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(54) Title: THERAPEUTIC AGENT

(57) Abstract: The present invention relates to methods and compositions for preventing and/or treating pyelonephritis and/or urosepsis.

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THERAPEUTIC AGENT

TECHNICAL FIELD

The present invention relates to methods and compositions for preventing and/or treating pyelonephritis and/or urosepsis.

BACKGROUND OF THE INVENTION

Urinary tract infections (UTIs) are common and may be dangerous. The clinical presentation and severity varies depending on the site of infection and molecular basis of disease. In acute pyelonephritis (APN), bacteria ascend into the renal pelvis, where they cause an intense mucosal inflammatory response with progression into the renal parenchyma. Symptoms include high fever, malaise, loin pain as well as poor feeding and irritability in infants. APN can lead to urosepsis.

In acute pyelonephritis, a pathogen-specific TLR4 response is activated by P fimbriated *E. coli*, through ceramide release and the successive phosphorylation of the TICAM-1 (TRIF) and TICAM-2 (TRAM) adaptors, CREB-1, c-FOS and c-JUN activates IRF- and API-dependent transcription. Additional involvement of MyD88, TIRAP and NF-kB depends on the virulence repertoire of the infecting strain. Genetic studies in the murine UTI model have identified IRF3-dependent gene expression and mCXCR2- dependent neutrophil activation as determinants of bacterial clearance and tissue homeostasis. Infected *Irf3*$^{-/-}$ or *mCxcrl*$^{-/-}$ mice develop severe APN and tissue damage after one week and relevance for human APN susceptibility has been demonstrated, through disease-associated IRF3 and CXCR1 polymorphisms in APN prone patients.

SUMMARY OF THE INVENTION

The inventors have now surprisingly identified agents that can be used to treat or prevent pyelonephritis, including APN, and as a result to prevent resulting urosepsis. Those agents include inhibitors of IL-1 receptors, particularly IL-1β, and NlpD proteins. Without being bound by theory, based on their understanding of IL-1β processing, the inventors have also identified that MMP7 inhibitors and agents that moderate the expression of MMP7 may also be useful in the invention. It is particularly surprising that these agents, known for their anti-inflammatory activities can be used to treat infection.

The present invention provides a method for preventing or treating pyelonephritis and / or urosepsis comprising administering to a patient in need thereof, an effective amount of an agent selected from the group consisting of IL-1 inhibitors, MMP inhibitors and NlpD proteins.

The invention also provides an agent selected from the group consisting of IL-1 inhibitors, MMP inhibitors and NlpD proteins, for use in the treatment or prevention of pyelonephritis and / or urosepsis.

In certain embodiments, the method or agent is for the treatment or prevention, preferably the treatment, of pyelonephritis. In certain embodiments, the pyelonephritis is acute pyelonephritis. In certain embodiments, the pyelonephritis is chronic or long-term. In certain embodiments, the method or agent is for the treatment or prevention, preferably the prevention, of urosepsis, particularly urosepsis caused by pyelonephritis.

In certain embodiments, the agent may be provided in a pharmaceutical composition, comprising a pharmaceutically acceptable carrier.

In particular, the agent is an IL-1 inhibitor. In certain embodiments, it is an IL-1β inhibitor. In certain embodiments, it is an IL-1 receptor antagonist inhibitor. Many IL-1 inhibitors are known in the art. These include, for example, small molecules such as anthraquinones, described for example in USP 4,244,968 including diacerein, as well as proteins and peptides such as an interleukin-1 receptor antagonist (IL-1 RA), for example anakinra and rilonacept, or pharmaceutically acceptable salts thereof, or prodrugs thereof, and combinations of these. In particular, the agent is an IL-1β receptor antagonist, such as anakinra (US Patent No 5,075,222).

Alternatively, the agent is an MMP inhibitor, and in particular an MMP7 inhibitor. A wide range of MMP inhibitors are known as described for example Durrant et al. Chem. Biol. Drug Des 20111; 78; 191-198, the content of which is incorporated herein by reference. Particular examples include batimastat, periostat (doxycycline hyclate), marimastat, or salts or prodrugs thereof, but in particular batimastat. It may also be an agent that reduces the expression of MMP, particularly MMP-7, such as a protein selected from ASC or NLRP-3, or an active fragment or variant thereof.

In certain embodiments, the NlpD protein is a bacterial protein, preferably a commensal bacteria or asymptomatic carrier. In certain embodiments, this is a commensal bacteria or asymptomatic carrier with respect to a human host. The bacteria may be asymptomatic bacteriuria (ABU). In certain embodiments, the bacteria strain is an *E. coli* strain, such as *E. coli* 83972.

In certain embodiments, the NlpD protein may comprise or consist of SEQ ID NO: 1 or a variant or active fragment thereof.

MSAGSPKFTV RRIAALSLVS LWLAGCSDT**S NPPAPVSSVN GNAPANTNSG MLITPPPKMG TTSTAQQPQI QPVQQPQIQA TQQPQIQPMQ PVAQQPVQME NGRIVYNRQY GNIPKGSYSG STYTVKKGDT LFYIAWITGN DFRDLAQRNN IQAPYALNVG**

QTLQVGNASG TPITGGNAIT QADAAEQGVV IKPAQNSTVA VASQPTITYS ESSGEQSANK MLPNNKPTAT TVTAPVTVPT ASTTEPIVSS TSTSTPISTW RWPTEGKVIE TFGASEGGNK GIDIAGSKGQ AIIATADGRV VYAGNALRGY GNLIIIKHND DYLSAYAHND TMLVREQQEV KAGQKIATMG STGTSSTRLH FEIRYKGKSV NPLRYLPQR (SEQ ID NO: 1)

One particular fragment of SEQ ID NO: 1 is represented in bold (which is SEQ ID NO: 2).

In certain embodiments, the NlpD protein, or variant or active fragment thereof, is of low molecular weight, for instance less than 3kDa in molecular weight. In other embodiments, the proteins can be larger, for example about 40 kDa.

As used herein, the expression 'fragment' refers to a peptide or protein which lacks one or more amino acids found in a full length protein but which still has the function of the full length protein.

The expression "variant" refers to proteins or polypeptides having a similar biological function but in which the amino acid sequence differs from the base sequence from which it is derived in that one or more amino acids within the sequence are substituted for other amino acids. Amino acid substitutions may be regarded as "conservative" where an amino acid is replaced with a different amino acid with broadly similar properties. Non-conservative substitutions are where amino acids are replaced with amino acids of a different type.

"Conservative substitution" means the substitution of an amino acid by another amino acid of the same class, in which the classes are defined as follows:

Class	Amino acid examples
Nonpolar:	A, V, L, I, P, M, F, W
Uncharged polar:	G, S, T, C, Y, N, Q
Acidic:	D, E
Basic:	K, R, H.

As is well known to those skilled in the art, altering the primary structure of a polypeptide by a conservative substitution may not significantly alter the activity of that polypeptide because the side-chain of the amino acid which is inserted into the sequence may be able to form similar bonds and contacts as the side chain of the amino acid which has been substituted out. This is so even when the substitution is in a region which is critical in determining the peptide's conformation.

Non-conservative substitutions are possible provided that these do not interrupt activity. Broadly speaking, fewer non-conservative substitutions will be possible without altering the biological activity of the polypeptides.

Determination of the effect of any substitution (and, indeed, of any amino acid deletion or insertion) is wholly within the routine capabilities of the skilled person, who can readily determine whether a variant polypeptide retains the fundamental properties and activity of the basic polypeptide. For example, when determining whether a variant of the polypeptide falls within the scope of the invention, the skilled person will determine whether the variant retains the biological activity of the native protein and whether the variant has at least 60%, preferably at least 70%, more preferably at least 80%, yet more preferably 90%, 95%, 96%, 97%, 98%, 99% or 100% activity of the native protein.

Variants of the polypeptide may comprise or consist essentially of an amino acid sequence with at least 70% identity, for example at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 96%, 97%, 98% or 99% identity to a native polypeptide sequence. The level of sequence identity is suitably determined using the BLASTP computer program with the native polypeptide sequences as the base sequence. This means that native polypeptide sequences form the sequence against which the percentage identity is determined. The BLAST software is publicly available at http://blast.ncbi.nlm.nih.gov/Blast.cgi (accessible on 13 October 2016).

The NlpD proteins may be isolated from bacteria. Where the NlpD protein is a variant or active fragment, it may be obtained by recombinant expression. Where the protein is obtained by recombinant expression, the protein sequence may comprise a sequence for use in purification, such as an N-terminal or C-terminal His tag. The use of purification tags is well-known in the art. In a preferred embodiment, the NlpD proteins, or variants or active fragments thereof, are synthetic. Typically, the NlpD protein, or variants or active fragments thereof, will be isolated or synthetic.

For administration to patients, the agent is suitably administered in the form of a pharmaceutical composition, which further comprise a pharmaceutically acceptable carrier. Such compositions are known in the art.

Suitable pharmaceutical compositions will be in either solid or liquid form. They may be adapted for administration by any convenient route, such as parenteral, oral or topical administration or for administration by inhalation or insufflation. The pharmaceutical acceptable carrier may include diluents or excipients which are physiologically tolerable and compatible with the active ingredient.

Parenteral compositions are prepared for injection, for example either subcutaneously or intravenously. They may be liquid solutions or suspensions, or they may be in the form of a

solid that is suitable for solution in, or suspension in, liquid prior to injection. Suitable diluents and excipients are, for example, water, saline, dextrose, glycerol, or the like, and combinations thereof. In addition, if desired the compositions may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, stabilizing or pH-buffering agents, and the like.

Oral formulations will be in the form of solids or liquids, and may be solutions, syrups, suspensions, tablets, pills, capsules, sustained-release formulations, or powders. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate, and the like.

Topical formulations will generally take the form of suppositories or intranasal aerosols. For suppositories, traditional binders and excipients may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient.

The amount of agent administered will vary depending upon factors such as the nature of the agent being used, the size and health of the patient, the nature of the condition being treated etc. in accordance with normal clinical practice. Typically, a dosage in the range of from ^g-50mg/Kg for instance from 2-20 mg/Kg, such as from 5- 15 mg/Kg would be expected to produce a suitable effect.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", mean "including but not limited to", and do not exclude other components, integers or steps. Moreover the singular encompasses the plural unless the context otherwise requires: in particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Preferred features of each aspect of the invention may be as described in connection with any of the other aspects. Within the scope of this application it is expressly intended that the various aspects, embodiments, examples and alternatives set out in the preceding paragraphs, in the claims and/or in the following description and drawings, and in particular the individual features thereof, may be taken independently or in any combination. That is, all embodiments and/or features of any embodiment can be combined in any way and/or combination, unless such features are incompatible.

BRIEF DESCRIPTION OF THE DRAWINGS

One or more embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 shows the effect of NlpD and IL-1RA in infected *Irf3*$^{-/-}$ mice, genetic model of acute pyelonephritis and urosepsis.

Figure 1A shows the experimental protocol, 1B shows urine bacterial and neutrophil counts, 1C shows kidney gross pathology at sacrifice day and 1D shows kidney bacterial numbers at sacrifice day.

DETAILED DESCRIPTION OF THE INVENTION

Example 1

Methods and Materials

Irf3$^{-/-}$ mice were infected with *E. coli* CFT073 (50 µl of 2.10^9 cfu/ml) by intravesical instillation. Intraperitoneal treatment was administered daily, starting 6 hours after infection and for 7 days. Mice were treated with recombinant NlpD protein (105 µg in 100 µl) or IL-1RA (Anakinra, 1 mg/kg, 100 µl). Control mice received PBS. Urine sampling for bacterial and neutrophil counts were done on day 1, 3, 5 and 7 in one group of animals (those sacrificed on day 7), and on day 1, 3, 5, 7, 21 and 42 in others.

Animals were sacrificed under anesthesia; kidneys and bladders were asceptically removed and in the case of bladders, macroscopic pathology was documented by photography. Tissues were fixed with 4% paraformaldehyde or frozen for sectioning and RNA extraction. Viable counts in homogenized tissues (Stomacher 80, Seward Medical) were determined on TSA (37°C, overnight). Urine samples were collected prior to and at regular times after infection and quantitatively cultured. Neutrophils in uncentrifuged urine were counted, using a hemocytometer.

Results

Urine bacterial and neutrophil counts.

As shown in figure 1B, treatments increased bacterial clearance from the urinary tract and decreased urine neutrophil infiltration. Two-way ANOVA, and Sidak's multiple comparison test were used to assess the results.

Kidney gross pathology.

Untreated *Irf3*$^{-/-}$ controls developed severe kidney pathology with evidence of renal abscesses. Treatments protected the mice from kidney pathology.

Kidney bacterial numbers (Kruskal-Wallis tests).

Kidney pathology in untreated mice was combined with high bacterial counts. Treated mice had very low or no kidney bacterial growth.

Urine bacterial and neutrophil counts

As shown in figure 2, treatment provided long term protection, against infection and inflammation in mice treated with either IL-1RA or NlpD. Infected and treated mice remained disease free with no bacterial growth in urine at day 21 and 42, and had low urine neutrophil numbers.

CLAIMS

1. An agent selected from the group consisting of IL-1 inhibitors, MMP inhibitors and NlpD proteins, for use in the treatment or prevention of pyelonephritis, particularly acute pyelonephritis and / or urosepsis.

2. A method for preventing or treating pyelonephritis, especially acute pyelonephritis, and / or urosepsis comprising administering to a patient in need thereof, an effective amount of an agent selected from the group consisting of IL-1 inhibitors, MMP inhibitors and NlpD proteins.

3. An agent according to claim 1, or a method according to claim 2, wherein the agent or method is for the treatment or prevention of acute pyelonephritis.

4. An agent according to claim 1, or a method according to claim 2, wherein the agent or method is for the prevention of urosepsis, caused by acute pyelonephritis.

5. An agent according to claim 1, 3 or 4, or a method according to claim 2, 3 or 4, wherein the agent an IL-1β inhibitor.

6. An agent according to claim 1, 3, 4 or 5, or a method according to claim 2, 3, 4 or 5, wherein the IL-1 inhibitor is an interleukin-1 receptor antagonist (IL-1 RA).

7. An agent or a method according to claim 6, wherein the IL-1RA is anakinra or rilonacept, or a pharmaceutically acceptable salt, or a prodrug thereof.

8. An agent according to claim 1, 3 or 4, or a method according to claim 2, 3 or 4, wherein the agent an MMP inhibitor.

9. An agent or a method according to claim 8, wherein the MMP inhibitor is an MMP7 inhibitor.

10. An agent or a method according to claim 8, wherein the MMP inhibitor is batimastat, periostat (doxycycline hyclate), marimastat, or a salt or prodrug thereof.

11. An agent according to claim 1, 3 or 4, or a method according to claim 2, 3 or 4, wherein the agent is an NlpD protein or fragment or variant thereof.

12. An agent or a method according to claim 11, wherein the NlpD protein is bacterial, particularly from a commensal bacteria or asymptomatic carrier.

13. An agent or a method according to claim 11, wherein the NlpD protein comprises or consists of an amino acid sequence selected from SEQ ID NO 1 or SEQ ID NO 2, or a variant or active fragment thereof.

Effect of NlpD and IL-1RA in infected *Irf3*$^{-/-}$ mice, genetic model of acute pyelonephritis and urosepsis

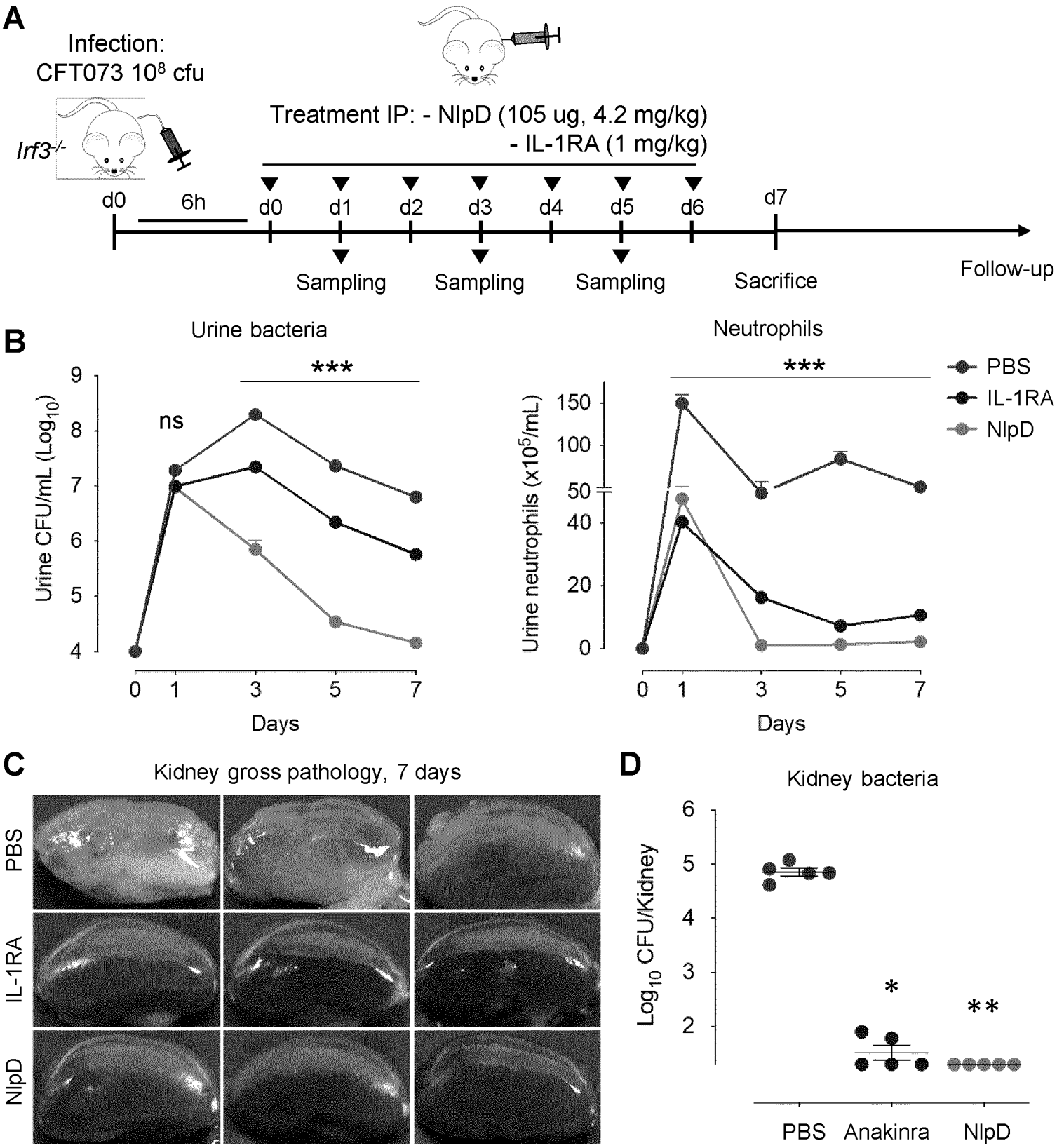

Figure 1

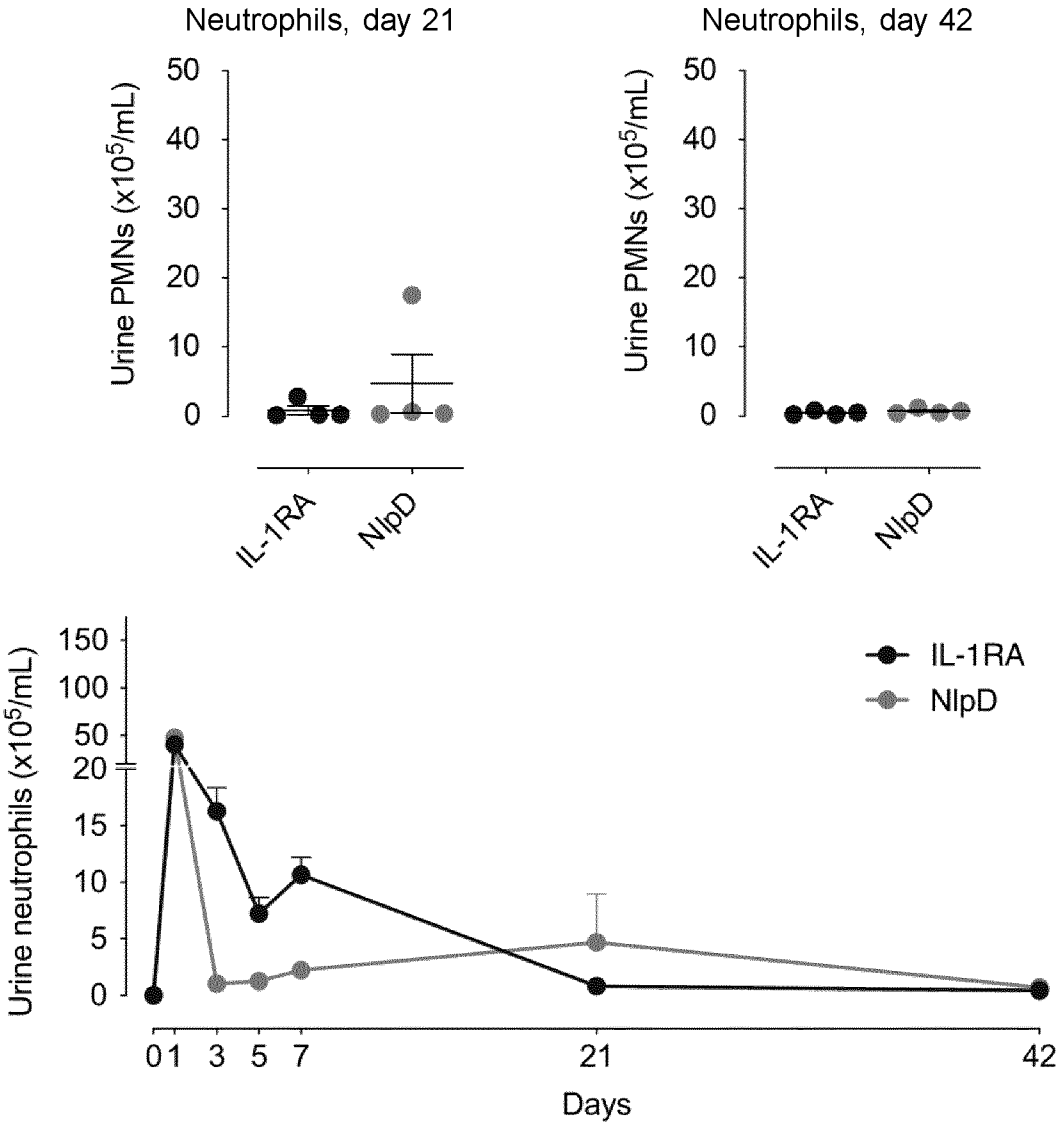
Neutrophils, day 21
Neutrophils, day 42
Urine PMNs (x10^5/mL)
50
40
30
20
10
0
IL-1RA
NlpD
Urine neutrophils (x10^5/mL)
150
100
50
20
15
10
5
0
0 1 3 5 7
21
42
Days
IL-1RA
NlpD

Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/052076

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/052076

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P13/00 A61K38/17 A61K38/00 A61K38/20 A61K31/65
A61K38/16 A61K38/44
ADD.
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)
A61K A61P

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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 880 719 A2 (CHIH-HSIUNG LIN [TW]) 23 January 2008 (2008-01-23)	1,2,8-10
Y	the whole document paragraph [0010]	1-13

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family 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 application or patent 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
25 April 2023	04/05/2023

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, Fax: (+31-70) 340-3016	Thalmair, Michaela

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/052076

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MULDERS-MANDERS C M ET AL: "Peri-and postoperative treatment with the interleukin-1 receptor antagonist anakinra is safe in patients undergoing renal transplantation: Case series and review of the literature", FRONTIERS IN PHARMACOLOGY, FRONTIERS RESEARCH FOUNDATION, CH, vol. 8, 31 May 2017 (2017-05-31), pages 342-1, XP009543719, ISSN: 1663-9812, DOI: 10.3389/FPHAR.2017.00342	1,2,6,7
Y	Case 2; page 2, right-hand column	1-7
X	BUSH I ET AL: "Intravenous and oral doxycycline therapy of urinary tract infections", CLINICAL MEDICINE,, vol. 81, no. 1, 1 January 1974 (1974-01-01), pages 27-28, XP009543724, ISSN: 0412-7994	1,2,8-10
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/052076

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