(54) Title: TREATMENT OF IgA NEPHROPATHY

\[
\begin{bmatrix}
 1 & 1 & 1 \\
 Z & J & B \\
 a & x & c
\end{bmatrix}
\quad \text{Cys} \quad \begin{bmatrix}
 2 & 2 & 2 \\
 B & J & Z \\
 d & y & b
\end{bmatrix}
\]

(I)

(57) Abstract

The present invention provides use of a peptide or ligand in the manufacture of a medicament for the treatment of IgA nephropathy. The peptide has general formula (I) wherein \(m = 0 \) or \(1\), \(n = 0 \) or \(1\), and \(m + n = 1 \) or \(2\); \(J^1\) and \(J^2\) represent sequences of positively charged amino acid residues; \(Z^1\), \(Z^2\), \(B^1\) and \(B^2\) represent sequences of residues of positively charged, negatively charged or neutral amino acid residues or sequences of any mixture of positively charged, negatively charged or neutral amino acid residues; \(x = 0 \) or \(1\), \(y = 0 \) or \(1\), and \(x + y = 1 \) or \(2\); \(c = 0 \) to \(4\), \(d = 0 \) to \(4\); and \(a = 0 \) to \(18\) and \(b = 0 \) to \(18\) with the proviso that when \(m = 0 \) at least one of \(B^2\) and \(Z^2\) is a positively charged amino acid residue and when \(n = 0 \) at least one of \(B^1\) and \(Z^1\) is a positively charged amino acid residue, and when \(m = n = 1\) and \(y = 0 \) at least one of \(Z^1\), \(B^1\), \(B^2\) and \(Z^2\) is a positively charged amino acid residue and when \(m = n = 1\) and \(x = 0\) at least one of \(Z^1\), \(B^1\), \(B^2\) and \(Z^2\) is a positively charged amino acid residue: \(B^1\) and \(B^2\) may also represent a non-peptide spacer arm of a length equivalent to that determined by the length of \(b\) and \(c\) residues of amino acids.
**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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Treatment of IgA Nephropathy

The present invention relates to use of a peptide or ligand in the manufacture of a medicament for the treatment of IgA nephropathy, and a method of treatment of the disease comprising administering an effective dose of a medicament comprising the peptide or ligand.

Amino acids and amino acid residues are represented herein by their standard codes as identified by IUPAC-IUB Biochemical Nomenclature Commission and represent D and L amino acids, their analogues or derivatives.

The clinical features of IgA Nephropathy are:
- recurrent episodes of macroscopic haematuria;
- mild proteinuria;
- a variety of glomerular changes;
- slow or no progression to renal failure.

Berger, J., Transplant. Proc. 1, 939-44, (1969), indicated that IgA nephropathy is connected with an IgA defect, but the connection has not been uncovered and no treatment has been proven to be effective. IgA nephropathy is now considered to be the most common form of glomerulonephritis in the world. It has become apparent that terminal renal failure eventually occurs in about 20% of patients with IgA nephropathy and that IgA nephropathy is responsible for about 10% of the cases of end-stage renal failure requiring dialysis or kidney transplantation.

Susuki, et al., Lancet 343, 8888, (1994), indicated that patients with IgA nephropathy have significantly more IgA
antibodies against *H. parainfluenzae* than patients with other glomerular diseases and D'Amigo, et al., Medicine (1984), 64, 49-60 indicated that total serum IgA is elevated in about 50% of patients with IgA nephropathy.

Stanworth, et al., WO 93/11153 have disclosed the use of a polypeptide or ligand for the treatment of the articular inflammatory disease rheumatoid arthritis (RA). The major pathological factor in RA is believed by Stanworth to be a covalently linked complex of serum IgA and α1-antitrypsin (α1AT), a major anti-protease. This disulphide-bridged complex is found to be present at abnormally high levels in the sera and joint fluids of RA patients and the complex has potent cytotoxicity. Stanworth et al identified a class of peptides capable of interacting with thiol-reactive IgA at a thiol-reactive cysteine residue, and capable of dissociating IgA-α1AT complex or preventing its formation. Hence, Stanworth proposed the use of these peptides in therapy for the IgA mediated disease RA.

It has now been recognised that there is an association between inflammatory diseases of the intestine (coeliac disease, Crohn's disease, ulcerative colitis etc.) and various polyarthritis; primary rheumatological disorders, including rheumatoid arthritis and seronegative spondyloarthritides, being linked with abnormalities in the gut. For instance, patients suffering from RA, ankylosing spondylitis or reactive arthritis often show signs of intestinal inflammation and hence increased intestinal permeability which does not appear to be caused by treatment with non-steroidal anti-inflammatory drugs. Moreover, abnormalities of the duodenojejunal mucosa, including partial or total villous atrophy, have been observed in patients with RA. Yet, despite there being evidence of a common underlying
mechanism, little has previously been known about the cause of these pathological associations.

The present inventors now believe that there is a link between the articular disease RA and the disease IgA Nephropathy, in that they are both IgA mediated to a certain extent.

In this description IgA Nephropathy will be referred to as IgAN.

According to the invention there is provided use of a peptide or ligand in the manufacture of a medicament for the treatment of IgAN, and a method of treatment of the disease comprising administering an effective dose of a medicament comprising the peptide or ligand.

The peptide has not more than 20 amino acid residues, and comprises a thiol-active cysteine residue and at least two positively charged amino acid residues situated at, adjacent or near to the N terminus or at, adjacent or near to the C terminus or at, adjacent or near to both termini; or this peptide and a pharmaceutically acceptable diluent or carrier.

Preferably the positively charged amino acid residues are separated from the thiol-active cysteine residue by a spacer, for example an amino acid residue sequence, a hydrocarbon chain or a chemical bond.

Preferably the spacer comprises 1-4 preferably neutrally charged amino acid residues.

Preferably the neutrally charged amino acid residues are glycine.
Preferably the peptide or analog comprises 3-20 amino acid residues; more preferably 4-10.

Preferably the peptide or analog comprises amino acid residues having a sequence selected from the group which comprises:

Cys-Lys-Lys

His-Cys-Lys-Lys (SEQ ID NO:1)

Preferably the C terminus of the peptide or analog is amidated to prolong its half life, thus enabling a shorter peptide to be used.

Also, the present invention can provide a method of treatment of IgAN comprising administering an effective dose of a peptide or analogue thereof having the following general formula:

\[
\begin{array}{cccc}
1 & 1 & 1 \\
Z & J & B \\
a & x & c & m \\
\end{array}
\begin{array}{cccc}
2 & 2 & 2 \\
Cys & B & J & Z \\
d & y & b & n \\
\end{array}
\]

wherein \( m \) is 0 or 1, \( n \) is 0 or 1 and \( m + n \) is 1 or 2;

\( J^1 \) and \( J^2 \) represent sequences of positively charged amino acid residues; \( Z^1, Z^2, B^1 \) and \( B^2 \) represent sequences of residues of positively charged, negatively charged or neutral amino acid residues or sequences of any mixture of positively charged, negatively charged or neutral amino acid residues;

\( x = 0 \) or 1, \( y = 0 \) or 1, and \( x + y = 1 \) or 2;

\( c = 0 \) to 4, \( d = 0 \) to 4; and

\( a = 0 \) to 18 and \( b = 0 \) to 18

with the proviso that when \( m = 0 \) at least one of \( B^2 \) and \( Z^2 \) is a positively charged amino acid residue and when \( n = 0 \) at least
one of B¹ and Z¹ is a positively charged amino acid residue, and when m = n = 1 and y is 0 at least one of Z¹, B¹, B² and Z² is a positively charged amino acid residue and when m = n = 1 and x = 0 at least one of Z¹, B¹, B² and Z is a positively charged amino acid residue: B¹ and B² may also represent a non-peptide spacer arm of a length equivalent to that determined by the length of b and c residues of amino acids.

Surprisingly, it appears that the ability of these compounds to dissociate IgA-α₁AT complex or prevent its formation causes the compounds to be effective in treatment of IgAN.

In a second aspect the present invention can provide a method of treatment of IgAN comprising administering an effective dose of a ligand comprising an antibody domain which can bind specifically to an antigenic determinant specific to a complex of human IgA and α₁-antitrypsin; or this ligand and a pharmaceutically acceptable diluent or carrier.

The antibody can be monoclonal or polyclonal or can comprise a fragment thereof; preferably it is humanised for example using the technique described in EP-0 239 400 (Winter).

In a third aspect the present invention can provide a use of the peptide or ligand described herein in the manufacture of a medicament for the treatment of IgAN.

Peptides for use according to the present invention were prepared using standard Fmoc chemistry as described in WO 93/11153 (Stanworth et al).

The present invention will now be illustrated with reference to
Figure 1 which shows levels of human IgA-α₁-antitrypsin complex (IgA-α₁,AT) in three groups: controls; patients with diagnosed IgAN; and patients with other glomerular nephropathies. The solid lines indicate each group mean. The broken line indicates the mean + 2SD of the control group and can be taken as a "normal upper limit". The mean level of IgA-α₁,AT in patients with IgAN lies above the normal upper limit.
SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: PEPTIDE THERAPEUTICS LIMITED
(B) STREET: 321 CAMBRIDGE SCIENCE PARK
(C) CITY: CAMBRIDGE
(D) STATE: CAMBRIDGE
(E) COUNTRY: ENGLAND
(F) POSTAL CODE (ZIP): CB4 4WG
(G) TELEPHONE: 01223 423333
(H) TELEFAX: 01223 423111

(ii) TITLE OF INVENTION: Treatment Of IgA Nephropathy

(iii) NUMBER OF SEQUENCES: 1

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPG)

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: GB 9416864.9
(B) FILING DATE: 19-AUG-1994

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

His Cys Lys Lys

1
Claims

1. Use of a peptide having not more than 20 amino acid residues, comprising a thiol-active cysteine residue and at least two positively charged amino acid residues situated at, adjacent or near to the N terminus or at, adjacent or near to the C terminus or at, adjacent to or near to both termini in the manufacture of a medicament for the treatment of IgA Nephropathy (IgAN).

2. Use of a peptide or analogue thereof having the following general formula:

\[
\begin{bmatrix}
1 & 1 & 1 \\
Z & J & B \\
\end{bmatrix} - \text{Cys} - \begin{bmatrix}
2 & 2 & 2 \\
B & J & Z \\
\end{bmatrix}
\]

\[
\begin{array}{ccc}
 a & x & c \\
 m \\
\end{array} \\
\begin{array}{ccc}
 d & y & b \\
 n \\
\end{array}
\]

wherein \( m \) is 0 or 1, \( n \) is 0 or 1 and \( m + n \) is 1 or 2;

\( J^1 \) and \( J^2 \) represent sequences of positively charged amino acid residues; \( Z^1, Z^2, B^1 \) and \( B^2 \) represent sequences of residues of positively charged, negatively charged or neutral amino acid residues or sequences of any mixture of positively charged, negatively charged or neutral amino acid residues;

\( x = 0 \) or 1, \( y = 0 \) or 1, and \( x + y = 1 \) or 2;

\( c = 0 \) to 4, \( d = 0 \) to 4; and

\( a = 0 \) to 18 and \( b = 0 \) to 18

with the proviso that when \( m = 0 \) at least one of \( B^1 \) and \( Z^1 \) is a positively charged amino acid residue and when \( n = 0 \) at least one of \( B^2 \) and \( Z^2 \) is a positively charged amino acid residue, and when \( m = n = 1 \) and \( y = 0 \) at least one of \( Z^1, B^1, B^2 \) and \( Z^2 \) is a positively charged amino acid residue and when \( m = n = 1 \) and \( x = 0 \) at least one of \( Z^1, B^1, B^2 \) and \( Z \) is a positively charged amino acid residue; \( B^1 \) and \( B^2 \) may also represent a non-peptide...
spacer arm of a length equivalent to that determined by the
length of b and c residues of amino acids in the manufacture of
a medicament for the treatment of IgA Nephropathy (IgAN).

3. Use of a peptide comprising the amino acid residue
sequence His-Cys-Lys-Lys (SEQ ID NO:1) in the manufacture of a
medicament for the treatment of IgAN.

4. A method of treatment of IgAN comprising administering
an effective dose of a peptide having not more than 20 amino
acid residues, comprising a thiol-active cysteine residue and
at least two positively charged amino acid residues situated at,
adjacent or near to the N terminus or at, adjacent or near to the
C terminus or at, adjacent or to near to both termini.

5. A method of treatment of IgAN comprising administering
an effective dose of a peptide or analogue thereof having the
following general formula:

\[
\begin{bmatrix}
1 & 1 & 1 \\
Z & - & J - B \\
a & x & c \\
\end{bmatrix}
- \text{Cys}
\begin{bmatrix}
2 & 2 & 2 \\
B & - & J - Z \\
d & y & b \\
\end{bmatrix}
\]

wherein \( m \) is 0 or 1, \( n \) is 0 or 1 and \( m + n \) is 1 or 2;
\( J^1 \) and \( J^2 \) represent sequences of positively charged amino acid
residues; \( Z^1, Z^2, B^1 \) and \( B \) represent sequences of residues of
positively charged, negatively charged or neutral amino acid
residues or sequences of any mixture of positively charged,
negatively charged or neutral amino acid residues;
\( x = 0 \) or 1, \( y = 0 \) or 1, and \( x + y = 1 \) or 2;
\( c = 0 \) to 4, \( d = 0 \) to 4; and
\( a = 0 \) to 18 and \( b = 0 \) to 18

with the proviso that when \( m = 0 \) at least one of \( B^2 \) and \( Z^2 \) is a
positively charged amino acid residue and when n is 0 at least one of B' and Z' is a positively charged amino acid residue, and when m = n = 1 and y is 0 at least one of Z', B', B' and Z' is a positively charged amino acid residue and when m = n = 1 and x = 0 at least one of Z', B', B' and Z' is a positively charged amino acid residue; B' and B' may also represent a non-peptide spacer arm of a length equivalent to that determined by the length of b and c residues of amino acids.

6. A method of treatment of IgAN comprising administering an effective dose of a peptide comprising the amino acid residue sequence His-Cys-Lys-Lys.

7. Use of a ligand comprising an antibody domain which can bind specifically to an antigenic determinant specific to a complex of human IgA and α1-antitrypsin in the manufacture of a medicament for the treatment of IgAN.

8. A method of treatment of IgAN comprising administering an effective dose of a ligand comprising an antibody domain which can bind specifically to an antigenic determinant specific to a complex of human IgA and α1-antitrypsin.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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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)

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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).

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**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
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  * '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.
  * 'A' member document of the same patent family

**Date of the actual completion of the international search**: 8 November 1995

**Date of mailing of the international search report**: 08.12.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HN Rijswijk
Tel.: (+31-70) 340-2040, Tx: 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Fernandez y Branas, F
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 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.: 4-6, 8
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark: Although claims 4-6, 8 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.

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 II  Observations where unity of invention is lacking (Continuation of item 2 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.
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