described herein, and detecting the formation of a complex of the antigen-binding molecule with IL-11 or a complex comprising IL-11.
- 30 The present invention also provides a method of selecting or stratifying a subject for treatment with an IL-11-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule described herein and detecting the formation of a complex of the antigen-binding molecule with IL-11 or a complex comprising IL-11.
- 35 The present invention also provides the use of an antigen-binding molecule described herein as an *in vitro* or *in vivo* diagnostic or prognostic agent.
- The present invention also provides a kit of parts comprising a predetermined quantity of: an antigen-binding molecule, a CAR, a nucleic acid or a plurality of nucleic acids, an expression vector or a plurality of expression vectors, a cell, or a composition described herein.
- 40 **Description**
- The present invention relates to novel IL-11-binding molecules having improved properties as compared to known anti-IL-11 antibodies. The IL-11-binding molecules of the present invention are provided with

combinations of desirable biophysical and functional properties as compared to IL-11-binding antigen-binding molecules disclosed in the prior art.

Interleukin 11 and receptors for IL-11

Interleukin 11 (IL-11), also known as adipogenesis inhibitory factor, is a pleiotropic cytokine and a member of the IL-6 family of cytokines that includes IL-6, IL-11, IL-27, IL-31, oncostatin, leukemia inhibitory factor (LIF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF) and neuropoietin (NP-1).

Interleukin 11 (IL-11) is expressed in a variety of mesenchymal cell types. IL-11 genomic sequences have been mapped onto chromosome 19 and the centromeric region of chromosome 71, and is transcribed with a canonical signal peptide that ensures efficient secretion from cells. The activator protein complex of IL-11, cJun/AP-1, located within its promoter sequence is critical for basal transcriptional regulation of IL-11 (Du and Williams., Blood 1997, Vol 89: 3897–3908). The immature form of human IL-11 is a 199 amino acid polypeptide whereas the mature form of IL-11 encodes a protein of 178 amino acid residues (Garbers and Scheller., Biol. Chem. 2013; 394(9):1145-1161). The human IL-11 amino acid sequence is available under UniProt accession no. P20809 (P20809.1 GI:124294; SEQ ID NO:1). Recombinant human IL-11 (oprelvekin) is also commercially available. IL-11 from other species, including mouse, rat, pig, cow, several species of bony fish and primates, have also been cloned and sequenced.

In this specification “IL-11” refers to an IL-11 from any species and includes isoforms, fragments, variants or homologues of an IL-11 from any species. As used herein, a “fragment”, “variant” or “homologue” of a protein may optionally be characterised as having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of the reference protein. In some embodiments fragments, variants, isoforms and homologues of a reference protein may be characterised by ability to perform a function performed by the reference protein.

A “fragment” generally refers to a fraction of the reference protein. A “variant” generally refers to a protein having an amino acid sequence comprising one or more amino acid substitutions, insertions, deletions or other modifications relative to the amino acid sequence of the reference protein, but retaining a considerable degree of sequence identity (e.g. at least 60%) to the amino acid sequence of the reference protein. An “isoform” generally refers to a variant of the reference protein expressed by the same species as the species of the reference protein. A “homologue” generally refers to a variant of the reference protein produced by a different species as compared to the species of the reference protein. Homologues include orthologues. A “fragment” may be of any length (by number of amino acids), although may optionally be at least 20% of the length of the reference protein (that is, the protein from which the fragment is derived) and may have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of the reference protein. A fragment of IL-11 may have a minimum length of 10 amino acids, and a maximum length of one of 15, 20, 25, 30, 40, 50, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 195 amino acids.

- In some embodiments, the IL-11 is IL-11 from a mammal (e.g. a primate (rhesus, cynomolgous, non-human primate or human) and/or a rodent (e.g. rat or murine) IL-11). Isoforms, fragments, variants or homologues of IL-11 may optionally be characterised as having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of an immature or mature IL-11 isoform from a given species, e.g. human. In some embodiments, the IL-11 of the present disclosure comprises, or consists of, an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:1.
- Isoforms, fragments, variants or homologues of an IL-11 may optionally be characterised by ability to bind an IL-11 receptor (e.g. IL-11R α , gp130 and/or a complex comprising IL-11R α and gp130, preferably from the same species) and stimulate signal transduction in cells expressing IL-11R α and gp130 (e.g. as described in Curtis et al. Blood, 1997, 90(11); or Karpovich et al. Mol. Hum. Reprod. 2003 9(2): 75-80).
- IL-11 signals through a homodimer of the ubiquitously expressed glycoprotein 130 (gp130; also known as glycoprotein 130, IL-6ST, IL-6-beta or CD130). Gp130 is a transmembrane protein that forms one subunit of the type I cytokine receptor with the IL-6 receptor family. Specificity is gained through an individual interleukin 11 receptor subunit alpha (IL-11R α), which does not directly participate in signal transduction, although the initial cytokine binding event to the α -receptor leads to the final complex formation with gp130.
- Human gp130 (including the 22 amino acid signal peptide) is a 918 amino acid protein, and the mature form is 866 amino acids, comprising a 597 amino acid extracellular domain, a 22 amino acid transmembrane domain, and a 277 amino acid intracellular domain. The extracellular domain of the protein comprises the cytokine-binding module (CBM) of gp130. The CBM of gp130 comprises the Ig-like domain D1, and the fibronectin-type III domains D2 and D3 of gp130. The amino acid sequence of human gp130 is available under UniProt accession no. P40189-1 (SEQ ID NO:2).
- Human IL-11R α is a 422 amino acid polypeptide (UniProt Q14626; SEQ ID NO:3) and shares ~85% nucleotide and amino acid sequence identity with the murine IL-11R α (Du and Williams., Blood Vol, 89, No,11, June 1, 1997). Two isoforms of IL-11R α have been reported, which differ in the cytoplasmic domain (Du and Williams, supra). The IL-11 receptor α -chain (IL-11R α) shares many structural and functional similarities with the IL-6 receptor α -chain (IL-6R α). The extracellular domain shows 24% amino acid identity including the characteristic conserved Trp-Ser-X-Trp-Ser (WSXWS) motif. The short cytoplasmic domain (34 amino acids) lacks the Box 1 and 2 regions that are required for activation of the JAK/STAT signalling pathway.
- The receptor binding sites on murine IL-11 have been mapped and three sites – sites I, II and III - identified. Binding to gp130 is reduced by substitutions in the site II region and by substitutions in the site III region. Site III mutants show no detectable agonist activity and have IL-11R α antagonist activity (Cytokine Inhibitors Chapter 8; edited by Gennaro Ciliberto and Rocco Savino, Marcel Dekker, Inc. 2001).

In this specification an IL-11 receptor/receptor for IL-11 (IL-11R) refers to a polypeptide or polypeptide complex capable of binding IL-11 and/or a complex comprising IL-11. In some embodiments an IL-11 receptor is capable of binding IL-11 and/or a complex comprising IL-11 and inducing signal transduction in cells expressing the IL-11 receptor. A "complex comprising IL-11" may be a non-covalent complex of IL-11 and a polypeptide capable of non-covalent association with IL-11.

An IL-11 receptor may be from any species and includes isoforms, fragments, variants or homologues of an IL-11 receptor from any species. In preferred embodiments the species is human (*Homo sapiens*).

In some embodiments the IL-11 receptor (IL-11R) may be IL-11R α . In some embodiments a receptor for IL-11 may be a polypeptide complex comprising IL-11R α . In some embodiments the IL-11 receptor may be a polypeptide complex comprising IL-11R α and gp130. In some embodiments the IL-11 receptor may be gp130 or a complex comprising gp130 to which IL-11 binds.

Isoforms, fragments, variants or homologues of an IL-11R α may optionally be characterised as having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of IL-11R α from a given species, e.g. human. Isoforms, fragments, variants or homologues of an IL-11R α may optionally be characterised by ability to bind IL-11 (preferably from the same species) and stimulate signal transduction in cells expressing the IL-11R α and gp130 (e.g. as described in Curtis et al. *Blood*, 1997, 90(11) or Karpovich et al. *Mol. Hum. Reprod.* 2003 9(2): 75-80). A fragment of an IL-11 receptor may be of any length (by number of amino acids), although may optionally be at least 25% of the length of the mature IL-11R α and have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of the mature IL-11R α . A fragment of an IL-11 receptor fragment may have a minimum length of 10 amino acids, and a maximum length of one of 15, 20, 25, 30, 40, 50, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 400, or 415 amino acids.

IL-11 signalling

IL-11 binds to IL-11R α with low affinity ($K_d \sim 10$ nmol/L), and interaction between these binding partners alone is insufficient to transduce a biological signal. The generation of a high affinity receptor ($K_d \sim 400$ to 800 pmol/L) capable of signal transduction requires co-expression of the IL-11R α and gp130 (Curtis et al (*Blood* 1997 Dec 1;90 (11):4403-12; Hilton et al., *EMBO J* 13:4765, 1994; Nandurkar et al., *Oncogene* 12:585, 1996). Binding of IL-11 to cell-surface IL-11R α induces heterodimerization, tyrosine phosphorylation, activation of gp130 and downstream signalling, predominantly through the mitogen-activated protein kinase (MAPK)-cascade and the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathway (Garbers and Scheller, *supra*).

In principle, a soluble IL-11R α can also form biologically active soluble complexes with IL-11 (Pflanz et al., 1999 *FEBS Lett*, 450, 117-122) raising the possibility that, similar to IL-6, IL-11 may in some instances bind soluble IL-11R α prior to binding cell-surface gp130 (Garbers and Scheller, *supra*). Curtis et al (*Blood* 1997 Dec 1;90 (11):4403-12) describe expression of a soluble murine IL-11 receptor alpha chain (sIL-11R) and examined signalling in cells expressing gp130. In the presence of gp130 but not transmembrane IL-11R the

IL-11R mediated IL-11 dependent differentiation of M1 leukemic cells and proliferation in Ba/F3 cells and early intracellular events including phosphorylation of gp130, STAT3 and SHP2 similar to signalling through transmembrane IL-11R. Activation of signalling through cell-membrane bound gp130 by IL-11 bound to soluble IL-11R α has recently been demonstrated (Lokau et al., 2016 Cell Reports 14, 1761–1773). This so-called IL-11 *trans* signalling may be a very important component of IL-11-mediated signalling, and may even be the most common form of IL-11-mediated signalling, because whilst the expression of IL-11R α is restricted to a relatively small subset of cell types, gp130 is expressed on a wide range of cell types.

As used herein, “IL-11 signalling” and “IL-11-mediated signalling” refers to signalling mediated by binding of IL-11, a fragment thereof having the function of the mature IL-11 molecule, or a complex comprising IL-11/a fragment thereof having the function of the mature IL-11 molecule to a receptor for IL-11.

As used herein, ‘IL-11 *trans* signalling’ is used to refer to signalling which is triggered by binding of IL-11 bound to IL-11R α , to gp130. The IL-11 may be bound to IL-11R α as a non-covalent complex. The gp130 is membrane-bound and expressed by the cell in which signalling occurs following binding of the IL-11:IL-11R α complex to gp130. In some embodiments the IL-11R α may be a soluble IL-11R α . In some embodiments, the soluble IL-11R α is a soluble (secreted) isoform of IL-11R α (e.g. lacking a transmembrane domain). In some embodiments, the soluble IL-11R α is the liberated product of proteolytic cleavage of the extracellular domain of cell membrane bound IL-11R α . In some embodiments, the IL-11R α may be cell membrane-bound, and signalling through gp130 may be triggered by binding of IL-11 bound to cell-membrane-bound IL-11R α , termed “IL-11 *cis* signalling”.

IL-11-mediated signalling has been shown to stimulate haematopoiesis and thrombopoiesis, stimulate osteoclast activity, stimulate neurogenesis, inhibit adipogenesis, reduce pro inflammatory cytokine expression, modulate extracellular matrix (ECM) metabolism, and mediate normal growth control of gastrointestinal epithelial cells (Du and Williams, supra).

The physiological role of Interleukin 11 (IL-11) remains unclear. IL-11 has been most strongly linked with activation of haematopoietic cells and with platelet production, but has also been suggested to be pro-inflammatory as well as anti-inflammatory, pro-angiogenic and important for neoplasia. It is known that TGF β 1 or tissue injury can induce IL-11 expression (Zhu, M. et al. PLOS ONE 10, (2015); Yashiro, R. et al. J. Clin. Periodontol. 33, 165–71 (2006); Obana, M. et al. Circulation 121, 684–91 (2010); Tang, W et al. J. Biol. Chem. 273, 5506–13 (1998)).

IL-11 is an important post-transcriptional modulator of TGF β -mediated signalling. TGF β 1 has been shown to stimulate the AP-1 promoter region of IL-11, and TGF β -induced secretion of IL-11 has been shown to induce activation of ERK p42/44 and p38 MAP kinases in intestinal myofibroblasts (Bamba et al. Am J Physiol Gastrointest Liver Physiol. (2003) 285(3):G529-38). MAP kinase inhibitors are able to significantly reduce TGF β -induced IL-11 secretion, and p38 MAP kinase-mediated stabilization of mRNA has been shown to be critical for TGF β -induced secretion of IL-11.

IL-11 mediated signalling has recently been demonstrated to play a key role in fibrotic processes in a wide variety of tissues; see for example WO 2017/103108 A1 and Schafer et al. (2017) Nature 552: 110–115, both of which are hereby incorporated by reference in their entirety.

5 WO 2017/103108 A1 (hereby incorporated by reference in its entirety) reports a pro-fibrotic role for IL-11, and establishes the therapeutic utility of antagonists of IL-11 mediated signalling in the treatment/prevention of fibrosis. Example 2 and Figures 7A and 7B of WO 2017/103108 A1 demonstrate that incubation of primary human atrial fibroblasts with recombinant human IL-11 increases deposition of collagen by fibroblasts, a well-established fibrotic process. Treatment with neutralising anti-IL-11 antibody (but not
10 isotype control antibody) was shown to abrogate collagen production induced by stimulation of the fibroblasts with TGF β 1 (a known pro-fibrotic stimulus). Example 3 and Figure 10 of WO 2017/103108 A1 further demonstrate the ability of neutralising anti-IL-11 antibody to abrogate increased collagen production by human atrial fibroblasts in response to various other pro-fibrotic stimuli (ANG2, PDGF, ET-1). Example 5.2 and Figures 20A-20E of WO 2017/103108 A1 provide further data supporting a pro-fibrotic role for IL-11 in
15 heart tissue. Human atrial fibroblasts were shown to display significantly increased production of extracellular matrix components (collagen, periostin) and increased expression of pro-fibrotic markers (α SMA, IL-6, MMP2, TIMP1) in response to treatment with human IL-11 protein, in the same way as production of these factors is increased in response to treatment with the pro-fibrotic stimulus TGF β 1. Example 5.3.1 and Figures 38A to 38D of WO 2017/103108 A1 likewise show increased production of extracellular matrix
20 components and increased expression of fibrotic markers by human primary liver fibroblasts in response to treatment with human IL-11, and also the ability of neutralising anti-IL-11 antibody to abrogate the profibrotic effects of stimulation with TGF β 1. Figures 22A to 22F and 23A and 23B of WO 2017/103108 A1 show that TGF β 1-mediated fibrosis can be inhibited by treatment with neutralising anti-IL-11 antibody, and Figure 24 moreover shows that IL-11-binding decoy receptor molecules, neutralising anti-IL-11R α antibodies and
25 oligonucleotides encoding siRNA for antisense knockdown of IL-11 and IL-11RA gene expression are similarly able to inhibit TGF β 1-mediated transition of fibroblasts to myofibroblasts (fibrosis effector cells). Further data showing inhibition of the TGF β 1-mediated fibrotic response using decoy IL-11 receptors is provided at Figures 32A and 32B of WO 2017/103108 A1. Example 5.3.3 and Figures 21B and 21C of WO 2017/103108 A1 provide *in vivo* data demonstrating IL-11 to be pro-fibrotic in a variety of tissues. Injection of
30 mice with recombinant mouse IL-11 caused an increase in the relative weight of heart, kidney, lung and liver (Figure 21B), and that this was associated with increased collagen content in these tissues (Figure 21C). Further *in vivo* data supporting a pro-fibrotic role for IL-11 is provided at Examples 7.2 and 7.3, and Figures 27A to 27D and Figure 28 of WO 2017/103108 A1. These experiments show that IL-11RA knockout mice are protected from fibrosis of the heart and kidney tissues induced by profibrotic stimuli, indicating signalling
35 through the IL-11 receptor as an important mediator of fibrotic processes. Further still, Figures 31A and 31B, summarised at the legend to Figure 31 of WO 2017/103108 A1 report that more fibrosis was detected in eye sections obtained from wildtype mice than IL-11RA knockout mice at 7 days following trabeculectomy. Thus WO 2017/103108 A1 provides abundant data from both *in vitro* and *in vivo* studies proving that IL-11/IL-11R signalling is a key mediator of fibrosis in a wide range of tissues, and demonstrates that inhibition of IL-11
40 mediated signalling reduces fibrosis, as determined by analysis of a variety of markers of the fibrotic response.

Antigen-binding molecules capable of binding to IL-11

The present invention provides antigen-binding molecules capable of binding to IL-11.

5 An "antigen-binding molecule" refers to a molecule which is capable of binding to a target antigen, and encompasses monoclonal antibodies, polyclonal antibodies, monospecific and multispecific antibodies (e.g., bispecific antibodies), and antibody fragments (e.g. Fv, scFv, Fab, scFab, F(ab')₂, Fab₂, diabodies, triabodies, scFv-Fc, minibodies, single domain antibodies (e.g. VhH), etc.), as long as they display binding to the relevant target molecule(s). By "antibody" we include fragments and derivatives thereof, including synthetic antibodies and fragments. As used herein, an antibody is a polypeptide capable of binding specifically to the relevant target molecule (i.e. the antigen for which the antibody is specific). Antibodies and antigen-binding molecules according to the present invention may be provided in isolated form.

15 In view of contemporary techniques in relation to monoclonal antibody technology, antibodies can be prepared to most antigens. The antigen-binding portion may be a part of an antibody (for example a Fab fragment) or a synthetic antibody fragment (for example a single chain Fv fragment [ScFv]). Suitable monoclonal antibodies to selected antigens may be prepared by known techniques, for example those disclosed in "Monoclonal Antibodies: A manual of techniques ", H Zola (CRC Press, 1988) and in "Monoclonal Hybridoma Antibodies: Techniques and Applications ", J G R Hurrell (CRC Press, 1982). Chimeric antibodies are discussed by Neuberger et al (1988, 8th International Biotechnology Symposium Part 2, 792-799).

20 Monoclonal antibodies (mAbs) are useful in the methods of the invention and are a homogenous population of antibodies specifically targeting a single epitope on an antigen.

25 Antigen binding fragments of antibodies, such as Fab and Fab₂ fragments may also be used/provided as can genetically engineered antibodies and antibody fragments. The variable heavy (V_H) and variable light (V_L) domains of the antibody are involved in antigen recognition, a fact first recognised by early protease digestion experiments. Further confirmation was found by "humanisation" of rodent antibodies. Variable domains of rodent origin may be fused to constant domains of human origin such that the resultant antibody retains the antigenic specificity of the rodent parent antibody (Morrison et al (1984) Proc. Natl. Acad. Sci. USA 81, 6851-6855).

30 In some embodiments, the antigen-binding molecule of the invention is a fully human antibody/antibody fragment. A fully human antibody/antibody fragment is encoded by human nucleic acid sequence(s). Fully human antibodies/antibody fragments are devoid of non-human amino acid sequences.

35 The two most commonly employed techniques to the production of fully human antibodies are (i) phage display, in which human antibody genes are expressed in phage display libraries, and (ii) production of antibodies in transgenic mice engineered to have human antibody genes (described in Park and Smolen Advances in Protein Chemistry (2001) 56: 369-421). Briefly, in the human antibody gene-phage display technique, genes encoding the V_H and V_L chains are generated by PCR amplification and cloning from "naive" human lymphocytes, and assembled into a library from which they can be expressed either as

disulfide-linked Fab fragments or as single-chain Fv (scFv) fragments. The Fab- or scFv-encoding genes are fused to a surface coat protein of filamentous bacteriophage and Fab or scFv capable of binding to the target of interest can then be identified by screening the library with antigen. Molecular evolution or affinity maturation procedures can be employed to enhance the affinity of the Fab/scFv fragment. In the transgenic mouse technique, mice in which the endogenous murine Ig gene loci have been replaced by homologous recombination with their human homologues are immunized with antigen, and monoclonal antibody is prepared by conventional hybridoma technology, to yield fully human monoclonal antibody.

In some embodiments, the antigen-binding molecule of the invention is a murine antibody/antibody fragment.

In some embodiments the antibody/antibody fragment may be prepared by phage display using a human naïve antibody gene library.

In some embodiments, the antigen-binding molecule of the invention is a mouse/human chimeric antibody/antibody fragment (e.g., an antigen-binding molecule comprising murine variable domains and human constant regions). In some embodiments, the antigen-binding molecule is a humanised antibody/antibody fragment (e.g., an antigen-binding molecule comprising murine CDRs and human framework and constant regions).

A mouse/human chimeric antigen-binding molecule can be prepared from a mouse monoclonal antibody by the process of chimerisation, e.g. as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 8 thereof, in particular section 3 of Chapter 8.

A humanised antigen-binding molecule can be prepared from a mouse antibody by the process of humanization, e.g. as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 7 thereof, in particular section 3.1 of Chapter 7 entitled 'Antibody Humanization'.

The antigen-binding molecule of the present invention comprises a moiety capable of binding to a target antigen(s). In some embodiments, the moiety capable of binding to a target antigen comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL) of an antibody capable of specific binding to the target antigen. In some embodiments, the moiety capable of binding to a target antigen comprises or consists of an aptamer capable of binding to the target antigen, e.g. a nucleic acid aptamer (reviewed, for example, in Zhou and Rossi Nat Rev Drug Discov. 2017 16(3):181-202). In some embodiments, the moiety capable of binding to a target antigen comprises or consists of an antigen-binding peptide/polypeptide, e.g. a peptide aptamer, thioredoxin, monobody, anticalin, Kunitz domain, avimer, knottin, fynomer, atrimer, DARPin, affibody, nanobody (i.e. a single-domain antibody (sdAb)) affilin, armadillo repeat protein (ArmRP), OBody or fibronectin – reviewed e.g. in Reverdatto et al., Curr Top Med Chem. 2015; 15(12): 1082–1101, which is hereby incorporated by reference in its entirety (see also e.g. Boersma et al., J Biol Chem (2011) 286:41273-85 and Emanuel et al., Mabs (2011) 3:38-48).

The antigen-binding molecules of the present invention generally comprise an antigen-binding domain comprising a VH and a VL of an antibody capable of specific binding to the target antigen. The antigen-binding domain formed by a VH and a VL may also be referred to herein as an Fv region.

- 5 An antigen-binding molecule may be, or may comprise, an antigen-binding polypeptide, or an antigen-binding polypeptide complex. An antigen-binding molecule may comprise more than one polypeptide which together form an antigen-binding domain. The polypeptides may associate covalently or non-covalently. In some embodiments the polypeptides form part of a larger polypeptide comprising the polypeptides (e.g. in the case of scFv comprising VH and VL, or in the case of scFab comprising VH-CH1 and VL-CL).
- 10 An antigen-binding molecule may refer to a non-covalent or covalent complex of more than one polypeptide (e.g. 2, 3, 4, 6, or 8 polypeptides), e.g. an IgG-like antigen-binding molecule comprising two heavy chain polypeptides and two light chain polypeptides.
- 15 The antigen-binding molecules of the present invention may be designed and prepared using the sequences of monoclonal antibodies (mAbs) capable of binding to IL-11. Antigen-binding regions of antibodies, such as single chain variable fragment (scFv), Fab and F(ab')₂ fragments may also be used/provided. An "antigen-binding region" is any fragment of an antibody which is capable of binding to the target for which the given antibody is specific.
- 20 Antibodies generally comprise six complementarity-determining regions CDRs; three in the heavy chain variable (VH) region: HC-CDR1, HC-CDR2 and HC-CDR3, and three in the light chain variable (VL) region: LC-CDR1, LC-CDR2, and LC-CDR3. The six CDRs together define the paratope of the antibody, which is the part of the antibody which binds to the target antigen.
- 25 The VH region and VL region comprise framework regions (FRs) either side of each CDR, which provide a scaffold for the CDRs. From N-terminus to C-terminus, VH regions comprise the following structure: N term-[HC-FR1]-[HC-CDR1]-[HC-FR2]-[HC-CDR2]-[HC-FR3]-[HC-CDR3]-[HC-FR4]-C term; and VL regions comprise the following structure: N term-[LC-FR1]-[LC-CDR1]-[LC-FR2]-[LC-CDR2]-[LC-FR3]-[LC-CDR3]-
- 30 [LC-FR4]-C term.
- There are several different conventions for defining antibody CDRs and FRs, such as those described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991), Chothia et al., J. Mol. Biol. 196:901-917 (1987), and VBASE2, as
- 35 described in Retter et al., Nucl. Acids Res. (2005) 33 (suppl 1): D671-D674. The CDRs and FRs of the VH regions and VL regions of the antibody clones described herein were defined according to the Kabat system.
- In some embodiments, the antigen-binding molecule comprises the CDRs of an antigen-binding molecule which is capable of binding to IL-11. In some embodiments, the antigen-binding molecule comprises the FRs of an antigen-binding molecule which is capable of binding to IL-11. In some embodiments, the antigen-binding molecule comprises the CDRs and the FRs of an antigen-binding molecule which is capable of
- 40

binding to IL-11. That is, in some embodiments the antigen-binding molecule comprises the VH region and the VL region of an antigen-binding molecule which is capable of binding to IL-11.

In some embodiments the antigen-binding molecule comprises a VH region and a VL region which is, or which is derived from, the VH/VL region of a IL-11-binding antibody clone described herein (e.g. anti-IL-11 antibody clone 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V, 02A, 02G, 02I, 02L, 02Q, 02S, 02T, 02V, 03A, 03G, 03I, 03L, 03Q, 03S, 03T, 03V, BSN-3C6 (comprising 3C6 VH 1, 3C6 VH 2, 3C6 VH 2.1, 3C6 VH 2.2, 3C6 VH 2.3, 3C6 VH 2.4 or 3C6 VH 2.5 and 3C6 VL 1, 3C6 VL 2, 3C6 VL 1.1, 3C6 VL 1.2, 3C6 VL 1.3, 3C6 VL 1.4, 3C6 VL 2.1, 3C6 VL 2.2, 3C6 VL 2.3 or 3C6 VL 2.4), BSN-1H2, BSN-7D4, BSN-8H11).

In some embodiments the antigen-binding molecule comprises a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:7, wherein the VL region comprises a substitution of the cysteine residue at position 91 of SEQ ID NO:7 to an amino acid other than cysteine. In some embodiments the amino acid other than cysteine is selected from alanine, glycine, isoleucine, leucine, glutamine, serine, threonine or valine.

In some embodiments the antigen-binding molecule comprises a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:9, wherein the VL region comprises a substitution of the cysteine residue at position 91 of SEQ ID NO:9 to an amino acid other than cysteine. In some embodiments the amino acid other than cysteine is selected from alanine, glycine, isoleucine, leucine, glutamine, serine, threonine or valine.

In some embodiments the antigen-binding molecule comprises a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:11, wherein the VL region comprises a substitution of the cysteine residue at position 91 of SEQ ID NO:11 to an amino acid other than cysteine. In some embodiments the amino acid other than cysteine is selected from alanine, glycine, isoleucine, leucine, glutamine, serine, threonine or valine.

In some embodiments the antigen-binding molecule comprises a VH region having less than 100% sequence identity to the amino acid sequence of SEQ ID NO:91. In some embodiments the antigen-binding molecule does not comprise a VH region comprising or consisting of the amino acid sequence of SEQ ID NO:91. In some embodiments the antigen-binding molecule does not comprise a peptide/polypeptide comprising or consisting of the amino acid sequence of SEQ ID NO:91.

In some embodiments the antigen-binding molecule comprises a VL region having less than 100% sequence identity to the amino acid sequence of SEQ ID NO:93. In some embodiments the antigen-binding molecule

does not comprise a VL region comprising or consisting of the amino acid sequence of SEQ ID NO:93. In some embodiments the antigen-binding molecule does not comprise a peptide/polypeptide comprising or consisting of the amino acid sequence of SEQ ID NO:93.

5 In some embodiments the antigen-binding molecule comprises a VH region according to one (1) or (2) below:

(1) (01X) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

10 HC-CDR3 having the amino acid sequence of SEQ ID NO:39,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(2) (02X, 03X) a VH region incorporating the following CDRs:

15 HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

20

In some embodiments the antigen-binding molecule comprises a VH region according to one of (3) to (5) below:

(3) (01X) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:65

25 HC-FR2 having the amino acid sequence of SEQ ID NO:67

HC-FR3 having the amino acid sequence of SEQ ID NO:68

HC-FR4 having the amino acid sequence of SEQ ID NO:70,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2, HC-FR3, or HC-FR4 are substituted with another amino acid.

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(4) (02X) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:65

HC-FR2 having the amino acid sequence of SEQ ID NO:67

HC-FR3 having the amino acid sequence of SEQ ID NO:69

35 HC-FR4 having the amino acid sequence of SEQ ID NO:70,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2, HC-FR3, or HC-FR4 are substituted with another amino acid.

(5) (03X) a VH region incorporating the following FRs:

40 HC-FR1 having the amino acid sequence of SEQ ID NO:66

HC-FR2 having the amino acid sequence of SEQ ID NO:67

HC-FR3 having the amino acid sequence of SEQ ID NO:69

HC-FR4 having the amino acid sequence of SEQ ID NO:70,
or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2, HC-FR3, or HC-FR4 are substituted with another amino acid.

- 5 In some embodiments the antigen-binding molecule comprises a VH region comprising the CDRs according to (1) or (2) above, and the FRs according to one of (3) to (5) above.

In some embodiments the antigen-binding molecule comprises a VH region according to one of (6) to (8) below:

- 10 (6) (01X) a VH region comprising the CDRs according to (1) and the FRs according to (3).

(7) (02X) a VH region comprising the CDRs according to (2) and the FRs according to (4).

(8) (03X) a VH region comprising the CDRs according to (2) and the FRs according to (5).

15

In some embodiments the antigen-binding molecule comprises a VH region according to one of (9) to (1) below:

- (9) (01X) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
20 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:6.

(10) (02X) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
25 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:8.

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(11) (03X) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:10.

- 30 In some embodiments the antigen-binding molecule comprises a VL region according to one (12) to (38) below:

(12) (01X) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

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LC-CDR3 having the amino acid sequence of SEQ ID NO:80,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(13) (01A) a VL region incorporating the following CDRs:

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LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:48,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(14) (01G) a VL region incorporating the following CDRs:

- 5 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:49,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

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(15) (01I) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:41
LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:50,
15 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(16) (01L) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:41
20 LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:51,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(17) (01Q) a VL region incorporating the following CDRs:

- 25 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:52,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
30 or LC-CDR3 are substituted with another amino acid.

(18) (01S) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:41
LC-CDR2 having the amino acid sequence of SEQ ID NO:44
35 LC-CDR3 having the amino acid sequence of SEQ ID NO:53,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(19) (01T) a VL region incorporating the following CDRs:

- 40 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:54,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(20) (01V) a VL region incorporating the following CDRs:

- 5 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
LC-CDR2 having the amino acid sequence of SEQ ID NO:44
LC-CDR3 having the amino acid sequence of SEQ ID NO:55,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

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(21) (02X) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:81,
15 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(22) (02A) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:42
20 LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:57,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

25 (23) (02G) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:58,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
30 or LC-CDR3 are substituted with another amino acid.

(24) (02I) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
35 LC-CDR3 having the amino acid sequence of SEQ ID NO:59,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(25) (02L) a VL region incorporating the following CDRs:

- 40 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:60,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(26) (02Q) a VL region incorporating the following CDRs:

- 5 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:61,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

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(27) (02S) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:62,
15 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(28) (02T) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:42
20 LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:63,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(29) (02V) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:64,
25 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

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(30) (03X) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
35 LC-CDR3 having the amino acid sequence of SEQ ID NO:80,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(31) (03A) a VL region incorporating the following CDRs:

- 40 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:48,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(32) (03G) a VL region incorporating the following CDRs:

- 5 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:49,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

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(33) (03I) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:50,
15 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(34) (03L) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:43
20 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:51,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(35) (03Q) a VL region incorporating the following CDRs:

- 25 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:52,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
30 or LC-CDR3 are substituted with another amino acid.

(36) (03S) a VL region incorporating the following CDRs:

- LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
35 LC-CDR3 having the amino acid sequence of SEQ ID NO:53,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
or LC-CDR3 are substituted with another amino acid.

(37) (03T) a VL region incorporating the following CDRs:

- 40 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:54,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(38) (03V) a VL region incorporating the following CDRs:

- 5 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:55,
 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
10 or LC-CDR3 are substituted with another amino acid.

10 In some embodiments the antigen-binding molecule comprises a VH region incorporating the CDRs according to (2) and a VL region incorporating the CDRs according to (22).

15 In some embodiments the antigen-binding molecule comprises a VL region according to one of (39) to (41) below:

(39) (01X) a VL region incorporating the following FRs:

- LC-FR1 having the amino acid sequence of SEQ ID NO:71
 LC-FR2 having the amino acid sequence of SEQ ID NO:74
 LC-FR3 having the amino acid sequence of SEQ ID NO:76
20 LC-FR4 having the amino acid sequence of SEQ ID NO:77,
 or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

(40) (02X) a VL region incorporating the following FRs:

- 25 LC-FR1 having the amino acid sequence of SEQ ID NO:72
 LC-FR2 having the amino acid sequence of SEQ ID NO:75
 LC-FR3 having the amino acid sequence of SEQ ID NO:76
 LC-FR4 having the amino acid sequence of SEQ ID NO:78,
 or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.
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(41) (03X) a VL region incorporating the following FRs:

- LC-FR1 having the amino acid sequence of SEQ ID NO:73
 LC-FR2 having the amino acid sequence of SEQ ID NO:74
35 LC-FR3 having the amino acid sequence of SEQ ID NO:76
 LC-FR4 having the amino acid sequence of SEQ ID NO:79,
 or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

- 40 In some embodiments the antigen-binding molecule comprises a VL region comprising the CDRs according to one of (12) to (38) above, and the FRs according to one of (39) to (41) above.

In some embodiments the antigen-binding molecule comprises a VL region according to one of (42) to (68) below:

- (42) (01X) a VL region comprising the CDRs according to (12) and the FRs according to (39).
- 5 (43) (01A) a VL region comprising the CDRs according to (13) and the FRs according to (39).
- (44) (01G) a VL region comprising the CDRs according to (14) and the FRs according to (39).
- (45) (01I) a VL region comprising the CDRs according to (15) and the FRs according to (39).
- 10 (46) (01L) a VL region comprising the CDRs according to (16) and the FRs according to (39).
- (47) (01Q) a VL region comprising the CDRs according to (17) and the FRs according to (39).
- 15 (48) (01S) a VL region comprising the CDRs according to (18) and the FRs according to (39).
- (49) (01T) a VL region comprising the CDRs according to (19) and the FRs according to (39).
- (50) (01V) a VL region comprising the CDRs according to (20) and the FRs according to (39).
- 20 (51) (02X) a VL region comprising the CDRs according to (21) and the FRs according to (40).
- (52) (02A) a VL region comprising the CDRs according to (22) and the FRs according to (40).
- 25 (53) (02G) a VL region comprising the CDRs according to (23) and the FRs according to (40).
- (54) (02I) a VL region comprising the CDRs according to (24) and the FRs according to (40).
- (55) (02L) a VL region comprising the CDRs according to (25) and the FRs according to (40).
- 30 (56) (02Q) a VL region comprising the CDRs according to (26) and the FRs according to (40).
- (57) (02S) a VL region comprising the CDRs according to (27) and the FRs according to (40).
- 35 (58) (02T) a VL region comprising the CDRs according to (28) and the FRs according to (40).
- (59) (02V) a VL region comprising the CDRs according to (29) and the FRs according to (40).
- (60) (03X) a VL region comprising the CDRs according to (30) and the FRs according to (41).
- 40 (61) (03A) a VL region comprising the CDRs according to (31) and the FRs according to (41).

- (62) (03G) a VL region comprising the CDRs according to (32) and the FRs according to (41).
- (63) (03I) a VL region comprising the CDRs according to (33) and the FRs according to (41).
- 5 (64) (03L) a VL region comprising the CDRs according to (34) and the FRs according to (41).
- (65) (03Q) a VL region comprising the CDRs according to (35) and the FRs according to (41).
- (66) (03S) a VL region comprising the CDRs according to (36) and the FRs according to (41).
- 10 (67) (03T) a VL region comprising the CDRs according to (37) and the FRs according to (41).
- (68) (03V) a VL region comprising the CDRs according to (38) and the FRs according to (41).
- 15 In some embodiments the antigen-binding molecule comprises a VL region according to one of (69) to (95) below:
- (69) (01X) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:82.
- 20 (70) (01A) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:12.
- 25 (71) (01G) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:13.
- (72) (01I) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:14.
- 30 (73) (01L) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:15.
- 35 (74) (01Q) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:16.
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- (75) (01S) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:17.
- 5 (76) (01T) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:18.
- 10 (77) (01V) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:19.
- 15 (78) (02X) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:83.
- 20 (79) (02A) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:20.
- (80) (02G) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:21.
- 25 (81) (02I) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:22.
- 30 (82) (02L) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:23.
- 35 (83) (02Q) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:24.
- 40 (84) (02S) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:25.

- (85) (02T) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:26.
- 5 (86) (02V) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:27.
- (87) (03X) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:84.
- 10 (88) (03A) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:28.
- 15 (89) (03G) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:29.
- 20 (90) (03I) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:30.
- (91) (03L) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:31.
- 25 (92) (03Q) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:32.
- 30 (93) (03S) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:33.
- 35 (94) (03T) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:34.
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(95) (03V) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:35.

- 5 In some embodiments the antigen-binding molecule comprises a VH region according to any one of (1) to (11) above, and a VL region according to any one of (12) to (95) above.

- In some embodiments the antigen-binding molecule comprises a VH region according to (7) or (10) and a VL region according to (52) or (79). In some embodiments the antigen-binding molecule comprises a VH region according to (7) and a VL region according to (52). In some embodiments the antigen-binding molecule comprises a VH region according to (10) and a VL region according to (79). In some embodiments the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:210. In some
- 10
- 15 embodiments the antigen-binding molecule comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:210.

- 20 In some embodiments the antigen-binding molecule comprises a VH region according to (96):
(96) (3C6 VH 1, 3C6 VH 2, 3C6 VH 2.1, 3C6 VH 2.2, 3C6 VH 2.3, 3C6 VH 2.4, 3C6 VH 2.5) a VH region incorporating the following CDRs:
- HC-CDR1 having the amino acid sequence of SEQ ID NO:95
HC-CDR2 having the amino acid sequence of SEQ ID NO:96
- 25 HC-CDR3 having the amino acid sequence of SEQ ID NO:97,
or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

- In some embodiments the antigen-binding molecule comprises a VH region according to one of (97) to (103) below:
- 30

(97) (3C6 VH 1) a VH region incorporating the following FRs:

- HC-FR1 having the amino acid sequence of SEQ ID NO:104
HC-FR2 having the amino acid sequence of SEQ ID NO:106
HC-FR3 having the amino acid sequence of SEQ ID NO:107
- 35 HC-FR4 having the amino acid sequence of SEQ ID NO:108,
or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2, HC-FR3, or HC-FR4 are substituted with another amino acid.

(98) (3C6 VH 2) a VH region incorporating the following FRs:

- 40 HC-FR1 having the amino acid sequence of SEQ ID NO:105
HC-FR2 having the amino acid sequence of SEQ ID NO:106
HC-FR3 having the amino acid sequence of SEQ ID NO:107

HC-FR4 having the amino acid sequence of SEQ ID NO:108,
or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2,
HC-FR3, or HC-FR4 are substituted with another amino acid.

5 (99) (3C6 VH 2.1) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:129

HC-FR2 having the amino acid sequence of SEQ ID NO:132

HC-FR3 having the amino acid sequence of SEQ ID NO:136

HC-FR4 having the amino acid sequence of SEQ ID NO:140,

10 or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2,
HC-FR3, or HC-FR4 are substituted with another amino acid.

(100) (3C6 VH 2.2) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:130

15 HC-FR2 having the amino acid sequence of SEQ ID NO:133

HC-FR3 having the amino acid sequence of SEQ ID NO:137

HC-FR4 having the amino acid sequence of SEQ ID NO:140,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2,
HC-FR3, or HC-FR4 are substituted with another amino acid.

20

(101) (3C6 VH 2.3) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:130

HC-FR2 having the amino acid sequence of SEQ ID NO:134

HC-FR3 having the amino acid sequence of SEQ ID NO:138

25 HC-FR4 having the amino acid sequence of SEQ ID NO:140,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2,
HC-FR3, or HC-FR4 are substituted with another amino acid.

(102) (3C6 VH 2.4) a VH region incorporating the following FRs:

30 HC-FR1 having the amino acid sequence of SEQ ID NO:131

HC-FR2 having the amino acid sequence of SEQ ID NO:134

HC-FR3 having the amino acid sequence of SEQ ID NO:139

HC-FR4 having the amino acid sequence of SEQ ID NO:140,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2,
35 HC-FR3, or HC-FR4 are substituted with another amino acid.

(103) (3C6 VH 2.5) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:131

HC-FR2 having the amino acid sequence of SEQ ID NO:135

40 HC-FR3 having the amino acid sequence of SEQ ID NO:139

HC-FR4 having the amino acid sequence of SEQ ID NO:140,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2, HC-FR3, or HC-FR4 are substituted with another amino acid.

In some embodiments the antigen-binding molecule comprises a VH region comprising the CDRs according to (96) above, and the FRs according to one of (97) to (103) above.

In some embodiments the antigen-binding molecule comprises a VH region according to one of (104) to (110) below:

(104) (3C6 VH 1) a VH region comprising the CDRs according to (96) and the FRs according to (97).

(105) (3C6 VH 2) a VH region comprising the CDRs according to (96) and the FRs according to (98).

(106) (3C6 VH 2.1) a VH region comprising the CDRs according to (96) and the FRs according to (99).

(107) (3C6 VH 2.2) a VH region comprising the CDRs according to (96) and the FRs according to (100).

(108) (3C6 VH 2.3) a VH region comprising the CDRs according to (96) and the FRs according to (101).

(109) (3C6 VH 2.4) a VH region comprising the CDRs according to (96) and the FRs according to (102).

(110) (3C6 VH 2.5) a VH region comprising the CDRs according to (96) and the FRs according to (103).

In some embodiments the antigen-binding molecule comprises a VH region according to one of (111) to (117) below:

(111) (3C6 VH 1) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:91.

(112) (3C6 VH 2) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:92.

(113) (3C6 VH 2.1) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:116.

(114) (3C6 VH 2.2) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:117.

- (115) (3C6 VH 2.3) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:118.
- 5 (116) (3C6 VH 2.4) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:119.
- (117) (3C6 VH 2.5) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:120.
- 10 In some embodiments the antigen-binding molecule comprises a VL region according to (118) or (119):
 (118) (3C6 VL 1, 3C6 VL 1.1, 3C6 VL 1.2, 3C6 VL 1.3, 3C6 VL 1.4) a VL region incorporating the following CDRs:
- 15 LC-CDR1 having the amino acid sequence of SEQ ID NO:98
 LC-CDR2 having the amino acid sequence of SEQ ID NO:99
 LC-CDR3 having the amino acid sequence of SEQ ID NO:100,
 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2,
 20 or LC-CDR3 are substituted with another amino acid.
- (119) (3C6 VL 2, 3C6 VL 2.1, 3C6 VL 2.2, 3C6 VL 2.3, 3C6 VL 2.4) a VL region incorporating the following CDRs:
- 25 LC-CDR1 having the amino acid sequence of SEQ ID NO:101
 LC-CDR2 having the amino acid sequence of SEQ ID NO:102
 LC-CDR3 having the amino acid sequence of SEQ ID NO:103,
 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.
- 30 In some embodiments the antigen-binding molecule comprises a VL region according to one of (120) to (129) below:
 (120) (3C6 VL 1) a VL region incorporating the following FRs:
- 35 LC-FR1 having the amino acid sequence of SEQ ID NO:109
 LC-FR2 having the amino acid sequence of SEQ ID NO:111
 LC-FR3 having the amino acid sequence of SEQ ID NO:113
 LC-FR4 having the amino acid sequence of SEQ ID NO:115,
 or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.
- 40 (121) (3C6 VL 2) a VL region incorporating the following FRs:
 LC-FR1 having the amino acid sequence of SEQ ID NO:110
 LC-FR2 having the amino acid sequence of SEQ ID NO:112

LC-FR3 having the amino acid sequence of SEQ ID NO:114

LC-FR4 having the amino acid sequence of SEQ ID NO:115,

or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

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(122) (3C6 VL 1.1) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:150

LC-FR2 having the amino acid sequence of SEQ ID NO:112

LC-FR3 having the amino acid sequence of SEQ ID NO:153

10 LC-FR4 having the amino acid sequence of SEQ ID NO:149,

or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

(123) (3C6 VL 1.2) a VL region incorporating the following FRs:

15 LC-FR1 having the amino acid sequence of SEQ ID NO:151

LC-FR2 having the amino acid sequence of SEQ ID NO:112

LC-FR3 having the amino acid sequence of SEQ ID NO:153

LC-FR4 having the amino acid sequence of SEQ ID NO:149,

20 or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

(124) (3C6 VL 1.3) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:152

LC-FR2 having the amino acid sequence of SEQ ID NO:112

25 LC-FR3 having the amino acid sequence of SEQ ID NO:154

LC-FR4 having the amino acid sequence of SEQ ID NO:149,

or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

(125) (3C6 VL 1.4) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:152

LC-FR2 having the amino acid sequence of SEQ ID NO:112

LC-FR3 having the amino acid sequence of SEQ ID NO:155

LC-FR4 having the amino acid sequence of SEQ ID NO:149,

35 or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

(126) (3C6 VL 2.1) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:141

40 LC-FR2 having the amino acid sequence of SEQ ID NO:144

LC-FR3 having the amino acid sequence of SEQ ID NO:146

LC-FR4 having the amino acid sequence of SEQ ID NO:149,

or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

(127) (3C6 VL 2.2) a VL region incorporating the following FRs:

- 5 LC-FR1 having the amino acid sequence of SEQ ID NO:141
LC-FR2 having the amino acid sequence of SEQ ID NO:145
LC-FR3 having the amino acid sequence of SEQ ID NO:147
LC-FR4 having the amino acid sequence of SEQ ID NO:149,
or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-
10 FR3, or LC-FR4 are substituted with another amino acid.

(128) (3C6 VL 2.3) a VL region incorporating the following FRs:

- LC-FR1 having the amino acid sequence of SEQ ID NO:142
LC-FR2 having the amino acid sequence of SEQ ID NO:145
15 LC-FR3 having the amino acid sequence of SEQ ID NO:148
LC-FR4 having the amino acid sequence of SEQ ID NO:149,
or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-
FR3, or LC-FR4 are substituted with another amino acid.

(129) (3C6 VL 2.4) a VL region incorporating the following FRs:

- 20 LC-FR1 having the amino acid sequence of SEQ ID NO:143
LC-FR2 having the amino acid sequence of SEQ ID NO:145
LC-FR3 having the amino acid sequence of SEQ ID NO:148
LC-FR4 having the amino acid sequence of SEQ ID NO:149,
25 or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-
FR3, or LC-FR4 are substituted with another amino acid.

In some embodiments the antigen-binding molecule comprises a VL region comprising the CDRs according to (118) or (119) above, and the FRs according to one of (120) to (129) above.

30 In some embodiments the antigen-binding molecule comprises a VL region according to one of (130) to (139) below:

(130) (3C6 VL 1) a VL region comprising the CDRs according to (118) and the FRs according to (120).

35 (131) (3C6 VL 2) a VL region comprising the CDRs according to (119) and the FRs according to (121).

(132) (3C6 VL 1.1) a VL region comprising the CDRs according to (118) and the FRs according to (122).

(133) (3C6 VL 1.2) a VL region comprising the CDRs according to (118) and the FRs according to (123).

40 (134) (3C6 VL 1.3) a VL region comprising the CDRs according to (118) and the FRs according to (124).

- (135) (3C6 VL 1.4) a VL region comprising the CDRs according to (118) and the FRs according to (125).
- (136) (3C6 VL 2.1) a VL region comprising the CDRs according to (119) and the FRs according to (126).
- 5 (137) (3C6 VL 2.2) a VL region comprising the CDRs according to (119) and the FRs according to (127).
- (138) (3C6 VL 2.3) a VL region comprising the CDRs according to (119) and the FRs according to (128).
- (139) (3C6 VL 2.4) a VL region comprising the CDRs according to (119) and the FRs according to (129).
- 10 In some embodiments the antigen-binding molecule comprises a VL region according to one of (140) to (141) below:
- (140) (3C6 VL 1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
15 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:93.
- (141) (3C6 VL 2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
20 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:94.
- (142) (3C6 VL 1.1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
25 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:125.
- (143) (3C6 VL 1.2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
30 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:126.
- (144) (3C6 VL 1.3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
35 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:127.
- (145) (3C6 VL 1.4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
40 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:128.
- (146) (3C6 VL 2.1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:121.

- (147) (3C6 VL 2.2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:122.
- 5 (148) (3C6 VL 2.3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:123.
- (149) (3C6 VL 2.4) a VL region comprising an amino acid sequence having at least 70% sequence identity
10 more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:124.
- In some embodiments the antigen-binding molecule comprises a VH region according to any one of (96) to (117) above, and a VL region according to any one of (118) to (149) above.
- 15 In some embodiments the antigen-binding molecule comprises a VH region according to (105) and a VL region according to (131). In some embodiments the antigen-binding molecule comprises a VH region according to (112) and a VL region according to (141).
- 20 In some embodiments the antigen-binding molecule comprises a VH region according to (107) and a VL region according to (137). In some embodiments the antigen-binding molecule comprises a VH region according to (107) and a VL region according to (136).
- In some embodiments the antigen-binding molecule comprises a VH region according to (114) and a VL region according to (147). In some embodiments the antigen-binding molecule comprises a VH region
25 according to (114) and a VL region according to (146).
- In some embodiments the antigen-binding molecule comprises a VH region according to (107) and a VL region according to (138). In some embodiments the antigen-binding molecule comprises a VH region
30 according to (114) and a VL region according to (148). In some embodiments the antigen-binding molecule comprises a VH region according to (107) and a VL region according to (139). In some embodiments the antigen-binding molecule comprises a VH region according to (114) and a VL region according to (149). In some embodiments the antigen-binding molecule comprises a VH region according to (108) and a VL region according to (137). In some embodiments the antigen-binding molecule comprises a VH region according to (115) and a VL region according to (147). In some embodiments the antigen-binding molecule comprises a
35 VH region according to (108) and a VL region according to (138). In some embodiments the antigen-binding molecule comprises a VH region according to (115) and a VL region according to (148).
- In some embodiments the antigen-binding molecule comprises a VH region according to one of (150) to (152) below:
- 40 (150) (1H2 VH) a VH region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:158

HC-CDR2 having the amino acid sequence of SEQ ID NO:159
HC-CDR3 having the amino acid sequence of SEQ ID NO:160,
or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2,
or HC-CDR3 are substituted with another amino acid.

5

(151) (7D4 VH) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:176

HC-CDR2 having the amino acid sequence of SEQ ID NO:177

HC-CDR3 having the amino acid sequence of SEQ ID NO:178,

10 or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

(152) (8H11 VH) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:194

15 HC-CDR2 having the amino acid sequence of SEQ ID NO:195

HC-CDR3 having the amino acid sequence of SEQ ID NO:196,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

20 In some embodiments the antigen-binding molecule comprises a VH region according to one of (153) to
(155) below:

(153) (1H2 VH) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:164

HC-FR2 having the amino acid sequence of SEQ ID NO:165

25 HC-FR3 having the amino acid sequence of SEQ ID NO:166

HC-FR4 having the amino acid sequence of SEQ ID NO:167,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2,
HC-FR3, or HC-FR4 are substituted with another amino acid.

30 (154) (7D4 VH) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:182

HC-FR2 having the amino acid sequence of SEQ ID NO:183

HC-FR3 having the amino acid sequence of SEQ ID NO:184

HC-FR4 having the amino acid sequence of SEQ ID NO:185,

35 or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2,
HC-FR3, or HC-FR4 are substituted with another amino acid.

(155) (8H11 VH) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:200

40 HC-FR2 having the amino acid sequence of SEQ ID NO:201

HC-FR3 having the amino acid sequence of SEQ ID NO:202

HC-FR4 having the amino acid sequence of SEQ ID NO:203,

or a variant thereof in which one or two or three amino acids in one or more of HC-FR1, HC-FR2, HC-FR3, or HC-FR4 are substituted with another amino acid.

5 In some embodiments the antigen-binding molecule comprises a VH region comprising the CDRs according to any one of (96) or (150) to (152) above, and the FRs according to any one of (97) to (103) or (153) to (155) above.

In some embodiments the antigen-binding molecule comprises a VH region according to one of (156) to (158) below:
10 (156) (1H2 VH) a VH region comprising the CDRs according to (150) and the FRs according to (153).

(157) (7D4 VH) a VH region comprising the CDRs according to (151) and the FRs according to (154).

(158) (8H11 VH) a VH region comprising the CDRs according to (152) and the FRs according to (155).
15

In some embodiments the antigen-binding molecule comprises a VH region according to one of (159) to (161) below:

(159) (1H2 VH) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
20 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:156.

(160) (7D4 VH) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
25 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:174.

(161) (8H11 VH) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:192.

30 In some embodiments the antigen-binding molecule comprises a VL region according to one of (162) to (164) below:

(162) (1H2 VL) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:161

LC-CDR2 having the amino acid sequence of SEQ ID NO:162

35 LC-CDR3 having the amino acid sequence of SEQ ID NO:163,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(163) (7D4 VL) a VL region incorporating the following CDRs:

40 LC-CDR1 having the amino acid sequence of SEQ ID NO:179

LC-CDR2 having the amino acid sequence of SEQ ID NO:180

LC-CDR3 having the amino acid sequence of SEQ ID NO:181,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(164) (8H11 VL) a VL region incorporating the following CDRs:

- 5 LC-CDR1 having the amino acid sequence of SEQ ID NO:197
LC-CDR2 having the amino acid sequence of SEQ ID NO:198
LC-CDR3 having the amino acid sequence of SEQ ID NO:199,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

10

In some embodiments the antigen-binding molecule comprises a VL region according to one of (165) to (167) below:

(165) (1H2 VL) a VL region incorporating the following FRs:

- 15 LC-FR1 having the amino acid sequence of SEQ ID NO:168
LC-FR2 having the amino acid sequence of SEQ ID NO:169
LC-FR3 having the amino acid sequence of SEQ ID NO:170
LC-FR4 having the amino acid sequence of SEQ ID NO:171,
or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

20

(166) (7D4 VL) a VL region incorporating the following FRs:

- LC-FR1 having the amino acid sequence of SEQ ID NO:186
LC-FR2 having the amino acid sequence of SEQ ID NO:187
LC-FR3 having the amino acid sequence of SEQ ID NO:188
25 LC-FR4 having the amino acid sequence of SEQ ID NO:189,
or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

(167) (8H11 VL) a VL region incorporating the following FRs:

- 30 LC-FR1 having the amino acid sequence of SEQ ID NO:204
LC-FR2 having the amino acid sequence of SEQ ID NO:205
LC-FR3 having the amino acid sequence of SEQ ID NO:206
LC-FR4 having the amino acid sequence of SEQ ID NO:207,
or a variant thereof in which one or two or three amino acids in one or more of LC-FR1, LC-FR2, LC-FR3, or LC-FR4 are substituted with another amino acid.

35

In some embodiments the antigen-binding molecule comprises a VL region comprising the CDRs according to any one of (118), (119) or (162) to (164) above, and the FRs according to any one of (120) to (129) or (165) to (167) above.

40

In some embodiments the antigen-binding molecule comprises a VL region according to one of (168) to (170) below:

(168) (1H2 VL) a VL region comprising the CDRs according to (162) and the FRs according to (165).

(169) (7D4 VL) a VL region comprising the CDRs according to (163) and the FRs according to (166).

5 (170) (8H11 VL) a VL region comprising the CDRs according to (164) and the FRs according to (167).

In some embodiments the antigen-binding molecule comprises a VL region according to one of (171) to (173) below:

10 (171) (1H2 VL) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:157.

(172) (7D4 VL) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:175.

(173) (8H11 VL) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:193.

20

In some embodiments the antigen-binding molecule comprises a VH region according to any one of (96) to (117) or (150) to (161), and a VL region according to any one of (118) to (149) or (162) to (173).

25 In some embodiments the antigen-binding molecule comprises a VH region according to (150) and a VL region according to (162).

In some embodiments the antigen-binding molecule comprises a VH region according to (159) and a VL region according to (171).

30 In some embodiments the antigen-binding molecule comprises a VH region according to (151) and a VL region according to (163).

In some embodiments the antigen-binding molecule comprises a VH region according to (160) and a VL region according to (172).

35

In some embodiments the antigen-binding molecule comprises a VH region according to (152) and a VL region according to (164).

40 In some embodiments the antigen-binding molecule comprises a VH region according to (161) and a VL region according to (173).

In some embodiments provided is an antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
- HC-CDR1 having the amino acid sequence of SEQ ID NO:158
- 5 HC-CDR2 having the amino acid sequence of SEQ ID NO:159
- HC-CDR3 having the amino acid sequence of SEQ ID NO:160; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:161
- LC-CDR2 having the amino acid sequence of SEQ ID NO:162
- 10 LC-CDR3 having the amino acid sequence of SEQ ID NO:163.

In some embodiments provided is an antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
- 15 HC-CDR1 having the amino acid sequence of SEQ ID NO:176
- HC-CDR2 having the amino acid sequence of SEQ ID NO:177
- HC-CDR3 having the amino acid sequence of SEQ ID NO:178; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:179
- 20 LC-CDR2 having the amino acid sequence of SEQ ID NO:180
- LC-CDR3 having the amino acid sequence of SEQ ID NO:181.

In some embodiments provided is an antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
- 25 HC-CDR1 having the amino acid sequence of SEQ ID NO:194
- HC-CDR2 having the amino acid sequence of SEQ ID NO:195
- HC-CDR3 having the amino acid sequence of SEQ ID NO:196; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- 30 LC-CDR1 having the amino acid sequence of SEQ ID NO:197
- LC-CDR2 having the amino acid sequence of SEQ ID NO:198
- LC-CDR3 having the amino acid sequence of SEQ ID NO:199.

35 In embodiments in accordance with the present invention in which one or more amino acids are substituted with another amino acid, the substitutions may conservative substitutions, for example according to the following Table. In some embodiments, amino acids in the same block in the middle column are substituted. In some embodiments, amino acids in the same line in the rightmost column are substituted:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar - uncharged	C S T M
		N Q
AROMATIC	Polar - charged	D E
		K R
		H F W Y

In some embodiments, substitution(s) may be functionally conservative. That is, in some embodiments the substitution may not affect (or may not substantially affect) one or more functional properties (e.g. target binding) of the antigen-binding molecule comprising the substitution as compared to the equivalent unsubstituted molecule.

In some embodiments substitution(s) relative to a reference VH or VL sequence may be focussed in a particular region or regions of the VH or VL sequence. For example, variation from a reference VH or VL sequence may be focussed in one or more of the framework regions (FR1, FR2, FR3 and/or FR4).

The VH and VL region of an antigen-binding region of an antibody together constitute the Fv region. In some embodiments, the antigen-binding molecule according to the present invention comprises, or consists of, an Fv region which binds to IL-11. In some embodiments the VH and VL regions of the Fv are provided as single polypeptide joined by a linker region, i.e. a single chain Fv (scFv).

In some embodiments the antigen-binding molecule of the present invention comprises one or more regions of an immunoglobulin heavy chain constant sequence. In some embodiments the immunoglobulin heavy chain constant sequence is, or is derived from, the heavy chain constant sequence of an IgG (e.g. IgG1, IgG2, IgG3, IgG4), IgA (e.g. IgA1, IgA2), IgD, IgE or IgM.

In some embodiments the immunoglobulin heavy chain constant sequence is human immunoglobulin G 1 constant (IGHG1; UniProt: P01857-1, v1; SEQ ID NO:85). Positions 1 to 98 of SEQ ID NO:85 form the CH1 region (SEQ ID NO:86). Positions 99 to 110 of SEQ ID NO:85 form a hinge region between CH1 and CH2 regions (SEQ ID NO:87). Positions 111 to 223 of SEQ ID NO:85 form the CH2 region (SEQ ID NO:88). Positions 224 to 330 of SEQ ID NO:85 form the CH3 region (SEQ ID NO:89).

In some embodiments a CH1 region comprises or consists of the sequence of SEQ ID NO:86, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:86. In some embodiments a CH1-CH2 hinge region comprises or consists of the sequence of SEQ ID NO:87, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:87. In some embodiments a CH2 region comprises or consists of the sequence of SEQ ID NO:88, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:88. In some embodiments a CH3 region comprises or consists of the sequence of SEQ ID NO:89 or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:89.

In some embodiments the immunoglobulin heavy chain constant sequence is human immunoglobulin G 4 constant (IGHG4; UniProt: P01861, v1; SEQ ID NO:211). Positions 1-98 of SEQ ID NO:211 form the CH1 region (SEQ ID NO:212). Positions 99-110 of SEQ ID NO:211 form a hinge region between CH1 and CH2

regions (SEQ ID NO:213). Positions 111-220 of SEQ ID NO:211 form the CH2 region (SEQ ID NO:214). Positions 221-327 of SEQ ID NO:211 form the CH3 region (SEQ ID NO:215).

In some embodiments a CH1 region comprises or consists of the sequence of SEQ ID NO:212, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:212. In some embodiments a CH1-CH2 hinge region comprises or consists of the sequence of SEQ ID NO:213, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:213. In some embodiments a CH2 region comprises or consists of the sequence of SEQ ID NO:214, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:214. In some embodiments a CH3 region comprises or consists of the sequence of SEQ ID NO:215 or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:215.

In some embodiments the immunoglobulin heavy chain constant sequence is human immunoglobulin G 4 constant (IGHG4; UniProt: P01861, v1) comprising amino acid substitutions which impart improved properties on the antigen-binding molecules of the invention. In some embodiments the immunoglobulin heavy chain constant sequence is human IgG4 comprising substitutions S241P and/or L248E. The S241P mutation is hinge stabilising while the L248E mutation further reduces the already low ADCC effector function of IgG4 (Davies and Sutton, Immunol Rev. 2015 Nov; 268(1):139–159; Angal et al *Mol Immunol*. 1993 Jan;30(1):105-8). The lower ADCC activity is advantageous for potential subcutaneous administration of the antibody.

In some embodiments the immunoglobulin heavy chain constant sequence is human immunoglobulin G 4 constant (IGHG4; UniProt: P01861, v1) comprising substitution S241P (numbered according to the Kabat system), as described in SEQ ID NO:216. Positions 1-98 of SEQ ID NO:216 form the CH1 region (SEQ ID NO:212). Positions 99-110 of SEQ ID NO:216 form a hinge region between CH1 and CH2 regions (SEQ ID NO:217) comprising the S241P substitution. Positions 111-220 of SEQ ID NO:216 form the CH2 region (SEQ ID NO:214). Positions 221-327 of SEQ ID NO:216 form the CH3 region (SEQ ID NO:215).

In some embodiments a CH1 region comprises or consists of the sequence of SEQ ID NO:212, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:212. In some embodiments a CH1-CH2 hinge region comprises or consists of the sequence of SEQ ID NO:217, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:217. In some embodiments a CH2 region comprises or consists of the sequence of SEQ ID NO:214, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:214. In some embodiments a CH3 region comprises or consists of the sequence of SEQ ID NO:215 or a

sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:215.

5 In some embodiments the immunoglobulin heavy chain constant sequence is human immunoglobulin G 4 constant (IGHG4; UniProt: P01861, v1) comprising substitutions S241P and L248E (numbered according to the Kabat system), as described in SEQ ID NO:218. Positions 1-98 of SEQ ID NO:218 form the CH1 region (SEQ ID NO:212). Positions 99-110 of SEQ ID NO:218 form a hinge region between CH1 and CH2 regions (SEQ ID NO:217) comprising the S241P substitution. Positions 111-220 of SEQ ID NO:218 form the CH2 region (SEQ ID NO:219), comprising the L248E substitution. Positions 221-327 of SEQ ID NO:218 form the
10 CH3 region (SEQ ID NO:215).

In some embodiments a CH1 region comprises or consists of the sequence of SEQ ID NO:212, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:212.
15 In some embodiments a CH1-CH2 hinge region comprises or consists of the sequence of SEQ ID NO:217, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:217. In some embodiments a CH2 region comprises or consists of the sequence of SEQ ID NO:219, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,
20 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:219. In some embodiments a CH3 region comprises or consists of the sequence of SEQ ID NO:215 or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:215.

25 In some embodiments the antigen-binding molecule of the present invention comprises one or more regions of an immunoglobulin light chain constant sequence. In some embodiments the immunoglobulin light chain constant sequence is human immunoglobulin kappa constant (IGKC; Cκ; UniProt: P01834-1, v2; SEQ ID NO:90). In some embodiments the immunoglobulin light chain constant sequence is a human immunoglobulin lambda constant (IGLC; Cλ), e.g. IGLC1, IGLC2, IGLC3, IGLC6 or IGLC7 (SEQ ID NO:231, 232, 233, 234 or 235). In some embodiments a CL region comprises or consists of the sequence of SEQ ID NO:90, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:90. In some embodiments a CL region comprises or consists of the sequence of SEQ ID NO:231, 232, 233, 234 or 235, or a sequence having at least 60%, preferably one of 70%, 75%, 80%, 85%, 90%,
30 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:231, 232, 233, 234 or 235.
35

The VL and light chain constant (CL) region, and the VH region and heavy chain constant 1 (CH1) region of an antigen-binding region of an antibody together constitute the Fab region. In some embodiments the
40 antigen-binding molecule comprises a Fab region comprising a VH, a CH1, a VL and a CL (e.g. Cκ or Cλ). In some embodiments the Fab region comprises a polypeptide comprising a VH and a CH1 (e.g. a VH-CH1 fusion polypeptide), and a polypeptide comprising a VL and a CL (e.g. a VL-CL fusion polypeptide). In some

embodiments the Fab region comprises a polypeptide comprising a VH and a CL (e.g. a VH-CL fusion polypeptide) and a polypeptide comprising a VL and a CH (e.g. a VL-CH1 fusion polypeptide); that is, in some embodiments the Fab region is a CrossFab region. In some embodiments the VH, CH1, VL and CL regions of the Fab or CrossFab are provided as single polypeptide joined by linker regions, i.e. as a single chain Fab (scFab) or a single chain CrossFab (scCrossFab).

In some embodiments, the antigen-binding molecule of the present invention comprises, or consists of, a Fab region which binds to IL-11.

In some embodiments, the antigen-binding molecule described herein comprises, or consists of, a whole antibody which binds to IL-11. As used herein, "whole antibody" refers to an antibody having a structure which is substantially similar to the structure of an immunoglobulin (Ig). Different kinds of immunoglobulins and their structures are described e.g. in Schroeder and Cavacini J Allergy Clin Immunol. (2010) 125(202): S41-S52, which is hereby incorporated by reference in its entirety.

Immunoglobulins of type G (i.e. IgG) are ~150 kDa glycoproteins comprising two heavy chains and two light chains. From N- to C-terminus, the heavy chains comprise a VH followed by a heavy chain constant region comprising three constant domains (CH1, CH2, and CH3), and similarly the light chain comprise a VL followed by a CL. Depending on the heavy chain, immunoglobulins may be classed as IgG (e.g. IgG1, IgG2, IgG3, IgG4), IgA (e.g. IgA1, IgA2), IgD, IgE, or IgM. The light chain may be kappa (κ) or lambda (λ).

In some embodiments, the antigen-binding molecule described herein comprises, or consists of, an IgG (e.g. IgG1, IgG2, IgG3, IgG4), IgA (e.g. IgA1, IgA2), IgD, IgE, or IgM which binds to IL-11.

In some embodiments, the antigen-binding molecule of the present invention is at least monovalent binding for IL-11. Binding valency refers to the number of binding sites in an antigen-binding molecule for a given antigenic determinant. Accordingly, in some embodiments the antigen-binding molecule comprises at least one binding site for IL-11.

In some embodiments the antigen-binding molecule comprises more than one binding site for IL-11, e.g. 2, 3 or 4 binding sites. The binding sites may be the same or different. In some embodiments the antigen-binding molecule is e.g. bivalent, trivalent or tetravalent for IL-11.

Aspects of the present invention relate to multispecific antigen-binding molecules. By "multispecific" it is meant that the antigen-binding molecule displays specific binding to more than one target. In some embodiments the antigen-binding molecule is a bispecific antigen-binding molecule. In some embodiments the antigen-binding molecule comprises at least two different antigen-binding domains (i.e. at least two antigen-binding domains, e.g. comprising non-identical VHs and VLs).

In some embodiments the antigen-binding molecule binds to IL-11 and another target (e.g. an antigen other than IL-11), and so is at least bispecific. The term "bispecific" means that the antigen-binding molecule is able to bind specifically to at least two distinct antigenic determinants.

It will be appreciated that an antigen-binding molecule according to the present invention (e.g. a multispecific antigen-binding molecule) may comprise antigen-binding molecules capable of binding to the targets for which the antigen-binding molecule is specific. For example, an antigen-binding molecule which is capable of binding to IL-11 and an antigen other than IL-11 may comprise: (i) an antigen-binding molecule which is capable of binding to IL-11, and (ii) an antigen-binding molecule which is capable of binding to an antigen other than IL-11.

It will also be appreciated that an antigen-binding molecule according to the present invention (e.g. a multispecific antigen-binding molecule) may comprise antigen-binding polypeptides or antigen-binding polypeptide complexes capable of binding to the targets for which the antigen-binding molecule is specific. For example, an antigen-binding molecule according to the invention may comprise e.g. (i) an antigen-binding polypeptide complex capable of binding to IL-11, comprising a light chain polypeptide (comprising the structure VL-CL) and a heavy chain polypeptide (comprising the structure VH-CH1-CH2-CH3), and (ii) an antigen-binding polypeptide complex capable of binding to an antigen other than IL-11, comprising a light chain polypeptide (comprising the structure VL-CL) and a heavy chain polypeptide (comprising the structure VH-CH1-CH2-CH3).

In some embodiments, a component antigen-binding molecule of a larger antigen-binding molecule (e.g. a multispecific antigen-binding molecule) may be referred to e.g. as an "antigen-binding domain" or "antigen-binding region" of the larger antigen-binding molecule.

In some embodiments the antigen-binding molecule comprises an antigen-binding molecule capable of binding to IL-11, and an antigen-binding molecule capable of binding to an antigen other than IL-11. In some embodiments, the antigen other than IL-11 is an immune cell surface molecule. In some embodiments, the antigen other than IL-11 is a cancer cell antigen. In some embodiments the antigen other than IL-11 is a receptor molecule, e.g. a cell surface receptor. In some embodiments the antigen other than IL-11 is a cell signalling molecule, e.g. a cytokine, chemokine, interferon, interleukin or lymphokine. In some embodiments the antigen other than IL-11 is a growth factor or a hormone.

A cancer cell antigen is an antigen which is expressed or over-expressed by a cancer cell. A cancer cell antigen may be any peptide/polypeptide, glycoprotein, lipoprotein, glycan, glycolipid, lipid, or fragment thereof. A cancer cell antigen's expression may be associated with a cancer. A cancer cell antigen may be abnormally expressed by a cancer cell (e.g. the cancer cell antigen may be expressed with abnormal localisation), or may be expressed with an abnormal structure by a cancer cell. A cancer cell antigen may be capable of eliciting an immune response. In some embodiments, the antigen is expressed at the cell surface of the cancer cell (i.e. the cancer cell antigen is a cancer cell surface antigen). In some embodiments, the part of the antigen which is bound by the antigen-binding molecule described herein is displayed on the external surface of the cancer cell (i.e. is extracellular). The cancer cell antigen may be a cancer-associated antigen. In some embodiments the cancer cell antigen is an antigen whose expression is associated with the development, progression or severity of symptoms of a cancer. The cancer-associated antigen may be associated with the cause or pathology of the cancer, or may be expressed abnormally as a consequence of

the cancer. In some embodiments, the cancer cell antigen is an antigen whose expression is upregulated (e.g. at the RNA and/or protein level) by cells of a cancer, e.g. as compared to the level of expression of by comparable non-cancerous cells (e.g. non-cancerous cells derived from the same tissue/cell type). In some embodiments, the cancer-associated antigen may be preferentially expressed by cancerous cells, and not expressed by comparable non-cancerous cells (e.g. non-cancerous cells derived from the same tissue/cell type). In some embodiments, the cancer-associated antigen may be the product of a mutated oncogene or mutated tumor suppressor gene. In some embodiments, the cancer-associated antigen may be the product of an overexpressed cellular protein, a cancer antigen produced by an oncogenic virus, an oncofetal antigen, or a cell surface glycolipid or glycoprotein.

An immune cell surface molecule may be any peptide/polypeptide, glycoprotein, lipoprotein, glycan, glycolipid, lipid, or fragment thereof expressed at or on the cell surface of an immune cell. In some embodiments, the part of the immune cell surface molecule which is bound by the antigen-binding molecule of the present invention is on the external surface of the immune cell (i.e. is extracellular). The immune cell surface molecule may be expressed at the cell surface of any immune cell. In some embodiments, the immune cell may be a cell of hematopoietic origin, e.g. a neutrophil, eosinophil, basophil, dendritic cell, lymphocyte, or monocyte. The lymphocyte may be e.g. a T cell, B cell, natural killer (NK) cell, NKT cell or innate lymphoid cell (ILC), or a precursor thereof (e.g. a thymocyte or pre-B cell). In some embodiments the immune cell surface molecule may be a costimulatory molecule (e.g. CD28, OX40, 4-1BB, ICOS or CD27) or a ligand thereof. In some embodiments the immune cell surface molecule may be a checkpoint inhibitor (e.g. PD-1, CTLA-4, LAG-3, TIM-3, TIGIT or BTLA) or a ligand thereof.

Multispecific antigen-binding molecules according to the invention may be provided in any suitable format, such as those formats described in Brinkmann and Kontermann MAb (2017) 9(2): 182-212, which is hereby incorporated by reference in its entirety. Suitable formats include those shown in Figure 2 of Brinkmann and Kontermann MAb (2017) 9(2): 182-212: antibody conjugates, e.g. IgG₂, F(ab')₂ or CovX-Body; IgG or IgG-like molecules, e.g. IgG, chimeric IgG, $\kappa\lambda$ -body common HC; CH1/CL fusion proteins, e.g. scFv2-CH1/CL, VHH2-CH1/CL; 'variable domain only' bispecific antigen-binding molecules, e.g. tandem scFv (taFv), triplebodies, diabodies (Db), dsDb, Db(kih), DART, scDB, dsFv-dsFv, tandAbs, triple heads, tandem dAb/VHH, tertravalent dAb.VHH; Non-Ig fusion proteins, e.g. scFv₂-albumin, scDb-albumin, taFv-albumin, taFv-toxin, miniantibody, DNL-Fab₂, DNL-Fab₂-scFv, DNL-Fab₂-IgG-cytokine₂, ImmTAC (TCR-scFv); modified Fc and CH3 fusion proteins, e.g. scFv-Fc(kih), scFv-Fc(CH3 charge pairs), scFv-Fc (EW-RVT), scFv-fc (HA-TF), scFv-Fc (SEEDbody), taFv-Fc(kih), scFv-Fc(kih)-Fv, Fab-Fc(kih)-scFv, Fab-scFv-Fc(kih), Fab-scFv-Fc(BEAT), Fab-scFv-Fc (SEEDbody), DART-Fc, scFv-CH3(kih), TriFabs; Fc fusions, e.g. Di-diabody, scDb-Fc, taFv-Fc, scFv-Fc-scFv, HCAB-VHH, Fab-scFv-Fc, scFv₄-Ig, scFv₂-Fcab; CH3 fusions, e.g. Dia-diabody, scDb-CH3; IgE/IgM CH2 fusions, e.g. scFv-EHD2-scFv, scFvMHD2-scFv; Fab fusion proteins, e.g. Fab-scFv (bibody), Fab-scFv₂ (tribody), Fab-Fv, Fab-dsFv, Fab-VHH, orthogonal Fab-Fab; non-Ig fusion proteins, e.g. DNL-Fab₃, DNL-Fab₂-scFv, DNL-Fab₂-IgG-cytokine₂; asymmetric IgG or IgG-like molecules, e.g. IgG(kih), IgG(kih) common LC, ZW1 IgG common LC, Biclonics common LC, CrossMab, CrossMab(kih), scFab-IgG(kih), Fab-scFab-IgG(kih), orthogonal Fab IgG(kih), DuetMab, CH3 charge pairs + CH1/CL charge pairs, hinge/CH3 charge pairs, SEED-body, Duobody, four-in-one-CrossMab(kih), LUZ-Y common LC; LUZ-Y scFab-IgG, FcFc*; appended and Fc-modified IgGs, e.g. IgG(kih)-Fv, IgG HA-TF-Fv,

IgG(kih)scFab, scFab-Fc(kih)-scFv2, scFab-Fc(kih)-scFv, half DVD-Ig, DVI-Ig (four-in-one), CrossMab-Fab; modified Fc and CH3 fusion proteins, e.g. Fab-Fc(kih)-scFv, Fab-scFv-Fc(kih), Fab-scFv-Fc(BEAT), Fab-scFv-Fc-SEEDbody, TriFab; appended IgGs - HC fusions, e.g. IgG-HC, scFv, IgG-dAb, IgG-taFv, IgG-CrossFab, IgG-orthogonal Fab, IgG-(CαCβ) Fab, scFv-HC-IgG, tandem Fab-IgG (orthogonal Fab) Fab-IgG(CαCβ Fab), Fab-IgG(CR3), Fab-hinge-IgG(CR3); appended IgGs - LC fusions, e.g. IgG-scFv(LC), scFv(LC)-IgG, dAb-IgG; appended IgGs - HC and LC fusions, e.g. DVD-Ig, TVD-Ig, CODV-Ig, scFv4-IgG, Zybody; Fc fusions, e.g. Fab-scFv-Fc, scFv4-Ig; F(ab')₂ fusions, e.g. F(ab')₂-scFv₂; CH1/CL fusion proteins e.g. scFv₂-CH1-hinge/CL; modified IgGs, e.g. DAF (two-in one-IgG), DutaMab, Mab²; and non-Ig fusions, e.g. DNL-Fab₄-IgG.

The skilled person is able to design and prepare bispecific antigen-binding molecules. Methods for producing bispecific antigen-binding molecules include chemically crosslinking of antigen-binding molecules or antibody fragments, e.g. with reducible disulphide or non-reducible thioether bonds, for example as described in Segal and Bast, 2001. Production of Bispecific Antigen-binding molecules. Current Protocols in Immunology.

14:IV:2.13:2.13.1–2.13.16, which is hereby incorporated by reference in its entirety. For example, *N*-succinimidyl-3-(2-pyridylthio)-propionate (SPDP) can be used to chemically crosslink e.g. Fab fragments via hinge region SH- groups, to create disulfide-linked bispecific F(ab)₂ heterodimers.

Other methods for producing bispecific antigen-binding molecules include fusing antibody-producing hybridomas e.g. with polyethylene glycol, to produce a quadroma cell capable of secreting bispecific antibody, for example as described in D. M. and Bast, B. J. 2001. Production of Bispecific Antigen-binding molecules. Current Protocols in Immunology. 14:IV:2.13:2.13.1–2.13.16.

Bispecific antigen-binding molecules according to the present invention can also be produced recombinantly, by expression from e.g. a nucleic acid construct encoding polypeptides for the antigen-binding molecules, for example as described in Antibody Engineering: Methods and Protocols, Second Edition (Humana Press, 2012), at Chapter 40: Production of Bispecific Antigen-binding molecules: Diabodies and Tandem scFv (Hornig and Färber-Schwarz), or French, How to make bispecific antigen-binding molecules, Methods Mol. Med. 2000; 40:333-339, the entire contents of both of which are hereby incorporated by reference. For example, a DNA construct encoding the light and heavy chain variable domains for the two antigen-binding fragments (i.e. the light and heavy chain variable domains for the antigen-binding fragment capable of binding IL-11, and the light and heavy chain variable domains for the antigen-binding fragment capable of binding to another target protein), and including sequences encoding a suitable linker or dimerization domain between the antigen-binding fragments can be prepared by molecular cloning techniques. Recombinant bispecific antibody can thereafter be produced by expression (e.g. *in vitro*) of the construct in a suitable host cell (e.g. a mammalian host cell), and expressed recombinant bispecific antibody can then optionally be purified.

In some embodiments the antigen-binding molecules of the present invention comprise an Fc region. An Fc region is composed of CH2 and CH3 regions from one polypeptide, and CH2 and CH3 regions from another polypeptide. The CH2 and CH3 regions from the two polypeptides together form the Fc region.

In some embodiments, the antigen-binding molecule of the present invention comprises an Fc region comprising modification in one or more of the CH2 and CH3 regions promoting association of the Fc region. Recombinant co-expression of constituent polypeptides of an antigen-binding molecule and subsequent association leads to several possible combinations. To improve the yield of the desired combinations of polypeptides in antigen-binding molecules in recombinant production, it is advantageous to introduce in the Fc regions modification(s) promoting association of the desired combination of heavy chain polypeptides. Modifications may promote e.g. hydrophobic and/or electrostatic interaction between CH2 and/or CH3 regions of different polypeptide chains. Suitable modifications are described e.g. in Ha et al., Front. Immunol (2016) 7:394, which is hereby incorporated by reference in its entirety. In some embodiments the antigen-binding molecule of the present invention comprises an Fc region comprising paired substitutions in the CH3 regions of the Fc region according to one of the following formats, as shown in Table 1 of Ha et al., Front. Immunol (2016) 7:394: KiH, KiH_{s-s}, HA-TF, ZW1, 7.8.60, DD-KK, EW-RVT, EW-RVT_{s-s}, SEED or A107.

Polypeptides

The present invention also provides polypeptide constituents of antigen-binding molecules. The polypeptides may be provided in isolated or substantially purified form.

The antigen-binding molecule of the present invention may be, or may comprise, a complex of polypeptides.

In the present specification where a polypeptide comprises more than one domain or region, it will be appreciated that the plural domains/regions are preferably present in the same polypeptide chain. That is, the polypeptide comprises more than one domain or region is a fusion polypeptide comprising the domains/regions.

In some embodiments a polypeptide according to the present invention comprises, or consists of, a VH as described herein. In some embodiments a polypeptide according to the present invention comprises, or consists of, a VL as described herein.

In some embodiments, the polypeptide additionally comprises one or more antibody heavy chain constant regions (CH). In some embodiments, the polypeptide additionally comprises one or more antibody light chain constant regions (CL). In some embodiments, the polypeptide comprises a CH1, CH2 region and/or a CH3 region of an immunoglobulin (Ig).

In some embodiments the polypeptide comprises one or more regions of an immunoglobulin heavy chain constant sequence. In some embodiments the polypeptide comprises a CH1 region as described herein. In some embodiments the polypeptide comprises a CH1-CH2 hinge region as described herein. In some embodiments the polypeptide comprises a CH2 region as described herein. In some embodiments the polypeptide comprises a CH3 region as described herein.

In some embodiments the polypeptide comprises a CH3 region comprising any one of the amino acid substitutions/combinations of amino acid substitutions shown in Table 1 of Ha et al., Front. Immunol (2016) 7:394, incorporated by reference hereinabove.

In some embodiments the CH2 and/or CH3 regions of the polypeptide comprise one or more amino acid substitutions for promoting association of the polypeptide with another polypeptide comprising a CH2 and/or CH3 region.

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In some embodiments the polypeptide comprises one or more regions of an immunoglobulin light chain constant sequence. In some embodiments the polypeptide comprises a CL region as described herein.

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In some embodiments, the polypeptide according to the present invention comprises a structure from N- to C-terminus according to one of the following:

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- (i) VH
- (ii) VL
- (iii) VH-CH1
- (iv) VL-CL
- (v) VL-CH1
- (vi) VH-CL
- (vii) VH-CH1-CH2-CH3
- (viii) VL-CL-CH2-CH3
- (ix) VL-CH1-CH2-CH3
- (x) VH-CL-CH2-CH3

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Also provided by the present invention are antigen-binding molecules composed of the polypeptides of the present invention. In some embodiments, the antigen-binding molecule of the present invention comprises one of the following combinations of polypeptides:

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- (A) VH + VL
- (B) VH-CH1 + VL-CL
- (C) VL-CH1 + VH-CL
- (D) VH-CH1-CH2-CH3 + VL-CL
- (E) VH-CL-CH2-CH3 + VL-CH1
- (F) VL-CH1-CH2-CH3 + VH-CL
- (G) VL-CL-CH2-CH3 + VH-CH1
- (H) VH-CH1-CH2-CH3 + VL-CL-CH2-CH3
- (I) VH-CL-CH2-CH3 + VL-CH1-CH2-CH3

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In some embodiments the antigen-binding molecule comprises more than one of a polypeptide of the combinations shown in (A) to (I) above. By way of example, with reference to (D) above, in some embodiments the antigen-binding molecule comprises two polypeptides comprising the structure VH-CH1-CH2-CH3, and two polypeptides comprising the structure VL-CL.

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In some embodiments, the antigen-binding molecule of the present invention comprises one of the following combinations of polypeptides:

- (J) VH (anti-IL-11) + VL (anti-IL-11)
- 5 (K) VH (anti-IL-11)-CH1 + VL (anti-IL-11)-CL
- (L) VL (anti-IL-11)-CH1 + VH (anti-IL-11)-CL
- (M) VH (anti-IL-11)-CH1-CH2-CH3 + VL (anti-IL-11)-CL
- (N) VH (anti-IL-11)-CL-CH2-CH3 + VL (anti-IL-11)-CH1
- (O) VL (anti-IL-11)-CH1-CH2-CH3 + VH (anti-IL-11)-CL
- 10 (P) VL (anti-IL-11)-CL-CH2-CH3 + VH (anti-IL-11)-CH1
- (Q) VH (anti-IL-11)-CH1-CH2-CH3 + VL (anti-IL-11)-CL-CH2-CH3
- (R) VH (anti-IL-11)-CL-CH2-CH3 + VL (anti-IL-11)-CH1-CH2-CH3

15 Wherein: "VH (anti-IL-11)" refers to the VH of an antigen-binding molecule capable of binding to IL-11 as described herein, e.g. as defined in any one of (1) to (11), (96) to (117) or (150) to (161); "VL (anti-IL-11)" refers to the VL of an antigen-binding molecule capable of binding to IL-11 as described herein, e.g. as defined in any one of (12) to (95), (118) to (149) or (162) to (173).

20 In some embodiments the polypeptide comprises or consists of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of one of SEQ ID NOs:6 to 35, 82 to 84, 91 to 94, 116 to 128, 156, 157, 174, 175, 192, 193 or 210.

In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:220. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:221. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:222. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:223. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:224. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:236. In

some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:237. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:238. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:239. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:240.

In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:225. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:226. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:227. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:228. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:229. In some embodiments the antigen-binding molecule of the present invention comprises a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of SEQ ID NO:230.

Linkers and additional sequences

In some embodiments the antigen-binding molecules and polypeptides of the present invention comprise one or more linker sequences between amino acid sequences. A linker sequence may be provided at one or both ends of one or more of a VH, VL, CH1-CH2 hinge region, CH2 region and a CH3 region of the antigen-binding molecule/polypeptide.

Linker sequences are known to the skilled person, and are described, for example in Chen et al., Adv Drug Deliv Rev (2013) 65(10): 1357-1369, which is hereby incorporated by reference in its entirety. In some embodiments, a linker sequence may be a flexible linker sequence. Flexible linker sequences allow for relative movement of the amino acid sequences which are linked by the linker sequence. Flexible linkers are known to the skilled person, and several are identified in Chen et al., Adv Drug Deliv Rev (2013) 65(10): 1357-1369. Flexible linker sequences often comprise high proportions of glycine and/or serine residues.

In some embodiments, the linker sequence comprises at least one glycine residue and/or at least one serine residue. In some embodiments the linker sequence consists of glycine and serine residues. In some embodiments, the linker sequence has a length of 1-2, 1-3, 1-4, 1-5 or 1-10 amino acids.

The antigen-binding molecules and polypeptides of the present invention may additionally comprise further amino acids or sequences of amino acids. For example, the antigen-binding molecules and polypeptides may comprise amino acid sequence(s) to facilitate expression, folding, trafficking, processing, purification or detection of the antigen-binding molecule/polypeptide. For example, the antigen-binding molecule/polypeptide may comprise a sequence encoding a His, (e.g. 6XHis), Myc, GST, MBP, FLAG, HA, E, or Biotin tag, optionally at the N- or C- terminus of the antigen-binding molecule/polypeptide. In some embodiments the antigen-binding molecule/polypeptide comprises a detectable moiety, e.g. a fluorescent, luminescent, immuno-detectable, radio, chemical, nucleic acid or enzymatic label.

The antigen-binding molecules and polypeptides of the present invention may additionally comprise a signal peptide (also known as a leader sequence or signal sequence). Signal peptides normally consist of a sequence of 5-30 hydrophobic amino acids, which form a single alpha helix. Secreted proteins and proteins expressed at the cell surface often comprise signal peptides.

The signal peptide may be present at the N-terminus of the antigen-binding molecule/polypeptide, and may be present in the newly synthesised antigen-binding molecule/polypeptide. The signal peptide provides for efficient trafficking and secretion of the antigen-binding molecule/polypeptide. Signal peptides are often removed by cleavage, and thus are not comprised in the mature antigen-binding molecule/polypeptide secreted from the cell expressing the antigen-binding molecule/polypeptide.

Signal peptides are known for many proteins, and are recorded in databases such as GenBank, UniProt, Swiss-Prot, TrEMBL, Protein Information Resource, Protein Data Bank, Ensembl, and InterPro, and/or can be identified/predicted e.g. using amino acid sequence analysis tools such as SignalP (Petersen et al., 2011 Nature Methods 8: 785-786) or Signal-BLAST (Frank and Sippl, 2008 Bioinformatics 24: 2172-2176).

Labels and conjugates

In some embodiments the antigen-binding molecules of the present invention additionally comprise a detectable moiety or a chemical moiety.

In some embodiments the antigen-binding molecule comprises a detectable moiety, e.g. a fluorescent label, phosphorescent label, luminescent label, immuno-detectable label (e.g. an epitope tag), radiolabel, chemical,

nucleic acid or enzymatic label. The antigen-binding molecule may be covalently or non-covalently labelled with the detectable moiety.

Fluorescent labels include e.g. fluorescein, rhodamine, allophycocyanin, eosine and NDB, green fluorescent protein (GFP) chelates of rare earths such as europium (Eu), terbium (Tb) and samarium (Sm), tetramethyl rhodamine, Texas Red, 4-methyl umbelliferone, 7-amino-4-methyl coumarin, Cy3, and Cy5. Radiolabels include radioisotopes such as Iodine¹²³, Iodine¹²⁵, Iodine¹²⁶, Iodine¹³¹, Iodine¹³³, Bromine⁷⁷, Technetium^{99m}, Indium¹¹¹, Indium^{113m}, Gallium⁶⁷, Gallium⁶⁸, Ruthenium⁹⁵, Ruthenium⁹⁷, Ruthenium¹⁰³, Ruthenium¹⁰⁵, Mercury²⁰⁷, Mercury²⁰³, Rhenium^{99m}, Rhenium¹⁰¹, Rhenium¹⁰⁵, Scandium⁴⁷, Tellurium^{121m}, Tellurium^{122m}, Tellurium^{125m}, Thulium¹⁶⁵, Thulium¹⁶⁷, Thulium¹⁶⁸, Copper⁶⁷, Fluorine¹⁸, Yttrium⁹⁰, Palladium¹⁰⁰, Bismuth²¹⁷ and Antimony²¹¹. Luminescent labels include as radioluminescent, chemiluminescent (e.g. acridinium ester, luminol, isoluminol) and bioluminescent labels. Immuno-detectable labels include haptens, peptides/polypeptides, antibodies, receptors and ligands such as biotin, avidin, streptavidin or digoxigenin. Nucleic acid labels include aptamers. Enzymatic labels include e.g. peroxidase, alkaline phosphatase, glucose oxidase, beta-galactosidase and luciferase.

In some embodiments the antigen-binding molecules of the present invention are conjugated to a chemical moiety. The chemical moiety may be a moiety for providing a therapeutic effect. Antibody-drug conjugates are reviewed e.g. in Parslow et al., *Biomedicines*. 2016 Sep; 4(3):14. In some embodiments, the chemical moiety may be a drug moiety (e.g. a cytotoxic agent). In some embodiments, the drug moiety may be a chemotherapeutic agent. In some embodiments, the drug moiety is selected from calicheamicin, DM1, DM4, monomethylauristatin E (MMAE), monomethylauristatin F (MMAF), SN-38, doxorubicin, duocarmycin, D6.5 and PBD.

Functional properties of the antigen-binding molecules

The antigen-binding molecules described herein may be characterised by reference to certain functional properties. In some embodiments, the antigen-binding molecule described herein may possess one or more of the following properties:

- a) Specific binding to IL-11 (e.g. human IL-11 and/or mouse IL-11);
- b) Binding to IL-11 (e.g. human IL-11) with an affinity of binding of EC₅₀ = less than 1000 ng/ml, e.g. as determined by ELISA;
- c) Inhibition of interaction between IL-11 and IL-11R α ;
- d) Inhibition of interaction between IL-11 and gp130;
- e) Inhibition of interaction between IL-11 and IL-11R α :gp130 receptor complex;
- f) Inhibition of interaction between IL-11:IL-11R α complex and gp130;
- g) Inhibition of interaction between IL-11 and IL-11;
- h) Inhibition of signalling mediated by IL-11;
- i) Inhibition of signalling mediated by binding of IL-11 to IL-11R α :gp130 receptor complex;
- j) Inhibition of signalling mediated by binding of IL-11:IL-11R α complex to gp130 (i.e. IL-11 *trans* signalling);
- k) Inhibition of fibroblast proliferation;
- l) Inhibition of myofibroblast generation from fibroblasts;

- m) Reversal/regression of myofibroblast generation from fibroblasts;
- n) Inhibition of myofibroblast generation from stellate cells, e.g. hepatic or pancreatic stellate cells;
- o) Reversal/regression of myofibroblast generation from stellate cells, e.g. hepatic or pancreatic stellate cells;
- 5 p) Inhibition of migratory and/or invasive behaviour (i.e. inhibition of migration and/or invasion) of fibroblasts, stellate cells or myofibroblasts;
- q) Inhibition of the presence of immune cells in an organ;
- r) Inhibition of a pathological process mediated by IL-11;
- s) Inhibition of fibrosis;
- 10 t) Reversal/regression of fibrosis;
- u) Inhibition of gene or protein expression in fibroblasts or stellate cells of one or more of collagen, fibronectin, periostin, IL-6, IL-11, α SMA (ACTA2), TIMP1, MMP2, TNF α , CCL2 e.g. following stimulation with a profibrotic factor;
- v) Inhibition of extracellular matrix production by fibroblasts or stellate cells;
- 15 w) Inhibition of proliferation and/or survival of cells of a cancer;
- x) Inhibition of development and/or progression of cancer *in vivo*;
- y) Inhibition of tumour growth;
- z) Killing of cells expressing/comprising IL-11 or a complex comprising IL-11.

20 Herein, 'inhibition' refers to a reduction, decrease or lessening relative to a control condition. For example, inhibition of a process by an antigen-binding molecule refers to a reduction, decrease or lessening of the extent/degree of that process in the absence of the antigen-binding molecule, and/or in the presence of an appropriate control antigen-binding molecule.

25 Inhibition may herein also be referred to as neutralisation or antagonism. That is, an IL-11 binding antigen-binding molecule which is capable of inhibiting a function or process (e.g. interaction, signalling or other activity mediated by IL-11 or a complex comprising IL-11) may be said to be a 'neutralising' or 'antagonist' antigen-binding molecule with respect to the relevant function or process. For example, antigen-binding molecule which is capable of inhibiting IL-11 mediated signalling may be referred to as an antigen-binding
30 molecule which is capable of neutralising IL-11 mediated signalling, or may be referred to as an antagonist of IL-11 mediated signalling.

The skilled person is able to identify an appropriate control condition for a given assay. For example, a control antigen-binding molecule may be an antigen-binding molecule directed against a target protein which
35 is known not to have a role involved in the property being investigated in the assay. A control antigen-binding molecule may be of the same isotype as the anti-IL-11 antigen-binding molecule being analysed, and may e.g. have the same constant regions.

The antigen-binding molecules described herein preferably display specific binding to IL-11. As used herein,
40 "specific binding" refers to binding which is selective for the antigen, and which can be discriminated from non-specific binding to non-target antigen. An antigen-binding molecule that specifically binds to a target molecule preferably binds the target with greater affinity, and/or with greater duration than it binds to other,

non-target molecules. In some embodiments the present antigen-binding molecules may bind with greater affinity to IL-11 than to one or more members of the IL-6 cytokine family. In some embodiments the present antigen-binding molecules may bind with greater affinity to IL-11 than to one or more of IL-6, leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CNTF), and cardiotrophin-like cytokine (CLC).

In embodiments, inhibition of IL-11-mediated signalling is achieved by disrupting IL-11-mediated *cis* signalling but not disrupting IL-11-mediated *trans* signalling, e.g. inhibition of IL-11-mediated signalling is achieved by inhibiting gp130-mediated *cis* complexes involving membrane bound IL-11R α . In embodiments, inhibition of IL-11-mediated signalling is achieved by disrupting IL-11-mediated *trans* signalling but not disrupting IL-11-mediated *cis* signalling, i.e. inhibition of IL-11-mediated signalling is achieved by inhibiting gp130-mediated *trans* signalling complexes such as IL-11 bound to soluble IL-11R α or IL-6 bound to soluble IL-6R. In embodiments, inhibition of IL-11-mediated signalling is achieved by disrupting IL-11-mediated *cis* signalling and IL-11-mediated *trans* signalling.

The ability of a given polypeptide to bind specifically to a given molecule can be determined by analysis according to methods known in the art, such as by ELISA, Surface Plasmon Resonance (SPR; see e.g. Hearty et al., Methods Mol Biol (2012) 907:411-442), Bio-Layer Interferometry (see e.g. Lad et al., (2015) J Biomol Screen 20(4): 498-507), flow cytometry, or by a radiolabeled antigen-binding assay (RIA) enzyme-linked immunosorbent assay. Through such analysis binding to a given molecule can be measured and quantified. In some embodiments, the binding may be the response detected in a given assay.

In some embodiments, the extent of binding of the antigen-binding molecule to a non-target molecule is less than about 10% of the binding of the antibody to the target molecule as measured, e.g. by ELISA, SPR, Bio-Layer Interferometry or by RIA. Alternatively, binding specificity may be reflected in terms of binding affinity where the antigen-binding molecule binds to IL-11 with a dissociation constant (K_D) that is at least 0.1 order of magnitude (i.e. 0.1×10^n , where n is an integer representing the order of magnitude) greater than the K_D of the antigen-binding molecule towards a non-target molecule. This may optionally be one of at least 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, or 2.0.

In some embodiments, the antigen-binding molecule displays binding to human IL-11. In some embodiments, the antigen-binding molecule displays binding to mouse IL-11. In some embodiments, the antigen-binding molecule displays binding to human IL-11 and mouse IL-11. That is, in some embodiments the antigen-binding molecule is cross-reactive for human IL-11 and mouse IL-11. In some embodiments the antigen-binding molecule of the present invention displays cross-reactivity with IL-11 of a non-human primate.

In some embodiments, the antigen-binding molecule according to the present invention binds to IL-11 with a K_D of 5 μ M or less, preferably one of ≤ 1 μ M, ≤ 500 nM, ≤ 100 nM, ≤ 75 nM, ≤ 50 nM, ≤ 40 nM, ≤ 30 nM, ≤ 20 nM, ≤ 15 nM, ≤ 12.5 nM, ≤ 10 nM, ≤ 9 nM, ≤ 8 nM, ≤ 7 nM, ≤ 6 nM, ≤ 5 nM, ≤ 4 nM ≤ 3 nM, ≤ 2 nM, ≤ 1 nM, ≤ 500 pM.

In some embodiments, the antigen-binding molecule according to the present invention binds to IL-11 with an affinity of binding (e.g. as determined by ELISA) of $EC_{50} = 1000$ ng/ml or less, preferably one of ≤ 900 ng/ml, ≤ 800 ng/ml, ≤ 700 ng/ml, ≤ 600 ng/ml, ≤ 500 ng/ml, ≤ 400 ng/ml, ≤ 300 ng/ml, ≤ 200 ng/ml, ≤ 100 ng/ml, ≤ 90 ng/ml, ≤ 80 ng/ml, ≤ 70 ng/ml, ≤ 60 ng/ml, ≤ 50 ng/ml, ≤ 40 ng/ml, ≤ 30 ng/ml, ≤ 20 ng/ml, ≤ 15 ng/ml, ≤ 10 ng/ml, ≤ 7.5 ng/ml, ≤ 5 ng/ml, ≤ 2.5 ng/ml, or ≤ 1 ng/ml.

Affinity of binding to IL-11 by an antigen-binding molecule may be analysed *in vitro* by ELISA assay. Suitable assays are well known in the art and can be performed by the skilled person, for example, as described in Antibody Engineering, vol. 1 (2nd Edn), Springer Protocols, Springer (2010), Part V, pp657-665. For example, the affinity of binding to IL-11 by an antigen-binding molecule may be analysed according to the methodology described herein in the experimental examples.

The ability of an antigen-binding molecule to inhibit interaction between two proteins can be determined for example by analysis of interaction in the presence of, or following incubation of one or both of the interaction partners with, the antigen-binding molecule. An example of a suitable assay to determine whether a given antigen-binding molecule is capable of inhibiting interaction between two interaction partners is a competition ELISA assay.

An antigen-binding molecule which is capable of inhibiting a given interaction (e.g. between IL-11 and IL-11R α , or between IL-11 and gp130, or between IL-11 and IL-11R α :gp130, or between IL-11:IL-11R α and gp130) is identified by the observation of a reduction/decrease in the level of interaction between the interaction partners in the presence of – or following incubation of one or both of the interaction partners with – the antigen-binding molecule, as compared to the level of interaction in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). Suitable analysis can be performed *in vitro*, e.g. using recombinant interaction partners or using cells expressing the interaction partners. Cells expressing interaction partners may do so endogenously, or may do so from nucleic acid introduced into the cell. For the purposes of such assays, one or both of the interaction partners and/or the antigen-binding molecule may be labelled or used in conjunction with a detectable entity for the purposes of detecting and/or measuring the level of interaction.

Ability of an antigen-binding molecule to inhibit interaction between two binding partners can also be determined by analysis of the downstream functional consequences of such interaction, e.g. receptor signalling. For example, downstream functional consequences of interaction between IL-11 and IL-11R α :gp130 or between IL-11:IL-11R α and gp130 may include proliferation of fibroblasts, myofibroblast generation from fibroblasts, or gene or protein expression of one or more of collagen, fibronectin, periostin, IL-6, IL-11, α SMA, TIMP1, MMP2.

Fibroblasts according to the present disclosure may be derived from any tissue, including liver, lungs, kidney, heart, blood vessels, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, and bone marrow. In particular embodiments, for the purposes of analysis of the antigen-binding molecule, the fibroblasts may be cardiac fibroblasts (e.g. atrial fibroblasts), skin fibroblasts, lung fibroblasts, kidney

fibroblasts or liver fibroblasts. Fibroblasts may be characterised by gene or protein expression of one or more of COL1A, ACTA2, prolyl-4-hydroxylase, MAS516, and FSP1.

Gene expression can be measured by various means known to those skilled in the art, for example by measuring levels of mRNA by quantitative real-time PCR (qRT-PCR), or by reporter-based methods.

Similarly, protein expression can be measured by various methods well known in the art, e.g. by antibody-based methods, for example by western blot, immunohistochemistry, immunocytochemistry, flow cytometry, ELISA, ELISPOT, or reporter-based methods.

In some embodiments, the antigen-binding molecule according to the present invention may inhibit protein expression of one or more markers of fibrosis, e.g. protein expression of one or more of collagen, fibronectin, periostin, IL-6, IL-11, α SMA, TIMP1, MMP2.

The ability of an antigen-binding molecule to inhibit interaction between IL-11 and IL-11R α :gp130 can, for example, be analysed by stimulating fibroblasts with TGF β 1, incubating the cells in the presence of the antigen-binding molecule and analysing the proportion of cells having α SMA-positive phenotype after a defined period of time. In such example, inhibition of interaction between IL-11 and IL-11R α :gp130 can be identified by observation of a lower proportion of cells having an α SMA-positive phenotype as compared to positive control condition in which cells are treated with TGF β 1 in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule), or in the presence of an appropriate control antigen-binding molecule.

Such assays are also suitable for analysing the ability of antigen-binding molecule to inhibit IL-11-mediated signalling.

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting interaction between IL-11 and IL-11R α to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11 and IL-11R α in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting interaction between IL-11 and IL-11R α to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of interaction between IL-11 and IL-11R α in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting interaction between IL-11 and gp130 to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or

- less, 5% or less, or 1% or less of the level of interaction between IL-11 and gp130 in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting interaction between IL-11 and gp130 to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of interaction between IL-11 and gp130 in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).
- In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting interaction between IL-11 and IL-11R α :gp130 to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11 and IL-11R α :gp130 in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting interaction between IL-11 and IL-11R α :gp130 to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of interaction between IL-11 and IL-11R α :gp130 in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).
- In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting interaction between IL-11:IL-11R α complex and gp130 to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11:IL-11R α complex and gp130 in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of inhibiting interaction between IL-11:IL-11R α complex and gp130 to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of interaction between IL-11:IL-11R α complex and gp130 in the absence of the antigen-binding molecule.
- Inhibition of IL-11 mediated signalling can also be analysed using ^3H -thymidine incorporation and/or Ba/F3 cell proliferation assays such as those described in e.g. Curtis et al. Blood, 1997, 90(11) and Karpovich et al. Mol. Hum. Reprod. 2003 9(2): 75-80. Ba/F3 cells co-express IL-11R α and gp130.
- As used herein, IL-11 mediated signalling and/or processes mediated by IL-11 includes signalling mediated by fragments of IL-11 and polypeptide complexes comprising IL-11 or fragments thereof. IL-11 mediated signalling may be signalling mediated by human IL-11 and/or mouse IL-11. Signalling mediated by IL-11 may

occur following binding of IL-11 or a complex comprising IL-11 to a receptor to which IL-11 or said complex binds.

- 5 In some embodiments, antibodies and fragments according to the present invention are capable of inhibiting the biological activity of IL-11 or a complex comprising IL-11. In some embodiments, the antigen-binding molecule binds to IL-11 or the complex comprising IL-11 in a region which is important for binding to a receptor for the IL-11 or complex comprising IL-11, e.g. gp130 or IL-11R α , and thereby disrupts binding to and/or signalling through the receptor.
- 10 In some embodiments, the antigen-binding molecule according to the present invention is an antagonist of one or more signalling pathways which are activated by signal transduction through receptors comprising IL-11R α and/or gp130, e.g. IL-11R α :gp130. In some embodiments, the antigen-binding molecule is capable of inhibiting signalling through one or more immune receptor complexes comprising IL-11R α and/or gp130, e.g. IL-11R α :gp130.
- 15 In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting IL-11-mediated signalling to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of signalling in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing IL-11 mediated signalling to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of signalling in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).
- 20 In some embodiments, the IL-11 mediated signalling may be signalling mediated by binding of IL-11 to IL-11R α :gp130 receptor. Such signalling can be analysed e.g. by treating cells expressing IL-11R α and gp130 with IL-11, or by stimulating IL-11 production in cells which express IL-11R α and gp130.
- 25 The IC₅₀ for antigen-binding molecule for inhibition of IL-11 mediated signalling may be determined, e.g. by culturing Ba/F3 cells expressing IL-11R α and gp130 in the presence of human IL-11 and the IL-11 binding agent, and measuring ³H-thymidine incorporation into DNA.
- 30 In some embodiments, the antigen-binding molecule of the present invention may exhibit an IC₅₀ of 10 μ g/ml or less, preferably one of ≤ 5 μ g/ml, ≤ 4 μ g/ml, ≤ 3.5 μ g/ml, ≤ 3 μ g/ml, ≤ 2 μ g/ml, ≤ 1 μ g/ml, ≤ 0.9 μ g/ml, ≤ 0.8 μ g/ml, ≤ 0.7 μ g/ml, ≤ 0.6 μ g/ml, or ≤ 0.5 μ g/ml in such an assay.
- 35 In some embodiments, the IL-11 mediated signalling may be signalling mediated by binding of IL-11:IL-11R α complex to gp130. In some embodiments, the IL-11:IL-11R α complex may be soluble, e.g. complex of extracellular domain of IL-11R α and IL-11, or complex of soluble IL-11R α isoform/fragment, and IL-11. In
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some embodiments, the soluble IL-11R α is a soluble (secreted) isoform of IL-11R α , or is the liberated product of proteolytic cleavage of the extracellular domain of cell membrane bound IL-11R α . IL-11 mediated signalling which is mediated by binding of IL-11 bound to IL-11R α , to gp130 is referred to herein as 'IL-11 *trans* signalling'.

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In some embodiments, the IL-11:IL-11R α complex may be cell-bound, e.g. complex of cell-membrane bound IL-11R α and IL-11. Signalling mediated by binding of IL-11:IL-11R α complex to gp130 can be analysed by treating cells expressing gp130 with IL-11:IL-11R α complex, e.g. recombinant fusion protein comprising IL-11 joined by a peptide linker to the extracellular domain of IL-11R α (e.g. hyper IL-11 as described herein).

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In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting signalling mediated by binding of IL-11:IL-11R α complex to gp130, and is also capable of inhibiting signalling mediated by binding of IL-11 to IL-11R α :gp130 receptor.

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In some embodiments, the binding agent may be capable of inhibiting interaction between IL-11 and IL-11 to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11 and IL-11 in the absence of the binding agent (or in the presence of an appropriate control binding agent). In some embodiments, the binding agent is capable of inhibiting interaction between IL-11 and IL-11 to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of interaction between IL-11 and IL-11 in the absence of the binding agent.

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In some embodiments, the antigen-binding molecule is capable of inhibiting fibroblast proliferation. Proliferation of fibroblasts can be determined by analysing cell division over a period of time. Cell division for a given population of fibroblasts can be analysed, for example, by *in vitro* analysis of incorporation of ^3H -thymidine or by CFSE dilution assay, e.g. as described in Fulcher and Wong, Immunol Cell Biol (1999) 77(6): 559-564, hereby incorporated by reference in entirety. Proliferating cells (e.g. proliferating fibroblasts) may also be identified by analysis of incorporation of 5-ethynyl-2'-deoxyuridine (EdU) by an appropriate assay, as described e.g. in Buck et al., Biotechniques. 2008 Jun; 44(7):927-9, and Sali and Mitchison, PNAS USA 2008 Feb 19; 105(7): 2415-2420, both hereby incorporated by reference in their entirety.

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Fibroblasts according to the present disclosure may be derived from any tissue, including liver, lungs, kidney, heart, blood vessels, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, and bone marrow. In particular embodiments, for the purposes of analysis of the antigen-binding molecule, the fibroblasts may be cardiac fibroblasts (e.g. atrial fibroblasts), skin fibroblasts, lung fibroblasts, kidney fibroblasts or liver fibroblasts.

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In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting fibroblast proliferation to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or

less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of fibroblast proliferation in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing fibroblast proliferation to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of fibroblast proliferation in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting a pathological process mediated by IL-11, e.g. following stimulation with a profibrotic factor (e.g. TGF β 1). Pathological processes mediated by IL-11 include fibrosis, and can be evaluated either *in vitro*, *ex vivo* or *in vivo*.

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting fibrosis. In some embodiments, the antigen-binding molecule according to the present invention is capable of reversing or regressing fibrosis. In some embodiments the fibrosis is established or severe fibrosis. Inhibiting or the inhibition of fibrosis, as used herein, refers to the ability of an antigen-binding molecule to reduce, restrain or prevent the development of fibrosis. In some embodiments inhibition of fibrosis refers to e.g. a prophylactic effect whereby fibrosis is prevented from developing. In some embodiments inhibition of fibrosis refers to e.g. a treatment effect whereby existing early or late-stage fibrosis is prevented from developing or advancing to a more advanced stage. Reversing/reversal of or regressing/regression of fibrosis, as used herein, refers to the ability of an antigen-binding molecule to ameliorate the fibrotic state from a more developed state to a less developed state, or to lessen the severity of the fibrosis itself or its symptoms. Reversing/reversal of fibrosis may be associated with an improvement in the fibrotic state.

In the experimental examples herein, inhibition, reversal or regression of fibrosis is analysed for example by measuring the number or percentage of ACTA2⁺ve cells using Operetta high-content imaging system, measuring cell or organ collagen content by assessing hydroxyproline content, measuring ERK activation/phosphorylation by western blotting, and/or measuring the expression level of inflammation markers such as TNF α and CCL2 or fibrotic markers such as TGF β 1, α SMA (ACTA2), TIMP1, COL1A1, COL1A2 or COL3A1 by quantitative PCR. In tissues such as the liver, inhibition, reversal or regression of fibrosis is analysed for example by determining triglyceride content and serum ALT levels.

Fibrosis may be of a particular tissue or several tissues, e.g. liver, lung, kidney, heart, blood vessel, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, or bone marrow. Fibrosis may be measured by means well known to the skilled person, for example by analysing gene or protein expression of one or more myofibroblast markers and/or gene or protein expression of one or more markers of fibrosis in a given tissue or tissues.

Myofibroblast markers may include one or more of increased α SMA, vimentin, palladin, cofilin or desmin. Markers of fibrosis include increased level of collagen, fibronectin, periostin, IL-6, IL-11, α SMA, TIMP1 and MMP2, extracellular matrix components, number/proportion of myofibroblasts, and organ weight.

5 Inhibition/reversal/regression of fibrosis can be measured *in vitro* or *in vivo*. For example, whether an antigen-binding molecule is capable of inhibiting/reversing/regressing fibrosis in a given tissue can be analysed *in vitro* by treating fibroblasts derived from that tissue with a profibrotic stimulus, and then analysing whether the antibody can reduce or reverse myofibroblast generation from the fibroblasts (or e.g. some other marker of fibrosis). Whether an antigen-binding molecule is capable of inhibiting/reversing/regressing fibrosis
10 can be analysed *in vivo*, for example, by administering the antigen-binding molecule to a subject (e.g. a subject that has been exposed to a profibrotic stimulus), and analysing tissue(s) for one or more markers of fibrosis.

In some embodiments, the antigen-binding molecule according to the present invention is capable of
15 inhibiting/reversing/regressing fibrosis to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of fibrosis in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding
20 molecule is capable of reducing/reversing/regressing fibrosis to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of fibrosis in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

25 In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting myofibroblast generation from fibroblasts or stellate cells (e.g. hepatic or pancreatic stellate cells), e.g. following exposure of the fibroblasts or stellate cells to profibrotic factor. Myofibroblast generation from fibroblasts or stellate cells can be investigated by analysis for myofibroblast markers. A profibrotic factor
30 according to the present disclosure may be e.g. TGF β 1, IL-11, IL-13, PDGF, ET-1, oncostatin M (OSM) or ANG2 (AngII). In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting fibroblast or stellate cell activation by profibrotic factor.

In some embodiments the antigen-binding molecule according to the present invention is capable of
35 promoting stellate cell senescence. Senescence may be measured by detecting expression of senescence markers such as P16, P21 and P53.

In some embodiments, the antigen-binding molecule is capable of inhibiting gene or protein expression in fibroblasts, stellate cells, or fibroblast/stellate cell-derived cells (e.g. myofibroblasts), of one or more of
40 collagen, fibronectin, periostin, IL-6, IL-11, α SMA, TIMP1, MMP2, TNF α , CCL2 e.g. following stimulation with a profibrotic factor. In some embodiments, the antigen-binding molecule is capable of inhibiting gene or

protein expression in fibroblasts, or fibroblast-derived cells (e.g. myofibroblasts), of one or more extracellular matrix components, e.g. following stimulation with a profibrotic factor.

In the experimental examples herein, myofibroblast generation from fibroblasts or stellate cells is analysed by measuring α SMA protein expression levels using Operetta High-Content Imaging System following stimulation of the fibroblasts with TGF β 1.

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting myofibroblast generation from fibroblasts or stellate cells to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of myofibroblast generation from fibroblasts or stellate cells in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing myofibroblast generation from fibroblasts or stellate cells to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of myofibroblast generation from fibroblasts or stellate cells in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting gene or protein expression in fibroblasts, stellate cells or myofibroblasts of one or more of collagen, fibronectin, periostin, IL-6, IL-11, α SMA, TIMP1, MMP2, TNF α , CCL2 e.g. following stimulation with a profibrotic factor (e.g. TGF β 1). In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting gene or protein expression to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of gene or protein expression in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing gene or protein expression to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of gene or protein expression in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting extracellular matrix production by fibroblasts or stellate cells, e.g. following stimulation with a profibrotic factor (e.g. TGF β 1). Extracellular matrix production can be evaluated, for example, by measuring the level of an extracellular matrix component. Extracellular matrix components according to the present invention include e.g. proteoglycan, heparan sulphate, chondroitin sulphate, keratan sulphate, hyaluronic acid, collagen, periostin, fibronectin, vitronectin, elastin, fibronectin, laminin, nidogen, gelatin and aggrecan.

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting collagen secretion from fibroblasts, stellate cells and/or myofibroblasts.

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting extracellular matrix production by fibroblasts or stellate cells to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of extracellular matrix production by fibroblasts or stellate cells in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing extracellular matrix production by fibroblasts or stellate cells to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of extracellular matrix production in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments the antigen-binding molecule according to the present invention is capable of upregulating gene or protein expression in hepatic cells of one or more genes/proteins involved in lipogenesis and/or β -oxidation. Such genes/proteins may be e.g. ACOX1 (acyl-CoA oxidase 1), SCD1 (stearoyl-CoA desaturase 1), FASN (fatty acid synthase), or SREBF1 (sterol regulatory element-binding protein 1). In some embodiments, the antigen-binding molecule according to the present invention is capable of upregulating gene or protein expression by more than 1 times, e.g. one of ≥ 1.01 times, ≥ 1.05 times, ≥ 1.1 times, ≥ 1.15 times, ≥ 1.2 times, ≥ 1.25 times, ≥ 1.3 times, ≥ 1.35 times, ≥ 1.4 times, ≥ 1.45 times, ≥ 1.5 times, ≥ 1.55 times, ≥ 1.6 times, ≥ 1.65 times, ≥ 1.7 times, ≥ 1.75 times, ≥ 1.8 times, ≥ 1.85 times, ≥ 1.9 times, ≥ 1.95 times, ≥ 2 times, ≥ 2.5 times, ≥ 3 times, ≥ 3.5 times, ≥ 4 times, ≥ 4.5 times, ≥ 5 times, ≥ 6 times, ≥ 7 times, ≥ 8 times, ≥ 9 times or ≥ 10 times the level of gene or protein expression in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments the antigen-binding molecule according to the present invention is capable of inhibiting migratory and/or invasive behaviour, i.e. inhibiting migration and/or invasion, of fibroblasts, stellate cells or myofibroblasts. Migration and invasion of such cells can be critical in the pathology of fibrosis. Migration of cells can be evaluated using e.g. polycarbonate membranes and invasive stimulants such as TGF β 1 or CCL2. Invasion of cells can be measured using e.g. Boyden chamber invasion assays or ECM-coated matrigel. In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting migration and/or invasion of fibroblasts, stellate cells or myofibroblasts to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of migration and/or invasion in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing migration and/or invasion to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4

times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of migration and/or invasion in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

- 5 In some embodiments the antigen-binding molecule according to the present invention is capable of inhibiting the presence of immune cells in an organ. In some embodiments the antigen-binding molecule according to the present invention is capable of reducing the number of immune cells in an organ. The organ may be an organ susceptible to, or suffering from, fibrosis, e.g. liver or kidney. The immune cells may be CD45⁺ cells, e.g. CD3⁺CD4⁺ T cells, CD3⁺CD8⁺ T cells, B lymphocytes, granulocytes and monocytes. The
- 10 immune cells may express murine monocyte marker LyC6. In some embodiments the antigen-binding molecule according to the present invention is capable of reducing the number of immune cells in an organ to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the number of
- 15 immune cells in an organ in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing the number of immune cells in an organ to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times,
- 20 ≤ 0.1 times the number of immune cells in an organ in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).
- In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting proliferation and/or survival of cells of a cancer. The skilled person is able to determine whether an antigen-binding molecule is capable of inhibiting proliferation and/or survival of cells of a cancer for example
- 25 by analysing the effect of the antigen-binding molecule on cells of the cancer. For example, proliferation of cells can be measured as described herein, e.g. by ³H thymidine incorporation or CFSE dilution assays. Cell survival can be analysed by measuring cells for markers of cell viability/cell death following treatment with the antigen-binding molecule.
- 30 In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting proliferation and/or survival of cells of a cancer to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of proliferation and/or survival of cells of a cancer in
- 35 the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing proliferation and/or survival of cells of a cancer to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of proliferation
- 40 and/or survival of cells of a cancer in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments, the antigen-binding molecule of the present invention inhibits the development and/or progression of cancer *in vivo*. In some embodiments the antigen-binding molecule causes killing of cancer cells, e.g. by effector immune cells. In some embodiments the antigen-binding molecule causes a reduction in the number of cancer cells *in vivo*, e.g. as compared to an appropriate control condition. In some
 5 embodiments the antigen-binding molecule inhibits tumor growth, e.g. as determined by measuring tumor size/volume over time.

The antigen-binding molecule of the present invention may be analysed for the ability to inhibit development and/or progression of cancer in an appropriate *in vivo* model. The cancer may be a cancer in which IL-11
 10 mediated signalling and/or cells expressing/comprising IL-11 or a complex comprising IL-11 are pathologically implicated. Such cancers include those described in Xu et al., Cancer Lett. (2016) 373(2):156-63 and Johnstone et al., Cytokine & Growth Reviews (2015) 26(5): 489-498, both of which are hereby incorporated by reference in their entirety.

In some embodiments, administration of an antigen-binding molecule according to the present invention may cause one or more of: inhibition of the development/progression of the cancer, a delay to/prevention of onset of the cancer, a reduction in/delay to/prevention of tumor growth, a reduction in/delay to/prevention of metastasis, a reduction in the severity of the symptoms of the cancer, a reduction in the number of cancer cells, a reduction in tumour size/volume, and/or an increase in survival (e.g. progression free survival), e.g.
 20 as determined in an appropriate *in vivo* model of the cancer. In some embodiments an antigen-binding molecule according to the present invention provides an additive effect when administered in conjunction, e.g. separately, simultaneously or sequentially, with a chemotherapeutic agent, compared to the chemotherapeutic agent administered alone. The additive effect may be any effect described herein, such as reduction of IL-11 signalling, inhibition of the development/progression of a cancer and/or inhibition of tumour
 25 growth.

In some embodiments, the antigen-binding molecule according to the present invention is capable of inhibiting tumour growth to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less,
 30 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of tumour growth in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule). In some embodiments, the antigen-binding molecule is capable of reducing tumour growth to less than 1 times, e.g. one of ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45
 35 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times the level of tumour growth in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments, the antigen-binding molecule of the present invention is capable of causing killing of cells expressing/comprising IL-11 or a complex comprising IL-11. Killing of cells expressing/comprising IL-11
 40 or a complex comprising IL-11 may be increased through an effector function of the antigen-binding molecule. In embodiments wherein antigen-binding molecule comprises an Fc region the antigen-binding

molecule may cause killing of cells expressing/comprising IL-11 or a complex comprising IL-11 through one or more of complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

5 An antigen-binding molecule which is capable of causing killing of cells expressing/comprising IL-11 or a complex comprising IL-11 can be identified by observation of a level of killing of cells expressing/comprising IL-11 or a complex comprising IL-11 in the presence of – or following incubation of the cells expressing/comprising IL-11 or a complex comprising IL-11 with – the antigen-binding molecule, as compared to the level of cell killing detected in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule), in an appropriate assay. Assays of CDC, ADCC and ADCP are well known to the skilled person. The level of killing of cells expressing/comprising IL-11 or a complex comprising IL-11 can also be determined by measuring the number/proportion of viable and/or non-viable cells expressing/comprising IL-11 or a complex comprising IL-11 following exposure to different treatment conditions.

15 In some embodiments, the antigen-binding molecule of the present invention is capable of causing killing of cells expressing/comprising IL-11 or a complex comprising IL-11 to more than 1 times, e.g. ≥ 1.01 times, ≥ 1.02 times, ≥ 1.03 times, ≥ 1.04 times, ≥ 1.05 times, ≥ 1.1 times, ≥ 1.2 times, ≥ 1.3 times, ≥ 1.4 times, ≥ 1.5 times, ≥ 1.6 times, ≥ 1.7 times, ≥ 1.8 times, ≥ 1.9 times, ≥ 2 times, ≥ 3 times, ≥ 4 times, ≥ 5 times, ≥ 6 times, ≥ 7 times, ≥ 8 times, ≥ 9 times or ≥ 10 times the level of killing observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

25 In some embodiments, the antigen-binding molecule of the present invention is capable of reducing the number of cells expressing/comprising IL-11 or a complex comprising IL-11 to less than less than 1 times, e.g. ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the number of cells expressing/comprising IL-11 or a complex comprising IL-11 detected following incubation in the absence of the antigen-binding molecule (or following incubation in the presence of an appropriate control antigen-binding molecule), in a comparable assay. Cell numbers and proportions can be determined e.g. by flow cytometry analysis using antibodies allowing detection of cell types.

35 In some embodiments, the antigen-binding molecule according to the present invention has one or more similar or improved properties as compared to a reference antibody/antigen-binding fragment thereof capable of binding to IL-11.

In some embodiments, the antigen-binding molecule of the present invention displays one or more of the following properties as compared to a reference antibody/antigen-binding fragment thereof capable of binding to IL-11:

40 (i) binds to IL-11 with similar or greater specificity (i.e. has similar or reduced cross-reactivity for proteins of the IL-6 cytokine family other than IL-11);

- (ii) binds to IL-11 (e.g. human IL-11 and/or mouse IL-11) with similar or greater affinity (e.g. has similar or lower EC50 as determined by ELISA; e.g. has similar or lower K_D as determined by SPR analysis);
- (iii) similar or greater inhibition of interaction between IL-11 and IL-11R α ;
- (iv) similar or greater inhibition of interaction between IL-11 and gp130;
- 5 (v) similar or greater inhibition of interaction between IL-11 and IL-11R α :gp130 receptor complex;
- (vi) similar or greater inhibition of interaction between IL-11:IL-11R α complex and gp130;
- (vii) similar or greater inhibition of interaction between IL-11 and IL-11;
- (viii) similar or greater inhibition of signalling mediated by IL-11 (e.g. has similar or lower IC50 as determined by ELISA in a suitable assay);
- 10 (ix) similar or greater inhibition of signalling mediated by binding of IL-11 to IL-11R α :gp130 receptor complex;
- (x) similar or greater inhibition of signalling mediated by binding of IL-11:IL-11R α complex to gp130 (i.e. IL-11 *trans* signalling);
- (xi) similar or greater inhibition of fibroblast proliferation;
- 15 (xii) similar or greater inhibition of myofibroblast generation from fibroblasts;
- (xiii) similar or greater inhibition reversal/regression of myofibroblast generation from fibroblasts;
- (xiv) similar or greater inhibition of myofibroblast generation from stellate cells, e.g. hepatic or pancreatic stellate cells;
- (xv) similar or greater reversal/regression of myofibroblast generation from stellate cells, e.g. hepatic or
- 20 pancreatic stellate cells;
- (xvi) similar or greater inhibition of migratory and/or invasive behaviour (i.e. inhibition of migration and/or invasion) of fibroblasts, stellate cells or myofibroblasts;
- (xvii) similar or greater inhibition of the presence of immune cells in an organ;
- (xviii) similar or greater inhibition of a pathological process mediated by IL-11;
- 25 (xix) similar or greater inhibition of fibrosis;
- (xx) similar or greater reversal/regression of fibrosis;
- (xxi) similar or greater inhibition of gene or protein expression in fibroblasts of one or more of collagen, fibronectin, periostin, IL-6, IL-11, α SMA (ACTA2), TIMP1, MMP2, TNF α , CCL2 e.g. following stimulation with a profibrotic factor;
- 30 (xxii) similar or greater inhibition of extracellular matrix production by fibroblasts or stellate cells;
- (xxiii) similar or greater inhibition of proliferation and/or survival of cells of a cancer;
- (xxiv) similar or greater inhibition of development and/or progression of cancer *in vivo*;
- (xxv) similar or greater inhibition of tumour growth;
- (xxvi) similar or greater killing of cells expressing/comprising IL-11 or a complex comprising IL-11.

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In some embodiments, "greater specificity" or "greater affinity" or "a greater inhibition" or "greater killing" refers, respectively, to a level of specificity, affinity, inhibition or killing which is greater than 1 times, e.g. ≥ 1.01 times, ≥ 1.02 times, ≥ 1.03 times, ≥ 1.04 times, ≥ 1.05 times, ≥ 1.06 times, ≥ 1.07 times, ≥ 1.08 times, ≥ 1.09 times, ≥ 1.1 times, ≥ 1.2 times, ≥ 1.3 times, ≥ 1.4 times, ≥ 1.5 times, ≥ 1.6 times, ≥ 1.7 times, ≥ 1.8 times, ≥ 1.9 times, ≥ 2 times, ≥ 2.1 times, ≥ 2.2 times, ≥ 2.3 times, ≥ 2.4 times, ≥ 2.5 times, ≥ 2.6 times, ≥ 2.7 times, ≥ 2.8 times, ≥ 2.9 times, ≥ 3 times, ≥ 3.5 times, ≥ 4 times, ≥ 4.5 times, ≥ 5 times, ≥ 6 times, ≥ 7 times, ≥ 8 times, ≥ 9 times, ≥ 10 times, ≥ 15 times, ≥ 20 times, ≥ 25 times, ≥ 30 times, ≥ 35 times, ≥ 40 times, ≥ 45 times, ≥ 50 times,

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≥60 times, ≥70 times, ≥80 times, ≥90 times, ≥100 times, ≥200 times, ≥300 times, ≥400 times, ≥500 times, ≥600 times, ≥700 times, ≥800 times, ≥900 times, ≥1000 times the level displayed by the reference antibody/antigen-binding fragment thereof capable of binding to IL-11, as determined in an appropriate assay.

5

In some embodiments, "similar specificity" or "similar affinity" or "a similar inhibition" or "similar killing" refers, respectively, to a level of specificity, affinity, inhibition or killing which is ≥ 0.2 times and ≤ 5 times, e.g. ≥ 0.3 times and ≤ 4 times, ≥ 0.4 times and ≤ 3 times, ≥ 0.5 times and ≤ 2 times, ≥ 0.6 times and ≤ 1.75 times, ≥ 0.7 times and ≤ 1.5 times, ≥ 0.75 times and ≤ 1.25 times, ≥ 0.8 times and ≤ 1.2 times, ≥ 0.85 times and ≤ 1.15 times, ≥ 0.9 times and ≤ 1.1 times, ≥ 0.91 times and ≤ 1.09 times, ≥ 0.92 times and ≤ 1.08 times, ≥ 0.93 times and ≤ 1.07 times, ≥ 0.94 times and ≤ 1.06 times, ≥ 0.95 times and ≤ 1.05 times, ≥ 0.96 times and ≤ 1.04 times, ≥ 0.97 times and ≤ 1.03 times, ≥ 0.98 times and ≤ 1.02 times, or ≥ 0.99 times and ≤ 1.01 times the level displayed by the reference antibody/antigen-binding fragment thereof capable of binding to IL-11, as determined in an appropriate assay.

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In some embodiments the reference antibody/antibody fragment capable of binding to IL-11 may comprise the CDRs of an anti-IL-11 antibody clone selected from YU100-H01, YU100-G08 or YU100-F11. In some embodiments the reference antibody/antibody fragment capable of binding to IL-11 may comprise or consist of the VH and VL sequences of an anti-IL-11 antibody clone selected from YU100-H01, YU100-G08 or YU100-F11.

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In some embodiments the reference antibody/antibody fragment capable of binding to IL-11 may comprise the CDRs of monoclonal mouse anti-human IL-11 antibody clone #22626; Catalog No. MAB218 (R&D Systems, MN, USA). In some embodiments the reference antibody/antibody fragment capable of binding to IL-11 may comprise or consist of the VH and VL sequences of monoclonal mouse anti-human IL-11 antibody clone #22626; Catalog No. MAB218 (R&D Systems, MN, USA).

25

Chimeric antigen receptors (CARs)

The present invention also provides Chimeric Antigen Receptors (CARs) comprising the antigen-binding molecules or polypeptides of the present invention.

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CARs are recombinant receptors that provide both antigen-binding and T cell activating functions. CAR structure and engineering is reviewed, for example, in Dotti et al., Immunol Rev (2014) 257(1), hereby incorporated by reference in its entirety. CARs comprise an antigen-binding region linked to a cell membrane anchor region and a signalling region. An optional hinge region may provide separation between the antigen-binding region and cell membrane anchor region, and may act as a flexible linker.

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The CAR of the present invention comprises an antigen-binding region which comprises or consists of the antigen-binding molecule of the present invention, or which comprises or consists of a polypeptide according to the invention.

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The cell membrane anchor region is provided between the antigen-binding region and the signalling region of the CAR and provides for anchoring the CAR to the cell membrane of a cell expressing a CAR, with the antigen-binding region in the extracellular space, and signalling region inside the cell. In some embodiments, the CAR comprises a cell membrane anchor region comprising or consisting of an amino acid sequence which comprises, consists of, or is derived from, the transmembrane region amino acid sequence for one of CD3- ζ , CD4, CD8 or CD28. As used herein, a region which is 'derived from' a reference amino acid sequence comprises an amino acid sequence having at least 60%, e.g. one of at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the reference sequence.

The signalling region of a CAR allows for activation of the T cell. The CAR signalling regions may comprise the amino acid sequence of the intracellular domain of CD3- ζ , which provides immunoreceptor tyrosine-based activation motifs (ITAMs) for phosphorylation and activation of the CAR-expressing T cell. Signalling regions comprising sequences of other ITAM-containing proteins such as Fc γ RI have also been employed in CARs (Haynes et al., 2001 J Immunol 166(1):182-187). Signalling regions of CARs may also comprise co-stimulatory sequences derived from the signalling region of co-stimulatory molecules, to facilitate activation of CAR-expressing T cells upon binding to the target protein. Suitable co-stimulatory molecules include CD28, OX40, 4-1BB, ICOS and CD27. In some cases CARs are engineered to provide for co-stimulation of different intracellular signalling pathways. For example, signalling associated with CD28 costimulation preferentially activates the phosphatidylinositol 3-kinase (PI3K) pathway, whereas the 4-1BB-mediated signalling is through TNF receptor associated factor (TRAF) adaptor proteins. Signalling regions of CARs therefore sometimes contain co-stimulatory sequences derived from signalling regions of more than one co-stimulatory molecule. In some embodiments, the CAR of the present invention comprises one or more co-stimulatory sequences comprising or consisting of an amino acid sequence which comprises, consists of, or is derived from, the amino acid sequence of the intracellular domain of one or more of CD28, OX40, 4-1BB, ICOS and CD27.

An optional hinge region may provide separation between the antigen-binding domain and the transmembrane domain, and may act as a flexible linker. Hinge regions may be derived from IgG1. In some embodiments, the CAR of the present invention comprises a hinge region comprising or consisting of an amino acid sequence which comprises, consists of, or is derived from, the amino acid sequence of the hinge region of IgG1.

Also provided is a cell comprising a CAR according to the invention. The CAR according to the present invention may be used to generate CAR-expressing immune cells, e.g. CAR-T or CAR-NK cells. Engineering of CARs into immune cells may be performed during culture, *in vitro*.

The antigen-binding region of the CAR of the present invention may be provided with any suitable format, e.g. scFv, scFab, etc.

Nucleic acids and vectors

The present invention provides a nucleic acid, or a plurality of nucleic acids, encoding an antigen-binding molecule, polypeptide or CAR according to the present invention.

5 In some embodiments, the nucleic acid is purified or isolated, e.g. from other nucleic acid, or naturally-occurring biological material. In some embodiments the nucleic acid(s) comprise or consist of DNA and/or RNA.

10 The present invention also provides a vector, or plurality of vectors, comprising the nucleic acid or plurality of nucleic acids according to the present invention.

The nucleotide sequence may be contained in a vector, e.g. an expression vector. A "vector" as used herein is a nucleic acid molecule used as a vehicle to transfer exogenous nucleic acid into a cell. The vector may be a vector for expression of the nucleic acid in the cell. Such vectors may include a promoter sequence
15 operably linked to the nucleotide sequence encoding the sequence to be expressed. A vector may also include a termination codon and expression enhancers. Any suitable vectors, promoters, enhancers and termination codons known in the art may be used to express a peptide or polypeptide from a vector according to the invention.

20 The term "operably linked" may include the situation where a selected nucleic acid sequence and regulatory nucleic acid sequence (e.g. promoter and/or enhancer) are covalently linked in such a way as to place the expression of nucleic acid sequence under the influence or control of the regulatory sequence (thereby forming an expression cassette). Thus a regulatory sequence is operably linked to the selected nucleic acid sequence if the regulatory sequence is capable of effecting transcription of the nucleic acid sequence. The
25 resulting transcript(s) may then be translated into a desired peptide(s)/polypeptide(s).

Suitable vectors include plasmids, binary vectors, DNA vectors, mRNA vectors, viral vectors (e.g. gammaretroviral vectors (e.g. murine Leukemia virus (MLV)-derived vectors), lentiviral vectors, adenovirus
30 vectors, adeno-associated virus vectors, vaccinia virus vectors and herpesvirus vectors), transposon-based vectors, and artificial chromosomes (e.g. yeast artificial chromosomes).

In some embodiments, the vector may be a eukaryotic vector, e.g. a vector comprising the elements necessary for expression of protein from the vector in a eukaryotic cell. In some embodiments, the vector may be a mammalian vector, e.g. comprising a cytomegalovirus (CMV) or SV40 promoter to drive protein
35 expression.

Constituent polypeptides of an antigen-binding molecule according to the present invention may be encoded by different nucleic acids of the plurality of nucleic acids, or by different vectors of the plurality of vectors.

Cells comprising/expressing the antigen-binding molecules and polypeptides

The present invention also provides a cell comprising or expressing an antigen-binding molecule, polypeptide or CAR according to the present invention. Also provided is a cell comprising or expressing a nucleic acid, a plurality of nucleic acids, a vector or a plurality of vectors according to the invention.

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The cell may be a eukaryotic cell, e.g. a mammalian cell. The mammal may be a primate (rhesus, cynomolgous, non-human primate or human) or a non-human mammal (e.g. rabbit, guinea pig, rat, mouse or other rodent (including any animal in the order Rodentia), cat, dog, pig, sheep, goat, cattle (including cows, e.g. dairy cows, or any animal in the order Bos), horse (including any animal in the order Equidae), donkey, and non-human primate).

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The present invention also provides a method for producing a cell comprising a nucleic acid(s) or vector(s) according to the present invention, comprising introducing a nucleic acid, a plurality of nucleic acids, a vector or a plurality of vectors according to the present invention into a cell. In some embodiments, introducing an isolated nucleic acid(s) or vector(s) according to the invention into a cell comprises transformation, transfection, electroporation or transduction (e.g. retroviral transduction).

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The present invention also provides a method for producing a cell expressing/comprising an antigen-binding molecule, polypeptide or CAR according to the present invention, comprising introducing a nucleic acid, a plurality of nucleic acids, a vector or a plurality of vectors according to the present invention in a cell. In some embodiments, the methods additionally comprise culturing the cell under conditions suitable for expression of the nucleic acid(s) or vector(s) by the cell. In some embodiments, the methods are performed *in vitro*.

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The present invention also provides cells obtained or obtainable by the methods according to the present invention.

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Producing the antigen-binding molecules and polypeptides

Antigen-binding molecules and polypeptides according to the invention may be prepared according to methods for the production of polypeptides known to the skilled person.

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Polypeptides may be prepared by chemical synthesis, e.g. liquid or solid phase synthesis. For example, peptides/polypeptides can be synthesised using the methods described in, for example, Chandrudu et al., Molecules (2013), 18: 4373-4388, which is hereby incorporated by reference in its entirety.

Alternatively, antigen-binding molecules and polypeptides may be produced by recombinant expression.

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Molecular biology techniques suitable for recombinant production of polypeptides are well known in the art, such as those set out in Green and Sambrook, Molecular Cloning: A Laboratory Manual (4th Edition), Cold Spring Harbor Press, 2012, and in Nat Methods. (2008); 5(2): 135-146 both of which are hereby incorporated by reference in their entirety. Methods for the recombinant production of antigen-binding molecules are also described in Frenzel et al., Front Immunol. (2013); 4: 217 and Kunert and Reinhart, Appl Microbiol Biotechnol. (2016) 100: 3451-3461, both of which are hereby incorporated by reference in their entirety.

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In some cases the antigen-binding molecule of the present invention are comprised of more than one polypeptide chain. In such cases, production of the antigen-binding molecules may comprise transcription and translation of more than one polypeptide, and subsequent association of the polypeptide chains to form the antigen-binding molecule.

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For recombinant production according to the invention, any cell suitable for the expression of polypeptides may be used. The cell may be a prokaryote or eukaryote. In some embodiments the cell is a prokaryotic cell, such as a cell of archaea or bacteria. In some embodiments the bacteria may be Gram-negative bacteria such as bacteria of the family Enterobacteriaceae, for example *Escherichia coli*. In some embodiments, the cell is a eukaryotic cell such as a yeast cell, a plant cell, insect cell or a mammalian cell, e.g. CHO, HEK (e.g. HEK293), HeLa or COS cells. In some embodiments, the cell is a CHO cell that transiently or stably expresses the polypeptides.

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In some cases the cell is not a prokaryotic cell because some prokaryotic cells do not allow for the same folding or post-translational modifications as eukaryotic cells. In addition, very high expression levels are possible in eukaryotes and proteins can be easier to purify from eukaryotes using appropriate tags. Specific plasmids may also be utilised which enhance secretion of the protein into the media.

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In some embodiments polypeptides may be prepared by cell-free-protein synthesis (CFPS), e.g. according using a system described in Zemella et al. *ChemBiochem* (2015) 16(17): 2420-2431, which is hereby incorporated by reference in its entirety.

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Production may involve culture or fermentation of a eukaryotic cell modified to express the polypeptide(s) of interest. The culture or fermentation may be performed in a bioreactor provided with an appropriate supply of nutrients, air/oxygen and/or growth factors. Secreted proteins can be collected by partitioning culture media/fermentation broth from the cells, extracting the protein content, and separating individual proteins to isolate secreted polypeptide(s). Culture, fermentation and separation techniques are well known to those of skill in the art, and are described, for example, in Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (4th Edition; incorporated by reference herein above).

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Bioreactors include one or more vessels in which cells may be cultured. Culture in the bioreactor may occur continuously, with a continuous flow of reactants into, and a continuous flow of cultured cells from, the reactor. Alternatively, the culture may occur in batches. The bioreactor monitors and controls environmental conditions such as pH, oxygen, flow rates into and out of, and agitation within the vessel such that optimum conditions are provided for the cells being cultured.

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Following culturing the cells that express the antigen-binding molecule/polypeptide(s), the polypeptide(s) of interest may be isolated. Any suitable method for separating proteins from cells known in the art may be used. In order to isolate the polypeptide it may be necessary to separate the cells from nutrient medium. If the polypeptide(s) are secreted from the cells, the cells may be separated by centrifugation from the culture media that contains the secreted polypeptide(s) of interest. If the polypeptide(s) of interest collect within the

cell, protein isolation may comprise centrifugation to separate cells from cell culture medium, treatment of the cell pellet with a lysis buffer, and cell disruption e.g. by sonification, rapid freeze-thaw or osmotic lysis.

It may then be desirable to isolate the polypeptide(s) of interest from the supernatant or culture medium, which may contain other protein and non-protein components. A common approach to separating protein components from a supernatant or culture medium is by precipitation. Proteins of different solubilities are precipitated at different concentrations of precipitating agent such as ammonium sulfate. For example, at low concentrations of precipitating agent, water soluble proteins are extracted. Thus, by adding different increasing concentrations of precipitating agent, proteins of different solubilities may be distinguished. Dialysis may be subsequently used to remove ammonium sulfate from the separated proteins.

Other methods for distinguishing different proteins are known in the art, for example ion exchange chromatography and size chromatography. These may be used as an alternative to precipitation, or may be performed subsequently to precipitation.

Once the polypeptide(s) of interest have been isolated from culture it may be desired or necessary to concentrate the polypeptide(s). A number of methods for concentrating proteins are known in the art, such as ultrafiltration or lyophilisation.

Compositions

The present invention also provides compositions comprising the antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors and cells described herein.

The antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors and cells described herein may be formulated as pharmaceutical compositions or medicaments for clinical use and may comprise a pharmaceutically acceptable carrier, diluent, excipient or adjuvant. The composition may be formulated for topical, parenteral, systemic, intracavitary, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, intraconjunctival, intratumoral, subcutaneous, intradermal, intrathecal, oral or transdermal routes of administration which may include injection or infusion.

Suitable formulations may comprise the antigen-binding molecule in a sterile or isotonic medium. Medicaments and pharmaceutical compositions may be formulated in fluid, including gel, form. Fluid formulations may be formulated for administration by injection or infusion (e.g. via catheter) to a selected region of the human or animal body.

In some embodiments the composition is formulated for injection or infusion, e.g. into a blood vessel or tumour.

In accordance with the invention described herein methods are also provided for the production of pharmaceutically useful compositions, such methods of production may comprise one or more steps selected from: producing an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof) or cell described herein; isolating an antigen-binding molecule,

polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof) or cell described herein; and/or mixing an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof) or cell described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

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For example, a further aspect the invention described herein relates to a method of formulating or producing a medicament or pharmaceutical composition for use in the treatment of a disease/condition (e.g. a cancer), the method comprising formulating a pharmaceutical composition or medicament by mixing an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof)

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or cell described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

Therapeutic and prophylactic applications

The antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors, cells and compositions described herein find use in therapeutic and prophylactic methods.

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The present invention provides an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein for use in a method of medical treatment or prophylaxis. Also provided is the use of an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein in the manufacture of a medicament for treating or preventing a disease or condition. Also provided is a

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method of treating or preventing a disease or condition, comprising administering to a subject a therapeutically or prophylactically effective amount of an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein.

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The methods may be effective to reduce the development or progression of a disease/condition, alleviation of the symptoms of a disease/condition or reduction in the pathology of a disease/condition. The methods may be effective to prevent progression of the disease/condition, e.g. to prevent worsening of, or to slow the rate of development of, the disease/condition. In some embodiments the methods may lead to an improvement in the disease/condition, e.g. a reduction in the symptoms of the disease/condition or reduction in some other correlate of the severity/activity of the disease/condition. In some embodiments the methods may prevent development of the disease/condition a later stage (e.g. a chronic stage or metastasis). In some embodiments the methods may be effective to reverse or regress the disease/condition, e.g. the pathology of a disease/condition may be reversed from a later developmental stage to an earlier developmental stage. In some embodiments the methods may be effective to reverse or regress the symptoms of the

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disease/condition or some other correlate of the severity/activity of the disease/condition. In some embodiments the methods may be effective to reverse/regress a disease/condition to a state similar to the state observed in a subject without the disease/condition.

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It will be appreciated that the articles of the present invention may be used for the treatment/prevention of any disease/condition that would derive therapeutic or prophylactic benefit from a reduction in the level of

(i.e. inhibition or antagonism of) IL-11 mediated signalling, or a reduction in the number and/or activity of cells expressing IL-11.

For example, the disease/condition may be a disease/condition in which IL-11 mediated signalling is pathologically implicated, e.g. a disease/condition in which an increased level of IL-11 mediated signalling is positively associated with the onset, development or progression of the disease/condition, and/or severity of one or more symptoms of the disease/condition, or for which an increased level of IL-11 mediated signalling is a risk factor for the onset, development or progression of the disease/condition.

For example, the disease/condition may be a disease/condition in which cells expressing IL-11 are pathologically implicated, e.g. a disease/condition in which an increased number/proportion of cells expressing IL-11 is positively associated with the onset, development or progression of the disease/condition, and/or severity of one or more symptoms of the disease/condition, or for which an increased number/proportion of cells expressing IL-11 is a risk factor for the onset, development or progression of the disease/condition.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present invention is a disease/condition characterised by an increase in the level of IL-11 mediated signalling or a correlate thereof (e.g. in an organ/tissue in which the symptoms of the disease/condition manifest) as compared to the level of IL-11 mediated signalling/correlate thereof in the absence of the disease/condition.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present invention is a disease/condition characterised by an increase in the number/proportion/activity of cells expressing IL-11, e.g. as compared to the number/proportion/activity of cells expressing IL-11 in the absence of the disease/condition.

In some embodiments, a subject may be selected for treatment/prophylaxis as described herein based on the detection of an increase in the level of IL-11 mediated signalling or a correlate thereof and/or an increase in the number/proportion/activity of cells expressing IL-11, e.g. in the periphery, or in an organ/tissue which is affected by the disease/condition (e.g. an organ/tissue in which the symptoms of the disease/condition manifest). The disease/condition may affect any tissue or organ or organ system. In some embodiments the disease/condition may affect several tissues/organs/organ systems.

In some embodiments a subject may be selected for therapy/prophylaxis in accordance with the present invention based on determination that the subject has an increase in the level of IL-11 mediated signalling or a correlate thereof and/or an increase in the number/proportion/activity of cells expressing IL-11, e.g. in the periphery, or in an organ/tissue relative to the level of IL-11 mediated signalling/correlate thereof, or number/proportion/activity of cells expressing IL-11 in a healthy subject.

The antigen-binding molecules of the present invention are preferably able to bind to and inhibit the biological activity of IL-11 and IL-11-containing molecules/complexes (e.g. IL-11:IL-11R α complex). Accordingly, the antigen-binding molecules of the present invention find use in the treatment or prevention of

diseases and disorders in which IL-11 is implicated in the pathology of the disease/disorder. That is, the antigen-binding molecules of the present invention find use in the treatment or prevention of diseases and disorders associated with IL-11 mediated signalling.

- 5 In some embodiments, the disease/disorder may be associated with increased IL-11, IL-11R α and/or gp130 gene or protein expression, e.g. as compared to the control (i.e. non-diseased) state. In some embodiments, the disease/disorder may be associated with an increased level of IL-11-mediated signalling as compared to the control state. In some embodiments, the disease/disorder may be associated with an increased level of signalling through ERK and/or STAT3 pathways as compared to the control state. In some embodiments, the increased expression/activity of IL-11, IL-11R α and/or gp130, and/or the increased level of IL-11-mediated signalling, may be observed in effector cells of the disease/disorder. In some embodiments, the increased expression/activity of IL-11, IL-11R α and/or gp130, and/or the increased level of IL-11-mediated signalling, may be observed in cells other than the effector cells.
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- 15 Signalling through ERK can be measured e.g. using an assay for ERK phosphorylation such as an assay described in Assay Guidance Manual: Phospho-ERK Assays, Kim E. Garbison, Beverly A. Heinz, Mary E. Lajiness, Jeffrey R. Weidner, and G. Sitta Sittampalam, Eli Lilly & Company, Sittampalam GS, Coussens NP, Nelson H, et al., editors Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004. Signalling through STAT3 can be measured e.g. using an assay for phosphorylation of STAT3, such as the Phospho-STAT3 (Tyr705) Cellular Assay Kit (Cisbio Assays).
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- In some embodiments, the treatment is of a disease/disorder for which a reduction in IL-11 mediated signalling is therapeutic. In some embodiments, the treatment is of a disease/disorder associated with excess ERK and/or STAT3 signalling. In some embodiments, the treatment is of a disease/disorder associated with excess proliferation or hyperactivation of fibroblasts, or associated with an excess of myofibroblasts.
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- In some embodiments, the treatment may be aimed at preventing or treating a disease/disorder by decreasing the number or proportion of myofibroblasts or α SMA-positive fibroblasts.
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- In some embodiments, the disease/disorder may be fibrosis, a fibrotic condition, or a disease/disorder characterised by fibrosis. As used herein, "fibrosis" refers to the formation of excess fibrous connective tissue as a result of the excess deposition of extracellular matrix components, for example collagen. Fibrous connective tissue is characterised by having extracellular matrix (ECM) with a high collagen content. The collagen may be provided in strands or fibers, which may be arranged irregularly or aligned. The ECM of fibrous connective tissue may also include glycosaminoglycans.
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- As used herein, "excess fibrous connective tissue" refers to an amount of connective tissue at a given location (e.g. a given tissue or organ, or part of a given tissue or organ) which is greater than the amount of connective tissue present at that location in the absence of fibrosis, e.g. under normal, non-pathological conditions. As used herein, "excess deposition of extracellular matrix components" refers to a level of
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deposition of one or more extracellular matrix components which is greater than the level of deposition in the absence of fibrosis, e.g. under normal, non-pathological conditions.

The cellular and molecular mechanisms of fibrosis are described in Wynn, J. Pathol. (2008) 214(2): 199-210, and Wynn and Ramalingam, Nature Medicine (2012) 18:1028-1040, which are hereby incorporated by reference in their entirety. The main cellular effectors of fibrosis are myofibroblasts, which produce a collagen-rich extracellular matrix.

In response to tissue injury, damaged cells and leukocytes produce pro-fibrotic factors such as TGF β , IL-13 and PDGF, which activate fibroblasts to α SMA-expressing myofibroblasts, and recruit myofibroblasts to the site of injury. Myofibroblasts produce a large amount of extracellular matrix, and are important mediators in aiding contracture and closure of the wound. However, under conditions of persistent infection or during chronic inflammation there can be overactivation and recruitment of myofibroblasts, and thus over-production of extracellular matrix components, resulting in the formation of excess fibrous connective tissue.

In some embodiments fibrosis may be triggered by pathological conditions, e.g. conditions, infections or disease states that lead to production of pro-fibrotic factors such as TGF β 1. In some embodiments, fibrosis may be caused by physical injury/stimuli, chemical injury/stimuli or environmental injury/stimuli. Physical injury/stimuli may occur during surgery, e.g. iatrogenic causes. Chemical injury/stimuli may include drug induced fibrosis, e.g. following chronic administration of drugs such as bleomycin, cyclophosphamide, amiodarone, procainamide, penicillamine, gold and nitrofurantoin (Daba et al., Saudi Med J 2004 Jun; 25(6): 700-6). Environmental injury/stimuli may include exposure to asbestos fibres or silica.

Fibrosis can occur in many tissues of the body. For example, fibrosis can occur in the lung, liver (e.g. cirrhosis), kidney, heart, blood vessels, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, and bone marrow. Fibrosis may also occur in multiple organs at once.

In embodiments herein, fibrosis may involve an organ of the gastrointestinal system, e.g. of the liver, small intestine, large intestine, or pancreas. In some embodiments, fibrosis may involve an organ of the respiratory system, e.g. the lungs. In embodiments, fibrosis may involve an organ of the cardiovascular system, e.g. of the heart or blood vessels. In some embodiments, fibrosis may involve the skin. In some embodiments, fibrosis may involve an organ of the nervous system, e.g. the brain. In some embodiments, fibrosis may involve an organ of the urinary system, e.g. the kidneys. In some embodiments, fibrosis may involve an organ of the musculoskeletal system, e.g. muscle tissue.

In some preferred embodiments, the fibrosis is cardiac or myocardial fibrosis, hepatic fibrosis, or renal fibrosis. In some embodiments cardiac or myocardial fibrosis is associated with dysfunction of the musculature or electrical properties of the heart, or thickening of the walls or valves of the heart. In some embodiments fibrosis is of the atrium and/or ventricles of the heart. Treatment or prevention of atrial or ventricular fibrosis may help reduce risk or onset of atrial fibrillation, ventricular fibrillation, or myocardial infarction.

In some preferred embodiments hepatic fibrosis is associated with chronic liver disease or liver cirrhosis. In some preferred embodiments renal fibrosis is associated with chronic kidney disease.

Diseases/disorders characterised by fibrosis in accordance with the present invention include but are not limited to: respiratory conditions such as pulmonary fibrosis, cystic fibrosis, idiopathic pulmonary fibrosis (IPF), progressive massive fibrosis, scleroderma, obliterative bronchiolitis, Hermansky-Pudlak syndrome, asbestosis, silicosis, chronic pulmonary hypertension, AIDS associated pulmonary hypertension, sarcoidosis, tumor stroma in lung disease, and asthma; chronic liver disease, primary biliary cirrhosis (PBC), schistosomal liver disease, liver cirrhosis, steatohepatitis, non-alcoholic steatohepatitis (NASH), early-stage NASH, late-stage NASH, alcoholic steatohepatitis, steatosis; pancreatic conditions such as chronic pancreatitis and pancreatic fibrosis; cardiovascular conditions such as hypertrophic cardiomyopathy, dilated cardiomyopathy (DCM), fibrosis of the atrium, atrial fibrillation, fibrosis of the ventricle, ventricular fibrillation, myocardial fibrosis, Brugada syndrome, myocarditis, endomyocardial fibrosis, myocardial infarction, fibrotic vascular disease, hypertensive heart disease, arrhythmogenic right ventricular cardiomyopathy (ARVC), tubulointerstitial and glomerular fibrosis, atherosclerosis, varicose veins, cerebral infarcts; neurological conditions such as gliosis and Alzheimer's disease; muscular dystrophy such as Duchenne muscular dystrophy (DMD) or Becker's muscular dystrophy (BMD); gastrointestinal conditions such as Chron's disease, microscopic colitis and primary sclerosing cholangitis (PSC); skin conditions such as scleroderma, nephrogenic systemic fibrosis and cutis keloid; arthrofibrosis; Dupuytren's contracture; mediastinal fibrosis; retroperitoneal fibrosis; myelofibrosis; Peyronie's disease; adhesive capsulitis; kidney disease (e.g., renal fibrosis, nephritic syndrome, Alport's syndrome, HIV associated nephropathy, polycystic kidney disease, Fabry's disease, diabetic nephropathy, chronic glomerulonephritis, nephritis associated with systemic lupus, kidney interstitial fibrosis (IF)); kidney injury e.g. acute kidney injury/renal failure; nephrotoxicity; progressive systemic sclerosis (PSS); chronic graft versus host disease; diseases/disorders of the eye and associated processes, such as Grave's ophthalmopathy, epiretinal fibrosis (e.g. diabetic retinopathy (DR)), glaucoma, subretinal fibrosis (e.g. associated with macular degeneration (e.g. wet or dry age-related macular degeneration (AMD))), macular edema, drusen formation, choroidal neovascularization (CNV), post-surgical fibrosis (e.g. of the posterior capsule following cataract surgery, or of the bleb following trabeculectomy for glaucoma), conjunctival fibrosis, subconjunctival fibrosis; arthritis; fibrotic pre-neoplastic and fibrotic neoplastic disease; and fibrosis induced by chemical or environmental insult (e.g., cancer chemotherapy, pesticides, radiation/cancer radiotherapy).

Early stage NASH refers herein to steatotic stages of fatty liver disease, e.g. NAFLD, which may bridge into a NASH state in which the liver has become inflamed. Late-stage NASH refers herein to states of persistent liver inflammation which may include fibrosis.

It will be appreciated that many of the diseases/conditions listed above are interrelated. For example, fibrosis of the ventricle may occur post myocardial infarction, and is associated with DCM, HCM and myocarditis.

In particular embodiments, the disease/disorder may be one of pulmonary fibrosis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), non-alcoholic steatohepatitis (NASH), cirrhosis, chronic kidney disease, scleroderma, systemic sclerosis, keloid, cystic

fibrosis, Crohn's disease, post-surgical fibrosis or retinal fibrosis, e.g. associated with wet age-related macular degeneration (AMD).

5 In some embodiments the methods may be effective to reverse or regress fibrosis. The fibrosis may be established or severe fibrosis and may be associated with any of the diseases/conditions described herein. In some embodiments the methods may be effective to reverse or regress any of the diseases/disorders provided herein.

10 Fibrosis can lead directly or indirectly to, and/or increase susceptibility to development of, diseases/disorders. For example, more than 80% of hepatocellular carcinomas (HCCs) develop in fibrotic or cirrhotic livers (Afo et al. 2016, Annu Rev Pathol.), suggesting an important role for liver fibrosis in the premalignant environment (PME) of the liver.

15 Accordingly, the antigen-binding molecules of the present invention find use in methods for the treatment and prevention of diseases/disorders associated with fibrosis, and/or for which fibrosis is a risk factor. In some embodiments, the disease/disorder associated with fibrosis, or for which fibrosis is a risk factor, is a cancer, e.g. cancer of the liver (e.g. hepatocellular carcinoma).

20 IL-11 is also implicated in the pathology of other diseases/disorders, and the antibodies and fragments of the present invention accordingly find use in methods to treat, prevent, alleviate and/or reverse or regress the symptoms of these diseases/disorders also.

25 In some embodiments, fibrosis may be associated with angiogenesis e.g. in the eye. In some embodiments, methods of treating or preventing fibrosis, methods of determining the suitability of a subject for such treatment/prevention and methods of diagnosing/prognosing fibrosis as described herein are also applicable to treating/preventing/diagnosing/prognosing angiogenesis, and vice versa. Fibrosis of the eye may be associated with choroidal neovascularization (CNV).

30 In some embodiments the antigen-binding molecules of the present invention are provided for use in methods to treat and/or prevent metabolic diseases. That is, the present invention provides for the treatment/prevention of metabolic diseases through inhibition of IL-11 mediated signalling, in e.g. a cell, tissue/organ/organ system/subject. As used herein, a "metabolic disease" refers to any disease or condition which is caused by, or which is characterised by, abnormal metabolism. "Metabolism" in this context refers to the bodily conversion/processing of sources of energy, e.g. substances consumed to provide nutrition, into
35 energy and/or for storage. "Normal metabolism" may be the metabolism of a healthy subject not having a disease, e.g. not having a metabolic disease, or not possessing a symptom/correlate of a metabolic disease.

40 A subject having a metabolic disease may display abnormal metabolism. A subject having a metabolic disease may have a symptom/correlate of abnormal metabolism. A subject having a metabolic disease may have been diagnosed as having metabolic disease. A subject may satisfy the diagnostic criteria for the diagnosis of a metabolic disease. In some embodiments, the present invention provides for the

treatment/prevention of diseases/conditions in a subject for which a metabolic disease provides a poor prognosis.

In some embodiments, the metabolic disease affects one or more of: the liver, pancreas, cardiovascular system, digestive system, the excretory system, the respiratory system, the renal system, the reproductive system, the circulatory system, the muscular system, the endocrine system, the exocrine system, the lymphatic system, the immune system, the nervous system, and/or the skeletal system.

In some embodiments the metabolic disease is, or comprises (e.g. is characterised by), obesity, type 2 diabetes (T2D), type 1 diabetes (T1D), pre-diabetes, being overweight, metabolic syndrome, pregnancy-associated hyperglycemia (i.e. gestational diabetes), cholestatic liver disease, hyperglycaemia, hyperlipidaemia, hypertriglyceridemia, hypercholesterolemia, wasting, cachexia, chemotherapy-associated weight loss, pancreatic insufficiency, pancreatitis, acute pancreatitis, chronic pancreatitis, steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), lipodystrophy, lipohypertrophy, lipoatrophy, insulin deficiency, insulin resistance and hyperglucagonemia. In some embodiments the metabolic disease is, or comprises, obesity. In some embodiments the metabolic disease is, or comprises, cholestasis, i.e. a reduced flow of bile from the liver to the duodenum. The disease may be cholestatic liver disease (Jansen et al., *Hepatology* (2017) 65(2):722-738 and Pollock and Minuk, *J Gastroenterol Hepatol* (2017) 32(7):1303-1309, both of which are hereby incorporated by reference in their entirety), including e.g. primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

Aspects of the present invention are concerned with the treatment and/or prevention of aberrant and/or insufficient function of cells/tissue(s)/organ(s)/organ systems having a role in metabolism. In particular, treatment and/or prevention of aberrant function and/or insufficient function of cells of the pancreas/pancreatic tissue/the pancreas is contemplated herein, as is the treatment and/or prevention of aberrant function and/or insufficient function of cells of the liver/hepatic tissue/the liver.

In some embodiments the metabolic disease is, or comprises, wasting. As used herein, the term "wasting" refers to involuntary weight loss, which may be progressive and/or degenerative. Wasting can be defined as loss of muscle with or without loss of fat mass, and typically involves significant, usually involuntary, loss of body mass (including skeletal muscle), and may or may not include loss of adipose tissue. In some instances, adipose tissue wasting can occur in isolation, as seen in lipodystrophy diseases. Wasting may be characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism (Fearon et al. *Lancet Oncol.* (2011) 12(5):489-95). Wasting can lead to progressive functional impairment, impaired quality of life, increased risk for morbidity and mortality. In some cases, wasting leads to asthenia (abnormal physical weakness or lack of energy) and/or anaemia (deficiency of red cells or haemoglobin in the blood). In some cases, wasting cannot be fully reversed by conventional nutritional support or by therapeutic interventions that have been trialled to date. Death usually occurs once weight loss has reached 30% of the patient's historic stable body weight (Tisdale, *Nature Reviews Cancer*, 2, 862-871 (2002)).

Diseases/conditions characterised by wasting include cachexia (non-age-related loss of muscle mass), sarcopenia (loss of muscle mass: e.g. age-related, disuse, space travel or denervation), anorexic disorders (protein-energy malnutrition), muscular dystrophies, lipodystrophies (e.g. abnormal or degenerative condition of adipose tissue), lipoatrophy (age-related loss of subcutaneous fat in the face and other tissues) and myopenia (muscle wasting in any chronic illness; proposed by Fearon et al. J Cachexia Sarcopenia Muscle. 2011; 2:1–3). Herein, diseases/conditions characterised by wasting are also referred to as “wasting disorders”. In some embodiments a wasting disorder according to the present disclosure is cachexia, pre-cachexia, refractory cachexia, sarcopenia, anorexia, lipodystrophy, lipoatrophy and/or myopenia. In some embodiments according to the various aspects described herein, the wasting disorder is cachexia, pre-cachexia and/or refractory cachexia.

Wasting disorders arising due to chronic illness may include “mild muscle wasting disease” (with or without frailty), “moderate muscle wasting disease” (with or without frailty; sometimes known as “pre-cachexia”), or “severe muscle wasting disease” (sometimes called “cachexia”, often with frailty present). Cachexia can be defined as involuntary weight loss of >5% from historical stable weight, a body mass index (BMI) of <20 kg/m² (person younger than 65) or <22 kg/m² (person aged 65 or older) with any degree of weight loss >2%, or a skeletal muscle index consistent with sarcopenia with any degree of weight loss >2%. The subject may also display <10% body fat and/or a low blood albumin level of <35 g/l. These criteria may also help to identify populations ‘at-risk’ of developing a wasting disorder (Fearon et al. Lancet Oncol. 2011; 12(5):489-95).

A three-step classification of cachexia has been proposed, with severity classified according to degree of depletion of energy stores and body protein (BMI) in combination with degree of ongoing weight loss.

1. Pre-cachexia – when a patient has weight loss <5 %, but has not yet developed serious complications.
2. Cachexia – where the syndrome is progressing, with weight loss exceeding the above-mentioned parameters, but still potentially able to be treated.
3. Refractory cachexia – the point at which the disease is no longer responsive to treatment or when treatment benefits are outweighed by burden and risk (Fearon et al, supra). Often, the refractory stage is dictated by the overall stage of an underlying illness, described below, and the condition of the patient.

Metabolic diseases may be present in acute or chronic disease settings. Aspects of the present invention provide for the treatment/prevention of diseases/conditions associated with metabolic diseases.

Disease/conditions associated with metabolic diseases include diseases/conditions that are positively associated with the onset of a metabolic disease. In some embodiments, the disease/condition associated with a metabolic disease is one which can cause/causes/has caused (i.e. can lead to, leads to or has led to) a metabolic disease.

Disease/conditions associated with metabolic diseases also include diseases/conditions which are caused and/or exacerbated (made worse, progressed and/or complicated) by a metabolic disease. In some embodiments a disease/condition associated with a metabolic disease, may be positively associated with the

onset of a metabolic disease and may also be exacerbated by a metabolic disease. An “associated” disease/condition may be one comprising a metabolic disease-related pathology.

- 5 In embodiments of the invention, a metabolic disease, or a disease/condition associated with a metabolic disease may be present in or affect any organ/tissue, such as the heart, liver, kidney, brain, skin, muscular system, stomach, small intestine, large intestine, pancreas, mouth, salivary glands, pharynx, oesophagus, gallbladder, trachea, larynx, bladder, ovary, uterus, testes, glands of the endocrine system e.g. pituitary or thyroid, the lymphatic system e.g. spleen.
- 10 In embodiments of the invention, a disease/condition associated with a metabolic disease may be one or more of cancer, cardiac disease, kidney disease, lung disease, liver disease, chronic infection, neurological degenerative diseases, acute injury, traumatic injury/trauma, post-operative conditions, or ageing/senescence.
- 15 In accordance with various aspects of the present invention, a method of treating and/or preventing a metabolic disease according to the present invention may comprise one or more of the following:
- Reducing blood lipid level;
 - Reducing blood glucose level;
 - Increasing glucose tolerance (e.g. of a glucose intolerant subject);
 - 20 Increasing insulin tolerance (e.g. of an insulin resistant subject);
 - Increasing pancreatic function
 - Reducing body weight (e.g. of an overweight/obese subject);
 - Reducing body fat mass;
 - Increasing lean mass;
 - 25 Reducing fasting blood glucose level;
 - Reducing serum triglyceride level;
 - Reducing serum cholesterol level;
 - Increasing glucose tolerance;
 - Increasing pancreatic function (e.g. exocrine and/or endocrine function);
 - 30 Increasing the growth of pancreatic tissue;
 - Regenerating pancreatic tissue;
 - Increasing pancreas weight;
 - Reducing pancreatic islet cell hyperplasia;
 - Reducing glucagon expression;
 - 35 Increasing insulin expression;
 - Increasing body weight (e.g. of a subject having a wasting disease, e.g. cachexia);
 - Reducing expression of IL-11 protein in the liver;
 - Reducing Erk activation in the liver;
 - Reducing steatosis, e.g. of the liver;
 - 40 Reducing liver triglyceride level;
 - Reducing serum ALT level;

Reducing expression of a pro-inflammatory factor (e.g. TNF α , CCL2, CCL5, IL-6, CXCL5, and/or CXCL1);

Reducing expression of a pro-fibrotic factor (e.g. IL-11, TIMP1, ACTA2, TGF β 1, MMP2, TIMP2, MMP9, COL1A2, COL1A1 and/or COL3A1);

5 Reducing serum TGF β 1 level;

Reducing expression/production by HSCs of IL-11, ACTA2, MMP2, TGF β 1, PDGF, ANG II, bFGF, CCL2 and/or H₂O₂;

Inhibiting HSC-to-myofibroblast transition by HSCs;

Reducing the number/proportion of myofibroblasts in the liver;

10 Reducing liver hydroxyproline level;

Increasing liver function;

Increasing the function of an organ/tissue affected by a metabolic disease;

Reducing liver damage; and

Reducing the number/proportion of CD45⁺ cells in the liver.

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IL-11 has been implicated in the development and progression of various cancers. Studies suggest that IL-11 is important for promoting chronic gastric inflammation and associated gastric, colonic, hepatocellular and breast cancer tumorigenesis through excessive activation of STAT3 (Ernst M, et al. J Clin Invest.

(2008);118:1727–1738), that IL-11 may promote tumorigenesis by triggering the JAK-STAT intracellular signalling pathway, and may also promote metastasis via signalling through the PI3K-AKT-mTORC1

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pathway (Xu et al., Cancer Letters (2016) 373(2): 156-163). Through STAT3, IL-11 promotes survival, proliferation, invasion angiogenesis and metastasis, the IL-11/GP130/JAK/STAT3 signalling axis may be rate-limiting for the progression of gastrointestinal tumors, and elevated IL-11 expression is associated with poor prognosis of breast cancer patients (Johnstone et al., Cytokine & Growth Reviews (2015) 26(5): 489-

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498). IL-11 has also been shown to influence breast cancer stem cell dynamics and tumor heterogeneity (Johnstone et al., Cytokine & Growth Reviews (2015) 26(5): 489-498). Recently, IL-11 signalling has been

implicated in chemoresistance of lung adenocarcinoma; cancer associated fibroblasts were found to

upregulate IL-11, and confer chemoresistance to lung cancer cells through activation of the IL-11/IL-

11R/STAT3 anti-apoptotic signalling pathway (Tao et al. 2016, Sci Rep. 6;6:38408). IL-11 signalling may

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promote the fibroblast-to-myofibroblast transition and extracellular matrix production by fibroblasts in the pre-malignant environment (PME) and tumour micro-environment (TME).

In some embodiments, the antigen-binding molecules of the present invention are provided for use in

methods to treat/prevent a cancer. In some embodiments, the cancer may be a cancer which leads directly

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or indirectly to inflammation and/or fibrosis.

A cancer may be any unwanted cell proliferation (or any disease manifesting itself by unwanted cell

proliferation), neoplasm or tumor or increased risk of or predisposition to the unwanted cell proliferation,

neoplasm or tumor. The cancer may be benign or malignant and may be primary or secondary (metastatic).

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A neoplasm or tumor may be any abnormal growth or proliferation of cells and may be located in any tissue.

In some embodiments, the antigen-binding molecules of the present invention are provided for use in methods to treat/prevent a cancer, e.g. an epithelial cell cancer, breast cancer, gastrointestinal cancer (e.g. esophageal cancer, stomach cancer, pancreatic cancer, liver cancer (e.g. HCC), gallbladder cancer, colorectal cancer, anal cancer, gastrointestinal carcinoid tumor, and lung cancer (e.g. non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)). In some embodiments, the cancer is a cancer for which acute and/or chronic inflammation is a risk factor. In some embodiments, the cancer is a cancer for which a disease/disorder characterised by fibrosis (e.g. as described herein) is a risk factor.

In some embodiments, the cancer may be associated with increased IL-11, IL-11R α and/or gp130 gene or protein expression. For example, cells of the cancer may have increased expression of IL-11, IL-11R α and/or gp130 as compared to comparable, non-cancerous cells, or may be associated with increased expression of IL-11, IL-11R α and/or gp130 by other cells (e.g. non-cancerous cells) as compared to the level of expression by comparable cells in the absence of a cancer (e.g. in a healthy control subject). In some embodiments, cells of the cancer may be determined to have an increased level of signalling through ERK and/or STAT3 pathways as compared to comparable non-cancerous cells.

In some embodiments, the cancer may be associated with a mutation in IL-11, IL-11R α and/or gp130. In some embodiments, such mutation may be associated with increased level of gene or protein expression, or may be associated with an increased level of IL-11/IL-11R signalling relative to the level of expression/signalling observed in the absence of the mutation.

IL-11 has also been implicated in diseases/disorders characterised by inflammation. Intra-articular injection of IL-11 has been shown to cause joint inflammation (Wong et al., Cytokine (2005) 29:72-76), and IL-11 has been shown to be proinflammatory at sites of IL-13-mediated tissue inflammation (Chen et al., J Immunol (2005) 174:2305-2313). IL-11 expression has also been observed to be significantly increased in chronic skin lesions in atopic dermatitis, and is known to be involved in bronchial inflammation (Toda et al., J Allergy Clin Immunol (2003) 111:875-881). IL-11-mediated signalling is implicated in inflammatory bowel disease (IBD) and asthma (Putoczki and Ernst, J Leuko Biol (2010) 88(6):1109-1117). IL-11 has also been identified as a risk factor for multiple sclerosis; IL-11 is elevated in the cerebrospinal fluid of patients with clinically isolated syndrome (CIS) as compared to control subjects, and serum levels of IL-11 are higher during relapses for patients with relapsing-remitting multiple sclerosis, and IL-11 may promote differentiation of CD4⁺ T cells to a TH17 phenotype – TH17 cells are important cells in the pathogenesis of multiple sclerosis (Zhang et al., Oncotarget (2015) 6(32): 32297-32298).

In some embodiments, the antigen-binding molecules of the present invention are provided for use in methods to treat/prevent a disease/disorder characterised by inflammation. In some embodiments, a disease or disorder characterised by inflammation may be a disease/disorder which leads directly or indirectly to a cancer and/or fibrosis. Diseases characterised by inflammation include e.g. allergic inflammation such as allergic asthma and bronchial inflammation, atopic dermatitis, allergic rhinitis and ocular allergic diseases, and autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, chronic active hepatitis, type 1 diabetes mellitus, celiac disease, Grave's disease, uveitis, pemphigus,

psoriasis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, anaemia and autoimmune thyroiditis.

In some embodiments, the antigen-binding molecules of the present invention are provided for use in methods to treat/prevent hepatotoxicity and diseases/disorders characterised by hepatotoxicity. As used herein, hepatotoxicity refers to damage to and/or death of liver cells/tissue. Hepatotoxicity can refer to a state of toxic damage to the liver, specifically with death of the hepatocyte cells within the liver. Hepatotoxicity may be determined/diagnosed by detection of one or more correlates of hepatotoxicity as described hereinbelow. Hepatotoxicity may arise as a consequence of hepatotoxic insult. As used herein "hepatotoxic insult" refers to any treatment, event or conditions giving rise to hepatotoxicity. For example, hepatotoxic insult may be caused by a chemical/physical treatment/experience, or gaseous conditions. In some embodiments hepatotoxic insult is chemical, e.g. in the case of drug-induced liver injury, e.g. APAP-induced hepatotoxicity. In some embodiments hepatotoxic insult is physical, e.g. in the case of hepatotoxicity arising as a result of surgical damage to liver tissue, which may occur e.g. surgery to treat a disease and/or for liver transplantation (e.g. the hepatotoxicity may have iatrogenic causes). In some embodiments hepatotoxic insult arises from hypoxia, e.g. as a consequence of ischaemia, or may result from reperfusion (e.g. the hepatotoxic insult may arise from IRI).

Hepatotoxicity may be chemical-driven liver damage, for example damage or injury caused by a medicine, chemical, ischaemia, reperfusion, sepsis or herbal or dietary supplements. In some embodiments hepatotoxicity refers to drug-induced liver injury (DILI). In some embodiments hepatotoxicity refers to liver injury caused by a hepatotoxin. A hepatotoxin may be alcohol. Hepatotoxicity may also be termed toxic hepatitis. Hepatotoxicity may refer to acute and/or chronic hepatotoxicity.

Hepatotoxicity may be caused, directly or indirectly, by alcohol ingestion e.g. chronic alcohol consumption. Hepatotoxicity as referred to herein may be caused, directly or indirectly, by fasting, malnutrition, infection by an infectious agent (e.g. a hepatitis virus (e.g. hepatitis A, B, C, D or E), HIV), cancer or drug interactions.

Hepatotoxicity may be present in association with other disorders, diseases and conditions. Disorders, diseases or conditions associated with hepatotoxicity include acute liver injury (ALI), acute liver failure, acute liver disease, chronic liver disease, liver damage, hepatitis e.g. viral hepatitis, alcoholic hepatitis, liver ischemia-reperfusion injury (IRI) e.g. 'warm' ischemia-reperfusion (WIR), radiation-induced liver disease (RILD), drug-induced liver injury (DILI), autoimmune liver injury, cholestatic liver disease, HIV and cancer.

Drug-induced liver injury (DILI) includes intrinsic and idiosyncratic hepatotoxicity, and idiosyncratic DILI further includes allergic and nonallergic reaction. The intrinsic mechanism is related to dose dependent hepatotoxicity, whereas idiosyncratic hepatotoxicity is not dose dependent and may happen in an unpredictable fashion. Allergic idiosyncratic hepatotoxicity is further characterized by the presence of symptoms and signs typical of an adaptive immune system reaction, including fever, skin reactions, eosinophilia, formation of autoantibodies, and a short latency time particularly after re-exposure (Khoury et al., J Clin Transl Hepatol. 2015 Jun 28; 3(2): 99–108).

In some embodiments antigen-binding molecules of the present invention may be used for the diagnosis, treatment and prophylaxis of acetaminophen (APAP)-induced hepatotoxicity. Acetaminophen is also known as N-acetyl-p-aminophenol or paracetamol, or by the brand names Tylenol and Panadol. Acetaminophen intoxication results in hepatotoxicity associated with increased serum concentrations of hepatocellular leakage enzymes such as aspartate aminotransferase, lactate dehydrogenase, and alanine aminotransferase, centrilobular degeneration and necrosis, and activation of Kupffer cells (Trepicchio WL et al., Toxicol Pathol. 2001; 29(2):242-9).

In some embodiments the antigen-binding molecules of the present invention are provided for use in methods to treat/prevent kidney injury, e.g. acute kidney injury (AKI; acute renal failure), or a disease/disorder associated with kidney injury. Kidney injury may be characterised by damage to tubular epithelial cells (TECs) and/or the transition of TECs to an epithelial-to-mesenchymal cell-like phenotype (i.e. EMT). Transition of TECs to a mesenchymal cell-like phenotype may be characterised e.g. by reduced expression of E-cadherin, increased expression of SNAIL and/or increased expression of ACTA2. The kidney injury may have any cause, examples include kidney injury resulting from mechanical (i.e. physical) damage or injury, chemical damage or injury, ischemia or genetic predisposition. The cause or damage will normally result in impaired kidney function, which may lead to kidney failure. Mechanical damage or injury may include physical injury to the subject, to the kidney, to TECs or to podocytes. It may also include tubular obstruction/blockage, e.g. of the urinary tract. In some embodiments the kidney injury is drug-induced kidney injury or drug-induced acute kidney injury.

Ischemic damage may arise from a decrease in blood flow to the kidney which may be caused by a number of factors such as low blood pressure e.g. due to sepsis, blood loss or surgery, or the effect of a chemical agent, e.g. a medicine or drug, administered to the subject to treat another disease, disorder or condition. Kidney injury caused by ischemia may be ischemia-induced kidney injury, or ischemia-induced acute kidney injury. Kidney injury caused by crush injury may be ischemia-induced kidney injury with vasoconstriction or can be caused by tubular cast mechanical factors or toxic effects of circulating factors e.g. myoglobin.

In some embodiments the kidney injury, which may be AKI, is characterised by damage to, which may in some cases include or lead to death of, tubular epithelial cells (TECs) of the kidney, i.e. renal tubular epithelial cells. The TECs may be proximal or distal, both of which may be damaged in AKI, as may also the podocytes in the kidney glomerulus. Damage to TECs may also be any type of damage, injury or insult, e.g. as described above this may be mechanical, chemical or ischemic damage. Damage to TECs is a common causative factor of kidney injury, particularly AKI. Proliferation of TECs provides a mechanism for recovery and restoration of kidney function, whereas failure of TECs to proliferate can lead to disease development and progression, e.g. to chronic kidney disease and renal failure. Proliferation of podocyte precursors to restore glomerulus function may also occur, but is not as well described as TEC proliferation. Mechanical damage may include e.g. unilateral ureteric obstruction (UUO).

In some embodiments the kidney injury is nephrotoxicity, referring to toxicity of the kidneys. Nephrotoxicity can arise as a result of toxic effects of certain substances on renal function, and may therefore be viewed as a consequence of chemical damage or injury. As with chemical damage or injury, nephrotoxicity may be a

side effect of the administration of an agent to treat a disease or condition not occurring in the kidney, or occurring both in the kidney and in one or more other tissues. In some embodiments nephrotoxicity may be a side effect of administration of a chemotherapeutic agent administered to the subject in order to prevent or treat cancer. As such, nephrotoxicity may be a form of drug-induced kidney injury or drug-induced acute kidney injury. In some embodiments kidney injury may be induced by folic acid, i.e. is folate-induced kidney injury.

In some embodiments, the antigen-binding molecules are provided for use in the diagnosis, treatment and/or prophylaxis of cisplatin-induced kidney injury. This may include cisplatin-induced acute kidney injury or cisplatin-induced nephrotoxicity. Cisplatin (dichlorodiamino platinum; SP-4-2)-diamminedichloroplatinum(II)) is a chemotherapeutic agent that is widely used to treat a range of cancers including head and neck, breast, lung, testis, ovarian, brain, and bladder cancers and is widely acknowledged to lead to kidney injury and dysfunction involving tubular damage and necrosis (e.g. Oh et al., *Electrolyte Blood Press* 2014 Dec; 12(2): 55-65; PA Arunkumar et al., *Asian Pac J Trop Biomed* 2012 Aug 2(8): 640-644). Other platinum-based chemotherapeutics agents also cause kidney damage.

It is recognised that a subject having kidney injury may also present with fibrosis of the kidney, either as a disease condition having a separable etiology or as a secondary effect of the kidney injury. In some embodiments the kidney injury being diagnosed, treated or prevented is not fibrosis of the kidney, e.g. renal fibrosis. In some embodiments the subject does not have fibrosis. In some embodiments TEC damage occurs in the absence of fibrosis. In some embodiments fibrosis arises separately (e.g. secondarily to) AKI, e.g. due to incomplete regeneration of TECs. In some embodiments, the damaged TECs in the subject are not pro-fibrotic TECs. In some embodiments, fibrosis does not arise.

In some embodiments, the antigen-binding molecules of the present invention are provided for use in methods to treat/prevent a disease/disorder associated with infection, in particular where infection leads directly or indirectly to fibrosis, cancer or inflammation. A disease associated with infection may be a disease which is caused or exacerbated by infection with the relevant infectious agent, or may be a disease for which infection with the relevant infectious agent is a risk factor.

An infection may be any infection or infectious disease, e.g. bacterial, viral, fungal, or parasitic infection. In particular embodiments, the disease/disorder may be associated with a viral infection. In some embodiments it may be particularly desirable to treat chronic/persistent infections, e.g. where such infections are associated with inflammation, cancer and/or fibrosis.

The infection may be chronic, persistent, latent or slow, and may be the result of bacterial, viral, fungal or parasitic infection. As such, treatment may be provided to patients having a bacterial, viral or fungal infection. Examples of bacterial infections include infection with *Helicobacter pylori* and *Mycobacterium tuberculosis* infection of the lung. Examples of viral infections include infection with EBV, HPV, HIV, hepatitis B or hepatitis C.

The treatment may involve ameliorating, treating, or preventing any disease/disorder/condition associated with IL-11 signalling, and/or described herein, by inhibiting the biological activity of IL-11 or a complex comprising IL-11. The treatment may involve reversing or regressing the disease/disorder by inhibiting the biological activity of IL-11 or a complex comprising IL-11. Such methods may include the administration of the antibodies/fragments/compositions according to the present invention to bind to and inhibit the biological activity of IL-11 or a complex comprising IL-11. Herein, inhibiting the biological activity of IL-11 or a complex comprising IL-11 may be referred to as 'neutralising'.

Methods of treatment may optionally include the co-administration of biological adjuvants (e.g., interleukins, cytokines, Bacillus Comette-Guerin, monophosphoryl lipid A, etc.) in combination with conventional therapies for treating cancer such as treatment with an agent for treating cancer (e.g. chemotherapy), radiation, or surgery. Methods of medical treatment may also involve in vivo, ex vivo, and adoptive immunotherapies, including those using autologous and/or heterologous cells or immortalized cell lines.

The treatment may be aimed at prevention of a disease/disorder associated with overactive/elevated IL-11 mediated signalling. As such, the antibodies, antigen binding fragments and polypeptides may be used to formulate pharmaceutical compositions or medicaments and subjects may be prophylactically treated against development of a disease state. This may take place before the onset of symptoms of the disease state, and/or may be given to subjects considered to be at greater risk of the disease or disorder.

Administration of the agents according to the present disclosure is preferably in a "therapeutically effective" or "prophylactically effective" amount, this being sufficient to show benefit to the subject. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the disease/condition and the nature of the agent. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disease/condition to be treated, the condition of the individual subject, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins.

The antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors, cells and compositions described herein are preferably formulated as a medicament or pharmaceutical together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The term "pharmaceutically acceptable" as used herein pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, adjuvant, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation. Suitable carriers, adjuvants, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's

Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 2nd edition, 1994.

5 The formulations may be prepared for administration as suitable for the disease/condition to be treated. For example, formulations may be formulated for topical, parenteral, systemic, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, local ocular (e.g. subconjunctival, intravitreal, retrobulbar, intracameral), intra-conjunctival, subcutaneous, oral, or transdermal routes of administration which may include injection. The agents of the present disclosure may be formulated in fluid or solid form. Fluid
10 formulations may be formulated for administration by injection or infusion to a selected region of the human or animal body. Injectable formulations may comprise the selected agent in a sterile or isotonic medium.

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into
15 association the active compound with carriers (e.g., liquid carriers, finely divided solid carrier, etc.), and then shaping the product, if necessary.

In accordance with the present invention methods are also provided for the production of pharmaceutically useful compositions, such methods of production may comprise one or more steps selected from: isolating
20 an antibody or antigen binding fragment as described herein; and/or mixing an isolated antibody or antigen binding fragment as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent. For example, a further aspect of the present invention relates to a method of formulating or producing a medicament or pharmaceutical composition for use in a method of medical treatment, the method comprising formulating a pharmaceutical composition or medicament by mixing an antibody or
25 antigen binding fragment as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

Multiple doses of the antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition may be provided. One or more, or each, of the
30 doses may be accompanied by simultaneous or sequential administration of another therapeutic agent.

Multiple doses may be separated by a predetermined time interval, which may be selected to be one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 days, or 1, 2, 3, 4, 5, or 6 months. By way of example, doses may be given once every 7, 14, 21 or 28 days (plus
35 or minus 3, 2, or 1 days).

The antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors, cells and compositions described herein may be administered alone or in combination with other therapeutic or prophylactic intervention. Such other therapeutic or prophylactic intervention may occur before, during and/or
40 after the therapies encompassed by the disclosure, and the deliveries of the other therapeutic or prophylactic interventions may occur via the same or different administration routes as the therapies of the disclosure.

In some embodiments, administration of the antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors, cells and compositions described herein may be accompanied by an agent for treating or preventing infection (e.g. an antibiotic, anti-viral, anti-fungal or anti-parasitic agent). In some embodiments, treatment with an antibody, antigen binding fragment or composition of the present invention may be accompanied by an agent for treating or preventing inflammation (e.g. a non-steroidal anti-inflammatory drug (NSAID)). In some embodiments, treatment with an antibody, antigen binding fragment or composition of the present invention may be accompanied by radiotherapy (i.e. treatment with ionising radiation, e.g. X-rays or γ-rays) and/or an agent for treating or preventing cancer (e.g. a chemotherapeutic agent). In some embodiments the chemotherapeutic agent is an alkylating agent, e.g. cisplatin. In some embodiments, the antibody, antigen binding fragment or composition of the present invention may be administered as part of a combination treatment with an immunotherapy.

Simultaneous administration refers to administration of the agents together, for example as a pharmaceutical composition containing the agents (i.e. a combined preparation), or immediately after each other and optionally via the same route of administration, e.g. to the same artery, vein or other blood vessel. In certain embodiments upon simultaneous administration the two or more of the agents may be administered via different routes of administration. In some embodiments simultaneous administration refers to administration at the same time, or within e.g. 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 8 hrs, 12 hrs, 24 hrs, 36 hrs or 48 hrs.

Sequential administration refers to administration of one or more of the agents followed after a given time interval by separate administration of another of the agents. It is not required that the two agents are administered by the same route, although this is the case in some embodiments. The time interval may be any time interval, including hours, days, weeks, months, or years. In some embodiments sequential administration refers to administrations separated by a time interval of one of at least 10 min, 30 min, 1 hr, 6 hrs, 8 hrs, 12 hrs, 24 hrs, 36 hrs, 48 hrs, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 6 weeks, 2 months, 3 months, 4 months, 5 months or 6 months.

Methods of detection

The invention also provides the articles of the present invention for use in methods for detecting, localizing or imaging IL-11 or a complex comprising IL-11, or cells expressing/comprising IL-11 or a complex comprising IL-11. The antigen-binding molecules described herein may be used in methods that involve binding of the antigen-binding molecule to IL-11 or a complex comprising IL-11. Such methods may involve detection of the bound complex of the antigen-binding molecule and IL-11 or a complex comprising IL-11.

Detection of IL-11 or a complex comprising IL-11 may be useful in methods of diagnosing/prognosing a disease/condition in which IL-11 mediated signalling and/or cells expressing/comprising IL-11 or a complex comprising IL-11 are pathologically implicated, identifying subjects at risk of developing such diseases/conditions, and/or may be useful in methods of predicting a subject's response to a therapeutic intervention.

As such, a method is provided, comprising contacting a sample containing, or suspected to contain, IL-11 or a complex comprising IL-11 or cells expressing/comprising IL-11 or a complex comprising IL-11 with an

antigen-binding molecule as described herein, and detecting the formation of a complex of the antigen-binding molecule and IL-11/a complex comprising IL-11. Also provided is a method comprising contacting a sample containing, or suspected to contain, a cell expressing/comprising IL-11 or a complex comprising IL-11 with an antigen-binding molecule as described herein and detecting the formation of a complex of the antigen-binding molecule and a cell expressing/comprising IL-11 or a complex comprising IL-11.

Suitable method formats are well known in the art, including immunoassays such as sandwich assays, e.g. ELISA. The methods may involve labelling the antigen-binding molecule, or target(s), or both, with a detectable moiety, e.g. a fluorescent label, phosphorescent label, luminescent label, immuno-detectable label, radiolabel, chemical, nucleic acid or enzymatic label. IL-11 expression may be measured by immunohistochemistry (IHC), for example of a tissue sample obtained by biopsy. In some embodiments, the label may be selected from: a radio-nucleotide, positron-emitting radionuclide (e.g. for positron emission tomography (PET)), MRI contrast agent or fluorescent label.

Detection techniques are well known to those of skill in the art and can be selected to correspond with the labelling agent. Analysis *in vitro* or *in vivo* of processes mediated by IL-11 may involve analysis by positron emission tomography (PET), magnetic resonance imaging (MRI), or fluorescence imaging, e.g. by detection of appropriately labelled species.

Methods of this kind may provide the basis of a method of diagnosis of a disease or condition requiring detection and or quantitation of IL-11 or a complex comprising IL-11. Such methods may be performed *in vitro* on a subject sample, or following processing of a subject sample. Once the sample is collected, the subject is not required to be present for the *in vitro* method of diagnosis to be performed and therefore the method may be one which is not practised on the human or animal body. In some embodiments the antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors, cell or compositions according to the present disclosure are provided for use in any method of diagnosis, detection or quantification described herein.

Such methods may involve detecting or quantifying IL-11 or a complex comprising IL-11, or cells expressing IL-11 or a complex comprising IL-11, e.g. in a patient sample. Where the method comprises quantifying the relevant factor, the method may further comprise comparing the determined amount against a standard or reference value as part of the diagnostic or prognostic evaluation. Other diagnostic/prognostic tests may be used in conjunction with those described herein to enhance the accuracy of the diagnosis or prognosis or to confirm a result obtained by using the tests described herein.

Detection in a sample of IL-11 or a complex comprising IL-11 may be used for the purpose of diagnosis of an infectious disease, autoimmune disorder or a cancerous condition in the subject, diagnosis of a predisposition to an infectious disease, autoimmune disorder or a cancerous condition or for providing a prognosis (prognosticating) of an infectious disease, autoimmune disorder or a cancerous condition. The diagnosis or prognosis may relate to an existing (previously diagnosed) infectious, inflammatory or autoimmune disease/disorder or cancerous condition.

- Where an increased level of IL-11 or a complex comprising IL-11 is detected, or where the presence of – or an increased number/proportion of – cells expressing/comprising IL-11 or a complex comprising IL-11 is detected in a sample obtained from a subject, the subject may be diagnosed as having a disease/condition a disease/condition according to the present disclosure, or being at risk of developing such a
- 5 disease/condition. In such methods, an “increased” level of expression or number/proportion of cells refers to a level/number/proportion which is greater than the level/number/proportion determined for an appropriate control condition, such as the level/number/proportion detected in a comparable sample (e.g. a sample of the same kind, e.g. obtained from the same fluid, tissue, organ etc.), e.g. obtained from a healthy subject.
- 10 Where an increased level of IL-11 or a complex comprising IL-11 is detected, or where the presence of – or an increased number/proportion of – cells expressing/comprising IL-11 or a complex comprising IL-11 is detected in a sample obtained from a subject, the subject may be determined to have a poorer prognosis as compared to a subject determined to have a lower level of IL-11 or a complex comprising IL-11, or a reduced number/proportion of cells expressing/comprising IL-11 or a complex comprising IL-11 in a comparable
- 15 sample (e.g. a sample of the same kind, e.g. obtained from the same fluid, tissue, organ etc.).

Thus the present invention provides methods for selecting/stratifying a subject for treatment with the antigen-binding molecules, polypeptides, CARs, nucleic acids, expression vectors, cell or compositions according to the present invention. In some embodiments a subject is selected for treatment/prevention in accordance

20 with the invention, or is identified as a subject which would benefit from such treatment/prevention, based on detection/quantification of IL-11 or a complex comprising IL-11, or cells expressing IL-11 or a complex comprising IL-11, e.g. in a sample obtained from the subject. The level of IL-11 or a complex comprising IL-11 present in a subject sample may be indicative that a subject may respond to treatment with an antigen-binding molecule or composition according to the present invention. The presence of a high level of IL-11 or

25 a complex comprising IL-11 in a sample may be used to select a subject for treatment as described herein. The antigen-binding molecules of the present invention may therefore be used to select a subject for treatment with IL-11-targeted therapy.

A sample may be taken from any tissue or bodily fluid. The sample may comprise or may be derived from: a

30 quantity of blood; a quantity of serum derived from the individual's blood which may comprise the fluid portion of the blood obtained after removal of the fibrin clot and blood cells; a tissue sample or biopsy; pleural fluid; cerebrospinal fluid (CSF); or cells isolated from said individual. In some embodiments, the sample may be obtained or derived from a tissue or tissues which are affected by the disease/disorder (e.g. tissue or tissues in which symptoms of the disease manifest, or which are involved in the pathogenesis of the

35 disease/disorder).

Methods of diagnosis or prognosis according to the present invention may be performed *in vitro* on a sample obtained from a subject, or following processing of a sample obtained from a subject. Once the sample is collected, the patient is not required to be present for the *in vitro* method of diagnosis or prognosis to be

40 performed and therefore the method may be one which is not practised on the human or animal body. The term “*in vitro*” is intended to encompass experiments with cells in culture whereas the term “*in vivo*” is intended to encompass experiments with and/or treatment of intact multi-cellular organisms.

The diagnostic and prognostic methods of the present invention may be performed on samples obtained from a subject at multiple time points throughout the course of the disease and/or treatment, and may be used monitor development of the disease/condition over time, e.g. in response to treatment administered to the subject. The results of characterisation in accordance with the methods may be used to inform clinical decisions as to when and what kind of therapy to administer to a subject.

Subjects

The subject in accordance with aspects the invention described herein may be any animal or human. The subject is preferably mammalian, more preferably human. The subject may be a non-human mammal, but is more preferably human. The subject may be male or female. The subject may be a patient. A subject may have been diagnosed with a disease or condition requiring treatment (e.g. a cancer), may be suspected of having such a disease/condition, or may be at risk of developing/contracting such a disease/condition.

The subject/patient may have a disease/disorder that would derive therapeutic or prophylactic benefit from a reduction in the level of (i.e. inhibition or antagonism of) IL-11 mediated signalling, or a reduction in the number and/or activity of cells expressing IL-11R α or a complex comprising IL-11R α . The subject/patient may have a disease/disorder as described herein. The subject/patient may have been diagnosed with a disease/disorder as described herein requiring treatment, may be suspected of having such a disease/disorder, or may be at risk of developing such a disease/disorder.

In embodiments according to the present invention the subject is preferably a human subject. In some embodiments, the subject to be treated according to a therapeutic or prophylactic method of the invention herein is a subject having, or at risk of developing, a cancer. In embodiments according to the present invention, a subject may be selected for treatment according to the methods based on characterisation for certain markers of such disease/condition.

Kits

In some aspects of the invention described herein a kit of parts is provided. In some embodiments the kit may have at least one container having a predetermined quantity of an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein.

In some embodiments, the kit may comprise materials for producing an antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein.

The kit may provide the antigen-binding molecule, polypeptide, CAR, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition together with instructions for administration to a patient in order to treat a specified disease/condition.

In some embodiments the kit may further comprise at least one container having a predetermined quantity of another therapeutic agent (e.g. anti-infective agent or chemotherapy agent). In such embodiments, the kit may also comprise a second medicament or pharmaceutical composition such that the two medicaments or pharmaceutical compositions may be administered simultaneously or separately such that they provide a combined treatment for the specific disease or condition. The therapeutic agent may also be formulated so as to be suitable for injection or infusion to a tumor or to the blood.

Sequence identity

As used herein, "sequence identity" refers to the percent of nucleotides/amino acid residues in a subject sequence that are identical to nucleotides/amino acid residues in a reference sequence, after aligning the sequences and, if necessary, introducing gaps, to achieve the maximum percent sequence identity between the sequences. Pairwise and multiple sequence alignment for the purposes of determining percent sequence identity between two or more amino acid or nucleic acid sequences can be achieved in various ways known to a person of skill in the art, for instance, using publicly available computer software such as ClustalOmega (Söding, J. 2005, Bioinformatics 21, 951-960), T-coffee (Notredame et al. 2000, J. Mol. Biol. (2000) 302, 205-217), Kalign (Lassmann and Sonnhammer 2005, BMC Bioinformatics, 6(298)) and MAFFT (Kato and Standley 2013, Molecular Biology and Evolution, 30(4) 772-780 software. When using such software, the default parameters, e.g. for gap penalty and extension penalty, are preferably used.

Sequences

SEQ ID NO:	DESCRIPTION	SEQUENCE
1	Human IL-11 (UniProt: P20809)	MNCVCRLVLVLSLWPD TAVAPGPPPGPPRVSPDPRAELDSTVLLTRSLADTRQLAAQLRDKFP ADGDHNLDSLPTLAMSAGALGALQLPGVLT RLRLADLLSYLRHVQWLR RAGGSSSLKTLEPELGT LQ ARLDRLRLRLQLLSRLALPQPPDP PAPP LAPPSSAWGGIRAAHAILGGLHLTLDWAVRG LLLLK TRL
2	Human gp130 (UniProt P40189-1)	MLTLQTWLVQALFIFLTTESTGELLDP CGYISPE SPVVQLHSNFTAVCVLKEKCMDFYHVNANYIV WKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIV NEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPT SCTVDYSTVYFVNIEVWVEA ENALGKVTSDHINFDPVYKVKPNPPHNL SVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDAST WSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAPSF WYKIDPSHTQGYRTVQLVWKTLP PFEANGKILDYEVLTTRWKS HLQNYTVNATKLT VNLTDNRYL ATLTVRNLVGKSDAAVL TIPACDFQATHPVM DLKAFPKDNMLWVEWTPRESVKKYILEWCVLSD KAPCITDWQEDGT VHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRT KKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHT EYTLSSLTSDTLYMVRMA AYTDEGGKDGPEFTFTTPKFAQGEIEAIVPVCLAFLLTLLGVLCFNKRDLIKKHIWPNVPDPSK SHIAQWSPHTPPRHNFNSKQMYSDGNFTDVS VVEIEANDKKPFEDLKS LDFLKKKEINTEGHS SGIGGSSCMSSSRPSISSDENESSQNTSSTVQYSTV VHSYRQHVPSVQVFSRSESTQPLLD S EERPEDLQLVDHVDGGD GILPRQYFKQNC SQHESSPDISHFERSKQVSSVNEEDFVRLKQQIS DHISQSCGSGQM KMFQEVSAADAFGPGTEGQVERFETVGM EAATDEGMPKSYLPQTVRQGGY MPQ
3	Human IL11RA (UniProt Q14626)	MSSSCSGLSRVLVAVATALVSASSPCQAWGPPGVQY GQPGRSVKLCCPGVTAGDPVSWFRD GEPKLLQGPD SGLGHELVL AQADSTDEGT YICQTLDGALGGTVTLQLGYPPARPV VSCQAADYE NFSC TWSPSQISGLPTRYLT SYRKKT VLGADSQRRSPSTGPWPCPDPLGAARC VVHGAEFWS QYRINVTEVNPLGASTRLLDVSLQ SILRPDP PQGLRVESVPGYPRRLRASWTYPASWPCQPHFLL KFRLQYRPAQHPAWSTVEPAGLEEVIDDAVAGL PHAVRVSARDFLDAGTWSTWSPEAWGTPST GTIPKEIPAWGQLHTQPEVEPQVDS PAPP RPSLQPHPRLLDHRDSVEQVAVLASLGILSFLGLVAG ALALGLWLRRLRRGGKDGSPKPGFLASVIPVDRRPGAPNL
4	IL-11:IL-11Ra fusion protein	MGWSCILFLVATATGVHSPQAWGPPGVQY GQPGRSVKLCCPGVTAGDPVSWFRD GEPKLLQG PDSGLGHELVL AQADSTDEGT YICQTLDGALGGTVTLQLGYPPARPV VSCQAADYENFSC TWS SQISGLPTRYLT SYRKKT VLGADSQRRSPSTGPWPCPDPLGAARC VVHGAEFWSQYRINVTEV NPLGASTRLLDVSLQ SILRPDP PQGLRVESVPGYPRRLRASWTYPASWPCQPHFLLKFRLQYRPA QHPAWSTVEPAGLEEVIDDAVAGL PHAVRVSARDFLDAGTWSTWSPEAWGTPSTGGPAGQSGG GGGSGGGSGGGSVPGPPGPPRVSPDPRAELDSTVLLTRSLADTRQLAAQLRDKFPADGDHN LDLPTLAMSAGALGALQLPGVLT RLRLADLLSYLRHVQWLR RAGGSSSLKTLEPELGT LQARLDRL LRLQLLSRLALPQPPDP PAPP LAPPSSAWGGIRAAHAILGGLHLTLDWAVRG LLLLKTRLHHH

		HHH
5	Nucleotide sequence encoding IL-11:IL-11Ra fusion protein	GAATTCCTCCGCGCCACCATGGGCTGGTCTGCATCATCCTGTTTCTGGTGGCCACAGCCACC GGCGTGCACCTCTCCACAGGCTTGGGGACCTCCAGGCGTGACATATGGCCAGCCTGGCAGAT CCGTGAAGCTGTGCTGTCTGGCGTGACAGCTGGCGACCCCTGTGTCTGGTTACAGATGG CGAGCCCCAAGCTGCTGCAGGGCCCAGATTCTGGACTGGGCCACGAAGTGGTGTGGCCAG GCCGATTCTACCGACGAGGGCACCTACATCTGCCAGACCTGGATGGCGCCCTGGGCGGAA CAGTGACACTGCAGCTGGGCTACCTCCCGCCAGACCTGTGGTGTCTTGTCTAGGCCGCCGA CTACGAGAAGCTTCAGCTGCACATGGTCCCCCAGCCAGATCAGCGGCCTGCCACACGATACC TGACCAGCTACCGGAAGAAAACCGTGTGGGCGCCGACAGCCAGAGAAGAAGCCCTTCTAC AGGCCCTGGCCCTGCCCTCAGGATCCTCTGGGAGCTGCCAGATGTGTGGTGCACGGCGCC GAGTTCTGGTCCCAGTACCGGATCAACGTGACCGAAGTGAACCCCTGGGCGCCTCCACAA GACTGCTGGATGTGTCCCTGCAGAGCATCCTGCGGCCGATCCTCCACAGGGCCTGAGAGT GGAAAGCGTGCCCGGCTACCCAGAAAGGCTGAGAGCCAGCTGGACATACCCCGCCTCTTGG CCTTGCCAGCCCCACTTCTGCTGAAGTTTCGGCTGCAGTACCGGCCAGCCAGCACCCCTG CTTGAGACACAGTGAACCTGCCGGCTGGAAGAAGTGATCACAGACGCCCTGGCCGGACT GCCTCATGCTGTGCGGGTCTCCGCCAGAGACTTTCTGGATGCCGGCACCTGGTCTACCTGG TCCCCAGAAGCTGGGGCACACCTTCTACTGGCGGACCTGCTGGACAGTCTGGCGGAGGCG GAGGAAGTGGCGGAGGATCAGGGGGAGGATCTGTGCCTGGACCTCCTCCAGGACCCCTA GAGTGTCCCCAGATCCTAGGGCCGAGCTGGACTCTACCGTGTGCTGACAGATCCTGTCT GGCCGACACAAGGACGCTGGCTGCCAGCTGAGAGACAAGTTCCCCGCCGACGGCGACCA CAACCTGGATAGCCTGCCTACCTGGCCATGTCTGCTGGCGCAGTGGGGCTCTGCAGCTG CCTGGGGTGTGACTAGACTGAGAGCCGACCTGCTGAGCTACCTGCGGCATGTGCAGTGGC TGAGAAGGGCTGGCGGCAGCAGCCTGAAACCTGGAACCTGAGCTGGGCACACTGCGAGGC CAGACTGGACAGACTGCTGCGCAGACTGCAGCTGCTGATGAGCAGACTGGCTCTGCCCCAG CCTCCTCCTGACCCCTCCTGCTCCTCACTGGCTCCTCAAGCTGCTTGGGGCGGAATTAG AGCCGCCCACGCCATTCTGGGAGGCCTGCACCTGACACTGGATTGGGCAGTGGGGGCTG CTGCTGCTGAAAACAGACTGCACCACCACCATCACCCTGATAAGCTT
6	YU100-H01 VH	QVQLVQSGGGVVPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADS VKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDDYWGQGLTVTVSS
7	YU100-H01 VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLG
8	YU100-G08 VH	QVQLVQSGGGVVPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYAD SVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGLTVTVSS
9	YU100-G08 VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQHPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCCSYAGRYTWMFGGGTKVTVLG
10	YU100-F11 VH	QVQLVESGGGVVPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADS VKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGLTVTVSS
11	YU100-F11 VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLG
12	01A VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCASYAGSYTWVFGGGTKLTVLG
13	01G VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCASYAGSYTWVFGGGTKLTVLG
14	01I VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCISYAGSYTWVFGGGTKLTVLG
15	01L VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCISYAGSYTWVFGGGTKLTVLG
16	01Q VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCQSYAGSYTWVFGGGTKLTVLG
17	01S VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCQSYAGSYTWVFGGGTKLTVLG
18	01T VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCTSYAGSYTWVFGGGTKLTVLG
19	01V VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCVSYAGSYTWVFGGGTKLTVLG
20	02A VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCASYAGRYTWMFGGGTKVTVLG
21	02G VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCASYAGRYTWMFGGGTKVTVLG
22	02I VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCISYAGRYTWMFGGGTKVTVLG
23	02L VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCISYAGRYTWMFGGGTKVTVLG
24	02Q VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCQSYAGRYTWMFGGGTKVTVLG
25	02S VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCQSYAGRYTWMFGGGTKVTVLG
26	02T VL	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCTSYAGRYTWMFGGGTKVTVLG

27	02V VL	QSALTQPRSVSGSPGQSVTLSTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCVSYAGRYTWMFGGGTQKTVTLG
28	03A VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCASYAGSYTWVFGGGTQLTVLG
29	03G VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCGSYAGSYTWVFGGGTQLTVLG
30	03I VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCISYAGSYTWVFGGGTQLTVLG
31	03L VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCLSYAGSYTWVFGGGTQLTVLG
32	03Q VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCQSYAGSYTWVFGGGTQLTVLG
33	03S VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCSSYAGSYTWVFGGGTQLTVLG
34	03T VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCTSYAGSYTWVFGGGTQLTVLG
35	03V VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMYDVTKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCVSYAGSYTWVFGGGTQLTVLG
36	YU100-H01 HC-CDR1	SYAMH
37	YU100-G08, YU100-F11 HC-CDR1	SYGMH
38	YU100-H01 YU100-G08 YU100-F11 HC-CDR2	VISYDGSNKYYADSVKG
39	YU100-H01 HC-CDR3	IMGYDYGDDYDVVDY
40	YU100-G08, YU100-F11 HC-CDR3	IGATDPLDY
41	YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V LC- CDR1	TGTSSDVAGYNYVS
42	YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T, 02V LC- CDR1	TGTSSDVGGYNYVS
43	YU100-F11, 03A, 03G, 03I, 03L, 03Q, 03S, 03T, 03V LC- CDR1	TGSSSDVAGYNYVS
44	YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V LC- CDR2	DVSERPS
45	YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T, 02V LC- CDR2	DVNERSS
46	YU100-F11, 03A, 03G, 03I, 03L, 03Q, 03S, 03T, 03V LC- CDR2	DVTKRPS
47	YU100-H01, YU100-F11 LC-CDR3	CSYAGSYTWV
48	01A, 03A, LC-CDR3	ASYAGSYTWV
49	01G, 03G LC-CDR3	GSYAGSYTWV
50	01I, 03I LC-CDR3	ISYAGSYTWV
51	01L, 03L LC-CDR3	LSYAGSYTWV
52	01Q, 03Q LC-CDR3	QSYAGSYTWV

53	01S, 03S LC-CDR3	SSYAGSYTWV
54	01T, 03T LC-CDR3	TSYAGSYTWV
55	01V, 03V LC-CDR3	VSYAGSYTWV
56	YU100-G08 LC-CDR3	CSYAGRYTWM
57	02A LC-CDR3	ASYAGRYTWM
58	02G LC-CDR3	GSYAGRYTWM
59	02I LC-CDR3	ISYAGRYTWM
60	02L LC-CDR3	LSYAGRYTWM
61	02Q LC-CDR3	QSYAGRYTWM
62	02S LC-CDR3	SSYAGRYTWM
63	02T LC-CDR3	TSYAGRYTWM
64	02V LC-CDR3	VSYAGRYTWM
65	YU100-H01, YU100-G08 HC-FR1	QVQLVQSGGGVWPGRSLRLSCAASGFTFS
66	YU100-F11 HC-FR1	QVQLVESGGGVWPGRSLRLSCAASGFTFS
67	YU100-H01 YU100-G08 YU100-F11 HC-FR2	WVRQAPGKGLEWVA
68	YU100-H01 HC-FR3	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
69	YU100-G08, YU100-F11 HC-FR3	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
70	YU100-H01 YU100-G08 YU100-F11 HC-FR4	WGQGTLVTVSS
71	YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V LC-FR1	QSALTQPRSVSGSPGQSVTISC
72	YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T, 02V LC-FR1	QSALTQPRSVSGSPGQSVTLSC
73	YU100-F11, 03A, 03G, 03I, 03L, 03Q, 03S, 03T, 03V LC- FR1	QSALTQPASVSGSPGQSITISC
74	YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V, YU100-F11, 03A, 03G, 03I, 03L, 03Q, 03S, 03T, 03V LC-FR2	WYQQHPGKAPKLMY
75	YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T, 02V LC-FR2	WYQHYPGKAPKLMIF
76	YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V, YU100-G08,	GVPDRFSGSKSGNTASLTISGLQAEDADYYC

	02A, 02G, 02I, 02L, 02Q, 02S, 02T, 02V, YU100-F11, 03A, 03G, 03I, 03L, 03Q, 03S, 03T, 03V LC-FR3	
77	YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V LC-FR4	FGGGTKLTVLG
78	YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T, 02V LC-FR4	FGGGTKVTVLG
79	YU100-F11, 03A, 03G, 03I, 03L, 03Q, 03S, 03T, 03V LC-FR4	FGGGTQLTVLG
80	01X 03X LC-CDR3	X ₁ SYAGSYTWV X ₁ = A, G, I, L, Q, S, T or V
81	02X LC-CDR3	X ₁ SYAGRYTWM X ₁ = A, G, I, L, Q, S, T or V
82	01X VL	QSALTQPRSVSGSPGQSVTLISCTGTSSDVGAYNYVSWYQQHPGKAPKLMIFYDVSERPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCX ₁ SYAGSYTWVFGGGTKLTVLG X ₁ = A, G, I, L, Q, S, T or V
83	02X VL	QSALTQPRSVSGSPGQSVTLISCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCX ₁ SYAGRYTWMFGGGTKVTVLG X ₁ = A, G, I, L, Q, S, T or V
84	03X VL	QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMIFYDVKRPSGVPDRF SGSKSGNTASLTISGLQAEDEADYYCX ₁ SYAGSYTWVFGGGTQLTVLG X ₁ = A, G, I, L, Q, S, T or V
85	Human IgG1 constant region (IGHG1; UniProt: P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK KDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKS LSLSPGK
86	CH1 IgG1 (positions 1-98 of P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKV
87	Hinge IgG1 (positions 99-110 of P01857-1, v1)	EPKSCDKTHTCP
88	CH2 IgG1 (positions 111-223 of P01857-1, v1)	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
89	CH3 IgG1 (positions 224-330 of P01857-1, v1)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF FLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
90	Cκ CL (IGCK; UniProt: P01834-1, v2)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
91	3C6 VH 1	QVQLQESGPPELVKPGASVKIPCKASGYTFTDYNMDWV/KQSHGKSLEWIGDINPHNGGPIYNQKF TGKATLTVDKSSSTAYMELRSLTSEDVAVYYCARGELGHWFYFDVWGTGTTVTVSS
92	3C6 VH 2	EVQLQQSGPELVKPGASVKIPCKASGYTFTDYNMDWV/KQSHGKSLEWIGDINPHNGGPIYNQKF TGKATLTVDKSSSTAYMELRSLTSEDVAVYYCARGELGHWFYFDVWGTGTTVTVSS
93	3C6 VL 1	NIVMTQSPKSMMSVGERVTLTCKASENVVTVSWYQQKPEQSPKLLIYGASNRYTGVPDRFTG SGSATDFTLTISVQAEDLADYHCGQGYSYPYTFGGGTKEIK
94	3C6 VL 2	DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYIHWWYQQKPGQPPKLLIYLASNLDSGVPARF SGSGSGTDFTLNIHPVEEEDAATYYCQHSRDLPTFGGGTKEIK
95	3C6 VH 1, 3C6 VH 2, 3C6 VH 2.1, 3C6 VH 2.2,	DYNMD

	3C6 VH 2.3, 3C6 VH 2.4, 3C6 VH 2.5 HC-CDR1	
96	3C6 VH 1, 3C6 VH 2, 3C6 VH 2.1, 3C6 VH 2.2, 3C6 VH 2.3, 3C6 VH 2.4, 3C6 VH 2.5 HC-CDR2	DINPHNGGPIYNQKFTG
97	3C6 VH 1, 3C6 VH 2, 3C6 VH 2.1, 3C6 VH 2.2, 3C6 VH 2.3, 3C6 VH 2.4, 3C6 VH 2.5 HC-CDR3	GELGHWYFDV
98	3C6 VL 1 3C6 VL 1.1, 3C6 VL 1.2, 3C6 VL 1.3, 3C6 VL 1.4 LC-CDR1	KASENVVTVYS
99	3C6 VL 1 3C6 VL 1.1, 3C6 VL 1.2, 3C6 VL 1.3, 3C6 VL 1.4 LC-CDR2	GASNRYT
100	3C6 VL 1, 3C6 VL 1.1, 3C6 VL 1.2, 3C6 VL 1.3, 3C6 VL 1.4 LC-CDR3	GQGYSYPYT
101	3C6 VL 2, 3C6 VL 2.1, 3C6 VL 2.2, 3C6 VL 2.3, 3C6 VL 2.4 LC-CDR1	RASKSVSTSGYSYIH
102	3C6 VL 2, 3C6 VL 2.1, 3C6 VL 2.2, 3C6 VL 2.3, 3C6 VL 2.4 LC-CDR2	LASNLDS
103	3C6 VL 2, 3C6 VL 2.1, 3C6 VL 2.2, 3C6 VL 2.3, 3C6 VL 2.4 LC-CDR3	QHSRDLPT
104	3C6 VH 1 HC-FR1	QVQLQESGPELVKPGASVKIPCKASGYTFT
105	3C6 VH 2 HC-FR1	EVQLQQSGPELVKPGASVKIPCKASGYTFT
106	3C6 VH 1, 3C6 VH 2 HC-FR2	WVKQSHGKSLEWIG
107	3C6 VH 1, 3C6 VH 2 HC-FR3	KATLTVDKSSSTAYMELRSLTSEDVAVYYCAR
108	3C6 VH 1, 3C6 VH 2 HC-FR4	WGTGTTVTVSS

109	3C6 VL 1 LC-FR1	NIVMTQSPKSM SMSVGERVTLTC
110	3C6 VL 2 LC-FR1	DIVLTQSPASLAVSLGQRATISC
111	3C6 VL 1 LC-FR2	WYQQKPEQSPKLLIY
112	3C6 VL 2, 3C6 VL 1.1, 3C6 VL 1.2, 3C6 VL 1.3, 3C6 VL 1.4LC-FR2	WYQQKPGQPPKLLIY
113	3C6 VL 1 LC-FR3	GVPDRFTGSGSATDFTLTISVQAEDLADYHC
114	3C6 VL 2 LC-FR3	GVPARFSGSGSGTDFTLNIHPVEEEDAATYYC
115	3C6 VL 1, 3C6 VL 2 LC-FR4	FGGGTKLEIK
116	3C6 VH 2.1	EVQLVQSGPELKKPGASVKISCKASGYTFTDYNMDWVKQAHGQRLEWIGDINPHNGGPIYNQKF TGRATLTVDKSASTAYMELRSLTSEDVAVYYCARGELGHWYFDVWGQGTITVTVSS
117	3C6 VH 2.2	EVQLVQSGAEVKKPGASVKISCKASGYTFTDYNMDWVKQAPGQRLEWIGDINPHNGGPIYNQKF TGRATLTVDKSASTAYMELSSLRSEDVAVYYCARGELGHWYFDVWGQGTITVTVSS
118	3C6 VH 2.3	EVQLVQSGAEVKKPGASVKISCKASGYTFTDYNMDWVRQAPGQRLEWIGDINPHNGGPIYNQKF TGRVTLTVDKSASTAYMELSSLRSEDVAVYYCARGELGHWYFDVWGQGTITVTVSS
119	3C6 VH 2.4	QVQLVQSGAEVKKPGASVKVSKASGYTFTDYNMDWVRQAPGQRLEWIGDINPHNGGPIYNQKF FTGRVTITVDKSASTAYMELSSLRSEDVAVYYCARGELGHWYFDVWGQGTITVTVSS
120	3C6 VH 2.5	QVQLVQSGAEVKKPGASVKVSKASGYTFTDYNMDWVRQAPGQRLEWIGDINPHNGGPIYNQ KFTGRVTITVDKSASTAYMELSSLRSEDVAVYYCARGELGHWYFDVWGQGTITVTVSS
121	3C6 VL 2.1	DIVLTQSPASLALSPGERATLSCRASKSVSTSGYSYIHWWYQQKPGQPPRLIYLASNLD SGV PARF SGSGSGTDFTLNIHPLEEEEDFATYYCQHSRDLPTFGQGTKEIK
122	3C6 VL 2.2	DIVLTQSPASLALSPGERATLSCRASKSVSTSGYSYIHWWYQQKPGQAPRLIYLASNLD SGV PARF SGSGSGTDFTLTISSEEDFATYYCQHSRDLPTFGQGTKEIK
123	3C6 VL 2.3	DIVLTQSPATLSLSPGERATLSCRASKSVSTSGYSYIHWWYQQKPGQAPRLIYLASNLD SGV PARF SGSGSGTDFTLTISSEEDFATYYCQHSRDLPTFGQGTKEIK
124	3C6 VL 2.4	EIVLTQSPATLSLSPGERATLSCRASKSVSTSGYSYIHWWYQQKPGQAPRLIYLASNLD SGV PARF SGSGSGTDFTLTISSEEDFATYYCQHSRDLPTFGQGTKEIK
125	3C6 VL 1.1	NIVMTQSPDSL SVSVGERATLNCKASENVVTVSWYQQKPGQPPKLLIYGASNRYTGVPDRFTG SGSATDFTLTISSLQAEDLADYHCGQGYSPYTFGQGTKEIK
126	3C6 VL 1.2	NIVMTQSPDSLAVSVGERATLNCKASENVVTVSWYQQKPGQPPKLLIYGASNRYTGVPDRFTG SGSATDFTLTISSLQAEDLADYHCGQGYSPYTFGQGTKEIK
127	3C6 VL 1.3	DIVMTQSPDSLAVSLGERATINCKASENVVTVSWYQQKPGQPPKLLIYGASNRYTGVPDRFSGS GSATDFTLTISSLQAEDLADYHCGQGYSPYTFGQGTKEIK
128	3C6 VL 1.4	DIVMTQSPDSLAVSLGERATINCKASENVVTVSWYQQKPGQPPKLLIYGASNRYTGVPDRFSGS GSATDFTLTISSLQAEDVAVYHCGQGYSPYTFGQGTKEIK
129	3C6 VH 2.1 HC-FR1	EVQLVQSGPELKKPGASVKISCKASGYTFT
130	3C6 VH 2.2, 3C6 VH 2.3 HC-FR1	EVQLVQSGAEVKKPGASVKISCKASGYTFT
131	3C6 VH 2.4, 3C6 VH 2.5 HC-FR1	QVQLVQSGAEVKKPGASVKVSKASGYTFT
132	3C6 VH 2.1 HC-FR2	WVKQAHGQRLEWIG
133	3C6 VH 2.2 HC-FR2	WVKQAPGQRLEWIG
134	3C6 VH 2.3, 3C6 VH 2.4 HC-FR2	WVRQAPGQRLEWIG
135	3C6 VH 2.5 HC-FR2	WVRQAPGQRLEWMG
136	3C6 VH 2.1 HC-FR3	RATLTVDKSASTAYMELRSLTSEDVAVYYCAR
137	3C6 VH 2.2 HC-FR3	RATLTVDKSASTAYMELSSLRSEDVAVYYCAR
138	3C6 VH 2.3 HC-FR3	RVTITVDKSASTAYMELSSLRSEDVAVYYCAR
139	3C6 VH 2.4,	RVTITVDKSASTAYMELSSLRSEDVAVYYCAR

	3C6 VH 2.5 HC-FR3	
140	3C6 VH 2.1, 3C6 VH 2.2, 3C6 VH 2.3, 3C6 VH 2.4, 3C6 VH 2.5 HC-FR4	WGQGTTVTVSS
141	3C6 VL 2.1, 3C6 VL 2.2 LC-FR1	DIVLTQSPASLALSPGERATLSC
142	3C6 VL 2.3 LC-FR1	DIVLTQSPATLSLSPGERATLSC
143	3C6 VL 2.4 LC-FR1	EIVLTQSPATLSLSPGERATLSC
144	3C6 VL 2.1 LC-FR2	WYQQKPGQPPRLIY
145	3C6 VL 2.2, 3C6 VL 2.3, 3C6 VL 2.4 LC-FR2	WYQQKPGQAPRLIY
146	3C6 VL 2.1 LC-FR3	GVPARFSGSGSGTDFTLNHPLEEDFATYYC
147	3C6 VL 2.2 LC-FR3	GVPARFSGSGSGTDFTLTISLEEDFATYYC
148	3C6 VL 2.3, 3C6 VL 2.4 LC-FR3	GVPARFSGSGSGTDFTLTISLEPEDFATYYC
149	3C6 VL 2.1 3C6 VL 2.2 3C6 VL 2.3 3C6 VL 2.4 3C6 VL 1.1 3C6 VL 1.2 3C6 VL 1.3 3C6 VL 1.4 LC-FR4	FGQGTKLEIK
150	3C6 VL 1.1 LC-FR1	NIVMTQSPDSLVSVERATLNC
151	3C6 VL 1.2 LC-FR1	NIVMTQSPDSLAVSVGERATLNC
152	3C6 VL 1.3, 3C6 VL 1.4 LC-FR1	DIVMTQSPDSLAVSLGERATINC
153	3C6 VL 1.1 3C6 VL 1.2 LC-FR3	GVPDRFTGSGSATDFTLTISLQAEDLADYHC
154	3C6 VL 1.3 LC-FR3	GVPDRFSGSGSATDFTLTISLQAEDLADYHC
155	3C6 VL 1.4 LC-FR3	GVPDRFSGSGSATDFTLTISLQAEDVAVYHC
156	1H2 VH	QAQLQQSGAELARPGASVKLSCKASGYTFTSYGITWVKQRTGGGLEWIGDIYPRSGNIYYNENFK GEATLTADKSSSTAYMQLSRLTSEDSAVYFCARSGWEGWFAYWGQGTLLVTVSV
157	1H2 VL	DIVMTQSHKFMSTSVGDRVNITCKASQDVGSAAVWYQQKPGQSPKVLIVWASTRHTGVPDRFTG SGSGTDFTLTISNVQSEDLADYFCQQYSSYRTFGGGTKLEIK
158	1H2 HC-CDR1	SYGIT
159	1H2 HC-CDR2	DIYPRSGNIYYNENFKG
160	1H2 HC-CDR3	SGWEGWFAY
161	1H2 LC-CDR1	KASQDVGSAAV
162	1H2 LC-CDR2	WASTRHT
163	1H2 LC-CDR3	QQYSSYRT
164	1H2 HC-FR1	QAQLQQSGAELARPGASVKLSCKASGYTFT

165	1H2 HC-FR2	WVKQRTGQGLEWIG
166	1H2 HC-FR3	EATLTADKSSSTAYMQLSRLTSEDSAVYFCAR
167	1H2 HC-FR4	WGQGTLLTVSV
168	1H2 LC-FR1	DIVMTQSHKFMSTSVGDRVNITC
169	1H2 LC-FR2	WYQQKPGQSPKVLII
170	1H2 LC-FR3	GVPDRFTGSGSGTDFTLTISNVQSEDLADYFC
171	1H2 LC-FR4	FGGGTKLEIK
172	1H2 VH	CAGGCTCAGCTGCAGCAGTCTGGAGCTGAGCTGGCGAGGCCTGGGGCTTCAGTGAAGCTGT CCTGCAAGGCTTCTGGCTACACCTTCACAAGCTATGGTATAACCTGGGTGAAGCAGAGAACT GGACAGGGCCTTGAGTGGATTGGAGATATTTATCCTAGAAGTGGTAATATTTATTACAATGAG AACTTCAAGGGCGAGGCCACATTGACTGCAGACAAATCCTCCAGCACAGCCTATATGCAGCT CAGCAGACTGACATCTGAGGACTCTGCAGTCTATTTCTGTGCAAGATCCGGGTGGGAAGGCT GGTTTGCTTATTGGGGCCAAGGGACTCTGGTCACTGTCTCTGTA
173	1H2 VL	GACATTGTGATGACCCAGTCTCACAATTCATGTCCACATCAGTAGGAGACAGGGTCAACATC ACCTGCAAGGCCAGTCAGGATGTGGGTAGTGTGTAGTCTGGTATCAACAGAAACAGGGCA ATCTCCTAAAGTACTGATTTACTGGGCATCCACCCGGCACACTGGAGTCCCTGATCGCTTCAC AGGCAGTGGCTCTGGGACAGATTTCACTCTCACCATTAGCAATGTGCAGTCTGAAGACTTGG CAGATTATTTCTGTGAGCAATATAGCAGTTATCGGACGTTCCGTGGAGGCACCAAGCTGGAAA TCAAA
174	7D4 VH	EVQLQQSGPELVKPGASVKISCKASGYTFTDYNMDWVKQSQGRLEWIGDINPNYGGTIYNQKF KGKATLTVDKSSSTAYMELRSLTSEDITVYYCTRGELGHWFYFDVWGTGTTVTVSS
175	7D4 VL	DIVLTQSPPSLTSLGQQRATISCRASKSVSASGYSYMHWYQQKPGQPPKLLIYLTSLNESGVPARF SGSGSGTDFTLNIHPVEEEDAATYYCQHSWDLPTTFGGGTKEIK
176	7D4 HC-CDR1	DYNMD
177	7D4 HC-CDR2	DINPNYGGTIYNQKFKG
178	7D4 HC-CDR3	GELGHWFYFDV
179	7D4 LC-CDR1	RASKSVSASGYSYMH
180	7D4 LC-CDR2	LTSNLES
181	7D4 LC-CDR3	QHSWDLPTT
182	7D4 HC-FR1	EVQLQQSGPELVKPGASVKISCKASGYTFT
183	7D4 HC-FR2	WVKQSQGRLEWIG
184	7D4 HC-FR3	KATLTVDKSSSTAYMELRSLTSEDITVYYCTR
185	7D4 HC-FR4	WGTGTTVTVSS
186	7D4 LC-FR1	DIVLTQSPPSLTSLGQQRATISC
187	7D4 LC-FR2	WYQQKPGQPPKLLIY
188	7D4 LC-FR3	GVPARFSGSGSGTDFTLNIHPVEEEDAATYYC
189	7D4 LC-FR4	FGGGTKLEIK
190	7D4 VH	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATAT CCTGCAAGGCTTCTGGATACACATTCAGTACTGACTACAACATGGACTGGGTGAAGCAGAGTCAA GGAAAGAGACTTGAGTGGATTGGAGATATTAATCCTAACTATGGTGGTACTATCTACAACCAG AAGTTCAAGGGCAAGGCCACATTGACTGTTGACAAGTCTCCAGCACAGCCTACATGGAGCT CCGCAGCCTGACATCTGAGGACACTACAGTCTATTACTGTACAAGAGGGGAAGTGGGTCACT GGTACTTCGATGTCTGGGGCACAGGGACACGGTCACCGTCTCCTCA
191	7D4 VL	GACATTGTGCTGACACAGTCTCCTCCTTAACTGTGTCTCTGGGGCAGAGGGCCACCAT CTCATGCAGGGCCAGTAAAGTGTGAGTGCCTGCTGGCTATAGTTATATGCACTGGTACCAACA GAAACCAGGACAGCCACCCAACTCCTCATCTATCTTACATCCAACCTAGAAATCTGGGGTCCC TGCCAGGTTCAAGTGGCAGTGGGTCTGGGACAGACTTCACCTCAACATCCATCCTGTGGAGG AGGAGGATGCTGCAACCTATTACTGTGACACAGTTGGGACCTTCCTCCGACGTTCCGTGGA

		GGCACCAAGCTGGAAATCAAA
192	8H11 VH	EVQLQQSGPELVKPGASVKIPCKASGYTFTDYNIDWVKQSHGKSLEWIGDINPNYGGTLYNQKFK GKATLTVDKSSSTAYMELRSLTSEDVAVYYCARGELGHWFYFDVWGTGTTVTVSS
193	8H11 VL	DIVLTQSPASLAVSLGQRATISCRASKSVSTSDYSYMHWYQQKPGHPPKLLIYLASNLESGVPARF SGSGSGTDFTLNHPVEEEDAATYFCQHSRDLPTFGGGTKLEIK
194	8H11 HC-CDR1	DYNID
195	8H11 HC-CDR2	DINPNYGGTLYNQKFKG
196	8H11 HC-CDR3	GELGHWFYFDV
197	8H11 LC-CDR1	RASKSVSTSDYSYMH
198	8H11 LC-CDR2	LASNLES
199	8H11 LC-CDR3	QHSRDLPT
200	8H11 HC-FR1	EVQLQQSGPELVKPGASVKIPCKASGYTFT
201	8H11 HC-FR2	WVKQSHGKSLEWIG
202	8H11 HC-FR3	KATLTVDKSSSTAYMELRSLTSEDVAVYYCAR
203	8H11 HC-FR4	WGTGTTVTVSS
204	8H11 LC-FR1	DIVLTQSPASLAVSLGQRATISC
205	8H11 LC-FR2	WYQQKPGHPPKLLIY
206	8H11 LC-FR3	GVPARFSGSGSGTDFTLNHPVEEEDAATYFC
207	8H11 LC-FR4	FGGGTKLEIK
208	8H11 VH	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATAC CCTGCAAGGCTTCTGGATACACATTCACTGACTACAACATAGACTGGGTGAAGCAGAGCCAT GGAAAGAGCCTTGAGTGGATTGGAGATATTAATCCTAATTATGGTGGTACTCTCTACAACCAAG AAGTTCAAGGGCAAGGCAACATTGACTGTAGACAAGTCCCTCCAGCACAGCCTACATGGAAC CCGCAGCCTGACATCTGAGGACACTGCAGTCTATTACTGTGCAAGAGGGGAACCTGGGTCAC GGTACTTCGATGTCTGGGGCACAGGACCACGGTCACCGTCTCTCTCA
209	8H11 VL	GACATTGTGCTGACACAGTCTCCTGCTTCTAGCTGTATCTCTGGGGCAGAGGGCCACCAT CTCATGCAGGGCCAGCAAAAGTGTGAGTACATCTGACTATAGTTATATGCACTGGTACCAACA GAAACCAGGACACCCACCCAACTCCTCATCTATCTTGATCCAACTAGAACTCTGGGGTCCC TGCCAGGTTCAAGTGGCAGTGGGTCTGGGACAGACTTACCCTCAACATCCATCCTGTGGAGG AGGAGGATGCTGCAACCTATTTCTGTGACACAGTAGGGACCTTCTCCGACGTTCCGGTGG GGCACCAAGCTGGAAATCAAA
210	YU100-G08 VH- 02A VL	QVQLVQSGGVSVPGRSLRLSCAASGFTSSYGMHWVRQAPGKGLEWVAVISYDGSNKKYYAD SVKGRFTISRDNKNTLYLQMNSLRADTAVYYCAKIGATDPLDYWGQGLTVTVSSGSASAPKLE EGEFSEARVQSALTQPRSVSGSPGQSVTLSTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVN ERSSGVPRDFSGSKSGNTASLTISGLQAEDADYYCASYAGRYTWMFGGGTKVTVLGLQPKAAP VTLFPPS
211	Human IgG4 constant region (IGHG4; UniProt: P01861, v1)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSL SLGK
212	CH1 IgG4 (positions 1-98 of P01861, v1)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRV
213	Hinge IgG4 (positions 99-110 of P01861, v1)	ESKYGPPCPSCP
214	CH2 IgG4 (positions 111-220 of P01861, v1)	APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKISKAK
215	CH3 IgG4 (positions 221-327 of P01861, v1)	GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSD DGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGK
216	Human IgG4 constant region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDT

	(IGHG4; UniProt: P01861, v1; S241P)	LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSLGLK
217	Hinge IgG4 (positions 99-110 of P01861, v1; S241P)	ESKYGPPCPPCP
218	Human IgG4 constant region (IGHG4; UniProt: P01861, v1; S241P and L248E)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSLGLK
219	CH2 IgG4 (positions 111-220 of P01861, v1; L248E)	APFEFGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAK
220	YU100-G08 VH - Human IgG1 constant region (IGHG1; UniProt: P01857-1, v1)	QVQLVQSGGGVVPGRSLRLSCAASGFTSSYGMHWVRQAPGKGLEWVAIVSYDGSNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKLSLSLSPGK
221	YU100-G08 VH - Human IgG4 constant region (IGHG4; UniProt: P01861, v1)	QVQLVQSGGGVVPGRSLRLSCAASGFTSSYGMHWVRQAPGKGLEWVAIVSYDGSNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLTVTSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTCTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSLGLK
222	YU100-G08 VH - Human IgG4 constant region (IGHG4; UniProt: P01861, v1; S241P)	QVQLVQSGGGVVPGRSLRLSCAASGFTSSYGMHWVRQAPGKGLEWVAIVSYDGSNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLTVTSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTCTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSLGLK
223	YU100-G08 VH - Human IgG4 constant region (IGHG4; UniProt: P01861, v1; S241P and L248E)	QVQLVQSGGGVVPGRSLRLSCAASGFTSSYGMHWVRQAPGKGLEWVAIVSYDGSNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLTVTSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTCTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSLGLK
224	02A VL-C κ CL (IGCK; UniProt: P01834-1, v2)	QSALTQPRSVSGSPGQSVTLSTCTGTSSDVGGYNYVSWYQHPGKAPKLMIFDVNERSSGVPDRFSGSKSGNTASLTISGLQAEDADYASYAGRYTWMFGGGTKVTFVAPVLPSSDQELKSGTASVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
225	3C6 VH 2.2 - Human IgG1 constant region (IGHG1; UniProt: P01857-1, v1)	EVQLVQSGAEVKKPGASVKISKASGYTFTDYNMDWVKQAPGQRLEWIGDINPHNGGPIYNQKFTGRATLTVDKSASTAYMELSSLRSEDTAVYYCARGELGHWYFDVWGQGTITVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMEALHNHYTQKLSLSLSPGK
226	3C6 VH 2.2 - Human IgG4 constant region (IGHG4; UniProt: P01861, v1)	EVQLVQSGAEVKKPGASVKISKASGYTFTDYNMDWVKQAPGQRLEWIGDINPHNGGPIYNQKFTGRATLTVDKSASTAYMELSSLRSEDTAVYYCARGELGHWYFDVWGQGTITVTSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTCTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSLGLK
227	3C6 VH 2.2 - Human IgG4 constant region (IGHG4; UniProt: P01861, v1; S241P)	EVQLVQSGAEVKKPGASVKISKASGYTFTDYNMDWVKQAPGQRLEWIGDINPHNGGPIYNQKFTGRATLTVDKSASTAYMELSSLRSEDTAVYYCARGELGHWYFDVWGQGTITVTSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTCTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSLGLK

228	3C6 VH 2.2 - Human IgG4 constant region (IGHG4; UniProt: P01861, v1; S241P and L248E)	EVQLVQSGAEVKKPGASVKISCKASGYTFTDYNMDWVKQAPGQRLEWIGDINPHNGGPIYNQKF TGRATLTVDKSASTAYMELSSLRSEDTAVYYCARGELGHWFYFDVWGQGTTVTVSSASTKGPSVF PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSS SLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSGFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK
229	3C6 VL 2.2 - Cκ CL (IGCK; UniProt: P01834-1, v2)	DIVLTQSPASLALSPGERATLSCRASKSVSTSGYSYIHWHYQQKPGQAPRLLIYASNLDSGVPARF SGSGSGTDFTLTISSELEEDFATYYCQHSRDLPTTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
230	3C6 VL 2.1 - Cκ CL (IGCK; UniProt: P01834-1, v2)	DIVLTQSPASLALSPGERATLSCRASKSVSTSGYSYIHWHYQQKPGQAPRLLIYASNLDSGVPARF SGSGSGTDFTLNIHPLEEEDFATYYCQHSRDLPTTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
231	C _L CL (IGLC1; UniProt: P0CG04, v1)	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
232	C _L CL (IGLC2; UniProt: P0DOY2, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTTTPSKQSNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
233	C _L CL (IGLC3; UniProt: P0DOY3, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTTTPSKQSNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
234	C _L CL (IGLC6; UniProt: P0CF74, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETTTTPSKQSNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS
235	C _L CL (IGLC7; UniProt: A0M8Q6, v3)	GQPKAAPSVTFLFPPSSEELQANKATLVCLVSDFNPGAVTVAWKADGSPVKGVETTKPSKQSNK KYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS
236	02A VL-C _L CL (IGLC1; UniProt: P0CG04, v1)	QSALTQPRSVSGSPGQSVTLSTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCASYAGRYTWMFGGGTKVTVLGQPKANPTVTLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNK YAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS
237	02A VL-C _L CL (IGLC2; UniProt: P0DOY2, v1))	QSALTQPRSVSGSPGQSVTLSTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCASYAGRYTWMFGGGTKVTVLGQPKAAPSVTFLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTTTPSKQSNK YAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS
238	02A VL-C _L CL (IGLC3; UniProt: P0DOY3, v1)	QSALTQPRSVSGSPGQSVTLSTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCASYAGRYTWMFGGGTKVTVLGQPKAAPSVTFLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTTTPSKQSNK YAASSYLSLTPEQWKSH KSYSCQVTHEGSTVEKTVAPTECS
239	02A VL-C _L CL (IGLC6; UniProt: P0CF74, v1)	QSALTQPRSVSGSPGQSVTLSTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCASYAGRYTWMFGGGTKVTVLGQPKAAPSVTFLFPPSSE ELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETTTTPSKQSNK YAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPAECS
240	02A VL-C _L CL (IGLC7; UniProt: A0M8Q6, v3)	QSALTQPRSVSGSPGQSVTLSTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVPDR FSGSKSGNTASLTISGLQAEDEADYYCASYAGRYTWMFGGGTKVTVLGQPKAAPSVTFLFPPSSE ELQANKATLVCLVSDFNPGAVTVAWKADGSPVKGVETTKPSKQSNK YAASSYLSLTPEQWKSH RSYSCRVTHEGSTVEKTVAPAECS

Numbered paragraphs (paras) relating to aspects and embodiments of the invention:

1. An antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

5 HC-CDR1 having the amino acid sequence of SEQ ID NO:36 or 37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39 or 40; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:41, 42 or 43

10 LC-CDR2 having the amino acid sequence of SEQ ID NO:44, 45 or 46

LC-CDR3 having the amino acid sequence of SEQ ID NO:80 or 81.

2. The antigen-binding molecule according to para 1, wherein the antigen-binding molecule comprises:
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 - HC-CDR1 having the amino acid sequence of SEQ ID NO:36
 - 5 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - LC-CDR1 having the amino acid sequence of SEQ ID NO:41
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:44
 - 10 LC-CDR3 having the amino acid sequence of SEQ ID NO:80.
3. The antigen-binding molecule according to para 1, wherein the antigen-binding molecule comprises:
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 - HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 - 15 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - LC-CDR1 having the amino acid sequence of SEQ ID NO:42
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:45
 - 20 LC-CDR3 having the amino acid sequence of SEQ ID NO:81.
4. The antigen-binding molecule according to para 1, wherein the antigen-binding molecule comprises:
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 - HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 - 25 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 - 30 LC-CDR3 having the amino acid sequence of SEQ ID NO:80.
5. The antigen-binding molecule according to para 1 or para 2, wherein the antigen-binding molecule comprises:
- (a)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 - 35 HC-CDR1 having the amino acid sequence of SEQ ID NO:36
 - HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - 40 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:44
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:48;

- (b)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:36
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 5 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
 LC-CDR2 having the amino acid sequence of SEQ ID NO:44
 LC-CDR3 having the amino acid sequence of SEQ ID NO:49;
- 10 (c)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:36
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 15 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
 LC-CDR2 having the amino acid sequence of SEQ ID NO:44
 LC-CDR3 having the amino acid sequence of SEQ ID NO:50;
- (d)
- 20 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:36
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 25 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
 LC-CDR2 having the amino acid sequence of SEQ ID NO:44
 LC-CDR3 having the amino acid sequence of SEQ ID NO:51;
- (e)
- 30 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:36
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:41
 35 LC-CDR2 having the amino acid sequence of SEQ ID NO:44
 LC-CDR3 having the amino acid sequence of SEQ ID NO:52;
- (f)
- 40 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:36
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:53;

(g)

5 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

10 LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:54; or

(h)

15 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:36

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

20 LC-CDR1 having the amino acid sequence of SEQ ID NO:41

LC-CDR2 having the amino acid sequence of SEQ ID NO:44

LC-CDR3 having the amino acid sequence of SEQ ID NO:55.

6. The antigen-binding molecule according to para 1 or para 3, wherein the antigen-binding molecule comprises:

25 (a)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

30 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:42

LC-CDR2 having the amino acid sequence of SEQ ID NO:45

LC-CDR3 having the amino acid sequence of SEQ ID NO:57;

(b)

35 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

40 LC-CDR1 having the amino acid sequence of SEQ ID NO:42

LC-CDR2 having the amino acid sequence of SEQ ID NO:45

LC-CDR3 having the amino acid sequence of SEQ ID NO:58;

- (c)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 5 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
 LC-CDR2 having the amino acid sequence of SEQ ID NO:45
 LC-CDR3 having the amino acid sequence of SEQ ID NO:59;
- 10 (d)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 15 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
 LC-CDR2 having the amino acid sequence of SEQ ID NO:45
 LC-CDR3 having the amino acid sequence of SEQ ID NO:60;
- (e)
- 20 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 25 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
 LC-CDR2 having the amino acid sequence of SEQ ID NO:45
 LC-CDR3 having the amino acid sequence of SEQ ID NO:61;
- (f)
- 30 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
 35 LC-CDR2 having the amino acid sequence of SEQ ID NO:45
 LC-CDR3 having the amino acid sequence of SEQ ID NO:62;
- (g)
- 40 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:63; or

(h)

- 5 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
10 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:64.

7. The antigen-binding molecule according to para 1 or para 3, wherein the antigen-binding molecule
15 comprises:

(a)

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
20 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:48;

25 (b)

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
30 (ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:49;

(c)

- 35 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
40 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
LC-CDR2 having the amino acid sequence of SEQ ID NO:46
LC-CDR3 having the amino acid sequence of SEQ ID NO:50;

- (d)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 5 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:51;
- 10 (e)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 15 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:52;
- (f)
- 20 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 25 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:53;
- (g)
- 30 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:43
 35 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:54; or
- (h)
- 40 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:43

LC-CDR2 having the amino acid sequence of SEQ ID NO:46

LC-CDR3 having the amino acid sequence of SEQ ID NO:55.

- 5 8. The antigen-binding molecule according to any one of paras 1 to 7, wherein the antigen-binding molecule comprises:
- a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6, 8 or 10; and
 - 10 a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:82, 83 or 84.
9. The antigen-binding molecule according to para 8, wherein the antigen-binding molecule comprises:
- a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and
 - 15 a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:82.
10. The antigen-binding molecule according to para 8, wherein the antigen-binding molecule comprises:
- 20 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
 - a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:83.
11. The antigen-binding molecule according to para 8, wherein the antigen-binding molecule comprises:
- 25 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and
 - a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:84.
- 30 12. The antigen-binding molecule according to para 8 or para 9, wherein the antigen-binding molecule comprises:
- (a)
 - a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and
 - 35 a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:12;
 - (b)
 - a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and
 - 40 a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:13;
 - (c)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:14;

5 (d)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:15;

10 (e)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:16;

15 (f)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:17;

20 (g)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:18; or

25 (h)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:6; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:19.

30

13. The antigen-binding molecule according to para 8 or para 10, wherein the antigen-binding molecule comprises:

(a)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

35

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:20;

(b)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and

40

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:21;

- (c)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:22;
- (d)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:23;
- (e)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:24;
- (f)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:25;
- (g)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:26; or
- (h)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:27.
14. The antigen-binding molecule according to para 8 or para 11, wherein the antigen-binding molecule comprises:
- (a)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:28;
- (b)
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:29;

(c)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:30;

(d)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:31;

(e)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:32;

(f)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:33;

(g)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:34; or

(h)

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:10; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:35.

15. An antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:95

HC-CDR2 having the amino acid sequence of SEQ ID NO:96

HC-CDR3 having the amino acid sequence of SEQ ID NO:97; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:98 or 101

LC-CDR2 having the amino acid sequence of SEQ ID NO:99 or 102

LC-CDR3 having the amino acid sequence of SEQ ID NO:100 or 103.

16. The antigen-binding molecule according to para 15, wherein the antigen-binding molecule comprises:

(a)

5 (i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:95

HC-CDR2 having the amino acid sequence of SEQ ID NO:96

HC-CDR3 having the amino acid sequence of SEQ ID NO:97; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

10 LC-CDR1 having the amino acid sequence of SEQ ID NO:98

LC-CDR2 having the amino acid sequence of SEQ ID NO:99

LC-CDR3 having the amino acid sequence of SEQ ID NO:100; or

(b)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

15 HC-CDR1 having the amino acid sequence of SEQ ID NO:95

HC-CDR2 having the amino acid sequence of SEQ ID NO:96

HC-CDR3 having the amino acid sequence of SEQ ID NO:97; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:101

20 LC-CDR2 having the amino acid sequence of SEQ ID NO:102

LC-CDR3 having the amino acid sequence of SEQ ID NO:103.

17. The antigen-binding molecule according to para 15 or 16, wherein the antigen-binding molecule comprises:

25 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:91, 92, 116, 117, 118, 119 or 120; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:93, 94, 121, 122, 123, 124, 125, 126, 127 or 128.

30 18. The antigen-binding molecule according to any one of paras 1 to 17, wherein the antigen-binding molecule is capable of inhibiting IL-11 mediated signalling.

19. An antigen-binding molecule, optionally isolated, comprising (i) an antigen-binding molecule according to any one of paras 1 to 18, and (ii) an antigen-binding molecule capable of binding to an antigen other than IL-11.

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20. The antigen-binding molecule according to any one of paras 1 to 19, wherein the antigen-binding molecule is capable of inhibiting interaction between IL-11 or a complex comprising IL-11 and an IL-11 receptor.

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21. A chimeric antigen receptor (CAR) comprising an antigen-binding molecule according to any one of paras 1 to 20.

22. A nucleic acid, or a plurality of nucleic acids, optionally isolated, encoding an antigen-binding molecule according to any one of paras 1 to 20 or a CAR according to para 21.
- 5 23. An expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids according to para 22.
24. A cell comprising an antigen-binding molecule according to any one of paras 1 to 20, a CAR according to para 21, a nucleic acid or a plurality of nucleic acids according to para 22, or an expression vector or a plurality of expression vectors according to para 23.
- 10 25. A method comprising culturing a cell comprising a nucleic acid or a plurality of nucleic acids according to para 22, or an expression vector or a plurality of expression vectors according to para 23, under conditions suitable for expression of the antigen-binding molecule or CAR from the nucleic acid(s) or expression vector(s).
- 15 26. A composition comprising an antigen-binding molecule according to any one of paras 1 to 20, a CAR according to para 21, a nucleic acid or a plurality of nucleic acids according to para 22, an expression vector or a plurality of expression vectors according to para 23, or a cell according to para 24.
- 20 27. An antigen-binding molecule according to any one of paras 1 to 20, a CAR according to para 21, a nucleic acid or a plurality of nucleic acids according to para 22, an expression vector or a plurality of expression vectors according to para 23, a cell according to para 24, or a composition according to para 26 for use in a method of medical treatment or prophylaxis.
- 25 28. An antigen-binding molecule according to any one of paras 1 to 20, a CAR according to para 21, a nucleic acid or a plurality of nucleic acids according to para 22, an expression vector or a plurality of expression vectors according to para 23, a cell according to para 24, or a composition according to para 26, for use in a method of treatment or prevention of fibrosis, a disease characterised by fibrosis, a cancer, inflammation, or a disease characterised by inflammation.
- 30 29. Use of an antigen-binding molecule according to any one of paras 1 to 20, a CAR according to para 21, a nucleic acid or a plurality of nucleic acids according to para 22, an expression vector or a plurality of expression vectors according to para 23, a cell according to para 24, or a composition according to para 26, in the manufacture of a medicament for use in a method of treatment or prevention of fibrosis, a disease characterised by fibrosis, a cancer, inflammation, or a disease characterised by inflammation.
- 35 30. A method of treating or preventing fibrosis, a disease characterised by fibrosis, a cancer, inflammation, or a disease characterised by inflammation, comprising administering to a subject a therapeutically or prophylactically effective amount of an antigen-binding molecule according to any one of paras 1 to 20, a CAR according to para 21, a nucleic acid or a plurality of nucleic acids according to para 22, an expression
- 40

vector or a plurality of expression vectors according to para 23, a cell according to para 24, or a composition according to para 26.

- 5 31. A method of inhibiting IL-11 mediated signalling, comprising contacting IL-11-expressing cells with an antigen-binding molecule according to any one of paras 1 to 20.
32. An *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to any one of paras 1 to 20 bound to IL-11 or a complex comprising IL-11.
- 10 33. A method comprising contacting a sample containing, or suspected to contain, IL-11 or a complex comprising IL-11 with an antigen-binding molecule according to any one of paras 1 to 20, and detecting the formation of a complex of the antigen-binding molecule with IL-11 or a complex comprising IL-11.
- 15 34. A method of selecting or stratifying a subject for treatment with an IL-11-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule according to any one of paras 1 to 20 and detecting the formation of a complex of the antigen-binding molecule with IL-11 or a complex comprising IL-11.
- 20 35. Use of an antigen-binding molecule according to any one of paras 1 to 20 as an *in vitro* or *in vivo* diagnostic or prognostic agent.
36. A kit of parts comprising a predetermined quantity of: an antigen-binding molecule according to any one of paras 1 to 20, a CAR according to para 21, a nucleic acid or a plurality of nucleic acids according to para 22, an expression vector or a plurality of expression vectors according to para 23, a cell according to para 24, or a composition according to para 26.

The invention includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

- 30 The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Aspects and embodiments of the present invention will now be illustrated, by way of example, with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art.

- 35 All documents mentioned in this text are incorporated herein by reference.

- Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.
- 40

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value.

5 Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment.

Where a nucleic acid sequence is disclosed herein, the reverse complement thereof is also expressly contemplated.

10

Methods described herein may preferably performed *in vitro*. The term “*in vitro*” is intended to encompass procedures performed with cells in culture whereas the term “*in vivo*” is intended to encompass procedures with/on intact multi-cellular organisms.

15

Brief Description of the Figures

Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures.

20

Figure 1. Table summarising panning strategies used to identify human anti-human IL-11 antibodies capable of binding to both human IL-11 and mouse IL-11.

Figure 2. Scatterplot showing strength of binding signal to human IL-11 and mouse IL-11 as determined by ELISA assay for 86 human anti-IL-11 antibody candidates.

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Figure 3. Table summarising the 56 human anti-human IL-11 antibody clones.

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Figures 4A and 4B. Bar charts showing inhibition by the human anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the percentage of α SMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with TGF β 1, in the presence of the human anti-IL-11 antibodies. **(4A)** Bar chart showing fold change in proportion of α SMA-positive cells relative to unstimulated cells (=1). **(4B)** Bar chart showing the percentage of α SMA-positive cells (activated fibroblasts).

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Figures 5A and 5B. Bar chart showing inhibition by the human anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in **(5A)** mouse atrial fibroblasts and **(5B)** mouse dermal fibroblasts, as determined by fold change in the percentage of α SMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with TGF β 1, in the presence of the human anti-IL-11 antibodies.

Figure 6. Bar chart showing inhibition by the human anti-IL-11 antibodies of IL-11 *trans* signalling mediated by hyper IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the percentage of α SMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with hyper IL-11, in the presence of the human anti-IL-11 antibodies.

Figure 7. Table summarising the fold-change data of Figures 4 to 6 for the 56 human anti-IL-11 antibodies. Antibody candidates numbered 1 to 56 correspond to clone designations as indicated in Figure 3. "Industry Standard" is monoclonal mouse anti-IL-11 IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA.

Figures 8A and 8B. Graphs showing fibroblast activation in response to hyper IL-11. Cells were stimulated with the indicated amount (in ng/ml) of hyper IL-11 or recombinant IL-11, and fibroblast activation was measured by analysis of the percentage of α -SMA positive cells. (8A) and (8B) present the results of two different experiments.

Figure 9. Graph showing induction of IL-11 secretion in primary fibroblasts by hyper IL-11. Cells were stimulated with hyper IL-11, and IL-11 RNA and native IL-11 protein levels were measured in the cell culture supernatant by ELISA at the indicated time points.

Figures 10A to 10F. Graphs showing binding of human anti-IL-11 antibodies to human IL-11 as determined by ELISA analysis. (10A) ELISA for clones YU45-A3, YU45-A10, YU45-D11, YU45-E11, YU45-D12 and YU33-A2(IgG). (10B) ELISA for clones YU45-G1, YU45-B2, YU45-A5, YU45-E3, YU45-F8 and YU33-H3(IgG). (10C) ELISA for clones YU45-G8, YU45-F9, YU45-H10, YU45-F2, YU45-H3 and YU33-E3(IgG). (10D) ELISA for clones YU45-A8, YU45-B5, YU45-D9, YU45-G7, YU45-B6 and YU45-F9. (10E) ELISA for clones YU45-F5, YU46-B5, YU45-C1, YU46-A8, YU46-B6 and YU45-F9. (10F) ELISA for clones YU46-E3, YU46-G8, YU46-D3, YU45-B6, YU45-C1 and YU45-F9.

Figure 11. Table summarising EC₅₀ values determined for binding of human anti-IL-11 antibodies to IL-11 as determined by ELISA analysis.

Figure 12. Schematic representation of the process of antibody light chain shuffling.

Figure 13. Table summarising the 16 mouse anti-human IL-11 antibody clones.

Figure 14. Bar chart showing inhibition by the mouse anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the percentage of α SMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with TGF β 1, in the presence of the mouse anti-IL-11 antibodies.

Figure 15. Bar chart showing inhibition by the mouse anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in mouse atrial fibroblasts, as determined by fold change in the percentage of α SMA positive cells as

compared to control (unstimulated) fibroblasts, following stimulation with TGF β 1, in the presence of the mouse anti-IL-11 antibodies.

Figure 16. Bar chart showing inhibition by the mouse anti-IL-11 antibodies of IL-11 *trans* signalling mediated by hyper IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the amount of MMP2 in the cell culture supernatant as compared to control (unstimulated) fibroblasts, following stimulation with hyper IL-11, in the presence of the mouse anti-IL-11 antibodies.

Figure 17. Table summarising the fold-change data of Figures 14 to 16 for the 16 mouse anti-IL-11 antibodies. Antibody candidates numbered 1 to 16 correspond to clone designations as indicated in Figure 13. Industry standard is monoclonal mouse anti-IL-11 IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA.

Figures 18A to 18H. (A-B) Table and bar chart showing binding of mouse-anti-IL-11 antibodies to human IL-11, as determined by iQue analysis (18A) Table summarising the results of the experiments. (18B) Bar chart showing strength of binding relative to the positive control anti-FLAG antibody (100%); numbers correspond to the clones as indicated in Figure 17. (C-E) Antibodies that neutralise IL-11 signalling in (18C) human and (18D) mouse fibroblasts stimulated with TGF β 1, or (18E) in human fibroblasts stimulated with Hyper IL-11 (IL-11:IL11RA). (18F) Neutralisation of fibrotic response by 3C6 in human fibroblasts stimulated with recombinant IL-11. (18G) Neutralisation of fibrotic response by 3C6 in human fibroblasts stimulated with Hyper IL-11 (IL-11:IL11RA). (18H) Neutralisation of fibrotic response by 3C6 in human HSCs stimulated with TGFB1 (left) or IL-11 (right).

Figure 19. Table summarising panning strategies used to identify human anti-human IL-11 antibodies capable of binding to both human IL-11 and mouse IL-11, after light chain shuffling.

Figure 20. Scatterplot showing binding signal to human IL-11 and mouse IL-11 as determined by ELISA assay for light chain-shuffled human anti-IL-11 antibodies. 66 antibodies displaying cross-reactive binding to human IL-11 and mouse IL-11 were identified (black circles). Antibodies displaying binding to mouse IL-11 only are indicated by grey circles.

Figures 21A and 21B. Bar chart (21A) and Table (21B) showing binding signal to human IL-11 and mouse IL-11 as determined by ELISA assay for the 64 unique light chain-shuffled human anti-IL-11 antibodies.

Figure 22. Bar chart showing EC50 values in ng/ml for binding of the indicated light-chain shuffled anti-IL-11 antibodies to human IL-11, as determined by ELISA.

Figures 23A to 23E. Bar chart showing the effect of anti-IL-11 antibodies on MMP2 secretion by human cardiac atrial fibroblasts in response to TGF β 1. 23A and 23B show the results of two separate experiments. Cells were cultured in the presence of TGF β 1 (5 ng/ml) for 24 hours, in the presence of the indicated light chain shuffled anti-IL-11 antibodies, or in the presence of human IgG1 isotype control. Basal MMP2 secretion by the cells in culture was measured by culture in the absence of TGF β 1, in the presence of human

IgG1 isotype control. Horizontal lines show basal MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of human IgG1 isotype control antibody in the absence of TGFβ1 (NEG); and MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of 5 ng/ml TGFβ and the human IgG1 isotype control antibody (POS). **23C** shows neutralisation of the fibrotic response *in vitro* assessed by monitoring MMP2 levels. Primary human fibroblasts were incubated with TGFβ1 (5ng/ml) and varying concentrations of antibody candidates in IgG1 format. MMP2 secretion into the supernatant by fibroblasts was assessed to estimate the % of inhibition. **23D** shows neutralisation of the fibrotic response *in vitro* for clones YU100-G08 and YU100-H01. **23E** shows neutralisation of *trans* IL-11 signalling for clones YU100-G08 and YU100-H01.

Figure 24. Table summarising the results of Figures 22, 23A and 23B relating to functional characterisation of the indicated light-chain shuffled anti-IL-11 antibody clones. N.D. = not determined.

Figures 25A and 25B. Images and graph showing the results of histological analysis of kidney sections from mice subjected to different treatments in a mouse model of kidney fibrosis. Kidney fibrosis was induced by intraperitoneal (IP) injection of folic acid (FA, 180 mg/kg) in vehicle (0.3M NaHCO₃) mice; control mice were administered vehicle alone. Mice were administered isotype control IgG2 (20mg/kg, 3 x per week, intraperitoneal), anti-IL-11 antibody (20mg/kg, 3 x per week, intraperitoneally) from day 1 post folic acid injury and for the duration of the experiment. Animals were sacrificed 28 days after folic acid-induced kidney damage and analysed for fibrosis histologically using Masson's Trichrome stain. **(25A)** Images of Masson's Trichrome stained kidney sections. Fibrotic areas containing collagen appear darker as compared to healthy areas that appear lighter. **(25B)** Graphs showing semi-quantitative analysis of collagen area expressed as a percentage (%) of the total kidney area (graph). ***, P< 0.001 compared to FA+IgG, ANOVA.

Figure 26. Graph showing the urinary albumin/creatinine ratio in mice subjected to different treatments in a mouse model of kidney fibrosis. Kidney fibrosis was induced by intraperitoneal (IP) injection of folic acid (FA, 180mg/kg) in vehicle (0.3M NaHCO₃) mice; control mice were administered vehicle alone. FA treated mice were administered isotype control IgG2 (20mg/kg, 3 x per week, intraperitoneal) or anti-IL11 antibody (20mg/kg, 3 x per week, intraperitoneal) from day 1 post folic acid injury and for the duration of the experiment. Mice were placed in metabolic cages and urinary creatinine and albumin measured using commercial assays (Abcam) according to the manufacturer's instructions. ***, P< 0.001 compared to FA+IgG, ANOVA.

Figures 27A to 27C. Graph showing total collagen in kidney tissue in mice subjected to different treatments in a mouse model of kidney fibrosis. **(27A)** Kidney fibrosis was induced by intraperitoneal (IP) injection of folic acid (FA, 180mg/kg) in vehicle (0.3M NaHCO₃) mice; control mice were administered vehicle alone. From day one of the experiment, mice in the treatment groups were given isotype control IgG2 (20mg/kg, 3 x per week) or neutralizing anti-IL11 antibody at varying doses: 20mg/kg x 3/week; 10mg/kg x 3/week; 10mg/kg x 2/week; 5mg/kg x 3/week; 5mg/kg x 2/week; 1mg/kg x 2/week), all intraperitoneal. Animals were sacrificed 28 days post-injection and kidney analysed for fibrosis (micrograms/g (μg/g)) by hydroxyproline assay using Quickzyme Total Collagen assay kit (Quickzyme Biosciences) according to the manufacturer's protocol. **, P<0.01; ***, P< 0.001 compared to FA+IgG, ANOVA. Dose-dependent effects of anti-IL-11

antibodies (27B) BSN-3C6 and (27C) YU100-G08_02A on kidney collagen content in folic-acid induced kidney fibrosis.

Figures 28A and 28B. Images and graph showing the results of histological analysis of kidney sections from mice subjected to different treatments in a mouse model of acute renal injury. (28A) Mice were treated by sham operation or ureteric obstruction of one ureter. Mice received IgG, anti-IL-11 antibody (20mg/kg on surgical days -1, 1, 3, 5) and injured kidneys (UUO IgG, IL-11) or contralateral (Con) uninjured kidneys (Con IgG, IL-11) were harvested on day 7 post surgery. (28B) Semi-quantitative assessment of tubular injury was determined by histological analysis of casts, tubular atrophy or tubular expansion blinded to experimental conditions (Tubular injury score: 0, none; 1, minimal; 2, mild; 3, moderate; 4, severe). *, P<0.05 compared to UUO IgG, ANOVA.

Figure 29. Image showing the results of ELISA western blot for IL-11 of human liver samples. Liver samples obtained from patients undergoing liver surgery were used for western blot analysis. Blotting of GAPDH was used as a loading control. Samples from normal human liver (NHL) had low levels of IL-11 protein, whereas samples from patients with fibrotic liver diseases including alcoholic liver disease (ALD), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) or non-alcoholic steatohepatitis (NASH) had higher levels of IL-11.

Figures 30A to 30C. IL-11 and liver fibrosis. (A) Bar chart showing the results of ELISA analysis of secretion of IL-11 by human PCLS subjected to different treatments. (B) Trans-differentiation of human hepatic stellate cells into myofibroblasts following IL-11 stimulation (24h) in the presence of 2ug/ml of IgG or anti-IL-11 antibody YU100-G08_02A. (C) YU100-G08_02A blocks fibrotic response in HSCs stimulate by endogenous and exogenous IL-11.

Figures 31A and 31B. Images and graph showing the results of analysis of liver tissue from mice subjected to different treatments in a mouse model of nonalcoholic steatohepatitis. Diabetic mice (db/db; deficient for the leptin receptor) were maintained for 8 weeks on a normal chow diet (left, round symbols) or on a NASH-inducing (methionine/choline deficient (MCD)) diet. In a subset of animals neutralizing anti-IL11 antibody was administered (20mg/kg, 3x/week, intraperitoneal) for the final 3 weeks of the 8 week NASH diet. Liver samples were photographed (31A) and assessed for collagen content per mg of liver tissue (31B); each symbol represents an individual animal. P values shown on graph, ANOVA.

Figures 32A to 32D. Bar chart and images showing the results of analysis of eye fibrosis from mice subjected to different treatments in a mouse model of retinal fibrosis. Mice (10 per group) were subjected to laser-induced retinal damage (4 burns per retina) and administered intraocularly with 0.5 µg of anti-IL-11 antibody or IgG control antibody on days 1, 7, 14 and 21. Eyes were harvested for histological analyses on day 28. The area of fibrosis at burn sites were measured by Masson's Trichrome staining. (32A) Bar chart showing quantification of the fibrosis areas in control (IgG) or anti-IL11 (IL11) treated mice. (32B) representative images showing staining of fibrotic areas in control antibody treated eyes (IGG, top panel) or anti-IL11 treated eyes (IL11, bottom panel). (32C) Mice were treated with Eylea + IgG control or an Eylea + BSN-3C6 combination therapy. Bar chart showing quantification of the fibrosis area in control, low anti-IL-11,

or high anti-IL-11 treatment. **(32D)** Bar chart showing area of leakage fold change in choroidal neovascularisation before and after intravitreal injections (IVT) of anti-IL-11 therapy (low and high concentration).

5 **Figures 33A to 33C.** Schematic, images and bar chart relating to analysis of skin fibrosis in mice subjected to different treatments in a mouse model of skin fibrosis. **(33A)** Schematic representation of experimental procedures for different treatment groups. Groups 1 and 2 were treated with bleomycin (BLM), and either anti-IL-11 antibody (Group 1) or IgG control antibody (Group 2). Group 3 were injected with vehicle (PBS) only and do not develop fibrosis. **(33B)** Images showing Masson's trichrome staining of skin section at equal
10 distances from the injection site. Dermal thickness is indicated by the black bar. **(33C)** Bar chart showing the results of analysis of dermal thickness (blinded for treatment groups). Average dermal thickness was determined from the bottom of epithelial layer to top of dermal white adipose tissue layer across 40 fields of view per sample. Each point indicates an animal. P value was calculated using an unpaired two-tailed t-test.

15 **Figure 34.** Images showing the results of histological analysis of heart fibrosis in mice subjected to different treatments in a mouse model of cardiac fibrosis. Mice (C57Bl6, male, 8-12 weeks old) were subjected to fibrosis-inducing transverse aortic constriction (TAC) or sham operations. TAC-treated animals received either control antibody (20mg/kg, 3x/week, intraperitoneal) or neutralizing anti-IL-11 antibody (20mg/kg, 3x/week, intraperitoneal). After two weeks hearts were harvested and assessed for fibrosis extent using
20 Masson's Trichrome stain.

Figures 35A to 35J. Sensorgrams and Table showing the results by Single Cycle Kinetics analysis of affinity of binding of different antibody clones to IL-11. **35A to 35I** show binding of YU100-G08 (**35A**), 02A (**35B**), 02G (**35C**), 02I (**35D**), 02L (**35E**), 02Q (**35F**), 02S (**35G**), 02T (**35H**) and 02V (**35I**). **35J** summarises the
25 kinetics determined for the binding of the different clones.

Figures 36A to 36J. Sensorgrams and Table showing the results by Single Cycle Kinetics analysis of affinity of binding of different antibody clones to IL-11. **36A to 36I** show binding of YU100-H01 (**36A**), 01A (**36B**), 01G (**36C**), 01I (**36D**), 01L (**36E**), 01Q (**36F**), 01S (**36G**), 01T (**36H**) and 01V (**36I**). **36J** summarises the
30 kinetics determined for the binding of the different clones.

Figures 37A to 37I. Graphs showing inhibition of IL-11 mediated signalling by different antibody clones, as determined by analysis *in vitro* of inhibition of production of MMP2 by human cardiac atrial fibroblasts following stimulation with TGFβ1. **37A to 37I** show the results obtained for clones YU100-H01 (**37A**), 01A (**37B**), 01G (**37C**), 01I (**37D**), 01L (**37E**), 01Q (**37F**), 01S (**37G**), 01T (**37H**) and 01V (**37I**).
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Figures 38A to 38M. Analysis of inhibition of IL-11 signalling. **(A-I)** Graphs showing inhibition of IL-11 mediated signalling by different antibody clones, as determined by analysis *in vitro* of inhibition of production of MMP2 by human cardiac atrial fibroblasts following stimulation with TGFβ1. **38A to 38I** show the results obtained for clones YU100-G08 (**38A**), 02A (**38B**), 02G (**38C**), 02I (**38D**), 02L (**38E**), 02Q (**38F**), 02S (**38G**), 02T (**38H**) and 02V (**38I**). **(J-M)** Cross-species reactivity for IL-11 antibodies YU100-G08_02A (human) and
40

3C6 (mouse) using macaque dermal fibroblasts: (J) % of ACTA positive cells, (K) secreted collagen, (L) periostin, (M) collagen concentration.

- Figures 39A to 39H.** Graphs showing effect of anti-IL-11 antibody in a mouse NASH model on (39A) hepatic triglyceride content, (39B) liver hydroxyproline content, (39C, 39D) expression of pro-inflammatory factors, (39E) serum ALT levels, and (39F) levels of phosphorylated ERK in livers. All measurements were compared to a steatosis control and IgG control. Dose-dependent effects of anti-IL-11 antibodies (39G) BSN-3C6 and (39H) YU100-G08_02A on serum ALT levels and liver hydroxyproline content in a NASH model.
- Figures 40A to 40D.** Therapeutic effect of anti-IL-11 antibody in mouse models of advanced NASH. (A-C) Western blot and graphs showing the effect of anti-IL-11 antibody on ERK activation (40A), liver hydroxyproline content (40B) and serum ALT levels (40C) in a mouse NASH model after high fat methionine/choline-deficient (HFMCD) diet or normal chow (NC) diet. (40D) Another NASH model was stimulated by a single subcutaneous injection of streptozotocin and mice were fed on a normal chow diet for 4 weeks, then HFMCD diet for 7 weeks along with anti-IL-11 antibody or IgG control. Graph shows RNA expression of fibrosis and inflammation genes after 7 weeks.
- Figures 41A to 41D.** Representative fluorescent images and graphs showing effect of anti-IL-11 antibody on HSC transformation to myofibroblasts when stimulated with different NASH-promoting factors. Representative fluorescent images show (41A) the number of ACTA2⁺ cells and (41B) cells producing collagen. Scale bars = 200 μ m. (41C) Percentage of ACTA2⁺ cells following treatment. (41D) Collagen production in cells following treatment.
- Figure 42.** Graph showing TGF β 1- and CCL2-induced matrigel invasion of HSCs pre-treated with anti-IL-11 antibody or IgG control.
- Figure 43.** Graph showing the effect of anti-IL-11 antibody on HSC CCL2 secretion without stimulus, stimulated with IL-11, or stimulated with TGF β 1 in the presence of IgG or anti-IL-11 antibody.
- Figures 44A to 44D.** The reversing effect of anti-IL-11 therapy on liver fibrosis. (44A) Liver hydroxyproline content indicating total hepatic collagen content (44B) Acta2 expression in HSCs. (44C) Percentage of ACTA2⁺ HSCs stimulated by TGF β 1 or PDGF. (44D) MMP2 concentration after HSC stimulation by TGF β 1 or PDGF.
- Figures 45A to 45H.** The effect of anti-IL-11 therapy in early stage NASH. (45A) Representative gross liver images. (45B) Western blot showing ERK activation in mice on HFMCD diet after treatment with anti-IL-11 antibody or IgG control. (45C) Triglyceride content in mice on HFMCD diet after treatment with anti-IL-11 antibody or IgG control. (45D) Representative Masson's Trichrome stained images of livers of mice of mice that received anti-IL-11 therapy or IgG control. (45E) Serum ALT levels in mice on HFMCD diet after treatment with anti-IL-11 antibody or IgG control. (45F) Differential expression heatmap of pro-fibrotic and pro-inflammatory genes Z-scores in mice on normal chow diet and mice on HFMCD diet after treatment with

anti-IL-11 antibody or IgG control. **(45G)** RNA expression of pro-inflammatory genes. **(45H)** RNA expression of pro-fibrotic genes.

Figures 46A to 46D. The effect of IL-11 on lung fibroblast activation, migration and invasion. **(46A)**

5 Representative immunostaining of IL-11 and ACTA2 in serial sections of lung tissue from an IPF patient and healthy donor (Control). Scale bars, 50 μ m. **(46B)** Total secreted collagen in the supernatant of IL-11 treated fibroblasts. **(46C)** Transwell migration and **(46D)** matrigel invasion indices of wild-type mouse lung fibroblasts induced by IL-11. Scale bars, 150 μ m.

10 **Figures 47A and 47B.** Graphs showing binding kinetics of **(47A)** human and **(47B)** mouse IL-11 to anti-IL-11 antibody BSN-3C6. Equilibrium binding constants are shown.

Figures 48A to 48E. The effect of anti-IL-11 therapy on lung fibrosis. **(48A)** Heatmaps showing the

15 immunofluorescence quantification of Acta2+ve cells and Col1 α 1 immunostaining (intensity/area) in mouse lung fibroblasts treated with multiple pro-fibrotic stimuli in the presence of anti-IL-11 antibody or IgG control. **(48B)** Quantification of ACTA2+ve cells, COL1 α 1 immunostaining (intensity/area) and collagen secretion of TGF β 1-differentiated human lung fibroblasts treated with anti-IL-11 antibody or IgG control. **(48C)** Inhibition of MMP2 from TGF β 1-stimulated primary human lung fibroblasts in the presence of anti-IL-11 antibody. **(48D)** Inhibition of Mmp2 from TGF β 1-stimulated primary mouse lung fibroblasts in the presence of anti-IL-11 antibody. **(48E)** Effect of anti-IL-11 antibody on migration and invasion of mouse lung fibroblasts.

Figures 49A to 49E. The effect of IL-11 therapy in a bleomycin (BLM)-induced mouse model of early

25 pulmonary fibrosis. Mice were treated with anti-IL-11 antibody or IgG control. **(49A)** Representative Masson's trichrome staining of lung sections. Scale bars, 100 μ m. **(49B)** Graphs showing indexed lung/body weight and lung hydroxyproline content. **(49C)** Densitometry analysis of western blots of Col3a1, fibronectin and IL-11 protein levels in lung homogenates. **(49D)** mRNA expression of *Col1a1*, *Col1a2*, *Col3a1*, *Fn1*, *Mmp2* and *Timp1* in lung lysates. **(49E)** Western blot of phosphorylation status and total levels of Erk and Stat3 in lung homogenates.

30 **Figures 50A to 50D.** The effect of IL-11 therapy in a bleomycin (BLM)-induced mouse model of established pulmonary fibrosis. **(50A)** Representative Masson's trichrome staining of lung sections. Scale bars, 100 μ m.

(50B) Graphs showing indexed lung/body weight and lung hydroxyproline content. **(50C)** Western blots of Col3a1, fibronectin and IL-11 protein levels in lung homogenates. **(50D)** Western blot of phosphorylation status and total levels of Erk and Stat3 in lung homogenates.

35 **Figures 51A to 51C.** Effect of anti-IL-11 antibody therapy on cancer. **(51A)** 3C6 prevents tumour growth in an HCC mouse flank model. **(51B)** 3C6 prevents IL-11 induced splenomegaly in a myelofibrosis mouse model expressing IL-11 in fibroblasts. **(51C)** 3C6 provides an additive effect on tumour volume inhibition in conjunction with cisplatin chemotherapy in a lung cancer (A549) mouse model. Anova with Tukey post hoc correction for multiple testing. Cisplatin + IgG vs cisplatin + 3C6: **, P<0.01; ***, P<0.001. Group sizes: no treatment, n=5; Cisplatin + IgG, n=10; Cisplatin + 3C6, n=10.

Figure 52. Role of IL-11 in pancreatic fibrosis. Mice received daily injections of 100µg/kg of recombinant mouse IL-11 or saline for 21 days. Collagen content of the pancreas was assessed using a calorimetric hydroxyproline assay.

5 **Figure 53A to 53C.** Graphs showing the effects of treatment with **(53A)** YU100-G08_02A or **(53B)** 3C6 on body weight and food consumption in a model of wasting-related weight loss. Mice fed a HFMCD diet were treated 2x/week with 0.5, 1, 5 or 10 mg/kg anti-IL-11 antibody. Control mice were either fed with normal chow (NC), or fed on a HFMCD diet and treated with IgG isotype control. **(53C)** Effect of anti-IL-11 antibody on mouse body weight after folate-induced kidney injury.

10 **Figures 54A and 54B.** Ability of humanised 3C6 clones VH 2.2/VL 2.1; VH 2.2/VL 2.2; VH 2.2/VL 2.3; VH 2.2/VL 2.4; VH 2.3/VL 2.2; and VH 2.3/VL 2.3 to block IL-11 signalling and inhibit MMP2 (fibrogenic protein) production in **(A)** primary human atrial fibroblasts and **(B)** human HSCs.

15 **Figures 55A to 55C.** Ability of YU100-G08_02A (IgG1) and YU100-G08_02A (IgG4) to block **(55A)** endogenous IL-11 signalling, **(55B)** exogenous IL-11 signalling and **(55C)** IL-11 *trans* signalling *in vitro* in human HSCs. MMP2 secretion into the supernatant by fibroblasts was assessed to estimate the % of inhibition.

20 **Figures 56A and 56B.** Comparison of ability of YU100-G08_02A (IgG1) and YU100-G08_02A (IgG4) to reverse liver damage and fibrosis in an *in vivo* NASH model. Serum ALT levels **(56A)** and hepatic collagen content (HPA assay; **56B**) were assessed after 4 weeks of diet and 3 weeks of antibody treatment.

Examples

25 In the following Examples, the inventors describe the generation of anti-IL-11 antibodies, and functional characterisation of the antibodies.

Example 1: Human anti-human IL-11 antibodies

Fully human anti-human IL-11 antibodies were developed via phage display.

30 Recombinant human IL-11 (Cat. No. Z03108-1) and recombinant murine IL-11 (Cat. No. Z03052-1) were obtained from GenScript (NJ, USA). Recombinant human IL-11 was expressed in CHO cells, both as an Fc-tagged version and a tag-free version. Tag-free murine IL-11 was expressed in HEK293 cells.

35 IL-11 bioactivity of recombinant human IL-11 and mouse IL-11 was confirmed by *in vitro* analysis using primary fibroblast cell cultures.

Recombinant, biotinylated human IL-11 and murine IL-11 were also prepared by biotinylation of the recombinant human IL-11 and murine IL-11 molecules, according to standard methods.

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Antibodies capable of binding to both human IL-11 and murine IL-11 (i.e. cross-reactive antibodies) were identified by phage display using a human naïve library by panning using biotinylated and non-biotinylated recombinant human and murine IL-11, based on 16 different panning strategies as summarised in Figure 1.

- 5 The phage display identified 175 scFv binders, as 'first hits'. Sequence analysis of the CDR sequences from these 175 scFv identified 86 unique scFv.

The soluble scFv were produced by recombinant expression in *E. coli*, and analysed for their ability to bind to human IL-11 and murine IL-11 by ELISA. Briefly, the respective antigen was coated to wells of an ELISA plate, the cell culture supernatant containing the respective scFv was added at a 1:2 dilution, and binding was detected.

The results of the ELISA analysis of binding to human IL-11 and murine IL-11 are shown in Figure 2. The analysis revealed:

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- 8 scFv capable of binding only to human IL-11;
 - 6 scFv capable of binding to murine IL-11 only;
 - 32 scFv displaying only weak binding to human/murine IL-11, with a high signal to noise ratio, and;
 - 40 scFv having cross-reactivity for both human IL-11 and murine IL-11.
- 20

From these 86 scFv, 56 candidates were selected for further functional characterisation. For further analyses, the scFv were cloned into scFv-Fc format in *E. coli*.

The antibody clone designations are shown in Figure 3.

25 The VH and VL sequences of the antibodies were cloned into expression vectors for the generation of scFv-Fc (human IgG1) antibodies. The vectors were transiently expressed in mammalian cells cultured in serum-free media, and isolated by protein A purification.

30 Example 2: Functional characterisation of human anti-human IL-11 antibodies

The antibodies described in Example 1 were analysed in *in vitro* assays for their ability to (i) inhibit human IL-11-mediated signalling, (ii) inhibit mouse IL-11-mediated signalling, and (iii) inhibit IL-11 *trans* signalling, by IL-11 in complex with IL-11RA. The affinity of the antibodies for human IL-11 was also analysed by ELISA.

35 2.1 Ability to inhibit human IL-11 mediated signalling

To investigate ability to neutralise human IL-11-mediated signalling, cardiac atrial human fibroblasts were cultured in wells of 96-well plates in the presence of TGFβ1 (5 ng/ml) for 24 hours, in the presence or absence of the anti-IL-11 antibodies. TGFβ1 promotes the expression of IL-11, which in turn drives the transistion of quiescent fibroblasts to activated, αSMA-positive fibroblasts. It has previously been shown that neutralising IL-11 prevents TGFβ1-induced transition to activated, αSMA-positive fibroblasts.

Expression of α SMA was analysed with the Operetta High-Content Imaging System in an automated high-throughput fashion.

In non-stimulated cultures, ~29.7% (= 1) of the fibroblasts were α SMA-positive, activated fibroblasts at the end of the 24 hour culture period, whilst ~52% (= 1.81) of fibroblasts were α SMA-positive in cultures that were stimulated with TGF β 1 in the absence of anti-IL-11 antibodies.

Anti-IL-11 antibodies (2 μ g/ml) were added to fibroblast cultures that were stimulated with TGF β 1, and at the end of the 24 hour culture period, the percentage of α SMA-positive fibroblasts was determined. The percentages were normalised based on the percentage of α SMA-positive fibroblasts observed in cultures of fibroblasts which had not been stimulated with TGF β 1.

The results of the experiments are shown in Figures 4A, 4B and 7. 28 of the antibodies were demonstrated to be capable of neutralising signalling mediated by human IL-11.

A commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA) was also analysed for ability to inhibit signalling by human IL-11 in the experiments. This antibody was found to be able to reduce the percentage of activated fibroblasts to 28.3% (=0.99).

Several of the clones neutralised signalling by human IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): YU45-C11/A10 (#6), YU45-G1 (#11), YU45-E3 (#16), YU45-F8 (#18), YU45-F9 (#21), YU45-H10 (#22), YU45-F2 (#24), YU45-H3 (#25), YU45-G7 (#33), YU45-B6 (#36), YU45-C1 (#42), YU46-B6 (#47), YU46-E3 (#50), YU46-G8 (#54) and YU46-D3 (#56).

2.2 Ability to inhibit mouse IL-11 mediated signalling

The ability of the human antibodies to inhibit mouse IL-11-mediated signalling was also investigated, following the same procedure as described in section 2.1 above, but using mouse atrial fibroblasts instead of human atrial fibroblasts.

After 24 hours in culture, about 31.8% (=1) of non-stimulated cells in culture were activated fibroblasts. Stimulation with TGF β 1 resulted in a ~2-fold increase in the percentage of activated fibroblasts (68.8% = 2.16) as compared to non-stimulated cultures.

The results of the experiments are shown in Figures 5A, 5B and 7. The antibodies were demonstrated to be capable of neutralising signalling mediated by mouse IL-11. Monoclonal Mouse IgG2A clone #22626, catalog No. MAB218 anti-IL-11 antibody was also analysed for ability to inhibit signalling by mouse IL-11. This antibody was found to be able to reduce the percentage of activated fibroblasts to 39.4% (=1.24).

Several of the clones neutralised signalling by IL-11 in mouse atrial fibroblasts to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): YU33-B4/YU45-G2/A3 (#3), YU45-H11/D12 (#9), YU45-G1 (#11), YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5 (#14), YU45-B3 (#15),

YU45-F8 (#18), YU45-H10 (#22), YU46-A10 (#23), YU45-A8/C6 (#27), YU45-D9/D3 (#31), YU45-B6 (#36), YU45-C1 (#42), YU46-A8 (#45), YU46-C1 (#48), YU46-H8 (#52), YU46-G8 (#54) and YU46-D3 (#56).

The ability of the human antibodies to inhibit mouse IL-11-mediated signalling was also investigated using mouse skin fibroblasts.

The results of the experiments are shown in Figure 7. The antibodies were demonstrated to be capable of neutralising signalling mediated by mouse IL-11.

Several of the clones neutralised signalling by IL-11 in mouse skin fibroblasts to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): YU45-B6 (#36), YU45-C1 (#42), and YU46-H8 (#52).

2.3 Ability to inhibit IL-11 *trans* signalling, by IL-11 in complex with IL-11RA

Trans signalling is recognised as a major aspect of IL-6 signalling, where a complex of IL-6 and soluble IL-6R α can activate cells that express gp130, but lack the IL-6 receptor (Hunter and Jones, 2015 Nature Immunology 16, 448–457).

It has recently been suggested that *trans* signalling by a complex of IL-11 and soluble IL-11RA is also important for IL-11 biology (Lokau et al., Cell Reports (2016) 14, 1761–1773). Using a recombinant fusion protein of IL-11 and IL-11R α (as described in Pflanz et al., Febs Lett (1999) 450: 117-122), anti-IL-11 antibodies were screened for the ability to inhibit *trans* signalling mediated by IL-11:IL-11R α complex.

Importantly, antibodies which are capable of inhibiting both classical IL-11 mediated signalling and IL-11 *trans* signalling by IL-11:IL-11R α complex are able to inhibit all known modes of IL-11/IL-11R signalling.

The IL-11:IL-11R α fusion protein (hereafter referred to as hyper IL-11) consists of the extracellular domain of the IL-11 receptor alpha (IL-11R α) linked to IL-11. The IL-11:IL-11R α fusion protein used in the present Example has the amino acid sequence of SEQ ID NO:4.

Hyper IL-11 was found to be a more potent activator of human fibroblasts than recombinant IL-11 protein. Briefly, in two separate experiments human fibroblasts were cultured without stimulation (Baseline), in the presence of different amounts of hyper IL-11 (0.008 ng/ml, 0.04 ng/ml, 0.2 ng/ml, 1 ng/ml and 5 ng/ml), or 5 ng/ml recombinant human IL-11 obtained from a commercial source, and fibroblast activation was analysed by determining the percentage of α SMA-positive cells as described herein. The results are shown in Figures 8A and 8B. Hyper-IL-11 activated fibroblasts in a dose-dependent fashion, and was a more potent activator than IL-11.

The IL-11:IL-11R α fusion protein was prepared as follows:

- DNA encoding IL-11:IL-11R α fusion protein was cloned into pTT5 vector, and transfected into 293-6E cells in culture in serum-free FreeStyle™ 293 Expression Medium (Thermo Fisher Scientific).

- Cells were maintained in Erlenmeyer Flasks (Corning Inc.) at 37°C with 5% CO₂ on an orbital shaker (VWR Scientific).
 - Cell culture supernatants were collected on day 6 were used for purification.
 - Cell culture supernatant was loaded onto an affinity purification column.
- 5 • After washing and elution with appropriate buffer, the eluted fractions were pooled and buffer exchanged to final formulation buffer.
- The purified IL-11:IL-11R α fusion protein was analyzed by SDS-PAGE, Western blot to confirm molecular weight and purity.
- 10 Fibroblasts cultured *in vitro* and stimulated with hyper IL-11 were shown to upregulate IL-11 protein expression, as determined by ELISA (Figure 9). Interestingly, an increase in IL-11 RNA level was not detected in response to stimulation with hyper IL-11. Unlike TGF β 1, which increases IL-11 expression at both the RNA and the protein level, hyper IL-11 seems to upregulate IL-11 expression only post-transcriptionally, at the protein level.
- 15 The ability of the human antibodies to inhibit signalling mediated by hyper IL-11 was investigated.
- Human atrial fibroblasts derived from 3 individuals were incubated for 24h with hyper IL-11 (0.2 ng/ml) in the presence of neutralising anti-IL-11 antibody or isotype control antibody. Following incubation, cells were
- 20 stained for α SMA to determine the fraction of myofibroblasts.
- After 24 hours in culture, about 26.5.% (=1) of non-stimulated cells in culture were activated fibroblasts. Stimulation with hyper IL-11 resulted in a ~2-fold increase in the percentage of activated fibroblasts (56.4% = 2.13) as compared to non-stimulated cultures.
- 25 The results of the experiments are shown in Figures 6 and 7. The antibodies were demonstrated to be capable of neutralising signalling mediated by hyper IL-11 (i.e. IL-11 *trans* signalling).
- Monoclonal Mouse IgG2A clone #22626, catalog No. MAB218 anti-IL-11 antibody was also analysed for
- 30 ability to inhibit signalling by hyper IL-11. This antibody was found to be able to reduce the percentage of activated fibroblasts to 33.8% (=1.28).
- Clone YU33-B4/YU45-G2/A3 (#3) neutralised IL-11 *trans* signalling by hyper IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard).
- 35 The results of the experimental procedures described in hereinabove identified antibody clones which possess functional properties which are relevant for their pre-clinical and clinical development of antibodies capable of inhibiting IL-11/IL-11-R signalling.
- 40 Clones YU33-B4/YU45-G2/A3 (#3), YU45-E3 (#16), YU45-F2 (#24), YU45-F5 (#39), YU46-A8 (#45) and YU46-G8 (#54) were identified as particularly promising candidates, showing good ability to inhibit signalling by both human and mouse IL-11, and good inhibition of IL-11 *trans* signalling.

2.4 Analysis of antibody affinity for human IL-11

The human anti-human IL-11 antibodies were analysed for their affinity of binding to human IL-11 by ELISA assay.

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Recombinant human IL-11 was obtained from Genscript and Horseradish peroxidase (HRP)-conjugated anti-human IgG (Fc-specific) antibody was obtained from Sigma. Corning 96-well ELISA plates were obtained from Sigma. Pierce 3,3',5,5'-tetramethylbenzidine (TMB) ELISA substrate kit was obtained from Life Technologies (0.4 g/mL TMB solution, 0.02 % hydrogen peroxide in citric acid buffer). Bovine serum albumin and sulphuric acid was obtained from Sigma. Wash buffer comprised 0.05% Tween-20 in phosphate buffered saline (PBS-T). ScFv-Fc antibodies were generated as described in Example 1. Purified mouse and human IgG controls were purchased from Life Technologies. Tecan Infinite 200 PRO NanoQuant was used to measure absorbance.

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Criss-cross serial dilution analysis was performed as described by Hornbeck et al., (2015) Curr Protoc Immunol 110, 2.1.1-23) to determine the optimal concentration of coating antigen, primary and secondary antibodies.

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An indirect ELISA was performed to assess the binding affinity of primary ScFv-Fc antibodies at 50% of effective concentration (EC_{50}) as previously described (Unverdorben et al., (2016) MAbs 8, 120–128.). ELISA plates were coated with 1 μ g/mL of recombinant human IL-11 overnight at 4°C and remaining binding sites were blocked with 2 % BSA in PBS. ScFv-Fc antibodies were diluted in 1% BSA in PBS, titrated to obtain working concentrations of 800, 200, 50, 12.5, 3.125, 0.78, 0.195, and 0.049 ng/mL, and incubated in duplicates for 2 hours at room temperature. Detection of antigen-antibody binding was performed with 15.625 ng/mL of HRP-conjugated anti-human IgG (Fc-specific) antibody. Following 2 hours of incubation with the detection antibody, 100 μ L of TMB substrate was added for 15 mins and chromogenic reaction stopped with 100 μ L of 2 M H_2SO_4 . Absorbance reading was measured at 450 nm with reference wavelength correction at 570 nm. Data were fitted with GraphPad Prism software with log transformation of antibody concentrations followed by non-linear regression analysis with the asymmetrical (five-parameter) logistic dose-response curve to determine individual EC_{50} values.

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The same materials and procedures as described above were performed to determine the affinity of binding for the murine monoclonal anti-IL-11 antibodies, with the exception that HRP-conjugated anti-mouse IgG (H&L) was used instead of HRP-conjugated anti-human IgG.

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The same materials and procedures as described above were performed to determine the affinity of binding for the human monoclonal anti-IL-11 antibodies and murine monoclonal anti-IL-11 antibodies to recombinant murine IL-11 obtained from Genscript.

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The results of the ELISA assays are shown in Figure 10A to 10F, and were used to determine EC_{50} values for the antibodies which are shown in Figure 11.

2.5 Ability to inhibit human IL-11 mediated signalling in a variety of tissues

Ability of the antibodies to neutralise IL-11-mediated signalling and *trans* signalling in fibroblasts obtained from a variety of different tissues is investigated, essentially as described in sections 2.1 and 2.3 except that instead of cardiac atrial human fibroblasts, human fibroblasts derived from liver, lung, kidney, eye, skin, pancreas, spleen, bowel, brain, and bone marrow are used for the experiments.

Anti-IL-11 antibodies are demonstrated to be capable of neutralising signalling in fibroblasts derived from the various different tissues, as determined by observation of a relative decrease in the proportion of α SMA-positive fibroblasts at the end of the 24 h culture period in the presence of the anti-IL-11 antibodies as compared to culture in the absence of the antibodies.

Example 3: Light chain shuffling of human anti-human IL-11 antibodies

Human IL-11 antibodies are affinity-matured by light chain shuffling to obtain antibodies having improved affinity for IL-11.

Chain shuffling to improve antibody affinity is a well-known technique in the field of antibody technology, and is described in detail in Marks, Antibody Affinity Maturation by Chain Shuffling, Antibody Engineering Methods and Protocols, Humana Press (2004) Vol. 248, pp327-343, incorporated by reference herein. In particular, Light chain shuffling is described in detail at sections 3.1 and 3.2 thereof.

The heavy chain variable regions of the human anti-human IL-11 antibodies are combined with a repertoire of light chain variable region partners to identify new VL/VH combinations having high affinity for IL-11.

A schematic representation of light chain shuffling is shown in Figure 12. Briefly, nucleic acid encoding the VH domain for an antibody is cloned into a phage display vector comprising a repertoire of VL chains, and scFv comprising new VH/VL combinations are analysed for binding to human IL-11 by ELISA.

The scFv having VH/VL combinations displaying the strongest binding affinity for IL-11 are then analysed for cross-reactivity against murine IL-11.

The VH/VL sequences of the scFv are then cloned into expression vectors for the generation of scFv-Fc (human IgG1) antibodies, the vectors are transiently expressed in mammalian cells cultured in serum-free media, and isolated by protein A purification.

Example 4: Mouse monoclonal anti-human IL-11 antibodies

Mouse monoclonal antibodies directed against human IL-11 protein were also generated, as follows.

cDNA encoding the amino acid for human IL-11 was cloned into expression plasmids (Aldevron GmbH, Freiburg, Germany).

Mice were immunised by intradermal application of DNA-coated gold-particles using a hand-held device for particle-bombardment ("gene gun"). Serum samples were collected from mice after a series of

immunisations, and tested in flow cytometry on HEK cells which had been transiently transfected with human IL-11 expression plasmids (cell surface expression of human IL-11 by transiently transfected HEK cells was confirmed with anti-tag antibodies recognising a tag added to the N-terminus of the IL-11 protein).

- 5 Antibody-producing cells were isolated from the mice and fused with mouse myeloma cells (Ag8) according to standard procedures.

Hybridomas producing antibodies specific for IL-11 were identified by screening for ability to bind to IL-11 expressing HEK cells by flow cytometry.

10

Cell pellets of positive hybridomas cells were prepared using an RNA protection agent (RNAlater, cat. #AM7020 by ThermoFisher Scientific) and further processed for sequencing of the variable domains of the antibodies.

15

In total, 16 mouse monoclonal anti-human IL-11 antibodies were prepared (Figure 13). The VH and VL sequences determined for clone BSN-3C6 are shown in SEQ ID NOs:91 to 94. The VH and VL sequences determined for clone BSN-1H2 are shown in SEQ ID NOs:156 and 157. The VH and VL sequences determined for clone BSN-7D4 are shown in SEQ ID NOs:174 and 175. The VH and VL sequences determined for clone BSN-8H11 are shown in SEQ ID NOs: 192 and 193.

20

Example 5: Functional characterisation of mouse monoclonal anti-human IL-11 antibodies

5.1 Ability to inhibit human IL-11 mediated signalling

The ability of the murine monoclonal anti-human IL-11 antibodies to inhibit signalling mediated by human IL-11 was investigated using the same assay as described in Example 2.1 above.

25

The results of the Experiments are shown in Figures 14 and 17. The antibodies were demonstrated to be capable of neutralising signalling mediated by human IL-11.

A commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA) was also analysed for ability to inhibit signalling by human IL-11 in the experiments. This antibody was found to be able to reduce the percentage of activated fibroblasts to 0.89 times.

30

Clone A7 (BSN-3C11) was found to neutralise signalling by human IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard).

35

5.2 Ability to inhibit mouse IL-11 mediated signalling

The ability of the murine monoclonal anti-human IL-11 antibodies to inhibit signalling mediated by murine IL-11 was investigated using the same assay as described in Example 2.2 above, but using mouse atrial fibroblasts instead of mouse dermal fibroblasts.

40

The results of the Experiments are shown in Figures 15 and 17. The antibodies were demonstrated to be capable of neutralising signalling mediated by murine IL-11.

A commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA) was also analysed for ability to inhibit signalling by human IL-11 in the experiments. This antibody was found to be able to reduce the percentage of activated fibroblasts to 43.0% (=1.44).

Several of the clones neutralised signalling by murine IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): A3 (BSN-2E1), A5 (BSN-2G6) and A6 (BSN-3C6).

9.3 Ability of mouse anti-IL-11 antibodies to inhibit IL-11 *trans* signalling, by IL-11 in complex with IL-11RA

The ability of the mouse anti-IL-11 antibodies to inhibit signalling mediated by hyper IL-11 was investigated.

Human atrial fibroblasts were incubated for 24h with hyper IL-11 (0.2 ng/ml) in the presence of anti-IL-11 antibodies (2 µg/ml) or isotype control antibody. Following incubation, cell culture supernatant was analysed for MMP2. Stimulation with hyper IL-11 results in an increase in the secretion of MMP2 as compared to non-stimulated cultures.

The results of the experiments are shown in Figures 16 and 17. The mouse anti-IL-11 antibodies were found to be capable of neutralising signalling mediated by hyper IL-11 (i.e. IL-11 *trans* signalling), and several were found to be capable of inhibiting *trans* signalling to a greater extent than the commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA): BSN-2G6 (A5), BSN-3C6 (A6), BSN-5B8 (A9) and BSN-7D4 (A12).

Clone BSN-3C6 (A6) was identified as a particularly promising candidate for further development (highlighted in Figure 17), showing good ability to inhibit both human IL-11 and mouse IL-11 mediated signalling, and good inhibition of IL-11 *trans* signalling.

5.4 Screening for ability of mouse anti-IL-11 antibodies to bind IL-11

The mouse hybridomas producing anti-human IL-11 antibodies were sub-cloned, and cell culture supernatant from the subcloned hybridomas was analysed by "mix-and-measure" iQue assay for (i) ability to bind to human IL-11, and (ii) cross reactivity for antigen other than IL-11.

Briefly, labelled control cells (not expressing IL-11 at the cell surface) and unlabelled target cells expressing human IL-11 at their surface (following transient transfection with a plasmid encoding a FLAG-tagged human IL-11) were mixed together with the cell culture supernatant (containing mouse-anti-IL-11 antibodies) and secondary detection antibodies (fluorescently-labelled anti-mouse IgG antibody).

The cells were then analysed using the HTFC Screening System (iQue) for the two labels (i.e. the cell label and the label on the secondary antibody). Detection of the secondary antibody on the unlabelled, IL-11 expressing cells indicated ability of the mouse-anti-IL-11 antibodies to bind to IL-11. Detection of the

secondary antibody on the labelled, control cells indicated cross-reactivity of the mouse-anti-IL-11 antibodies for target other than IL-11.

As a positive control condition, labelled and unlabelled cells were incubated with a mouse anti-FLAG tag antibody as the primary antibody.

The results are shown in Figures 18A and 18B. The majority of the subcloned hybridomas expressed antibody which was able to bind to human IL-11, and which recognised this target with high specificity.

Clones BSN-2G6, BSN-5B8 and BSN-7F9 displayed some binding to cells not expressing IL-11, and so may have cross-reactivity for target(s) other than IL-11. Antibody produced by subclone BSN-3C11 was found not to bind to human IL-11.

13 of the 16 antibodies displayed stronger signal for binding to IL-11 than signal for the positive control anti-tag antibody for the tag, indicating that these antibodies bind to IL-11 with high affinity.

Human fibroblasts were stimulated with a maximum dose of TGFB1 (5ng/ml), the strongest stimulator of IL-11 expression in atrial fibroblasts. This usually results in an IL-11 concentration of ~500pg/ml – 1ng/ml in the supernatant after 24h, depending also on the genotype of the primary atrial fibroblasts. The advantage of this approach is that it ensures the inhibition of correctly folded, endogenously produced IL-11 at physiologically relevant maximum levels of production. The fibrosis-relevant autocrine activity of IL-11 directly on fibroblasts is neutralised in this assay. TGFB1 stimulates the expression of IL-11, which subsequently drives the transition from quiescent fibroblasts to activated (ACTA2-positive) fibroblasts. Neutralising IL-11 antibodies inhibit this transition. Thus, antibodies lowering the percentage of activated fibroblasts after TGFB1 stimulation in our in vitro screening can be considered neutralisers and anti-fibrotic agents.

Figure 18C shows the antibodies that neutralise IL-11 signalling. Human fibroblast activation was monitored to identify neutralising clones. 100% inhibition indicates myofibroblast (ACTA2+ve) levels of unstimulated fibroblasts and 0% corresponds to fully activated fibroblasts and the maximum amount of myofibroblasts.

The experiment was repeated in mouse fibroblasts. The results are shown in Figure 18D.

The antibodies were also tested for their ability to inhibit *trans* signalling using Hyper IL-11 (IL-11:IL11RA) activation of human fibroblasts. Antibodies that specifically bind IL-11 were incubated with IL-11:IL11RA-stimulated primary fibroblasts. Human fibroblast activation was monitored to identify neutralising clones. 100% inhibition indicates levels of unstimulated fibroblasts and 0% to fully activated fibroblasts.

Figure 18E shows the antibodies that neutralise IL-11 *trans* signalling.

IC50 values were determined for clone 3C6 in primary atrial human fibroblasts stimulated with human recombinant IL-11 (2ng/ml, 24h). The fibrotic response was determined by measuring MMP2 and TIMP1 concentrations in the supernatant. A similar experiment was performed using 200pg/ml of hyper IL-11 for 24h

to assess blockage of *trans* signalling. Protein secretion into the supernatant by fibroblasts was assessed to estimate the % of inhibition.

Figures 18F and 18G show neutralisation of the fibrotic response in both cases.

5

The experiment was repeated using human hepatic stellate cells (HSCs) incubated with TGFB1 (5ng/ml) or IL-11 (2ng/ml) and determining MMP2 secretion into the supernatant by fibroblasts to estimate the % of inhibition. Figure 18H shows neutralisation of the fibrotic response by 3C6 in HSCs stimulated with TGFB1 (left) or IL-11 (right).

10 Example 6: Chimeric and humanised versions of the mouse anti-human IL-11 antibodies

Mouse/human chimeric and humanised versions of the mouse monoclonal anti-human IL-11 antibodies of Example 4 are prepared according to standard methods.

6.1 Mouse/human chimeric antibodies

15 Mouse/human chimeric antibodies are prepared from the mouse monoclonal anti-human IL-11 antibodies as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 8 thereof.

20 Briefly, the DNA sequences encoding the VH and VL of hybridomas producing the mouse anti-human IL-11 antibodies are determined, and combined with DNA sequence encoding human immunoglobulin constant regions to produce a mouse/human chimeric antibody sequence, from which a chimeric mouse/human antibody is expressed in mammalian cells.

6.2 Humanised antibodies

25 Humanised antibodies are prepared from the mouse monoclonal anti-human IL-11 antibodies as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 7 thereof, in particular at section 3.1 of Chapter 7 entitled 'Antibody Humanization'.

30 Humanised versions of BSN-3C6 sequences were also designed, and these are shown in SEQ ID NOs:116 to 128.

35 Briefly, the DNA sequences encoding the VH and VL of hybridomas producing the mouse anti-human IL-11 antibodies are determined, and inserted into DNA sequence encoding human antibody variable region framework regions and immunoglobulin constant regions, to produce a humanised antibody sequence, from which a humanised antibody is expressed in mammalian cells.

40 Primary human atrial fibroblasts were incubated with TGFB1 (5ng/ml) and varying concentrations of humanised 3C6 clones: VH 2.2/VL 2.1; VH 2.2/VL 2.2; VH 2.2/VL 2.3; VH 2.2/VL 2.4; VH 2.3/VL 2.2; and VH 2.3/VL 2.3.

Name	Heavy chain	Light chain
VH 2.2/VL 2.1	SEQ ID NO:117	SEQ ID NO:121
VH 2.2/VL 2.2	SEQ ID NO:117	SEQ ID NO:122
VH 2.2/VL 2.3	SEQ ID NO:117	SEQ ID NO:123
VH 2.2/VL 2.4	SEQ ID NO:117	SEQ ID NO:124
VH 2.3/VL 2.2	SEQ ID NO:118	SEQ ID NO:122
VH 2.3/VL 2.3	SEQ ID NO:118	SEQ ID NO:123

Primary human atrial fibroblasts were incubated with TGFB1 (5ng/ml) and varying concentrations of humanised 3C6 clones. MMP2 secretion into the supernatant by human atrial fibroblasts was assessed to estimate the % of inhibition.

5

Figure 54A shows that the antibodies bind to IL-11 and block endogenously produced IL-11 from interacting. IL-11 signalling is neutralised, which inhibits fibrogenic protein production.

10

The experiment was repeated using human HSCs and clones VH 2.2/VL 2.1, VH 2.2/VL 2.2, VH 2.2/VL 2.3 and VH 2.2/VL 2.4.

Figure 54B shows that the antibodies bind to IL-11 and block endogenously produced IL-11 from interacting. IL-11 signalling is neutralised, which inhibits fibrogenic protein production.

Example 7: Further biochemical analysis of anti-IL-11 antibodies

15

The antibodies described herein are subjected to further biochemical analysis.

The antibodies are analysed by BIAcore, Biolayer interferometry (BLI) and MicroScale Thermophoresis (MST) analysis to determine the affinity of binding to human IL-11 and mouse IL-11.

20

BIAcore determination of antibody affinity by surface plasmon resonance (SPR) analysis is performed as described in Rich et al., Anal Biochem. 2008 Feb 1; 373(1):112-20.

Biolayer interferometry analysis of antibody affinity is performed as described in Concepcion et al., Comb Chem High Throughput Screen. 2009 Sep; 12(8):791-800.

25

MicroScale Thermophoresis analysis of antibody affinity is performed as described in Jerabek-Willemsen et al., Assay Drug Dev Technol. 2011 Aug; 9(4): 342–353.

30

Aggregation of the antibodies is analysed by size exclusion chromatography (SEC), as described in Iacob et al., J Pharm Sci. 2013 Dec; 102(12): 4315–4329.

Hydrophobicity of the antibodies is analysed by Hydrophobic interaction chromatography (HIC) as described in Haverick et al., MAbs. 2014 Jul-Aug;6(4):852-8.

The melting temperature of the antibodies is analysed by Differential scanning fluorimetry (DSF) as described in Menzen and Friess, J Pharm Sci. 2013 Feb;102(2):415-28.

Example 8: Inhibition of fibrosis *in vivo* using anti-IL-11 antibodies

The therapeutic utility of the anti-human IL-11 antibodies is demonstrated in *in vivo* mouse models of fibrosis for various different tissues. The mice used in the experiments are wildtype (i.e. IL-11RA+/+) mice.

8.1 Heart fibrosis

A pump is implanted, and mice are treated with AngII (2mg/kg/day) for 28 days.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. At the end of the experiment, collagen content is assessed in the atria of the mice using a calorimetric hydroxyproline-based assay kit, and the level of RNA expression of the markers or fibrosis Col1A2, α SMA (ACTA2) and fibronectin (Fn1) were analysed by qPCR.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in heart tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

8.2 Kidney fibrosis

A mouse model for kidney fibrosis is established, in which fibrosis is induced by intraperitoneal injection of folic acid (180mg/kg) in vehicle (0.3M NaHCO₃); control mice were administered vehicle alone.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. Kidneys are removed at day 28, weighed and either fixed in 10% neutral-buffered formalin for Masson's trichrome and Sirius staining or snap-frozen for collagen assay, RNA, and protein studies.

Total RNA is extracted from the snap-frozen kidney using Trizol reagent (Invitrogen) and Qiagen RNeasy column (Qiagen) purification. The cDNA is prepared using iScriptTM cDNA synthesis kit, in which each reaction contained 1 μ g of total RNA, as per the manufacturer's instructions.

Quantitative RT-PCR gene expression analysis is performed on triplicate samples with either TaqMan (Applied Biosystems) or fast SYBR green (Qiagen) technology using StepOnePlusTM (Applied Biosystem) over 40 cycles. Expression data are normalized to GAPDH mRNA expression level and the 2- $\Delta\Delta$ Ct method is used to calculate the fold-change. The snap-frozen kidneys are subjected to acid hydrolysis by heating in 6M HCl at a concentration of 50 mg/ml (95°C, 20 hours). The amount of total collagen in the hydrolysate is quantified based on the colorimetric detection of hydroxyproline using Quickzyme Total Collagen assay kit (Quickzyme Biosciences) as per the manufacturer's instructions.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in kidney tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

8.3 Lung fibrosis

Mice are treated by intratracheal administration of bleomycin on day 0 to establish a fibrotic response in the lung (pulmonary fibrosis).

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. Mice are sacrificed at day 21, and analysed for differences in fibrosis markers.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in lung tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

8.4 Skin fibrosis

Mice are treated by subcutaneous administration of bleomycin on day 0 to establish a fibrotic response in the skin.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. Mice are sacrificed at day 21, and analysed for differences in fibrosis markers.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in skin tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

8.5 Eye fibrosis

To analyse fibrosis in the eye, IL-11RA $-/-$ mice and IL-11RA $+/+$ mice undergo trabeculectomy (filtration surgery) on day 0 to initiate a wound healing response in the eye. This mouse model of glaucoma filtration surgery has been shown to be an efficient model to evaluate the wound healing response in the eye (Khaw et al. 2001, Curr Opin Ophthalmol 12, 143–148; Seet et al. 2011, Mol. Med. 17, 557–567) and has successfully shown the beneficial effect of fibrotic modulators *in vivo* (Mead et al. 2003, Invest. Ophthalmol. Vis. Sci. 44, 3394–3401; Wong et al. 2003 Invest. Ophthalmol. Vis. Sci. 44, 1097–1103; Wong et al. 2005, Invest. Ophthalmol. Vis. Sci. 46, 2018–2022).

Briefly, the conjunctiva are dissected to expose the underlying sclera, after which an incision is made through the sclera into the anterior chamber of the eye using a 30-gauge needle. The created fistula allows aqueous humor to exit into and underneath the conjunctiva. The dissected conjunctiva is then secured and closed at the limbus by a 10-0 (0.2 metric) Ethilon black monofilament nylon scleral suture. Fucithalamic ointment is instilled at the end of the procedure. The surgery is performed under anaesthesia by intraperitoneal injection of a 0.1 ml ketamine/xylazine mixture, as well as topical application of one drop per eye of 1% xylocaine. Fucithalamic ointment is instilled post-surgery to prevent infection. Surgery is performed with 70% propyl alcohol sterilized surgical scissors and forceps and sterile needles.

The accumulated fluid underneath the sutured conjunctiva is observed as a conjunctival bleb. Mice are euthanized on day 7 post-surgery for analyses. For qualitative immune-histological analyses, eyes from mice are harvested by enucleation and then sectioned. Maturation of collagen fibres is evaluated with using the picro-sirius red/polarization light technique (Szendrői et al. 1984, Acta Morphol Hung 32, 47–55); orange-red indicates mature collagen, and yellow/green indicates newly formed immature collagen.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection, and fibrosis is monitored in the eye tissue.

- 5 Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in eye tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

8.6 Other tissues

- 10 The effect of treatment with neutralising anti-IL-11 antibodies on fibrosis is also analysed in mouse models of fibrosis for other tissues, such as the liver, kidney, bowel, and is also analysed in a model relevant to multiorgan (i.e. systemic) fibrosis.

- 15 The fibrotic response is measured and compared between mice treated with neutralising anti-IL-11 antibodies and mice treated with control antibodies. Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

Example 9: Treatment of cancer *in vivo* using anti-IL-11 antibodies

- 20 The effect of treatment with neutralising anti-IL-11 antibodies on cancer is analysed in mouse models of cancer.

Models of breast, lung, and gastrointestinal cancers are established in mice, the mice are treated by administration of neutralising anti-IL-11 antibodies, or control antibodies, and the development/progression of cancer is monitored.

- 25 An anti-cancer effect is observed for the neutralising anti-IL-11 antibodies, as evidenced by reduced symptoms of cancer and/or increased survival as compared to mice treated with control antibodies.

Anti-IL-11 antibodies were assessed for their effect on tumour growth.

- 30 A number of different cancer models were investigated.

Liver cancer cells (HCC) were implanted into mice (flank model) and tumour volume was monitored for 3 weeks after implantation. Mice were treated either with 3C6 or IgG control antibodies. Tumour size was monitored.

- 35 Figure 51A shows that tumour size was found to be significantly reduced during anti-IL-11 antibody treatment alone, indicating a therapeutic effect of inhibiting IL-11 signalling in liver cancer.

- 40 A murine model demonstrating IL-11 over-expression in fibroblasts was created which developed severe global organ fibrosis due to IL-11 secretion from fibroblasts. The spleen increases in size 2-fold over a period of 3 weeks and shows profound and easily measured IL-11 related changes, likely driven by myelofibrosis (a

type of bone marrow cancer). 3C6 antibody prevents IL-11 induced splenomegaly in a transgenic mouse expressing IL-11 in fibroblasts in the myelofibrosis model, as shown in Figure 51B.

The effect of anti-IL-11 antibody 3C6 was assessed in a lung cancer model in conjunction with cisplatin chemotherapy.

Mice were inoculated subcutaneously with A549 tumor cells (5×10^6 ; day 0). Mice were either left untreated, or treated with cisplatin (6mg/kg, twice weekly) supplemented by either IgG antibody (10mg/kg x 2/week, IP) or 3C6 (10mg/kg x 2/week, IP) for 5 weeks. Tumor volume was measured twice per week.

The results are shown in Figure 51C. Anti-IL-11 therapy provides an additive effect for inhibition of tumour volume when administered in combination with cisplatin chemotherapy.

Example 10: Treatment of AMD using anti-IL-11 antibodies

The effect of treatment with neutralising anti-IL-11 antibodies is investigated in wet age-related macular degeneration (AMD).

Neutralising anti-IL-11 antibody is administered to subjects having wet AMD. In some treatment conditions, subjects are administered with VEGF antagonist therapy (e.g. ranibizumab, bevacizumab, pegaptanib, brolucizumab or aflibercept), PDGF antagonist therapy (e.g. pegpleranib), or are treated by laser coagulation therapy in addition to treatment with anti-IL-11 antibody.

A reduction in wet AMD pathology and/or improvement in the symptoms of wet AMD is observed in subjects treated with anti-IL-11 antibody as compared to subjects not treated with anti-IL-11 antibody.

Example 11: Light Chain Shuffled Antibodies

Light chain shuffling was performed as represented schematically in Figure 12.

The heavy chains of the following IL-11-binding antibody clones were used for light chain shuffling: YU45-E03, YU45-F02, YU45-F05, YU45-G02, YU46-A08, YU46-G08.

Variable regions of the heavy chains were amplified by PCR, and the resulting amplicons were pooled and cloned into phagemid vectors (phagemids) each containing a specific VL chain, and representing naïve lambda and kappa light chain library repertoires. The VH and VL containing phagemids were used to produce a new library of antibody-phages, which was used to select clones displaying binding to IL-11 under stringent conditions (i.e. antigen limitation, large number washing steps).

Antibodies capable of binding to both human IL-11 and murine IL-11 (i.e. cross-reactive antibodies) were identified by phage display by panning using biotinylated and non-biotinylated recombinant human and murine IL-11, based on the panning strategy shown in Figure 19.

The analysis identified 66 cross-reactive antibodies (Figure 20). Sequence analysis identified 64 unique antibody clones.

The 64 antibody clones were analysed for binding signal to human IL-11 and murine IL-11 in an ELISA assay. The results are shown in Figures 21A and 21B.

Example 12: Functional Characterisation of the Light Chain Shuffled Antibodies

54 of the light chain shuffled antibodies were analysed for their ability to bind IL-11 and inhibit IL-11 mediated signalling.

12.1 Binding to human IL-11

The light chain shuffled anti-IL-11 antibodies were analysed to determine the EC50 for binding to human IL-11 by ELISA according to standard methods. Briefly, wells of microtiter plates were coated with recombinant human IL-11 (100 ng/well), scFv-Fc comprising the VH and VL domains of the clones were added in a dilution series and antibody binding was detected using a polyclonal antibody detection system.

The results of the ELISA assays were used to calculate EC50 values (ng/ml) for the light chain shuffled antibody clones, and these are shown in Figure 22.

12.2 Ability to inhibit human IL-11 mediated signalling

To investigate the ability of light chain shuffled antibody clones to neutralise human IL-11-mediated signalling, cardiac atrial human fibroblasts were cultured in wells of 96-well plates in the presence of TGFβ1 (5 ng/ml) for 24 hours, in the presence of anti-IL-11 antibodies in scFv-human IgG1-Fc format, or in the presence of human IgG1 isotype control antibody, at a final concentration of 2 mg/ml. Levels of the pro-fibrotic marker MMP2 in the cell culture supernatant were then measured by ELISA. Basal MMP2 secretion by the cells in culture was measured by culture in the absence of TGFβ1, in the presence of human IgG1 isotype control (2 mg/ml).

The results of two separate experiments are shown in Figures 23A and 23B. Horizontal lines in the bar charts represent the basal MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of human IgG1 isotype control antibody in the absence of TGFβ1 stimulation ('NEG' in Figures 23A and 23B), and MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of 5 ng/ml TGFβ and the human IgG1 isotype control antibody ('POS' in Figures 23A and 23B).

The light chain shuffled anti-IL-11 antibodies were shown to be able to bind to human IL-11, and to inhibit IL-11 mediated signalling. The results are summarised in Figure 24.

Nine clones were assessed further based on their performance and were screened for neutralisation of endogenous IL-11, as above. MMP2 secretion into the supernatant by fibroblasts was assessed to estimate the % of inhibition.

Figure 23C shows that several of the antibodies bind to endogenously produced IL-11, neutralise IL-11 signalling in the fibroblasts and inhibit fibrogenic protein production.

To more accurately estimate the IC₅₀ values of clones YU100-G08 and YU100-H01, the above experiment was repeated using lower antibody concentrations (range: 0.061, 0.244, 0.976, 3.9, 15.625, 62.5, 250, 1000 and 4000 ng/ml) and primary atrial fibroblasts. MMP2 secretion into the supernatant by fibroblasts was assessed to estimate the % of inhibition.

Figure 23D shows that both antibodies bind to endogenously produced IL-11, neutralise IL-11 signalling in the fibroblasts and inhibit fibrogenic protein production. Stimulation of human fibroblasts with recombinant IL-11 (2ng/ml, 24h) also showed that both antibodies neutralise IL-11 signalling in the fibroblasts and inhibit fibrogenic protein production.

The ability of YU100-G08 and YU100-H01 to inhibit *trans* IL-11 signalling was assessed. Primary human fibroblasts were stimulated with IL-11:IL11RA (hyperIL-11; 0.2ng/ml, 24h). MMP2 secretion into the supernatant by fibroblasts was assessed to estimate the % of inhibition.

Figure 23E shows that both antibodies neutralise *trans* IL-11 signalling and inhibit fibrogenic protein production.

Example 13: Inhibition of kidney fibrosis or kidney injury using anti-IL-11 antibodies

10–12 week old littermate mice of similar weight had kidney fibrosis induced by intraperitoneal (i.p.) injection of folic acid (180 mg kg⁻¹) in vehicle (0.3 M NaHCO₃); control mice were administered vehicle alone.

Anti-IL11 antibody clone BSN-3C6 was administered one day after folic acid treatment and then 3 times per week at a dose of 20 mg/kg. Mice were euthanized 28 days post-injection.

The mouse plasma levels of urea and creatinine were quantified using urea assay kit (ab83362, Abcam) and creatinine assay kit (ab65340, Abcam), respectively according to the manufacturer's instructions. The amount of total collagen in the kidney was quantified on the basis of colourimetric detection of hydroxyproline using a Quickzyme Total Collagen assay kit (Quickzyme Biosciences). All colourimetric assays were performed according to the manufacturer's instructions.

Tissues were paraffin-embedded, and kidneys were sectioned at 3 µm. For paraffin sections, tissues were fixed for 24 h, at room temperature in 10% neutral-buffered formalin (Sigma-Aldrich), dehydrated and embedded in paraffin. For cryosections, freshly dissected organs were embedded with Tissue-Tek Optimal Cutting Temperature compound (VWR International). Cryomoulds were then frozen in a metal beaker with isopentane cooled in liquid nitrogen and sections were stored in -80 °C. Total collagen was stained with Masson's trichrome stain kit (HT15, Sigma-Aldrich) according to the manufacturer's instructions. Images of the sections were captured and blue-stained fibrotic areas were semi-quantitatively determined with ImageJ software (version 1.49). For immunohistochemistry, the tissue sections were incubated with anti-ACTA2 antibody (ab5694, Abcam). Primary antibody staining was visualized using an ImmPRESS HRP Anti-Rabbit

IgG Polymer Detection kit (Vector Laboratories) with ImmPACT DAB Peroxidase Substrate (Vector Laboratories) as the chromogen. The sections were then counterstained with Mayer's haematoxylin (Merck).

5 Figures 25A and 25B show that mice treated with anti-IL11 antibody were found to have significantly reduced staining for collagen, indicating that anti-IL-11 antibody treatment had inhibited kidney fibrosis.

Figure 26 shows that the urinary albumin/creatinine ratio was significantly reduced by treatment with anti-IL11 antibody, indicating a reduced level of kidney damage in mice treated with anti-IL-11 antibody.

10 Figure 27A shows that treatment with the anti-IL-11 antibody inhibited folic acid-induced kidney fibrosis in a dose-dependent fashion.

15 Anti-IL-11 antibodies BSN-3C6 and YU100-G08 02A were assessed for their ability to reduce folic acid-induced kidney fibrosis at different concentrations (0.5, 1, 5 and 10 mg/kg). IgG (10 mg/kg) was used as a control. Antibody injections were initiated one day before folate treatment and performed biweekly. Animals were sacrificed three weeks after folate induced injury to assess renal collagen content using the HPA assay. Figures 27B and 27C show that anti-IL-11 therapy was found to reduce kidney collagen content in folic acid-induced kidney fibrosis in a dose-dependent fashion.

20 In another experiment a mouse model of acute renal injury was induced by unilateral ureteric obstruction (UUO). Briefly, mice were treated by sham operation or ureteric obstruction of one ureter. Mice received IgG, anti-IL-11 antibody clone BSN-3C6 (20mg/kg; on surgical days -1, 1, 3, 5) and injured kidneys ('UUO') or contralateral uninjured kidneys (Con) were harvested on day 7 post surgery.

25 Semi-quantitative assessment of tubular injury was performed by histological analysis of casts, tubular atrophy or tubular expansion blinded to experimental conditions (Tubular injury score: 0, none; 1, minimal; 2, mild; 3, moderate; 4, severe).

30 Figures 28A and 28B show that treatment with anti-IL-11 antibody reduced tubular damage in a mouse model of acute renal injury.

Example 14: IL-11 and liver fibrosis

35 Protein expression of IL-11 in healthy and diseased livers was confirmed by western blots in matched samples of human livers. Matched frozen liver samples were prepared for western blotting and levels of IL11 determined using Human IL-11 Antibody Monoclonal Mouse IgG2A Clone # 22626, catalog number MAB218 from R&D Systems. Film images were generated.

The results are shown in Figure 29. Increased expression of IL-11 was detected in most diseased tissue as compared to normal healthy livers.

To determine whether IL-11 expression changed with disease, an ELISA was performed on media from Precision Cut Liver Slices (PCLS) using Human IL-11 DuoSet 15 plate kit, catalog number DY218 from R&D Systems.

- 5 Human PCLS were cut and incubated with media treatments after a 24 h rest period for acclimatisation to media plates. Samples were treated with media only (control), media with LPS, a combination of profibrogenic stimuli inducing TGF β 1, or a combination of profibrogenic stimuli inducing TGF β 1 and the TGF β 1 inhibitor ALK5.
- 10 The results are shown in Figure 30A. The profibrogenic stimuli induced upregulation of IL-11 protein expression, and ALK5 inhibitor was found to inhibit TGF β 1 receptor signalling, which reduced the expression of IL-11 protein down to control levels.

- 15 Hepatic stellate cells (HSCs) are the precursors of myofibroblasts in the liver. BSN-3C6 and YU100-G08_02A were assessed for their ability to block the HSC-to-myofibroblast transition, indicated by a reduction of ACTA2⁺ cells when HSCs were incubated with TGF β 1 (24h) and neutralising antibodies (2ug/ml).

- 20 Figure 30B shows that both anti-IL-11 antibodies inhibited the trans-differentiation of HSCs into myofibroblasts following IL-11 stimulation by TGF β 1.

- The IC₅₀ of YU100-G08_02A was determined by measuring MMP2 concentration from HSCs stimulated with IL-11. Primary human HSCs were incubated with TGF β 1 (5ng/ml) (left) or IL-11 (2ng/ml) (right) and varying concentrations of antibody. MMP2 secretion into the supernatant by fibroblasts was assessed to estimate the % of inhibition.
- 25

Figure 30C shows that YU100-G08_02A neutralises the fibrotic response in HSCs.

14.1 Inhibition of liver fibrosis using anti-IL-11 antibodies in a preclinical model of NASH

- 30 Non-alcoholic steatohepatitis (NASH) is a common liver disease characterised by progression from inflammation to fibrosis and eventually liver failure.

- 35 Diabetic mice (db/db; deficient for the leptin receptor) were maintained for 8 weeks on a normal chow diet or on a NASH-inducing (methionine/choline deficient (MCD)) diet. To test the efficacy of neutralizing anti-IL11 antibodies, anti-IL-11 antibody clone BSN-3C6 was administered (20mg/kg, 3x/week, intraperitoneally) for the final 3 weeks of the 8 week NASH diet (Figure 31A, bottom panels). Gross liver histology was assessed at time of euthanasia, and collagen content of the liver was analysed by hydroxyproline assay.

- 40 The results are shown in Figures 31A and 31B. Inhibition of IL-11 mediated signalling by anti-IL-11 antibody treatment improved liver histology in a mouse model of nonalcoholic steatohepatitis (Figure 31A) as evidenced by partial restoration of liver morphology and texture in anti-IL-11 antibody-treated animals on NASH diet as compared to untreated animals on NASH diet. Livers from mice treated with anti-IL-11

antibody on NASH diet were also found to have reduced collagen content as compared to untreated animals on NASH diet (Figure 31B).

In the same NASH model using diabetic mice, animals were fed on a normal chow (NC) diet for 12 weeks to reach the steatosis stage. Mice were then fed a MCD diet for 8 weeks to induce NASH. For those 8 weeks, mice were administered with 20 mg/kg anti-IL-11 antibody BSN-3C6 or IgG control twice per week.

Liver triglycerides (TG) measurements were performed using triglyceride colorimetric assay kit (10010303, Cayman). Total hydroxyproline content in the livers was measured using Quickzyme Total Collagen assay kit (Quickzyme Biosciences). Serum levels of alanine aminotransferase (ALT) was measured using Alanine Transaminase Activity Assay Kit (ab105134, abcam). To quantify expression of pro-inflammatory factors, total RNA was extracted from snap-frozen liver tissues using Trizol (Invitrogen) followed by RNeasy column (Qiagen) purification. The cDNAs were synthesized with iScript™ cDNA synthesis kit (Bio-Rad) according to manufacturer's instructions. Gene expression analysis was performed on duplicate samples with either TaqMan (Applied Biosystems) or fast SYBR green (Qiagen) technology using StepOnePlus™ (Applied Biosystem) over 40 cycles. Expression data were normalized to GAPDH mRNA expression and fold change was calculated using 2- $\Delta\Delta C_t$ method. Total and phosphorylated ERK levels in livers were measured by Western blot. All measurements were compared to a steatosis control.

The results are shown in Figures 39A to 39F. Anti-IL-11 3C6 therapy was found to reduce hepatic triglyceride content (39A), liver hydroxyproline content (39B), expression of pro-inflammatory factors (39C, 39D), ALT serum levels (39E), and levels of phosphorylated ERK in livers (39F).

Thus, anti-IL-11 therapy was found to reduce hepatic steatosis, fibrosis, and inflammation in late-stage NASH compared to controls.

The effects of different concentrations of anti-IL-11 antibodies BSN-3C6 and YU100-G08_02A (0.5, 1, 5 and 10 mg/kg) were assessed in the NASH model after 4 weeks on the NASH (HFMCD) diet to induce liver damage and fibrosis. After one week of the NASH diet (at which time there is an established and robust steatohepatitis and ALT levels are ~800u/L (~40-fold increase compared to normal chow)), animals were started on either IgG control antibody or ENx108A biweekly for a four-week period. Mice fed on the normal chow diet and IgG (10 mg/kg) were used as controls. Serum ALT levels and liver collagen content were measured as described above.

The results are shown in Figures 39G and 39H. Anti-IL-11 therapy was found to have a dose-dependent ameliorative effect on fibrosis indicators serum ALT levels and liver collagen content.

In a separate experiment, five-week old male C57BL/6N mice were fed MCD diet supplemented with 60 kcal% fat (A06071302, Research Diets) (HFMCD diet) to induce NASH. Control mice were fed with normal chow (NC, Specialty Feeds). After 6 weeks on the HFMCD diet, anti-IL-11 antibody BSN-3C6 (10 mg/kg) was administered biweekly for 4 weeks. Livers and serum were collected at week 10 and analysed for ERK activation, liver hydroxyproline content, and serum ALT levels, measured as previously described.

The results are shown in Figures 40A to 40C. Anti-IL-11 antibody was found to have abolished ERK activation (40A) and inhibited the progression of liver fibrosis (40B) and serum ALT levels (40C). FC: fold change.

5

Anti-IL-11 therapy was investigated in another model of advanced NASH. 2 day old C57BL/6 mice were administered a single subcutaneous injection of 200 µg streptozotocin and fed on a normal chow diet for 4 weeks. Mice were then switched onto a HFMCD diet for 7 weeks and then treated along with the HFMCD diet with 10 mg/kg anti-IL-11 antibody BSN-3C6 or IgG control 3x per week for a subsequent 7 weeks. RNA expression was measured for fibrosis and inflammation genes *Col1a1*, *Col1a2*, *Col1a3*, *Timp1*, *Tgfb1*, *Mmp2*, *Tnfa*, *Ccl2* and *Ccl5*.

10

The results are shown in Figure 40D. Anti-IL-11 therapy was found to robustly inhibit expression of genes indicative of fibrosis and inflammation.

15

Thus, anti-IL-11 therapy inhibits hepatic fibrosis and liver damage.

14.2 Inhibition of myofibroblast activation using anti-IL-11 antibodies

Hepatic stellate cells (HSCs) play an important role in the pathogenesis of NASH. Pro-fibrotic stimuli e.g. TGFβ1, PDGF and pro-inflammatory factors can activate and transform HSCs into liver myofibroblasts which share features with fibroblast-derived myofibroblasts.

20

HSCs were treated with NASH-promoting factors in the presence or absence of anti-IL-11 antibody to investigate the transformation of HSCs to myofibroblasts.

25

HSCs were seeded in 96-well plates at a density of 5×10^3 cells per well and treated with TGFβ1 (5 ng ml⁻¹), PDGF (20 ng ml⁻¹), AngII (100 nM), bFGF (10 ng ml⁻¹), or CCL2 (5 ng ml⁻¹) in the presence of IgG control or anti-IL-11 antibody clone BSN-3C6 for 24 hours. Cells were then fixed in 4% paraformaldehyde (PFA, 28908, Thermo Fisher Scientific), permeabilized with 0.1% Triton X-100 (Sigma) and non-specific sites were blocked with 0.5% BSA and 0.1% Tween-20 in PBS. Cells were incubated overnight (4°C) with primary antibodies (1:500), followed by incubation with the appropriate AlexaFluor 488 secondary antibodies (1:1000). EdU-Alexa Fluor 488 was incorporated using a Click-iT EdU Labelling kit (C10350, Thermo Fisher Scientific) according to manufacturer's protocol. Cells were counterstained with 1 µg ml⁻¹ DAPI (D1306, Thermo Fisher Scientific) in blocking solution. Each condition was imaged from duplicated wells and a minimum of 7 fields per well using Operetta high-content imaging system 1483 (PerkinElmer). The quantification of ACTA2⁺ cells was measured using Harmony v3.5.2 (PerkinElmer). The measurement of fluorescence intensity per area of Collagen I (normalized to the number of cells) was performed with Columbus 2.7.1 (PerkinElmer).

30

35

40

Anti-IL-11 antibody treatment was found to block transition of HSCs into myofibroblasts driven by NASH-promoting factors. The results are shown in Figures 41A to 41D. Representative fluorescent images show that anti-IL-11 antibody BSN-3C6 reduced the number of ACTA2⁺ cells (41A) and the production of

collagen I by HSCs (41B), scale bars = 200 μm . The percentage of ACTA2⁺ cells (41C) and collagen I production (41D) for each treatment was quantified, showing that fewer treated HSCs were ACTA2-positive or producing collagen, i.e. antibody treatment blocked the stimuli-driven transition of HSCs into myofibroblasts.

5

The effect of anti-IL-11 therapy on the invasive behaviour of human HSCs was assessed using 24-well Boyden chamber invasion assays (Cell Biolabs Inc.). HSCs were pre-treated with anti-IL-11 antibody clone BSN-3C6 or IgG control for 15 minutes prior to adding stimuli. Equal numbers of HSCs in serum-free HSC media were seeded in triplicates onto the ECM-coated matrigel and were allowed to invade towards HSC media containing 0.2% FBS. After 48 hours of incubation with invasive stimulants PDGF (20 ng ml⁻¹) or CCL2 (5 ng ml⁻¹), media was aspirated and non-invasive cells were removed using cotton swabs. The cells that invaded towards the bottom chamber were stained with cells staining solution (Cell Biolabs), imaged and counted under 40x magnification.

15 The results are shown in Figure 42. Anti-IL-11 antibody was found to prevent PDGF- and CCL2-induced matrigel invasion of HSCs.

14.3 Blocking IL-11 signalling inhibits liver inflammation in NASH

Beyond their role in liver fibrosis, HSCs have a central role in hepatic inflammation through the secretion and paracrine activity of pro-inflammatory cytokines and chemokines.

It was determined that IL-11 loss of function led to consistently lower levels of inflammation markers *TNF α* , *CCL2* and *CCL5*. A study was performed to determine whether the effects on inflammation *in vivo* were related to the action of IL-11 on HSCs. CCL2 was measured by ELISA in the supernatants of HSCs (n=4/group) without stimulus (-), with IL-11, or with TGF β 1 in the presence of IgG control or anti-IL-11 antibody BSN-3C6; IL-11 (5 ng/ml), TGF β 1 (5 ng/ml), IgG, BSN-3C6 (2 $\mu\text{g/ml}$).

The results are shown in Figure 43. It was found that IL-11 stimulated HSC secretion of CCL2 whereas IL-11 inhibition by anti-IL-11 antibody blocked CCL2 secretion. This reveals an unappreciated role for IL-11 in stromal immunity and shows that IL-11 neutralisation inhibits paracrine effects of pro-inflammatory factors secreted from HSCs on other cells in the hepatic niche.

14.4 Neutralisation of IL-11 signalling reverses hepatic fibrosis

Severe liver fibrosis was established by feeding mice the NASH MCD diet for 10 weeks. Feed was then switched to normal chow (NC) and mice were treated with anti-IL-11 antibody BSN-3C6 (20 mg/kg) twice per week for six weeks. Mice fed on NC diet for the duration of the experiment and IgG antibody were used as controls. Liver hydroxyproline content, i.e. total collagen content, was measured as previously described.

The results are shown in Figure 44A. Hepatic collagen content was significantly reversed after three weeks of anti-IL-11 antibody treatment and even greater reversal was seen at six weeks. Notably, hepatic collagen content remained unchanged in IgG control-treated animals for the duration of the experiment.

Reversal of hepatic fibrosis is favoured when transformed HSCs undergo senescence or reversion to an inactive, ACTA2^{-ve} cellular state. Figure 44B shows that anti-IL-11 therapy was found to decrease *Acta2* expression.

5 To check directly if IL-11 signalling is required to maintain HSCs in a transformed state, HSCs were stimulated with TGFβ1 or PDGF for 72 hours and then treated with anti-IL-11 antibody BSN-3C6 for a further 24 or 48 hours in the presence of ongoing TGFβ1 or PDGF stimulation. Unstimulated HSCs were used as a non-fibrotic control.

10 The results are shown in Figure 44C. Within 24 h of IL-11 inhibition, the percentage of ACTA2⁺ cells was reversed to near baseline levels, whether HSCs were stimulated with TGFβ1 or PDGF. The amount of secreted collagen was also reversed to near baseline levels.

The MMP2 concentration was measured after 24 or 48 hours of treatment with anti-IL-11 therapy. The results are shown in Figure 44D. Anti-IL-11 therapy reduced MMP2 concentration after 24h and reversed MMP2 concentration to near baseline levels after 48h.

Therefore, inhibition of IL-11-dependent HSC transformation causes HSC senescence/reversion and favourable matrix remodelling leading to fibrosis regression.

20 The effect of anti-IL-11 therapy in early stage NASH was investigated. In the HFMCD diet model of NASH, inflammation peaks at six weeks and is then followed by a phase of severe fibrosis. Mice were fed the HFMCD diet for one week and then treated twice a week for a further five weeks on the diet with 10 mg/kg anti-IL-11 antibody BSN-3C6 or IgG control. ERK phosphorylation, triglyceride content and serum ALT levels were assessed as before. Liver tissues were fixed for 48 hours at RT in 10% neutral-buffered formalin (NBF), dehydrated, embedded in paraffin blocks and sectioned at 7μm. Sections stained with Masson's Trichrome were examined by light microscopy, scale bars 100 μm.

30 The results are shown in Figures 45A to 45E. Inhibition of IL-11 signalling during early steatohepatitis using anti-IL-11 therapy was found to result in mice having livers which were strikingly less steatotic (45A) and which had lesser ERK activation (45B). At the molecular level, there was a significant reduction in triglyceride content (45C) and livers of mice that received anti-IL-11 therapy did not show lipid droplets compared to IgG control (45D). HFMCD diet induces marked steatohepatitis and liver damage after one week (ALT>700 U L⁻¹), which was reversed in a dose-dependent manner to near normal after three weeks of anti-IL-11 treatment (45E). The mice that received anti-IL-11 therapy did not develop fibrosis during the experiment, reaffirming the strong anti-fibrotic effects associated with inhibition of IL-11 signalling.

The effect of anti-IL-11 treatment on the expression of pro-fibrotic and pro-inflammatory genes in the NASH mouse model was assessed using RNA-seq and qPCR.

40 The results are shown in Figures 45F to 45H. Upregulation of pro-fibrotic and pro-inflammatory genes was abolished after treatment with anti-IL-11 antibody. Differential expression heatmap of pro-fibrotic and pro-

inflammatory genes Z-scores (Transcripts Per Million mapped reads, TPM) shows that anti-IL-11 treatment produced similar expression of pro-fibrotic and pro-inflammatory genes as observed in mice on a NC control diet (non-NASH) (45F). Neither inflammation markers *Tnfa* and *Ccl2* (45G) nor pro-fibrotic markers *Tgfb1*, *Acta2*, *Timp1*, *Col1a1*, *Col1a2* or *Col3a1* (45H) were upregulated in mice treated with anti-IL-11 antibody.

Thus, neutralisation of IL-11 signalling reverses liver damage in early stage NASH.

In summary, IL-11 is required for HSC activation and transformation and has a central role in HSC pathobiology. IL-11 neutralising antibodies show disease-modifying therapeutic impact beyond anti-fibrotic effects alone. IL-11 antibodies could reverse hepatic stellate cell (HSC) activation downstream of TGFβ1 or PDGF. Inhibition of IL-11 signalling prevents inflammation and steatosis and can reverse liver fibrosis and hepatocyte damage during late stages of the disease. When given earlier, during steatohepatitis, anti-IL-11 therapy blocks inflammatory signals from HSCs and prevents hepatocyte damage.

Example 15: Inhibition of eye fibrosis using anti-IL-11 antibodies

The anti-fibrotic effect of anti-IL-11 antibody treatment was assessed in a mouse model of retinal fibrosis in which Bruch's membrane is disrupted, as described in Caballero et al., Exp Eye Res. (2009) Mar;88(3):367-77.

Briefly, mice were subjected to laser-induced retinal damage (4 burns per retina) and were then treated by intraocular administration of antibodies (0.5 µg of either IgG control or anti-IL11 antibody clone BSN-3C6) on days 1, 7, 14 and 21. Eyes were harvested for histological analyses on day 28. The area of fibrosis at burn sites was measured using Masson's Trichrome staining, blinded to treatment.

The results are shown in Figures 32A and 32B. The area of fibrosis was significantly greater in control IgG-treated mice as compared to anti-IL11 antibody treated mice.

In a separate experiment, mice (n=10) were subjected to retinal burns by laser (4 per eye) and treated with either Eylea (Aflibercept; Regeneron) + IgG control or an Eylea + BSN-3C6 combination therapy. Four weeks after injury, retina were stained/quantified for collagen (blinded).

The results are shown in Figure 32C. Anti-IL-11 therapy was found to reduce the area of fibrosis in the eye compared to IgG control. Thus, anti-IL-11 therapies reduce the fibrotic response in the context of anti-VEGF therapies.

Choroidal neovascularisation (CNV) was assessed using fluorescein fundus angiogram analysis. CNV lesions were monitored 7 and 28 days after laser-induced rupture of Bruch's membrane.

The results are shown in Figure 32D. Measurements indicate the extent of CNV by area of leakage fold change before and after intravitreal injections (IVT) of antibodies. Anti-IL-11 therapy reduced the area of leakage fold change.

Example 16: Inhibition of skin fibrosis using anti-IL-11 antibodies

The anti-fibrotic effect of anti-IL-11 antibody treatment was analysed in a mouse model of skin fibrosis established by subcutaneous injection of bleomycin (BLM, Sigma B2434, 50 µg/day).

5 Briefly, the fur on the middle of the back of the mice (~9 cm²) was trimmed using scissors, and hair removal cream was applied to remove fur completely. Subcutaneous injections of 100 µL of bleomycin dissolved in PBS at a concentration of 0.5 mg/ml were performed on the top half of the injection site. Subcutaneous
10 injections of 60 µL of anti-IL11 antibody clone BSN-3C6 or control IgG antibody were subsequently performed on the bottom half of the injection site (dosage = 15mg/kg/day). Injections were performed daily for 21 days and animals were sacrificed one day after the final injection and analysed histologically for dermal thickness and collagen content (by Masson's trichrome staining). Figure 33A shows a schematic representation of experimental procedures for different treatment groups.

15 Figures 33B and 33C show that dermal thickness was significantly reduced in mice treated with neutralising anti-IL-11 antibody as compared to control IgG-treated mice. Increased collagen staining can also be seen for the control IgG-treated group (Figure 33B, middle panel).

Example 17: Inhibition of heart fibrosis using anti-IL-11 antibodies

The anti-fibrotic effect of anti-IL-11 antibody treatment was analysed in a mouse model of cardiac fibrosis.

20 Briefly, transverse aortic constriction (TAC) was performed in male mice as described previously (Tarnavski, O. et al. Mouse cardiac surgery: comprehensive techniques for the generation of mouse models of human diseases and their application for genomic studies. *Physiol. Genomics* 16, 349–360 (2004)). Age-matched mice underwent a sham operative procedure without TAC. Trans-thoracic two-dimensional Doppler
25 echocardiography was used to confirm increased pressure gradients (>40 mm Hg), indicative of successful TAC.

Mice were euthanized at 2 weeks post-TAC for histological and molecular assessment. Anti-IL-11 antibody clone BSN-3C6 or control IgG antibody were administered intraperitoneally 3 times per week at a dose of 20
30 mg/kg. After two weeks hearts were harvested and assessed for fibrosis extent using Masson's Trichrome stain kit (HT15, Sigma-Aldrich), in accordance with the manufacturer's instructions.

The results of the analysis is shown in Figure 34. Mice treated with neutralising anti-IL-11 antibody were found to have reduced levels of fibrosis in the epicardium, endocardium and in perivascular regions as
35 compared to mice treated with IgG control antibody.

Example 18: Variant anti-IL-11 antibody clones

The cysteine residue at position 91 of the light chain variable region sequences shown in SEQ ID NOs:7, 9 and 11 was substituted with A, G, I, L, Q, S, T or V. The variant light chain variable region sequences are
40 shown in SEQ ID NOs:12 to 35.

HEK293 EBNA cells were transfected with vectors encoding scFv corresponding to YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T, 01V, YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T or 02V.

5 Example 19: Analysis of affinity of binding of variant clones to IL-11

The 01 and 02 variant anti-IL-11 antibody clones described in Example 18 were analysed for affinity of binding to human IL-11 by Single Cycle Kinetics analysis using a BIAcore T200.

10 Briefly, recombinant human IL-11 was immobilised on a CM5 chip, and associations were performed by flowing increasing concentrations of purified anti-IL-11 antibodies corresponding to the different clones in IgG1 format over the chip at a flow rate of 30 µl/min, with no dissociation step between runs. A single dissociation step was used, and the surface was regenerated using 3.8 M MgCl₂.

15 For YU100-G08 and 02 variant clones, the following concentrations of antibody were used in the associations: 3.125 nM, 6.25 nM, 12.5 nM and 25 nM. For YU100-H01 and 01 variants the following concentrations of antibody were used: 37.5 nM, 75 nM, 150 nM

20 For YU100-G08 and 02 variants the analyte injection time was 150 seconds, and for YU100-H01 and 01 variants the analyte injection time was 400 seconds.

For YU100-G08 and 02 variants the analyte dissociation time was 500 seconds, and for YU100-H01 and 01 variants the analyte dissociation time was 700 seconds.

25 The analysis of the raw data obtained was performed using BIAcore T200 evaluation software V3.0, fitting the background-subtracted data to a 1:1 interaction model.

30 The results obtained for YU100-G08 and the 02 variants are shown in Figures 35A to 35J. Variants 02A, 02I, 02L, 02Q and 02S displayed an affinity of binding to human IL-11 with greater affinity or within two-fold of the affinity of YU100-G08.

The results obtained for YU100-H01 and the 01 variants are shown in Figures 36A to 36J. Variants 01A, 01I, 01L, and 01T displayed an affinity of binding to human IL-11 with greater affinity or within two-fold of the affinity of YU100-H01.

35 Example 20: Analysis of inhibition of IL-11 mediated signalling for variant clones

The 01 and 02 variant anti-IL-11 antibody clones described in Example 18 were analysed for their ability to inhibit IL-11 mediated signalling in an *in vitro* assay.

Cardiac atrial human fibroblasts were cultured in wells of 96-well plates in the presence of TGFβ1 (5 ng/ml) for 24 hours, in the presence of different concentrations of the YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S,

01T, 01V, YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T or 02V anti-IL-11 antibodies in scFv-human IgG1-Fc format.

Levels of the pro-fibrotic marker MMP2 in the cell culture supernatant were then measured by ELISA. Basal MMP2 secretion by the cells in culture was measured by culture in the absence of TGF β 1.

MMP2 levels determined were used to derive IC50 values for inhibition of IL-11 mediated signalling by the different clones.

The results for YU100-H01, 01A, 01G, 01I, 01L, 01Q, 01S, 01T and 01V are shown in Figures 37A to 37I.

The results for YU100-G08, 02A, 02G, 02I, 02L, 02Q, 02S, 02T and 02V are shown in Figures 38A to 38I.

12.3 Cross-species reactivity

Macaque skin fibroblasts were stimulated with recombinant macaque IL-11 (5ng/ml) for 24h in the presence of IgG control, YU100-G08_02A, or 3C6 antibodies at 2 μ g/ml. Collagen, ACTA2+ve and EdU+ve cells were quantified using the Operetta High content imaging platform. Secreted collagen was quantified using the calorimetric Sirius Red collagen assay.

The results are shown in Figures 38J to 38M. Both antibodies blocked IL-11 signalling in macaque fibroblasts. 3C6 was also tested in rat and pig cardiac fibroblasts and was found to inhibit the fibrotic response in these cells.

Example 21: IL-11 and lung fibrosis

Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease characterised by invasive pulmonary myofibroblasts that deposit ECM components e.g. collagen and destroy lung integrity.

Lung sections from healthy individuals and IPF patients were immunostained for IL-11 and alpha smooth muscle actin (ACTA2), a marker for myofibroblasts. Human IPF tissues were obtained from lung transplant patients with IPF and normal control human lung tissues were obtained from IIAM (International Institute for the 197 Advancement of Medicine). Human lung tissue were fixed in 10% formalin overnight and embedded in paraffin. Tissue sections were incubated with primary antibodies (Anti-IL-11 (PA5-36544, ThermoFisher Scientific), Anti-ACTA2 (ab7817 and ab5694, abcam) overnight and visualized using an ImmPRESS HRP anti-rabbit IgG polymer detection kit (Vector Laboratories) with ImmPACT DAB Peroxidase Substrate (Vector 209 Laboratories).

The results are shown in Figure 46A. IL-11 was found to be expressed at a low level in normal lung tissue, but markedly elevated in IPF lung samples along with ACTA2.

The role of IL-11 in lung fibroblast activation, migration and invasion was investigated. Murine pulmonary fibroblasts were incubated with recombinant mouse IL-11 (5 ng ml⁻¹, 24h) and total secreted collagen in the supernatant of IL-11 treated fibroblasts was quantified by Sirius red collagen assay (n = 5/group). Fibroblasts

were cultured in serum-free DMEM for 24h prior to cell migration or invasion assays. Equal numbers of fibroblast in serum-free DMEM were seeded in duplicates onto apical chambers containing polycarbonate membranes for migration assays or onto ECM-coated matrigel for invasion assays. Fibroblasts were allowed to migrate towards IL-11 or TGF β 1 as chemoattractants. For invasion assays, fibroblasts were allowed to invade towards DMEM containing 2% FBS. After 24h of incubation at 37°C, media was removed and non-migratory or non-invasive cells were removed using cotton swabs. The cells that migrated or invaded towards the bottom chamber were stained with cell staining solution (Cell Biolabs Inc.). Cells that migrated were colourimetrically quantified at 540 nm. Invasive cells from 5 non-overlapping fields of each membrane were imaged and counted under 40x magnification.

The results are shown in Figures 46B (secreted collagen), 46C (migration) and 46D (invasion). IL-11 induced marked fibroblast activation, proliferation, ECM production, migration and invasion.

Thus, IL-11 is upregulated in the lung in IPF which drives fibroblast-to-myofibroblast transformation and induces fibrosis.

21.1 Anti-IL-11 therapy and lung fibrosis

Anti-IL-11 antibodies were generated as described herein.

Real-time binding kinetics of anti-IL-11 antibody BSN-3C6 to human and mouse IL-11 were measured by surface plasmon resonance (SPR) using a BIAcore T200 system (GE Healthcare, USA). The association and dissociation were measured for 250 s and 500 s respectively. The equilibrium binding constant K_D was determined by the ratio of the binding rate constants k_d/k_a .

The results are shown in Figures 47A and 47B. Binding of BSN-3C6 to human IL-11 showed a K_D of 4.14 nM (47A) and binding of BSN-3C6 to mouse IL-11 showed a K_D of 2.38 nM (47B).

The effects of anti-IL-11 antibody BSN-3C6 on fibrotic characteristics were assessed.

Mouse lung fibroblasts were treated with multiple pro-fibrotic stimuli in the presence of BSN-3C6 or IgG control antibody. Cells were immunostained, as before, for Acta2 and Col1 α 1 (Anti-ACTA2 (ab7817 and ab5694, abcam), anti-COL1A1 (ab34710, abcam)) and the immunofluorescence was quantified. Secreted collagen in the cell culture supernatant was quantified using a Sirius red collagen detection kit.

The results are shown in Figure 48A. Heatmaps show the immunofluorescence quantification of Acta2⁺ cells and Col1 α 1 immunostaining (intensity/area) in mouse lung fibroblasts treated with multiple pro-fibrotic stimuli was reduced in the presence of anti-IL-11 antibody when compared to IgG control. Collagen secretion in culture supernatant was reduced in the presence of anti-IL-11 antibody.

TGF β 1-differentiated human lung fibroblasts (5 ng ml⁻¹, 24h pretreatment) were treated with BSN-3C6 or IgG control antibody (2 μ g ml⁻¹, 24h). The percentage of ACTA2⁺ cells, COL1 α 1 immunostaining (intensity/area) and collagen secretion were determined.

The results are shown in Figure 48B. Anti-IL-11 antibody was found to reduce fibroblast activation, COL1 α 1 production and collagen secretion in pre-activated human lung fibroblasts, thus demonstrating that anti-IL-11 therapy can reverse fibrosis.

5

Primary mouse and human fibroblasts were stimulated with species-specific recombinant TGF β 1 (5 ng ml⁻¹, 24h) and secreted MMP2 levels were monitored in the presence of purified anti-IL-11 BSN-3C6 antibody (6 μ g ml⁻¹).

10 The results are shown in Figures 48C (human) and 48D (mouse). The anti-IL-11 antibody effectively inhibits TGF β 1-driven secretion of the pro-fibrotic marker MMP2 from both human and mouse fibroblasts by neutralizing the downstream IL-11 autocrine loop.

15 The effects of anti-IL-11 antibody BSN-3C6 on TGF β 1-induced migration or invasion of mouse lung fibroblasts was investigated. Fibroblasts were pretreated with anti-IL-11 antibody BSN-3C6 or IgG control antibodies for 15 min prior to addition of chemoattractants

The results are shown in Figure 48E. Anti-IL-11 antibody was found to reduce both migration and invasion.

20 Therefore, anti-IL-11 antibody BSN-3C6 was found to block fibroblast activation and ECM production, and inhibit fibroblast invasion and migration downstream of multiple stimuli. Anti-IL-11 antibody was also found to inhibit multiple fibrotic phenotypes of IPF patient-derived lung fibroblasts after TGF β 1 stimulation.

25 Importantly, anti-IL-11 therapy was not only able to prevent or inhibit fibrosis, but was also able to reverse the fibrotic phenotypes of established populations of TGF β 1-transformed pulmonary myofibroblasts (Figure 48B).

21.2 Anti-IL-11 therapy prevents pulmonary fibrosis

The potential of anti-11-therapy to prevent pulmonary fibrosis was investigated in a mouse model of IPF.

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The half-life of anti-IL-11 antibody BSN-3C6 in mouse blood was measured to be ~9 days using freshly labeled [¹²⁵I]BSN-3C6 (4.2 μ Ci/2.5 μ g/100 μ l) in PBS. Antibody was administered by retro orbital injections, mice were anesthetized with 2% isoflurane and blood collected at several time points: 2, 5, 10, 15, 30 min, 2h, 6h, 8h and 2d post injection via submandibular bleeding.

35

8-10 week old C57BL/6 female wild type mice were allowed to acclimatize for one week before bleomycin (BLM) administration. Mice were administered anti-IL-11 antibody BSN-3C6 (20 mg kg⁻¹, in PBS) via intraperitoneal injections on day 7, 9, 11, 14, 16, 18 and lungs were harvested on day 21 post-BLM challenge. Lung sections from anti-IL-11 antibody or IgG control were stained with Masson's trichrome: sections were subjected to Bouin's fixative, Beibrich Scarlet-Acid Fuchsin and differentiated in 5% Phosphomolybdic-phosphotungstic acid, counterstained in 2.5% Aniline blue and further differentiated in 1% Acetic acid. Total hydroxyproline content in the lungs (right superior lobe) of mice was measured using a

40

Quickzyme Total Collagen assay kit (Quickzyme Biosciences). Protein expression of Col3a1, fibronectin, and IL-11 protein levels, and phosphorylation status and total levels of Erk and Stat3 in lung homogenates were detected by Western Blot analysis and visualised using the ECL detection system (Pierce). mRNA expression in lung lysates was quantified by RT-PCR over 40 cycles and normalised to GAPDH expression.

TaqMan probes were obtained from Thermo Fisher Scientific (Col1a1, Mm00801666_g1; Col1a2, Mm00483888_m1; Col3a1, Mm01254476_m1; Fn1, Mm01256744_m1; Mmp2, Mm00439498_m1; Timp1, Mm01341361_m1; Gapdh, Mm99999915_g1).

The results are shown in Figures 49A to 49D. Lungs from mice treated with anti-IL-11 antibody were less fibrotic (49A). Mice treated with anti-IL-11 therapy were found to have reduced lung/body weight and lung hydroxyproline content (49B) and reduced expression of collagen proteins Col3a1 and fibronectin (49C) compared to those treated with IgG control. Anti-IL-11 treatment was found to reduce fibrosis marker RNA expression. Furthermore, anti-IL-11 antibody-treated mice were also found to have developed an RNA expression signature of preferential ECM remodelling which promotes fibrillar collagen degradation and fibrosis resolution (49D). Blocking IL-11 signalling was found to reduce non-canonical IL-11 signalling (Erk activation) whereas canonical (Stat3) signalling was unchanged (49E).

21.3 Anti-IL-11 therapy reverses pulmonary fibrosis

The potential of anti-IL-11-therapy to treat and reverse pulmonary fibrosis was investigated in the BLM-induced IPF mouse model.

Mice were injected with anti-IL-11 antibody BSN-3C6 (20 mg kg⁻¹, alternate days) or IgG control starting at day 14 (late intervention) after BLM treatment, when collagen levels plateau. Lungs were assessed, as above, on day 28 post-BLM administration.

The results are shown in Figure 50A to 50D. Fibrosis regression was observed in the lungs of mice treated with anti-IL-11 antibody compared to IgG control (50A). Mice treated with anti-IL-11 therapy were found to have reduced lung/body weight and lung hydroxyproline content (50B). Protein levels of Col3a1 and fibronectin were notably decreased by anti-IL-11 therapy, as was IL-11 (50C). Blocking IL-11 signalling was found to reduce non-canonical IL-11 signalling (Erk activation) whereas canonical (Stat3) signalling was unchanged (50D).

In summary, neutralising IL-11 signalling using an anti-IL-11 antibody blocks the fibrotic response of lung fibroblasts and reverses TGFβ1-transformed myofibroblast activation. In a mouse model of IPF, where IL-11 is strongly upregulated, administration of anti-IL-11 therapy either early or late after BML challenge resulted in prevention or reversal of lung fibrosis, respectively.

Example 22: Effect of IL-11 on pancreatic fibrosis

100µg/kg of recombinant mouse IL-11 or saline were injected into mice daily subcutaneously for 21 days. Collagen content of the pancreas was then assessed using the calorimetric hydroxyproline assay.

The results are shown in Figure 52. IL-11 induces collagen production in the pancreas. Pancreatic fibrosis will therefore benefit from therapy with anti-IL-11 antibodies.

Example 23: Effect of anti-IL-11 antibodies on wasting disorders

Animals on an HFMCD diet lose weight and become very unwell, see also Example 14. Inhibition of IL-11 signalling ameliorates HFMCD-induced loss of weight and 9A7 antibody showed a dose dependent effect on weight gain.

Five-week old male mice were fed on the HFMCD or normal chow (NC) diet as before for one week to induce wasting, resulting in a ~15% loss in body weight in MCD mice. After the initial week, mice were intraperitoneally injected twice per week with 0.5, 1, 5 or 10 mg/kg of anti-IL-11 antibody YU100-G08_02A or 3C6. 10 mg/kg of IgG isotype antibody was used as a control. Body weight and food consumption were measured weekly. For food consumption, average food intake was measured (g/mouse/week) in food hoppers from cages (n=3 mice per cage).

The results are shown in Figures 53A and 53B. Anti-IL-11 therapies (53A) YU100-G08_02A and (53B) 3C6 were found to provide a dose-dependent gain in body weight and food consumption, indicating reversal of wasting. The highest doses showed the greatest wasting-reversing effect. Mice fed with an NC diet steadily gained weight, whilst mice fed on the HFMCD diet and treated with IgG control lost ~30% of body weight over the course of the treatment. The highest doses had the greatest effect on food consumption, whereas mice treated with IgG control showed a slight reduction in food consumption.

Acute disease, e.g. trauma or sepsis, can also be associated with anorexia and cachexia, and so the inventors next investigated the effects of antagonism of IL-11-mediated signalling on anorexia and cachexia in mouse models of acute kidney injury.

Kidney injury was induced by IP injection of folic acid (180 mg/kg) in vehicle (0.3M NaHCO₃) to 10-week old male mice; control mice were administered vehicle alone. Animals were sacrificed 28 days post-injection. Mice were intraperitoneally injected every 3 days with 20 mg/kg of anti-IL-11 antibody or identical concentration of IgG isotype control starting from 1 hour before folic acid administration until the mice were sacrificed.

It was found that folate-induced kidney injury resulted in rapid anorexia/cachexia-associated weight loss associated with the acute phase of severe and bilateral kidney injury. Mice (n=7/group) receiving anti-IL-11 therapy at the time of injury, and for the duration of the injury, regained weight more quickly compared to the IgG control and returned to normal, or near normal, weight by 3 weeks later.

Separately, kidney injury is induced as before by IP injection of folic acid. Mice are only treated with anti-IL-11 antibody or IgG control from 21 days after kidney injury. Animal weight is assessed before and after antibody treatment. Healthy mice that do not receive folic acid were used as a control.

Figure 53C shows that mice treated with anti-IL-11 antibody start to regain weight upon initiation of treatment showing that wasting-associated weight loss can be improved in late-stage disease.

Example 24: Effect of anti-IL-11 antibodies on metabolic disorders

The effect of anti-IL-11 antibody is investigated in mice with metabolic diseases such as obesity and type II diabetes. Western diet along with fructose (WDF) is used to establish metabolic disorders that closely resemble those in humans during obesity, type II diabetes and non-alcoholic fatty liver disease (NAFLD) (Baena et al., Sci Rep (2016) 6: 26149, Machado et al., PLoS One (2015) 10:e0127991). Mice are fed Western diet (D12079B, Research Diets), supplemented with 15% weight/volume fructose in drinking water (WDF) for 16 weeks, from 12 weeks of age. Control subjects are fed normal chow (NC, Specialty Feeds) and drinking water. IgG antibody is used as a control.

Anti-IL-11 antibody-treated mice fed on WDF show significant reduction in body weight (A) and fat mass (B) when compared to control IgG antibody-treated mice fed on WDF. An increase in lean mass is also observed in mice treated with anti-IL-11 antibody compared to IgG control-treated mice, suggesting that inhibition of IL-11 signalling during WDF-induced metabolic pathogenesis recovered muscle mass. Furthermore, intraperitoneal glucose tolerance test (ipGTT) results show, along with fasting glucose, significant improvement in glucose tolerance in mice treated with anti-IL-11 antibody.

The analysis is extended to the effects on the pancreas. Anti-IL-11 antibody-treated mice fed on WDF are found to display remarkable protection against WDF-induced loss of pancreas whether treated from 8 to 16 weeks (for protecting against effects associated with metabolic disease) or treated from 16 to 24 week (for reversing effects associated with metabolic disease) when compared to IgG control-treated mice.

Anti-IL-11 antibody-treated mice fed on WDF show significantly lower serum cholesterol levels compared to control IgG antibody-treated mice fed on WDF, and show significantly lower serum triglyceride levels compared to control IgG antibody-treated mice fed on WDF. Anti-IL-11 antibody-treated mice fed on WDF show significantly lower fasting blood glucose levels compared to control IgG antibody-treated mice fed on WDF.

Immune-histology of pancreas reveals increase in glucagon and insulin staining in pancreatic islets along with islet hyperplasia in IgG treated WDF fed mice, which are classical features of type II diabetes (Bonner-Weir and O'Brien Diabetes (2008) 57:2899-2904). Anti-IL-11 antibody treatment in WDF fed mice from 16 to 24 weeks remarkably reduces islet hyperplasia and glucagon staining as well improved insulin expression in the islets of mice fed on WDF, suggesting that antagonism of IL-11 mediated signalling is useful to improve and reverse metabolic diseases caused by a Western-type diet.

The HFMCD model has early onset steatotic hepatitis followed by fibrosis. However, this model is not obese or insulin resistant. A model of WDF-induced NASH is used to test effects of anti-IL-11 therapy in the context of obesity, insulin resistance and diabetes. Mice are fed WDF for 16 weeks by which time they were obese and insulin resistant with liver steatosis, inflammation and fibrosis. Treatment with anti-IL11 antibody is then initiated. Hepatic Erk activation is inhibited in NASH livers when IL-11 signalling was targeted (e.g. Figure

40A). Despite similar weight gain, reversal of liver fibrosis, steatosis, inflammation, and reduction in serum ALT levels in mice on anti-IL11 therapy is observed. This is accompanied by a reduction in serum glucose, triglycerides and cholesterol levels. Neutralizing anti-IL11 therapy reverses WDF-induced NASH pathologies.

- 5 Severe liver fibrosis is established using HFMCD for 10 weeks, then mice are converted to normal chow, mimicking a robust metabolic intervention, and anti-IL-11 antibody treatment is initiated in parallel.

Upon removal of the metabolic stimulus, Erk activation is found to slowly regress, which is accelerated by antibody treatment. Fibrosis is unchanged in IgG treated animals for the duration of the experiment,
10 suggesting complete metabolic correction alone does not reverse fibrosis, or very slowly reverses fibrosis. In contrast, hepatic collagen content is significantly reversed in the early stages of antibody treatment with further reversal in later stages, showing a progressive and sustained effect.

Regression of fibrosis is associated with lower TIMP and higher MMP levels, which promotes favorable
15 matrix remodelling. Consistent with this, anti-IL11 antibody treated mice with severe fibrosis are found to rapidly upregulate Mmp2 and downregulate Timp1. Reversal of hepatic fibrosis is favoured when transformed HSCs undergo apoptosis, senescence and/or revert to an inactive ACTA2-ve state. To check if IL-11 is required to maintain HSCs in a transformed state, HSCs are stimulated with TGFβ1 or PDGF followed by inhibition of IL-11 signalling. Within 24h of IL-11 inhibition, the percentage of ACTA2+ve cells and
20 the amount of secreted collagen are reversed to near baseline levels, and ERK activity is largely diminished despite ongoing TGFβ1/PDGF stimulation.

Example 25: Effect of inhibiting IL-11 signalling in hepatotoxicity

25.1 Effect of anti-IL-11 therapy on hepatotoxicity

IL-11 directly causes hepatocyte cell death and drives hepatocyte to dysfunctional partial epithelial-
25 mesenchymal cell transition (EMT) state that is known to limit the regenerative capacity of the liver (Grant Rowe et al. Molecular and Cellular Biology 2011; 31 (12): 2392–2403). Primary human hepatocytes were found to highly express the IL-11Rα receptor, IL-11 stimulation was found to induce dose-dependent hepatocyte cell death as evidenced by a progressive increase in alanine aminotransferase (ALT) over the physiologically relevant dose range, and stimulation of human hepatocytes with H₂O₂ results in IL-11
30 upregulation by 10-fold in the supernatant.

A mouse model of acetaminophen (APAP)-induced liver injury is employed to investigate the effect of anti-IL-11 therapy on hepatotoxicity. 12-14 weeks old male mice are starved and intraperitoneally (IP) injected with
35 10 mg/kg of anti-IL-11 antibody or IgG isotype control 16 hours prior to APAP injection (IP, 400 mg/kg). Mice were sacrificed 24 hours post-APAP administration. The levels of IL-11 in mouse serum and hepatocyte supernatant are quantified. Liver samples are excised and fixed for 48 hours at room temperature in 10% neutral-buffered formalin (NBF), dehydrated, embedded in paraffin blocks and sectioned at 7μm. Sections are stained with Hematoxylin&Eosin (H&E) according to standard protocol and examined by light
40 microscopy.

Mice receiving anti-IL-11 antibody are found to have lower ALT levels, i.e. less liver damage, and prevent APAP-induced loss of liver mass, which reflects destruction of liver cells. Antibody treated mice are also found to have normal mobility and activity, compared to control IgG-treated mice were found to be static/moribund with visible features of ill health (e.g. piloerection, hunched posture).

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Inhibiting IL-11 signalling by blocking IL-11 is found to prevent hepatotoxicity in the accepted, translational model of APAP-induced liver injury (drug induced liver injury; DILI).

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Severe APAP overdose (400 mg/kg) or an equivalent volume of saline is administered to 12-14 weeks old male mice by IP injection, and 10 hours later mice are administered IP with 20 mg/kg of antagonist anti-IL11R α antibody, isotype-matched IgG control antibody, or untreated. Anti-IL-11 antibody administered 10 hours after severe APAP overdose is found to restore gross liver morphology to that mice which had not been treated with APAP. Liver function is also rescued in mice treated with anti-IL-11 antibody. Antagonist antibody inhibitor of IL-11 mediated signalling administered 10 hours after lethal APAP overdose is demonstrated to rescue mice from DILI-associated inhibition of liver function. 10 hours is thought to be equivalent to about 24 hours after overdose in humans.

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Example 26: Isotype selection

Clones YU100-G08_02A, 3C6 VH2.2/VL2.2 and 3C6 VH2.2/VL2.1 were generated in the human IgG1 and IgG4 formats. The IgG4 version contains the S241P L248E double mutation (Kabat numbering). The S241P mutation is hinge stabilising while the L248E mutation further reduces the already low ADCC effector function of IgG4 (Davies and Sutton, Immunol Rev. 2015 Nov; 268(1):139–159; Angal et al Mol Immunol. 1993 Jan;30(1):105-8). The lower ADCC activity may be advantageous for subcutaneous administration of the antibody.

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Forced degradation studies were performed to examine the effects of oxidation and deamidation on the integrity of the YU100-G08_02A antibodies. Forced oxidation using 0.5% v/v H₂O₂ showed that YU100-G08_02A (IgG4) was not susceptible to the effects of oxidation as assessed by micro-capillary zone electrophoresis (micro-CZE), whereas YU100-G08_02A in IgG1 format were slightly affected. SEC-HPLC analyses of both clones indicated a stable IgG4 clone after the oxidation treatment, whereas the IgG1 clone appeared to partially fragment into light and heavy chains. When antibodies were treated with 1% w/v ammonium bicarbonate, deamidation of YU100-G08_02A (IgG4) was observed, however this did not have an impact on antibody integrity. YU100-G08_02A in IgG1 format appeared less stable after deamidation in comparison.

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Stability studies were performed, in which both clones were stored in either PBS -or- 10mM Histidine pH 6.5, 10% Trealose, 0.02% Polysorbate 80 -or- 25mM Citrate pH 5.5, 150mM Arginine, 0.02% Polysorbate 80. Antibodies were stored at -20, 25 or 45 degree Celsius. Stability was assessed using UV-Vis, SEC-HPLC, CE-SDS and CE-CZE at 0, 2, 4 and 12 weeks. Both antibodies appeared stable at similar levels with slight increase in degradation at 45 degrees Celsius.

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YU100-G08_02A (IgG1) and YU100-G08_02A (IgG4) were tested in *in vitro* cellular assays. Primary hepatic stellate cells were activated with either TGFB1 (5ng/ml), IL-11 (2ng/ml) or hyperIL-11 (200pg/ml) and incubated with varying concentrations of either antibody to determine IC50 values, as described previously. Neutralisation of the fibrotic response *in vitro* assessed by monitoring MMP2 secretion into the supernatant.

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Figures 55A to 55C show that YU100-G08_02A in both formats block (A) endogenous IL-11 signalling, (B) exogenous IL-11 signalling and (C) IL-11 *trans* signalling. Fibrogenic protein production was inhibited in each case.

10

The performance of both antibodies *in vivo* was tested in the HFMCD preclinical model of NASH, as described in Example 14. Animals were fed with HFMCD or normal chow for 4 weeks. For the final 3 weeks of the diet, animals were also treated with varying amounts of YU100-G08_02A IgG1 or IgG4. Serum ALT levels and hepatic collagen content (HPA assay) were assessed after 4 weeks of diet and antibody treatment. Identical baseline and IgG control animals are plotted for each antibody to facilitate data

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interpretation.

The results are shown in Figures 56A and 56B. Both antibody formats were able to reduce serum ALT levels (A) and liver collagen (B), thus indicating reversal of liver damage and fibrosis. YU100-G08_02A IgG4 performed slightly better than the IgG1 version.

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Claims:

1. An antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:
- 5 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
- 10 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:81.
2. The antigen-binding molecule according to claim 1, wherein the antigen-binding molecule comprises:
- 15 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:37
HC-CDR2 having the amino acid sequence of SEQ ID NO:38
HC-CDR3 having the amino acid sequence of SEQ ID NO:40; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
- 20 LC-CDR1 having the amino acid sequence of SEQ ID NO:42
LC-CDR2 having the amino acid sequence of SEQ ID NO:45
LC-CDR3 having the amino acid sequence of SEQ ID NO:57;
3. The antigen-binding molecule according to claim 1 or claim 2, wherein the antigen-binding molecule comprises:
- 25 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:83.
- 30 4. The antigen-binding molecule according to claim 3, wherein the antigen-binding molecule comprises:
a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:8; and
a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:20.
- 35 5. An antigen-binding molecule, optionally isolated, which is capable of binding to IL-11, wherein the antigen-binding molecule comprises:
- 40 (i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:95
HC-CDR2 having the amino acid sequence of SEQ ID NO:96
HC-CDR3 having the amino acid sequence of SEQ ID NO:97; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:101

LC-CDR2 having the amino acid sequence of SEQ ID NO:102

LC-CDR3 having the amino acid sequence of SEQ ID NO:103.

5

6. The antigen-binding molecule according to claim 5, wherein the antigen-binding molecule comprises:

a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:92, 116, 117, 118, 119 or 120; and

10 a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:94, 121, 122, 123, 124, 125, 126, 127 or 128.

7. The antigen-binding molecule according to claim 5 or claim 6, wherein the antigen-binding molecule comprises:

15 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:117; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:122.

8. The antigen-binding molecule according to claim 5 or claim 6, wherein the antigen-binding molecule comprises:

20 a VH region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:117; and

a VL region comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:121.

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9. The antigen-binding molecule according to any one of claims 1 to 8, wherein the antigen-binding molecule is capable of inhibiting IL-11 mediated signalling.

10. An antigen-binding molecule, optionally isolated, comprising (i) an antigen-binding molecule according to any one of claims 1 to 9, and (ii) an antigen-binding molecule capable of binding to an antigen other than IL-11.

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11. The antigen-binding molecule according to any one of claims 1 to 10, wherein the antigen-binding molecule is capable of inhibiting interaction between IL-11 or a complex comprising IL-11 and an IL-11 receptor.

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12. A chimeric antigen receptor (CAR) comprising an antigen-binding molecule according to any one of claims 1 to 11.

13. A nucleic acid, or a plurality of nucleic acids, optionally isolated, encoding an antigen-binding molecule according to any one of claims 1 to 11 or a CAR according to claim 12.

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14. An expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids according to claim 13.
- 5 15. A cell comprising an antigen-binding molecule according to any one of claims 1 to 11, a CAR according to claim 12, a nucleic acid or a plurality of nucleic acids according to claim 13, or an expression vector or a plurality of expression vectors according to claim 14.
- 10 16. A method comprising culturing a cell comprising a nucleic acid or a plurality of nucleic acids according to claim 13, or an expression vector or a plurality of expression vectors according to claim 14, under conditions suitable for expression of the antigen-binding molecule or CAR from the nucleic acid(s) or expression vector(s).
- 15 17. A composition comprising an antigen-binding molecule according to any one of claims 1 to 11, a CAR according to claim 12, a nucleic acid or a plurality of nucleic acids according to claim 13, an expression vector or a plurality of expression vectors according to claim 14, or a cell according to claim 15.
- 20 18. An antigen-binding molecule according to any one of claims 1 to 11, a CAR according to claim 12, a nucleic acid or a plurality of nucleic acids according to claim 13, an expression vector or a plurality of expression vectors according to claim 14, a cell according to claim 15, or a composition according to claim 17 for use in a method of medical treatment or prophylaxis.
- 25 19. An antigen-binding molecule according to any one of claims 1 to 11, a CAR according to claim 12, a nucleic acid or a plurality of nucleic acids according to claim 13, an expression vector or a plurality of expression vectors according to claim 14, a cell according to claim 15, or a composition according to claim 17, for use in a method of treatment or prevention of fibrosis, a disease characterised by fibrosis, a cancer, inflammation, a disease characterised by inflammation, hepatotoxicity, a disease characterised by hepatotoxicity, a metabolic disease, a wasting disorder, kidney injury, nephrotoxicity or a disease characterised by hepatotoxicity.
- 30 20. A method of inhibiting IL-11 mediated signalling, comprising contacting IL-11-expressing cells with an antigen-binding molecule according to any one of claims 1 to 11.
- 35 21. An *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to any one of claims 1 to 11 bound to IL-11 or a complex comprising IL-11.
22. A method comprising contacting a sample containing, or suspected to contain, IL-11 or a complex comprising IL-11 with an antigen-binding molecule according to any one of claims 1 to 11, and detecting the formation of a complex of the antigen-binding molecule with IL-11 or a complex comprising IL-11.
- 40 23. A method of selecting or stratifying a subject for treatment with an IL-11-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule according to any

one of claims 1 to 11 and detecting the formation of a complex of the antigen-binding molecule with IL-11 or a complex comprising IL-11.

5 24. Use of an antigen-binding molecule according to any one of claims 1 to 11 as an *in vitro* or *in vivo* diagnostic or prognostic agent.

10 25. A kit of parts comprising a predetermined quantity of: an antigen-binding molecule according to any one of claims 1 to 11, a CAR according to claim 12, a nucleic acid or a plurality of nucleic acids according to claim 13, an expression vector or a plurality of expression vectors according to claim 14, a cell according to claim 15, or a composition according to claim 17.