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(54) Title: INHIBITORS OF PACE4 FOR THE TREATMENT OF ARTHRITIS

(57) Abstract: Disclosed are methods and compositions for the treatment of arthritis using inhibitors of PACE4.

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INHIBITORS OF PACE4 FOR THE TREATMENT OF ARTHRITIS

FIELD OF THE INVENTION

The present invention relates to methods of treating and prevention osteoarthritis, and more particularly, methods of inhibiting proprotein convertases responsible for processing precursor enzymes that degrade components of cartilage.

BACKGROUND OF THE INVENTION

Degradation of articular cartilage, resulting in the loss of its biomechanical properties, is the hallmark of osteoarthritis (OA). The primary cause of this process is elevated levels of proteolytic enzymes that degrade cartilage aggrecan and type II collagen. Aggrecan loss, which is an early and perhaps the most critical event in the progression of arthritis, can be ascribed to increased activity of aggrecanases that cleave the core protein. Two cartilage aggrecanases, aggrecanase-1 and aggrecanase-2, have been identified. They are zinc metalloproteinases belonging to the a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family, and are designated ADAMTS-4 and ADAMTS-5, respectively. Both are synthesized by chondrocytes in a latent, inactive form, thus requiring activation before they exert their activities against aggrecan.

Proprotein convertases (PC) are serine proteases whose major function is the proteolytic processing of precursor proteins into their functionally active forms through cleavage at the C-terminus of the consensus sequence RXXR. PC's are intracellular enzymes found in the cytosol, transgolgi membrane, cellular vesicles and the cell membrane. Some PC's are membrane bound, while others are free. A subgroup of proprotein convertases that cleave precursor proteins at a pair of basic amino acid residues within the precursor protein are called PACE, an acronym for paired-basic amino acid cleaving enzymes. One member of the PACE family of proprotein convertase enzymes is known as PACE4.

Several inhibitors of PACE4 are known, such as polyarginine peptides and the chloromethylketone peptide inhibitor RVKR-CMK. Unlike the homolog PC PACE, PACE4 is not significantly inhibited by the mutant serine protease inhibitor (serpin) α1 antitrypsin Pittsburgh (α1-AT_p), and equivocally inhibited by the mutant α1 antitrypsin

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Portland (α1-PDX). Inhibitors of PACE4 gene expression are also known, such as hASH-1 and MASH-1 . To date, few PACE4 substrates well characterized, the most notable being vonWillibrand factor.

SUMMARY OF THE INVENTION

It has now been discovered that PACE4 is responsible, at least in part, for the processing and activation of aggrecanase-1 (ADAMTS-4) and aggrecanase-2 (ADAMTS-5). PACE4 is secreted by articular chondrocytes into the extracellular matrix of OA cartilage resulting in the activation of ADAMTS-4 and ADAMTS-5 and subsequent aggrecan degradation. Aggrecanase-1 is believed to be responsible, at least in part, for the degradation of cartilage in arthritis conditions, especially in osteoarthritis. Therefore, an embodiment of the present invention is directed to a method of preventing or treating an arthritis condition by inhibition of PACE4 in a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "PACE4," as used herein, means the dibasic proprotein convertase enzyme with the SWISSPROT accession number P29122, SEQ ID NO. 1, Chemical Abstracts Registry Number: 151662-24-7, described in U.S. Patent No. 5,863,756 issued to Barr et al., herein incorporated by reference. PACE4 is also known as protein convertase 6, Endoprotease PACE4; PACE4 proteinase; Paired basic amino acid cleaving enzyme 4; Precursor convertase PACE4; Propeptidase PACE4; Proprotein convertase PACE4; and Proprotein convertase SPC4.

The term "aggrecanase," as used herein, and unless otherwise qualified, means either the enzyme aggrecanase-1 (also known as ADAMTS-4), and aggrecanase-2 (also known as ADAMTS-5).

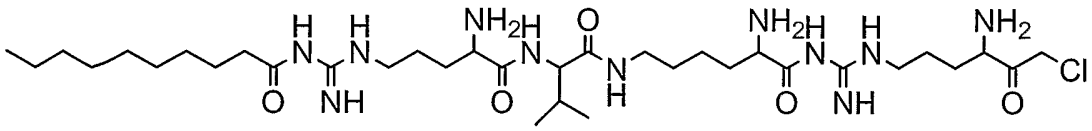
The terms "latent aggrecanase, precursor aggrecanase, immature aggrecanase, or pre-aggrecanase," as used interchangeably herein, means the unprocessed form of aggrecanase, that is to say, the form of aggrecanase prior to processing by a proprotein

convertase, particularly PACE4. This form of aggrecanase is not enzymatically active, that is, not functional to cleave aggrecan.

The terms "active aggrecanase, functional aggrecanase, mature aggrecanase, or processed aggrecanase," as used interchangeably herein, means the form of aggrecanase that is enzymatically active, that is, functional to cleave aggrecan.

The term "α1-PDX," as used herein, means alpha1-antitrypsin variant Portland, an engineered serpin (that is, serine protease inhibitor) that contains the minimal SPC consensus motif in its reactive loop.

The term "RVKR-CMK," as used herein, means the irreversible chloromethylketone peptide inhibitor, Decanoyl-Arg-Val-Lys-Arg-chloromethylketone, a broad PC inhibitor. RVKR-CMK has the following structure:



$C_{34}H_{66}ClN_{11}O_5$
Exact Mass: 743.49
Mol. Wt.: 744.41
C, 54.86; H, 8.94; Cl, 4.76; N, 20.70; O, 10.75

The term "hASH-1," as used herein, means human *achaete–scute* homologue 1. It is believed that hASH-1 down-regulates PACE-4 gene expression.

The term "MASH-1," as used herein, means mammalian *achaete–scute* homologue 1, a mammalian homologue of the *Drosophila achaete–scute* complex. It is believed that MASH-1 down-regulates PACE-4 gene expression.

A pharmaceutically acceptable carrier includes, but is not limited to, physiological saline, Ringer's, phosphatesolution or buffer, buffered saline, and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a

tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

Also included in the compositions of the invention are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine,

chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

"Effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is readily determined by one or ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used; the nature and severity of the illness to be treated as well as on the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

"Co-administration" and "co-administered" mean both taken in a single delivery vehicle, taken together contemporaneously, or taken within a period of time sufficient to receive a beneficial effect from both of the constituent agents of the combination.

The term "subject" for purposes of treatment includes any human or animal subject who has any one of the known arthritis disorders, and is preferably a human subject. For methods of prevention, the subject is any human or animal subject, and preferably is a human subject who is at risk for obtaining arthritis. The subject may be at risk due to genetic predisposition, injury, age and the like.

The term "treatment," as used herein, unless otherwise qualified, means prophylactic, palliative, restorative or curative treatment.

The term "prophylactic treatment," as used herein, means preventative treatment for a subject predisposed to a PACE4 mediated condition. The predisposition may be due to genetic factors, age, sex, injury, and the like.

The term "palliative treatment," as used herein, means treatment with the objective of relieving symptoms of a condition, without significantly mitigating or eliminating the underlying condition.

The term "restorative treatment," as used herein, means treatment effective to mitigate the underlying condition.

The term "curative treatment," as used herein, means treatment effective to cause the complete remission of the underlying condition.

The term "arthritis," as used herein, and unless otherwise qualified, includes without limitation rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis.

The singular indefinite articles "a" and "an," when used in a Markush group, are intended to include the plural.

Both ADAMTS-4 and ADAMTS-5 have a PC cleavage site, $RAKR^{212}$ and $RRRR^{261}$ (Arg-Ala-Lys-Arg^{212} and Arg-Arg-Arg-Arg^{261}) respectively, located within their pro-domain downstream from the cysteine switch, suggesting that one or more PC's activate these proteinases. Addition of several recombinant PC's, including furin, PC5/6, PC7 and PACE4, to unstimulated live or dead bovine or human cartilage explants triggered aggrecan catabolism, suggesting activation of constitutively present latent aggrecanases. Furthermore, IL-1-induced aggrecan breakdown could be blocked with the irreversible chloromethylketone peptide inhibitor, RVKR-CMK (Decanoyl-Arg-Val-Lys-Arg-chloromethylketone), a broad PC inhibitor, but not with the potent furin inhibitor alpha1-PDX. Endogenous PC activity was detected in the extracellular matrix of IL-1-stimulated bovine cartilage and human OA cartilage, but not in that of normal cartilage, suggesting that a PC is secreted from chondrocytes in pathological conditions. We went on to purify the endogenous PC activity from the extracellular matrix of OA cartilage using conventional and affinity chromatography. The enzymatic profile of this activity was found to be identical to that of PACE4, and its identity was confirmed to be PACE4 by immunoprecipitation. Recombinant PACE4 was shown to activate recombinant proADAMTS-4 and proADAMTS-5 in what appears to be a 2-step activation requiring cleavage at the PC cleavage site located within the N-terminal domain and at another PC cleavage site located within the C-terminal thrombospondin domain at $RRTR^{565}$ (Arg-Arg-Thr-Arg^{565}) and $RAIYR^{614}$ (Arg-Ala-Ile-Tyr-Arg^{614}) of ADAMTS-4 and ADAMTS-5, respectively. Finally, evaluation of human OA cartilage by immunohistochemistry demonstrated that PACE4 is co-localized with ADAMTS-4 protein, with the aggrecanase-generated aggrecan neoepitope, $NITEGE^{373}$ (Asn-Ile-Thr-Glu-Gly-Glu^{373}), and with areas of aggrecan depletion.

Inhibition of PACE4 may be accomplished by reducing or halting expression of the PACE4 gene. The bHLH transcription factors Hash-1, Hash-2, Mash-1 and Mash-2

are known to inhibit expression of PACE4. Therefore, in one embodiment of the present invention, a therapeutically effective amount of a transcription factor selected from Hash-1, Hash-2, Mash-1 and Mash-2 is administered to a subject suffering from arthritis, to prevent expression of PACE4 and subsequent processing of aggrecanase.

Inhibition of PACE4 may in addition be accomplished by administering an antibody that is specific for and capable of inactivating PACE4. In one embodiment of the present invention, a monoclonal antibody that is specific for PACE4 and is capable of inactivating PACE4 is administered to a subject in need thereof. In another embodiment, one or more polyclonal antibodies that are specific for PACE4 and capable of inactivating PACE4 are administered to a subject in need thereof.

Numerous variations will occur to those skilled in the art in light of the foregoing disclosure. Such variations are intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

1. A method for treating arthritis, in a subject in need of such treatment, comprising administering to the subject a treatment effective amount of a blocker of PACE4.

2. The method of claim 1 wherein said blocker of PACE4 is an inhibitor of PACE4 enzyme.

3. The method of claim 2 wherein said inhibitor of PACE4 enzyme is one or more compounds selected from the group consisting of: a monoclonal antibody specific to and capable of inactivating PACE4; one or more polyclonal antibodies specific to and capable of inactivating PACE5; a polyarginine compound; and the chloromethylketone peptide inhibitor RVKR-CMK.

4. The method of claim 1 wherein said blocker of PACE4 is an inhibitor of PACE4 gene expression.

5. The method of claim 4 wherein said inhibitor of PACE4 gene expression is one or two compounds selected from the group consisting of hASH-1 and MASH-1.

6. The use of an inhibitor of PACE4 in the manufacture of a medicament for the treatment of arthritis.

7. A pharmaceutical composition comprising an arthritis treatment effective amount of a blocker of PACE4, together with a suitable, pharmaceutically acceptable carrier.

8. The pharmaceutical composition of claim 7 wherein the blocker of PACE4 is an inhibitor of PACE4 enzyme.

9. The pharmaceutical composition of claim 8 wherein said inhibitor of PACE4 enzyme is one or more compounds selected from the group consisting of: a monoclonal antibody specific to and capable of inactivating PACE4; a polyarginine compound, and the chloromethylketone peptide inhibitor RVKR-CMK.

10. The pharmaceutical composition of claim 7 wherein said blocker of PACE4 is an inhibitor of PACE4 gene expression.

11. The pharmaceutical composition of claim 10 wherein said inhibitor of PACE4 gene expression is one or two compounds selected from the group consisting of hASH-1 and MASH-1.

12. A method of preventing the activation of precursor aggrecanase into functionally active aggrecanase in a subject in need of aggrecanase inhibition comprising treating said subject with an effective amount of a blocker of PACE4.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002948

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/55 A61K39/395 A61P19/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	MILNER J M ET AL: "Inhibition of furin-like enzymes blocks interleukin-1alpha/oncostatin M-stimulated cartilage degradation." ARTHRITIS AND RHEUMATISM. APR 2003, vol. 48, no. 4, April 2003 (2003-04), pages 1057-1066, XP002318175 ISSN: 0004-3591 page 1057 - page 1058	1-12
P,X	WO 2004/009113 A (RENOVO LIMITED; FERGUSON, MARK, WILLIAM, JAMES; BRUNNER, GEORG) 29 January 2004 (2004-01-29) page 10 page 14	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2005	07/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Wagner, R

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P,X	WANG PING ET AL: "Proprotein convertase furin interacts with and cleaves pro-ADAMTS4 (Aggrecanase-1) in the trans-Golgi network." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 9 APR 2004, vol. 279, no. 15, 9 April 2004 (2004-04-09), pages 15434-15440, XP002318176 ISSN: 0021-9258 page 15434 page 15439	1-12
A	GAO GUI ET AL: "Activation of the proteolytic activity of ADAMTS4 (Aggrecanase-1) by C-terminal truncation" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 13, 29 March 2002 (2002-03-29), pages 11034-11041, XP002318177 ISSN: 0021-9258 the whole document	1-121
A	MALFAIT ANNE-MARIE ET AL: "Inhibition of ADAM-TS4 and ADAM-TS5 prevents aggrecan degradation in osteoarthritic cartilage" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 25, 21 June 2002 (2002-06-21), pages 22201-22208, XP002318178 ISSN: 0021-9258 page 22208	1-12
A	WO 03/004607 A (WYETH; AGOSTINO, MICHAEL, J; DI BLASIO, ELIZABETH; LAVALLIE, EDWARD, R) 16 January 2003 (2003-01-16) page 24	1-12
A	YOSHIDA I ET AL: "Proprotein convertase PACE4 is down-regulated by the basic helix-loop-helix transcription factor hASH-1 and MASH-1." THE BIOCHEMICAL JOURNAL. 15 DEC 2001, vol. 360, no. Pt 3, 15 December 2001 (2001-12-15), pages 683-689, XP002318179 ISSN: 0264-6021 abstract	4,5

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	CAMERON A ET AL: "Polyarginines Are Potent Furin Inhibitors" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 275, no. 47, 24 November 2000 (2000-11-24), pages 36741-36749, XP002251991 ISSN: 0021-9258 the whole document	3,9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/002948

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-5,12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/002948

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004009113 A	29-01-2004	WO 2004009113 A1	29-01-2004
WO 03004607 A	16-01-2003	BR 0210835 A	13-07-2004
		CA 2451374 A1	16-01-2003
		EP 1409658 A2	21-04-2004
		JP 2004533841 T	11-11-2004
		MX PA03011715 A	19-03-2004
		WO 03004607 A2	16-01-2003
		US 2003148306 A1	07-08-2003