Use of a cathepsin S inhibitor against the formation of anti-drug antibodies

The present invention is directed in particular to a cathepsin S inhibitor for use in a method for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent.

Protein-based biologics, namely Immunomodulatory drugs, are effective therapeutic agents and their clinical applications have significantly grown during the past years due to its high specificity to immune targets (Leader, Baca et al., Nat Rev Drug Discov 2008, 7(1): 21-39). However, along with its superior efficacy and safety profile compared with small-molecules, some adverse reactions, including immunogenicity, are often reported (Sathish, Sethu et al., Nat Rev Drug Discov 2013, 12(4): 306-324; Boehncke and Brembilla, Expert Rev Clin Immunol 2018, 14(6): 513-523). Immunogenicity is characterized by anti-drug-antibody (ADA) formation which can be innocuous but can also lead to loss or reduced efficacy, altered pharmacokinetics, infusion reactions, crossreactivity to endogenous protein and in severe cases to anaphylactic reactions (Abramowicz, Crusiaux et al., N Engl J Med 1992, 327(10): 736, Baudouin, Crusiaux et al., Transplantation 2003, 76(3): 459-463). These unwanted effects are often the reason for therapy discontinuation and hence explain the urgent need for strategies aimed to mitigate ADA in the clinic. For this purpose, B-cell depleting agents, like Gazyva, have been applied in the clinic in combination with cancer immunotherapy (CIT) treatments and showed to supress *de novo* ADA responses. However, the complete ablation of B-cells may be undesired to patients as the role of B-cells in the mode of action of CITs is not completely known.

Mammalian cathepsins are cysteine-type proteases involved in key steps of biological and pathological events. Cathepsins are considered tractable drug targets as it is feasible to inhibit enzymatic activity with small molecules and are therefore of interest to the pharmaceutical industry (Bromme, D. (2001), 'Papain-like cysteine proteases', Curr Protoc Protein Sci, Chapter 21, Unit 21 2; Roberts, R. (2005), 'Lysosomal cysteine

proteases: structure, function and inhibition of cathepsins', Drug News Perspect, 18 (10), 605-14).

Cathepsin S is prominently expressed in antigen presenting cells like macrophages and dendritic cells and smooth muscle cells. (Hsing, L. C. and Rudensky, A. Y. (2005), 'The lysosomal cysteine proteases in MHC class II antigen presentation', Immunol Rev, 207, 229-41; Rudensky, A. and Beers, C. (2006), 'Lysosomal cysteine proteases and antigen presentation', Ernst Schering Res Found Workshop, (56), 81-95). While Cathepsin S is only weakly expressed in normal arterial tissue, strong upregulation is seen in atherosclerotic arteries (Liu, J., et al. (2006), 'Increased serum cathepsin S in patients with atherosclerosis and diabetes', Atherosclerosis, 186 (2), 411-9; Sukhova, G. K., et al. (1998), 'Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells', J Clin Invest, 102 (3), 576-83).

Preclinical data suggest that the function of Cathepsin S is critical for atherosclerosis as Cathepsin S deficient mice have a reduced atherosclerosis-phenotype when tested in appropriate mouse models. In LDL-Rec deficient mice reduced lipid accumulation, elastin-fibre breakdown and chronic arterial inflammation is reported. In APO E deficient mice, a significant reduction of acute plaque rupture events was reported. When chronic renal disease is introduced into CatS/In APO-E deficient mice a strong reduction of accelerated calcification is seen on top of the anti atherosclerotic activity in arteries and heart valves (Aikawa, E., et al. (2009), 'Arterial and aortic valve calcification abolished by elastolytic cathepsin S deficiency in chronic renal disease', Circulation, 119 (13), 1785-94; de Nooijer, R., et al. (2009), 'Leukocyte cathepsin S is a potent regulator of both cell and matrix turnover in advanced atherosclerosis', Arterioscler Thromb Vasc Biol, 29 (2), 188-94; Rodgers, K. J., et al. (2006), 'Destabilizing role of cathepsin S in murine atherosclerotic plaques', Arterioscler Thromb Vasc Biol, 26 (4), 851-6; Sukhova, G. K., et al. (2003), 'Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice', J Clin Invest, 111 (6), 897-906). This suggests a potential inhibitor of Cathepsin S would stabilise atherosclerotic plaque by reducing extracellular matrix breakdown, by reducing the proinflammatory state and by reducing accelerated calcification and subsequently its clinical manifestations.

These phenotypes described in atherosclerosis models are in agreement with known cellular functions of Cathepsin S. Firstly, Cathepsin S is involved in the degradation of extracellular matrix that stabilises the plaque. In particular, Cathepsin S has potent elastinolytic activity and can exert this at neutral pH, a feature that distinguishes Cathepsin S from all other Cathepsins. Secondly, Cathepsin S is the major protease involved in antigen processing, in particular cleavage of the invariant chain in antigen presenting cells (APCs), resulting in reduced contribution of T cells to the chronic inflammation of the

atherosclerotic tissue. Elevated inflammation results in further oxidative and proteolytic tissue damage and subsequently plaque destabilisation (Cheng, X. W., et al. (2004), 'Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries', Am J Pathol, 164 (1), 243-51; Driessen, C., et al. (1999), 'Cathepsin S controls the trafficking and maturation of MHC class II molecules in dendritic cells', J Cell Biol, 147 (4), 775-90; Rudensky, A. and Beers, C. (2006), 'Lysosomal cysteine proteases and antigen presentation', Ernst Schering Res Found Workshop, (56), 81-95).

The anti-inflammatory and anti-elastinolytic properties of a Cat S inhibitor make it also a prominent target for chronic obstructive pulmonary disease (Williams, A. S., et al. (2009), 'Role of cathepsin S in ozone-induced airway hyperresponsiveness and inflammation', Pulm Pharmacol Ther, 22 (1), 27-32). Furthermore due to its extracellular functions in matrix degradation, inhibition of cathepsin S will impact neointima formation and angiogenesis (Burns-Kurtis, C. L., et al. (2004), 'Cathepsin S expression is up-regulated following balloon angioplasty in the hypercholesterolemic rabbit', Cardiovasc Res, 62 (3), 610-20; Cheng, X. W., et al. (2004), 'Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries', Am J Pathol, 164 (1), 243-51; Shi, G. P., et al. (2003), 'Deficiency of the cysteine protease cathepsin S impairs microvessel growth', Circ Res, 92 (5), 493-500; Wang, B., et al. (2006), 'Cathepsin S controls angiogenesis and tumor growth via matrix-derived angiogenic factors', J Biol Chem, 281 (9), 6020-9). An inhibitor of Cathepsin S might therefore be useful in several different disease settings.

Cathepsin S plays also a role in the reduction of tumor growth and tumor cell invasion as described by Roberta E. Burden in Clin Cancer Res 2009;15(19). In addition, nephrectomized Cathepsin S knock out mice showed a significant reduction of arterial calcification when compared to nephrectomized wild type mice. This indicates that inhibition of Cathepsin S may have a beneficial effect on the reduction of cardiovascular events in chronic kidney disease patients (Elena Aikawa, Circulation, 2009, 1785-1794).

We have surprisingly found that inhibition of cathepsin S (CatS) with a CatS inhibitor reduced or prevented ADA formation to immunogenic compounds, in particular to immunomodulatory antibody drugs.

One of the early steps in the cycle of anti-tumor immunity is the capture and presentation of tumor-associated antigens by dendritic cells in the context of MHC-I or MHC-II molecules. Therefore, for cancer immunotherapy (CIT), it sounds counterintuitive to use a compound supressing MHC-II maturation and antigen presentation. Nevertheless, recent studies have shown that the cathepsins upregulated in a wide range of cancers are

associated with tumor growth, invasion and metastasis (Pogorzelska, Zolnowska et al. ,Biochimie, 2018, 85-106; Tan, Qian et al., Oncology Reports, 2018, 111-122). Taking this into account, inhibition of Cathepsin S with a CatS inhibitor can even play an additive effect, together with the immunomodulatory drug, in fighting cancer, by restoring the activity of the immunomodulatory anti-cancer drug and at the same time downregulating cathepsin S.

Brief description of the figures.

Figure 1 represents the adalimumab-specific IgG response in hIgG1 Tg mice determined by ELISA before and after adalimumab immunization and administration of a cathepsin S inhibitor (dashed line) or vehicle (filled circles). The cathepsin S inhibitor reduces ADA to adalimumab in hIgG1 transgenic mice. Data shown represent mean ± SEM of 10 mice/group. ***$P < 0.001$.

Figure 2 represents the CEA-specific IgG response in hIgG1 Tg mice (Figure 2A) and wild-type mice (Figure 2B) determined by ELISA before and after immunization with CEA-IL2v and administration of a cathepsin S inhibitor (dashed symbols) or vehicle (filled symbols). The cathepsin S inhibitor prevents ADA to CEA-IL2v in hIgG transgenic mice and reduces its levels in wild-type mice. Data shown represent mean ± SEM of 10 mice/group. ***P < 0.01 and **$P < 0.001$, respectively.

Figure 3 represents the high affinity NP-specific IgG response in wild-type mice determined by ELISA over time (x-axis). The high dose of cathepsin S inhibitor (40mg/kg/day) significantly reduces NP-specific IgG levels compared to vehicle-treated animals. Data shown represent mean ± SEM of 10 mice/group. ***P < 0.001.

Figure 4 represents the adalimumab-specific IgG response in hIgG1 Tg mice determined by ELISA over time (x-axis) before and after adalimumab immunization and administration of a cathepsin S inhibitor (dashed line) or vehicle (filled circles). The cathepsin S inhibitor reduces ADA to adalimumab in hIgG1 transgenic mice. Data shown represent mean ± SEM of 10 mice/group. ***$P < 0.001$.

Figure 5 represents the CEA-specific IgG response in hIgG1 Tg mice (Figure 2A) and wild-type mice (Figure 2B) determined by ELISA over time (x-axis) before and after immunization with CEA-IL2v and administration of a cathepsin S inhibitor (dashed symbols) or vehicle (filled symbols). The cathepsin S inhibitor prevents ADA to CEA-IL2v in hIgG transgenic mice and reduces its levels in wild-type mice. Data shown represent mean ± SEM of 10 mice/group. ***P < 0.001 and **$P < 0.01$, respectively.

Figure 6 represents levels of CEA-IL2v in serum (y-axis) plotted over time (x-axis) in hlgG1 Tg mice (Figure 6A) and wild-type mice (Figure 6B). The CEA-IL2v exposure in cathepsin S inhibitor (dashed symbols) and vehicle (filled symbols) treated animals are shown. Data shown represent mean ± SEM of 10 mice/group.

Figure 7 represents the PD effect of CEA-IL2v in blood of hlgG1 Tg mice (A and B) and. The percentages of TCRβ+CD8+ CD8 T cells (A and C) and NK1.1+ NKp46+ NK cells (B and D) are depicted on the y-axis over time (x-axis). Data shown represent mean ± SEM of 10 mice/group.

Figure 8 represents the IgG response to murine surrogate FAP-OX40 in wild-type mice determined by ELISA. ADA specific to FAP (VHVL) is shown in Figure 8A whereas OX40-specific ADA is shown in Figure 8B. The cathepsin S inhibitor (dashed symbols) prevents ADA to FAP (A) as well as OX40 (B) domains in wild-type mice. Data shown represent mean ± SEM of 10 mice/group. ***P < 0.001.

Figure 9 represents the IgG response to murine surrogate PD-L1 in wild-type mice determined by ELISA before and after PD-L1 immunization and administration of a cathepsin S inhibitor. The cathepsin S inhibitor significantly reduced ADA to mPD-L1 in wild-type mice. Data shown represent mean ± SEM of 10 mice/group. ***P < 0.001.

Figure 10 represents the IgG response to murine hemi-surrogate CEA-TCB in hlgG1 Tg mice. CEA-specific ADA is shown in Figure 10A whereas ADA specific to CD3 binder (2C11) is shown in Figure 10B. Cathepsin S inhibitor (dashed symbols) and vehicle (filled symbols) treated animals are shown. The cathepsin S inhibitor significantly reduced ADA to CD3 binder (B), whereas the reduction of CEA-specific ADA was not significant compared to vehicle-treated animals (A). Data shown represent mean ± SEM of 10 mice/group. **$P < 0.01$.

The term “biologic”, which can be changed with “biopharmaceutical”, “biological medicinal product” or “biological”, refers to any pharmaceutical drug product manufactured in, extracted from, or semisynthesized from biological sources. Different from totally synthesized pharmaceuticals, they include vaccines, blood, blood components, allergenics, somatic cells, gene therapies, tissues, recombinant therapeutic protein and living cells used in cell therapy. Biologics can be composed of sugars, proteins or nucleic acids or complex combinations of these substances, or may be living cells or tissues. They (or their precursors or components) are isolated from living sources - human, animal, plant, fungal or microbial.

The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal

antibodies, multispecific antibodies (e.g. bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen binding activity.

The terms “full length antibody,” “intact antibody,” and “whole antibody” are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure.

The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab’-SH, $F(ab')_2$, diabodies, linear antibodies, single-chain antibody molecules (e.g. scFv), and single-domain antibodies. For a review of certain antibody fragments, see Hudson et al., Nat Med 9, 129-134 (2003). For a review of scFv fragments, see e.g. Plückthun, in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); see also WO 93/16185; and U.S. Patent Nos. 5,571,894 and 5,587,458. For discussion of Fab and $F(ab')_2$ fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see U.S. Patent No. 5,869,046. Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al., Nat Med 9, 129-134 (2003); and Hollinger et al., Proc Natl Acad Sci USA 90, 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., Nat Med 9, 129-134 (2003). Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a

portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; see e.g. U.S. Patent No. 6,248,516 B1). Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g. E. coli or phage), as described herein.

A "Fab molecule" refers to a protein consisting of the VH and CH1 domain of the heavy chain (the "Fab heavy chain") and the VL and CL domain of the light chain (the "Fab light chain") of an immunoglobulin.

The term "bispecific" means that the antibody is able to specifically bind to at least two distinct antigenic determinants. Typically, a bispecific antibody comprises two antigen binding sites, each of which is specific for a different antigenic determinant. In certain embodiments the bispecific antibody is capable of simultaneously binding two antigenic determinants, particularly two antigenic determinants expressed on two distinct cells.

The term "T-cell bispecific antibody" refers to an antibody designed to simultaneously bind to a surface antigen on a target cell, e.g., a tumor cell, and to an activating, invariant component of the T cell receptor (TCR) complex, such as CD3, for retargeting of T cells to kill target cells. A T-cell bispecific antibody thus has an antigen binding moiety capable of forming an antigen binding moiety-antigen complex with an antigenic determinant found on the surface of T-cells.

A "BiTE" (bispecific T cell engager) is a molecule wherein two scFv molecules are fused by a flexible linker (see, e.g., WO 2004/106381, WO 2005/061547, WO 2007/042261, and WO 2008/119567, Nagorsen and Bäuerle, Exp Cell Res 317, 1255-1260 (2011)).

The term "antibody-drug conjugate" (ADC) refers to an antibody which is conjugated to one or more therapeutic agents such as for example cytotoxic agents, chemotherapeutic agents, drugs, growth inhibitory agents, toxins (e.g., protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof) or radioactive isotopes. The antibody is typically connected to one or more of the therapeutic agents using linkers. An overview of ADC technology including examples of therapeutic agents and drugs and linkers is set forth in Pharmacol Review 68:3-19 (2016).

"Recombinant immunotoxins" are antibody-toxin chimeric molecules that kill cancer cells via binding to a surface antigen, internalization and delivery of the toxin moiety to the cell cytosol.

The term "immunogenicity", and hence "immunogenic", refers to the ability of a particular substance to provoke an immune response in the body of a human and other animal. In other words, immunogenicity is the ability to induce a humoral and/or cell-mediated immune responses. Distinction has to be made between wanted and unwanted immunogenicity. Wanted immunogenicity is typically related with vaccines, where the injection of an antigen (the vaccine) provokes an immune response against the pathogen (virus, bacteria...) aiming at protecting the organism. Unwanted immunogenicity is an immune response by an organism against a therapeutic agent (ex. recombinant protein, or monoclonal antibody). This reaction leads to production of anti-drug-antibodies (ADA) inactivating the therapeutic effects of the treatment and, in somes cases, inducing adverse effects.

An "anti-drug antibody" or "ADA" refers to an antibody that binds to a therapeutic agent and may influence serum concentrations and function of the therapeutic agent in a subject. The presence of ADA may increase clearance of the therapeutic agent through formation of immune complexes between therapeutic agent and antibody (neutralizing, non-neutralizing or both), thus reducing the therapeutic agent's half-life. Furthermore, the activity and effectiveness of the therapeutic agent may be decreased through binding of antibody to the therapeutic agent (particularly in the case of neutralizing ADA). ADA can also be associated with allergic or hypersensitivity reactions and other adverse events as neutralization of host proteins.

The term "vector", as used herein, refers to an altered virus, including adeno-associated virus (AAV), where its viral genes are removed, not causing disease. Viral vectors such as rAAV are intended to transport missing or mutated genes to a cell in order to restore the function of the protein. As a consequence of its repetitive structure, viral vectors frequently induce humoral immunity characterized by generation of neutralizing antibodies, which represents the most effective barrier to successful gene transfer with AAV vectors.

The term "activity" refers to the beneficial pharmacological activity of a drug on living matter. Therefore, in the context of the present invention, the expression "increasing the activity of a therapeutic agent" refers in particular to the increase in beneficial pharmacological activity of said therapeutic agent. In the present invention, an increase in activity can be associated with or due to for example an increased exposure, increased half-life or increased bioavailability.

The term "bioavailability" refers to the fraction of an administered dose of unchanged drug that reaches the systemic circulation. In pharmacology, bioavailability is a

measurement of the rate and extent to which a drug reaches at the site of action. Both definitions can be used in the context of the present invention.

The term "half-life" of a substance or therapeutic agent, in the present invention, is the time it takes for half of said substance or therapeutic agent to disappear from the target tissue or from the circulation.

The term "exposure" refers to the concentration of a drug in a body compartment (usually blood) as a function of time.

It is self-evident that the inhibitors are administered to the patient in a "therapeutically effective amount" (or simply "effective amount") which is the amount of the respective compound or combination that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

Examples of cathepsin S inhibitor useful in the present invention are described in They are described in WO 2010/121918 and WO2017/144483 which are herein incorporated by reference.

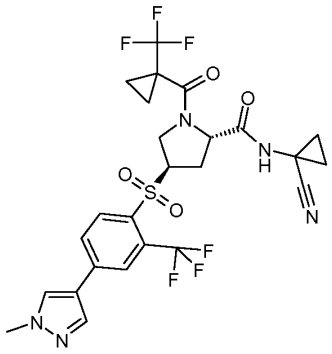
Advantageous cathepsin S inhibitor according to the invention are

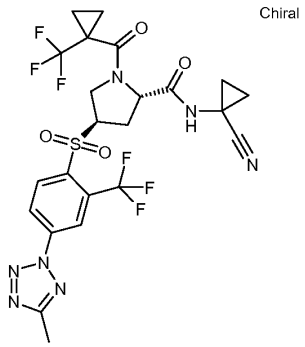
(2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; or

(2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

or a pharmaceutically acceptable salt thereof;

They are described in WO 2010/121918 and WO2017/144483. They are represented below.





(2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide is a particular advantageous cathepsin S inhibitor according to the invention.

Among the therapeutic agents that benefit most of the invention are antibodies, in particular antibodies used in oncology, more particularly immune activating compounds, e.g. cancer immunotherapy agents, including check point inhibitory antibodies like for example anti-PD-L1 or anti-PD-1 antibodies, for example atezolizumab, durvalumab, avelumab, pembrolizumab or nivolumab.

T-cell bispecific antibodies, BiTEs, cytokines, immunocytokines and immunomodulatory antibodies are particular examples of such therapeutic agents. Antibodies used in ophtlamology (e.g. Lucentis®), diabetes (Lantus®) or inflammatory and autoimmune diseases also benefit from the invention.

Examples of therapeutic agents according to the invention are alemtuzumab (LEMTRADA®), atezolizumab (TECENTRIQ®), bevacizumab (AVASTIN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), pertuzumab (OMNITARG®, 2C4), trastuzumab (HERCEPTIN®), tositumomab (Bexxar®), abciximab (REOPRO®), adalimumab (HUMIRA®), apolizumab, aselizumab, atlizumab, bapineuzumab, basiliximab (SIMULECT®), bavituximab, belimumab (BENLYSTA®) briankinumab, canakinumab (ILARIS®), cedelizumab, certolizumab pegol (CIMZIA®), cidfusituzumab, cidtuzumab, cixutumumab, clazakizumab, crenezumab, daclizumab (ZENAPAX®), dalotuzumab, denosumab (PROLIA®, XGEVA®), eculizumab (SOLIRIS®), efalizumab, emicizumab (HEMLIBRA®), epratuzumab, erlizumab, felvizumab, fontolizumab, golimumab (SIMPONI®), ipilimumab, imgatuzumab, infliximab (REMICADE®), labetuzumab, lebrikizumab, lexatumumab, lintuzumab, lucatumumab, lulizumab pegol, lumretuzumab, mapatumumab, matuzumab, mepolizumab, mogamulizumab, motavizumab, motovizumab, muronomab, natalizumab (TYSABRI®), necitumumab

(PORTRAZZA®), nimotuzumab (THERACIM®), nolovizumab, numavizumab, obinutuzumab (GAZYVA®/GAZYVARO®), ocrelizumab (OCREVUS®), olokizumab, omalizumab (XOLAIR®), onartuzumab (also known as MetMAb), palivizumab (SYNAGIS®), pascolizumab, pecfusituzumab, pectuzumab, pegylated interferon (PEGAZYS®), pembrolizumab (KEYTRUDA®), pexelizumab, priliximab, ralivizumab, ranibizumab (LUCENTIS®), reslivizumab, reslizumab, resyvizumab, rituximab (MABTHERA®), robatumumab, rontalizumab, rovelizumab, ruplizumab, sarilumab, secukinumab, seribantumab, sifalimumab, sibrotuzumab, siltuximab (SYLVANT®) siplizumab, sontuzumab, tadocizumab, talizumab, tefibazumab, tocilizumab (ACTEMRA®), toralizumab, trastuzumab emtansine (KADCYLA®), tucusituzumab, umavizumab, urtoxazumab, ustekinumab (STELARA®), vedolizumab (ENTYVIO®), visilizumab, zanolimumab and zalutumumab.

In the above list and in the rest of the application, tradenames are indicated in brackets for illustrative purposes. It is understood that the INN defines the therapeutic agents according to the invention, therefore covering also the biosimilars of the originator products.

Particular therapeutic agents according to the invention are IgG antibodies, in particular human IgG antibodies, IgG1 antibodies, in particular human, humanized or chimeric IgG1antibodies, IgG1 antibody-drug conjugates, in particular chimeric IgG1 antibody-drug conjugates, IgG2 antibodies, in particular human or humanized IgG2 antibodies, IgG4 antibodies, in particular human or humanized IgG4 antibodies, IgG2/4 antibodies, in particular human or humanized IgG2/4 antibodies, Fab fragments, in particular IgG Fab fragments or IgG1 Fab fragments, in particular humanized IgG Fab fragments or humanized or chimeric IgG1 Fab fragments, humanized IgG4-toxin conjugate, human monoclonal antitoxin antibodies, humanized IgG4-toxin conjugates or recombinant immunotoxins.

Antibody-drug conjugates are a particular type of therapeutic agent according to the invention.

Particular therapeutic agents according to the invention are antibodies against GPIIb/IIIa, TNF-alpha, CD-52, PCSK-9, PD-L1, CD-25, BLyS, CD-125, VEGF, C. difficile Toxin B, CD-30, IL-17RA, IL-1ß, PD-1, EGFR, CD-38, RANKL, IL-4Ralpha, Complement C5, SLAMF7, Factor VIII, CGRPR, CGRP, CD-33, CD-4, CTLA-4, IL-5, CCR4, CD-22, VLA-4, CD-20, PDGFR-alpha, IgE, F-protein of RS virus, HER-2, VEGF-A, IL-17a, cCLB8, IL-23, IL-6 receptor, IL-12, IL-23, Integrin-alpha4b7, CEA or CD3.

Particular therapeutic agents according to the invention are the following antibodies: abciximab, adalimumab, alemtuzumab, alirocumab, atezolizumab, avelumab, basiliximab, belimumab, benralizumab, bevacizumab, bezlotoxumab, brentuximab, brodalumab, canakinumab, catumaxomab, cemiplimab, certolizumab pegol, cetuximab, daratumumab, denosumab, dupilumab, durvalumab, eculizumab, elotuzumab, emicizumab, erenumab, etanercept, evolocumab, fremanezumab, galcanezumab, gemtuzumab ozogamicin, golimumab, ibalizumab, infliximab, ipilimumab, mepolizumab, mogamulizumab, moxetumomab, natalizumab, necitumumab, nivolumab, obinutuzumab, ocrelizumab, ofatumumab, olaratumab, omalizumab, palivizumab, panitumumab, pembrolizumab, pertuzumab, ramucirumab, ranibizumab, reslizumab, rituximab, secukinumab, siltuximab, tildrakizumab, tocilizumab, trastuzumab, ustekinumab and vedolizumab.

Other particular therapeutic agents according to the invention are protein products, like for example interferon-gamma, interferon-beta, erythropoietin, antihemophilic factor VIII, CD-2 inhibitor, coagulation factor Xa, Interferon-beta mimetic, follicle-stimulating hormone, GLP-1 agonist, b-glucocerebrosidase mimetic, erythropoietin mimetic, KGF mmetic, insulin mimetic, acid alpha-glucosidase mimetic, G-CSF mimetic, IL-11 mimetic, CD-80/86 blocker, metabolizing enzyme, IL-2 mimetic, rhDNAse, fibrin sealant of wounds or direct thrombin inhibitor.

Particular therapeutic agents according to the invention are the following proteins: Alteplase, Octocog alfa, Alefacept, Andexxa, Interferon Beta-1a, Interferon beta-1b, Urofollitropin, Exenatide, Alglucerase, Idursulfase, Eloctate, Epoetin alfa, Palifermin, Insulin detemir, Alglucosidase alfa, Pegfilgrastim, Neumega, Belatacept, Pegvaliase, Aldesleukin, Dornase alfa, Raplixa, ReFacto, Lepirudin or Albiglutide.

Further particular therapeutic agents according to the invention are protein replacement therapies, like for example recombinant human acid aslpha-glucosidase (rhGAA), factor VIII or interferon beta.

Adalimumab (HUMIRA®) is a particular therapeutic agent for use in the invention. It is used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa and juvenile idiopathic arthritis. Adalimumab is a TNF-inhibiting, anti-inflammatory, biologic medication. It binds to tumor necrosis factor-alpha (TNFα), which normally binds to TNFα receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNFα, adalimumab reduces this inflammatory response. Because TNFα is also part of the immune system, which protects the body from infection, treatment with adalimumab may increase the risk of infections. Like other TNF inhibitors, it is an immunomodulatory medication, used to treat autoimmune diseases such as rheumatoid

arthritis. It is associated with high incidence of immunogenicity in clinical trials (Bartelds GM et al, Ann Rheum Dis, 2007, 921-926; Bartelds GM et at, JAMA, 2011, 146-1468). It cross-reacts with mouse TNF leading to high ADA responses (Bitoun S et al, Ann Rheum Dis, 2018, 1463-1470), thus Adalimumab is a suitable model compound to demonstrate the efficacy of the present invention in pre-clinical mouse models.

Cergutuzumab amunaleukin (CEA-IL2v, RG7813) is a particular therapeutic agent for use in the invention. It is a monomeric CEA-targeted immunocytokine that comprises a single IL-2 variant (IL2v) moiety with abolished CD25 binding, fused to the C-terminus of a high affinity, bivalent carcinoembryonic antigen (CEA)-specific antibody devoid of Fc-mediated effector functions. It is described in WO 2012/107417 and WO 2012/146628.

T cell activating bispecific antibodies are a novel class of cancer therapeutics, designed to engage cytotoxic T cells against tumor cells. The simultaneous binding of such an antibody to CD3 on T cells and to an antigen expressed on the tumor cells will force a temporary interaction between tumor cell and T cell, causing activation of the T cell and subsequent lysis of the tumor cell. They are particular therapeutic agents according to the invention.

CEA TCB (RG7802, RO6958688, cibisatamab) is a novel T cell activating bispecific antibody targeting CEA on tumor cells and CD3ε on T cells. In mouse models, CEA TCB displays potent anti-tumor activity, leads to increased intratumoral T cell infiltration, increased release of pro-inflammatory cytokines such as IFNγ, TNF and Granzyme B, and up-regulates the PD-L1/PD-1 pathway and its activation. The increase in PD-L1/PD-1 pathway is a sign of fully activated T cells as it is one of the suppressive pathways that is turned on during T cell activation. It is a particular therapeutic agent according to the invention.

FAP-OX40 (RO7194691) is a bispecific antibody construct in development. It simultaneously binds to Fibroblast activation protein (FAP) highly expressed on stroma cells in various solid tumors and the activation induced T-cell specific surface molecule OX40. The mode of action relies on FAP binding (tumor specific targeting) and stimulation of OX40 expressing tumor infiltrating T-cells; thus enhancing the T-cell mediated immune response (cytokine secretion, expansion) against tumor cells in patients. It is in particular described in WO 2017/060144 and WO 2019/086497. It comprises a first heavy chain comprising an amino acid sequence of SEQ ID NO:1, a second heavy chain comprising an amino acid sequence of SEQ ID NO:2, and four light chains comprising an amino acid sequence of SEQ ID NO:3. It is a particular therapeutic agent according to the invention. The murine antibody used in the examples has a first heavy chain comprising an amino acid sequence of SEQ ID NO:4, a second heavy chain comprising an amino acid

sequence of SEQ ID NO:5, and four light chains comprising an amino acid sequence of SEQ ID NO:6.

Table 1: Sequences

SEQ ID NO:	Name	Sequence
1	HC 1 (49B4) VHCH1_VHCH1 Fc knob VH (4B9)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFS SYAISWVRQAPGQGLEWMGGIIPIFGTANYA QKFQGRVTITADKSTSTAYMELSSLRSEDTA VYYCAREYYRGPYDYWGQGTTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDGGGGSGGGGSQVQLVQSGAEV KKPGSSVKVSCKASGGTFSSYAISWVRQAPG QGLEWMGGIIPIFGTANYAQKFQGRVTITAD KSTSTAYMELSSLRSEDTAVYYCAREYYRG PYDYWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPCRDELTKNQVSLWCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGGGGGSGGGGSGGGGSGGGGSEV QLLESGGGLVQPGGSLRLSCAASGFTFSSYA MSWVRQAPGKGLEWVSAIIGSGASTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKGWFGGFNYWGQGTLVTVSS
2	HC 2 (49B4) VHCH1_VHCH1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFS SYAISWVRQAPGQGLEWMGGIIPIFGTANYA QKFQGRVTITADKSTSTAYMELSSLRSEDTA

	Fc hole VL (4B9)	VYYCAREYYRGPYDYWGQGTTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDGGGGSGGGGSQVQLVQSGAEV KKPGSSVKVSCKASGGTFSSYAISWVRQAPG QGLEWMGGIIPIFGTANYAQKFQGRVTITAD KSTSTAYMELSSLRSEDTAVYYCAREYYRG PYDYWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALGAPIEKTISKAKGQPREPQ VCTLPPSRDELTKNQVSLSCAVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLVSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGGGGGSGGGGSGGGGSGGGGSEIV LTQSPGTLSLSPGERATLSCRASQSVTSSYLA WYQQKPGQAPRLLINVGSRRATGIPDRFSGS GSGTDFTLTISRLEPEDFAVYYCQQGIMLPPT FGQGTKVEIK
3	LC (49B4)	DIQMTQSPSTLSASVGDRVTITCRASQSISSW LAWYQQKPGKAPKLLIYDASSLESGVPSRFS GSGSGTEFTLTISSLQPDDFATYYCQQYSSQP YTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
4	HC 1 (P1AD4396)	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTG YNLHWVRQPPGKGLEWMGRMRYDGDTYY NSVLKSRLSISRDTSKNQVFLKMNSLQTDDT AIYYCTRDGRGDSFDYWGQGVMVTVSSAK TTPPSVYPLAPGSAAQTNSMVTLGCLVKGYF PEPVTVTWNSGSLSSGVHTFPAVLQSDLYTL

		SSSVTVPSSTWPSQTVTCNVAHPASSTKVDK KIVPRDCGGGGSGGGGSQVQLKESGPGLVQ PSQTLSLTCTVSGFSLTGYNLHWVRQPPGKG LEWMGRMRYDGDTYYNSVLKSRLSISRDTS KNQVFLKMNSLQTDDTAIYYCTRDGRGDSF DYWGQGVMVTVSSAKTTPPSVYPLAPGSAA QTNSMVTLGCLVKGYFPEPVTVTWNSGSLS SGVHTFPAVLQSDLYTLSSSVTVPSSTWPSQ TVTCNVAHPASSTKVDKKIVPRDCGCKPCIC TVPEVSSVFIFPPKPKDVLTITLTPKVTCVVV AISKDDPEVQFSWFVDDVEVHTAQTKPREE QINSTFRSVSELPIMHQDWLNGKEFKCRVNS AAFGAPIEKTISKTKGRPKAPQVYTIPPPKKQ MAKDKVSLTCMITNFFPEDITVEWQWNGQP AENYKNTQPIMKTDGSYFVYSKLNVQKSNW EAGNTFTCSVLHEGLHNHHTEKSLSHSPGGG GGSGGGGSGGGGSGGGGSEVQLLESGGGLV QPGGSLRLSCAASGFTFSSHAMSWVRQAPG KGLEWVSAIWASGEQYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCAKGWLG NFDYWGQGTLVTVSS
5	HC2 (P1AD4396)	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTG YNLHWVRQPPGKGLEWMGRMRYDGDTYY NSVLKSRLSISRDTSKNQVFLKMNSLQTDDT AIYYCTRDGRGDSFDYWGQGVMVTVSSAK TTPPSVYPLAPGSAAQTNSMVTLGCLVKGYF PEPVTVTWNSGSLSSGVHTFPAVLQSDLYTL SSSVTVPSSTWPSQTVTCNVAHPASSTKVDK KIVPRDCGGGGSGGGGSQVQLKESGPGLVQ PSQTLSLTCTVSGFSLTGYNLHWVRQPPGKG LEWMGRMRYDGDTYYNSVLKSRLSISRDTS KNQVFLKMNSLQTDDTAIYYCTRDGRGDSF DYWGQGVMVTVSSAKTTPPSVYPLAPGSAA QTNSMVTLGCLVKGYFPEPVTVTWNSGSLS SGVHTFPAVLQSDLYTLSSSVTVPSSTWPSQ TVTCNVAHPASSTKVDKKIVPRDCGCKPCIC TVPEVSSVFIFPPKPKDVLTITLTPKVTCVVV AISKDDPEVQFSWFVDDVEVHTAQTKPREE

		QINSTFRSVSELPIMHQDWLNGKEFKCRVNS AAFGAPIEKTISKTKGRPKAPQVYTIPPPKEQ MAKDKVSLTCMITNFFPEDITVEWQWNGQP AENYDNTQPIMDTDGSYFVYSDLNVQKSNW EAGNTFTCSVLHEGLHNHHTEKSLSHSPGGG GGSGGGGSGGGGSGGGGSEIVLTQSPGTLSL SPGERATLSCRASQSVSRSYLAWYQQKPGQ APRLLIIGASTRATGIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYCQQGQVIPPTFGQGTKVEI K
6	LC (P1AD4396)	DIVMTQGALPNPVPSGESASITCRSSQSLVYK DGQTYLNWFLQRPGQSPQLLTYWMSTRASG VSDRFSGSGSGTYFTLKISRVRAEDAGVYYC QQVREYPFTFGSGTKLEIKRADAAPTVSIFPP SSEQLTSGGASVVCFLNNFYPKDINVKWKID GSERQNGVLNSWTDQDSKDSTYSMSSTLTL TKDEYERHNSYTCEATHKTSTSPIVKSFNRN EC

Atezolizumab (MPDL3280A, trade name Tecentriq®) is a fully humanized, engineered monoclonal antibody of IgG1 isotype against the protein programmed cell death-ligand 1 (PD-L1) and is a particular therapeutic agent according to the invention.

Infliximab (REMICADE®) and adalimuab (HUMIRA®) are particular therapeutic agents according to the invention since they are both known to be highly immunogenic. They are anti-TNFalpha antibodies indicated in particular for the treatment of Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis (infliximab) and rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa, uveitis and juvenile idiopathic arthritis (adalimumab).

Crohn’s disease and ulcerative colitis are the principal forms of inflammatory bowel disease (IBD). IBD is a severely debilitating disease that impacts in particular young patients. It can cause bloody diarrhea with urgency, repeated flares, abdominal pain and can necessitate frequent surgical interventions and hospitalizations. The disease burden comprises bowel perforation, toxic megacolon, fistulae, strictures, infertility, abscesses and ileostomy. Patients with IBD have an increased risk of colon cancer, high rates of

depression, anxiety, increased suicide, high rates of severe fatigue (47%), disability (34%), and chronic pain (38%).

The currently available treatments of IBD comprise anti-TNFalpha antibodies like infliximab and adalimumab, anti-α4β7 integrin antibodies like vedolizumab, anti-p40 antibodies like ustekinumab, JAK1 or JAK3i inhibitors like tofacitinib and anti-IL23 antibodies like risankizumab as therapeutic agents.

However, no broad sustained remission is observed with only 10-20% of patients remaining in remission at 1 year of treatment. The onset of some of the above therapeutic agents is slow, taking up to 12 weeks. Low rates of endoscopic and histologic healing are observed, together with increased risk of serious infection and malignancy. And furthermore, the current standard of care, infliximab and adalimumab, generate a high immunogenicity, with reported immunogenicity rates of up to 51% and 26%, respectively.

Efficiently treating IBD remains in consequence a high unmet medical.

Since administering a cathepsin S according to the invention reduces or prevents the formation of anti-drug antibodies (ADA) against a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent, the cathepsin S inhibitor is particularly useful in the treatment of IBD.

The cathepsin S inhibitor according to the invention, in particular the two specific cathepsin S inhibitors described above, can be administered at a dose of between 50 mg/kg/day and 400 mg/kg/day, in particular between 75 mg/kg/day and 250 mg/kg/day, more particularly at 100 mg/kg/day or 200 mg/kg/day.

The cathepsin S inhibitor according to the invention, in particular the two specific cathepsin S inhibitors described above, are particularly advantageously administered at dose of 200 mg/kg/day, in particular 100 mg/kg b.i.d.

100 mg/kg b.i.d has been established as the safest and most efficacious dose of the cathepsin S inhibitor in human according to the invention, in particular for the two specific cathepsin S inhibitors described above. The doses employed in the examples have been adapted to the murine species.

The first dose of the cathepsin S inhibitor is advantageously administered to the subject prior to the first dose of the therapeutic agent, in particular between at least 1 day and 2 weeks before the first dose of the therapeuthic agent, in particular between at least 1 day and 1 week before the first dose of the therapeutic agent, more particularly 1 week before the first dose of the therapeutic agent.

It is therefore understood that the expression "a patient who is receiving a treatment with a therapeutic agent" encompasses patient who are about to start a treatment with said therapeutic agent and which will be dosed with the cathepsin S inhibitor prior to the first dose of the therapeutic agent.

The invention thus relates in particular to:

A cathepsin S inhibitor for use in a method for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent;

A method for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a patient in need thereof who is receiving a treatment with said therapeutic agent, comprising administering an effective amount of a cathepsin S inhibitor to said patient;

A cathepsin S inhibitor for use in a method for increasing the activity of a therapeutic agent in a patient who is receiving a treatment with said therapeutic agent, wherein the activity of said therapeutic agent has been reduced by the subject's immune system;

A method for increasing the activity of a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent, wherein the activity of said therapeutic agent has been reduced by the subject's immune system, comprising the administration of an effective amount of a cathepsin S inhibitor to said patient;

A cathepsin S inhibitor for use in a method for increasing the activity of a therapeutic agent in a patient who is receiving a treatment with said therapeutic agent, wherein the therapeutic agent has a lower activity in the absence of said cathepsin S inhibitor;

A method for increasing the activity of a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent, comprising the administration of an effective amount of a cathepsin S inhibitor to said patient, wherein the therapeutic agent has a lower activity in the absence of said cathepsin S inhibitor;

A cathepsin S inhibitor for use in a method for increasing the bioavailability of a therapeutic agent in a patient who is receiving a treatment with said therapeutic agent;

A method for increasing the bioavailability of a therapeutic agent in a patient in need thereof who is receiving a treatment with said therapeutic agent, comprising the administration of an effective amount of a cathepsin S inhibitor to said patient;

A method for treating or preventing a disease comprising administering an effective amount of a therapeutic agent against said disease to a patient in need thereof and of a cathepsin S inhibitor, wherein the cathepsin S inhibitor is administered in an amount that is sufficient to reduce or prevent the formation of ADA against said therapeutic agent;

The use of a cathepsin S inhibitor in the manufacture of a medicament for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent;

A method for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a patient in need thereof who is receiving a treatment with said therapeutic agent comprising administering an effective amount of a cathepsin S inhibitor to said patient;

The use of a cathepsin S inhibitor in the manufacture of a medicament for increasing the activity of a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent, wherein the activity of said therapeutic agent has been reduced by the subject's immune system;

The use of a cathepsin S inhibitor in the manufacture of a medicament for increasing the activity of a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent, wherein the therapeutic agent has a lower activity in the absence of said cathepsin S inhibitor;

The use of a cathepsin S inhibitor in the manufacture of a medicament for increasing the bioavailability of a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent;

A kit for the prevention or reduction of the formation of ADA against a therapeutic agent in a subject, wherein the kit comprises a cathepsin S inhibitor and instructions for using the cathepsin S inhibitor in a method of treatment comprising the administration of the cathepsin S inhibitor and the therapeutic agent to said subject;

A kit for the prevention or treatment of a disease in a subject, wherein the kit comprises a therapeutic agent and instructions for using the therapeutic agent in a method of treatment comprising the administration of a cathepsin S inhibitor and the therapeutic agent to said subject;

A kit according to the invention comprising:

(a) a therapeutic agent;

(b) a cathepsin S inhibitor; and

(c) instructions for using the therapeutic agent and the cathepsin S inhibitor in a method of treatment comprising the administration of effective amounts of said therapeutic agent and said cathepsin S inhibitor to a patient in need thereof;

A kit according to the invention wherein the cathepsin S inhibitor is administered in an amount that is sufficient to reduce or prevent the formation of ADA against the therapeutic agent;

A cathepsin S inhibitor for use in the treatment of IBD;

A method of treatment of IBD, comprising administering an effective amount of a cathepsin S inhibitor to a patient in need thereof;

A cathepsin S inhibitor for use in the treatment of IBD in a patient who is receiving a treatment with a therapeutic agent;

A method of treatment of IBD, comprising administering an effective amount of a cathepsin S inhibitor to a patient in need thereof, wherein the patient is receiving a treatment with a therapeutic agent;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the first dose of the cathepsin S inhibitor is administered to the subject before the first dose of the therapeutic agent;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the method or the instructions comprise the following consecutive steps:

(a) administering a first effective dose of the cathepsin S inhibitor to the subject;

(b) optionally continuing the administration of the cathepsin S inhibitor before the therapeutic agent is administered to the subject;

(c) administering a first effective dose of the therapeutic agent to the subject; and

(d) continuing the administration of the cathepsin S inhibitor and/or the therapeutic agent to the subject;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the first dose of the cathepsin S inhibitor is administered to the subject prior to the first dose of the therapeutic agent, in particular between at least 1 day and 2 weeks before the first dose of the therapeuthic agent, in particular between at least 1 day and 1 week

before the first dose of the therapeutic agent, more particularly 1 week before the first dose of the therapeutic agent;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the first dose of the cathepsin S inhibitor is administered to the subject on the same day as the first dose of the therapeutic agent;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent does not interfere with the MHC-II antigen presentation;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent does not rely on MHC-II antigen presentation;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the ADA are produced through a T-cell dependent immune response;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the ADA are produced through a T-helper cell dependent immune response;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the ADA are produced by a MHC-II dependent immune response;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the ADA are produced from a cognate interaction between an MHC-II/peptide complex and a T-cell receptor;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is a biologic, in particular a protein, more particularly a polypeptide, an antibody, more particularly a bispecific antibody, in particular a T-cell bispecific antibody, an antibody fragment, an antibody-drug conjugate, a BiTE, a cytokine or a gene therapy vectors like for example AAV vector;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is an immune activating compound, in particular a cancer immunotherapy agent, including check point inhibitory antibodies.

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is an anti-PD-L1 antibody, like for example, atezolizumab, durvalumab oravelumab, in particular atezolizumab;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is an anti-PD-1 anibody, like for example, nivolumab or pembrolizumab;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is a biologic which induces, enhances or suppresses an immune response;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is immunogenic;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is indicated for the treatment of cancer, a metabolic disease like e.g. diabetes, an eye disease, an autoimmune or inflammatory disease;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is indicated for the treatment of inflammatory bowel disease;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is a monoclonal antibody, in particular a monoclonal antibody selected from alemtuzumab (LEMTRADA®), atezolizumab (TECENTRIQ®), bevacizumab (AVASTIN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), pertuzumab (OMNITARG®, 2C4), trastuzumab (HERCEPTIN®), tositumomab (Bexxar®), abciximab (REOPRO®), adalimumab (HUMIRA®), apolizumab, aselizumab, atlizumab, bapineuzumab, basiliximab (SIMULECT®), bavituximab, belimumab (BENLYSTA®) briankinumab, canakinumab (ILARIS®), cedelizumab, certolizumab pegol (CIMZIA®), cidfusituzumab, cidtuzumab, cixutumumab, clazakizumab, crenezumab, daclizumab (ZENAPAX®), dalotuzumab, denosumab (PROLIA®, XGEVA®), eculizumab (SOLIRIS®), efalizumab, emicizumab (HEMLIBRA®), epratuzumab, erlizumab, felvizumab, fontolizumab, golimumab (SIMPONI®), ipilimumab, imgatuzumab, infliximab (REMICADE®), labetuzumab, lebrikizumab, lexatumumab, lintuzumab, lucatumumab, lulizumab pegol, lumretuzumab, mapatumumab, matuzumab, mepolizumab, mogamulizumab, motavizumab, motovizumab, muronomab, natalizumab (TYSABRI®), necitumumab (PORTRAZZA®), nimotuzumab (THERACIM®), nolovizumab, numavizumab, obinutuzumab (GAZYVA®/GAZYVARO®), ocrelizumab (OCREVUS®), olokizumab, omalizumab (XOLAIR®), onartuzumab (also known as MetMAb), palivizumab (SYNAGIS®), pascolizumab, pecfusituzumab, pectuzumab, pegylated interferon (PEGAZYS®), pembrolizumab (KEYTRUDA®), pexelizumab, priliximab, ralivizumab, ranibizumab (LUCENTIS®), reslivizumab, reslizumab, resyvizumab, rituximab (MABTHERA®),

robatumumab, rontalizumab, rovelizumab, ruplizumab, sarilumab, secukinumab, seribantumab, sifalimumab, sibrotuzumab, siltuximab (SYLVANT®) siplizumab, sontuzumab, tadocizumab, talizumab, tefibazumab, tocilizumab (ACTEMRA®), toralizumab, trastuzumab emtansine (KADCYLA®), tucusituzumab, umavizumab, urtoxazumab, ustekinumab (STELARA®), vedolizumab (ENTYVIO®), visilizumab, zanolimumab and zalutumumab;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is a recombinant fusion protein comprised of a human monoclonal antibody directed against fibroblast activation protein-alpha (FAP) linked to an engineered variant form of interleukin-2 (IL-2v);

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is cergutuzumab amunaleukin;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is an anti-TNFalpha antibody;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the therapeutic agent is infliximab (REMICADE®) or adalimumab (HUMIRA®);

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is

(2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; or

(2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

or a pharmaceutically acceptable salt thereof;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-

trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is infliximab (REMICADE®);

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is infliximab (REMICADE®);

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is adalimumab (HUMIRA®);

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is adalimumab (HUMIRA®);

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is cergutuzumab amunaleukin;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is cergutuzumab amunaleukin;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is CEA-TCB;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is CEA-TCB;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is FAP-OX40;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is FAP-OX40;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is atezolizumab;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is atezolizumab;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is CEA-TCB in combination with atezolizumab;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof and the therapeutic agent is CEA-TCB in combination with atezolizumab;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is administered in an amount that is sufficient to reduce or prevent the formation of ADA against the therapeutic agent;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is administered at dose of between 50 mg/kg/day and 400 mg/kg/day, in particular between 75 mg/kg/day and 250 mg/kg/day, more particularly at 100 mg/kg/day or 200 mg/kg/day; and

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is administered at dose of 200 mg/kg/day, in particular 100 mg/kg b.i.d.;

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is administered at dose of 200 mg/kg/day, in particular 100 mg/kg b.i.d. and wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof; and

A cathepsin S inhibitor for use, a method, a use or a kit according to the invention, wherein the cathepsin S inhibitor is administered at dose of 200 mg/kg/day, in particular 100 mg/kg b.i.d. and wherein the cathepsin S inhibitor is (2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide or a pharmaceutically acceptable salt thereof.

The above doses are given for the free base. If a salt is administered, the dose shall be adapted so that in the end the above doses of free base are available to the patient.

In the cathepsin S inhibitor for use in the treatment of IBD, the patient is advantageously receiving a treatment with a therapeutic agent selected from an anti-TNFalpha antibody like infliximab or adalimumab, an anti-α4β7 integrin antibody like vedolizumab, an anti-p40 antibody like ustekinumab, a JAK1 or JAK3i inhibitor like

tofacitinib or an anti-IL23 antibody like risankizumab, more particulary an anti-TNFalpha antibody like infliximab or adalimumab.

In the method of treatment of IBD, comprising administering a cathepsin S inhibitor to a patient in need thereof, the patient is advantageously receiving a treatment with a therapeutic agent selected from an anti-TNFalpha antibody like infliximab or adalimumab, an anti-α4β7 integrin antibody like vedolizumab, an anti-p40 antibody like ustekinumab, a JAK1 or JAK3i inhibitor like tofacitinib or an anti-IL23 antibody like risankizumab, more particulary an anti-TNFalpha antibody like infliximab or adalimumab.

The invention will now be illustrated by the following examples which have no limiting character.

Examples

Example 1: Mitigation of ADA against HUMIRA® (adalimumab) and CEA-IL2v (28 days)

Adalimumab and CEA-IL2v are known to be immunogenic in the clinic (Bartelds, Krieckaert et al. JAMA 2011, 305(14): 1460-1468, van Schouwenburg, Rispens et al. Nat Rev Rheumatol 2013, 9(3): 164-172).

Adalimumab is an anti-TNFα inhibiting antibody shown to be highly immunogenic in mice.

In contrast, CEA-IL2v is an immunomodulatory drug for oncology indication.

For immunogenicity assessment, we used the previously described human IgG1 immune-tolerant mouse model (Bessa, Boeckle et al. Pharm Res 2015, 32(7): 2344-2359). Since this human IgG transgenic mouse is tolerant to a broad range of human IgG1 antibodies (Abs), ADA responses elicited in this system are taken to reflect intrinsic immunogenic attributes of the eliciting Ab compounds also expected to cause ADA in humans.

(2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide is a cathepsin S inhibitor known to inhibit MHCII maturation and antigen presentation by antigen-presenting cells (WO 2010/121918; Theron, Bentley et al. 2017, Front Immunol 8: 806). It is used in the experiements below.

- Immunization

15-week-old mice C57BL/6 wild type and C57BL/6-Tg (hIgG1,k,l) were purchased from Taconic (Denmark) and housed at the animal facilities under a 12 hour (h) light 12 h dark cycle with cycles of air ventilation and free access to water and food. 7x 10µg of CEA-IL2v or 7x 10µg of Humira (Adalimumab, Abbvie Germany GmbH) were injected respectively at day 0, 4, 7, 11, 14, 18 and 21 subcutaneously in the right flank or the left flank alternatively. The dosage of the cathepsin S inhibitor consumption was 40 mg/kg/day. The food admix (Ssniff Spezialdiäten, Germany) was given daily one day before the first immunization until day 28 for the mice immunized with Humira. The food admix was given daily one week before the first immunization until day 28 for the mice immunized with CEA-IL2v (RO6895882). At day -12, 7, 14 and 28 blood samples were taken.

- ADA measurement

Nunc Maxisorp flat-bottom 96 well ELISA plates were coated with 100µl per well of Humira or CEA-PGLALA (3.42mg/ml, ID 8037) respectively at 5µg/mL in NaHCO3 100mM buffer overnight at +4°C. The next day the ELISA plates were washed 3 times with PBS+0.05% Tween. For blocking, 100µl of PBS +2%BSA were added to each well and the ELISA plates were incubated 2 hours at room temperature. The sera were diluted 1 to 50 in PBS +1%FBS in the first raw of round bottom dilution plate, following by a 1 to 3 serial dilution step, 7 times in PBS +1%FBS. The ELISA plates were washed 3 times with PBS+0.05% Tween and 100µl of the diluted sera were transferred from the dilution plate to the ELISA plate. After 2 hours of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. For detection of ADA, 100µl per well of goat anti mouse IgG Alkaline Phosphatase conjugated (Jackson Cat n° 115-055-071) diluted 1:2000 in PBS +1% BSA were added. After 1 hour of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. 100µl of substrate P-nitrophenyl phosphate ready to use (Life Technologies Cat n°002212) were added per well and after 10 min incubation at room temperature, the OD at 405 nm was read as an end-point measurement with a Versamax ELISA reader.

The results are shown in Figures 1-2.

These results show that animals fed with a cathepsin S inhibitor and immunized with adalimumab showed reduced ADA levels compared to vehicle treated animals (Fig.1). Interestingly, the effect was more pronounced at later time-points and at higher serum dilutions, suggesting that either the cathepsin S inhibitor has a preferential effect in inhibiting the late emerging high affinity antibody responses or that one day prior immunization was not sufficient to prevent a certain degree of antigen presentation by APCs.

Our experiments also revealed that prophylactic treatment with a cathepsin S inhibitor (7 days prior immunization) lead to complete abrogation of ADA to CEA-IL2v in hIgG transgenic mice (Fig. 2A). In contrast, only partial reduction of ADA was achieved in wild-type (WT) mice (Fig. 2B). This is likely explained by the overall higher magnitude of ADA induced in WT animals (anti-Fc and anti-idiotypic ADA) in comparison to hIgG Tg mice (only anti-idiotypic ADA).

Example 2: Abrogation of T-cell dependent IgG response

- Immunization by NP-OVAL

6 to 8-weeks-old female mice C57BL/6-Tg (hIgG1,k,l) were purchased from Charles River Laboratories (Germany) and housed at the animal facilities in room with air-conditioned under a 12 hours light/dark cycle in macrolon boxes with enriched

environment and free access to water and food. The mice were injected at day -2 subcutaneously with 20µg/mouse of NP-OVAL (4-Hydroxy-3-nitrophenylacetyl hapten conjugated to ovalbumin, Biosearch Technologies, USA, Batch N° 060368) with adjuvant (Alhydrogel, InvivoGen#vac-alu-250) at the both flanks or without adjuvant at day 28. The dosage of (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide consumption was 0 (vehicle), 1, 10, 40mg/kg/day. The cathepsin S antagonist (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide was given via food admix (Ssniff Spezialdiäten, Germany) daily from two days before the first NP-OVAL immunization until day 35. At day -2, 1, 7, 12, 21, 28 and 35 blood samples from the tail were taken in BD Microtainer tubes SST. After 30min of resting the tubes were centrifuged at 10'000g for 10 min and stored at -20°C.

- NP specific IgG measurement

Nunc Maxisorp flat-bottom 96 well ELISA plates were coated with 100µl per well of NP(4)-BSA (Biosearch Technologies N-5050L; 1 mg/mL) at 1µg/mL in NaHCO3 100mM buffer and incubated overnight at +4°C. The next day the ELISA plates were washed 3 times with PBS+0.05% Tween. For blocking, 100µl of PBS +2%BSA were added to each well and the ELISA plates were incubated 2 hours at room temperature. The sera were diluted 1 to 50 in PBS +1%FBS in the first raw of round bottom dilution plate, following by a 1 to 3 serial dilution step, 7 times in PBS +1%FBS. The ELISA plates were washed 3 times with PBS+0.05% Tween and 100µl of the diluted sera were transferred from the dilution plate to the ELISA plate. After 2 hours of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. For detection of NP specific IgG, 100µl per well of goat anti mouse IgG Alkaline Phosphatase conjugated (Jackson Cat n° 115-055-071) diluted 1:2000 in PBS +1% BSA were added. After 1 hour of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. 100µl of substrate P-nitrophenyl phosphate ready to use (Life Technologies, Cat n°002212) were added per well and after 10 min incubation at room temperature, the OD at 405 nm was read as an end-point measurement with a Versamax ELISA reader.

The results are shown in Figure 3.

The dose of 40 mg/kg/day of the cathepsin S antagonist was capable of effectively abrogating the T-cell dependent IgG response against NP.

Example 3: Mitigation of ADA against HUMIRA® (adalimumab) (63 days)

- Immunization

15-week-old female mice C57BL/6-Tg (hIgG1,k,l) were purchased from Taconic (Denmark) and housed at the animal facilities in room with air-conditioned under a 12 hours light/dark cycle in macrolon boxes with enriched environment and free access to water and food. 7x 10µg of Humira (Adalimumab, Abbvie Germany GmbH) were injected at day 0, 4, 7, 11, 14, 18 and 21 subcutaneously in the right flank or the left flank alternatively. The dosage of (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide consumption was 40 mg/kg/day. (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide was given via food admix (Ssniff Spezialdiäten, Germany) daily from one day before the first Humira immunization until day 28. At day -4, 7, 14, 21, 28, 42, 49 and 56 blood samples from the tail were taken in BD Microtainer tubes SST before dosing. After 30min of resting the tubes were centrifuged at 10'000g for 10 min and stored at -20°C.

- ADA measurement

Nunc Maxisorp flat-bottom 96 well ELISA plates were coated with 100µl per well of Humira or CEA-PGLALA respectively at 5µg/mL in NaHCO3 100mM buffer overnight at +4°C. The next day the ELISA plates were washed 3 times with PBS+0.05% Tween. For blocking, 100µl of PBS +2%BSA were added to each well and the ELISA plates were incubated 2 hours at room temperature. The sera were diluted 1 to 50 in PBS +1%FBS in the first raw of round bottom dilution plate, following by a 1 to 3 serial dilution step, 7 times in PBS +1%FBS. The ELISA plates were washed 3 times with PBS+0.05% Tween and 100µl of the diluted sera were transferred from the dilution plate to the ELISA plate. After 2 hours of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. For detection of ADAs, 100µl per well of goat anti mouse IgG Alkaline Phosphatase conjugated (Jackson Cat n° 115-055-071) diluted 1:2000 in PBS +1% BSA were added. After 1 hour of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. 100µl of substrate P-nitrophenyl phosphate ready to use (Life Technologies, Cat n°002212) were added per well and after 10 min incubation at room temperature, the OD at 405 nm was read as an end-point measurement with a Versamax ELISA reader.

The results are shown in Figure 4.

Example 4: Mitigation of ADA against CEA-IL2v (63 days)

- Immunization

15-week-old mice C57BL/6-Tg (hIgG1,k,l) and C57BL/6 wild type mixed gender were purchased from Taconic (Denmark) and housed at the animal facilities in room with air-conditioned under a 12 hours light/dark cycle in macrolon boxes with enriched environment and free access to water and food. 7x 10µg of CEA-IL2v (Batch n°GLI0144-01) were injected at day 0, 4, 7, 11, 14, 18 and 21 for the primary response, and at day 49, 53, 56 and 60 for the memory response. The CEA-IL2v injections were done subcutaneously in the right flank or the left flank alternatively. The dosage of (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide consumption was 40 mg/kg/day. (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide was given via food admix (Ssniff Spezialdiäten, Germany) daily from one week before the first CEA-IL2v immunization until day 28 for the primary response and from day 42 (one week before boost with CEA-IL2v) until day 78 for the memory response. At day -12, 7, 14, 28, 42, 56 and 63 blood samples from the tail were taken before dosing. For serum and PK samples Sarstedt Micro tubes 1,1ml Z gel (cat. n°41.1378.005) were used. After 30min of resting the tubes were centrifuged at 10'000g for 10 min and stored at -20°C. For PD samples Sarstedt Microvette® 100 µl, Lithium-Heparin tubes (cat. n°20.1282) were used and kept at room temperature until measurement the same day.

- ADA measurement

Nunc Maxisorp flat-bottom 96 well ELISA plates were coated with 100µl per well of Humira or CEA-PGLALA respectively at 5µg/mL in NaHCO3 100mM buffer overnight at +4°C. The next day the ELISA plates were washed 3 times with PBS+0.05% Tween. For blocking, 100µl of PBS +2%BSA were added to each well and the ELISA plates were incubated 2 hours at room temperature. The sera were diluted 1 to 50 in PBS +1%FBS in the first raw of round bottom dilution plate, following by a 1 to 3 serial dilution step, 7 times in PBS +1%FBS. The ELISA plates were washed 3 times with PBS+0.05% Tween and 100µl of the diluted sera were transferred from the dilution plate to the ELISA plate. After 2 hours of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. For detection of ADAs, 100µl per well of goat anti mouse IgG Alkaline Phosphatase conjugated (Jackson Cat n° 115-055-071) diluted 1:2000 in PBS +1% BSA were added. After 1 hour of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. 100µl of substrate P-nitrophenyl phosphate ready to use (Life Technologies, Cat n°002212) were added per well and after 10 min incubation at room temperature, the OD at 405 nm was read as an end-point measurement with a Versamax ELISA reader.

The results are shown in Figures 5A and 5B.

Exemple 5: CEA-IL2v exposure in Tg and wild-type mices

- PK measurement

Serum samples from C56BL/6 hIgG tg and wildtype mice treated with CEA-IL2v (Example 4) were analysed using an enzyme-linked immunosorbent assay (ELISA) under non-GLP conditions. For the ELISA method capture antibody (mAb<CEA>M-Bi), calibrators (RO6895882), diluted serum samples, detection antibody (mAb<CEA>M-Dig) and anti-digoxigenin-POD are added successively to a streptavidin coated microtiter plate (SA-MTP). Formed immobilized immune complexes are detected by addition of the substrate solution ABTS. The color intensity was determined photometrically and was proportional to the analyte concentration in the test sample.

The results are shown in Figures 6A and 6B.

The cathepsin S inhibitor significantly increases and prolongs CEA-IL2v exposure.

- PD measurement

From Example 4, 50µl of lithium heparin whole blood were transferred into a 5ml polystyrene round-bottom tubes (BD Falcon, Cat. n°352058) and 2 ml of freshly prepared 1x Pharm Lyse™ lysing buffer (BD Bioscience, Cat. n°555899) with UltraPur™ distilled water (Invitrogen, Cat. n°10977-035) were added. The samples were vortexed thoroughly and incubated for 15 min at room temperature. After the incubation time, the tubes were spin down at 300g for 5 min, the supernatants were removed and the cells pellets were washed with 2ml DPBS (Gibco, Cat.n°14190-094) +2% Fetal bovine serum (Gibco, Cat.n°10082147). The tubes were spin down at 300g for 5 min and the supernatants were removed. 100µl of TruStain fcX™ (BioLegend, Cat.n°101320) diluted at 1:100 in DPBS+2%FBS were added to the cell pellets, carefully vortexed and incubated for 15 at room temperature. A master mix was prepared with 0.5µl of BV510-conjugated anti mouse CD45 (Biolegend, Cat.n°103138), 0.4µl of PE-Cy5-conjugated anti mouse TCRb (Biolegend, Cat.n°109210), 0.5µl of BUV737-conjugated anti mouse CD4 (BD Biosciences, Cat.n°564298), 0.5µl of BUV395-conjugated anti mouse CD8 (BD Biosciences, Cat.n°563786), 0.5µl of BV605 –conjugated anti mouse NKP46 (BD Biosciences, Cat.n°564069), and 0.5µl of BV605-conjugated anti mouse NK1.1 (Biolegend, Cat.n°108740) per sample. 3 µl of the master mix were added to the samples. After 30 min of incubation at +4°C in the dark, 2ml of DPBS+2%FBS were added and the tubes were spin down at 300g, +4°C. The supernatants were removed and the pellets were

re-suspend with 150µl of DPBS+2%FBS. Data were acquired with the BD FACSDiva software v8.0 on BD LSRFortessa™ cytometer and analyzed with FlowJo™ V10.

The results are shown in Figures 7A-7D.

CEA-IL2v pharmacology is preserved in cathepsin S inhibitor treated animals.

Example 6: Mitigation of ADA against FAP-OX40

- Immunization

10-week-old female mice C57BL/6 were purchased from Charles River Laboratories (Germany) and housed at the animal facilities in room with air-conditioned under a 12 hours light/dark cycle in macrolon boxes with enriched environment and free access to water and food. 12.5mg/kg of muFAP-OX40iMab (P1AD4396-005) were injected at day 1, 4 and 8 intravenously to the group 2 (n=10 mice) and at day 1, 4, 8, 11, 15, 18 and 22 to the group 3 (n=10 mice) respectively. The dosage of (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide consumption was 40 mg/kg/day. (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide was given via food admix (Ssniff Spezialdiäten, Germany) daily from one week before the first muFAP-OX40iMab immunization until day 23 to the group 3. The group 2 were feed with chow diet provided by Ssniff for the same time. At day -7, 8, 15, and 23 blood samples from the tail were taken in Sarstedt Micro tubes 1,1ml Z gel (cat. n°41.1378.005) before dosing. After 30min of resting the tubes were centrifuged at 10'000g for 10 min and stored at -20°C.

- ADA measurement

Nunc Maxisorp flat-bottom 96 well ELISA plates were coated with 100µl per well of FAP(28H1)-OX40(49B4) PGLALA (P1AD4523) or anti OX40 moIgG2a (P1AD4561) respectively at 5µg/mL in NaHCO3 100mM buffer overnight at +4°C. The next day the ELISA plates were washed 3 times with PBS+0.05% Tween. For blocking, 100µl of PBS +2%BSA were added to each well and the ELISA plates were incubated 2 hours at room temperature. The sera were diluted 1 to 50 in PBS +1%FBS in the first raw of round bottom dilution plate, following by a 1 to 3 serial dilution step, 7 times in PBS +1%FBS. The ELISA plates were washed 3 times with PBS+0.05% Tween and 100µl of the diluted sera were transferred from the dilution plate to the ELISA plate. After 2 hours of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. For detection of ADAs, 100µl per well of goat anti mouse IgG Alkaline

Phosphatase conjugated (Jackson Cat n° 115-055-071) diluted 1:2000 in PBS +1% BSA were added. After 1 hour of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. 100µl of substrate P-nitrophenyl phosphate ready to use (Life Technologies, Cat n°002212) were added per well and after 10 min incubation at room temperature, the OD at 405 nm was read as an end-point measurement with a Versamax ELISA reader.

The results are shown in Figures 8A and 8B.

Example 7: Mitigation of ADA against PD-L1

- Immunization

10-week-old female mice C57BL/6 were purchased from Charles River Laboratories (Germany) and housed at the animal facilities in room with air-conditioned under a 12 hours light/dark cycle in macrolon boxes with enriched environment and free access to water and food. 10mg/kg of muPD-L1 (P1AE4930-001) were injected at day 1, 8 and 15 intravenously to the group 4 (n=10 mice) and at day 1, 8, 15 and 22 to the group 5 (n=10 mice) respectively. The dosage of (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide consumption was 40 mg/kg/day. (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide was given via food admix (Ssniff Spezialdiäten, Germany) daily from one week before the first muPD-L1 immunization until day 23 to the group 5. The group 4 were feed with chow diet provided by Ssniff for the same time. At day -7, 8, 15, and 23 blood samples from the tail were taken in Sarstedt Micro tubes 1,1ml Z gel (cat. n°41.1378.005) before dosing. After 30min of resting the tubes were centrifuged at 10'000g for 10 min and stored at -20°C.

- ADA measurement

Nunc Maxisorp flat-bottom 96 well ELISA plates were coated with 100µl per well of anti muPD-L1 (P1AE4930-001) at 5µg/mL in NaHCO3 100mM buffer overnight at +4°C. The next day the ELISA plates were washed 3 times with PBS+0.05% Tween. For blocking, 100µl of PBS +2%BSA were added to each well and the ELISA plates were incubated 2 hours at room temperature. The sera were diluted 1 to 50 in PBS +1%FBS in the first raw of round bottom dilution plate, following by a 1 to 3 serial dilution step, 7 times in PBS +1%FBS. The ELISA plates were washed 3 times with PBS+0.05% Tween and 100µl of the diluted sera were transferred from the dilution plate to the ELISA plate. After 2 hours of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. For detection of ADAs, 100µl per well of goat anti mouse IgG

Alkaline Phosphatase conjugated (Jackson Cat n° 115-055-071) diluted 1:2000 in PBS +1% BSA were added. After 1 hour of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. 100µl of substrate P-nitrophenyl phosphate ready to use (Life Technologies, Cat n°002212) were added per well and after 10 min incubation at room temperature, the OD at 405 nm was read as an end-point measurement with a Versamax ELISA reader.

The results are shown in Figure 9.

Example 8: Mitigation of ADA against CEA-TCB

- Immunization

11-15-week-old mice C57BL/6-Tg (hIgG1,k,l) mixed gender(n=20) were purchased from Taconic (Denmark) and housed at the animal facilities in room with air-conditioned under a 12 hours light/dark cycle in macrolon boxes with enriched environment and free access to water and food. 7x 10µg of CEA-TCB (P1AE3536, huCEA binder CH1A1A/mouse CD3 binder 2C11) were injected at day 0, 4, 7, 11, 14, 18 and 21 subcutaneously in the right flank or the left flank alternatively. The dosage of (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide consumption was 40 mg/kg/day. (2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide was given via food admix (Ssniff Spezialdiäten, Germany) daily from one week before the first CEA-TCB immunization until day 28 to the group 2 (n=10). The group 1 (n=10) were feed with chow diet provided by Ssniff for the same time. At day -7, 8, 15, and 28 blood samples from the tail were taken in Sarstedt Micro tubes 1,1ml Z gel (cat. n°41.1378.005) before dosing. After 30min of resting the tubes were centrifuged at 10'000g for 10 min and stored at -20°C.

- ADA measurement

Nunc Maxisorp flat-bottom 96 well ELISA plates were coated with 100µl per well of huCEA IgG PGLALA (P1AD9477) or hu anti mouse CD3 (P1AE2779-001-01)respectively at 5µg/mL in NaHCO3 100mM buffer overnight at +4°C. The next day the ELISA plates were washed 3 times with PBS+0.05% Tween. For blocking, 100µl of PBS +2%BSA were added to each well and the ELISA plates were incubated 2 hours at room temperature. The sera were diluted 1 to 50 in PBS +1%FBS in the first raw of round bottom dilution plate, following by a 1 to 3 serial dilution step, 7 times in PBS +1%FBS. The ELISA plates were washed 3 times with PBS+0.05% Tween and 100µl of the diluted sera were transferred from the dilution plate to the ELISA plate. After 2 hours of

incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. For detection of ADA against CEA, 100µl per well of goat anti mouse IgG Alkaline Phosphatase conjugated (Jackson Cat n° 115-055-071) diluted 1:2000 in PBS +1% BSA were added. For detection of ADA against CD3 binder, 100µl per well of goat anti mouse IgG2c Alkaline Phosphatase conjugated (Jackson Cat n° 115-055-208) diluted 1:2000 in PBS +1% BSA were added. After 1 hour of incubation at room temperature, the ELISA plates were washed 3 times with PBS+0.05% Tween. 100µl of substrate P-nitrophenyl phosphate ready to use (Life Technologies, Cat n°002212) were added per well and after 10 min incubation at room temperature, the OD at 405 nm was read as an end-point measurement with a Versamax ELISA reader.

The results are shown in Figures 10A and 10B.

Claims

1. A cathepsin S inhibitor for use in a method for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a subject who is receiving a treatment with said therapeutic agent.

2. A method for reducing or preventing the formation of anti-drug antibodies (ADA) against a therapeutic agent in a patient in need thereof who is receiving a treatment with said therapeutic agent comprising administering an effective amount of a cathepsin S inhibitor to said patient.

3. A kit for the prevention or reduction of the formation of ADA against a therapeutic agent in a subject, wherein the kit comprises a cathepsin S inhibitor and instructions for using the cathepsin S inhibitor in a method of treatment comprising the administration of an effective amount of the cathepsin S inhibitor and the therapeutic agent to said subject.

4. A kit according to claim 3 comprising:

(a) a therapeutic agent;

(b) a cathepsin S inhibitor; and

(c) instructions for using the therapeutic agent and the cathepsin S inhibitor in a method of treatment comprising the administration of an effective amount of said therapeutic agent and said cathepsin S inhibitor to a patient in need thereof.

5. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 4, wherein the first dose of the cathepsin S inhibitor is administered to the subject before the first dose of the therapeutic agent.

6. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 5, wherein the method or the instructions comprise the following consecutive steps:

(a) administering a first effective dose of the cathepsin S inhibitor to the subject;

(b) optionally continuing the administration of the cathepsin S inhibitor before the therapeutic agent is administered to the subject;

(c) administering a first effective dose of the therapeutic agent to the subject; and

(d) continuing the administration of the cathepsin S inhibitor and/or the therapeutic agent to the subject.

7. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 6, wherein the first dose of the cathepsin S inhibitor is administered to the subject prior to the first dose of the therapeutic agent, in particular between at least 1 day and 2 weeks before the first dose of the therapeuthic agent, in particular between at least 1 day and 1 week before the first dose of the therapeutic agent, more particularly 1 week before the first dose of the therapeutic agent.

8. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 7, wherein the therapeutic agent does not rely on MHC-II antigen presentation.

9. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 8, wherein the ADA are produced through a T-cell dependent immune response.

10. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 9, wherein the ADA are produced through a T-helper cell dependent immune response.

11. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 10, wherein the ADA are produced by a MHC-II dependent immune response.

12. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 7, wherein the therapeutic agent is a biologic in particular an antibody.

13. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 12, wherein the therapeutic agent is a biologic which induces, enhances or suppresses an immune response.

14. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 13, wherein the therapeutic agent is a biologic, in particular a protein, more particularly a polypeptide, an antibody, more particularly a bispecific antibody, in particular a T-cell bispecific antibody, an antibody fragment, an antibody-drug conjugate, a BiTE, a cytokine or a vector like for example a gene therapy vector.

15. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 14, wherein the therapeutic agent is a monoclonal antibody, in particular a monoclonal antibody selected from alemtuzumab (LEMTRADA®), atezolizumab (TECENTRIQ®), bevacizumab (AVASTIN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), pertuzumab (OMNITARG®, 2C4), trastuzumab (HERCEPTIN®), tositumomab (Bexxar®), abciximab (REOPRO®), adalimumab

(HUMIRA®), apolizumab, aselizumab, atlizumab, bapineuzumab, basiliximab (SIMULECT®), bavituximab, belimumab (BENLYSTA®) briankinumab, canakinumab (ILARIS®), cedelizumab, certolizumab pegol (CIMZIA®), cidfusituzumab, cidtuzumab, cixutumumab, clazakizumab, crenezumab, daclizumab (ZENAPAX®), dalotuzumab, denosumab (PROLIA®, XGEVA®), eculizumab (SOLIRIS®), efalizumab, emicizumab (HEMLIBRA®), epratuzumab, erlizumab, felvizumab, fontolizumab, golimumab (SIMPONI®), ipilimumab, imgatuzumab, infliximab (REMICADE®), labetuzumab, lebrikizumab, lexatumumab, lintuzumab, lucatumumab, lulizumab pegol, lumretuzumab, mapatumumab, matuzumab, mepolizumab, mogamulizumab, motavizumab, motovizumab, muronomab, natalizumab (TYSABRI®), necitumumab (PORTRAZZA®), nimotuzumab (THERACIM®), nolovizumab, numavizumab, obinutuzumab (GAZYVA®/GAZYVARO®), ocrelizumab (OCREVUS®), olokizumab, omalizumab (XOLAIR®), onartuzumab (also known as MetMAb), palivizumab (SYNAGIS®), pascolizumab, pecfusituzumab, pectuzumab, pegylated interferon (PEGAZYS®), pembrolizumab (KEYTRUDA®), pexelizumab, priliximab, ralivizumab, ranibizumab (LUCENTIS®), reslivizumab, reslizumab, resyvizumab, rituximab (MABTHERA®), robatumumab, rontalizumab, rovelizumab, ruplizumab, sarilumab, secukinumab, seribantumab, sifalimumab, sibrotuzumab, siltuximab (SYLVANT®) siplizumab, sontuzumab, tadocizumab, talizumab, tefibazumab, tocilizumab (ACTEMRA®), toralizumab, trastuzumab emtansine (KADCYLA®), tucusituzumab, umavizumab, urtoxazumab, ustekinumab (STELARA®), vedolizumab (ENTYVIO®), visilizumab, zanolimumab and zalutumumab.

16. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 15, wherein the therapeutic agent is a recombinant fusion protein comprised of a human monoclonal antibody directed against fibroblast activation protein-alpha (FAP) linked to an engineered variant form of interleukin-2 (IL-2v).

17. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 15, wherein the therapeutic agent is cergutuzumab amunaleukin.

18. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 15, wherein the therapeutic agent is an anti-TNFalpha antibody.

19. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 15, wherein the therapeutic agent is infliximab (REMICADE®) or adalimumab (HUMIRA®).

20. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 19, wherein the cathepsin S inhibitor is

(2S,4R)-4-[4-(1-methyl-1H-pyrazol-4-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide; or

(2S,4R)-4-[4-(5-methyl-tetrazol-2-yl)-2-trifluoromethyl-benzenesulfonyl]-1-(1-trifluoromethyl-cyclopropanecarbonyl)-pyrrolidine-2-carboxylic acid (1-cyano-cyclopropyl)-amide;

or a pharmaceutically acceptable salt thereof.

21. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 20, wherein the cathepsin S inhibitor is administered in an amount that is sufficient to reduce or prevent the formation of ADA against the therapeutic agent.

22. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 21, wherein the cathepsin S inhibitor is administered at dose of between 50 mg/kg/day and 400 mg/kg/day, in particular between 75 mg/kg/day and 250 mg/kg/day, more particularly at 100 mg/kg/day or 200 mg/kg/day.

23. A cathepsin S inhibitor for use, a method or a kit according to any one of claims 1 to 21, wherein the cathepsin S inhibitor is administered at dose of 200 mg/kg/day, in particular 100 mg/kg b.i.d.

24. The invention as hereinbefore described.

***