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(54) Title: METHOD FOR PREVENTING OR TREATING SEXUALLY TRANSMITTED INFECTIONS

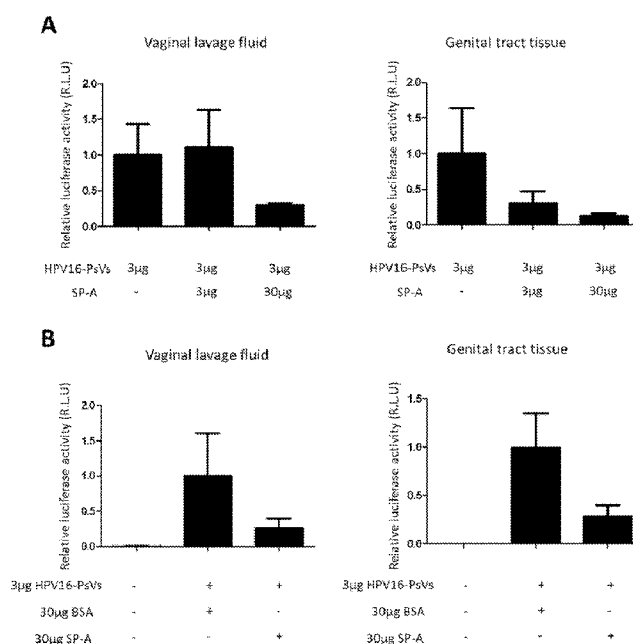


Figure 4

(57) **Abstract:** Surfactant protein A (SP-A) is described for preventing and/or treating a sexually transmitted infection (STI) in a subject. The STI is caused by a DNA virus, such as Human papillomavirus (HPV) and/or Herpes simplex virus (HSV). SP-A can thus be used to prevent cervical cancer, genital warts and/or genital ulcers. Pharmaceutical compositions and kits comprising SP-A are also described, as is a method for preventing and/or treating STIs caused by DNA viruses, the method comprising administering an effective amount of SP-A to a subject in need thereof.



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METHOD FOR PREVENTING OR TREATING SEXUALLY TRANSMITTED INFECTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to United Kingdom patent application no. 1711423.2 filed on 17 July 2017 which is incorporated by reference herein.

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FIELD OF THE INVENTION

The invention relates to the use of surfactant protein A (SP-A) for preventing or treating sexually transmitted infections (STIs).

10

BACKGROUND TO THE INVENTION

It is estimated that over a billion people have sexually transmitted infections (STIs) other than HIV/AIDS, and that these STIs result in over 100,000 deaths each year.

15

Human papillomavirus (HPV) is the most common sexually transmitted infection and a principle cause of various anogenital cancers, including cervical cancer. The majority of cervical cancer cases occur in low and middle-income countries (LMIC). Prophylactic vaccines exist to combat HPV infection but accessibility to these in LMIC is limited. Alternative preventative measures against HPV infection are therefore also needed to control cervical cancer risk.

20

Herpes simplex virus is also a highly prevalent sexually transmitted virus which causes significant disease burden worldwide (HSV-2 is the principal cause of genital ulcers). Like HPV, HSV infection is currently incurable.

25

STIs can also be caused by other viruses, bacteria and parasites.

There is therefore still a need for a new treatment which prevents or reduces the risk of a subject acquiring a STI.

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SUMMARY OF THE INVENTION

5 According to a first embodiment, the invention provides surfactant protein A (SP-A), or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating a sexually transmitted infection (STI) in a subject, wherein the STI is caused by a DNA virus.

10 More particularly, the DNA virus may be human papillomavirus (HPV) and/or herpes simplex virus (HSV). The HPV may be any type of HPV, such as types 6, 11, 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82. The HSV may be HSV-1 or HSV-2.

The subject may be a mammal, such as a human. More particularly, the subject may be a female human.

15 The SP-A may comprise the sequence shown in SEQ ID NO: 1, or the SP-A fragment, homologue, variant or derivative may comprise an amino acid sequence having at least 70% sequence identity over at least 50 amino acid residues of SEQ ID NO:1.

20 SP-A, or the fragment, homologue, variant or derivative thereof, may bind to HPV or HSV.

SP-A, or the fragment, homologue, variant or derivative thereof may neutralize the ability of HPV or HSV to successfully infect the host.

25 SP-A bound HPV or SP-A bound HSV may be preferentially internalised by immune cells (such as macrophages).

The SP-A, or the fragment, homologue, variant or derivative thereof, may be administered to the genital area or reproductive tract of the subject.

30 The SP-A, or the fragment, homologue, variant or derivative thereof, may be administered in combination with an antimicrobial therapy.

In a second embodiment, the invention provides a nucleic acid encoding SP-A, or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating a STI in a subject, wherein the STI is caused by a DNA virus.

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In a third embodiment, the invention provides a pharmaceutical composition comprising SP-A, or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating a STI in a subject, wherein the STI is caused by a DNA virus.

5

The composition may further comprise a pharmaceutical excipient and/or carrier.

In a further embodiment, the invention provides the use of SP-A, or a fragment, homologue, variant or derivative thereof, in the manufacture of a medicament for preventing and/or treating a STI in a subject, wherein the STI is caused by a DNA virus.

10

In a further embodiment, the invention provides a kit comprising SP-A, or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating a STI, wherein the STI is caused by a DNA virus.

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The kit may optionally be in the form of a pharmaceutical combination further comprising an antimicrobial therapy and/or pharmaceutical composition.

The kit may include an applicator for administering the SP-A into the reproductive tract.

20

In yet a further embodiment, the invention provides a method for preventing and/or treating a STI in a subject, wherein the STI is a DNA virus, the method comprising a step of administering SP-A, or a fragment, homologue, variant or derivative thereof, to the subject.

25

Further embodiments of the invention extend to SP-A, a nucleic acid encoding SP-A, or a pharmaceutical composition or kit comprising SP-A, for use in preventing cervical cancer, genital warts and/or genital ulcers; to the use of SP-A in the manufacture of a medicament for preventing cervical cancer, genital warts and/or genital ulcers; and to a method for preventing cervical cancer, genital warts and genital ulcers in a subject, the method comprising administering SP-A to the subject.

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BRIEF DESCRIPTION OF THE FIGURES

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Figure 1 shows that binding of HPV16-PsVs to SP-A but not SP-D results in increased viral uptake by RAW264.7 macrophages but not HeLa cervical epithelial cells. **A-C)** Co-

immunoprecipitation experiments displaying the input, flow through (FT) and eluate samples of **(A)** HPV16-PsVs and SP-A alone (controls), **(B)** HPV16-PsVs and SP-A together and **(C)** HPV16-PsVs and SP-D together.

5 Figure 2 shows that uptake of SP-A-mediated HPV16-PsVs by RAW264.7 macrophages is calcium-dependent, but not dependent on the CRD.

Figure 3 shows that infection of C57BL/6 mice with HPV16-PsVs does not alter SP-A expression.

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Figure 4 shows that SP-A reduces HPV16-PsVs infection in C57BL/6 mice.

DETAILED DESCRIPTION OF THE INVENTION

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Surfactant protein A (SP-A) has been identified and characterised previously, in for example, Wright, J.R. et al., "Surfactant apoprotein Mr = 26,000-36,000 enhances uptake of liposomes by type II cells", J Biol Chem 1987 262(6):2888-94. SP-A is an innate immune system collectin which is primarily expressed in the lungs and facilitates phagocytosis of e.g. microbes by alveolar macrophages through opsonisation. The function of SP-A proteins is primarily understood in the lung, but they are also expressed at other sites of the body, including the female reproductive tract.

20

The inventors have now surprisingly found that administration of SP-A to the reproductive tract of a subject reduces the risk of the subject acquiring a sexually transmitted infection (STI) caused by a DNA virus such as HPV or HSV.

25

Innate mucosal immune responses in the female reproductive tract, the first barrier associated with clearance of incoming HPV, are an underexplored area. Due to several immune evasion mechanisms, infiltration and activation of macrophages and dendritic cells (as the most likely antigen presenting cells) upon HPV infection are usually relatively ineffective, thereby leading to inept humoral and cellular immunity.

30

The inventors have identified that host innate immunity which protects against Human papillomavirus (HPV) can be enhanced by raising the levels of SP-A in the female reproductive tract. Enhanced immune recognition of HPV reduces the risk of the virus reaching squamous

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epithelial cells where it could establish a persistent infection, thereby increasing the risk of viral induction of invasive cancer. Raising levels of SP-A in the female reproductive tract could therefore lead to reduced HPV infection and other STI infections and their pathological consequences.

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More specifically, the examples below show that:

- SP-A binds to HPV;
- SP-A bound HPV is preferentially internalised by macrophages; and
- HPV infection in a mouse model is reduced when exogenous SP-A is added to the female

10

reproductive tract.

SP-A may also bind to HSV (e.g. HSV-1 or HSV-2) and lead to reduced HSV-infection in a subject.

15 SP-A was therefore identified as being suitable for use in topical microbicides which provide protection against viral infections of the female reproductive tract, and in particular against DNA viral infections.

As used herein, SP-A refers to any SP-A polypeptide or nucleic acid (as the context requires).

20 The SP-A polypeptide or nucleic acid for use according to the present invention may be a human SP-A having the NCBI Reference Sequence: NG_021189 or the GenBank accession number NM_005411.

The amino acid sequence of such a human SP-A is shown in SEQ ID NO: 1, and two examples

25 of nucleic acid sequences encoding human SP-A are shown in SEQ ID NOs: 2 and 3.

SEQ ID NO: 1

30 MWLCPLALNL ILMAASGAVC EVKDVCVGSP GIPGTPGSHG LPGRDGRDGL KGDPGPPGPM
GPPGEMPCPP GNDGLPGAPG IPGECGEKGE PGERGPPGLP AHLDEELQAT LHDFRHQILQ
TRGALSLQGS IMTVGEKVFS SNGQSITFDA IQEACARAGG RIAVPRNPPEE NEAIASFVKK
YNTYAYVGLT EGPSPGDFRY SDGTPVNYTN WYRGEPAGRG KEQCVEMYTD GQWDRNCLY
SRLTICEF

The amino acid sequence of SP-A may be lacking the signal sequence (e.g. the amino acid

35 sequence may lack residues 1 to 20 of SEQ ID NO: 1).

SEQ ID NO: 2

1 gacttggagg cagagaccca agcagctgga ggctctgtgt gtgggtgagt ttagcccat
61 cccctaggtg ttctccagct tgaggatcgc aggcagagag gaccagcca gcagccacag

	121	gcctgaccaa	agcccaggct	gggaaggagg	gcaactcccc	atthttccact	gggagggtgtt
	181	tcacagcaca	gtcaacatag	gtgacctgca	aagatccctca	tgtttgttat	tttctttggc
	241	cagatccatc	cctacagggt	tcagcagggc	ctacaggagg	ggcagtgaga	gaacagaccc
5	301	caaaaagaaa	ggggactcca	tgactgacca	ccttgagggg	ggccaggctg	cgggccccgt
	361	tcattctttt	tcattctcag	gtcgtgtatt	tcttgaggcc	tgaanaagaaa	gtaacacagc
	421	agggatgagg	acagatgggt	tgagtcaagt	agtgaagtac	ctgactaata	gcctgggagg
	481	gacagggcag	gttttctgca	gagcacggaa	gattcagctg	aagtcaagaa	ggtgaagcca
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	781	cccagcttcc	tgagtctctg	cagagcacag	tgggggagat	gttggcagag	gtggcagatg
	841	ggctcacggc	catccctcct	gcaggagcag	cgactggacc	cagagccatg	tggctgtgcc
	901	ctctggccct	caacctcatc	ttgatggcag	cctctggtgc	tgtgtgcgaa	gtgaaggacg
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	1021	acgggagaga	tgggtctcaa	ggagaccctg	gccctccagg	tactgtgctg	cagaccccac
	1081	cctcagctga	gggacacaga	ccccttttca	ggaggcccat	ctgtccaggc	ccctaggctg
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	1501	gggtggggca	ggtgggcagt	ggaaacatgg	gcacagcgac	cctgaagtca	gttacacggg
25	1561	gatgatgggg	atcagacaaa	ccctacaggt	tccccagggg	catttggctc	aacctaahta
	1621	agagaggata	agcttgaggg	agaaagctga	ggtgtctggg	gagtgtgggt	acaattcagg
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		actggctctg	ctttctcctt	tcattaatcc	attcaccag	atatttcatt	aaaattatca
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		actcctgagc	tgaataaaga	tgatttaagc	ttaataaatc	gtgaatgtgt	tcacaaaaaa
		aaaaaaaaa					

The present invention provides a SP-A polypeptide, variant, homologue, fragment or derivative for use in preventing and/or treating one or more STIs in a subject.

The terms "variant" or "derivative" in relation to the amino acid sequences for use according to the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acids from or to the sequence providing the resultant amino acid sequence retains substantially the same activity as the unmodified sequence, preferably having at least the same activity as the SP-A polypeptide shown in SEQ ID NO: 1.

Polypeptides having the amino acid sequence of SEQ ID NO: 1, or fragments or homologues thereof may be modified for use as described herein. Typically, modifications are made that maintain the biological activity of the sequence. Amino acid substitutions may be made, for example from 1, 2 or 3 to 10, 20 or 30 substitutions provided that the modified sequence retains the biological activity of the unmodified sequence. Alternatively, modifications may be made to deliberately inactivate one or more functional domains of the polypeptides described here.

Conservative substitutions may be made, for example according to Table 1. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other:

Table 1: Conservative amino acid substitutions

ALIPHATIC	Non-polar	G A P I L V
	Polar - uncharged	C S T M N Q
	Polar - charged	D E K R
AROMATIC		H F W Y

Preferred fragments include those having one or more biological activities of SP-A.

SP-A polypeptides also generally include any recombinant fragment of SP-A.

The SP-A, SP-A polypeptide or SP-A fragment for use according to the present invention also includes homologous sequences obtained from any source, for example related viral/bacterial proteins, cellular homologues and synthetic peptides, as well as variants or derivatives thereof.

Thus polypeptides also include those encoding homologues of SP-A from other species including animals such as mammals (e.g. mice, rats or rabbits), especially primates, more especially humans. More specifically, homologues include human homologues.

5 Thus, the SP-A for use according to the present invention may be a variant, homologue or derivative of the amino acid sequence of the SP-A sequence shown in SEQ ID NO: 1, as well as a variant, homologue or derivative of a nucleotide sequence encoding the amino acid sequence.

10 As used herein, a homologous sequence is taken to include an amino acid sequence which is at least 15, 20, 25, 30, 40, 50, 60, 70, 80 or 90% identical, preferably at least 95 or 98% identical at the amino acid level over at least 50 or 100, preferably 200 amino acids with the sequence of SP-A shown in SEQ ID NO: 1. In particular, homology should typically be considered with
15 non-essential neighbouring sequences. This is especially important when considering homologous sequences from distantly related organisms.

Although homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions), in the context of the present invention it is
20 preferred to express homology in terms of sequence identity.

Homology comparisons can be conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These publicly and commercially available computer programs can calculate % homology between two or more sequences. % homology may be
25 calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in one sequence directly compared with the corresponding amino acid in the other sequence, one residue at a time. This is called an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of residues (for example less than 50 contiguous amino acids).

30 Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause the following amino acid residues to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence
35 comparison methods are designed to produce optimal alignments that take into consideration

possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting "gaps" in the sequence alignment to try to maximise local homology.

However, these more complex methods assign "gap penalties" to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared sequences - will achieve a higher score than one with many gaps. "Affine gap costs" are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimised alignments with fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is preferred to use the default values when using such software for sequence comparisons. For example when using the GCG Wisconsin Bestfit package (see below) the default gap penalty for amino acid sequences is -12 for a gap and -4 for each extension.

Calculation of maximum % homology therefore firstly requires the production of an optimal alignment, taking into consideration gap penalties. A suitable computer program for carrying out such an alignment is the GCG Wisconsin Bestfit package (University of Wisconsin, U.S.A; Devereux et al., 1984, Nucleic Acids Research 12:387). Examples of other software than can perform sequence comparisons include, but are not limited to, the BLAST package (see Ausubel et al., 1999 *ibid*--Chapter 18), FASTA (Atschul et al., 1990, J. Mol. Biol., 403-410) and the GENWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (see Ausubel et al., 1999 *ibid*, pages 7-58 to 7-60). However it is preferred to use the GCG Bestfit program.

Although the final % homology can be measured in terms of identity, the alignment process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled similarity score matrix is generally used that assigns scores to each pairwise comparison based on chemical similarity or evolutionary distance. An example of such a matrix commonly used is the BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin programs generally use either the public default values or a custom symbol comparison table if supplied (see user manual for further details). It is preferred to use the public default values for the GCG package, or in the case of other software, the default matrix, such as BLOSUM62.

Once the software has produced an optimal alignment, it is possible to calculate % homology, preferably % sequence identity. The software typically does this as part of the sequence comparison and generates a numerical result.

- 5 The variants, homologues, fragments or derivatives of SP-A for use according to the present invention may encompass related polypeptides which provide one or more of the biological activities of SP-A.

10 The SP-A polypeptides, variants, homologues, fragments and derivatives for use as described herein may be in a substantially isolated form. It will be understood that such polypeptides may be mixed with carriers or diluents which will not interfere with the intended purpose of the protein and still be regarded as substantially isolated. A SP-A variant, homologue, fragment or derivative may also be in a substantially purified form, in which case it will generally comprise the protein in a preparation in which more than 90%, e.g. 95%, 98% or 99% of the protein in the
15 preparation is a protein.

As used herein, the terms "polynucleotide", "nucleotide", and nucleic acid are intended to be synonymous with each other. "Polynucleotide" generally refers to any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA.
20 "Polynucleotides" include, without limitation single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions
25 comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications has been made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of
30 polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

It will be understood by a skilled person that numerous different polynucleotides and nucleic
35 acids can encode the same polypeptide as a result of the degeneracy of the genetic code. In addition, it is to be understood that skilled persons may, using routine techniques, make

nucleotide substitutions that do not affect the polypeptide sequence encoded by the polynucleotides described here to reflect the codon usage of any particular host organism in which the polypeptides are to be expressed.

5 SP-A nucleic acids, variants, fragments, derivatives and homologues may comprise DNA or RNA. They may be single-stranded or double-stranded. They may also be polynucleotides which include within them synthetic or modified nucleotides. For the purposes of the use as described herein, it is to be understood that the polynucleotides may be modified by any method available in the art. Such modifications may be carried out in order to enhance the *in vivo*
10 activity or life span of polynucleotides of interest.

The terms "variant", "homologue" or "derivative" in relation to a nucleotide sequence include any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) nucleic acid from or to the sequence. Preferably said variant, homologues or derivatives
15 code for a polypeptide having biological activity.

As indicated above, with respect to sequence homology, preferably there is at least 50 or 75%, more preferably at least 85%, more preferably at least 90% homology to SEQ ID NO: 2 or SEQ ID NO: 3. More preferably there is at least 95%, more preferably at least 98%, homology.
20 Nucleotide homology comparisons may be conducted as described above. A preferred sequence comparison program is the GCG Wisconsin Bestfit program described above. The default scoring matrix has a match value of 10 for each identical nucleotide and -9 for each mismatch. The default gap creation penalty is -50 and the default gap extension penalty is -3 for each nucleotide.

25 The nucleic acid sequence may have at least 80, 85, 90, 95, 98 or 99% identity to the sequence shown as SEQ ID NO. 2 or SEQ ID NO: 3, provided that it encodes a SP-A polypeptide suitable for use as defined in the first embodiment of the invention.

30 SP-A can be used in order to prevent or treat sexually transmitted infections caused by DNA viruses. Examples of DNA viruses causing STIs are Human papillomavirus (HPV), Herpes simplex virus (HSV) and Molluscum contagiosum virus (MCV). These viruses are classified in virus Group 1 (dsDNA) and are distinguishable from HIV (Group VI - ssRNA-RT viruses) and Hepatitis B virus (HBV) and Hepatitis C virus (HCV) (Group VII - dsDNA-RT viruses). Viruses
35 such as HIV are therefore excluded from the present invention. The SP-A may neutralize the ability of the virus to successfully infect the host.

Treatment with SP-A is effective against any type of HPV.

5 The SP-A can be used as a broad spectrum treatment for preventing or treating both HPV and HSV infection. Moreover, as the binding of the SP-A to HPV is not dependent on the type of HPV, it can be used to prevent or treat a broad range of HPV types, including HPV types 6 and 11 (which cause genital warts and laryngeal papillomatosis) and HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82 (which are carcinogenic). Thus, SP-A can be used to prevent cervical and other cancers (including cancer of the vulva and vagina), genital
10 warts and genital ulcers (caused by HSV).

When used for the prevention of STIs, the invention relates to the prophylactic use of SP-A. In this aspect, exogenous SP-A may be administered to a subject who has not yet contracted the infection and/or who is not showing any symptoms of disease associated with the infection to
15 prevent or impair the cause of the infection or to reduce or prevent development of at least one symptom associated with the infection.

When used for the treatment of STIs, the invention relates to the therapeutic use of SP-A. Herein exogenous SP-A may be administered to a subject having an existing infection in order
20 to lessen, reduce or improve at least one symptom associated with the infection and/or to slow down, reduce or block the progression of the infection.

The SP-A can be administered on its own or in combination with an additional treatment. For example, the additional treatment could be an antimicrobial formulation containing a microbicide
25 such as an antiretroviral (e.g. tenofovir, dapivirine or UC-781), cellulose sulphate, dextrin sulphate, nonoxynol-9, carrageenan or *Lactobacillus crispatus*. Addition of SP-A to the formulation could enhance its antimicrobial activity.

The administration of SP-A can be accomplished using any of a variety of routes that make the
30 active ingredient bioavailable. For example, the SP-A can be formulated into a topical composition in the form of a gel, cream, lotion, aerosol spray, film, suppository or vaginal ring for insertion into the vagina or rectum, or could be in a formulation for oral administration, such as a tablet or syrup.

35 Preferably, SP-A is administered such that it is available in an active form in the reproductive tract of the subject to which it is administered.

Typically, a physician will determine the actual dosage that is most suitable for an individual subject and it will vary with the age, weight and response of the particular patient. The dosage is such that it is sufficient to prevent and/or treat an STI.

5

The present invention also provides a pharmaceutical composition comprising SP-A for use in preventing and/or treating STIs caused by a DNA virus.

SP-A may be administered with a pharmaceutically acceptable carrier, diluent, excipient or adjuvant. The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as (or in addition to) the carrier, excipient or diluent, any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s) and other carrier agents.

15

The present invention also provides a kit comprising SP-A for use in preventing and/or treating one or more STIs caused by DNA viruses. The kit comprises SP-A as defined above, and may be in the form of a pharmaceutical combination further comprising an antimicrobial treatment and/or pharmaceutical composition as defined above. The kit may also include an applicator for administering the SP-A into the reproductive tract.

20

The present invention further relates to a method for preventing and/or treating one or more STIs caused by a DNA virus, the method comprising the step of administering exogenous SP-A to a subject. The method may also comprise the use of an antimicrobial therapy and/or a pharmaceutical composition as defined above.

25

The present invention also relates to use of SP-A in the manufacture of a medicament for preventing and/or treating a STI in a subject, wherein the STI is caused by a DNA virus.

The invention will now be described in more detail by way of the following non-limiting examples.

30

Examples

Binding of SP-A to HPV

5 Co-immunoprecipitation and flow cytometry experiments were conducted to determine whether SP-A and the closely related surfactant protein D (SP-D) bind to HPV16 pseudovirions (HPV16-PsVs) (1-3). Native human SP-A purified from bronchoalveolar lavage fluid (4) was used. Co-immunoprecipitation experiments displaying the input, flow through (FT) and eluate samples of (A) HPV16-PsVs and SP-A alone (controls) (Figure 1A), HPV16-PsVs and SP-A together
10 (Figure 1B) and HPV16-PsVs and SP-D together (Figure 1C). Complexes were incubated for 1h at 4°C, followed by precipitations with either anti-HPV16-L1 (CamVir), anti-SP-A or anti-SP-D antibodies. Western Blots were performed using the CamVir antibody to detect the presence of HPV16-L1.

15 SP-A bound HPV16-PsVs and the resulting HPV16-SP-A complex showed enhanced uptake by RAW264.7 murine macrophages. SP-D bound HPV16-PsVs weakly and had no effect on viral uptake.

SP-A was found to enhance viral recognition of HPV, and both impairs initial infection and
20 stimulates anti HPV host innate immunity.

Functional virus assays

RAW264.7 cells were infected with fluorescently labelled HPV16-PsVs (pre-absorbed with
25 purified proteins where indicated) for 1h at 37°C (Figure 1D). Cells were washed extensively and lifted with trypsin/EDTA to remove surface-bound virions, thereby allowing detection of internalised viral particles by flow cytometry. Experiments were performed in triplicates, quantified by quadrant analysis of the dot plot of three independent experiments and presented as x-fold increase relative to the mean fluorescence intensity of cells infected with untreated
30 HPV16-PsVs which was set as 1. Significances were calculated by means of one-way ANOVA and Tukey post-hoc tests. *** indicates statistical significance between uptake of HPV16-PsVs in the presence of SP-A as compared to the other tested conditions (*** = $p < 0.001$). The murine macrophage cell line RAW264.7 and the human epithelial cell line HeLa were infected with HPV16-PsVs encapsidating the firefly luciferase reporter plasmid pGL3 for 48h (Figure 1E).
35 Where indicated, the viral particles were pre-absorbed with purified SP-A protein before infection. Firefly luciferase activities in the cell lysates as a measure for successful infection is

presented as Relative Light Units relative to RAW264.7 cells infected with untreated HPV16-PsVs which was set as 1.

Infection of RAW264.7 macrophages with fluorescently labelled HPV16-PsVs for 1h at 37°C demonstrated that pre-incubation of viral particles with recombinant SP-A but not SP-D enhanced uptake by RAW264.7 cells (Figure 1(D)). Enhanced infectious internalisation of SP-A-coated HPV16-PsVs was only seen in RAW264.7 macrophages but not HeLa epithelial cells (Figure 1(E)).

AF488-HPV16-PsVs were incubated in the presence of 10-fold (w/w) excess SP-A and with or without 2mM or 5mM calcium chloride in the presence or absence of 10mM EDTA as indicated (Figure 2A), or with various concentrations of mannose (Figure 2B). Shown are summaries of viral internalisation experiments as determined by FACS as described in Figure 1D. Fluorescent readings are displayed relative to HPV16-PsVs internalisation in the presence of SP-A only which was set as 1. Quantification of three independent experiments performed in duplicate are shown. Statistical significance was determined using one-way ANOVA and Tukey post-hoc tests. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. Bars depict mean values, with error bars showing SEM.

Effect of exogenous SP-A on HPV16-PsVs infection levels in mice

To assess if this relationship persisted *in vivo* HPV16-PsVs infections were carried out using the well-established murine HPV16-PsVs cervicovaginal challenge model system (Roberts et al., Longet et al.). Surprisingly, neither naïve nor C57BL/6 mice challenged with HPV16-PsVs expressed SP-A in the female genital tract. However, pre-incubation of HPV16-PsVs with purified SP-A at a 1:10 weight per weight ratio reduced the level of HPV16-PsV infection.

Female wildtype C57/BL6 mice were assessed for SP-A expression in various organs and body fluids. Figure 2(A) shows a Western Blot probed for SP-A in the lung, bronchoalveolar lavage fluid (BAL), genital tract tissue (GT), and vaginal lavage fluid. 20µg of each sample was loaded per lane, while 0.5µg of purified human SP-A protein was loaded as control. No endogenous SP-A was detected in the female genital tract.

Figure 3A shows a mouse model for HPV16-PsVs infection using C57BL/6 mice, adapted from Roberts *et al.*, 2007 (Nature Med). Briefly, 6-10 weeks old female wildtype C57/BL6 mice per

group were injected with 2mg Depo-Provera (s.c.) for 4 days, and then pre-treated with 25µl 4% N9 in 3% CMC i.vag. for 6h prior to HPV16-PsVs infection. 4-6 mice per group were i.vag. infected with the viral particles encapsidating the reporter gene firefly luciferase ($1\mu\text{g} = 3 \times 10^{10}\text{IU}$). After 1-3 days, tissues were harvested for analysis. Western Blot assessing SP-A expression in various organs and body fluids of naïve female wildtype C57BL/6 mice is shown in Figure 3B. No endogenous SP-A was detected in the female genital tract of naïve mice. Four mice per group were i.vag. infected with 3µg HPV16-PsVs encapsidating the pGL3 reporter plasmid. Genital tract tissue was harvested 24 hours later and RNA extracted for gene expression analysis to confirm successful HPV infection (Figure 3C). RNA from C) was assessed for SP-A expression, with lung RNA used as positive control. Gapdh was used as a reference gene (Figure 3D). Four mice per group were i.vag. infected with 3µg HPV16-PsVs. Vaginal lavages were performed 24 and 72 hours p.i. and assessed by Western Blot for the presence of SP-A. 20µg of each sample was loaded per lane, while 0.5µg purified human SP-A protein was loaded as control. *Loading control corresponds to a 45kDa cellular protein that cross-reacts with the CamVir primary antibody (Shafti-Keramat *et al.*, 2003, J Virol) (Figure 3E). Four mice per group were i.vag. infected with 3µg HPV16-PsVs and genital tract tissue was harvested 24 hours or 72 hours p.i., homogenised and assessed by Western Blot for the presence of SP-A as described in E) (Figure 3E).

6-10 weeks old female wildtype C57BL/6 mice per group were pre-treated as described in Figure 3A. HPV16-PsVs encapsidating firefly luciferase were pre-incubated with increasing amounts of purified SP-A protein for 1 hour on ice (Figure 4A). 3µg HPV16-PsVs were pre-incubated with 30µg purified SP-A protein or 30µg BSA for 1 hour on ice (Figure 4B).

Mice were euthanised 72 hours p.i., and tissue harvested for analysis. Firefly luciferase activity was measured in vaginal lavage fluid (left panels) and homogenised genital tract tissue (right panels). Data were normalised to total protein in the samples and are presented as x-fold to average control (no SP-A) which was set as 1. Figure 4A shows the data from one experiment with four mice per condition. Figure 4B shows pooled data from two independent experiments, with a total of ten mice per condition. Bars depict mean values, with error bars showing SEM.

Addition of exogenous SP-A into the female reproductive tract was thus shown to reduce the level of HPV16-PsVs infection.

It appears that SP-A binds to HPV in a type-unspecific manner, leading to enhanced uptake by macrophages, thereby providing protection against a wide range of incoming HPV particles.

Thus, while current prophylactic vaccines type-specifically prevent new HPV infections, SP-A as an innate immune modulator may broadly interact with incoming pathogens. SP-A therefore represents a tractable antiviral candidate for preventing HPV and other related viral infections and/or viral shedding in the genital tract.

5

Binding of SP-A to HSV

Studies will be conducted on the binding of SP-A to HSV. These will be carried out as described above but using live HSV instead of HPV-PsVs.

10

Based on previous studies by the applicant (results now shown), it is expected that SP-A will also be shown to bind to HSV and thereby reduce the risk of a subject who is exposed to HSV from becoming infected with the virus. However, final data confirming this expectation is not yet available.

15

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1. Surfactant protein A (SP-A), or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating one or more sexually transmitted infections (STIs) in a subject, wherein the STI is a DNA virus infection.
2. The SP-A or fragment, homologue, variant or derivative thereof for use according to claim 1, wherein the STI is caused by Human papillomavirus (HPV) and/or Herpes simplex virus (HSV).
3. The SP-A or fragment, homologue, variant or derivative thereof for use according to claim 2, wherein the STI is caused by Human papillomavirus (HPV).
4. The SP-A or fragment, homologue, variant or derivative thereof for use according to claim 3, wherein the STI is caused by any type of Human papillomavirus (HPV).
5. The SP-A or fragment, homologue, variant or derivative thereof for use according to claim 2, wherein the STI is caused by Herpes simplex virus (HSV).
6. The SP-A or fragment, homologue, variant or derivative thereof for use according to any one of claims 1 to 5, wherein the subject is a female human.
7. The SP-A or fragment, homologue, variant or derivative thereof for use according to any one of claims 1 to 6, wherein the SP-A or fragment, homologue, variant or derivative thereof has an amino acid sequence which has at least 70% identity to SEQ ID NO: 1.
8. The SP-A or fragment, homologue, variant or derivative thereof for use according to any one of claims 1 to 7, wherein the SP-A or fragment, homologue, variant or derivative thereof has an amino acid sequence which is identical to SEQ ID NO: 1.
9. The SP-A or fragment, homologue, variant or derivative thereof for use according to any one of claims 1 to 8, wherein the SP-A or fragment, homologue, variant or derivative thereof is formulated for delivery into the female reproductive tract.
10. The SP-A or fragment, homologue, variant or derivative thereof for use according to any one of claims 1 to 9, wherein the SP-A or fragment, homologue, variant or derivative thereof is formulated for topical application or as a suppository.

11. The SP-A or fragment, homologue, variant or derivative thereof for use according to any one of claims 1 to 10, wherein the SP-A or fragment, homologue, variant or derivative thereof is combined with a microbicide.
12. A nucleic acid encoding SP-A or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating one or more STIs in a subject, wherein the STI is a DNA virus infection.
13. The nucleic acid of claim 12, wherein the DNA virus is Human papillomavirus (HPV) and/or Herpes simplex virus 2 (HSV-2).
14. A pharmaceutical composition comprising SP-A or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating one or more STIs in a subject, wherein the STI is a DNA virus infection.
15. The pharmaceutical composition of claim 14, wherein the DNA virus is Human papillomavirus (HPV) and/or Herpes simplex virus (HSV).
16. The pharmaceutical composition of claim 14 or 15, which further comprises a pharmaceutical excipient and/or carrier.
17. The pharmaceutical composition of any one of claims 14 to 16, which further comprises a microbicide.
18. The pharmaceutical composition of any one of claims 14 to 17, which is formulated for delivery into the female reproductive tract.
19. The pharmaceutical composition of any one of claims 14 to 18, which is formulated for topical application or as a suppository.
20. The use of SP-A or a fragment, homologue, variant or derivative thereof in the manufacture of a medicament for preventing and/or treating one or more STIs in a subject, wherein the STI is a DNA virus infection.
21. The use of claim 20, wherein the DNA virus is Human papillomavirus (HPV) and/or Herpes simplex virus (HSV).

22. The use of claim 20 or 21, wherein the medicament further comprises a microbicide.
23. A kit comprising SP-A or a fragment, homologue, variant or derivative thereof, for use in preventing and/or treating one or more STIs, wherein the STI is a DNA virus infection.
24. The kit of claim 23, wherein the DNA virus is Human papillomavirus (HPV) and/or Herpes simplex virus (HSV).
25. The kit of claim 23 or 24, which further comprises a microbicide.
26. The kit of any one of claims 23 to 25, which further comprises an applicator for administering the SP-A into the reproductive tract.
27. A method for preventing and/or treating at least one STI in a subject, wherein the STI is a DNA virus infection, the method comprising a step of administering an effective amount of SP-A or a fragment, homologue, variant or derivative thereof to the subject.
28. The method of claim 27, wherein the DNA virus is Human papillomavirus (HPV) and/or Herpes simplex virus 2 (HSV-2).
29. The method of claim 27 or 28, wherein the SP-A or fragment, homologue, variant or derivative thereof is administered to the genital area or reproductive tract of the subject.
30. The method of claim 29, wherein the SP-A or fragment, homologue, variant or derivative thereof is administered in combination with a microbicide.
31. Surfactant protein A (SP-A), or a fragment, homologue, variant or derivative thereof, for use in preventing cervical cancer, genital warts and genital ulcers in a subject.
32. A nucleic acid encoding SP-A or a fragment, homologue, variant or derivative thereof, for use in preventing cervical cancer, genital warts and genital ulcers in a subject.
33. A pharmaceutical composition comprising SP-A or a fragment, homologue, variant or derivative thereof, for use in preventing cervical cancer, genital warts and genital ulcers in a subject.

34. The use of SP-A or a fragment, homologue, variant or derivative thereof in the manufacture of a medicament for preventing cervical cancer, genital warts and genital ulcers in a subject.
35. A kit comprising SP-A or a fragment, homologue, variant or derivative thereof, for use in preventing cervical cancer, genital warts and genital ulcers in a subject.
36. A method for preventing cervical cancer, genital warts and genital ulcers in a subject, the method comprising a step of administering an effective amount of SP-A or a fragment, homologue, variant or derivative thereof to the subject.

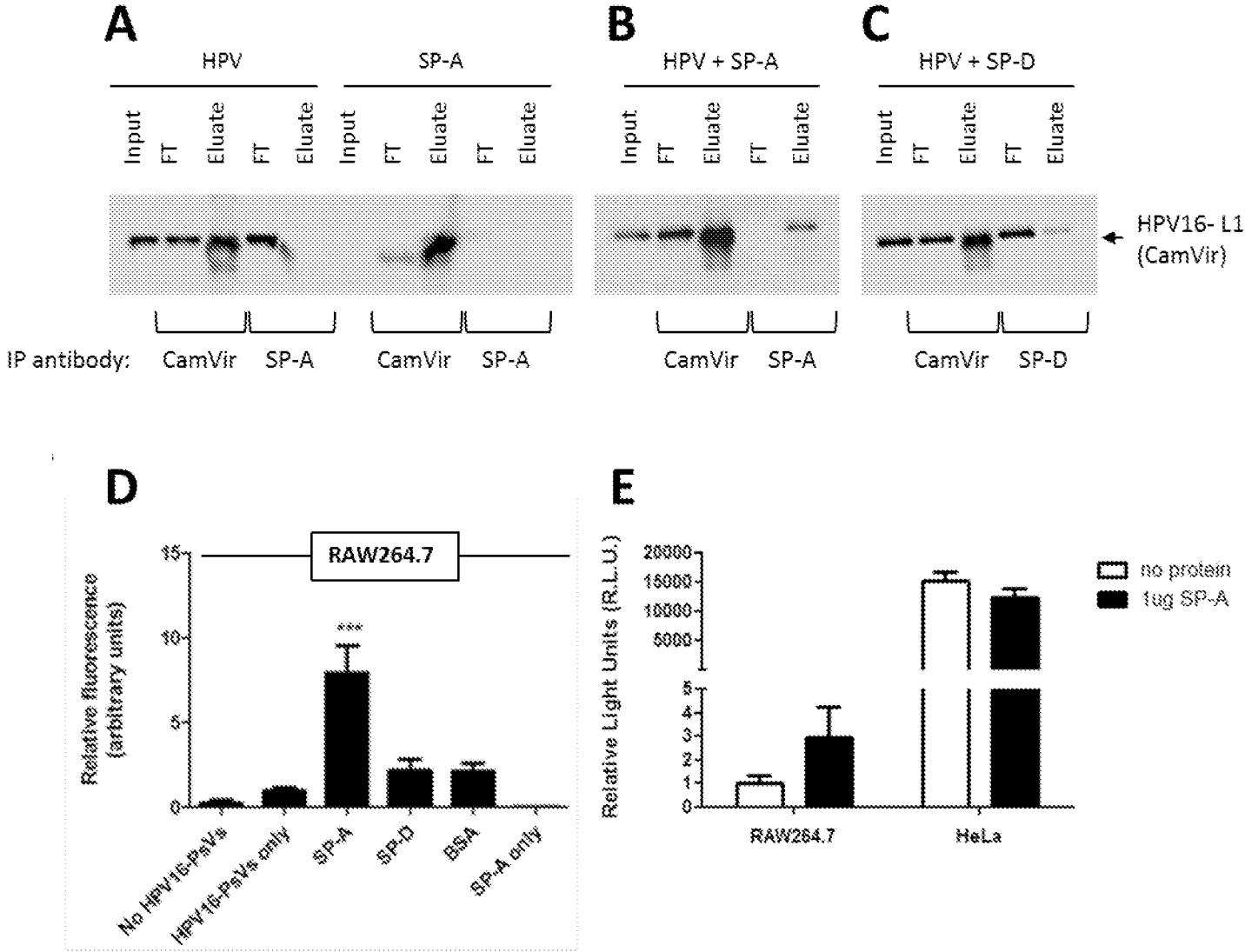


Figure 1

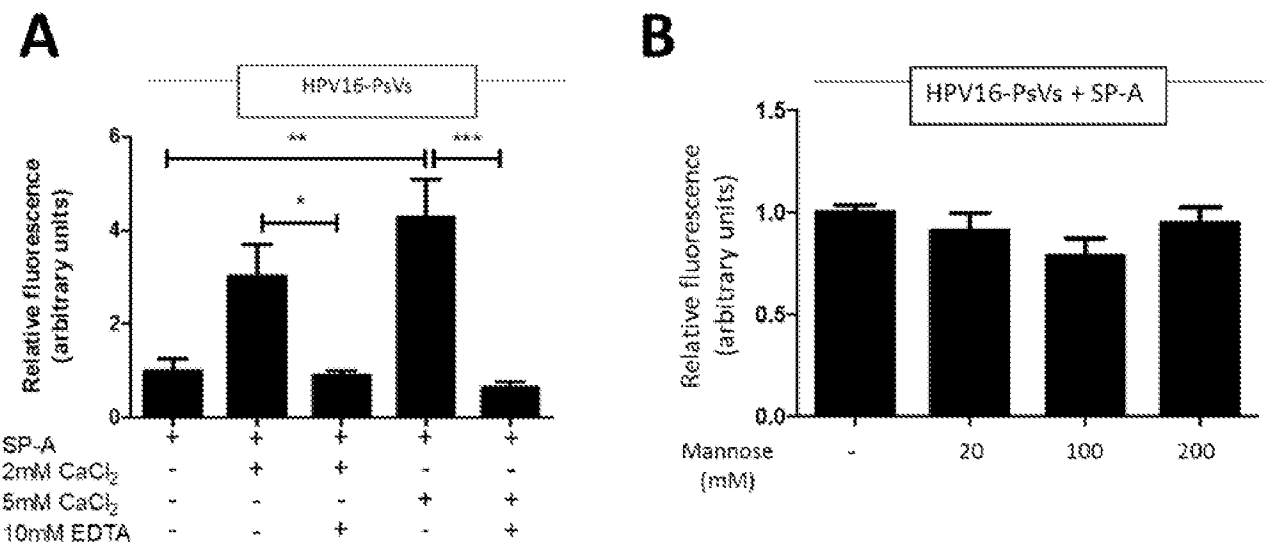


Figure 2

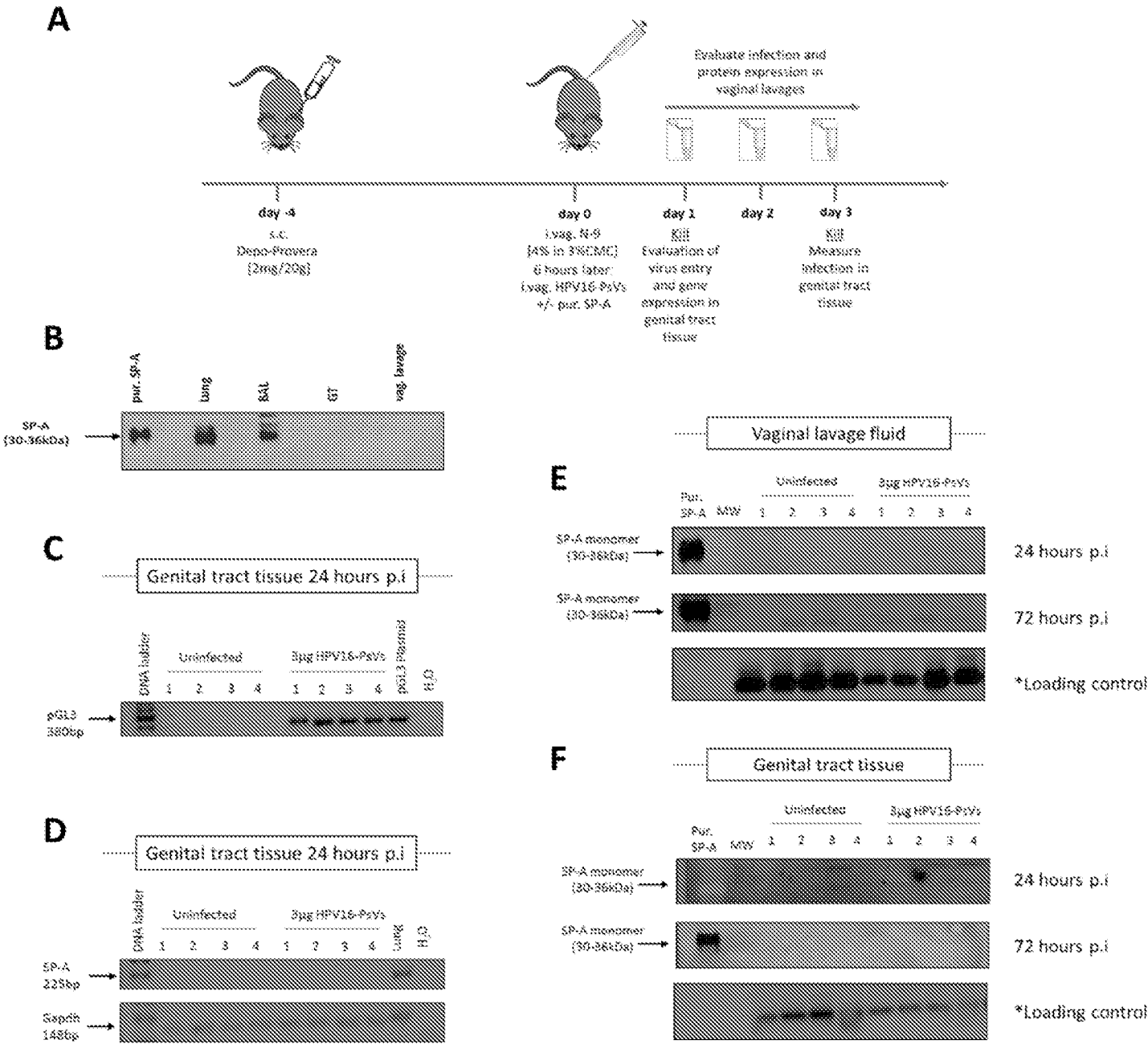


Figure 3

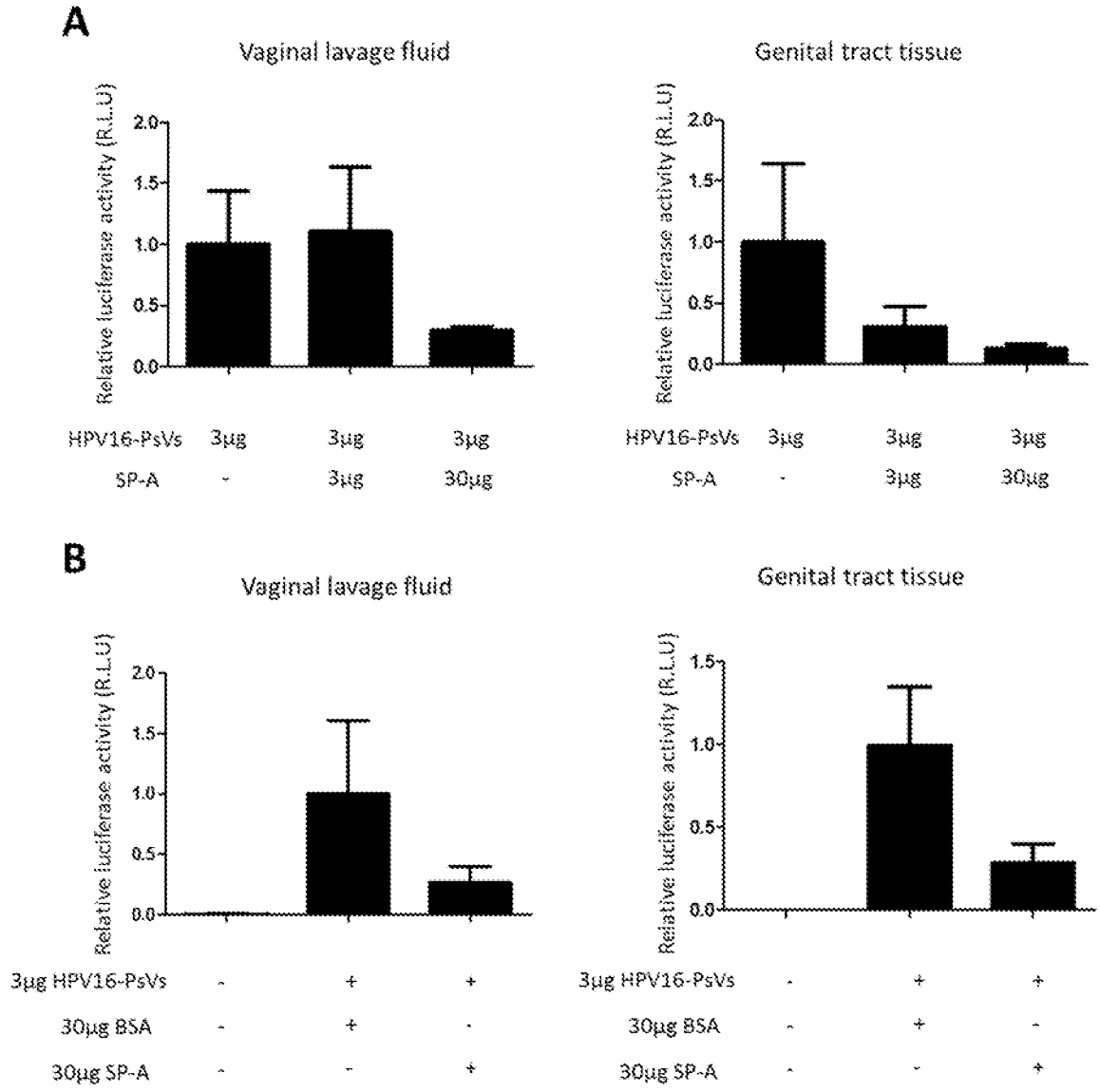


Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/055290

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/17 A61P31/12
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)

EP0-Internal, BIOSIS, EMBASE, 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	REISING S F ET AL: "In vitro inhibitory activity of surfactant protein A (SP-A) on herpes simplex virus type-2 (HSV-2)", ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 35, no. 0, 1995, page 198, XP009508360, & 35TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY; SAN FRANCISCO, CALIFORNIA, USA; SEPTEMBER 17-20, 1995	1-30
Y	Abstract H103 ----- -/--	1-30

☒ Further documents are listed in the continuation of Box C.

☐ 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

28 September 2018

Date of mailing of the international search report

10/01/2019

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/055290

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHARLES R. WIRA ET AL: "Innate Immunity in the Human Female Reproductive Tract: Endocrine Regulation of Endogenous Antimicrobial Protection Against HIV and Other Sexually Transmitted Infections", AMERICAN JOURNAL OF REPRODUCTIVE IMMUNOLOGY, vol. 65, no. 3, 7 February 2011 (2011-02-07), pages 196-211, XP055510561, US ISSN: 1046-7408, DOI: 10.1111/j.1600-0897.2011.00970.x abstract page 196, left-hand column, paragraph 1 - page 206, right-hand column, paragraph 1 -----	1-30
Y	PETER R LAWSON ET AL: "The roles of surfactant proteins A and D in innate immunity", IMMUNOLOGICAL REVIEWS., vol. 173, no. 1, 28 February 2002 (2002-02-28), pages 66-78, XP055510704, US ISSN: 0105-2896, DOI: 10.1034/j.1600-065X.2000.917308.x abstract page 66, right-hand column, paragraph 1 - page 74, right-hand column, paragraph 1 -----	1-30
Y	IWAARDEN VAN J F ET AL: "Binding of surfactant protein A (SP-A) to herpes simplex virus type 1-infected cells is mediated by the carbohydrate moiety of SP-A", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 267, no. 35, 15 December 1992 (1992-12-15), pages 25039-25043, XP002389974, ISSN: 0021-9258 abstract page 25039, left-hand column, paragraph 1 - page 25042, right-hand column, paragraph 4 ----- -/--	1-30

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/055290

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHARLES R WIRA ET AL: "The innate immune system: gatekeeper to the female reproductive tract", IMMUNOLOGY, vol. 111, no. 1, 15 December 2003 (2003-12-15), pages 13-15, XP055510562, DOI: 10.1111/j.1365-2567.2004.01796.x pages 13-14 -----	1-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/055290

Box No. 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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 No. 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:

see additional sheet

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 fees, this Authority did not invite payment of additional fees.
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.:

1-30

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-30

Use of a surfactant protein A (SP-A) in a method of prevention and/or treatment, wherein the method is for the prevention and/or treatment of one or more sexually-transmitted DNA virus infections.

2. claims: 31-36

Use of a surfactant protein A (SP-A) in a method of prevention and/or treatment, wherein the method is for the prevention and/or treatment of cervical cancer, genital warts and genital ulcers.
