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).

Summary

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.

In one aspect, the present disclosure provides a cathepsin S inhibitor for use in 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, wherein the therapeutic agent is a biologic.

In another aspect, the present disclosure provides a 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 patient in need thereof who is receiving a treatment with said therapeutic agent, wherein the therapeutic agent is a biologic.

In another aspect, the present disclosure provides a kit for use in 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, wherein the therapeutic agent is a biologic.

In another aspect, the present disclosure provides a use of a cathepsin S inhibitor in the manufacture of a kit for the prevention or reduction of the formation of ADA against a therapeutic agent in a subject, wherein the kit further comprises 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, wherein the therapeutic agent is a biologic.

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

Claims

1. A cathepsin S inhibitor for use in 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, wherein the therapeutic agent is a biologic.

2. 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 patient in need thereof who is receiving a treatment with said therapeutic agent, wherein the therapeutic agent is a biologic.

3. A kit for use in 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, wherein the therapeutic agent is a biologic.

4. A kit for use 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. Use of a cathepsin S inhibitor in the manufacture of a kit for the prevention or reduction of the formation of ADA against a therapeutic agent in a subject, wherein the kit further comprises 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, wherein the therapeutic agent is a biologic.

6. The use according to claim 5, wherein the kit comprises:

(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.

7. A cathepsin S inhibitor for use according to claim 1, use according to any one of claims 2, 5 or 6 or a kit for use according to claim 3 or 4, wherein the first dose of the cathepsin S inhibitor is to be administered to the subject before the first dose of the therapeutic agent.

8. A cathepsin S inhibitor for use according to claim 1 or 7, use according to any one of claims 2 or 5 to 7 or a kit for use according to any one of claims 3, 4 or 7, wherein the reducing or preventing or the instructions comprises:

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

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

(c) a first effective dose of the therapeutic agent is to be administered to the subject; and

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

9. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 8, use according to any one of claims 2 or 5 to 8 or a kit for use according to any one of claims 3, 4 or 7 to 8, wherein the first dose of the cathepsin S inhibitor is to be 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.

10. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 9, use according to any one of claims 2 or 5 to 9 or a kit for use according to any one of claims 3, 4 or 7 to 9, wherein the therapeutic agent does not rely on MHC-II antigen presentation.

11. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 10, use according to any one of claims 2 or 5 to 10 or a kit for use according to any one of claims 3, 4 or 7 to 10, wherein the ADA are produced through a T-cell dependent immune response.

12. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 11, use according to any one of claims 2 or 5 to 11 or a kit for use according to any one of claims 3, 4 or 7 to 11, wherein the ADA are produced through a T-helper cell dependent immune response.

13. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 12, use according to any one of claims 2 or 5 to 12 or a kit for use according to any one of claims 3, 4 or 7 to 12, wherein the ADA are produced by a MHC-II dependent immune response.

14. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 9, use according to any one of claims 2 or 5 to 9 or a kit for use according to any one of claims 3, 4 or 7 to 9, wherein the therapeutic agent is an antibody.

15. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 14, use according to any one of claims 2 or 5 to 14 or a kit for use according to any one of claims 3, 4 or 7 to 14, wherein the therapeutic agent is a biologic which induces, enhances or suppresses an immune response.

16. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 15, use according to any one of claims 2 or 5 to 15 or a kit for use according to any one of claims 3, 4 or 7 to 15, 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.

17. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 16, use according to any one of claims 2 or 5 to 16 or a kit for use according to any one of claims 3, 4 or 7 to 16, 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.

18. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 17, use according to any one of claims 2 or 5 to 17 or a kit for use according to any one of claims 3, 4 or 7 to 17, 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).

19. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 17, use according to any one of claims 2 or 5 to 17 or a kit for use according to any one of claims 3, 4 or 7 to 17, wherein the therapeutic agent is cergutuzumab amunaleukin.

20. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 17, use according to any one of claims 2 or 5 to 17 or a kit for use according to any one of claims 3, 4 or 7 to 17, wherein the therapeutic agent is an anti-TNFalpha antibody.

21. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 17, use according to any one of claims 2 or 5 to 17 or a kit for use according to any one of claims 3, 4 or 7 to 17, wherein the therapeutic agent is infliximab (REMICADE®) or adalimumab (HUMIRA®).

22. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 21, use according to any one of claims 2 or 5 to 21 or a kit for use according to any one of claims 3, 4 or 7 to 21, 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.

23. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 22, use according to any one of claims 2 or 5 to 22 or a kit for use according to any one of claims 3, 4 or 7 to 22, wherein the cathepsin S inhibitor is to be administered in an amount that is sufficient to reduce or prevent the formation of ADA against the therapeutic agent.

24. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 23, use according to any one of claims 2 or 5 to 23 or a kit for use according to any one of claims 3, 4 or 7 to 23, wherein the cathepsin S inhibitor is to be 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.

25. A cathepsin S inhibitor for use according to any one of claims 1 or 7 to 23, use according to any one of claims 2 or 5 to 23 or a kit for use according to any one of claims 3, 4 or 7 to 23, wherein the cathepsin S inhibitor is to be administered at dose of 200 mg/kg/day, in particular 100 mg/kg b.i.d.

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