The invention relates to monoclonal antibodies, in particular against a peptide of the BAMB1 protein, as well as the uses thereof and methods comprising same. Preferably, the antibodies are used for the treatment of autoimmune diseases. Specification includes a Sequence Listing.
Fig. 1 A

B6  KO

54 kDa  54 kDa

27 kDa  27 kDa

mAb B101-37  mAb B143-14
(IgG1)  (IgM)

Fig. 1 B

Hum

54 kDa

27 kDa

B101-37
Fig. 2 B

B

Not Stimulated

Not Stimulated

54 kDa

54 kDa

27 kDa

27 kDa

21 kDa

21 kDa

BAMBI

N-Ras

CD3 + CD28

CD3 + CD28
Fig. 4 A

A

Clinical Severity

**

IgG1-C 0.3 2

B101-37 mg/week

Fig. 4 B

Radiological Score (8 weeks)

**

Edema

Joint Space Narrowing

**

Juxta-Articular Osteopenia

Bone Erosion

IgG1-C 0.3 2

B101-37 mg/week
Fig. 5 A

Psoriasis

Day

100 80 60 40 20 0

% of Thickening

Arthritis

Days

B10RIII

B10RIII.KO

Clinical Severity

B10RIII + B101.37

*** ** *
Fig. 5 B

B10R III Mannan
B101-37

B10R III.KO Mannan

B10R III Mannan

B10R III Not Treated
Fig. 7

A

Psoriasis

- WT + IgG1 IC
- KO + IgG1 IC
- WT + B101-37

Clinical Score

Day

B

WT

WT Imiq. + IgG1 IC

WT Imiq. + B101-37

KO Imiq. + IgG1 IC

Epidermal Thickness  Dermal Thickness

Increase vs. Control

WT + IgG1 IC

WT + B101-37

KO + IgG1 IC

WT + B101-37

KO + IgG1 IC
MONOClonAL ANTIMIBES AGAINST BAMB1 AND USe FOR THE TREATMENT OF INFAMMATORY DISEASES

[0001] The present invention relates to antibodies against the BAMB1 (BMP and Activin Membrane Bound Inhibitor) protein and the use thereof for the treatment and prevention of inflammatory diseases. Therefore, the present invention falls within the field of medicine.

STATE OF THE ART

[0002] Under the name “autoimmune or chronic inflammatory” disease, there are currently more than 100 nosological entities that globally affect approximately 10% of the world’s population (Shoenfeld Y et al. 2008 J Autoimmun 31:325). Autoimmune diseases are the result of the action of multiple environmental agents on a specific genetic and/or epigenetic background. The accumulation of all of these factors in an individual alters the regulation of the immune response, causing aberrant immune responses against external agents or the reaction of the system against itself. The consequence is the development of autoimmune and/or autoimmune diseases.

[0003] Among the autoimmune diseases, rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, spondyloarthritides and systemic lupus erythematosus are included, which share a series of etiopathogenic mechanisms, as well their response to similar or equal immunomodulatory or immunosuppressive treatments. RA is the most common autoimmune rheumatic disease.

[0004] Especially involved in autoimmune-based diseases are CD4+ T lymphocytes, a term that refers to multiple effector (TH1, TH2, TH17, TFH) or regulatory (Treg, Tr1) sub-populations, basically defined by the cytokine patterns they secrete (Zhu J et al. 2010 Annu Rev Immunol 28:445; Zygmont B et al. 2011 Adv Immunol 109:159). Alterations in the control of mechanisms that regulate the differentiation and activation of the different functional CD4+ T lymphocytes sub-populations have been implicated in the development of immune-based pathologies. In this sense, some severe autoimmune diseases have been associated with the uncontrolled increase in the differentiation and/or functionality of TH17 lymphocytes (Rohn T A et al. 2006 Eur J Immunol 36:2857; Kebir H et al. 2007 Nat Med 13:1173; multiple sclerosis or rheumatoid arthritis, among others) or TFH (Tangye S G et al. 2013 Nat Rev Immunol 13:412; systemic lupus erythematosus). On the other hand, the reduction in the number and/or suppressive activity of Treg cells is critical in IPEX syndrome, seen in patients with foxp3 gene mutations (Bennett C L et al. 2001 Nat Genet 27:20) or in securin-deficient mice (Khattri R et al. 2003 Nat. Immunol 4:337).

[0005] For the treatment of autoimmune diseases, immunosuppressive drugs with a low degree of specificity have been used, and therefore they have multiple adverse side effects. More recently, cytokine-specific monoclonal antibodies or soluble receptors of said factors (globally known as biological drugs) have been used. These compounds have an advantage in that they have a high degree of specificity and the results obtained from them have been very positive. However, the use of biological drugs is not exempt from serious side effects, and furthermore, resistance appearance to the same is common, which forces the treatments to be stopped. Therefore, it is essential to develop highly specific therapies using monoclonal antibodies against new biological targets.

DESCRIPTION OF THE INVENTION

[0006] The present invention shows the use of monoclonal antibodies against BAMB1 for the treatment and prevention of autoimmune diseases, the same being exemplified with recognized models of arthritis, psoriasis and colitis.

[0007] In the first aspect the present invention relates to a monoclonal antibody that specifically recognizes an amino acid sequence that comprises a peptide with at least an 80% identity with SEQ ID NO: 1, preferably an 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, wherein the length of said amino acid sequence is between 15 and 30 amino acids (15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 amino acids), preferably 25 amino acids.

[0008] The term “antibody”, as used in the present invention, relates to immunoglobulin molecules and immunologically active portions (or fragments) of immunoglobulin molecules. That is, it refers to molecules that specifically bind (are immunoreactive) to an antigen, such as, for example, a peptide or a protein (an immunogen or epitope). The term “antibody” comprises monoclonal antibodies and polyclonal antibodies, and in the present invention the antibody is monoclonal, and it refers to an antibody that is intact or to immunologically active fragments of the same, and includes human, humanized and non-human, recombinant, chimeric and synthetic antibodies. In the context of this invention, the term antibody refers to the immunoglobulin that the animal or a hybrid cell has specifically synthesized against the sequence described in the first aspect of the present invention.

[0009] Examples of portions or fragments of immunologically active immunoglobulins include fragments F(ab) and F(ab')2, which can be generated by treating the antibody with an enzyme, such as pepsin.

[0010] “Monoclonal antibodies” are homogeneous populations of identical antibodies, produced by a hybridoma, that is, a hybrid cell that is the product of the fusion of a clone of B lymphocytes descendant of a single and unique stem cell and a plasma cell tumor, which are directed against a specific site or antigenic determinant. The method for obtaining monoclonal antibodies of the invention can be carried out according to conventional methods known in the state of the art. Optionally, said antibodies can be purified by conventional means, such as affinity chromatography, protein A-Sepharose, hydroxyapatite chromatography, gel electrophoresis or dialysis.

[0011] As is known by a person skilled in the art, there are five isotypes or main classes of immunoglobulins: immunoglobulin M (IgM), immunoglobulin D (IgD), immunoglobulin G (IgG) (which in turn have the following subtypes in mice: IgG1, IgG2a, IgG2b and IgG3), immunoglobulin A (IgA) and immunoglobulin E (IgE). The monoclonal antibodies included in the present invention are: clone B101-37 (IgG1) and clone B143-14 (IgM).
[0012] In a preferred embodiment of the first aspect of the invention, the antibody specifically recognizes the sequence SEQ ID NO: 1: murine BAMBI (109-133) peptide:

LEAVLSPKSEASQQQRVHDSSR

SEQ ID NO: 2: human BAMBI peptide (109-133):
LEAVLSPKSEASQQQRVHDSSR.

[0013] A more preferred embodiment of the first aspect of the invention relates to the antibody wherein said antibody is expressed from the cell line (hybridoma) deposited in an international authority.

[0014] In a specific embodiment the antibody can comprise a detectable label. An even more preferred embodiment of the first aspect of the invention relates to the antibody wherein said antibody is conjugated with a fluorochrome, an enzyme, a gold particle, a nanoparticle, a peptide or another protein of interest, for example a protein or peptide ligand of a receptor.

[0015] The term “detectable label” or “tag” in the present invention refers to a molecular tag that allows for the detection, location and/or identification of a molecule to which is bound, by means of suitable detection methods and equipment, either by spectroscopic, photochemical, biochemical, immunological or chemical means. Examples of detectable labels for marking compounds include, but are not limited to, radioactive isotopes, enzymatic substrates, cofactors, ligands, chemoluminescent agents, fluorophores, enzymes (for example peroxidase), receptors and combinations thereof. In a specific embodiment the antibody is marked with biotin, avidin, streptavidin, alkaline phosphatase or horseradish peroxidase (HRP). Methods for marking and guiding the selection of suitable labels for different purposes are known by a person skilled in the art.

[0016] The monoclonal antibody can be biochemically altered, by genetic manipulation or it can be synthetic; it may also lack portions.

[0017] In a more preferred embodiment of the first aspect of the invention, the antibody specifically comprises a heavy chain comprising the sequence SEQ ID NO: 3 and/or a light chain comprising the sequence SEQ ID NO: 4.

[0018] In another more preferred embodiment of the first aspect of the invention, the antibody comprises a heavy chain which comprises the sequence SEQ ID NO: 5 and/or a light chain which comprises the sequence SEQ ID NO: 6.

[0019] In a preferred embodiment, the antibody is the antibody in the present invention named clone B101:37 (IgG1, K anti-BAMBI) and/or clone B143-14 (IgM, K anti-BAMBI).

[0020] In a specific embodiment, the present invention also relates to a gene construction that is able to generate the antibody of the first aspect of the present invention.

[0021] The term “identity”, as used in this specification, refers to the proportion of identical amino acids between two compared peptides or proteins. The methods for comparing sequences are known in the state of the art, and include, but not limited to, the programs BLASTP or BLASTN, ClustalW and FASTA. We can consider that peptides or proteins with percent identities of at least 80% will maintain the same properties as the sequence SEQ ID NO: 1.

[0022] “Specific recognition”, “specific binding” is understood as the binding (reaction, interaction or specific binding) between the antibody of the invention and the sequence described in the first aspect of the invention.

[0023] A second aspect of the present invention relates to an antiserum comprising the antibody of the first aspect of the invention.

[0024] The term “antiserum” relates to a serum obtained after the immunization of an animal with an immunogen. The antiserum comprises specific antibodies of said immunogen generated after the immune response produced in the animal. In the context of the present invention, the immunogen is the peptide with at least 80% identity with the sequence SEQ ID NO: 1 (preferably 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100%), preferably SEQ ID NO: 1 or SEQ ID NO: 2, and the antiserum comprises specific monoclonal antibodies generated against said sequence.

[0025] A third aspect of the present invention relates to a cell that expresses the antibody of the first aspect of the invention (hybridoma).

[0026] A fourth aspect of the present invention relates to the use of the antibody of the first aspect of the invention or of the antiserum of the second aspect of the invention for the inhibition of BMP and Activin Membrane Bound Inhibitor (BAMBI).

[0027] A fifth aspect of the present invention relates to the use of the antibody of the first aspect of the invention or of the antiserum of the second aspect of the invention for the manufacture of a medicament. Alternatively, the present invention further relates to the antibody of the first aspect of the invention or of the antiserum of the second aspect of the invention, for use as a medicament.

[0028] A sixth aspect of the present invention relates to the use of the antibody of the first aspect of the invention or of the antiserum of the second aspect of the invention for the manufacture of a medicament for the treatment or prevention of autoimmune diseases. Alternatively, the present invention also relates to the antibody of the first aspect of the invention or of the antiserum of the second aspect of the invention for use as a medicament for the treatment or prevention of autoimmune diseases.

[0029] In the present invention the term “autoimmune disease” is understood as a disease in which the cells of the immune system trigger a chronic inflammatory response in one or several tissues of the individual, causing the deterioration or even destruction thereof. In the present invention, the terms “autoimmune disease” and “chronic inflammatory disease” are used interchangeably.

[0030] The autoimmune disease is preferably autoimmune arthritis, inflammatory bowel disease, psoriasis, spondyloarthropathy or systemic lupus erythematosus. In an even more preferred embodiment the autoimmune arthritis is recent-onset arthritis or rheumatoid arthritis.

[0031] For this reason, in a more preferred embodiment of the sixth aspect of the invention, the autoimmune diseases are chosen from the list consisting of: autoimmune arthritis, spondyloarthropathy, psoriasis, systemic lupus erythematosus, and inflammatory bowel disease. Preferably, the inflammatory bowel disease is ulcerative colitis or Crohn’s disease.

[0032] In the present invention the term “autoimmune arthritis” include both the terms “Rheumatoid Arthritis” and “Undifferentiated Arthritis”, regardless of whether it is recent-onset or well-established arthritis.

[0033] In the present invention, “Recent-Onset Arthritis Disability” (ROAD) (or early arthritis) is a disease consist-
ing of inflammation of at least one joint, in less than one year of development, which complies with the pre-established criteria by the American College of Rheumatology (ACR) and EULAR of “Rheumatoid Arthritis or RA” (Aletaha, Neogi et al. Ann Rheum Dis 2010; 69:1580-1588) or, without complying with said criteria, does not comply with criteria of other autoimmune, degenerative or metabolic diseases that may explain the symptoms. This last case is termed “Undifferentiated Arthritis” (UA) which, in many cases, if left untreated, ends up becoming RA. In this invention the terms ROAD, RA or UA refer to a chronic and progressive systemic autoimmune disease which causes chronic inflammation, primarily in the joints, and which, given the progressive nature thereof, causes the destruction thereof, resulting in deformation and loss of functional ability thereof. Furthermore, this disease can cause extrarticular alterations in different organs.

[0034] In the present invention the term “spondyloarthritis” is understood as any autoimmune disease, axial and/or peripheral, which meets the classification criteria of the Assessment of SpondyloArthritis International Society (ASAS) (Rudwaleit et al. Ann Rheum Dis 2011; 70:25-31).

[0035] In the present invention, “systemic lupus erythematosus” is understood as any systemic autoimmune disease defined by the criteria of the American College of Rheumatology (Tan et al. Arthritis Rheum• 1982; 25:1271-1277).

[0036] In the present invention, the term “inflammatory bowel disease” or “IBD” refers to chronic inflammation of the intestine in an individual, wherein said inflammation is due to the very immune system of the individual. The two most common forms are ulcerative colitis and Crohn’s disease. Therefore, in a preferred embodiment, the autoimmune disease is ulcerative colitis or Crohn’s disease.

[0037] In the present invention, “psoriasis” is understood as any skin disease that is characterized by an improper functioning of the immune system which causes an excessive production of skin cells. This disease causes the formation of red bumps covered by dry scales. Furthermore, excessive cell production also causes the infiltration of white blood cells on the skin. Generally, injuries are located in areas with the greatest friction, such as, although not limited to, the elbows, knees or groin area.

[0038] A seventh aspect of the present invention relates to a pharmaceutical composition comprising the monoclonal antibody of the first aspect of the invention or of the antisera of the second aspect of the invention.

[0039] In this specification, the term “pharmaceutical composition” refers to any substance used for the diagnosis, prevention, alleviation, treatment or cure of a disease in a human being or in animals. The pharmaceutical composition of the invention can be used alone or in combination with other pharmaceutical compositions. In a preferred embodiment, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier or excipient.

[0040] The term “excipient” refers to a substance which helps the absorption of the pharmaceutical composition, comprising the antibody of the invention, stabilizes said pharmaceutical composition or helps in the manufacture thereof in the sense of giving it consistency, form, flavor or any other special functional characteristic. Thus, excipients could have the function of keeping the ingredients bound together, such as for example starches, sugars or celluloses, a sweetening function, a colorant function, a protection function, such as for example isolating it from the air and/or moisture, a filler function for a tablet, capsule or any other form of formulation, such as for example dibasic calcium phosphate, a disintegrating function to facilitate the dissolution of the components and their absorption, without excluding other types of excipients not mentioned in this paragraph.

[0041] A “pharmaceutically acceptable carrier” (or “pharmacologically acceptable”) refers to any substance, or combination of substances, known in the pharmaceutical sector, used in the manufacture of pharmaceutical forms of administration and includes, but is not limited to, solids, liquids, solvents or surfactants. The carrier can be an inert substance or have a similar action to any of the compounds of the present invention, having the function of facilitating the incorporation of the drug as well as other compounds, allowing for an improved dosage and administration or providing consistency and form to the pharmaceutical composition. When the dosage form is liquid, the carrier is the diluent. The term “pharmacologically acceptable” refers to the fact that the compound referred to is allowed and evaluated so that it does not cause harm to the organisms to which it is administered.

[0042] The pharmaceutical composition of this invention can be facilitated through any route of administration, and as such, said composition shall be formulated in the pharmaceutical form suitable to the chosen route of administration.

[0043] An eighth aspect of the present invention relates to the in vitro use of the antibody of the first aspect of the invention or of the antisera of the second aspect of the invention for the screening of drugs, preferably drugs for the treatment or prevention of autoimmune diseases. The autoimmune diseases are preferably chosen from a list that consists of: autoimmune arthritis, spondyloarthritits, psoriasis, systemic lupus erythematous, and inflammatory bowel disease. More preferably the inflammatory bowel disease is ulcerative colitis or Crohn’s disease.

[0044] The term “in vitro” relates to the fact that the method of the invention is done outside of the body of the subject. That is, it is done on a biological sample of a subject.

[0045] In the present invention, the term “biological sample” refers to any sample that allows for the screening of drugs, and includes, but is not limited to, biological fluids or tissues of an individual, obtained by means of any method known by a person skilled in the art that serves for said end. For example, the biological sample could be, but is not limited to, a fluid sample, such as blood, plasma, serum or tissue. The biological sample of the present invention can be fresh, frozen, fixed or fixed and paraffin embedded.

[0046] In the present invention the terms “subject” and “individual” are used interchangeably. As used in the present document, the term “subject” or “individual” refers to all animals classified as mammals and includes, but is not limited to, farm and domestic animals, primates and humans, for example human beings, non-human primates, cows, horses, pigs, sheep, goats, dogs, cats or rodents. Preferably, the subject is a human being, male or female, of any age or race.

[0047] A ninth aspect of the present invention relates to a method for obtaining a monoclonal antibody that recognizes an amino acid sequence comprising a peptide with at least an 80% identity with the sequence SEQ ID NO: 1, comprising:

[0048] a. obtaining previously extracted serum from a non-human animal immunized with a recombinant pro-
tein comprising an amino acid sequence comprising a peptide with at least an 80% identity with the sequence SEQ ID NO: 1;

[0049] b. obtaining a hybridoma from step a) which generates specific monoclonal antibodies against an amino acid sequence comprising a sequence with at least an 80% identity with SEQ ID NO: 1.

[0050] In a more preferred embodiment of the ninth aspect of the invention, the method further comprises a step (c) of isolating the monoclonal antibody from the hybridoma generated in step (b).

[0051] In another more preferred embodiment of the ninth aspect of the invention, in step (a) the amino acid sequence is the sequence SEQ ID NO: 1 or SEQ ID NO: 2.

[0052] In an even more preferred embodiment of the sixth aspect of the invention, the non-human animal is a mammal that is chosen from a list consisting of pigs, chimpanzees, mice, rats, rabbits and guinea pigs.

[0053] A tenth aspect of the present invention relates to a kit and/or device, hereinafter shall be referred to “kit of the invention” or “device of the invention”, comprising the antibody, the antisera, the cell, as described in the invention, and/or any combination thereof.

[0054] The kit and/or device of the invention can further comprise, but is not limited to, probes, buffers, enzymes, agents for preventing contamination, etc. On the other hand, the kit can include all of the necessary supports and containers for the setup and operation thereof. The kit can further contain other proteins, including antibodies or antigens, which serve as positive and negative controls. Preferably, this kit further comprises the instructions for detecting the BAMBI protein, preferably by means of an immunohistochemical assay, more preferably by means of ELISA, Western blot or immunofluorescence.

[0055] Optionally, the antibody of the invention in the kit is marked or immobilized.

[0056] The term “marked”, as used in the present description, refers to the fact that the antibody is conjugated with a label. A high number of labels that can be conjugated to an antibody are known in the state of the art. Examples of labels that can be used for marking an antibody are, without limitation, radioisotopes (for example, 32P, 35S or 3H) fluorescent or luminescent markers [for example, fluorescein isothiocyanate (FITC), rhodamine, Texas red, phycoerythrin (PE), allophycocyanin, 6-carboxyfluorescin (6-FAM), 6-carboxy-2′,7′-dimethoxy-4′,5′-dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2′,4′,7,4′,7′-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N′,N′-tetracyanethyl-6-carboxyrhodamine (TAMRA)]; antibodies, fragments F(ab)2], affinity labels [for example, biotin, avidin, aagarose, bone morphogenetic protein (BMP) hapten], enzymes or enzyme substrates [for example, alkaline phosphatase (AP) and spicy horseradish peroxidase (HRP)].

[0057] The term “immobilized”, as used in the present description, refers to the fact that the antibody of the invention can be bound to a support without losing its activity. Preferably, the support can be the surface of an array (for example, a nylon array), a microtitrator plate (for example, with 96 wells) or a similar plastic support, or beads (spheres, for example, agarose spheres or small superparamagnetic microspheres made up of biodegradable arrays).

[0058] Another aspect of the invention relates to the in vitro use of the kit of the invention for detecting a peptide with at least an 80% identity with SEQ ID NO: 1. In a more preferred embodiment, the kit is used for detecting the peptide of SEQ ID NO: 1 or SEQ ID NO: 2.

[0059] In another aspect, the present invention relates to the in vitro use of the kit and/or device of the invention for the treatment and/or prevention of autoimmune diseases. In a more specific embodiment of this aspect, the autoimmune diseases are chosen from a list that consists of: autoimmune arthritis, spondyloarthritides, psoriasis, systemic lupus erythematosus, and inflammatory bowel disease, more specifically the inflammatory bowel disease is ulcerative colitis or Crohn’s disease.

[0060] Another object of the invention is constituted by a method for treating and/or preventing autoimmune diseases which comprises administering a therapeutically effective amount of the antibody of the invention, of the antisera of the invention, or of the composition of the invention to a subject in need thereof.

[0061] For the purposes of the present invention, the term “treatment” refers to an intervention performed with the intention of preventing the development or altering the pathology of a disorder. Thus, “treatment” refers both to therapeutic treatment as well as to prophylactic or preventive measures. A “subject in need of treatment” includes any case in which said subject already has the disorder, as well as any case in which the disorder is to be prevented. In the treatment of an immunological type disease, a therapeutic agent can directly alter the magnitude of the response of an immune response component, or make the disease more susceptible to treatment by other therapeutic agents, such as antibiotics, antifungals, anti-inflammatory agents, chemotherapy agents, etc. Administration can take place “in combination with” one or more therapeutic agents and includes simultaneous (concurrent) and consecutive administration in any order.

[0062] For the purposes of the present invention, the term “therapeutically effective amount” refers to the amount of antibody, antisera or composition of the invention required to achieve an appreciable improvement in the state, for example, a pathology, of the disease or condition which is the object of the treatment.

[0063] In a preferred embodiment of the method of treatment and/or prevention of the invention, the same is characterized in that the autoimmune diseases are chosen from a list that consists of: autoimmune arthritis, spondyloarthritides, psoriasis, systemic lupus erythematosus and inflammatory bowel disease, and more specifically the inflammatory bowel disease is ulcerative colitis or Crohn’s disease.

[0064] Throughout the description and the claims, the word “comprises” and its variants are not intended to exclude other technical characteristics, additives, components or steps. For those skilled in the art, other objects, advantages and characteristics of the invention may be deduced from both the description and the practical use of the invention. The following examples and drawings are provided by way of illustration, and are not meant to limit the present invention.

BRIEF DESCRIPTION OF THE FIGURES

of human BAMBI by the mAb B101-37 evaluated by Western Blot in human heart cell membrane lysates. C) CDR sequence of heavy and light chains of the mAbs B101-37 and B143-14. The VDJ and VJ recombination of the heavy and light chains, respectively, of both mAbs are indicated.

**0066** FIG. 2. The induction of BAMBI expression in murine and human CD4+T lymphocytes after the activation thereof. A) Comparative analysis by means of flow cytometry of the expression of BAMBI in CD4+T lymphocytes of normal B6 and B6.BAMBI-KO mice before, and 48 hours after in vitro activation thereof with anti-CD3 and anti-CD28 antibodies in the presence or absence of TGF-β or IL-2 (top panels). On the bottom panels, the staining with B101-37 of the CD4+T lymphocytes activated in B6.BAMBI-KO mice is compared with that of the IgG1 isotype control in CD4+T lymphocytes activated in normal mice. B) Induction of BAMBI in human T lymphocytes stimulated in vitro for 48 hours with anti-CD3 and anti-CD28 mAbs. The BAMBI expression was analyzed by Western Blot in plasma membrane lysates. As loading control, the N-Ras expression was compared in the same lysates.

**0067** FIG. 3: The effect of the BAMBI inhibition on the in vitro differentiation of murine and human CD4+T lymphocytes into Treg and TH17 cells. A) Naive CD4+CD25-CD62L+CD44- T cells of normal B6 and B6.BAMBI-KO mice were stimulated for 5 days with anti-CD3 and anti-CD28 antibodies in Treg (top panels) or TH17 (bottom panels) polarizing conditions in the presence of mAb B143-14 (IgM anti-BAMBI) or a mouse polyclonal IgM (Sigma). B) Human naive CD4+T lymphocytes purified by magnetic separation were activated in vitro for 10 days with anti-CD3 and anti-CD28 antibodies conjugated to beads in THO or Treg differentiation conditions and in the presence of mAb B143-14 (IgM anti-BAMBI) or a mouse polyclonal IgM. The percentages of CD4+FoxP3+ cells are shown, analyzed by means of flow cytometry in THO differentiation conditions (white bars) and Treg differentiation conditions (black bars). C) Human CD4+T lymphocytes, purified by magnetic separation, were activated in vitro for 10 days with anti-CD3 and anti-CD28 antibodies conjugated to beads in THO or TH17 differentiation conditions. The inhibition effect of BAMBI with the mAb B143-14 on the differentiation into TH17 cells, either IFNγ producers or not, analyzed by means of flow cytometry, is shown. The statistical differences are represented as: *p<0.01.

**0068** FIG. 4: MAb B101-37 inhibits the development of arthritis in the CIA model. A and B) For CIA induction, normal B10RIIl mice were immunized with bovine type II collagen emulsified in CFA. The different experimental groups received treatments with 2 mg/mouse/week, 0.3 mg/mouse/week of B101-37 or with 2 mg/mouse/week of irrelevant murine IgG1 (IgG1-C) during the first 4 weeks after immunization. The clinical degree of severity of each mouse (A) and of different radiological injuries (average±SD) associated with articular destruction at the eighth week after immunization is shown (B). As controls for the aforementioned experiments, the development of CIA between normal B10RIII and B1001-KO mice was compared. The evolution of the clinical severity of arthritis in these animals, expressed as average±SD. C) and of different radiological injuries (average±SD) associated with the articular destruction at the eighth week after immunization is shown (D). The statistical differences are represented as: *p<0.05, **p<0.01.

**0069** FIG. 5: The effect of the treatment with B101-37 on the development of psoriatic arthritis induced by mannan injection. A) Normal B10RIII or BAMBI-KO mice treated or not treated from the beginning of the experiment with mAb B101-37 (2 mg/mouse/week) received an IP injection of 10 mg of mannan obtained from the yeast *Saccharomyces cerevisiae*. The evolution of the severity of the arthritis and of the percentage of the increase in ear thickness (average±SD) in the different experimental groups is shown. B) Photographs showing the macroscopic appearance of the auricle of the experimental groups described in (A). The statistical differences are represented as: *p<0.05, **p<0.01, ***p<0.001.

**0070** FIG. 6: The therapeutic effect of treatment with B101-37 in the development of chronic psoriatic arthritis. Normal B10RIII mice received a weekly injection of 10 mg of mannan (white arrows) and were treated with mAb B101-37 (2 mg/mouse/week) from the moment of the first mannan injection (preventive B101-37) or from the appearance of the first signs of the disease (therapeutic B101-37) until the end of the experiment (black arrows). As controls, mice treated with 2 mg/mouse/week of one irrelevant murine IgG1 (IgG1-C) were used. It shows the evolution of the clinical severity of the arthritis (top panel) and the ear thickness (bottom panel) as a marker of the severity of the cutaneous psoriasis. The statistical differences are represented as: *p<0.05, **p<0.01, ***p<0.001.

**0071** FIG. 7: The effect of treatment with B101-37 in the development of imiquimod-induced psoriasis. 12.5 mg of imiquimod (Aldara®) was applied for 6 days on the right ears of the B10RIII mice, BAMBI deficient or not. The different experimental groups were treated from the moment of the first application of imiquimod with a single dose of 2 mg of B101-37 or of irrelevant murine IgG1 (IgG1-C). A) Evolution of the clinical severity of the cutaneous injuries, evaluating the appearance and severity of erythema, desquamation of the skin and thickness of the ear treated in comparison with the non-treated contralateral ear. B) Histologic severity of the cutaneous injuries. The top photographs show representative examples (x10) of histologic cuts of the ears stained with haematoxylin and eosin. The lower panels show the values of the thickness of the epidermis (left panel) and of the dermis (right panel) in the different animals of each experimental group. The statistical differences are represented as: *p<0.05, ***p<0.001.

**0072** FIG. 8: Therapeutic effect of the treatment with B101-37 on the development of DSS colitis. Normal B6 or BAMBI-KO mice, treated or not from the beginning of the experiment with mAb B101-37 (2 mg/mouse/week) received DSS dissolved at a ratio of 3% in the water of the bottle for 5 days. The severity of the colitis was assessed by means of DAI quantification (A) or analyzing the shortening of the colon (B). C) Mortality in the different experimental groups. The statistical differences are represented as: *p<0.05, **p<0.01.

**EXAMPLES**

**0073** The invention is illustrated below by means of tests carried out by the inventors which reveal the effectiveness of the product of the invention.
Material and Methods.

Obtention and Characterization of the Murine Anti-BAMBI Monoclonal Antibodies.

B6.BAMBI-KO mice were immunized with the murine BAMBI(109-133) peptide conjugated to keyhole limpet hemocyanin (KLH) and emulsified in complete Freund's adjuvant (CFA). The mice were immunized on two more occasions (with one month difference between each immunization) with the same peptide emulsified in incomplete Freund's adjuvant (IFA). The murine BAMBI(109-133) peptide is located in the extracellular region of BAMBI and differs from its human homologue by 4 amino acids (positions 8, 9, 10 and 23 of the SEQ ID NO: 1).

The presence of murine anti-BAMBI(109-133) circulating antibodies in immunized mice was evaluated 15 days after each immunization by means of ELISA. Mice with higher titers of these antibodies were used for obtaining the murine anti-BAMBI monoclonal antibodies (mAb). To do so, spleen cell suspensions were fused with non-secreting myeloma cell line SP2/O-Ag14 as was previously described (Yokoyama W M. et al. Curr Protoc Immunol. 2013, Unit 2.5). Hybridoma that produce human anti-BAMBI mAb were selected by enzyme-linked immunosorbent assay (ELISA). In the present invention, two of the mAbs obtained have been characterized; clone B101-37 (igG1, k anti-BAMBI) and clone B143-14 (igM, k anti-BAMBI). The specificity of the mAbs was subsequently evaluated by means of Western Blot in heart cell membrane of hearts from normal B6 and B6.BAMBI-KO mice and of human myocardial samples obtained from surgical biopsies.

Ribonucleic acid (RNA) of mAbs B101-37 and B143-14 were isolated by means of the commercial kit RNeasy Mini Kit (Qiagen). For defining the encoding sequences for the complementarity-determining regions of (CDRs) in the heavy and light chain of both mAbs, RT-PCRs were carried out based on the purified RNAs, as previously described (Wang Z. et al. J Immunol Methods. 2000, 233: 167). For defining the CDR of the heavy chain of B101-37, the following steps were used: degenerate amplification from the FR1 region of the heavy chain: 5'-CTT CCG GAA TTC SAR GTN MAG CTG SAG SAG TC-3' (SEQ ID NO: 7); amplification of the constant region of IgG1; 5'-GGA AGA TCT AEA GAC AGA TGG GGG TGT CTT TTI GCC G-3' (SEQ ID NO: 8). For defining the CDR of the heavy chain of B143-14, the previously mentioned degenerate amplification from the FR1 region of the heavy chain and the amplification of the constant region of IgM were used: 5'-GGA AGA TCT GAC ATT TGG GAA GGA CTG ACT CTC-3' (SEQ ID NO: 9). For defining the CDR of the heavy chain of B101-37 and B143-14, the following steps were used: degenerate amplification from the FR1 region of the light chain k: 5'-GGG GAG CTC CAG ATT GTG MTG ACM CAR WCT MCA-3' (SEQ ID NO: 10); amplification of the constant region of the light chain k: 5'-GGG GCC TGC GGA TAC AGT TGG TGC AGC ATC-3' (SEQ ID NO: 11). The PCR products were subsequently sequenced (STABI Vida, Caparica, Portugal) and the sequences were analyzed by means of the IgBLAST program.

Study of BAMBI Expression in Murine and Human CD4+ T Lymphocytes.

By means of flow cytometry BAMBI expression in CD4+ T lymphocytes of normal B6 mice after the stimulation thereof using biotinylated mAb B101-37. The isolated CD4+ T lymphocytes of the spleen of normal B6 mice were stimulated in vitro for 48 hours with antibodies anti-CD3 (1 μg/ml) and anti-CD28 (0.5 μg/ml) bound to the plate in the presence or absence of 2 ng/ml of recombinant murine TGFβ and/or 1 ng/ml of recombinant murine IL-2 (PeproTech, London). As negative controls, spleen cells of B6.BAMBI-KO mice stimulated in the same way and colored with biotinylated B101-37 and normal B6 mice colored with a biotinylated isotype control were used. The colored cells were analyzed in a FACSCanto II cyometer equipped with FACS DIVA software (BD Biosciences).

BAMBI expression in human CD4+ T lymphocytes after the in vitro stimulation thereof was analyzed by means of Western Blot. Said lymphocytes were purified from 50 ml of buffy coats coming from healthy donors of the Blood and Tissues Bank of Cantabria (Marques de Valdecilla University Hospital, Santander). The monoclonal cells obtained after the Ficoll gradient were subjected to a positive selection after marking with specific mAb of CD4 conjugated to magnetic microparticles (MACS) using a magnetic separator (AutoMACS, Miltenyi Biotec). The CD4+ T lymphocytes were subsequently stimulated in vitro for 48 hours with antibodies anti-CD3 (1 μg/ml) and anti-CD28 (0.5 μg/ml) bound to the culture plate. The cell membrane lysates of the activated lymphocytes were obtained as described above.

In Vitro Differentiation Cultures of Murine and Human CD4+ T Lymphocytes into Treg and TH17 Cells.

The inhibiting capability of anti-BAMBI mAbs directed against the BAMBI(109-133) peptide were explored in vitro in murine and human CD4+ T lymphocyte cultures differentiated into Treg and TH17 cells. In these experiments, mAb B143-14 was used. In the experiments with murine lymphocytes, naïve CD4+ cells (CD4+CD25-CD62L+CD44-) from spleens of normal B6 mice were purified by means of cell sorting (FACSARia, BD Biosciences). 5×10⁵ naïve CD4+ cells were stimulated for 5 days with anti-CD3 and anti-CD28 antibodies bound to the plastic of the culture plate, in Treg polarizing conditions (2 ng/ml of murine TGFβ) or TH17 (1 ng/ml of murine TGFβ and 10 ng/ml of murine IL-6) in the presence of 20 μg/ml of B143-14 or 20 μg/ml of murine IgM (Sigma, St Louis, Mo.) as an isotype control. The percentages of lymphocytes TCD4+FoxP3+ (Treg) and CD4+IL-17+ (TH17) at the end of the culture were analyzed by means of flow cytometry, as was previously described (Iglesias M. et al. Arthritis Rheum 2013, 65:343).

Human naïve CD4+ T lymphocytes (in Treg differentiation) or CD45RO+ memory T lymphocytes (in TH17 differentiation), purified by magnetic separation, were activated in vitro for 10 days with anti-CD3 and anti-CD28 antibodies (aBs) conjugated to beads in Treg differentiation conditions (5 μg/ml of TGFβ) or TH17 (20 ng/ml of IL-1β, 30 ng/ml of IL-6, 30 ng/ml of IL-23, 3 ng/ml of TGFβ1, 1 μg/ml of anti-IFNy and 2.5 μg/ml of anti-IL-4) in the presence of 20 μg/ml of B143-14 or 20 μg/ml of murine IgM. The percentages of lymphocytes TCD4+FoxP3+ (Treg) and CD4+IL-17+ (TH17) at the end of the culture were analyzed by means of flow cytometry.

Experimental Model of Arthritis after Immunization with Bovine Type II Collagen Emulsified in CFA (CIA).

Groups of 10 Balb/c (H-2d) BAMBI-deficient or not mice were immunized twice the 12th week of age by intradermal route at the root of the tail with 150 μg of bovine type II collagen (MD Biosciences, Zurich) emul-
sified (vol. 1/1) in CFA containing a concentration of *Mycobacterium tuberculosis* of 4 mg/ml (MD Biosciences) as was previously described (Iglesias M. et al. Arthritis Rheum 2013, 65:343). To study the effect of BAMBI inhibition in the development of CIA, normal B10RIII mice were intra-peritoneally (IP) treated during the first 4 weeks after immunization with 2 or 0.3 mg/week of B101-37 or with 2 mg/week of anti-TNP IgG1 used as an isotype control (IgG1-C). The evolution of arthritis was monitored on a weekly basis from the 3rd week (the date on which arthritis began) to the eighth week after immunization. The severity of the arthritis was evaluated in each of the four extremities by means of the method described by Wooley et al. (Wooley P H. et al. J Immunol 1985, 135:2443). Likewise, on the eighth week of immunization the articular injuries on the front and back legs were evaluated by means of radiology, as we previously described (Iglesias M. et al. Arthritis Rheum 2013, 65:343).

[0086] Experimental Model of Dextran Sulfate Sodium Colitis (DSS-Colitis).

[0087] For the induction of colitis, DSS (MPbio.com), DSS was dissolved in water at 3%. This solution (with daily changes of water) was administered in a bottle to the mice of the different experimental groups for a variable time period [until the mice of the control group reached an activity ratio of the disease (DAI) of between 1.5-2 (approximately 4-5 days)]. The water consumed by each experimental group was measured daily and the DAI was evaluated calculating the clinical score of the following parameters: A) weight loss: 0=no weight loss, 1=weight loss of 1.5%, 2=weight loss of 5-10%, 3=weight loss of 10-20%, 4=weight loss of more than 20%; B) fecal consistency (the same value is given to all animals that are in the same box). 0=normal fecal consistency, 2=soft feces and 4=diarrhea; C) rectal bleeding (the same value is given to all animals that are in the same box): 0=no blood, 2=minor bleeding and 4=intense bleeding. The final DAI value was calculated by adding the values of the different parameters and dividing by 3.

[0088] Mannan Induced Psoriatic Arthritis.

[0089] For the induction of acute symptoms of psoriatic arthritis, groups of B10RIII BAMBI-deficient mice, or mice not BAMBI-deficient received an IP injection of 10 mg of mannan obtained from *S. cerevisiae* yeast (Sigma-Aldrich) dissolved in 200 μl of PBS (Kihomalazde I. et al. Proc Nat Acad Sci USA 2014, 111:E3660). Additionally, a chronic form of the process was induced in non-transgenic B10RIII mice by means of repeated injections of the same mannan dose once a week. To study the effect of the treatment with B101-37 on the prevention of psoriatic arthritis, mice that received a single mannan injection were treated from the moment of the administration of mannan (induction of the disease) with 2 mg/week of B101-37 or with 2 mg/week of an anti-TNP IgG1 used as IgG1-C. To evaluate the therapeutic effect of the treatment with B101-37, the non-transgenic B10RIII mice with the chronic form of the disease were treated with 2 mg/week of B101-37 (divided into 3 equal doses every two days) from the moment of the first mannan injection with (preventative treatment) or from the moment the first clinical signs of the process were observed (3 days after the first manna injection; therapeutic treatment) until the end of the experiment. Once again, as controls, non-transgenic B10RIII mice treated with an anti-TNP IgG1 from the moment of the appearance of the first signs of the disease were analyzed. The psoriatic injuries were evaluated at the level of the auricles, quantifying the thickness of the same with the help of a digital gauge. The severity of the arthritis was evaluated in each of the four legs, on a scale of 0-10 (total range of 0-40) in the following way: severe inflammation of the carpus/tarsus=5 points, adding an additional point for each inflamed toe. If the inflammation is minor–3 points per carpus/tarsus=4.5 points for each inflamed toe.

[0090] Experimental Model of Iniquimod Induced Cutaneous Psoriasis.

[0091] For the induction of cutaneous psoriasis, 12.5 mg of imiquimod (Alara®) was topically applied for 6 days on the right ears of B10RIII mice, BAMBI deficient or not. The different experimental groups were treated at the moment of the first application of imiquimod with a single dose of 2 mg of B101-37 or of irrelevant murine IgG1. Erythema, desquamation and the increase in the thickness of the ear were evaluated daily. Erythema and desquamation were evaluated using a clinical score of 0 to 4 in the following way: none=0, minor=1, moderate=2, severe=3, highly severe=4. The increase in the thickness of the treated ear was calculated with the help of a digital gauge in comparison with the thickness of the non-treated left ear in the following way: no increase=0, increase of 0.1-10%=1, decrease of 10.1-20%=2, increase of 20.1-30%=3, increase of 30.1-40%=4, increase of 40.1-50%=5. The animals were sacrificed 24 hours after the last application of imiquimod and skin samples were collected for the histological study. The thickness of the epidermis and the dermis in the histological samples from the ears treated with imiquimod were quantified in each animal using the ImageJ program, in relation to the respective thicknesses of the histological samples from the contralateral ears that were not treated.

Example 1: Molecular Characterization of Anti-BAMBI mAb

[0092] The specificity of the anti-BAMBI B101-37 and B143-14 mAbs was initially determined by means of ELISA (during the hybridoma screening process) and subsequently by means of Western Blot. Both mAbs recognize a band of approximately 27-29 kDa and another of approximately 54 kDa, compatible with BAMBI monomers and dimers resistant to sodium dodecyl sulfate (SDS) and reducing conditions, as was previously described (Xavier S et al. 2010 PLoS One 5:e12995) in lysates of B6 mice but not in those of B6.BAMBIKO mice (FIG. 1A).

[0093] Although the murine BAMBI(109-133) peptide used for the development of anti-BAMBI mAb differs from its human homologue in 4 amino acids studied by Western Blot in myocardial plasma membrane lysates indicate that B101-37 also recognizes human BAMBI (FIG. 1B).

[0094] We subsequently characterize the CDRs of the heavy and light chains of both anti-BAMBI mAbs by means of deoxyribonucleic acid (DNA) sequencing (SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6). The comparison of the DNA sequences with the IgBLAST database indicates that the CDR of the heavy and light chains of mAb B101-37 are the result of the reordering of the V9-3/D1-3/J1 and V15-103/J5 segments, respectively, while the CDRs of the heavy and light chains of mAb B143-14 are the result of the reordering of the V1-55/D4-1/J2 and V5-43/J1 segments, respectively.
Example 2: BAMBI Expression in CD4+ T Lymphocytes

[0095] CD4+ T lymphocytes play a fundamental role in the development of inflammatory and autoimmune pathologies. For this reason, the regulation of BAMBI expression in this lymphocytic population in mice is studied by means of flow cytometry and subsequently in humans by means of Western Blot, in both cases using mAb B101-37. In murine naïve CD4+ T lymphocytes BAMBI expression was not detected, but it was induced 48 hours after the in vitro stimulation thereof with anti-CD3 and anti-CD28 antibodies (FIG. 2A). This expression increased after the addition of TGFβ, but not of IL-2, to the activated CD4+ T cells (FIG. 2A). As specificity controls of mAb B101-37, markers in flow cytometry were not detected in activated CD4+ T lymphocytes of BAMB1-KO mice colored B101-37 or in normal B6 mice colored with an isotype control IgG1, respectively (FIG. 2A, bottom panels).

[0096] Just like in the mouse, BAMBI expression was very low in human naïve CD4+ lymphocytes, being induced after the stimulation thereof with anti-CD3 and anti-CD28 antibodies (FIG. 2B).

Example 3: BAMBI Inhibition with Murine Anti-BAMBI(109-133) mAb B143-14 Alters In Vitro Differentiation of the CD4+ T Lymphocytes of Mice and Humans into Subtypes Treg and TH17

[0097] In previous studies we showed that the absence of BAMBI in CD4+ T lymphocytes of BAMB1-KO mice strengthened and inhibited the in vitro differentiation thereof into Treg and TH17 populations, respectively (Postigo J et al. Doctoral Thesis defended on 19 Apr, 2013, University of Cantabria). To evaluate the inhibiting effect of the anti-BAMBI mAbs directed against the murine BAMBI(109-133) epitope, we analyzed the capability of B143-14 to alter the functional differentiation of the CD4+ T lymphocytes of normal mice in the same sense as observed in BAMB1-KO mice. To do so, naïve CD4+ T lymphocytes of normal B6 and BAMB1-KO mice were activated in vitro in polarization conditions to Treg or TH17 cells, in the presence of B143-14 mAb or a murine IgM used as an isotype control. Just as observed with the lymphocytes of BAMB1-KO mice, the BAMBI inhibition after the addition to the B143-14 culture, but not of the IgM control, increased and reduced the Treg and TH17 in vitro differentiation, respectively, of CD4+ T lymphocytes of normal B6 mice (FIG. 3A).

[0098] Lastly, we observed that in the presence of mAb B143-14, but not of the IgM control, in the in vitro differentiation of human naïve CD4+ T lymphocytes (a Treg) or memory T lymphocytes (a Th17) activated in polarizing conditions to Treg (FIG. 3B) or TH17 (FIG. 3C) is altered in the same way as in the mouse: an increase in Treg and reduction in TH17.

Example 4: The Therapeutic Effect of mAb B101-37 in the Development of CIA, Mannan Induced Psoriatic Arthritis, Imiquimod Induced Psoriasis and DSS Colitis

[0099] The previous results indicate that: 1) we have mAbs able to recognize BAMBI in mice and humans, 2) the expression of BAMBI is induced in the CD4+ T lymphocytes after the activation thereof in mice and humans; and 3) in both species the in vitro inhibition of BAMBI with a murine anti-BAMBI(109-133) mAb alters the functional differentiation of the CD4+ T lymphocytes in the same was as that described in B6.BAMB1-KO mice (increase in Treg cells and reduction of TH17 cells). These findings raise the possibility that the in vivo inhibition of BAMBI has a therapeutic effect on inflammatory/autoimmune pathologies.

[0100] In the present invention we have characterized the therapeutic potential of B101-37 in the development of CIA (the experimental model for rheumatoid arthritis most used by the scientific community), mannan induced psoriatic arthritis, imiquimod induced psoriasis (the experimental model of cutaneous psoriasis most used by the scientific community) and DSS colitis.

[0101] Both from a clinical and radiological point of view, the treatment of the normal B10RIII mice with 2 mg/week of B101-37 during the first 4 weeks after immunization with bovine type II collagen inhibited the development of CIA in these animals, unlike that which was observed in mice treated with 0.3 mg/week of B101-37 or with 2 mg/week of IgG1-C (FIGS. 4A and 4B). CIA inhibition after treatment with the high dose of B101-37 was similar to that observed in B10RIII.BAMB1-KO immunized mice (FIGS. 4C and 4D).

[0102] Just like the CIA model, treatment with 2 mg/week of B101-37 from the moment of mannan administration to the normal B10RIII mice reduced the severity of the articular and cutaneous lesions in a highly significant way in this experimental model of acute psoriatic arthritis induced after a single mannan injection, similar to that which is observed in B10RIII.BAMB1-KO (FIG. 5).

[0103] The present results show a preventive effect of treatment with B101-37 on the development of acute cutaneous and articular injuries after the administration of a single injection of mannan. The therapeutic potential of B101-37 in the chronic variety of this experimental model was subsequently analyzed. FIG. 6 shows that the weekly mannan injection into B10RIII mice causes the appearance of articular and cutaneous injuries that are maintained over time. Preventive treatment with 2 mg/week of B101-37 37 (begun at the moment of the mannan injection and maintained until the end of the experiment) significantly reduced the severity of said injuries throughout the study (FIG. 6). Likewise, a significant reduction, similar to that observed in preventative treatment, of the cutaneous and articular manifestations was observed after the beginning of the treatment with B101-37 once the first signs of the disease were already apparent (three days after the first mannan injection (FIG. 6).

[0104] The therapeutic potential of B101-37 in psoriasis was confirmed in the cutaneous psoriasis experimental model most widely used in the scientific community, imiquimod induced psoriasis. The topical application of imiquimod for 6 consecutive days to non-transgenic B10RIII mice induces cutaneous lesions with histological characteristics of psoriasis (FIG. 7). Unlike the previous model, the administration of imiquimod does not cause the development of arthritis. The treatment of non-transgenic B10RIII mice with B101-37, from the moment of the first application of imiquimod and with the same dose used in the preceding models, significantly reduced the severity of the disease from a clinical (FIG. 7A) and histological (FIG. 7B) point of view, as observed in B10RIII.BAMB1-KO mice.

[0105] Lastly, we evaluated the therapeutic effect of B101-37 in the experimental model of DSS colitis. Just like in B6.BAMB1-KO mice, normal B6 mice treated with 2
mg/week of B101-37 from the moment of the administration of DSS developed a significantly less severe colitis than the non-treated controls (FIG. 8A). However, the protective effect of the treatment with B101-37 in B6 mice was not as important as that observed in BAMBI-KO animals, especially with regard to the degree of shortening of the colon (FIG. 8A, right panel). It is worth pointing out that both in the B6 animals treated with B1010-37 and in BAMBI-KO mice, the mortality associated with the induction of DSS colitis was entirely prevented (FIG. 8B).

Therefore, the present invention demonstrates the use of monoclonal antibodies against BAMBI for the treatment and prevention of autoimmune diseases.

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1. A monoclonal antibody that specifically recognizes an amino acid sequence that comprises a peptide with at least an 80% identity with SEQ ID NO: 1, wherein the length of said amino acid sequence is between 15 and 30 amino acids.

2. The antibody according to claim 1, wherein said antibody specifically recognizes the sequence SEQ ID NO: 1 or SEQ ID NO: 2.

3. The antibody according to claim 1, wherein the antibody comprises a heavy chain that comprises the sequence SEQ ID NO: 3 and/or a light chain which comprises the sequence SEQ ID NO: 4.

4. The antibody according to claim 1, wherein the antibody comprises a heavy chain that comprises the sequence SEQ ID NO: 5 and/or a light chain which comprises the sequence SEQ ID NO: 6.

5. An antiseraum that comprises the antibody according to claim 1.

6. A cell that expresses the antibody according to claim 1.

7. A method of inhibition of BMP and Activin Membrane Bound Inhibitor (BAMBI) by the administering to a subject an effective amount of an antibody according to claim 1.

8. A method of treating or preventing of autoimmune diseases in a subject, comprising administering to the subject in need thereof an effective amount of an antibody according to claim 1.

9. (canceled)

10. The method according to claim 8 wherein the autoimmune diseases are selected from the list that consists of: autoimmune arthritis, spondyloarthritis, psoriasis, systemic lupus erythematosus, and inflammatory bowel disease.

11. The method according to claim 10 wherein the inflammatory bowel disease is ulcerative colitis or Crohn's disease.
12. A pharmaceutical composition comprising the monoclonal antibody according to claim 1.
13. (canceled)
14. A method for obtaining a monoclonal antibody that recognizes an amino acid sequence that comprises a sequence with at least an 80% identity with the sequence SEQ ID NO: 1, comprising:
   a. obtaining previously extracted serum from a non-human animal immunized with a recombinant protein comprising an amino acid sequence that comprises a peptide with at least an 80% identity with the sequence SEQ ID NO: 1;
   b. obtaining a hybridoma from the serum of step a) which generates specific monoclonal antibodies against an amino acid sequence comprising a sequence with at least an 80% identity with SEQ ID NO: 1.
15. The method according to claim 14, which further comprises a step (c) of isolating the monoclonal antibody from the hybridoma generated in stage (b).
16. The method according to claim 14 where, in the step (a), the amino acid sequence is the sequence SEQ ID NO: 1 or SEQ ID NO: 2.
17. The method according to claim 14, wherein the non-human animal is a mammal selected from the list consisting of pigs, chimpanzees, mice, rats, rabbits and guinea pigs.
18. A kit and/or device comprising the antibody according to claim 1.
19.-23. (canceled)
24. A method of inhibition of BMP and Activin Membrane Bound Inhibitor (BAMBI) by the administering to a subject an effective amount of an antiserum according to claim 5.
25. A method of treating or preventing of autoimmune diseases in a subject, comprising administering to the subject in need thereof an effective amount of an antiserum according to claim 5.
26. A pharmaceutical composition comprising the antiserum according to claim 5.
27. A kit and/or device comprising the antiserum according to claim 5.

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