(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 June 2013 (27.06.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/092875 A1

(51) International Patent Classification:
A61K 39/00 (2006.01) *C07K 14/52* (2006.01)
C07K 16/44 (2006.01) *C07K 16/00* (2006.01)
A61K 39/12 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/EP2012/076404

(22) International Filing Date:
20 December 2012 (20.12.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/578,542 21 December 2011 (21.12.2011) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

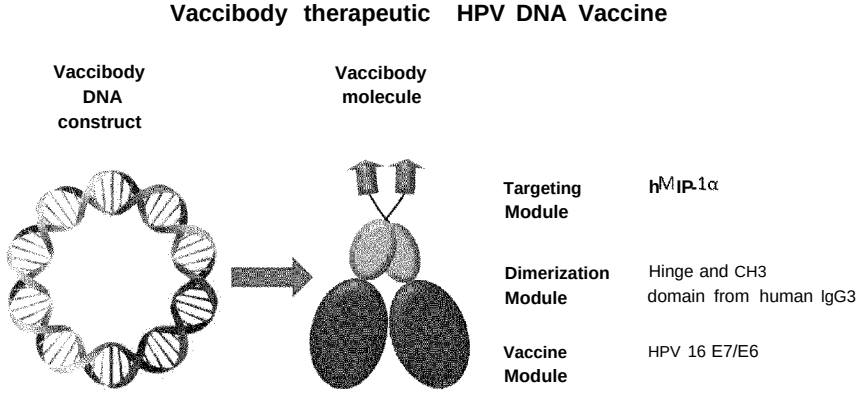
Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: VACCINES AGAINST HPV

Figure 1



(57) Abstract: The present invention relates to therapeutic compounds, such as vaccines against human papillomavirus (HPV) and in particular to DNA vaccines against HPV16 or HPV18. The invention further relates to protein construct encoding homodimeric peptides, which peptides may be released from a DNA vaccine or used separately. Further described are pharmaceutical formulations, host cells and methods for producing the vaccines, as well as methods for the treatment of various HPV induced diseases, such as cancers and infectious diseases by application.

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VACCINES AGAINST HPV

FIELD OF THE INVENTION

The present invention relates to therapeutic compounds, such as vaccines against human papillomavirus (HPV) and in particular to DNA vaccines against HPV16 and/or HPV18. The invention further relates to protein construct encoding homodimeric peptides, which peptides may be released from a DNA vaccine or used separately. Further described are pharmaceutical formulations, host cells and methods for producing the vaccines, as well as methods for the treatment of various HPV induced diseases, such as cancers and infectious diseases by application.

BACKGROUND OF THE INVENTION

It is now well established that human papillomavirus (HPV) is the cause of cervical cancer and other HPV-associated malignancies such as anogenital (anus, vulvar, vaginal and penile) cancers and a subset of head and neck cancers. In particular, HPV16 and HPV 18 are responsible for about 70% of all cervical cancers worldwide.

To date, two prophylactic HPV vaccines are on the market (Gardasil and Cervarix). The aim of the prophylactic vaccines is to induce humoral immune responses by stimulating the production of neutralizing antibodies specific for the HPV viral capsid proteins, LI and L2. Although the preventive vaccines are an important milestone for the control of HPV induced cervical cancer and possibly other HPV-associated malignancies, the effect of these vaccines will not be significantly observed for 20-40 years (Ma B et al., Current Cancer Therapy Reviews, 2010). Moreover, since the coverage of mass vaccination for the prophylactic vaccines are to date limited in addition to a substantial population worldwide that already are HPV infected, HPV-associated malignancies will continue to progress. Thus, it will be important to develop HPV-specific therapeutic vaccines in order to reduce the mortality and morbidity of HPV-associated malignancies and its precursor lesions (Ma B et al., Current Cancer Therapy Reviews, 2010).

The development of various cancer vaccines and cancer immunotherapy strategies has throughout the last two decades expanded. Still, only one therapeutic cancer vaccine, called Provenge (Dendreon INC) has so far been approved to be applied as standard therapy for prostate cancer. Notably, due to ethical reasons the majority of therapeutic cancer vaccines are tested on a patient group bearing a late stage tumor. This patient group is substantially immunosuppressed meaning that the tumor cells have for long escaped the immune system

and contributed to induce immunological tolerance to the tumor along carcinogenesis. In addition, the choice of antigens (tumor-specific vs. tumor-associated) applied as vaccines are critical in order to induce tumor-specific immune responses and avoid killing of healthy cells in the patients which may lead to serious adverse events. Thus, the major challenges in cancer immunotherapy are to break the immunological tolerance and activate tumor-specific effector functions to recognize and kill tumor cells. Although some case reports show clinical response to therapeutic cancer vaccines in late stage tumor patients, the most common primary endpoint is to observe the impact on overall survival compared to conventional therapy (surgery, chemo and radiation therapy). However, most studies are either not conclusive or that they completely fail to show this. One reason for the negative results lies in the patient group carrying end-stage tumors that are challenging to treat in the first place. A possible strategy could be to include patients with early-stage tumors in therapeutic vaccine trials.

One strategy is to target pre-cancerous lesions. The challenges for this strategy are mainly the lack of reliable biomarkers that are specifically expressed by precancerous lesions for many tissues and poor medical screening (either non-existing or that the existing method suffers from lack of sensitivity). Exceptionally, this is not the case for HPV-induced malignancies. For instance, the majority of western countries have good screening programs for cervical dysplasia and cervical cancer by performing the Papanicolaou test (Pap smear test). If there are unclear or abnormal results from Pap smear test, colposcopy will be performed (National Cervical Cancer Coalition). HPV-testing may also be recommended for some patients to detect the presence of "high-risk" HPV-type in the precancerous lesion. Thus, HPV represents a potential biomarker for HPV-associated precancerous lesions, in particular cervical intraepithelial dysplasia (CIN).

DNA vaccines have shown increasing promise for the treatment of human diseases, in particular cancer. DNA vaccines induce strong antigen-specific immune responses and can be repeatedly administered to maintain the target-specific immune responses. Such vaccines are considered to be safe and simple and cheap to produce on a large scale compared to other cancer therapeutic formats. Numerous immunotherapeutic interventions fail to induce immunological memory. Exceptionally, DNA vaccination ensures sustained release of the vaccine product in vivo which enhances antigen-specific immunological memory. Direct delivery of antigens to professional antigen-presenting cells (APCs) stimulates both CD4+ and CD8+ T cell immune responses in vivo. Such strong cellular immune responses have been demonstrated to specifically recognize and kill antigen-positive malignant cells efficiently both in vitro and in vivo.

There is still a need in the art for improved vaccines for inducing strong and specific immune responses against HPV responsible for both infectious diseases and cancers.

OBJECT OF THE INVENTION

It is an object of embodiments of the invention to provide specific and highly effective therapeutic compounds, such as DNA vaccines against diseases and conditions caused by HPV.

SUMMARY OF THE INVENTION

It has been found by the present inventors that by combining the antigens of the early gene products E6 and E7 from HPV, such as from HPV16 and/or HPV18 with the targeting module of hMIP-1a, therapeutic vaccines are provided, wherein the strong immunogenic epitopes of HPV gene products are presented with high efficiency to APCs to induce a specific and strong immune response. The products according to the present invention is primarily envisioned as therapeutic nucleic acid vaccines, such as DNA vaccines, wherein a nucleic acid construct encoding the vaccibody construct is used as the therapeutic compound leading to in vivo production of the protein product within the person receiving the vaccine. However, as an alternative the protein product itself may be formulated and used directly in the vaccine.

Accordingly, in a first aspect the present invention relates to a homodimeric protein of two identical amino acid chains, each amino acid chain comprising (1) a signal peptide, (2) a targeting unit, (3) a dimerization motif, and (4) an antigenic unit, said targeting unit comprising an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1, and an antigenic unit comprising an amino acid sequence of human papillomavirus (HPV), such as an antigenic unit comprising an amino acid sequence of HPV16 and/or HPV18, such as an antigenic unit derived from early proteins E6 and/or E7 of HPV16 and/or HPV18.

In a second aspect the present invention relates to an amino acid chain comprising (1) a signal peptide, (2) a targeting unit, (3) a dimerization motif, and (4) an antigenic unit, said targeting unit comprising an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1, and an antigenic unit comprising an amino acid sequence of human papillomavirus (HPV), such as an antigenic unit comprising an amino acid sequence of HPV16 and/or HPV18, such as an antigenic unit derived from early proteins E6 and/or E7 of HPV16 and/or HPV18, which amino acid chain is able to form a homodimeric protein according to the invention.

In a third aspect the present invention relates to a nucleic acid molecule, such as a DNA, encoding an amino acid chain comprising (1) a signal peptide, (2) a targeting unit, (3) a dimerization motif, and (4) an antigenic unit, said targeting unit comprising an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1, and an antigenic unit comprising an amino acid sequence of human papillomavirus (HPV), such as an antigenic unit comprising an amino acid sequence of HPV16 and/or HPV18, such as an antigenic unit derived from early proteins E6 and/or E7 of HPV16 and/or HPV18, which amino acid chain is able to form a homodimeric protein according to the invention.

In a further aspect the present invention relates to a homodimeric protein according to the invention, or an amino acid chain according to the invention, or the nucleic acid molecule according to the invention for use as a medicament.

In a further aspect the present invention relates to a pharmaceutical composition comprising a homodimeric protein according to the invention, or an amino acid chain according to the invention, or the nucleic acid molecule according to the invention.

In a further aspect the present invention relates to a host cell comprising the nucleic acid molecule according to the invention.

In a further aspect the present invention relates to a method for preparing a homodimeric protein according to the invention, or an amino acid chain of the invention, the method comprising a) transfecting the nucleic acid molecule according to the invention into a cell population; b) culturing the cell population; c) collecting and purifying the homodimeric protein, or amino acid chain expressed from the cell population.

In a further aspect the present invention relates to a method for preparing a vaccine, such as a DNA vaccine, comprising an immunologically effective amount of a nucleic acid molecule according to the invention, the method comprising a) preparing a nucleic acid molecule according to the invention; b) dissolving the nucleic acid molecule obtained under step a) in a pharmaceutically acceptable carrier, diluent, or buffer.

In a further aspect the present invention relates to a vaccine against HPV comprising an immunologically effective amount of a homodimeric protein according to the invention, or an amino acid chain according to the invention, or nucleic acid molecule, such as a DNA, according to the invention, wherein said vaccine is able to trigger both a T-cell- and B-cell immune response.

In a further aspect the present invention relates to a method of treating or preventing a HPV induced disease or condition, such as a cancer or an infectious disease caused by HPV in a patient, the method comprising administering to the patient in need thereof, a homodimeric protein according to the invention, or an amino acid chain according to the invention, or the nucleic acid molecule, such as a DNA, according to the invention.

LEGENDS TO THE FIGURE

Figure 1: The overall structure of vaccibody vaccines with E7/E6 fusion antigen. Shown are both DNA and protein formats. The vaccibody consist of three functional modules; the chemokine human MIP-1α (LD78β) in the targeting module, hinge and CH3 sequences from human IgG3 in the dimerization module and full-length E7 and/or E6 fusion in the vaccine module.

Figure 2: The suggested mode of action for a Vaccibody DNA vaccine against HPV -induced malignancies. Naked DNA plasmid encoding vaccibody is injected intradermal followed by electroporation. The plasmid is taken up by local cells and vaccibody proteins are produced and secreted. The chemotactic targeting modules attract CCRl and CCR5 expressing antigen presenting cells (APC) and ensure binding and uptake into dendritic cells (DC). The DC will present antigenic peptides to CD4+ and CD8+ T cells and the CD8+ T cells will kill HPV infected and transformed cells in the cervix.

Figure 3: ELISPOT results showing the number of E7 and E6 specific T cell responses as a function of different amounts of vaccine administered. C57BL/6 mice were injected i.d. with naked DNA plasmids encoding VB1009 and VB1016 and their corresponding controls followed by electroporation (Cellectis, France) on day 0 and day 7. Splenocytes were harvested at day 21 and stimulated with MHC class I-restricted E7 or E6 peptide for 24h. The number of IFNy secreting splenocytes was calculated by ELISPOT. (A) E7-specific responses after i.d. vaccination with 25µg of VB1009, control 1 (antigen alone) and pUMVC4a (empty vector). (B) E7-specific responses after i.d. vaccination with 12.5 and 1.4µg of VB1016, control 2 (antigen alone) and pUMVC4a (empty vector). (C) E6-specific responses after i.d. vaccination with 12.5 and 1.4µg of VB1016, control 2 (antigen alone) and pUMVC4a (empty vector).

Figure 4.Therapeutic effect of VB1016 shown by measured tumor volume. C57BL/6 mice were injected s.c. with $5xl0^5$ TC-1 cells at day 0. At day 3 and day 10, the mice were injected i.d. with 12.5µg naked DNA plasmids encoding VB1016, control 2 or empty vector followed by electroporation (Cellectis, France). The tumor sizes were measured by caliper two to three times a week and tumor volume calculated.

Figure 5.Therapeutic effect of VB1016 shown by measured tumor volume. C57BL/6 mice were injected s.c. in the neck area with 5xl 0^4 TC-1 cells at day 0. At day 3,7 and day 10, the mice were injected i.d. with 20µg or 2µg naked DNA plasmids encoding VB1016, control 2 or empty vector followed by electroporation (Cellectis, France). The tumor sizes were measured by caliper two to three times a week and tumor volume calculated.

Figure 6.Therapeutic effect of VB1020 and VB1021 shown by measured tumor volume. C57BL/6 mice were injected s.c. in the thigh with 5xl0 ^{4} TC-1 cells at day 0. At day 3 and day 10, the mice were injected i.d. with 10µg naked DNA plasmids encoding VB1016, VB1020, VB1021 or empty vector followed by electroporation (Cellectis, France). The tumor sizes were measured by caliper two to three times a week and tumor volume calculated.

DETAILED DISCLOSURE OF THE INVENTION

The constructs and DNA vaccine technology described herein by the inventors of the present invention (also referred to as "vaccibody" molecules/vaccines/constructs) represents a novel vaccine strategy to induce strong and specific immune responses for both infectious diseases and cancer. The HPV E6/E7, such as HPV16 or HPV18 E6/E7 vaccine described herein may be administered as a DNA vaccine by intradermal injection, preferably followed by electroporation. This results in the uptake of the DNA-construct encoding the vaccibody-HPV16 and/or HPV18 E6/E7 vaccine in cells at the site of injection (dermis) including dendritic cells (Langerhans cells), leading to in vivo production of the vaccibody-E6/E7 molecule.

The early gene products E6 and E7 from "high-risk" HPV types such as HPV16 and 18 may be responsible for transformation of the basal-epithelium cells and induction of precancerous lesions. Both proteins consist of highly immunogenic epitopes and are shown herein to induce strong immune responses leading to specific eradication of "high-risk" HPV positive tumor cells both in vitro and in vivo.

The vaccibody molecule described herein is a homodimer consisting of three modules; targeting module, dimerization module and the vaccine module (Figure 1). Genes encoding the three modules are genetically engineered to be expressed as one gene. When expressed in vivo, the vaccibody molecule targets antigen presenting cells (APCs) which results in an enhanced vaccine potency compared to identical, non-targeted antigens. In vivo expression of the chemokine human macrophage inflammatory protein 1 alpha (hMIP-1a/ LD78β) leads to attraction of DCs, neutrophils and other immune cells carrying the CCR1 and CCR5 receptors to the site of expression. Thus, the vaccibody molecule consisting of hMIP-1a as the targeting

module, will not only target the antigens to specific cells, but in addition give a response-amplifying effect (adjuvant effect) by recruiting specific immune cells to the injection site. This unique mechanism may be of great importance in a clinical setting where patients can receive the vaccine without any additional adjuvants since the vaccine itself gives the adjuvant effect.

The inventors of the present invention describes herein vaccine constructs where the antigenic module consist of the E7 full length genetic sequence in fusion to the E6 full length sequence originating from the HPV16 or HPV18 subtype. The advantage of this format is that both E6 and E7 will be present in one construct and may thus be equally expressed *in vivo.* Consequently, one vaccibody molecule consisting of a multi-antigenic unit may represent equal levels of E6 and E7 for the immune system. The HPV16 E6 and E7 gene products are oncogenic in their natural form. To neutralize their oncogenic properties, mutations at specific sites may be introduced in the E6 and E7 genetic sequence.

The mutations, including deletions, may be introduced at specific sites, known to inhibit the oncogenic properties of E6 and E7, such as any one described in any of *Dalai S et al., J Virol, 1996; Munger K et al., EMBO, 1989; Nakagawa S et al., Virology, 1995; Crook T et al., Cell, 1991; Munger K et al., HPV Compendium Online, 1997 (http://www.stdgen. lanl. gOv/COMPENDIUM_PDF/97PDF/3/E7.pdf); Nguyen, M et al., J Virol, 2002; Nomine Y et a., Molecular Cell, 2006; Moody C et al., Nat Rev Cancer, 201 0, Polakova I et al., Vaccine, 201 0; Xie Q, Virologica Sinica, 201 1; Mesplede T et al., J Virol, 2012;* US 2008/0 102084 and US6306397, which references are hereby incorporated by reference. Accordingly, in some aspects of the invention, the constructs according to the present invention contain HPV16 E6, E7 or HPV16 E6/E7 chimeric constructs with one or more mutations in either of HPV16 E6, E7 or both at a position known to inhibit the oncogenic properties as described in Dalai S et al., J Virol, 1996; Münger K et al., EMBO, 1989; Nakagawa S et al., Virology, 1995; Crook T et al., Cell, 1991; Münger K et al., HPV Compendium Online, 1997 (http ://www.stdgen .lanl.gOv/COMPENDIUM_PDF/97PDF/3/E7 .pdf) ; *Nguyen, M et al., J Virol, 2002; Nomine Y et a., Molecular Cell, 2006;* Moody C et al., Nat Rev Cancer, 2010, *Polakova I et al., Vaccine, 201 0; Xie Q, Virologica Sinica, 201 1; Mesplede T et al., J Virol, 2012;* US 2008/0 102084 or US6306397 . In other aspects of the invention, the constructs according to the present invention contain HPV18 E6, E7 or HPV18 E6/E7 chimeric constructs with one or more mutations in either of HPV18 E6, E7 or both at a position known to inhibit the oncogenic properties as described in Dalai S et al., J Virol, 1996; Münger K et al., EMBO, 1989; Nakagawa S et al., Virology, 1995; Crook T et al., Cell, 1991; Münger K et al., HPV Compendium Online, 1997 (http ://www.stdgen .lanl.gOv/COMPENDIUM_PDF/97PDF/3/E7 .pdf) ; Moody C et al., Nat Rev Cancer, 2010, US 2008/0 102084 and US6306397 .

There is a possibility that the vaccibody-moiety (targeting and dimerization modules) may eradicate the oncogenic properties of E6 and E7 wildtype proteins in the final fusion protein. Thus, in yet another aspect of the invention is the utilization of the wildtype full-length E6 and/or E7 sequences in the vaccibody construction.

The invention describes several variant of Vaccibody HPV therapeutic DNA vaccines all based on the overall format described in figure 1, the therapeutic vaccibody-HPV DNA vaccines encodes genes that are naturally expressed in humans; the *targeting module* genes encode the chemokine hMIP-1a, which binds to its cognate receptors, CCR1 and CCR5 expressed on the cell surface of APCs. The *dimerization module* genes may encode hinge regions and constant heavy chain 3, such as from human IgG3 which connects two vaccibody monomers generating a homodimer molecule. Genes encoding the *vaccine module* for the current strategy consist of HPV, such as HPV16 and/or HPV18 E7 and E6 antigens, such as the full length HPV16 E7 and E6 antigens, optionally comprising one or more mutation to inhibit the oncogenic properties. Once administered *in vivo* by i.d. injection followed by electroporation, dermal cells taking up the vaccine construct will express the vaccibody-HPV molecule. The *in vivo* produced vaccibody vaccines target to CCR1 and CCR5 expressed on the surface of APCs in the skin, in particular DCs. The binding of the vaccibody molecule to its cognate receptors leads to internalization of the complex in the APC, degradation of the proteins into small peptides that are loaded onto MHC molecules and presented to $CD4^+$ and $CD8^+$ T cells to induce HPV16 E6 and E7 specific immune responses. Once stimulated and with help from activated $CD4^+$ T cells, $CD8^+$ T cells will target and kill HPV16 E6 and E7 expressing cells (Figure 2). Such enhanced immune responses to a vaccine with a "built-in" adjuvant effect may potentially overcome tumor-escape (tumor immune surveillance) by breaking immunological tolerance and efficiently kill malignant cells. The hMIP-1a targeting unit may be connected through a dimerization motif, such as a hinge region, to an antigenic unit, wherein the later is in either the COOH-terminal or the NH2-terminal end. The present invention not only relates to a DNA sequence coding for this recombinant protein, but also to expression vectors comprising these DNA sequences, cell lines comprising said expression vectors, to treatment of mammals preferentially by immunization by means of Vaccibody DNA, Vaccibody RNA, or Vaccibody protein, and finally to pharmaceuticals and a kit comprising the said molecules.

The dimerization motif in the proteins according to the present invention may be constructed to include a hinge region and an immunoglobulin domain (e.g. Cγ3 domain), e.g. carboxyterminal C domain (C_H3 domain), or a sequence that is substantially identical to said C domain. The hinge region may be Ig derived and contributes to the dimerization through the formation of an intercahin covalent bond(s), e.g. disulfide bridge(s). In addition, it functions as a flexible spacer between the domains allowing the two targeting units to bind simultaneously to two target molecules on APC expressed with variable distances. The immunoglobulin

domains contribute to homodimerization through non-covalent interactions, e.g. hydrophobic interactions. In a preferred embodiment the C_H3 domain is derived from IgG. These dimerization motifs may be exchanged with other multimerization moieties (e.g. from other Ig isotypes/subclasses). Preferably the dimerization motif is derived from native human proteins, such as human IgG.

It is to be understood that the dimerization motif may have any orientation with respect to antigenic unit and targeting unit. In one embodiment the antigenic unit is in the COOH-terminal end of the dimerization motif with the targeting unit in the N-terminal end of the dimerization motif. In another embodiment the antigenic unit is in the N-terminal end of the dimerization motif with the targeting unit in the COOH-terminal end of the dimerization motif.

International application WO 2004/076489, which is hereby incorporated by reference discloses nucleic acid sequences and vectors, which may be used according to the present invention.

The proteins according to the present invention include an antigenic unit derived from HPV, such as HPV16 E7 and E6 antigens, such as the full length HPV16 E7 and E6 antigens, as well as immunogenic fragments or variants thereof. The antigenic sequence should be of sufficient length. The minimal length of such antigenic unit may be around 9 amino acids. Accordingly in some embodiments, the antigenic unit derived from HPV comprises an amino acid sequence of at least 9 amino acids corresponding to at least about 27 nucleotides in a nucleic acids sequence encoding such antigenic unit. Preferably the antigenic unit derived from HPV is considerably longer, such as the full length HPV16 E7 and E6 antigens. Diversity arises within a given HPV genotype through limited nucleotide changes in the coding (at a frequency of <2%) and non-coding (at a frequency of <5%) regions (Bernard, HU et al., Int J Cancer, 2006). Such variants phylogenetically segregate based on their geographical origin and are therefore labeled European, African, Asian, Asian-American and North American. Insertion of such sequences in a Vaccibody format might lead to activation of both arms of the immune response.

Immunization by means of Vaccibody protein, Vaccibody DNA, or Vaccibody RNA, the latter two executed e.g. by intramuscular or intradermal injection with or without a following electroporation, are all feasible methods according to the present invention.

As discussed above, the present invention relates to a vaccine composition against cancer or infectious diseases caused by HPV, the vaccine composition comprising an immunologically effective amount of the nucleic acid encoding the molecule of the invention or degenerate variants thereof. The vaccine may be able to trigger both a T-cell- and B-cell immune

response. The present invention also relates to a kit comprising Vaccibody DNA, RNA, or protein for diagnostic, medical or scientific purposes.

The invention further relates to a method of preparing the recombinant molecule of the invention comprising, transfecting the vector comprising the molecule of the invention into a cell population; culturing the cell population; collecting recombinant protein expressed from the cell population; and purifying the expressed protein.

The above described nucleotide sequences may be inserted into a vector suited for gene therapy, e.g. under the control of a specific promoter, and introduced into the cells. In some embodiments the vector comprising said DNA sequence is a virus, e.g. an adenovirus, vaccinia virus or an adeno-associated virus. In some embodiments a retroviruses is used as vector. Examples of suitable retroviruses are e.g. MoMuLV or HaMuSV. For the purpose of gene therapy, the DNA/RNA sequences according to the invention can also be transported to the target cells in the form of colloidal dispersions. They comprise e.g. liposomes or lipoplexes.

The present invention encompasses the use of a targeting unit as well as an antigenic unit having minimum degree of sequence identity or sequence homology with amino acid sequence(s) defined herein or with a polypeptide having the specific properties defined herein. The present invention encompasses, in particular, the use of peptide variants or peptide units to be used in the constructs according to the present invention having a degree of sequence identity with any one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34. Here, the term "variant" means an entity having a certain degree of sequence identity with the subject amino acid sequences or the subject nucleotide sequences, where the subject amino acid sequence preferably is SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, or SEQ ID NO:34.

In one aspect, the variant or fragment amino acid sequence and/or nucleotide sequence should provide and/or encode a polypeptide which retains the functional activity and/or enhances the activity of a polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID

NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34.

In the present context, a variant sequence is taken to include an amino acid sequence which may be at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99%, identical to the subject sequence. Typically, the variants used according to the present invention will comprise the same active sites etc. as the subject amino acid sequence. 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 preferred to express homology in terms of sequence identity.

Sequence identity comparisons can be conducted by eye, or more usually, with the aid of readily available sequence comparison computer programs. These commercially available computer programs use complex comparison algorithms to align two or more sequences that best reflect the evolutionary events that might have led to the difference(s) between the two or more sequences. Therefore, these algorithms operate with a scoring system rewarding alignment of identical or similar amino acids and penalising the insertion of gaps, gap extensions and alignment of non-similar amino acids. The scoring system of the comparison algorithms include:

i) assignment of a penalty score each time a gap is inserted (gap penalty score),

ii) assignment of a penalty score each time an existing gap is extended with an extra position (extension penalty score),

iii) assignment of high scores upon alignment of identical amino acids, and

iv) assignment of variable scores upon alignment of non-identical amino acids.

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.

The scores given for alignment of non-identical amino acids are assigned according to a scoring matrix also called a substitution matrix. The scores provided in such substitution matrices are reflecting the fact that the likelihood of one amino acid being substituted with another during evolution varies and depends on the physical/chemical nature of the amino acid to be substituted. For example, the likelihood of a polar amino acid being substituted with another polar amino acid is higher compared to being substituted with a hydrophobic amino acid. Therefore, the scoring matrix will assign the highest score for identical amino

acids, lower score for non-identical but similar amino acids and even lower score for non-identical non-similar amino acids. The most frequently used scoring matrices are the PAM matrices (Dayhoff et al. (1978), Jones et al. (1992)), the BLOSUM matrices (Henikoff and Henikoff (1992)) and the Gonnet matrix (Gonnet et al. (1992)).

Suitable computer programs for carrying out such an alignment include, but are not limited to, Vector NTI (Invitrogen Corp.) and the ClustalV, ClustalW and ClustalW2 programs (Higgins DG & Sharp PM (1988), Higgins et al. (1992), Thompson et al. (1994), Larkin et al. (2007). A selection of different alignment tools is available from the ExPASy Proteomics server at www.expasy.org. Another example of software that can perform sequence alignment is BLAST (Basic Local Alignment Search Tool), which is available from the webpage of National Center for Biotechnology Information which can currently be found at http://www.ncbi.nlm.nih.gov/ and which was firstly described in Altschul et al. (1990) J. Mol. Biol. 215; 403-4 10.

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

In one embodiment, it is preferred to use the ClustalW software for performing sequence alignments. Preferably, alignment with ClustalW is performed with the following parameters for pairwise alignment:

Substitution matrix:	Gonnet 250
Gap open penalty:	20
Gap extension penalty:	0.2
Gap end penalty:	None

ClustalW2 is for example made available on the internet by the European Bioinformatics Institute at the EMBL-EBI webpage www.ebi.ac.uk under tools - sequence analysis - ClustalW2. Currently, the exact address of the ClustalW2 tool is www.ebi.ac.uk/Tools/clustalw2.

In another embodiment, it is preferred to use the program AlignX in Vector NTI (Invitrogen) for performing sequence alignments. In one embodiment, ExplO has been may be used with default settings:

Gap opening penalty: 10

Gap extension penalty: 0.05

Gapseparation penalty range: 8

Score matrix: blosum62mt2

Thus, the present invention also encompasses the use of variants, fragments, and derivatives of any amino acid sequence of a protein, polypeptide, motif or domain as defined herein, particularly those of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34.

The sequences, particularly those of variants, fragments, and derivatives of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34, may also have deletions, insertions or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent substance. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues as long as the secondary binding activity of the substance is retained. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine, valine, glycine, alanine, asparagine, glutamine, serine, threonine, phenylalanine, and tyrosine.

The present invention also encompasses conservative substitution (substitution and replacement are both used herein to mean the interchange of an existing amino acid residue, with an alternative residue) that may occur i.e. like-for-like substitution such as basic for basic, acidic for acidic, polar for polar etc. Non-conservative substitution may also occur i.e. from one class of residue to another or alternatively involving the inclusion of unnatural amino acids such as ornithine (hereinafter referred to as Z), diaminobutyric acid ornithine (hereinafter referred to as B), norleucine ornithine (hereinafter referred to as O), pyriylalanine, thienylalanine, naphthylalanine and phenylglycine.

Conservative substitutions that may be made are, for example within the groups of basic amino acids (Arginine, Lysine and Histidine), acidic amino acids (glutamic acid and aspartic acid), aliphatic amino acids (Alanine, Valine, Leucine, Isoleucine), polar amino acids (Glutamine, Asparagine, Serine, Threonine), aromatic amino acids (Phenylalanine, Tryptophan and Tyrosine), hydroxyl amino acids (Serine, Threonine), large amino acids (Phenylalanine and Tryptophan) and small amino acids (Glycine, Alanine).

Replacements may also be made by unnatural amino acids include; alpha* and alpha-disubstituted* amino acids, N-alkyl amino acids*, lactic acid*, halide derivatives of natural amino acids such as trifluorotyrosine*, p-Cl- phenylalanine*, p-Br-phenylalanine*, p-I-phenylalanine*, L-allyl-glycine*, β-alanine*, L-a-amino butyric acid*, L-y-amino butyric acid*, L-a-amino isobutyric acid*, L-e-amino caproic acid*, 7-amino heptanoic acid*, L-methionine sulfone**, L-norleucine*, L-norvaline*, p-nitro-L-phenylalanine*, L-hydroxyproline*, L-thioproline*, methyl derivatives of phenylalanine (Phe) such as 4-methyl-Phe*, pentamethyl-Phe*, L-Phe (4-amino)#, L-Tyr (methyl)*, L-Phe (4-isopropyl)*, L-Tic (l,2,3,4-tetrahydroisoquinoline-3-carboxyl acid)*, L-diaminopropionic acid* and L-Phe (4-benzyl)*. The notation * has been utilised for the purpose of the discussion above (relating to homologous or non-conservative substitution), to indicate the hydrophobic nature of the derivative whereas # has been utilised to indicate the hydrophilic nature of the derivative, #* indicates amphipathic characteristics.

Variant amino acid sequences may include suitable spacer groups that may be inserted between any two amino acid residues of the sequence including alkyl groups such as methyl, ethyl or propyl groups in addition to amino acid spacers such as glycine or β-alanine residues. A further form of variation, involves the presence of one or more amino acid residues in peptoid form, will be well understood by those skilled in the art. For the avoidance of doubt, "the peptoid form" is used to refer to variant amino acid residues wherein the oc-carbon substituent group is on the residue's nitrogen atom rather than the oc-carbon. Processes for preparing peptides in the peptoid form are known in the art, for example Simon RJ *et al.* (1992), Horwell DC. (1995).

In one embodiment, the variant targeting unit used in the homodimeric protein according to the present invention is variant having the sequence of amino acids at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity therewith.

In one aspect, preferably the protein or sequence used in the present invention is in a purified form. The term "purified" means that a given component is present at a high level. The component is desirably the predominant active component present in a composition.

A "variant" or "variants" refers to proteins, polypeptides, units, motifs, domains or nucleic acids. The term "variant" may be used interchangeably with the term "mutant." Variants include insertions, substitutions, transversions, truncations, and/or inversions at one or more locations in the amino acid or nucleotide sequence, respectively. The phrases "variant polypeptide", "polypeptide", "variant" and "variant enzyme" mean a polypeptide/protein that has an amino acid sequence that has been modified from the amino acid sequence of SEQ ID

NO: 1. The variant polypeptides include a polypeptide having a certain percent, e.g., 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, of sequence identity with the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34.

"Variant nucleic acids" can include sequences that are complementary to sequences that are capable of hybridizing to the nucleotide sequences presented herein. For example, a variant sequence is complementary to sequences capable of hybridizing under stringent conditions, e.g., 50°C and 0.2X SSC (1X SSC = 0.15 M NaCl, 0.015 M sodium citrate, pH 7.0), to the nucleotide sequences presented herein. More particularly, the term variant encompasses sequences that are complementary to sequences that are capable of hybridizing under highly stringent conditions, e.g., 65°C and 0.1X SSC, to the nucleotide sequences presented herein. The melting point (Tm) of a variant nucleic acid may be about 1, 2, or 3°C lower than the Tm of the wild-type nucleic acid. The variant nucleic acids include a polynucleotide having a certain percent, e.g., 80%, 85%, 90%, 95%, or 99%, of sequence identity with the nucleic acid encoding SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34, encoding the monomeric protein which can form the homodimeric protein according to invention.

A specific category of mutations are the mutations in E6 and E7:

The E6 protein may be detoxified by rendering the p53 binding impossible. Five positions in the full length HPV16 E6 protein are sites for mutations for inactivation of E6 functionality, F47, L50, C63, C106 and I128. Any amino acid substitution in these positions may lead to inactivation of E6 and induces tumor suppression. Substitutions in any one of these positions with any one different amino acid may potentially be utilized. Sites for potential mutations are shown in SEQ ID NO:22.

In the E7 protein there are conserved regions associated with oncogenic properties (see Phelps et al J. Virol. April 1992, vol. 66, no. 4 24 18-242; Gulliver et al J Virol. 1997, August; 71(8)) including an N-terminal Rb (retinoblastoma binding protein) binding-site motif (LXCXE) and two conserved regions 3 (upstream and downstream) with a Zn- binding motif (CXXC). The preferred mutation sites in the LXCXE-motif are C24 and E26. Preferred sites in

the two CXXC motifs are C58, C61, C91 and C94. However, any mutations in these regions can be envisaged to be substituted for the reduction of binding functions and thus abolish the oncogenic effects of E7. Sites for potential mutations are shown in SEQ ID NO:23.

Signal peptide:

A signal peptide at the N-terminal end of the nascent polypeptide directs the molecule into the ER before transport to into the Golgi complex. The signal peptide is cleaved off by signal peptidase once it has served its purpose of targeting and importing the protein to the ER. These signal peptides are generally between 15 and 30 amino acids, but can have more than 50 residues *(Martoglio, B. et al., Trends in Cell Biology, 1998, Knappskog, S. et al., J Biotechnol, 2007)*. The native signal peptide may be replaced by signal peptides from any mammalian, prokaryotic or marine origin. Commonly used signal peptides are e.g. humanIL-2 and human albumin due to their natural ability to secrete large amounts of protein. The choice of signal peptide can have a considerable impact on the amount of synthesized and secreted protein.

In some embodiments, the signal peptide used in the protein construct according to the present invention is derived from a chemokine protein, such as the signal sequence of LD78beta.

In some embodiments the signal peptide is not derived from pLNOH2 (Bl-8 variable immunoglobulin leader) disclosed in the international application with International Application No: PCT/EP2011/060628.

In some embodiments the signal peptide is not derived from an immunoglobulin gene.

The term "homodimeric protein" as used herein refers to a protein comprising two individual identical strands of amino acids, or subunits held together as a single, dimeric protein by hydrogen bonding, ionic (charged) interactions, actual covalent disulfide bonding, or some combination of these interactions.

The term "dimerization motif", as used herein, refers to the sequence of amino acids between the antigenic unit and the targeting unit comprising the hinge region and the optional second domain that may contribute to the dimerization. This second domain may be an immunoglobulin domain, and optionally the hinge region and the second domain are connected through a linker. Accordingly the dimerization motif serves to connect the antigenic unit and the targeting unit, but also contain the hinge region that facilitates the dimerization of the two monomeric proteins into a homodimeric protein according to the invention.

The term "targeting unit" as used herein refers to a unit that delivers the protein with its antigen to mouse or human APC for MHC class II-restricted presentation to CD4+ T cells or for providing cross presentation to CD8+ T cells by MHC class I restriction. The targeting unit used in the constructs according to the present invention is derived from or identical to mature LD78-beta.

The term "antigenic unit" as used herein refers to any molecule, such as a peptide which is able to be specifically recognized by an antibody or other component of the immune system, such as a surface receptor on T-cells. Included within this definition are also immunogens that are able to induce an immune response. The terms "epitope" or "antigenic epitope" is used to refer to a distinct molecular surface, such as a molecular surface provided by a short peptide sequence within an antigenic unit. In some embodiments the antigenic unit comprises two ore more antigenic epitopes. The antigenic unit used in the constructs according to the present invention is derived from or identical to the early gene products E6 and E7 from HPV, such as from HPV16 or HPV18.

The term "hinge region" refers to a peptide sequence of the homodimeric protein that facilitates the dimerization, such as through the formation of an interchain covalent bond(s), e.g. disulfide bridge(s). The hinge region may be Ig derived, such as hinge exons h1+h4 of an Ig, such as IgG3.

Specific embodiments of the invention:

As described above, the present invention relates to a homodimeric protein of two identical amino acid chains, each amino acid chain comprising (1) a signal peptide, (2) a targeting unit, (3) a dimerization motif, and (4) an antigenic unit, said targeting unit comprising an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1, and an antigenic unit comprising an amino acid sequence of human papillomavirus (HPV), such as an antigenic unit comprising an amino acid sequence of HPV16 and/or HPV18, such as an antigenic unit derived from early proteins E6 and/or E7 of HPV16 and/or HPV18. In some embodiments according to the present invention, the targeting unit, dimerization motif and antigenic unit in the amino acid chain are in the N-terminal to C-terminal order of targeting unit, dimerization motif and antigenic unit.

In some embodiments, the antigenic unit used in the constructs according to the present invention is derived from HPV16, such as from early proteins E6 and/or E7.

In some embodiments, the antigenic unit used in the constructs according to the present invention is derived from E6 of HPV16.

In some embodiments, the antigenic unit used in the constructs according to the present invention is derived from E7 of HPV16.

In some embodiments, the antigenic unit used in the constructs according to the present invention is derived from HPV18, such as from early proteins E6 and/or E7.

In some embodiments, the antigenic unit used in the constructs according to the present invention is derived from E6 of HPV18.

In some embodiments, the antigenic unit used in the constructs according to the present invention is derived from E7 of HPV18.

In some embodiments according to the present invention, the signal peptide consists of an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 1-23 of SEQ ID NO:1.

In some embodiments according to the present invention, the signal peptide consists of an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as 100% sequence identity to the amino acid sequence 1-23 of SEQ ID NO:1.

In some embodiments according to the present invention, the targeting unit consists of an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1.

In some embodiments according to the present invention, the dimerization motif comprises a hinge region and optionally another domain that facilitate dimerization, such as an immunoglobulin domain, optionally connected through a linker.

In some embodiments according to the present invention, the hinge region is Ig derived, such as derived from IgG3.

In some embodiments according to the present invention, the hinge region has the ability to form one, two, or several covalent bonds. In some embodiments according to the present invention, the covalent bond is a disulphide bridge.

In some embodiments according to the present invention, the immunoglobulin domain of the dimerization motif is a carboxytermina l C domain, or a sequence that is substantially identical to the C domain or a variant thereof.

In some embodiments according to the present invention, the carboxyterminal C domain is derived from IgG.

In some embodiments according to the present invention, the immunoglobulin domain of the dimerization motif has the ability to homodimerize.

In some embodiments according to the present invention, the immunoglobulin domain has the ability to homodimerize via noncovalent interactions. In some embodiments according to the present invention, the noncovalent interactions are hydrophobic interactions.

In some embodiments according to the present invention, the dimerization domain does not comprise the CH2 domain.

In some embodiments according to the present invention, the dimerization motif consists of hinge exons hi and h4 connected through a linker to a C_H3 domain of human IgG3.

In some embodiments according to the present invention, the dimerization motif consist of an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 94-237 of SEQ ID NO:3.

In some embodiments according to the present invention, the linker is a $G_3S_2G_3SG$ linker.

In some embodiments according to the present invention, the antigenic unit and the dimerization motif is connected through a linker, such as a GLGGL linker or a GLSGL linker.

In some embodiments according to the present invention, the targeting unit consists of amino acids 24-93 of SEQ ID NO:l, or a variant thereof.

In some embodiments according to the present invention, the homodimeric protein have increased affinity for any one chemokine receptor selected from CCR1, CCR3 and CCR5 as compared to the affinity of the same homodimeric protein with the targeting unit consisting of amino acids 24-93 of SEQ ID NO:1, or a variant thereof.

In some embodiments according to the present invention, the antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-293 of SEQ ID NO:3.

In some embodiments according to the present invention, the antigenic unit consists of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-293 of SEQ ID NO:3.

In some embodiments according to the present invention, the antigenic unit comprises one or more amino acid substitutions at a position selected from the list consisting of F47, L50, C63, C106 and I128 of SEQ ID NO:22, or a deletion involving one or more amino acid selected from the list consisting of Y43-L50 of SEQ ID NO:22.

In some embodiments according to the present invention, the antigenic unit comprises not more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18 or 20 amino acid substitutions and/or deletions relative to SEQ ID NO:22.

In some embodiments according to the present invention, the antigenic unit comprises the amino acid sequence 243-293 of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, or SEQ ID NO:9, or a variant or antigenic fragment thereof.

In some embodiments according to the present invention, the antigenic unit consists of the amino acid sequence 243-293 of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, or SEQ ID NO:9, or a variant or antigenic fragment thereof.

In some embodiments according to the present invention, the antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-340 of SEQ ID NO:11.

In some embodiments according to the present invention, the antigenic unit consists of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-340 of SEQ ID NO:11.

In some embodiments according to the present invention, the antigenic unit comprises one or more amino acid substitutions at a position selected from the list consisting of C24, E26, C58, C61, C91, and C94 of SEQ ID NO:23, or a deletion involving one or more amino acid selected from the list consisting of L22-E26 and/or C58-C61 and/or C91-S95 of SEQ ID NO:23.

In some embodiments according to the present invention, the antigenic unit comprises not more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18 or 20 amino acid substitutions and/or deletions relative to SEQ ID NO:23.

In some embodiments according to the present invention, the antigenic unit comprises the amino acid sequence 243-340 of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:17, or a variant or antigenic fragment thereof.

In some embodiments according to the present invention, the antigenic unit consists of the amino acid sequence 243-340 of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:17, or a variant or antigenic fragment thereof.

In some embodiments according to the present invention, the antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at

least 99% sequence identity to the amino acid sequence 243-501 of SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, or SEQ ID NO:34.

In some embodiments according to the present invention, the antigenic unit consists of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-501 of SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, or SEQ ID NO:34.

In some embodiments according to the present invention, the antigenic unit comprising an amino acid sequence of human papillomavirus 16 (HPV16) derived from both early proteins E6 and E7.

In some embodiments according to the present invention, the antigenic unit comprising an amino acid sequence of human papillomavirus 18 (HPV18) derived from both early proteins E6 and E7.

In some embodiments according to the present invention, the antigenic unit comprises one or more amino acid substitutions at a position selected from the list consisting of F47, L50G, C63, C106, I128T of SEQ ID NO:22 and C24, E26, C58, C61, C91, C94 of SEQ ID NO:23.

In some embodiments according to the present invention, the antigenic unit comprises not more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18 or 20 amino acid substitutions and/or deletions relative to SEQ ID NO:22 and SEQ ID NO:23.

In some embodiments according to the present invention, the antigenic unit consists of the amino acid sequence 243-501 of SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, or SEQ ID NO:34, or a variant or antigenic fragment thereof.

In some embodiments according to the present invention, the amino acid chain consists of an amino acid sequence selected from the list consisting of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, and SEQ ID NO:34, or a variant or antigenic fragment thereof.

In some embodiments according to the present invention, the antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to any one amino acid sequence selected from SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, and SEQ ID NO:25.

In some embodiments according to the present invention, the antigenic unit consist of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to any one amino acid sequence selected from SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, and SEQ ID NO:25.

In some embodiments the homodimeric protein according to the present invention, is in its mature form without any signal peptide sequence.

In some embodiments the nucleic acid molecule according to the present invention is human codon optimized.

It is to be understood that a human codon optimized nucleic acid molecule according to the present invention comprises one or more nucleic acid substitution as compared to the wild type sequence, which substitution provides for a codon with higher frequency of usage in human coding regions. Frequency of codon usage in homo sapiens can be found at http://biowiki.edu-wiki.org/en/codon_table

In some embodiments the nucleic acid molecule according to the present invention is comprising any one of nucleotide sequences selected from the list consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:31 and SEQ ID NO:33, or a variant thereof.

In some embodiments the nucleic acid molecule according to the present invention is comprised by a vector.

In some embodiments the nucleic acid molecule according to the present invention is formulated for administration to a patient to induce production of the homodimeric protein in said patient.

In some embodiments the vaccine according to the present invention further comprises a pharmaceutically acceptable carrier and/or adjuvant.

In some embodiments, the method of treating or preventing a HPV induced disease or condition, such as a cancer or an infectious disease caused by HPV in a patient according to the present invention comprises administering to the patient in need thereof of a nucleic acid molecule, such as a DNA, according to the present invention with a subsequent step of electroporation. In some embodiments the administration is performed intradermal or intramuscular.

EXAMPLE 1

Construction and expression of the vaccines.

Gene sequences were designed according to the following structure: 1: native leader sequence for human LD78b, 2: full length LD78b sequence. 3: Human hinge-region 1 from IgG3. 4: Human hinge region 4 from IgG3. 5: Glycine- Serine linker. 6: Human CH3 domain from IgG3. 7: Glycine-Leucine linker. 8: wildtype and mutant Human papilloma virus oncogenes E6, E7 and fusion proteins of both E6 and E7 divided by a Glycine- Serine linker. The constructs are designated according to their E6 and or E7 composition as follows:

VB1001: Vaccibody-E6 wild type;

VB1005: Vaccibody-E7 wild type;

The mutants are designated according to the amino acid position in the corresponding native E6 or E7 sequence.

VB1002: Vaccibody-E6 C63R;

VB1003: Vaccibody-E6 C106R;

VB1004: Vaccibody-E6 F47R, C63R, C106R;

VB1006: Vaccibody-E7 C24G, E26G;

VB1007: Vaccibody-E7 C24G, E26G, C58G, C61G;

VB1008: Vaccibody-E7 C24G, E26G, C91G, C94G;

VB1009: Vaccibody- E7 C24G, E26G/ E6 F47R, C63R, C106R;

VB1016: Vaccibody- E7 C24G, E26G/ E6 C63R, C106R;

VB1020: Vaccibody- E7 C24G, E26G/ E6 F47R, C63R, C106R human codon optimized

VB1021: Vaccibody- E7 C24G, E26G/ E6 F47R, L50G, C106R, I128T human codon optimized

Control vaccines composed of only the antigens were included:

Control 1: E7 C24G, E26G/ E6 F47R, C63R, C106R;

Control 2: E7 C24G, E26G/ E6 C63R, C106R

All gene sequences were ordered from Aldevron (Fargo ND, USA) or Eurofins MWG GmbH and cloned into the expression vector pUMVC4a.

All constructs were transfected in to 293E cells and verified expression of intact vaccibody proteins were performed by dot blot and ELISA (data not shown). All amino acid sequences except for Controls 1 and 2 are shown as SEQ IDs.

EXAMPLE 2.

Immune response studies

VB 1009,VB1016, VB1020 and VB1021 were selected as vaccine candidates with their corresponding controls 1 and 2 respectively. As a negative control empty pUMVC4a vector was utilized.

25, 12.5 and 1.4 µg plasmid DNA of each candidate was injected intradermal in the lower back of C57BI/6 mice followed by electroporation, Dermavax, Cellectis (Paris, France). 7 days later the mice were boosted with similar amounts of vaccines and control plasmids. At day 21 the mice were killed and spleens were harvested.

The T cell responses were calculated by ELISPOT. (Figures 3 a, b and c)

EXAMPLE 3.

Therapeutic effect

VB1016, VB1020 and VB1021 with the corresponding controls 1 and 2 were selected as the vaccine candidate for therapeutic vaccine studies.

5xl0 ^{4} or 5xl0 ^{5} TC-1 cells (Johns Hopkins University, Baltimore, USA, *Lin KY et al., Cancer Res, 1996)* were injected in the neck or thigh region of C57BI/6 mice. After days 3 and 10 or day 3,7 and 10, the mice were vaccinated with 2µg, 10µg, 12.5 pg or 20µg of plasmid DNA

followed by electroporation, Dermavax, Cellectis France. Tumor size were measured two to three times a week up until day 49 after TC-1 cell injection (Figure 4, 5 and 6)

EXAMPLE 4.

A therapeutic DNA vaccine to be used may be prepared by GMP manufacturing of the plasmid vaccine according to regulatory authorities' guidelines, including GMP cell banking, GMP manufacturing of drug substance and drug product, ICH stability studies and Fill & Finish of the DNA vaccine. The DNA vaccine may be formulated by dissolving in a saline solution, such as IOηM Tris, ImM EDTA at a concentration of 2-5 mg/ml. The vaccine may be administered either intra-dermal or intra-muscular with or without following electroporation.

SEQUENCES:

C-C motif chemokine 3-like 1 precursor including signal peptide (aa 1-23 in bold) and mature peptide (LD78-beta), aa 24-93 (SEQ ID NO:l):

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQN FIADYFETSSQCSKPSVIFLTKR GRQVCADPSEEWVQKYVSDLELSA

The specific DNA and corresponding amino acid sequences of vaccibody HPV constructs:

E6 or E7 single constructs:

For the purpose of illustration only, the different domains of the constructs are separated by an "|"with the domains in the following order: Signal peptide |human MIP-Iα|Hinge hi |Hinge h4 |Gly-Ser Linker or Gly-Leu linker|hCH3 IgG3 |Gly-Ser Linker or Gly-Leu linker|wildtype or mutant full length E6 or E7. Amino acids or nucleotides in bold illustrates sites of mutations.

DNA sequence of VB100 1 (SEQ ID NO:2):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A |GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA |*GGCCTCGGTGGCCTG* |ATGTTTCAGGACCCACAGGAGCGACCCAGAAAGTTACCACAGTTATGCACAGAGCTG
CAAACAACTATACATGATATAATATTAGAATGTGTGTACTGCAAGCAACAGTTACTGCGACGTGAGGTATATGACTTTG
CTTTTCGGGATTTATGCATAGTATATAGAGATGGGAATCCATATGCTGTATGTGATAAATGTTTAAAGTTTTATTCTAA
AATTAGTGAGTATAGACATTATTGTTATAGTTTGTATGGAACAACATTAGAACAGCAATACAACAAACCGTTGTGTGAT
TTGTTAATTAGGTGTATTAACTGTCAAAAGCCACTGTGTCCTGAAGAAAAGCAAAGACATCTGGACAAAAAGCAAAGAT
TCCATAATATAAGGGGTCGGTGGACCGGTCGATGTATGTCTTGTTGCAGATCATCAAGAACACGTAGAGAAACCCAGCT
GTAA

Protein sequence of VB1001 (Homodimeric construct according to the invention with E6, SEQ ID NO:3): Amino acid sequence 393 amino acids.

MQVSTAALAVLLCTMALCNQVLS |APLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA |ELKTPLG
DTTHT**C**EPKSCDTPPPCPRCP |GGGSSGGGSG |GQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK |GLGGL |MFQDPQER
PRKLPQLCTELQTTIHDIILECVYCKQQLLRREVYDFAFRDLCIVYRDGN
PYAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINCQK
PLCPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRRETQL*

DNA sequence of VB1002 (SEQ ID NO:4):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**C**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**C***GGCCTCGGTGGCCTG* |ATGTTTCAGGACCCACAGGAGCGACCCAGAAAGTTACCACAGTTATGCACAGAGCTG
CAAACAACTATACATGATATAATATTAGAATGTGTGTACTGCAAGCAACAGTTACTGCGACGTGAGGTATATGACTTTG
CTTTTCGGGATTTATGCATAGTATATAGAGATGGGAATCCATATGCTGTA CGAGATAAATGTTTAAAGTTTTATTCTAA
AATTAGTGAGTATAGACATTATTGTTATAGTTTGTATGGAACAACATTAGAACAGCAATACAACAAACCGTTGTGTGAT
TTGTTAATTAGGTGTATTAACTGTCAAAAGCCACTGTGTCCTGAAGAAAAGCAAAGACATCTGGACAAAAAGCAAAGAT
TCCATAATATAAGGGGTCGGTGGACCGGTCGATGTATGTCTTGTTGCAGATCATCAAGAACACGTAGAGAAACCCAGCT
GTAA

Protein sequence of VB1002 (Homodimeric construct according to the invention, SEQ ID NO:5): Amino acid sequence, 393 amino acids.

MQVSTAALAVLLCTMALCNQVLS |APLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA |ELKTPLG
DTTHT**C**EPKSCDTPPPCPRCP |GGGSSGGGSG |GQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK |GLGGL |MFQDPQER
PRKLPQLCTELQTTIHDIILECVYCKQQLLRREVYDFAFRDLCIVYRDGN
PYAVRDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINCQK
PLCPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRRETQL*

DNA sequence of VB 1003 (SEQ ID NO:6):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**C**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**C***GGCCTCGGTGGCCTG* |ATGTTTCAGGACCCACAGGAGCGACCCAGAAAGTTACCACAGTTATGCACAGAGCTG
CAAACAACTATACATGATATAATATTAGAATGTGTGTACTGCAAGCAACAGTTACTGCGACGTGAGGTATATGACTTTG
CTTTTCGGGATTTATGCATAGTATATAGAGATGGGAATCCATATGCTGTATGTGATAAATGTTTAAAGTTTTATTCTAA
AATTAGTGAGTATAGACATTATTGTTATAGTTTGTATGGAACAACATTAGAACAGCAATACAACAAACCGTTGTGTGAT
TTGTTAATTAGGTGTATTAAC CGACAAAAGCCACTGTGTCCTGAAGAAAAGCAAAGACATCTGGACAAAAAGCAAAGAT
TCCATAATATAAGGGGTCGGTGGACCGGTCGATGTATGTCTTGTTGCAGATCATCAAGAACACGTAGAGAAACCCAGCT
GTAA

Protein sequence of VB1003 (Homodimeric construct according to the invention, SEQ ID NO:7): Amino acid sequence, 393 amino acids.

MQVSTAALAVLLCTMALCNQVLS |APLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA |ELKTPLG
DTTHT**I**EPKSCDTPPPCPRCP |GGGSSGGGSG |GQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK |GLGGL |MFQDPQER
PRKLPQLCTELQTTIHDI ILECVYCKQQLLRREVYDFAFRDLCIVYRDGN
PYAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINRQK
PLCPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRRETQL*

DNA sequence of VB1004 (SEQ ID NO:8):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**I**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**I***GGCCTCGGTGGCCTG* |ATGTTTCAGGACCCACAGGAGCGACCCAGAAAGTTACCACAGTTATGCACAGAGCTG
CAAACAACTATACATGATATAATATTAGAATGTGTGTACTGCAAGCAACAGTTACTGCGACGTGAGGTATATGACTTTG
CTCGACGGGATTTATGCATAGTATATAGAGATGGGAATCCATATGCTGTA CGAGATAAATGTTTAAAGTTTTATTCTAA
AATTAGTGAGTATAGACATTATTGTTATAGTTTGTATGGAACAACATTAGAACAGCAATACAACAAACCGTTGTGTGAT
TTGTTAATTAGGTGTATTAAC CGACAAAAGCCACTGTGTCCTGAAGAAAAGCAAAGACATCTGGACAAAAAGCAAAGAT
TCCATAATATAAGGGGTCGGTGGACCGGTCGATGTATGTCTTGTTGCAGATCATCAAGAACACGTAGAGAAACCCAGCT
GTAA

Protein sequence of VB1004 (Homodimeric construct according to the invention, SEQ ID NO:9): Amino acid sequence, 393 amino acids.

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSAELKTPLG
DTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGKGLGGLMFQDPQER
PRKLPQLCTELQTTIHDI ILECVYCKQQLLRREVYDFARRDLCIVYRDGN
PYAVRDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINRQK
PLCPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRRETQL*

DNA sequence of VB1005 (SEQ ID NO:10):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**I**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**I***GGCCTCGGTGGCCTG* |ATGCATGGAGATACACCTACATTGCATGAATATATGTTAGATTTGCAACCAGAGACA
ACTGATCTCTACTGTTATGAGCAATTAAATGACAGCTCAGAGGAGGAGGATGAAATAGATGGTCCAGCTGGACAAGCAG
AACCGGACAGAGCCCATTACAATATTGTAACCTTTTGTTGCAAGTGTGACTCTACGCTTCGGTTGTGCGTACAAAGCAC
ACACGTAGACATTCGTACTTTGGAAGACCTGTTAATGGGCACACTAGGAATTGTGTGCCCCATCTGTTCTCAGAAACCA
TAA

Protein sequence of VB1005 (Homodimeric construct according to the invention with E7, SEQ ID NO:111): Amino acid sequence, 340 amino acids.

MQVSTAALAVLLCTMALCNQVLS |APLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA |ELKTPLG
DTTHT**I**EPKSCDTPPPCPRCP |GGGSSGGGSG |GQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK |GLGGL |MHGDTPTL
HEYMLDLQPETTDLYCYEQLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFC
CKCDSTLRLCVQSTHVDIRTLEDLLMGTLGIVCPICSQKP*

DNA sequence of VB1006 (SEQ ID NO:12):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**I**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**I***GGCCTCGGTGGCCTG* |ATGCATGGAGATACACCTACATTGCATGAATATATGTTAGATTTGCAACCAGAGACA
ACTGATCTCTAC<u>GGA</u>TAT<u>GGA</u>CAATTAAATGACAGCTCAGAGGAGGAGGATGAAATAGATGGTCCAGCTGGACAAGCAG
AACCGGACAGAGCCCATTACAATATTGTAACCTTTTGTTGCAAGTGTGACTCTACGCTTCGGTTGTGCGTACAAAGCAC
ACACGTAGACATTCGTACTTTGGAAGACCTGTTAATGGGCACACTAGGAATTGTGTGCCCCATCTGTTCTCAGAAACCA
TAA

Protein sequence of VB1006 (Homodimeric construct according to the invention, SEQ ID NO:13): Amino acid sequence, 340 amino acids.

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSAELKTPLG
DTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGKGLGGLMHGDTPTL
HEYMLDLQPETTDLY<u>G</u>Y<u>G</u>QLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFC
CKCDSTLRLCVQSTH<u>V</u>D<u>I</u>RTLEDLLMGTLGIVCPICSQKP*

DNA sequence of VB1007 (SEQ ID NO:14):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**I**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**I***GGCCTCGGTGGCCTG* |ATGCATGGAGATACACCTACATTGCATGAATATATGTTAGATTTGCAACCAGAGACA
ACTGATCTCTAC<u>GGA</u>TAT<u>GGA</u>CAATTAAATGACAGCTCAGAGGAGGAGGATGAAATAGATGGTCCAGCTGGACAAGCAG
AACCGGACAGAGCCCATTACAATATTGTAACCTTT <u>GGA</u>TGCAAG<u>GGA</u>GACTCTACGCTTCGGTTGTGCGTACAAAGCAC
ACACGTAGACATTCGTACTTTGGAAGACCTGTTAATGGGCACACT<u>AGG</u>AATTGTGTGCCCCATCTGTTCTCAGAAACCA
TAA

Protein sequence of VB1007 (Homodimeric construct according to the invention, SEQ ID NO:15): Amino acid sequence, 340 amino acids.

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIAD

YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSAELKTPLG
DTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGKGLGGLMHGDTPTL
HEYMLDLQPETTDLYGYGQLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFG
CKGDSTLRLCVQSTHVDIRTLEDLLMGTLGIVCPICSQKP*

DNA sequence of VB1008 (SEQ ID NO:16):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**T**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**T**GGCCTCGGTGGCCTG |ATGCATGGAGATACACCTACATTGCATGAATATATGTTAGATTTGCAACCAGAGACA
ACTGATCTCTACGGATATGGACAATTAAATGACAGCTCAGAGGAGGAGGATGAAATAGATGGTCCAGCTGGACAAGCAG
AACCGGACAGAGCCCATTACAATATTGTAACCTTTTGTTGCAAGTGTGACTCTACGCTTCGGTTGTGCGTACAAAGCAC
ACACGTAGACATTCGTACTTTGGAAGACCTGTTAATGGGCACACTAGGAATTGTGGGACCCATCGGATCTCAGAAACCA
TAA

Protein sequence of VB1008 (Homodimeric construct according to the invention, SEQ ID NO:17): Amino acid sequence, 340 amino acids.

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSAELKTPLG
DTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGKGLGGLMHGDTPTL
HEYMLDLQPETTDLYGYGQLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFC
CKCDSTLRLCVQSTHVDIRTLEDLLMGTLGIVGPIGSQKP*

Constructs with E6 and E7:

For the purpose of illustration only, the different domains of the constructs are separated by an "**I**" with the domains in the following order: Signal peptide |human MIP-Iα|Hinge hi **I**Hinge h4 |Gly-Ser Linker or Gly-Leu linker |hCH3 IgG3 |Gly-Ser Linker or Gly-Leu linker|E7 mutant | Gly-Ser Linker or Gly-Leu linker|E6 mutant. Amino acids or nucleotides in bold illustrates sites of mutations .

DNA sequence of VB1009 (SEQ ID NO:18):

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**T**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA**T**GGCCTCGGTGGCCTG |ATGCATGGAGATACACCTACATTGCATGAATATATGTTAGATTTGCAACCAGAGACA
ACTGATCTCTACGGATATGGACAATTAAATGACAGCTCAGAGGAGGAGGATGAAATAGATGGTCCAGCTGGACAAGCAG
AACCGGACAGAGCCCATTACAATATTGTAACCTTTTGTTGCAAGTGTGACTCTACGCTTCGGTTGTGCGTACAAAGCAC

ACACGTAGACATTCGTACTTTGGAAGACCTGTTAATGGGCACACTAGGAATTGTGTGCCCCATCTGTTCTCAGAAACCA
IGGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |ATGTTTCAGGACCCACAGGAGCGACCCAGAAAGTTACCACAGTTATG
CACAGAGCTGCAAACAACTATACATGATATAATATTAGAATGTGTGTACTGCAAGCAACAGTTACTGCGACGTGAGGTA
TATGACTTTGCT CGACGGGATTTATGCATAGTATATAGAGATGGGAATCCATATGCTGTA CGAGATAAATGTTTAAAGT
TTTATTCTAAAATTAGTGAGTATAGACATTATTGTTATAGTTTGTATGGAACAACATTAGAACAGCAATACAACAAACC
GTTGTGTGATTTGTTAATTAGGTGTATTAAC CGACAAAAGCCACTGTGTCCTGAAGAAAAGCAAAGACATCTGGACAAA
AAGCAAAGATTCCATAATATAAGGGGTCGGTGGACCGGTCGATGTATGTCTTGTTGCAGATCATCAAGAACACGTAGAG
AAACCCAGCTGTAA

Protein sequence of VB1009 (Homodimeric construct according to the invention, SEQ ID NO:19) : Amino acid sequence, 501 amino acids .

MQVSTAALAVLLCTMALCNQVLS |APLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA |ELKTPLG
DTTHTIEPKSCDTPPPCPRCP |GGGSSGGGSG |GQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK |GLGGL |MHGDTPTL
HEYMLDLQPETTDLYGYGQLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFC
CKCDSTLRLCVQSTHVDIRTLEDLLMGTLGIVCPICSQKP |GGGSSGGGSG |
MFQDPQERPRKLPQLCTELQTTIHDI ILECVYCKQQLLRREVYDFARRDL
CIVYRDGNPYAVRDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLL
IRCINRQKPLCPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRRETQ
L*

DNA sequence of VB1016 (SEQ ID NO:20) :

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
AIGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAAIGGCCTCGGTGGCCTG |ATGCATGGAGATACACCTACATTGCATGAATATATGTTAGATTTGCAACCAGAGACA
ACTGATCTCTAC GGATAT GGACAATTAAATGACAGCTCAGAGGAGGAGGATGAAATAGATGGTCCAGCTGGACAAGCAG
AACCGGACAGAGCCCATTACAATATTGTAACCTTTTGTTGCAAGTGTGACTCTACGCTTCGGTTGTGCGTACAAAGCAC
ACACGTAGACATTCGTACTTTGGAAGACCTGTTAATGGGCACACTAGGAATTGTGTGCCCCATCTGTTCTCAGAAACCA
IGGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |ATGTTTCAGGACCCACAGGAGCGACCCAGAAAGTTACCACAGTTATG
CACAGAGCTGCAAACAACTATACATGATATAATATTAGAATGTGTGTACTGCAAGCAACAGTTACTGCGACGTGAGGTA
TATGACTTTGCTTTTCGGGATTTATGCATAGTATATAGAGATGGGAATCCATATGCTGTA CGAGATAAATGTTTAAAGT
TTTATTCTAAAATTAGTGAGTATAGACATTATTGTTATAGTTTGTATGGAACAACATTAGAACAGCAATACAACAAACC
GTTGTGTGATTTGTTAATTAGGTGTATTAAC CGACAAAAGCCACTGTGTCCTGAAGAAAAGCAAAGACATCTGGACAAA
AAGCAAAGATTCCATAATATAAGGGGTCGGTGGACCGGTCGATGTATGTCTTGTTGCAGATCATCAAGAACACGTAGAG
AAACCCAGCTGTAA

Protein sequence of VB1016 (Homodimeric construct according to the invention, SEQ ID NO:21) : Amino acid sequence, 501 amino acids

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSAELKTPLG
DTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGKGLGGLMHGDTPTL
HEYMLDLQPETTDLYGYGQLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFC
CKCDSTLRLCVQSTHVDIRTLEDLLMGTLGIVCPICSQKPGGGSSGGGSG
MFQDPQERPRKLPQLCTELQTTIHDI ILECVYCKQQLLRREVYDFAFRDL
CIVYRDGNPYAVRDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLL
IRCINRQKPLCPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRRETQ
L*

SEQ ID NO:22:
>tr|Q778I6|Q778I6_HPV16 E6 protein OS=Human papillomavirus type 16 GN=E6 PE=4 SV=1; (Underlined amino acids denotes amino acids that may be deleted; Potential amino acids that may be mutated are highlighted)
MFQDPQERPRKLPQLCTELQTTIHDIILECVYCKQQLLRREVYDFAFRDLCIVYRDG NPYAVCDKCLKFYS KISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINCQKPLCPEEKQRH LDKKQRFH NIRGRWTG RCMSCCR SSRTRRETQL

SEQ ID NO:23:
>sp|P03129|VE7_HPV16 Protein E7 OS=Human papillomavirus type 16 GN=E7 PE=1 SV=1; (Underlined amino acids denotes amino acids that may be deleted; Potential amino acids that may be mutated are highlighted)
MHGDTPTLHEYMLDLQPETTDLYCYEQLNDSSEEEDEIDG PAGQAEPDRAHYNIVTFCCKCDSTLRLCVQ STHVDIRTLEDLLMGTLGIVCPICSQKP

SEQ ID NO:24:
>sp|P06463|VE6_HPV18 Protein E6 OS=Human papillomavirus type 18 GN=E6 PE=1 SV=1
MARFEDPTRRPYKLPDLCTELNTSLQDIEITCVYCKTVLELTEVFEFAFKDLFVVYRDSI PHAACHKCIDFYSRIRELRHYSDSVYG DTLEKLTNTGLYNLLIRCLRCQKPLN PAEKLRH LNEKRRFHNIAG HYRGQCH SCCN RARQERLQRRRETQV

SEQ ID NO:25:
>sp|P06788|VE7_HPV18 Protein E7 OS=Human papillomavirus type 18 GN=E7 PE=3 SV=2
MHGPKATLQDIVLH LEPQNEIPVDLLCHEQLSDSEEEN DEIDGVN HQH LPARRAEPQRHT MLCMCCKCEARIKLVVESSADDLRAFQQLFLNTLSFVCPWCASQQ

SEQ ID NO:26:
Hinge regions (IgG3 UH hinge), 12 amino acids: ELKTPLGDTTHT

SEQ ID NO:27:
Hinge region (IgG3, MH hinge, 15 amino acids): EPKSCDTPPPCPRCP

SEQ ID NO:28:
Gly-Ser Linker: GGGSSGGGSG

SEQ ID NO:29: hCH3 IgG3:
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPM LDSDGSFFLYSKL TVDKSRWQQG NIFSCSVM HEALH NRFTQKSLSLSPGK

SEQ ID NO:30: Linker: GLGGL

SEQ ID NO:31: DNA sequence of VB1020:

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT|GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC|GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A |GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA|GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA|
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA|GGCCTCGGTGGCCTG/ATGCATGGCGATACCCCAACACTCCATGAGTACATGCTGGACCTTCAGCCCGAGAC
TACGGATCTGTATGGCTATGGGCAGTTGAATGACTCATCTGAGGAGGAGGACGAAATAGACGGCCCAGCTGGTCAAGCC
GAACCGGATAGAGCCCACTACAACATTGTGACCTTTTGCTGTAAGTGTGACAGCACTCTGAGACTGTGTGTTCAGTCCA
CTCATGTCGACATACGCACATTGGAGGATCTCCTGATGGGAACACTGGGAATTGTGTGTCCCATCTGTTCCCAAAAGCC
T/GGAGGTGGAAGCAGTGGAGGCGGTTCAGGC/ATGTTCCAAGATCCTCAAGAACGTCCTCGTAAGCTGCCACAGCTGT
GTACCGAGCTTCAGACCACCATTCACGACATCATCCTGGAGTGCGTCTATTGCAAACAGCAGCTCCTTAGAAGGGAAGT

GTACGATTTTGCACGGAGGGACCTCTGCATCGTGTATCGGGACGGCAATCCCTATGCGGTACGGGATAAATGCCTGAAG
TTCTACAGCAAAATCTCCGAGTACCGGCACTACTGCTACTCTCTCTATGGGACGACTCTGGAACAGCAGTACAACAAGC
CCTTGTGCGATCTGCTGATTCGCTGCATTAATCGCCAGAAACCTCTGTGCCCAGAAGAGAAGCAAAGACACCTGGACAA
GAAACAGCGATTCCACAACATCCGAGGGAGATGGACAGGGAGGTGTATGAGCTGCTGTCGGAGTTCTAGGACAAGGCGC
GAAACCCAGCTTTGA

SEQ ID NO:32: Protein sequence of VB1020 (Homodimeric construct according to the invention Amino acid sequence, 501 amino acids:

MQVSTAALAVLLCTMALCNQVLS |APLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA |ELKTPLG
DTTHT**I**EPKSCDTPPPCPRCP |GGGSSGGGSG |GQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK |GLGGL |MHGDTPTL
HEYMLDLQPETTDLYGYGQLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFC
CKCDSTLRLCVQSTHVDIRTLEDLLMGTLGIVCPICSQKP |GGGSSGGGSG |
MFQDPQERPRKLPQLCTELQTTIHDI ILECVYCKQQLLRREVYDFARRDL
CIVYRDGNPYAVRDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLL
IRCINRQKPLCPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRRETQ
L*

SEQ ID NO:33: DNA sequence of VB1021:

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCT |GCACCACTT
GCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTG
AGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCCAGTGA
GGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC |GAGCTCAAAACCCCACTTGGTGACACAACTCACAC
A**I**GAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCA |GGCGGTGGAAGCAGCGGAGGTGGAAGTGGA |
GGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCGGAGAACAACTACAACAC
CACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
GGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA/GGCCTCGGTGGCCTG/ATGCATGGTGACACACCAACCCTGCACGAATACATGCTCGATCTGCAGCCAGAG
ACTACCGACCTTTACGGCTATGGGCAGTTGAACGACAGCTCTGAGGAGGAGGACGAGATCGATGGTCCTGCTGGA
CAAGCAGAACCAGACAGAGCCCACTACAACATCGTAACCTTTTGCTGCAAGTGTGACAGTACCCTTCGTTTGTGCG
TTCAGAGCACGCATGTCGACATTCGGACACTGGAGGATCTGCTCATGGGGACTCTGGGGATTGTGTGTCCTATTTG
CAGCCAGAAACCA/GGCGGAGGATCTTCAGGAGGCGGGAGTGGC/ATGTTCCAAGACCCTCAGGAACGCCCTCGG
AAACTGCCCCAATTGTGTACTGAGCTCCAGACAACGATACACGACATAATCCTGGAGTGCGTGTATTGCAAGCAGC
AGCTTCTGAGGAGGGAAGTGTACGATTTTGCCAGGAGAGATGGCTGCATTGTCTACCGAGATGGCAATCCCTATG
CGGTGTGTGATAAGTGTCTGAAGTTCTATTCCAAAATCAGCGAATATCGGCATTATTGCTACTCACTGTACGGAACT
ACCCTCGAACAGCAGTACAACAAACCGCTCTGTGATCTGCTGATCAGATGCATCAATCGGCAGAAACCCCTTTGTC
CCGAAGAGAAGCAAAGACACCTGGACAAGAAGCAGAGGTTCCACAATACCCGAGGTCGTTGGACTGGGCGCTGC
ATGTCCTGTTGTCGCTCCTCTCGCACAAGGAGAGAGACACAACTGTGA

SEQ ID NO:34: Protein sequence of VB1021 (Homodimeric construct according to the invention. Amino acid sequence, 501 amino acids:

MQVSTAALAVLLCTMALCNQVLS |APLAADTPTACCFSYTSRQIPQNFIAD
YFETSSQCSKPSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA |ELKTPLG
DTTHT**I**EPKSCDTPPPCPRCP |GGGSSGGGSG |GQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKL
TVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK |GLGGL |MHGDTPTL
HEYMLDLQPETTDLYGYGQLNDSSEEEDEIDGPAGQAEPDRAHYNIVTFC
CKCDSTLRLCVQSTHVDIRTLEDLLMGTLGIVCPICSQKP |GGGSSGGGSG |
MFQDPQERPRKLPQLCTELQTTIHDI ILECVYCKQQLLRREVYDFARRDG
CIVYRDGNPYAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLL
IRCINRQKPLCPEEKQRHLDKKQRFHNTRGRWTGRCMSCCRSSRTRRETQ
L*

Claims

1. A homodimeric protein of two identical amino acid chains, each amino acid chain comprising (1) a signal peptide, (2) a targeting unit, (3) a dimerization motif, and (4) an antigenic unit, said targeting unit comprising an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1, and an antigenic unit comprising an amino acid sequence of human papillomavirus (HPV), such as an antigenic unit comprising an amino acid sequence of HPV16 and/or HPV18, such as an antigenic unit derived from early proteins E6 and/or E7 of HPV16 and/or HPV18.

2. The homodimeric protein according to claim 1, wherein said targeting unit, dimerization motif and antigenic unit in said amino acid chain are in the N-terminal to C-terminal order of targeting unit, dimerization motif and antigenic unit.

3. The homodimeric protein according to any one of claims 1 or 2, wherein said signal peptide consists of an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 1-23 of SEQ ID NO:1.

4. The homodimeric protein according to claim 3, wherein said signal peptide consists of an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as 100% sequence identity to the amino acid sequence 1-23 of SEQ ID NO:1.

5. The homodimeric protein according to any one of claims 1-4, wherein said targeting unit consists of an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1.

6. The homodimeric protein according to any one of claims 1-5, wherein the dimerization motif comprises a hinge region and optionally another domain that facilitate dimerization, such as an immunoglobulin domain, optionally connected through a linker.

7. The homodimeric protein according to claim 6, wherein the hinge region is Ig derived, such as derived from IgG3.

8. The homodimeric protein according to any one of claims 6-7, wherein the hinge region has the ability to form one, two, or several covalent bonds.

9. The homodimeric protein according to claim 8, wherein the covalent bond is a disulphide bridge.

10. The homodimeric protein according to any one of claims 6-9, wherein the immunoglobulin domain of the dimerization motif is a carboxyterminal C domain, or a sequence that is substantially identical to said C domain or a variant thereof.

11. The homodimeric protein according to claim 10, wherein the carboxyterminal C domain is derived from IgG.

12. The homodimeric protein according to any one of claims 6-11, wherein the immunoglobulin domain of the dimerization motif has the ability to homodimerize.

13. The homodimeric protein according to any one of claims 6-12, wherein said immunoglobulin domain has the ability to homodimerize via noncovalent interactions.

14. The homodimeric protein according to claim 13, wherein said noncovalent interactions are hydrophobic interactions.

15. The homodimeric protein according to any one of claims 1-14, wherein said dimerization domain does not comprise the CH2 domain.

16. The homodimeric protein according to any one of claims 1-15, wherein the dimerization motif consist of hinge exons h1 and h4 connected through a linker to a C_H3 domain of human IgG3.

17. The homodimeric protein according to any one of claims 1-16, wherein the dimerization motif consist of an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 94-237 of SEQ ID NO:3.

18. The homodimeric protein according to any one of claims 2-17, wherein said linker is a G3S2G3SG linker.

19. The homodimeric protein according to any one of claims 1-18, where in said antigenic unit and the dimerization motif is connected through a linker, such as a GLGGL linker or a GLSGL linker.

20. The homodimeric protein according to any one of claims 1-19, where in said targeting unit consists of amino acids 24-93 of SEQ ID NO:1, or a variant thereof.

21. The homodimeric protein according to any one of claims 1-20, which homodimeric protein have increased affinity for any one chemokine receptor selected from CCR1, CCR3 and CCR5 as compared to the affinity of the same homodimeric protein with the targeting unit consisting of amino acids 24-93 of SEQ ID NO:1, or a variant thereof.

22. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-293 of SEQ ID NO:3.

23. The homodimeric protein according to any one of claims 1-22, wherein said antigenic unit consists of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-293 of SEQ ID NO:3.

24. The homodimeric protein according to 22 or 23, wherein said antigenic unit comprises one or more amino acid substitutions at a position selected from the list consisting of F47, L50, C63, C106 and I128 of SEQ ID NO:22, or a deletion involving one or more amino acid selected from the list consisting of Y43-L50 of SEQ ID NO:22.

25. The homodimeric protein according to any one of claims 1-23, wherein said antigenic unit comprises the amino acid sequence 243-293 of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, or SEQ ID NO:9, or a variant or antigenic fragment thereof.

26. The homodimeric protein according to any one of claims 1-23, wherein said antigenic unit consists of the amino acid sequence 243-293 of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, or SEQ ID NO:9, or a variant or antigenic fragment thereof.

27. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-340 of SEQ ID NO:11.

28. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit consists of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-340 of SEQ ID NO:11.

29. The homodimeric protein according to claims 27 or 28, wherein said antigenic unit comprises one or more amino acid substitutions at a position selected from the list consisting of C24, E26, C58, C61, C91, and C94 of SEQ ID NO:23, or a deletion involving one or more amino acid selected from the list consisting of L22-E26 and/or C58-C61 and/or C91-S95 of SEQ ID NO:23.

30. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit comprises the amino acid sequence 243-340 of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:17, or a variant or antigenic fragment thereof.

31. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit consists of the amino acid sequence 243-340 of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:17, or a variant or antigenic fragment thereof.

32. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at

least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-501 of SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, or SEQ ID NO:34.

33. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit consists of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to the amino acid sequence 243-501 of SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, or SEQ ID NO:34.

34. The homodimeric protein according to any one of claims 1-22, 24-25, 27, 29-30, 32-33, wherein said antigenic unit comprising an amino acid sequence of human papillomavirus 16 (HPV16) derived from both early proteins E6 and E7.

35. The homodimeric protein according to claims 32-34, wherein said antigenic unit comprises one or more amino acid substitutions at a position selected from the list consisting of F47, L50, C63, C106 and I128 of SEQ ID NO:22 and C24, E26, C58, C61, C91, C94 of SEQ ID NO:23.

36. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit consists of the amino acid sequence 243-501 of SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, or SEQ ID NO:34, or a variant or antigenic fragment thereof.

37. The homodimeric protein according to any one of claims 1-21, wherein said amino acid chain consists of an amino acid sequence selected from the list consisting of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:32, and SEQ ID NO:34, or a variant or antigenic fragment thereof.

38. The homodimeric protein according to any one of claims 1-21, wherein said antigenic unit comprises an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at

least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to any one amino acid sequence selected from SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, and SEQ ID NO:25.

39. The homodimeric protein according to any one of claims 1-21, where in said antigenic unit consist of an amino acid sequence having at least 80%, such as at least 81%, such as at least 82%, such as at least 83%, such as at least 84%, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity to any one amino acid sequence selected from SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, and SEQ ID NO:25.

40. The homodimeric protein according to any one of claims 1-39, in its mature form without any signal peptide sequence.

41. An amino acid chain comprising (1) a signal peptide, (2) a targeting unit, (3) a dimerization motif, and (4) an antigenic unit, said targeting unit comprising an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1, and an antigenic unit comprising an amino acid sequence of human papillomavirus (HPV), such as an antigenic unit comprising an amino acid sequence of HPV16 and/or HPV18, such as an antigenic unit derived from early proteins E6 and/or E7 of HPV16 and/or HPV18, which amino acid chain is able to form a homodimeric protein according to any one of clams 1-40.

42. A nucleic acid molecule, such as a DNA, encoding the amino acid chain according to claim 41.

43. The nucleic acid molecule according to claim 42, which nucleic acid molecule is human codon optimized.

44. A nucleic acid molecule comprising any one of nucleotide sequences selected from the list consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:31 and SEQ ID NO:33, or a variant thereof.

45. The nucleic acid molecule according to claims 42-44 comprised by a vector.

46. The nucleic acid molecule according to any one of claims 42-45 formulated for administration to a patient to induce production of the homodimeric protein in said patient.

47. The homodimeric protein according to any one of claims 1-40, or an amino acid chain according to claim 41, or the nucleic acid molecule according to any one of claims 42-46 for use as a medicament.

48. A pharmaceutical composition comprising the homodimeric protein according to any one of claims 1-40, or an amino acid chain according to claim 41, or the nucleic acid molecule according to any one of claims 42-46.

49. A host cell comprising the nucleic acid molecule according to any one of claims 42-46.

50. A method for preparing a homodimeric protein according to any one of claims 1-40, or an amino acid chain of claim 41, the method comprising

a) transfecting the nucleic acid molecule according to any one of claims 41-45 into a cell population;

b) culturing the cell population;

c) collecting and purifying the homodimeric protein, or amino acid chain expressed from the cell population.

51. A method for preparing a vaccine, such as a DNA vaccine, comprising an immunologically effective amount of a nucleic acid molecule according to any one of claims 42-46, the method comprising

a) preparing a nucleic acid molecule according to any one of claims 41-45;

b) dissolving the nucleic acid molecule obtained under step a) in a pharmaceutically acceptable carrier, diluent, or buffer.

52. A vaccine against HPV comprising an immunologically effective amount of a homodimeric protein according to any one of claims 1-40, or an amino acid chain according to claim 41, or nucleic acid molecule, such as a DNA, according to any one of claims 42-46, wherein said vaccine is able to trigger both a T-cell- and B-cell immune response.

53. The vaccine according to claim 52 further comprising a pharmaceutically acceptable carrier and/or adjuvant.

54. A method of treating or preventing a HPV induced disease or condition, such as a cancer or an infectious disease caused by HPV in a patient, the method comprising administering to the patient in need thereof, a homodimeric protein according to any one of claims 1-40, or an amino acid chain according to claim 41, or the nucleic acid molecule, such as a DNA, according to one of claims 42-46.

55. The method according to claim 54, wherein the method comprises administering to the patient in need thereof of a nucleic acid molecule, such as a DNA, according to one of claims 42-46 with a subsequent step of electroporation .

56. The method according to claims 54 or 55, wherein the administration is performed intradermal or intramuscular.

Figure 1

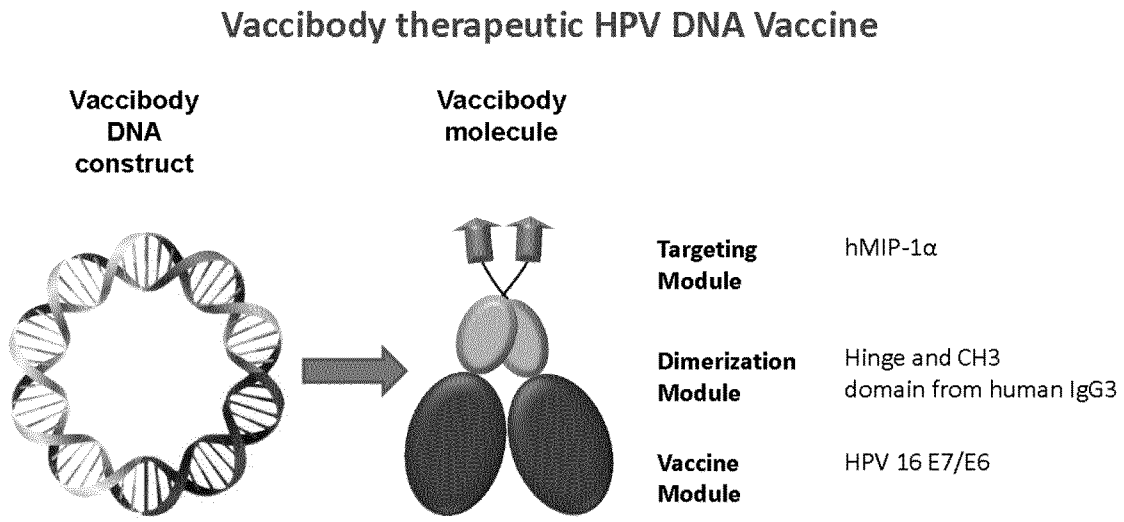

Vaccibody therapeutic HPV DNA Vaccine
Vaccibody DNA construct
Vaccibody molecule
Targeting Module
hMIP-1α
Dimerization Module
Hinge and CH3 domain from human IgG3
Vaccine Module
HPV 16 E7/E6

Figure 2

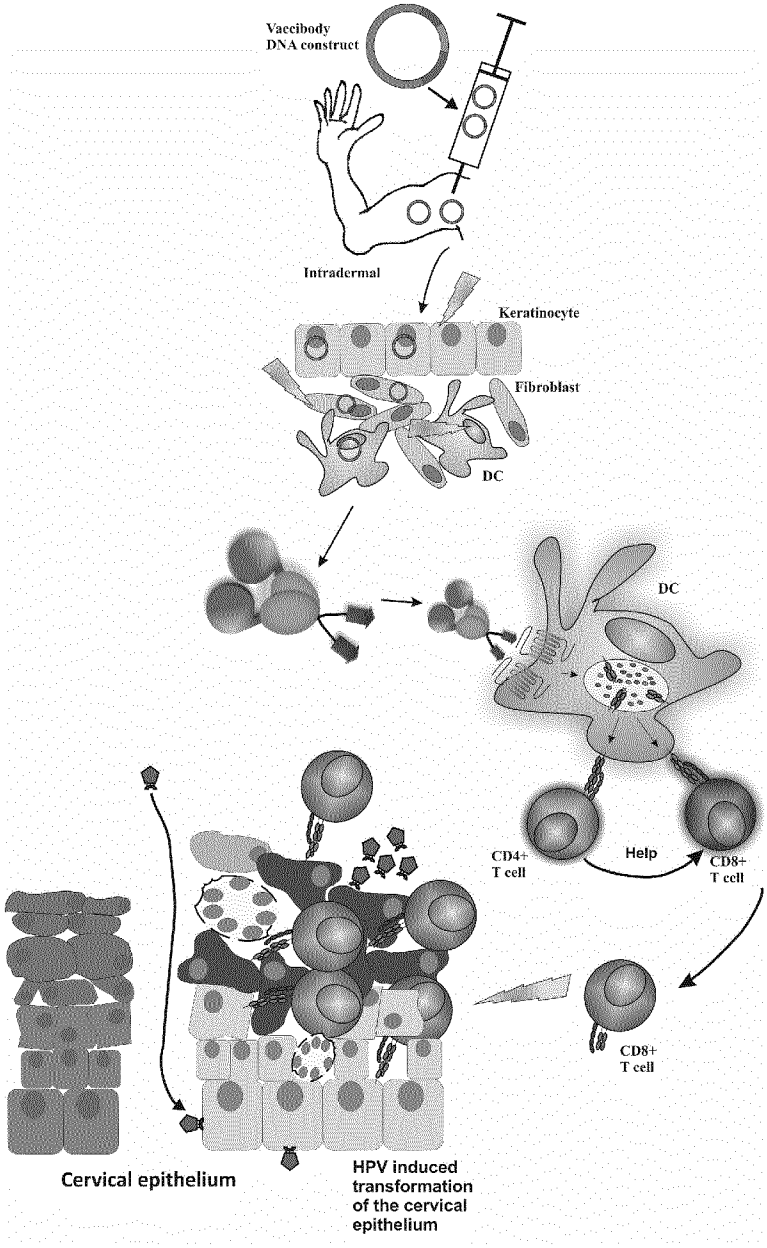
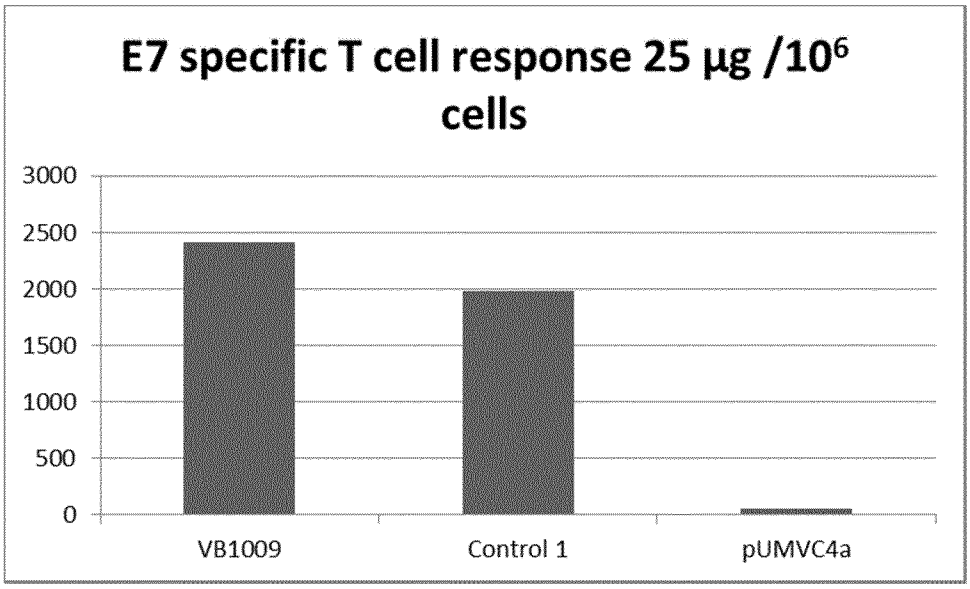
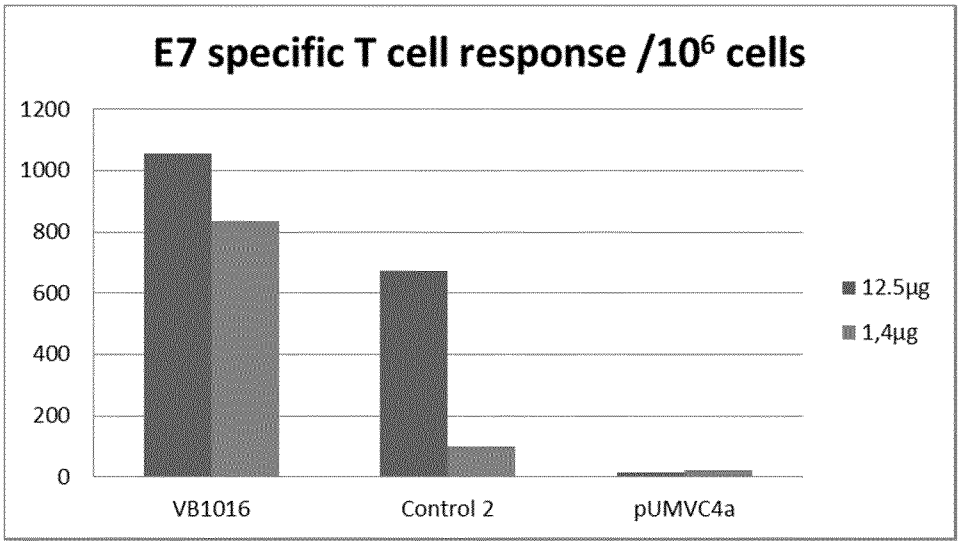

Vaccibody
DNA construct
Intradermal
Keratinocyte
Fibroblast
DC
DC
CD4+
T cell
Help
CD8+
T cell
CD8+
T cell
Cervical epithelium
HPV induced
transformation
of the cervical
epithelium

Figure 3.

A:


E7 specific T cell response 25 µg /10^6 cells
3000
2500
2000
1500
1000
500
0
VB1009
Control 1
pUMVC4a

B:


E7 specific T cell response /10^6 cells
1200
1000
800
600
400
200
0
VB1016
Control 2
pUMVC4a
12.5µg
1,4µg

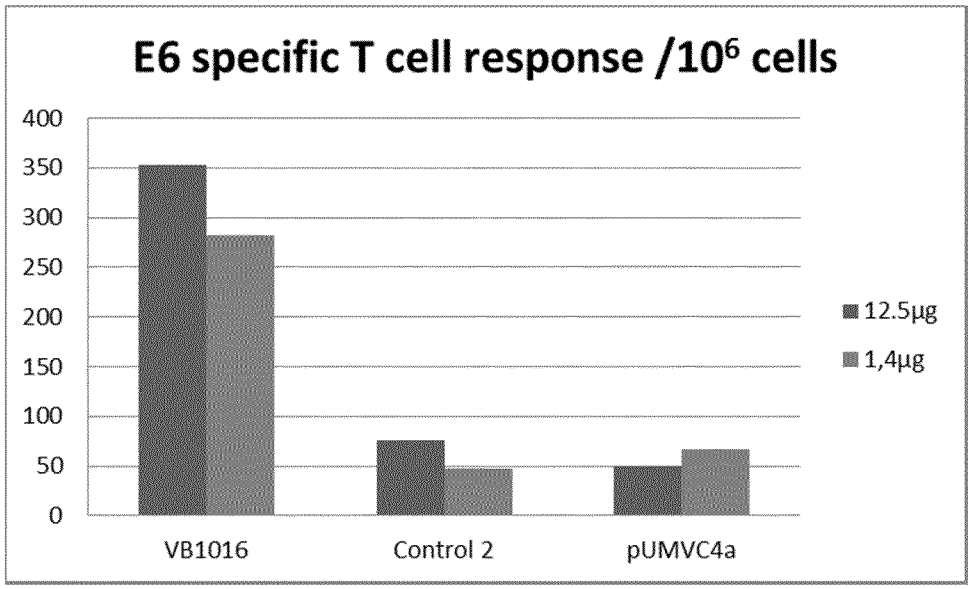


Fig. 3C

Figure 4:

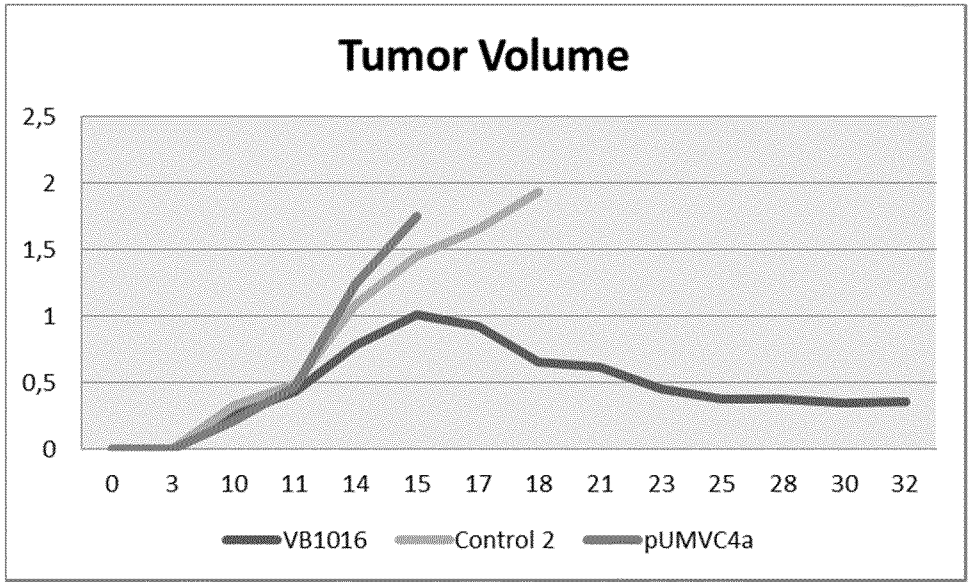


Figure 5:

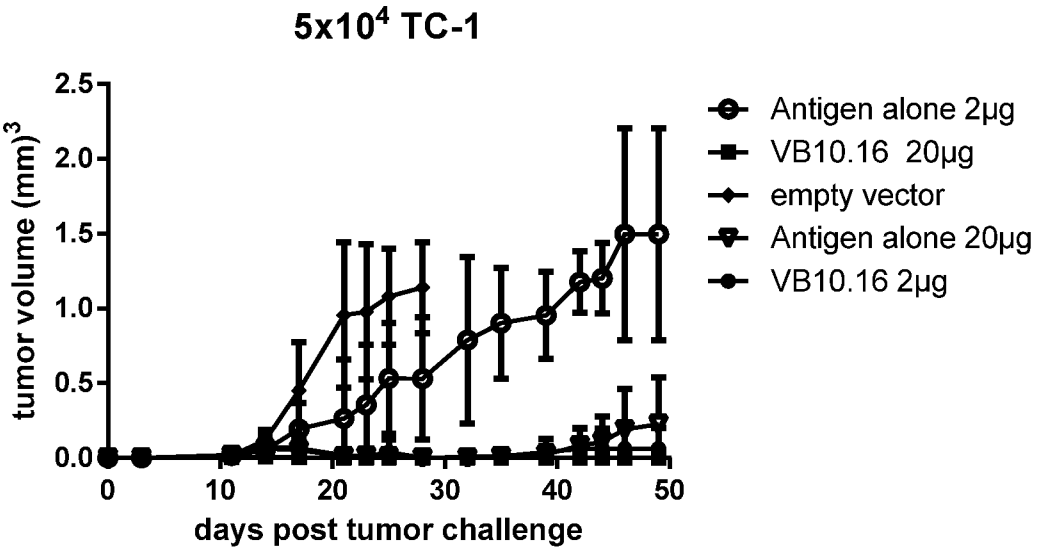
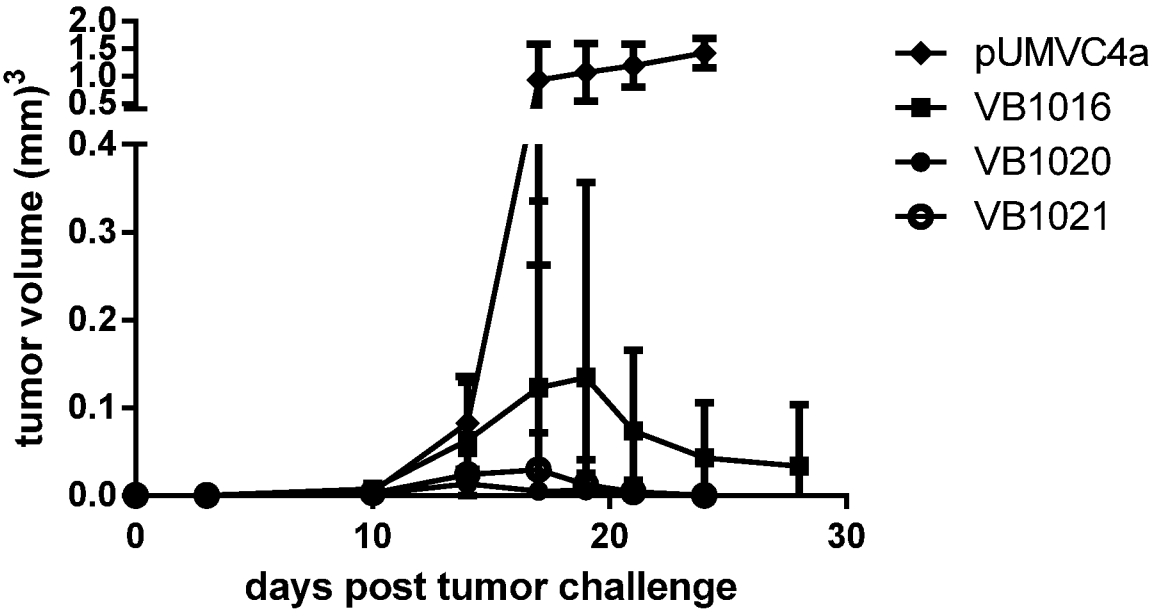


Figure 6:



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/076404

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K19/00 A61K39/00 C07K16/44 A61K39/12 C07K14/52
C07K16/00 A61P35/00
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 C07K

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 , WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RUFFINI P A ET AL: "Human chemokine MIP1alpha increases efficiency of targeted DNA fusion vaccines", VACCINE, ELSEVIER LTD, GB, vol. 29, no. 2, 16 December 2010 (2010-12-16), pages 191-199, XP027539078, ISSN: 0264-410X [retrieved on 2010-11-04] abstract figure 1 page 198, left-hand column, paragraph 3 page 195, left-hand column, paragraph 3 page 196, right-hand column, paragraph 1 ----- -/--	1-56

[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" documentwhich may throw doubts on priority claim(s) orwhich 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
13 March 2013	25/03/2013

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	Irion, Andrea

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AGNETE BRUNSVIK FREDRIKSEN ET AL: "Chemokine-idiotype fusion DNAvaccines are potentiated by bivalency and xenogeneic sequences", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 110, 1 January 2007 (2007-01-01), pages 1797-1805, XP007915509, ISSN: 0006-4971, DOI: 10.1182/BL00D-2006-06-032938 [retrieved on 2007-05-31] abstract page 1804, left-hand column, paragraph 2	1-56
Y	Ã YNEBRÃTEN I ET AL: "P19-39. Vaccibodies: a novel vaccine strategy for HIV that target viral antigens to APC", RETR0VIR0LOGY, BI0MED CENTRAL LTD., LONDON, GB, vol. 6, no. Suppl 3, 22 October 2009 (2009-10-22), page P359, XP021064082, ISSN: 1742-4690, DOI: 10.1186/1742-4690-6-S3-P359 abstract	1-56
Y	FREDRIKSEN ET AL: "DNA Vaccines Increase Immunogenicity of Idiotypic Tumor Antigen by Targeting Novel Fusion Proteins to Antigen-Presenting Cells", MOLECULAR THERAPY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 13, no. 4, 1 April 2006 (2006-04-01), pages 776-785, XP005358612, ISSN: 1525-0016, DOI: 10.1016/J.YMTHE.2005.10.019 abstract	1-56
A	TUNHEIM GR0 ET AL: "Human receptors of innate immunity (CD14, TLR2) are promising targets for novel recombinant immunoglobulin-based vaccine candidates", VACCINE, vol. 25, no. 24, June 2007 (2007-06), pages 4723-4734, XP022095376, ISSN: 0264-410X abstract	1-56
A	FR0YLAND MARIANNE ET AL: "Targeted idiotype-fusion DNA vaccines for human multiple myeloma: preclinical testing", EUROPEAN JOURNAL OF HAEMAT0L0GY, vol. 86, no. 5, May 2011 (2011-05), pages 385-395, XP055056142, abstract page 386, right-hand column, paragraph 2	1-56

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/076489 A1 (MEDINNOVA AS [NO] ; BOGEN BJARNE [NO] ; FREDRIKSEN AGNETE BRUNSVIK [NO] ;) 10 September 2004 (2004-09-10) page 4, lines 10-16 page 11, line 4 - page 12, line 25 page 28, lines 2-9 page 30, lines 3-34	1-56
Y	WO 2005/089792 A1 (PASTEUR INSTITUT [FR] ; BIOTEST PHARMA [FR] ; INST NAT SANTE RECH MED [FR] ; C) 29 September 2005 (2005-09-29) page 4, paragraph 2 page 7, paragraph 5 page 11, paragraph 4 page 12, paragraph 3-5 page 1, paragraph 5	1-56
X, P	WO 2011/161244 A1 (VACCIB0DY AS [NO] ; RUFFINI PIER ADELCHI [IT] ; BOGEN BJARNE [NO] ; FREDR) 29 December 2011 (2011-12-29) page 15, line 27 - page 16, line 24 page 20, line 22 - line 24 claims 16,20	1-56

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/076404

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 and necessary to the claimed invention, the international search was carried out on the basis of:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purpose of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/076404

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		SI 1576967 T1	29-02-2008
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