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Title: ANTIBODIES FOR THE TREATMENT OF HCV

Abstract: Scavenger receptor class B type 1 (SR-B1) specific antibodies and the use of SR-B1 specific antibodies in the treatment of HCV.
ANTIBODIES FOR THE TREATMENT OF HCV

The present invention relates to novel scavenger receptor class B type 1 (SR-B1) specific antibodies and the use of SR-B1 specific antibodies in the treatment of Hepatitis C virus (HCV).

Background of the Invention

HCV is a global blood-borne pathogen with 3% of the world's population chronically infected. Most infections are asymptomatic, but 60-to-80% of them become persistent and lead to severe fibrosis and cirrhosis, hepatic failure or hepatocellular carcinoma (HCC; see Shepard, C. W., L. Finelli, and M. J. Alter. 2005. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 5:558-67; and Wasley, A., and M. J. Alter. 2000. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis 20:1-16). Currently available therapies are limited and are expensive, often unsuccessful, and carry the risk of significant side effects. Thus, development of novel therapeutic approaches against HCV remains a high-priority. Targeting the early steps of HCV infection may represent a viable option and much effort is being devoted to uncovering the mechanism of viral attachment and entry.

The current view is that HCV entry into target cells occurs after attachment to specific cellular receptors via its surface glycoproteins E1 and E2. The molecules to which HCV initially bind might constitute a diverse collection of cellular proteins, carbohydrates, and lipids that concentrate viruses on the cell surface and determine to a large extent which cell types, tissues, and organisms HCV can infect.

The mannose binding C-type lectins, DC-SIGN and L-SIGN, and liver-specific glycosaminoglycans (GAGs) such as highly sulfated heparan sulfate proteoglycans (HSPGs) have been proposed as putative attachment factors for HCV (see e.g. Barth, H., et al., 2003, "Cellular binding of hepatitis C virus envelope glycoprotein E2 requires cell surface heparan sulphate", J Biol Chem 278:41003-12). L-SIGN is highly expressed in liver sinusoidal endothelial cells (LSEC), which are located in the wall of the liver sinusoids, but not in hepatocytes, while DC-SIGN is expressed in Kupffer cells, which are resident liver macrophages localized close to LSEC and hepatocytes. L-SIGN and DC-SIGN have been shown to capture and transmit HCV to hepatocytes, thereby facilitating receptor binding events.

With the adaptation of the HCV virus to several anti-viral agents, there is a need for novel compounds that are capable of not only conferring a protection against an infection but that can also be administered to patients that have already contracted the disease.

SUMMARY OF THE INVENTION

Based on the above-mentioned data obtained in vivo with the anti-CD81 antibodies, there was a strong belief in the field that predicted similar results, when using antibodies against other putative HCV receptors, i.e. that antibodies against such receptors would inhibit
entry of HCV and thus would prove to be good prophylactic agents but would not be useful for therapy. Thus it was an unexpected finding, particularly also in light of the above-mentioned observation that down-regulation of SR-BI receptor via RNAi appeared not to protect the cells against an HCV infection, of the present inventors that antibodies specific for the SR-BI receptor could successfully be used not only for the prevention but also for the therapy of an HCV infection (see examples herein below).

SR-BI is a lipoprotein receptor of 509 amino acids with cytoplasmic C- and N-terminal domains separated by a large extracellular domain (see Acton, S. et al., 1996, "Identification of scavenger receptor SR-BI as a high density lipoprotein receptor", Science 271:518-20; and see also: Calvo, D., and M. A. Vega, 1993, "Identification, primary structure, and distribution of CLA-1, a novel member of the CD36/LIMPII gene family", J Biol. Chem. 268:18929-35). It is expressed in a large number of tissues, and notably at high levels in liver and steroidogenic tissues, where it mediates selective cholesteryl ester uptake from HDL and may act as an endocytic receptor (Rhaids, D., and L. Brissette, 2004, "The role of scavenger receptor class B type 1 (SR-BI) in lipid trafficking, defining the rules for lipid traders", Int. J. Biochem. Cell. Biol. 36:39-77; and see also: Silver, D. et al., 2001, "High density lipoprotein (HDL) particle uptake mediated by scavenger receptor class B type 1 results in selective sorting of HDL cholesterol from protein and polarized cholesterol secretion", J. Biol. Chem. 276:25287-93). SR-BI was originally identified as a putative receptor for HCV because it binds soluble E2 (sE2) through interaction with the E2 hypervariable region 1 (HVR1). This finding suggested that SR-BI next to other receptors may function in HCV attachment to the target cell and, therefore it could act at the level of virus entry (Scarselli, E. et al, 2002. The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. EMBO J. 21:5017-5025).

The inventors have generated new human monoclonal antibodies with an improved dissociation constant against SR-BI which unexpectedly were found to not only inhibit HCV entry, i.e. endocytosis, but in addition, also proved to be potent inhibitors of virus transmission from cell-to-cell. As the novel anti-SR-BI antibodies unexpectedly inhibited cell-to-cell spread these new antibodies are capable of blocking virus spread and expansion in vivo and, thus, can be used not only for prophylactic medical use against HCV but can also be used for therapy, e.g. to treat a HCV infection. The antibodies of the present invention and fragments thereof are, thus, preferable administered to patients that already have contracted the HCV disease. Further experimental data showed that one of the new antibodies, namely anti-SRBI mAb8 exhibited an especially potent inhibitory effect at low concentrations. For
example, the antibody anti-SRBl mAb8, when used at a concentration of 0.008 μg/mL, was capable of reducing HCV infection by more than 50% (cf. Figure 5).

Thus, the present invention provides improved antibodies that can be used for the prevention and treatment of an HCV infection.

In a first aspect the present invention provides an antibody or fragment thereof, which binds to the scavenger receptor class B type 1 (SR-B1).

In a preferred embodiment of this aspect

(i) the heavy chain of said antibody or fragment thereof comprises a CDR3 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 13, 15, 17, 19, 21, and 23; wherein said CDR3 domain of the heavy chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion; and

(ii) the light chain of said antibody or fragment thereof comprises a CDR3 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 14, 16, 18, 20, 22, and 24; wherein said CDR3 domain of the light chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion.

In a second aspect the present invention provides a polynucleotide encoding the antibody or fragment of the first aspect of the invention.

In a third aspect the present invention provides a cell comprising the antibody or fragment thereof according to the first aspect of the invention and/or the polynucleotide of the second aspect of the invention.

In a fourth aspect the present invention provides a pharmaceutical composition comprising the antibody according to the first aspect of the invention or the polynucleotide of the second aspect of the invention and further comprising one or more pharmaceutically acceptable diluents; carriers; excipients; fillers; binders; lubricants; glidants; disintegrants; adsorbents; and/or preservatives.

In a fifth aspect the present invention provides an antibody or antibody of the first aspect of the invention or a polynucleotide of the second aspect of the invention or a pharmaceutical composition of the fourth aspect of the invention for use in the treatment of HCV.

DETAILED DESCRIPTION OF THE INVENTION

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the
purpose of describing particular embodiments only, and is not intended to limit the scope of
the present invention which will be limited only by the appended claims. Unless defined
otherwise, all technical and scientific terms used herein have the same meanings as commonly
understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary
of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and
Klbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland) and as described
in "Pharmaceutical Substances: Syntheses, Patents, Applications" by Axel Kleemann and
Jurgen Engel, Thieme Medical Publishing, 1999; the "Merck Index: An Encyclopedia of
Chemicals, Drugs, and Biologicals", edited by Susan Budavari et al., CRC Press, 1996, and
the United States Pharmacopeia-25/National Formulary-20, published by the United States

Throughout this specification and 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 feature, integer or step or group of features,
integers or steps but not the exclusion of any other feature, integer or step or group of integers
or steps. In the following passages different aspects of the invention are defined in more
detail. Each aspect so defined may be combined with any other aspect or aspects unless
clearly indicated to the contrary. In particular, any feature indicated as being preferred or
advantageous may be combined with any other feature or features indicated as being preferred
or advantageous.

Several documents are cited throughout the text of this specification. Each of the
documents cited herein (including all patents, patent applications, scientific publications,
manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby
incorporated by reference in their entirety. Nothing herein is to be construed as an admission
that the invention is not entitled to antedate such disclosure by virtue of prior invention.

In the following, some definitions of terms frequently used in this specification are
provided. These terms will, in each instance of its use, in the remainder of the specification
have the respectively defined meaning and preferred meanings.

The term "antibody or fragment thereof, as used herein, refers to immunoglobulin
molecules and immunologically active portions of immunoglobulin molecules, i.e. molecules
that contain an antigen binding site that specifically binds an antigen. Also comprised are
immunoglobulin-like proteins that are selected through techniques including, for example,
phage display to specifically bind to a target molecule, e.g. to the target protein SR-B1. The
immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgGl, IgG2, IgG3, IgG4, IgAl and IgA2) or subclass of immunoglobulin molecule. "Antibodies and fragments thereof suitable for use in the present invention include, but are not limited to, polyclonal, monoclonal, monovalent, bispecific, heteroconjugate, multispecific, human, humanized (in particular CDR-grafted), deimmunized, or chimeric antibodies, single chain antibodies (e.g. scFv), Fab fragments, F(ab')2 fragments, fragments produced by a Fab expression library, diabodies or tetrabodies (Holliger P. et al., 1993), nanobodies, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above.

In some embodiments the antibody fragments are mammalian, preferably human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (dsFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable domain(s) alone or in combination with the entirety or a portion of the following: hinge region, CL, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable domain(s) with a hinge region, CL, CH1, CH2, and CH3 domains.

Antibodies usable in the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, simian (e.g. chimpanzee, bonobo, macaque), rodent (e.g. mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. It is particularly preferred that the antibodies are of human or murine origin. As used herein, "human antibodies" include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described for example in U.S. Patent No. 5,939,598 by Kucherlapati & Jakobovits.

In the context of this invention the unique part of an antigen recognized by an antibody or fragment thereof of the invention is called an "epitope".

The terms "SR-B1" and "SR-BI" are used interchangeably herein and refer to the Scavenger receptor class B, type I (SR-BI) which is an integral membrane protein found in numerous cell types, including liver and adrenal cells. This receptor mediates the uptake of cholesteryl esters from high-density lipoproteins in the liver. An amino acid sequence of
human SR-B1 receptor can be found e.g. under accession number: NP_005496.4 (NCBI sequence).

As used herein, a first compound (e.g. an antibody or antibody fragment) is considered to "specifically bind" to a second compound (e.g. an antigen, such as a target protein), if it has a dissociation constant $K_D$ to said second compound of 100 $\mu$M or less, preferably 50 $\mu$M or less, preferably 30 $\mu$M or less, preferably 20 $\mu$M or less, preferably 10 $\mu$M or less, preferably 5 $\mu$M or less, more preferably 1 $\mu$M or less, more preferably 900 nM or less, more preferably 900 nM or less, more preferably 800 nM or less, more preferably 700 nM or less, more preferably 600 nM or less, more preferably 500 nM or less, more preferably 400 nM or less, more preferably 300 nM or less, more preferably 200 nM or less, even more preferably 100 nM or less, even more preferably 90 nM or less, even more preferably 80 nM or less, even more preferably 70 nM or less, even more preferably 60 nM or less, even more preferably 50 nM or less, even more preferably 40 nM or less, even more preferably 30 nM or less, even more preferably 20 nM or less, and even more preferably 10 nM or less. For example, in a particularly preferred embodiment of the antibody or fragment thereof of the present invention has a dissociation constant $K_D$ to the scavenger receptor class B type 1 (SR-B1) and/or to an extra-cellular part thereof of less than 10 nM.

As used herein, a "patient" means any mammal or bird who may benefit from a treatment with the antibody of the invention or a fragment thereof. It is particularly preferred that the "patient" is a human being.

As used herein, "treat", "treating" or "treatment" of a disease or disorder means accomplishing one or more of the following: (a) reducing the severity of the disorder; (b) limiting or preventing development of symptoms characteristic of the disorder(s) being treated; (c) inhibiting worsening of symptoms characteristic of the disorder(s) being treated; (d) limiting or preventing recurrence of the disorder(s) in patients that have previously had the disorder(s); and (e) limiting or preventing recurrence of symptoms in patients that were previously symptomatic for the disorder(s). In contrast to "prevention" or "prophylaxis" of a disease, the terms "treat", "treating" or "treatment" in all instances means that treatment occurs after the patient has contracted the disease.

As used herein, "administering" includes in vivo administration, as well as administration directly to tissue ex vivo, such as vein grafts.

An "effective amount" is an amount of a therapeutic agent sufficient to achieve the intended purpose. The effective amount of a given therapeutic agent will vary with factors such as the nature of the agent, the route of administration, the size and species of the animal
to receive the therapeutic agent, and the purpose of the administration. The effective amount
in each individual case may be selected as described herein or determined empirically by a
skilled artisan according to established methods in the art.

"Pharmaceutically acceptable" means approved by a regulatory agency of the Federal
or a state government or listed in the U.S. Pharmacopeia or other generally recognized
pharmacopeia for use in animals, and more particularly in humans.

The following Table 1 provides an overview over the sequences referred to herein:

<table>
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<tr>
<th>Antibody</th>
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<th>Sequence designation</th>
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<td>14</td>
<td>mAb8 VL - CDR3</td>
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<tr>
<td>mAb6</td>
<td>48</td>
<td>mAb6 VL - CDR2</td>
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</tbody>
</table>

As used herein, the term "isolated" refers to a molecule which is substantially free of other molecules with which it is naturally associated with. An isolated molecule is thus free of other molecules that it would encounter or contact in a living animal in nature, i.e. outside an experimental setting. Preferably, the antibody or fragment thereof of the present invention is an isolated antibody or fragment thereof.

As used herein, the term "protein", "peptide", "polypeptide", "peptides" and "polypeptides" are used interchangeably throughout. These terms refer to both naturally occurring peptides and synthesized peptides that may include naturally or non-naturally occurring amino acids. Peptides can be also chemically modified by modifying a side chain or a free amino or carboxy-terminus of a natural or non-naturally occurring amino acid. This chemical modification includes the addition of further chemical moieties as well as the modification of functional groups in side chains of the amino acids, such as a glycosylation. A peptide is a polymer preferably having at least 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45,
50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or at least 100 amino acids, most preferably at least 30 amino acids.

The term "vector" as used herein includes any vectors known to the skilled person including plasmid vectors, cosmId vectors, phage vectors such as lambda phage, filamentous phage vectors, viral vectors, adenovirus vectors, adeno-associated virus (AAV) vectors (e.g., AAV type 5 and type 2), alphavirus vectors (e.g., Venezuelan equine encephalitis virus (VEE), sindbis virus (SIN), semliki forest virus (SFV), and VEE-SIN chimeras), herpes virus vectors, measles virus vectors, pox virus vectors (e.g., vaccinia virus, modified vaccinia virus Ankara (MVA), NYVAC (derived from the Copenhagen strain of vaccinia), and avipox vectors: canarypox (ALVAC) and fowlpox (FPV) vectors), and vesicular stomatitis virus vectors, retrovirus, lentivirus, viral like particles, or bacterial spores. A vector is preferably a DNA or RNA polynucleotide and also includes expression vectors, cloning vectors and vectors that are useful to generate e.g. antibodies and fragments thereof in host cells.

The term "CDR" in the context of the antibody of the invention or fragment thereof, refers to any of the antibodies complementarity determining regions. In the variable (V) domain of an antibody there are three CDRs (CDR1, CDR2 and CDR3). Since antibodies are typically composed of two polypeptide chains, there is a frequency of about six CDRs for each antigen receptor that can come into contact with the antigen (each heavy and light chain contains three CDRs). Among these, CDR3 shows the greatest variability. CDR domains have been extensively studied and, thus, the average skilled person is well capable of identifying CDR regions, i.e. CDR1, CDR2 and CDR3 within a polypeptide sequence of a VL and VH domain of an antigen receptor. In one preferred method, the CDR1, CDR2 and CDR3 regions of the VL domain are determined as follows:

CDR1 of the VL domain:

The first amino acid of CDR1 is located at approx. residue 23 or 24 of the VL domain. The residue before the first amino acid of the CDR1 is a conserved Cys residue. The residues following the last amino acid of the CDR1 region is a conserved Trp residue followed typically by Tyr-Gln, but also, Leu-Gln, Phe-Gln or Tyr-Leu. The length of the CDR1 of the VL domain is between 10 and 17 residues.

CDR2 of the VL domain:

CDR2 is located 16 residues after the end of CDR1. The residues before the first amino acid of CDR2 are generally Ile-Tyr, but also, Val-Tyr, Ile-Lys, Ile-Phe or similar. The length of the CDR2 region is generally 7 residues.

CDR3 of the VL domain:
CDR3 region of the VL domain starts 33 residues after the end of the CDR2 region. The preceding residue before the first amino acid of CDR3 is always Cys. CDR3 is followed by the amino acids Phe-Gly-XXX-Gly. The length of the CDR3 region is typically between 7 to 11 residues.

In one preferred method, the CDR1, CDR2 and CDR3 regions of the VH domain are determined as follows:

CDR1 of the VH domain:
The first amino acid of CDR1 is located at approx. residue 26 of the VH domain (always 4 or 5 residues after a Cys). The amino acid after the CDR1 will be a Tip (Typically Trp-Val, but also, Trp-Ile or Tip-Ala). The length of the CDR1 of the VH domain is between 10 to 12 residues.

CDR2 of the VH domain:
The CDR2 domain starts at residue 15 after the end of the CDR1 of the VH domain. The CDR2 domain is preceded typically by the amino acids Leu-Glu-Trp-Ile-Gly or a variation thereof. The CDR2 domain will be followed by the three amino acids (Lys/Arg)-(Leu/Ile/Val/Phe/Tyr/Ala)-(Thr/Ser/Ile/Ala) and comprises a total of about 16 to 19 residues.

CDR3 of the VH domain:
The first amino acid of the CDR3 of the VH domain will be located 33 residues after the end of the CDR2 of the VH domain and will start always 3 amino acids after a conserved Cys residue (the preceding sequence is typically Cys-Ala-Arg). The residues following the CDR3 will be Trp-Gly-XXX-Gly. The CDR3 of the VH domain will typically have a length of between 3 to 25 residues.

As mentioned above the inventors identified novel therapeutic antibodies with enhanced binding affinities to SR-B1. Thus, in a first aspect the invention provides an antibody or fragment thereof, which specifically binds to the scavenger receptor class B type 1 (SR-B1). Preferably, the antibody or fragment thereof specifically binds to an extracellular part of the scavenger receptor class B type 1 (SR-B1).

In a preferred embodiment, the antibody or fragment thereof of the invention is capable of specifically binding to the same SR-B1 epitope that also an antibody is capable of specifically binding to which comprises a heavy chain with a VH domain and a light chain with a VL domain, wherein the VH and VL domains respectively have an amino acid sequence of any of i) through viii):

<table>
<thead>
<tr>
<th>VH-domain (SEQ ID NO)</th>
<th>VL-domain (SEQ ID NO):</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) 1</td>
<td>2;</td>
</tr>
</tbody>
</table>
As depicted in the multiple sequence alignment shown in Figure 1, the VH and VL chains of the novel antibodies of the invention comprise improved CDR1, CDR2 and CDR3 sequences with improved binding affinities to SR-BI. Among the CDRs, CDR3 shows not only the greatest variability but also the greatest contribution for specific binding. Thus, in a preferred embodiment of the first aspect

(i) the heavy chain of said antibody or fragment thereof comprises a CDR3 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 13, 15, 17, 19, 21, and 23; wherein said CDR3 domain of the heavy chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion; and

(ii) the light chain of said antibody or fragment thereof comprises a CDR3 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 14, 16, 18, 20, 22, and 24; wherein said CDR3 domain of the light chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion.

Antibodies of the invention and fragment thereof can be modified to enhance stability and to enhance antigen binding. Factors effecting stability include exposure of hydrophobic residues that are hidden at the interface of a whole Ig molecule at the constant domain interface; hydrophobic region exposure on the Fv surface leading to intermolecular interaction; and hydrophilic residues in the interior of the Fv beta sheet or at the normally interface between VH and VL. (Chowdhury et al., Engineering scFvs for Improved Stability, p. 237-254 in Recombinant Antibodies for Cancer Therapy Methods and Protocols, (Eds. Welschof and Krauss) Humana Press, Totowa, New Jersey, 2003.) Stability can be enhanced by substituting problematic residues impacting on stability. Such modifications can be achieved by e.g. effecting said single amino acid substitution, deletion, modification and/or insertion. Techniques for enhancing single chain antibody stability taking into account problematic residue are well known in art. (Chowdhury et al., Engineering scFvs for Improved Stability, p. 237-254 in Recombinant Antibodies for Cancer Therapy Methods and Protocols, (Eds. Welschof and Krauss) Humana Press, Totowa, New Jersey, 2003.)
In a further preferred embodiment of the antibody or fragment thereof of the invention the antibody or fragment thereof comprises a pair of polypeptides that are selected from the group consisting of:

SEQ ID NO: 13, SEQ ID NO: 14;
SEQ ID NO: 15, SEQ ID NO: 16;
SEQ ID NO: 17, SEQ ID NO: 18;
SEQ ID NO: 19, SEQ ID NO: 20;
SEQ ID NO: 21, SEQ ID NO: 22; and
SEQ ID NO: 23, SEQ ID NO: 24;

wherein each polypeptide pair is respectively a CDR3 domain of the heavy chain and a CDR3 domain of the light chain of said antibody or fragment thereof; wherein each CDR3 domain optionally comprises one amino acid substitution, deletion or addition.

In another embodiment of the antibody of the invention or fragment thereof,

(i) the heavy chain of said antibody or fragment thereof comprises a CDR3 domain having an amino acid sequence as specified in (iii); and

(ii) the light chain of said antibody or fragment thereof comprises a CDR3 domain having an amino acid sequence as specified in (iii); and

(iii) the pair of CDR3 domains defined in (i) and (ii) is selected from the following list:

<table>
<thead>
<tr>
<th>Heavy chain CDR3 domain</th>
<th>Light chain CDR3 domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSEQID NO: 1133;</td>
<td>SEQ ID NO: 14;</td>
</tr>
<tr>
<td>SEQ ID NO: 15;</td>
<td>SEQ ID NO: 16;</td>
</tr>
<tr>
<td>SEQ ID NO: 17;</td>
<td>SEQ ID NO: 18;</td>
</tr>
<tr>
<td>SEQ ID NO: 19;</td>
<td>SEQ ID NO: 20;</td>
</tr>
<tr>
<td>SEQ ID NO: 21;</td>
<td>SEQ ID NO: 22; and</td>
</tr>
<tr>
<td>SSEQID NO: 2233;</td>
<td>SEQ ID NO: 24.</td>
</tr>
</tbody>
</table>

It is further preferred that the antibody or fragment thereof of the invention additionally comprises one or more of the following:

(i) the heavy chain of said antibody or fragment thereof comprises a CDR1 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 25, 27, 29, 31, 33, and 35; wherein said CDR1 domain of the heavy chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion;

(ii) the light chain of said antibody or fragment thereof comprises a CDR1 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 26, 28, 30,
32, 34 and 36; wherein said CDR1 domain of the light chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion;

(iii) the heavy chain of said antibody or fragment thereof comprises a CDR2 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 37, 39, 41, 43, 45 and 47; wherein said CDR2 domain of the heavy chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion; and

(iv) the light chain of said antibody or fragment thereof comprises a CDR2 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 38, 40, 42, 44, 46 and 48; wherein said CDR2 domain of the light chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion.

In a preferred embodiment of the antibody or fragment of the invention:

(i) the VH domain of the heavy chain of said antibody or fragment thereof comprises the amino acid sequence selected from SEQ ID NO: 1, 3, 5, 7, 9 and 11; wherein said VH domain may optionally comprise between 1 and 10, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 single amino acid substitutions, deletions, modifications and/or insertions, preferably each of the CDR1, CDR2 and CDR3 sequences do not exhibit more than one substitution, deletion, modification and/or insertion; and

(ii) the VL domain of the light chain of said antibody or fragment thereof comprises the amino acid sequence selected from SEQ ID NO: 2, 4, 6, 8, 10 and 12; wherein said VL domain may optionally comprise between 1 and 10, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 single amino acid substitutions, modifications, deletions and/or insertions, preferably each of the CDR1, CDR2 and CDR3 sequences do not exhibit more than one substitution, deletion, modification and/or insertion.

Further preferred is an antibody or fragment thereof of the invention, wherein the following VH domain and VL domain are paired together 1 and 2; 3 and 4; 5 and 6; 7 and 8; 9 and 10; and 11 and 12 and together comprise between 0 and 15, more preferably between 0 and 10 i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and most preferably between 0 and 3 single amino acid substitutions, deletions and insertions or amino acid substitutions, deletions or insertions, preferably substitutions, preferably with the proviso that not more than one or none of said substitutions, deletions, modifications and/or insertions are located within the CDR1, CDR2 or CDR3 domains of the heavy chain or light chain. In the context of the antibody or fragment thereof of the invention the phrase "specifically binds" means that said antibody or fragment thereof binds to said SR-BI receptor, preferably with a dissociation constant as defined herein above.
In one particularly preferred embodiment, "specifically binds" means that said antibody or fragment thereof of the invention binds to said SR-B1 receptor with a dissociation constant (Ko) of less than 10 nM as measured by binding titration on CHO cells expressing SR-B1 receptor. Whole cell binding assays are well known in the art. For example, the average skilled person may determine said ¾ to CHO cells that are stably transfected with human SR-B1 as follows:

CHO/SR-B1 cells (number of cells = 5x10^5) are incubated for 1h at room temperature with an anti-SR-B1 antibody or fragment thereof of the invention [primary antibodies] in 50 µι of phosphate-buffered saline (PBS)-0.2% bovine serum albumin (BSA)-HEPES at 10 mM (fluorescence-activated cell sorter [FACS] buffer). Antibody binding is then determined by APC conjugated AffiniePure anti-human IgG goat F(ab’)2 fragments (Jackson Immunoresearch, cat# 109-136-170) [secondary antibody]. After incubation with primary antibodies cells are washed with 5ml of FACS buffer, centrifuged at 1200 rpm, supernatant is decanted and cells are resuspended in 50 µι of 1:500 dilution of secondary antibody and incubated 45min at room temperature. Following incubation cells are washed with 5ml of FACS buffer, centrifuged at 1200 rpm, supernatant is decanted and cells are resuspended in 400 µι FACS buffer for acquisition. A binding reaction without the primary antibody is used to determine the background signal. Next, mean fluorescence intensities (MFIs) obtained without the primary antibody are subtracted from MFIs at each anti-SR-B1 MAb concentration, i.e. by titrating the antibody or fragment thereof of the invention. FACS acquisitions and analysis are preferably performed with a FACScalibur (Becton Dickinson) according to specifications of the manufacturer.

To calculate the K_D, saturation curves for each antibody were fitted to experimental data with the Sigma Plot program. MFIs obtained without the IgG were subtracted.

It is within the skill of the artisan to experimentally determine also by other means, if an antibody or fragment thereof interacts with an antigen such as with the SR-B1 receptor. For example, assays as described in the examples below may be used. Additionally, it is possible to analyze the interaction between the antibody or fragment thereof and SR-B1 or a fragment thereof (such as its extracellular domain) using a pull down assay. For example, the SR-B1 or a fragment thereof may be purified and immobilized on a solid phase such as beads. In one embodiment, the beads linked to SR-B1 may be contacted with the antibody or fragment thereof, washed and probed with a secondary antibody specific for an invariant part of the antibody or fragment thereof, available in the state of the art. Also other binding assays well known in the art and suitable to determine binding affinities between two binding
partners can be used such as e.g. ELISA-based assays, fluorescence resonance energy transfer (FRET)-based assays, co-immunoprecipitation assays and plasmon-resonance assays. The binding can be detected by fluorescence means, e.g. using a fluorescently labelled secondary antibody, or enzymatically as is well known in the art. Also radioactive assays may be used to assess binding. Thus, any of the aforementioned exemplary methods can be used to determine if an antibody or fragment thereof of the invention binds to SR-B1 and optionally also to determine with what dissociation constant $K_D$ the antibody or fragment thereof binds the mentioned antigen.

It is further preferred that the antibody or fragment thereof of the invention is capable of inhibiting transmission of HCV from an HCV infected mammalian cell to another cell, preferably to an non-infected cell contacting said infected cell. Preferably the viral cell-to-cell transmission is inhibited to such degree that the HCV viral load of a subject can be reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or even more compared to a control subject, which does not receive the antibody or fragment thereof of the invention.

In a preferred embodiment, the antibody of the invention is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody, a human antibody, a diabody, a tetrabody, a nanobody, a chimeric antibody, and a deimmunized antibody.

In a preferred embodiment, the fragment of the antibody of the invention is an antibody fragment selected from the group consisting of Fab, F(ab')$_2$, Fd, Fv, single-chain Fv, and disulfide-linked Fvs (dsFv).

In a further aspect the invention provides a polynucleotide encoding the VH and/or VL domain of the antibody or fragment thereof according to the invention. In one embodiment the polynucleotide of the invention may be a composition comprising a first and a second polynucleotide, wherein the first polynucleotide comprises or consists of a polynucleotide that encodes a VL region according to any of SEQ ID NO: 2, 4, 6, 8, 10 and 12 optionally comprising not more than two, preferably a single amino acid substitution, deletion, modification and/or insertion and the second polynucleotide comprises or consists of a polynucleotide encoding a VH region according to any of SEQ ID NO: 1, 3, 5, 7, 9 and 11 optionally comprising not more than two, preferably a single amino acid substitution, deletion, modification and/or insertion.

In a preferred embodiment, the polynucleotide of the invention is comprised in a vector as defined herein.
An antibody of the invention or a fragment thereof can be generated e.g. by recombinant expression of a polynucleotide of the invention or by or through the use of a hybridoma. A hybridoma is an immortalized cell line producing the antigen binding protein. A hybridoma is an immortalized antibody producing cell line. A hybridoma can be produced using techniques such as those described in Ausubel Current Protocols in Molecular Biology, John Wiley, 1987-1998, Harlow et al., Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, 1988, and Kohler et al, Nature 256, 495-497, 1975.

In one embodiment the polynucleotide of the invention can be expressed in a host cell, preferably a human cell. The expression can be carried out by using a vector comprising a polynucleotide of the invention. Thus, in one embodiment, the vector is an expression vector or viral, e.g. adenoviral vector. The viral vector is preferably capable of expressing the polynucleotide of the invention in a target cell and thus useful for transgenic expression of antibodies of the invention and/or fragments thereof in such target cell which is preferably a human cell. The expression vector may further comprise regulatory elements for protein expression. Generally, the regulatory elements that can be used include a transcriptional promoter, a ribosome binding site, a terminator, and an operator. A preferred element for processing in eukaryotic cells is a polyadenylation signal. Antibody associated introns may also be present. Examples of expression cassettes for antibody or antibody fragment production are well known in art. (E.g., Persic et al. Gene 187:9-18, 1997, Boel et al, J. Immunol. Methods 239: 153-166, 2000, Liang et al, J. Immunol. Methods 247: 119-130, 2001.) If the vector is an expression vector, the vector may further comprise also an origin of replication for autonomous replication in a host cell, a selectable marker, a limited number of useful restriction enzyme sites, and a potential for high copy number. Examples of expression vectors for antibody and antibody fragment production are well known in art. (E.g., Persic et al., Gene 757:9-18, 1997, Boel et al., J. Immunol. Methods 239:153-166, 2000, Liang et al, J. Immunol Methods 247: 119-130, 2001.). If desired, a polynucleotide of the invention may be integrated into the host chromosome using techniques well known in the art. (See, Ausubel, Current Protocols in Molecular Biology, John Wiley, 1987-1998, Marks et al, International Application Number WO 95/17516, International Publication Date June 29, 1995.) A variety of different cell lines can be used for recombinant antigen binding protein expression, including those from prokaryotic organisms (e.g., E. coli, Bacillus, and Streptomyces) and from Eukaryotic organisms (e.g., yeast, insect and mammalian). (Breitling et al., Recombinant Antibodies, John Wiley & Sons, Inc. and Spektrum Akademischer Verlag, 1999.)
Preferred hosts for recombinant expression of the antibody of the invention or a fragment thereof are mammalian cells able to produce antigen binding protein with proper post translational modifications. Post translational modifications include disulfide bond formation and glycosylation. Another type of post translational modification is signal peptide cleavage. Proper glycosylation can be important for antibody function. (Yoo et al., Journal of Immunological Methods 261:1-20, 2002.) Naturally occurring antibodies typically contain at least one N-linked carbohydrate attached to a heavy chain. (Id.) Additional N-linked carbohydrates and O-linked carbohydrates may be present and may be important for antibody function. (Id.)

Different types of mammalian host cells can be used to provide for efficient post-translational modifications. Examples of such host cells include Chinese hamster ovary (CHO), HeLa, C6, PC12, and myeloma cells (see e.g. Yoo et al, Journal of Immunological Methods 267:1-20, 2002, Persic et al, Gene 787:9-18, 1997).

In some embodiments of the antibody of the invention and fragments thereof, in particular if the antibody of the invention is a single-chain antibody, the variable regions and/or complementary determining regions from the heavy and light chains (SEQ ID NO: 1-14, respectively) can be used and incorporated into said single chain antibody. Techniques for incorporating a variable region into an antibody or an antibody fragment are well known in the art. (E.g., Azzazy et al., Clinical Biochemistry 35:425-445, 2002, Persic et al., Gene 757:9-18, 1997.) In one example the average skilled person can follow the technique as described in the following:

The Fv domains are separately amplified using PCR primers specific for the VH and VL regions, the primers can include additional nucleotides for introducing unique restriction sites, for providing splice sites, and encoding additional amino acids. Next, the amplified variable encoding regions are incorporated into mammalian expression cassettes. VH encoding nucleic acid can be inserted into a plasmid containing a cassette for expressing a human heavy (e.g., human gamma 4 heavy chain), while the VL encoding region can be introduced into a vector expressing a light chain (e.g., human lambda light chain). Both vectors should carry an intron between the leader sequence and the constant region sequence of the antibody. The intron should contain unique restriction sites suitable for cloning the amplified Fv domains. In a next step, IgG production is achieved by co-transfecting the VH and VL expression vector in 293-EBNA cells. Numerous variations of the outlined procedure can be performed to incorporate a variable region into an antibody or an antibody fragment. Such variations
include, for example, using a vector encoding different types of antibody light and heavy chains or fragments thereof, using a single vector, and using different types of host cells.

Technique for grafting complementary determining regions into an antibody or antibody fragment as defined herein are also well known in art. Such techniques are generally described with reference to humanizing murine antibodies by grafting murine variable regions onto a human antibody framework and, if needed making further modifications. (E.g., O’Brien et al, Humanization of Monoclonal Antibodies by CDR Grafting, p 81-100, From Methods in Molecular Biology Vol 207: Recombinant antibodies for Cancer Therapy: Methods and Protocols (Eds Welschof and Krauss) Humana Press, Totowa, New Jersey, 2003.)

In a further aspect, the invention provides a cell comprising the antibody or fragment thereof according to the invention and/or the polynucleotide according to the invention.

In yet another aspect the invention provides a pharmaceutical composition comprising the antibody or fragment thereof according to the invention and/or the a polynucleotide of the invention and further comprising one or more pharmaceutically acceptable diluents; carriers; excipients, fillers, binders, lubricants, glidants, disintegrants, adsorbents; adjuvants and/or preservatives.

It is particularly preferred that the pharmaceutical composition of the invention can be used in the form of systemically administered medicaments. These include parenterals, which comprise among others injectables and infusions. Injectables are formulated either in the form of ampoules or as so called ready-for-use injectables, e.g. ready-to-use syringes or single-use syringes and aside from this in puncturable flasks for multiple withdrawal. The administration of injectables can be in the form of subcutaneous (s.c), intramuscular (i.m.), intravenous (i.v.) or intracutaneous (i.e.) application. In particular, it is possible to produce the respectively suitable injection formulations as a suspension of crystals, solutions, nanoparticulate or a colloid dispersed systems like, e.g. hydrosols.

Injectable formulations can further be produced as concentrates, which can be dissolved or dispersed with aqueous isotonic diluents. The infusion can also be prepared in form of isotonic solutions, fatty emulsions, liposomal formulations and micro-emulsions. Similar to injectables, infusion formulations can also be prepared in the form of concentrates for dilution. Injectable formulations can also be applied in the form of permanent infusions both in in-patient and ambulant therapy, e.g. by way of mini-pumps.

It is possible to add to parenteral drug formulations, for example, albumin, plasma, expander, surface-active substances, organic diluents, pH-influencing substances, complexing substances or polymeric substances, in particular as substances to influence the adsorption of
the pharmaceutical composition of the invention to proteins or polymers or they can also be added with the aim to reduce the adsorption of the pharmaceutical composition of the invention to materials like injection instruments or packaging-materials, for example, plastic or glass.

The pharmaceutical composition of the invention can in some embodiments also be bound to microcarriers or nanoparticles in parenterals like, for example, to finely dispersed particles based on poly(meth)acrylates, polylactates, polyglycolates, polyamino acids or polyether urethanes. The pharmaceutical composition of the invention can also be modified as depot preparations, e.g. based on the "multiple unit principle", if the composition of the invention is introduced in finely dispersed, dispersed and suspended form, respectively, or as a suspension of crystals in the medicament or based on the "single unit principle" if the composition of the invention is enclosed in a formulation, e.g. in a tablet or a rod which is subsequently implanted. These implants or depot medicaments in single unit and multiple unit formulations often consist out of so called biodegradable polymers like e.g. polyesters of lactic and glycolic acid, polyether urethanes, polyamino acids, poly(meth)acrylates or polysaccharides.

Adjuvants in a composition of the invention may preferably be aqua sterilisata (sterilized water), pH value influencing substances like, e.g. organic or inorganic acids or bases as well as salts thereof, buffering substances for adjusting pH values, substances for isotonization like e.g. sodium chloride, sodium hydrogen carbonate, glucose and fructose, tensides and surfactants, respectively, and emulsifiers like, e.g. partial esters of fatty acids of polyoxyethylene sorbitans (for example, Tween®) or, e.g. fatty acid esters of polyoxyethylenes (for example, Cremophor®), fatty oils like, e.g. peanut oil, soybean oil or castor oil, synthetic esters of fatty acids like, e.g. ethyl oleate, isopropyl myristate and neutral oil (for example, Miglyol®) as well as polymeric adjuvants like, e.g. gelatine, dextran, polyvinylpyrrolidone, additives which increase the solubility of organic solvents like, e.g. propylene glycol, ethanol, N,N-dimethylacetamide, propylene glycol or complex forming substances like, e.g. citrate and urea, preservatives like, e.g. benzoic acid hydroxypropyl ester and methyl ester, benzyl alcohol, antioxidants like e.g. sodium sulfite and stabilizers like e.g. EDTA.

When formulating the pharmaceutical composition of the present invention as suspension in a preferred embodiment thickening agents to prevent the setting of the pharmaceutical composition of the invention or, tensides and polyelectrolytes to assure the resuspendability of sediments and/or complex forming agents like, for example, EDTA are
added. It is also possible to achieve complexes of the active ingredient with various polymers. Examples of such polymers are polyethylene glycol, polystyrol, carboxymethyl cellulose, Pluronics® or polyethylene glycol sorbit fatty acid ester. In particular embodiments dispersing agents can be added as further adjuvants. For the production of lyophilisates scaffolding agents like mannite, dextran, saccharose, human albumin, lactose, PVP or varieties of gelatine can be used.

A particular advantage of the antibody and fragment thereof of the invention is that they are effective against an HCV infection. Thus, the invention also provides the antibody according to the invention or the pharmaceutical composition according to the invention for treating or preventing a HCV infection, preferably a chronic HCV infection. In this context the term "chronic HCV infection" is preferably defined as the persistence of HCV RNA in the blood for one month or more, preferably of two months or more or most preferably for six months or more. In people with chronic hepatitis C, the immune system has failed to clear the virus from the body. Therefore, individuals with chronic hepatitis C will persistently have an elevated HCV RNA. Once a person is chronically infected with HCV, the potential exists for liver damage and cirrhosis along with its complications, including liver failure and liver cancer. Approximately 60-85 percent of HCV infected people develop chronic hepatitis C.

In a further aspect the invention relates to anti-SR-BI antibodies, which specifically bind to the scavenger receptor class B type 1 for the treatment of chronic HCV.

It has been recognized in the art that an alternative way of administering an antibody is the administration of a nucleic acid encoding the antibody, which is then expressed in the patient. Expression can be achieved by numerous technologies known in the art comprising transfection of mRNA or transfection or infection of encoding nucleotides in vectors, which include viral vectors and plasmid vectors. Accordingly, the invention also relates to a nucleic acids encoding the antibody of the invention for the treatment or prophylaxis of HCV infection, in particular for the treatment of chronic HCV infection.

As mentioned, antibodies of the present invention, such as the antibody anti-SRBI mAb8, when used at a concentration of 0.008 µg/ml, is capable of reducing an HCV infection by more than 50% (cf. Figure 5). Thus, in a preferred embodiment, the antibodies of the invention are capable of reducing HCV infection when used at a concentration of 0.008 µg/ml, by more than 50% compared to an HCV infection that is observed, when no antibodies are used. Preferably said reduction in infection is determined using RT-PCR, for example as outlined in example 4 below. An average skilled person can determine the reduction of
infection of HCV by e.g. using the neutralization/blocking assay set forth in the examples below.

As used throughout this application, the phrase "a single amino acid substitution, deletion, modification and/or insertion" of a protein or polypeptide generally refers to a modified version of the recited protein or polypeptide, e.g. one amino acid of the protein or polypeptide may be deleted, inserted, modified and/or substituted. If the polypeptide or protein comprises several single amino acid substitutions, deletions, modifications and/or insertions then the total number of such substitutions, deletions, modifications and/or insertions is indicated in each case. Said insertion is an insertion of the indicated number of single amino acids into the original polypeptide or protein. An amino acid of the protein or polypeptide may also be modified, e.g. chemically modified by the total number of modifications indicated. For example, the side chain or a free amino or carboxy-terminus of an amino acid of the protein or polypeptide may be modified by e.g. glycosylation, amidation, phosphorylation, ubiquitination, e.t.c. The chemical modification can also take place in vivo, e.g. in a host-cell, as is well known in the art. For examples, a suitable chemical modification motif, e.g. glycosylation sequence motif present in the amino acid sequence of the protein will cause the protein to be glycosylated. If the polypeptide or protein comprises one or more single amino acid substitutions, said substitutions may in each case independently be a conservative or a non-conservative substitution, preferably a conservative substitution. In a most preferred embodiment, all substitutions are of conservative nature as further defined below. In some embodiments, a substitution also includes the exchange of a naturally occurring amino acid with a not naturally occurring amino acid. A conservative substitution comprises the substitution of an amino acid with another amino acid having a chemical property similar to the amino acid that is substituted. Preferably, the conservative substitution is a substitution selected from the group consisting of:

(i) a substitution of a basic amino acid with another, different basic amino acid;
(ii) a substitution of an acidic amino acid with another, different acidic amino acid;
(iii) a substitution of an aromatic amino acid with another, different aromatic amino acid;
(iv) a substitution of a non-polar, aliphatic amino acid with another, different non-polar, aliphatic amino acid; and
(v) a substitution of a polar, uncharged amino acid with another, different polar, uncharged amino acid.

A basic amino acid is preferably selected from the group consisting of arginine, histidine, and lysine. An acidic amino acid is preferably aspartate or glutamate. An aromatic
amino acid is preferably selected from the group consisting of phenylalanine, tyrosine and tryptophane. A non-polar, aliphatic amino acid is preferably selected from the group consisting of glycine, alanine, valine, leucine, methionine and isoleucine. A polar, uncharged amino acid is preferably selected from the group consisting of serine, threonine, cysteine, proline, asparagine and glutamine. In contrast to a conservative amino acid substitution, a non-conservative amino acid substitution is the exchange of one amino acid with any amino acid that does not fall under the above-outlined conservative substitutions (i) through (v).

If a protein or polypeptide comprises one or an indicated number of single amino acid deletions, then said amino acid(s) present in the reference polypeptide or protein sequence have been removed.

The pharmaceutical composition of the invention can be administered by various well known routes, including oral, rectal, intragastrical and parenteral administration (see also above), e.g. intravenous, intramuscular, intranasal, intradermal, subcutaneous and similar administration routes. Parenteral-, intramuscular- and intravenous administration is preferred. Preferably the pharmaceutical according to the invention is formulated as syrup, an infusion or injection solution, a tablet, a capsule, a caplet, lozenge, a liposome, a suppository, a plaster, a band-aid, a retard capsule, a powder, or a slow release formulation. Preferably the diluent is water, a buffer, a buffered salt solution or a salt solution and the carrier preferably is selected from the group consisting of cocoa butter and vitebesole.

Particular preferred pharmaceutical forms for the administration of the pharmaceutical according to the invention during the use of the present invention are forms suitable for injectable use and include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. Typically, such a solution or dispersion will include a solvent or dispersion medium, containing, for example, water-buffered aqueous solutions, e.g. biocompatible buffers, ethanol, polyol, such as glycerol, propylene glycol, polyethylene glycol, suitable mixtures thereof, surfactants or vegetable oils.

Infusion or injection solutions can be accomplished by any number of art recognized techniques including but not limited to addition of preservatives like anti-bacterial or anti-fungal agents, e.g. parabene, chlorobutanol, phenol, sorbic acid or thimersal. Further, isotonic agents, such as sugars or salts, in particular sodium chloride may be incorporated in infusion or injection solutions.

Preferred diluents of the present invention are water, physiological acceptable buffers, physiological acceptable buffer salt solutions or salt solutions. Preferred carriers are cocoa
butter and vitebesole. Excipients which can be used with the various pharmaceutical forms of the pharmaceutical according to the invention can be chosen from the following non-limiting list:

a) binders such as lactose, mannitol, crystalline sorbitol, dibasic phosphates, calcium phosphates, sugars, microcrystalline cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrrolidone and the like;

b) lubricants such as magnesium stearate, talc, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil, leucine, glycerids and sodium stearyl fumarates,

c) disintegrants such as starches, croscarmelllose, sodium methyl cellulose, agar, bentonite, alginic acid, carboxymethyl cellulose, polyvinyl pyrrolidone and the like.

Other suitable excipients can be found in the Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association, which is herein incorporated by reference.

Certain amounts of the pharmaceutical composition according to the invention are preferred for the therapy of a disease. It is, however, understood that depending on the severity of the disease, the type of the disease, as well as on the respective patient to be treated, e.g. the general health status of the patient, etc., different doses of the pharmaceutical composition according to the invention are required to elicit a therapeutic effect. The determination of the appropriate dose lies within the discretion of the attending physician.

Similarly, the antibodies, nucleic acids encoding such antibodies or the pharmaceutical compositions of the invention can be used in method of treating or preventing HCV infection, preferably of chronic HCV infection.

Various modifications and variations of the invention will be apparent to those skilled in the art without departing from the scope of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the relevant fields are intended to be covered by the present invention.

The following Figures are merely illustrative of the present invention and should not be construed to limit the scope of the invention as indicated by the appended claims in any way.
BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 CDR regions of anti-SR-Bl monoclonal antibodies - VH regions. The alignment illustrates the different VH regions of the monoclonal antibodies mAb 8 (SEQ ID NO: 1), mAb 8-1 (SEQ ID NO: 3), mAb 15 (SEQ ID NO: 5), mAb 15-1 (SEQ ID NO: 7), mAb 15-2 (SEQ ID NO: 9) and mAb 6 (SEQ ID NO: 11).

Fig. 2 CDR regions of anti-SR-Bl monoclonal antibodies - VL regions. The alignment illustrates the different VL regions of the monoclonal antibodies mAb 8 (SEQ ID NO: 2), mAb 8-1 (SEQ ID NO: 4), mAb 15 (SEQ ID NO: 6), mAb 15-1 (SEQ ID NO: 8), mAb 15-2 (SEQ ID NO: 10) and mAb 6 (SEQ ID NO: 12).

Fig. 3 Inhibition of HCVcc cell-to-cell spread in Huh-7.5/shSR-B1/KRAB cell line.

Fig. 4 HCVcc infection inhibited by anti-SRBl mAb measured by q-PCR. Huh7 cells were infected with HCVcc (J6/JFH1) after pre-incubation with anti-SR-Bl mAbs at a concentration of 10 µg/mL. Infectivity was measured by RT PCR assay 3 days post-infection. On the vertical axis it is shown the percentage of HCVcc infection in the presence of mAbs, relative to that measured in the absence of anti-SRB 1 mAb.

Fig. 5 Neutralization of J6/JFH1 HCVcc infection by anti-SR-Bl mAbs. Huh7.5 cells were infected with HCVcc upon pre-incubation with increasing concentrations (ng/ml) of anti-SR-Bl mAbs (indicated on the horizontal axis on a logarithmic scale). Infectivity was measured 3 days post-infection. On the vertical axis is shown the percentage of HCV (% infection) measured in cells infected in the presence of mAbs, relative to the number of HCV copies measured in no-antibody-treated cells. Neutralization curves were extrapolated by fitting experimental data with the Sigma Plot program.

Fig. 6 Efficacy of mAb8 in prevention mode: mAb8 can prevent HCV infection in vivo.

Fig. 7 Efficacy of mAb8 in post-exposure therapeutic mode: mAb8 reduces HCV post exposure in vivo.

Fig. 8 Apparent affinity of anti-SRBl mAbs.

EXAMPLES

Example 1: SRBl mediates cell-to-cell spread

Inhibition of HCVcc cell-to-cell spread in Huh-7.5/shSR-B1/KRAB cell line. Huh-7.5/shSR-B1/KRAB cells are stable derivatives of the human hepatoma Huh-7.5 cell line, where endogenous SR-B1 expression can be reversibly downregulated by a stably transfected

Huh-7.5/shSR-BI/KRAB cells, pre-treated or not with 100ng/ml doxycycline (DOX) for 6 days, were infected with HCVcc in the presence or absence of DOX. Cell monolayers grown on polylysine-coated wells were fixed, permeabilized and stained with an anti HCV core antibody conjugated to HRP at 3 days post HCV infection (Figure 3, Exp n.1) or with an anti HCV NS5a antibody conjugated to HRP at 2 days post HCV infection (Figure 3, Exp n.2). As shown in Figure 3, downregulation of SR-BI reduces the number of cell foci that are positive for HCV infection (+DOX). Images representative of the wells are shown in Figure 3.

Example 2: Selection of scFv from phage displayed libraries

scFv were selected from single-chain Fv (scFv) libraries. The library provides single-chain antibody fragments containing a variable domain of heavy chain and light chain exposed on the surface of a filamentous phage as a fusion to the coat protein pill.

$10^{11}$ transducing units from a scFv phage-displayed library were panned on HuH7 cells. Different selection experiments were performed. In each selection the phage library was incubated with MPBS (3% powdered non-fat dry milk in PBS solution) for 30 min at room temperature (RT). HuH7 cells used in the selection were detached from the plate using 2.5 mM EDTA in PBS and re-suspended to a final concentration of $1 \times 10^7$ cells/mL. Following centrifugation, cells were re-suspended with pre-adsorbed phage-Abs solution and incubated for 1 hour at RT. After extensive washing with PBS, cell-bound phage were centrifuged 5 min at 2 k rpm and re-suspended in 800 μL of elution buffer (0.1 M HCl adjusted to pH 2.5 with glycine, 1mg/ml BSA) and neutralised with 2 M Tris-HCl pH 9. E. Coli TGI cells (New England Biolabs, Beverly, MA) were infected with eluted phage and plated on 2X TY agar containing 2% glucose and 100 mg/mL ampicillin (2X TYAG). Phage rescue and amplification was carried out as described (Hegmans JP, Radosevic K, Voerman JS, Burgers JA, Hoogsteden HC, et al. (2002) A model system for optimising the selection of membrane antigen-specific human antibodies on intact cells using phage antibody display technology. J Immunol Methods 262: 191-204). The selected phage were panned again on the same cell line. A variable number of clones (in the range 100-1,000) were randomly chosen from the pool of selected phage and tested by phage ELISA for their ability to bind HuH7 cells by whole-cell phage-ELISA. Cells were seeded overnight in 96 well plates at the concentration of $4 \times 10^4$ cells in 100 mL of propagation medium per well. Following blocking with MPBS,
single phage supernatants were added to each well and incubated for 1 hour at RT. After washing with PBS, binding of phage-scFvs was revealed with HRPconjugated anti-M13 antibody (Amersham Biosciences, Pittsburg, PA) in MPBS, using tetramethylenbenzidine (Sigma Aldrich, Chicago, IL) as substrate. Phage-scFvs whose binding to the target cell line was at least three fold higher than that observed with an unrelated phage and higher than 0.3 units were defined as positive. Specific binding to SR-B1 was confirmed by a similar procedure of whole-cell phage-ELISA on CHO cells stably transfected with human SR-B1 (CHO/SR-B1). Parental CHO cells were used as negative control.

Heavy and Light chain amino acid sequences from phage8, phage81, phage 15, phage 151, phage 152 and phage6 are shown in Figures 1 and 2, respectively.

Example 3: Conversion of scFv into full human IgG

mAbs 8, 81, 15, 151, 152 and 6 were generated by subcloning the variable regions from the different phages specifically binding CHO/SR-B1 into two eukaryotic vectors for the expression of heavy (immunoglobulin G4 [IgG4] isotype) and light chains, as previously described (Persic, L., A. Roberts, J. Wilton, A. Cattaneo, A. Bradbury, and H. R. Hoogenboom. 1997. An integrated vector system for the eukaryotic expression of antibodies or their fragments after phage display libraries. Gene 10:9-18.). These two plasmids were cotransfected into HEK-293 EBNA cells with Lipofectamine (Invitrogen), and whole human IgG4 was purified from culture medium with Hi-Trap protein A columns (Amersham Biosciences). HEK-293 EBNA cells were grown in DMEM with 10% FBS, 1% nonessential amino acids, and G418 at 0.25 mg/ml.

Example 4: mAb 6, 8, 81, 15, 151 and 152 are capable of preventing HCVcc infection in vitro of human hepatoma cells HuH7.5

Neutralization activity of anti-SR-B1 mAbs was tested using HCVcc virus generated from plasmids carrying HCV (J6/JFH1-genotype 2a) genomic cDNA.

HuH 7.5 cells were seeded in 24-well plates (2.5 x 10^4 cells/well) in DEMEM-10% FBS. For neutralization assay, the cells were preincubated for 1h with 250 μL of medium with increasing concentrations of antibodies. After 1h HCVcc containing supernatant was added at a Multiplicity of Infection (m.o.i.) of 0.1 and the mixture was incubated for 3h. After 3h the virus was removed and the medium was replaced with fresh medium containing the mAb at the same concentration used in the pre-incubation. The infection was allowed to proceed for 3 days. After 3 days RNA was extracted and quantified (RNeasy mini kit from Qiagen). The
TaqMan was performed in 98-well plate using 50 ng of total RNA. The total volume of each sample was 25 μL (One-Step RT-PCR Master mix Reagent - Applied Biosystems). The primers and probe used in experiments were:

a) HCV-JFH1 Taqman probe, 5'-6FAM-AAA GGA CCC AGT CTT CCC GGC AA-TAMRA-3' (SEQ ID NO: 49)

b) HCV-JFH1-S147, 5'-TCT GCG GAA CCG GTG AGT A-3' (Forward Primer; SEQ ID NO: 50)

c) HCV-JFH1-A221, 5'-GGG CAT AGA GTG GGT TTA TCC A-3' (Reverse Primer, SEQ ID NO: 51)

Reactions were carried out in four stages:

- 50°C for 30 min for reverse transcription
- 95°C for 10 min to activate the AmpliTaq.
- 95°C for 15 sec for denaturation.
- 60°C for 60 sec for annealing and extension. The last 2 steps were repeated 40 times.

All treatments were performed in duplicate and the error bars represent the standard.

As shown in Figure 4, mAbs 6, 8, 15, 151, and 152 are able to reduce infection of HuH7.5 cell by HCVcc.

A dose response of the inhibitory activity of mAbs 6, 8, 81, 15, 151, and 152 was performed to calculate the activity of the antibodies (EC50). The experiment was performed as described above.

In all cases, HCVcc infection was reduced in dose-dependent manner. Figure 5 shows the inhibitory curves of mAbs 6, 8, and 151. In table 1 are reported the inhibitory activities of all six mAbs.

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<td>0.35</td>
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<tr>
<td>mAb6</td>
<td>0.48</td>
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<td>mAb8</td>
<td>0.63</td>
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<td>mAb81</td>
<td>0.62</td>
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<td>mAb152</td>
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<td>mAb15</td>
<td>0.54</td>
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Table 1, EC50 values were estimated according to a nonlinear regression curves fitted to experimental data with SigmaPlot program.

Example 5: mAb8 inhibits infection of HCV in AlbUPA-SCID chimeric mice
uPA-SCID mice were transplanted with cryopreserved primary human hepatocytes (BD Biosciences). HCV RNA in mouse plasma was quantified using a commercial real-time PCR (Roche TaqMan48). Depending on the dilution of the plasma, the detection limit of this assay ranged from 375 IU/ml to 1,500 IU/ml.


Chimeric mice were injected intraperitoneally (IP) with 400 µg anti-SR-BI mAb on days -1, 1, 5, 8 and 12. On day 0, all animals received an IP injection containing 5x10^4 IU of H77 virus (genotype 1a). The viral dose is the lowest amount of virus needed to induce a robust infection in all injected chimeric mice. Control animals were injected with the virus but were not treated with the antibody.

HCV infection was measured by quantitative PCR on total RNA extracted from blood. Values below the limit of detection (LOD) were arbitrarily set at 375 IU/ml. As shown in Figure 6 mAb8 prevents HCV infection in vivo. Thus, antibodies against SRB1 can prevent infection of HCV virus.

**Example 6: mAb8 prevent virus spread and amplification when they are administered after challenge**

Inhibition of HCV spread and amplification in AlbUPA-SCID chimeric mice was measured by an experiment of post-exposure therapy.

Chimeric mice were injected with 10^4 or 10^5 IU of H77 virus on day 0. Three days later, plasma was harvested and HCV RNA was quantified. HCV-positive animals were divided in different groups to receive 5 doses of 400 µg of mAb8 (days 3, 5, 7, 10 and 12), or no antibody as a control. All animals were bled on a weekly basis and the evolution of HCV RNA was monitored via RT-qPCR. As shown in Figure 7, all control animals experienced a rapid increase in viral load during the first two weeks after inoculation. In contrast, HCV RNA remained detectable in mAb8 treated animals but was several logs below the level of untreated animals and, in some cases, below the linear range of the RT-PCR test (+, < 375 IU/ml) and was therefore not quantifiable. 1 out of 2 animals in the mAb8 treated group remained at the limit of detection of the RT-qPCR test until the end of the observation (day 21).
Thus, as shown in Figure 7 mAb8 inhibits virus spread and amplification \textit{in vivo} when it is administered after HCV infection.

**Example 7: Determination of apparent affinities of mAb6, 8, 15 and 151**

The apparent affinity of the antibodies was determined as follows. Human hepatoma HepG2 cells were grown in Dulbecco's modified essential medium (DMEM; Invitrogen) supplemented with 10% FBS. 7.5 x 10^5 cells were incubated for 3 hours at room temperature with different amounts of anti-SR-BI mAbs in phosphate-buffered saline (PBS)-0.2% bovine serum albumin (BSA)-HEPES at 10 mM (fluorescence-activated cell sorter [FACS] buffer). Anti-SR-BI MAb binding was revealed by Fc (gamma) fragment specific, allophycocyanin-conjugated goat anti-human IgG. As a control, isotype-matched human IgG4 was used. FACS acquisitions and analysis were performed with a FACScalibur (Becton Dickinson) and CellQuest software.

The apparent affinities of anti-SRBI mAbs 6, 8, 15, and 151 are shown in Figure 8.
CLAIMS

1. An antibody or fragment thereof, which specifically binds to the scavenger receptor class B type 1 (SR-B1).

2. The antibody or fragment thereof of claim 1, wherein said antibody or fragment thereof is capable of specifically binding to the same SR-B1 epitope that also a reference antibody is capable of specifically binding to which comprises a heavy chain with a VH domain and a light chain with a VL domain, wherein the VH and VL domains respectively have an amino acid sequence of any of i) through viii):

   VH-domain (SEQ ID NO)  VL-domain (SEQ ID NO):
   i) 7  8
   ii) 11  12;
   iii) 5  6;
   iv) 3  4;
   v) 1  2; and
   vi) 9  10.

3. The antibody or fragment thereof of claim 1 or 2, wherein
   (i) the heavy chain of said antibody or fragment thereof comprises a CDR3 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 19, 23, 17, 15, 13 and 21; wherein said CDR3 domain of the heavy chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion; and
   (ii) the light chain of said antibody or fragment thereof comprises a CDR3 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 20, 24, 18, 16, 14 and 22; wherein said CDR3 domain of the light chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion.

4. The antibody or fragment thereof of any of claims 1 - 3, wherein the antibody or fragment thereof comprises a pair of polypeptides that are selected from the group of polypeptide pairs consisting of:

   SEQ ID NO: 19, SEQ ID NO: 20;
SEQ ID NO: 23, SEQ ID NO: 24;
SEQ ID NO: 17, SEQ ID NO: 18;
SEQ ID NO: 15, SEQ ID NO: 16;
SEQ ID NO: 13, SEQ ID NO: 14; and
SEQ ID NO: 21, SEQ ID NO: 22;
wherein each polypeptide pair is respectively a CDR3 domain of the heavy chain and a CDR3 domain of the light chain of said antibody or fragment thereof; wherein each CDR3 domain of the light and/or heavy chain optionally comprises one amino acid substitution, deletion or addition.

5. The antibody or fragment thereof of any of claims 1-4, wherein said antibody or fragment thereof additionally comprises one or more of the following:

(i) the heavy chain of said antibody or fragment thereof comprises a CDR1 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 31, 35, 29, 27, 25 and 33; wherein said CDR1 domain of the heavy chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion;

(ii) the light chain of said antibody or fragment thereof comprises a CDR1 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 32, 36, 30, 28, 26 and 34; wherein said CDR1 domain of the light chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion;

(iii) the heavy chain of said antibody or fragment thereof comprises a CDR2 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 43, 47, 41, 39, 37 and 45; wherein said CDR2 domain of the heavy chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion; and

(iv) the light chain of said antibody or fragment thereof comprises a CDR2 domain selected from a group of amino acid sequences consisting of SEQ ID NO: 44, 48, 42, 40, 38 and 46; wherein said CDR2 domain of the light chain may optionally comprise a single amino acid substitution, deletion, modification and/or insertion.

6. The antibody or fragment thereof of any of claims 1-5, wherein
(i) the VH domain of the heavy chain of said antibody or fragment thereof comprises the amino acid sequence selected from SEQ ID NO: 7, 11, 5, 3, 1, and 9; wherein said VH domain may optionally comprise between 1 and 10 single amino acid substitutions, deletions, modifications and/or insertions; and

(ii) the VL domain of the light chain of said antibody or fragment thereof comprises the amino acid sequence selected from SEQ ID NO: 8, 12, 6, 4, 2 and 10; wherein said VL domain may optionally comprise between 1 and 10 single amino acid substitutions, modifications, deletions and/or insertions.

7. The antibody or fragment thereof of any of claims 1-6, wherein said VH domain and VL domain together comprise between 0 and 15 single amino acid substitutions, deletions and/or insertions with the proviso that said substitutions, deletions, modifications and/or insertions are not located within the CDR1, CDR2 or CDR3 domains of the heavy chain or light chain.

8. The antibody or fragment thereof of any of claims 1-7, wherein said antibody or fragment thereof binds to CHO cells stably expressing said SR-B1 receptor with a KD of less than 10 nM.

9. The antibody or fragment thereof of any of claims 1-8, wherein said antibody or fragment thereof is capable of inhibiting a HCV virus to bind to the SR-B1 receptor.

10. The antibody or fragment thereof of any of claims 1-9, wherein said antibody or fragment thereof is capable of inhibiting transmission of HCV from an HCV infected mammalian cell to another cell.

11. The antibody or fragment thereof of any of claims 1-10, wherein said antibody is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody, a human antibody, a single-chain antibody, a diabody, a tetrabody, a nanobody, a chimeric antibody, and a deimmunized antibody.

12. The antibody or fragment thereof of any of claims 1-9, wherein said fragment is selected from the group consisting of Fab, F(ab')2, Fd, Fv, single-chain Fv, and disulfide-linked Fvs (dsFv).
13. Polynucleotide encoding the VH and/or VL domain of the antibody or fragment thereof according to any of claims 1-12.

14. Cell comprising the antibody or fragment thereof according to any of claims 1-12 and/or the polynucleotide according to claim 13.

15. Pharmaceutical composition comprising the antibody or fragment thereof according to any one of claims 1-12 and/or the polynucleotide according to claim 12 and further comprising one or more pharmaceutically acceptable diluents; carriers; excipients; fillers; binders; lubricants; glidants; disintegrants; adsorbents; adjuvants and/or preservatives.

16. Antibody according to any one of claims 1-12, the polynucleotide according to claim 13 or the pharmaceutical composition according to claim 15 for the preparation of a medicament for the treatment of an HCV infection.
Figure 1

CLUSTAL W (1.83) multiple sequence alignment

\( \text{\textbackslash leftarrow CDR1} \rightarrow \text{\textbackslash leftarrow CDR2} \)

H8  QLQLQESGPGGLVPSETLSTLCNVSGVSISD--DLWSWIRQSPGKLEWIGNIYYS-GIT
H81 QLQLQESGPGGLVPSETLSTCTVGGSISD--DLWSWIRQPPGKLEWIGNIYYS-GIT
H15 EVQVLQSGAEVKPGSSVKVSCKASGGFTSN--YGFSSWVRQAPQQGLEWWMGIGIPFDTT
H151 QVQVLQSGAEVKPGSSVKVSCKASGGFTSN--YGFSSWVRQAPQQGLEWWMGIGIPFDTT
H152 QVQVLQSGAEVKPGSSVKVSCKASGGFTSD--YGFSSWVRQAPQQGLEWWMGIGIPFDTT
H6  QLQLQESGPGGLVPSETLSTLCNVSGSSSSTSSTYWGWRPPGKLEWIGNIYNS-NT

\( \text{\textbackslash leftarrow CDR3} \rightarrow \)

H8  DYSPSLKSRLRMSVDSTTNQPSLRLSSVTAADTAVYFCARL--TLRG--FQNWQGTLV
H81 DYSPSLKSRTVISVTDKNQFSLKLSSVTAADTAVYCARL--TLRG--FQNWQGTLV
H15 NYAQNPQGRVTITADESTSTYMEELSSLRSEDTAVYCARDFPDPDTGYYAPEIWGQGTLV
H151 NYAQNPQGRVTITADESTSTYMEELSSLRSEDTAVYCARDFPDPDTGYYAPEIWGQGTLV
H152 NYAQNPQGRVTITADESTSTYMEELSSLRSEDTAVYCARDFPDPDSAGYAPEIWGQGTLV
H6  YYNPSLRSVMSVTDKNQFSLKLTSVTAADTAMYYCARQ--EGWDPNFDXWGRTGLV

\* \* \* \* \* \* \* \* \* \* \* \*

H8  TVSS
H81 TVSS
H15 TVSS
H151 TVSS
H152 TVSS
H6  TVSS

\* \* \* \* \* \* \*
Figure 2

CLUSTAL W (1.83) multiple sequence alignment

L8 QSVLTQPPSASGTPGQRVTISCSSGSSSNIGSS-TVNYWQQLPGTAPKLILICNNQRPSCV
L81 QSVLTQPPSASGTPGQRVTISCSSGSSSNIGSS-TVNYWQQLPGTAPKLILICNNQRPSCV
L15 QSAALTQASVGSPQGQSIASCAATGGATAFNPVYYNYQRRPGKAPRLLIYVDVSNRPSCV
L151 QSAALTQASVGSPQGQSIASCAATGGATAFNPVYYNYQRRPGKAPRLLIYVDVSNRPSCV
L152 QSAALTQASVGSPQGQSIASCAATGGATAFNPVYYNYQRRPGKAPRLLIYVDVSNRPSCV
L6 LPVLQTPPSASGTPGQRVTISCSSGSSSN-YVSWYQQLPGTAPKLILYRMNRRPSCV

L8 PDRFGSGSKGTSAISGLQSSEADYFCAAWDDSPNGVIFGGGTKLTLV
L81 PDRFGSGSKGTSAISGLQSSEADYFCAAWDDSPNGVIFGGGTKLTLV
L15 SDRFGSGSKGTSAITISGLQAEADDYYCPSYADN--NNVFQGGGTKLTLV
L151 SDRFGSGSKGTSAITISGLQAEADDYYCPSYADN--NNVFQGGGTKLTLV
L152 SDRFGSGSKGTSAITISGLQAEADDYYCPSYADN--NNVFQGGGTKLTLV
L6 PDRFGSGSKGTSAISGLRSSEADYFCAAWDDSDSSWVGGGTKLTLV
**Figure 4**

![Bar chart showing % infection across various treatments.](Image)

**Figure 5**

![Line graph showing % infection vs. concentration (ng/mL) across different mAbs.](Image)
Figure 8
INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/00Q157

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2006/005465 AI (LETTI SPA ISTITUTO DI RICERCHE [IT]; CORTESE RICCARDO [IT]; LUZZAGO AL) 19 January 2006 (2006-01-19) claims 8, 12-13; figures 3-8; examples 1-5; sequences 1-4</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
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  - "O" document referring to an oral disclosure, use, exhibition or other means
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  - "Z" document member of the same patent family

Date of the actual completion of the international search
24 March 2011

Date of mailing of the international search report
04/04/2011

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer
Luyten , Kattie
### DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CATANESE MARIA TERESA ET AL: “High-avidity monoclonal antibodies against the human scavenger class B type I receptor efficiently block hepatitis C virus infection in the presence of high-density lipoprotein”, JOURNAL OF VIROLOGY, vol. 81, no. 15, August 2007 (2007-08), pages 8063-8071, XP002629861, ISSN: 0022-538X whole document, especially the Abstract; page 8065; page 8069, right-hand column, paragraph 3; page 8070, last phrase of Discussion; Figures 1, 5-6</td>
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### Box No. 1  Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
   
   a. **(means)**
   - [X] on paper
   - [X] in electronic form
   
   b. **(time)**
   - [X] in the international application as filed
   - [X] together with the international application in electronic form subsequently to this Authority for the purpose of search

2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
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