

Multimerizing polypeptides derived from jelly roll fold domain of adenovirus penton base

The present invention relates to the design and production of novel polypeptide scaffolds for optimized presentation of oligopeptides, polypeptide sequences, protein domains, proteins and/or protein complexes made up of two, several or many subunits. These oligopeptides, polypeptide sequences, protein domains and/or proteins presented by the polypeptide scaffolds of the invention can include antigenic entities that stimulate the immune system to trigger an immune response, for example for vaccination purposes, or for preparing antibodies or other binder molecules in cell culture, or *in vivo*, or *in vitro* in a test tube. In a preferred embodiment, the polypeptides of the invention are assembled into Virus Like Particles (VLPs) optimized for presentation of antigens useful in the context of vaccination against infectious agents or tumors.

A prerequisite for successful protein scaffold design for presentation of oligopeptides, polypeptide sequences, protein domains, proteins and/or protein complexes, is a compact, stable multimerization domain which can accommodate modalities representing exposed and flexible loop structures that can accommodate such oligopeptides, polypeptide sequences, protein domains, proteins and/or protein complexes. Preferably, these displayed entities can represent immunogenic antigens that are presented to an immune system. Penton base proteins (protomers) from a number of Adenovirus (Ad) serotypes assemble into pentamers which then form dodecahedra, resembling virus-like particles. In contrast to live virus, they carry no genetic material such that these VLPs are beneficial under safety considerations.

Adenovirus is one of the most commonly used gene therapy vector in humans. The adenovirus shell is predominantly made up of two distinct proteins, the hexon protein, and the penton base protein, with the latter forming pentameric assemblies to which attach the fibres characteristic for this virus. Penton base proteins of certain adenovirus serotypes were shown to spontaneously self-assemble into a multimeric superstructure when expressed recombinantly in absence of other adenoviral components. This superstructure represents a dodecamer, formed by a total of 60 adenovirus base proteins arranged in twelve identical copies of a pentameric 'crown-shaped' assembly (Fig. 1). The adenovirus base protein itself adopts a two-domain architecture with one domain representing a beta-barrel conjoined to a

second domain stabilized by alpha-helices (Fig. 1B). The former mediates multimerization into the dodecahedron as evidenced by mutational studies, while the latter presents extended loops to the solvent on the dodecahedron surface. These loops are extremely variable in length and sequence content in different adenovirus serotypes, while the remainder of the base protein is highly conserved throughout the species. The adenovirus dodecahedron represents a highly versatile display scaffold for example for immunogenic peptides that can be inserted into the loops replacing naturally occurring sequences. Literally hundreds of heterologous peptides can thus be displayed efficiently on a single dodecahedron, if all insertion sites are occupied. The dodecahedron can be produced recombinantly in very high amount, it is exceptionally stable and can be stored at ambient temperature for indefinite time. Exploiting these highly advantageous characteristics, synthetic dodecahedron-based particles displaying immunogenic peptides in their exposed loops have been engineered for potential use in a range of applications including onco-immunology and emergent infectious disease.

WO2017167988 A1 describes synthetic adenovirus dodecahedrons facilitating epitope insertion into the exposed loops and also discloses an adenovirus base protein production protocol.

The problem underlying the present invention is the provision of a novel system for presenting antigens or other cargo through protein scaffolds which can assemble into VLP structures.

The above technical problem is provided by the embodiments of the present invention as defined in the claims as well as further described herein and illustrated by the accompanying drawings.

The present invention is based, at least in part, on the finding that the architecture of the adenovirus penton base proteins represents a *bona fide* two-domain structure which may have arisen during evolution by gene fusion (Fig. 1B). The two domains as it appeared could be easily split into two distinct compact entities: the beta-barrel containing the multimerization information, and the alpha-helical domain resembling a "crown".

Therefore, according to the present invention, there is provided a "minimal" multimerization polypeptide which can be coupled to antigen or other cargo carrying entities which utmost versatility and flexibility. The thus engineered polypeptide of the invention is derived from the amino acid sequences of adenovirus penton bases (also referred to herein as "penton base

protomers") which form the beta-barrel domain of the adenovirus penton base. The beta-barrel domain of adenovirus penton base proteins forms a so-called jellyroll fold domain comprising eight beta-sheets 1 through 8 (see Fig. 2); cf. Zubieta et al. (2005) Mol. Cell 17, 121-135. According to the present invention, it has been surprisingly found that, for effective
5 multimerization and thus, display of coupled cargo such as oligopeptides or polypeptides like antigens or other coupled entities, e.g. drugs, labels, nucleic acids, the two loops (forming the "crown" domain) interspersed in the sequence between the amino acid stretches forming the jellyroll fold domain, can be completely, or in other embodiments partially, replaced by desired non-adenoviral sequences such as oligopeptide linkers (to which antigens or other
10 cargo can in turn be coupled) or any desired amino acid sequence such as polypeptides, proteins, protein domains, protein complexes etc.

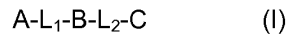
Therefore, in preferred embodiments of the invention, a nucleic acid, a drug, label and/or binding partner of a biological binding pair is/are coupled to L₁ and/or L₂. "Biological binding"
15 pair according to the invention are pairs of biological entities or compounds, respectively, which are typically found in nature or which are at least derived from binding pairs found in nature. Examples include, but are not limited to, antigens, antibodies, antibody fragments, diabodies, antibody mimetics, receptors and their ligands, biotin, streptavidin and the like.

20 Such entities may be coupled to L₁ and/or L₂ via means known in the art. If necessary linkers of any type can be linked to a suitable group at a position in L₁ and/or L₂, which linker is then coupled to the desired entity. Typical groups present in L₁ and/or L₂ which can be engaged into a chemical coupling include NH₂ and SH groups of amino acid residues present in L₁ and/or L₂. However, the coupling of cargo to L₁ and/or L₂ is not restricted to chemical bonds
25 but also include any other interaction such as ionic interactions, hydrogen bonds and Van der Waals interactions.

The jellyroll fold domain according to the invention is formed by three amino acid stretches (which also may be referred to as, e.g. "segments" or "regions"): an N-terminal stretch, an
30 intermediate stretch, and a C-terminal stretch. In the native adenovirus penton base protomer, the loop segments are found between the N-terminal amino acid stretch and the intermediate stretch (large loop) and between the intermediate amino acid stretch and the C-terminal amino acid stretch (small loop). As outlined above, the typically non-adenoviral sequences of the polypeptide of the present invention, which may be denoted herein as
35 "linkers", replace the loop segments of the native adenovirus penton base protomer. In other embodiments of the invention, one of the large loops and the small loop of the native penton base may be present in the polypeptide of the invention and forming L₁ or L₂.

Therefore, the polypeptide according to the invention generally has a structure represented by the following general formula (I)

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wherein

A is an N-terminal amino acid stretch of an adenovirus penton base protein;

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B is an amino acid stretch of an adenovirus penton base protein;

C is a C-terminal amino acid stretch of an adenovirus penton base;

wherein B is an amino acid stretch located between A and C in the sequence of said adenovirus penton base;

wherein A, B and C form the jellyroll fold domain of said adenovirus penton base protein.

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L₁ and L₂ are the linkers as outlined above. Thus, L₁ and L₂ can be selected from almost any amino acid sequence (as long as the same does not interfere with the multimerization of the polypeptide). Thus, L₁ and L₂ may be the same or different and are independently from one another selected from the group consisting of an oligopeptide, a polypeptide, a protein and a protein complex. The sequences of L₁ and L₂ are typically non-adenoviral, i.e. have an amino acid sequence of at least 5, 6, 7, 8, 9 10 or more amino acids, which sequence does not exist or occur in the known penton base protomer sequences of any adenovirus serotype, more preferably in any adenoviral protein.

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25 In an alternative embodiment of the invention, the linkers L₁ and L₂ may be selected from the loop sequences (i.e. regions comprising the first and second RGD loops and/or the variable loop as defined in WO 2017/167988 A1) of a penton base of an adenovirus. However, in this embodiment, the sequences of the loop segments are derived from an adenovirus having a different serotype compared to the serotype of the adenovirus from which said amino acid stretches A, B and C are derived. Accordingly, this embodiment of the invention provides chimeras of penton base protomers where the beta-barrel, jellyroll fold domain is derived from one adenovirus subtype, whereas L₁ and L₂ are polypeptides comprising RGD loop segments and/or VL variable loop segments (forming the "crown" domain) are derived from an adenovirus subtype different from the adenovirus subtype the jellyroll fold domain is
35 derived from.

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In a preferred embodiment of the invention, referring to Fig. 2, amino acid stretch A comprises beta-sheets 1, 2 and 3 of the jellyroll fold domain of the adenovirus penton base protomer, amino acid stretch B comprises beta sheets 4 and 5 of the jellyroll fold domain of said adenovirus penton base protomer, and amino acid stretch C comprises beta sheets 6, 7
 5 and 8 of the jellyroll fold domain of said adenovirus penton base protomer. It is to be understood that each segment A, B, and C can be independently derived from the same or different adenoviruses.

Preferably, amino acid stretches A, B, and C have an amino acid sequence which is each
 10 independently derived from penton base sequences selected from the group consisting of penton bases of human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype
 15 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53
 20 (rhAd53).

Preferred amino acid sequences of the above-indicated adenovirus penton bases are laid down in generally accessible databases such as UniProt and UniProtE, and especially preferred sequences referred to herein for the above-mentioned adenovirus subtypes are
 25 laid down in UniProt Acc. No. Q2Y0H9 (human adenovirus serotype 3; SEQ ID NO: 1), UniProt Acc. No. P03276 (human adenovirus serotype 2; SEQ ID NO: 2), UniProt Acc. No. Q2KSF3 (human adenovirus serotype 4; SEQ ID NO: 3), UniProt Acc. No. P12538 (human adenovirus serotype 5; SEQ ID NO: 4), UniProt Acc. No. Q9JFT6 (human adenovirus serotype 7; SEQ ID NO: 5), UniProt Acc. No. D2DM93 (human adenovirus serotype 11; SEQ
 30 ID NO: 6), UniProt Acc. No. P36716 (human adenovirus serotype 12; SEQ ID NO: 7), UniProt Acc. No. F1DT65 (human adenovirus serotype 17; SEQ ID NO: 8), UniProt Acc. No. M0QUK0 (human adenovirus serotype 25; SEQ ID NO: 9), UniProt Acc. No. Q7T941 (human adenovirus serotype 35; SEQ ID NO: 10), UniProt Acc. No. Q912J1 (human adenovirus serotype 37; SEQ ID NO: 11), UniProt Acc. No. F8WQN4 (human adenovirus serotype 41;
 35 SEQ ID NO: 12), UniProt Acc. No. E5L3Q9 (gorilla adenovirus; SEQ ID NO: 13), UniProt Acc. No. G9G849 (chimpanzee adenovirus; SEQ ID NO: 14), UniProt Acc. No. H8PFZ9 (simian adenovirus serotype 18; SEQ ID NO: 15), UniProt Acc. No. F6KSU4 (simian

adenovirus serotype 20; SEQ ID NO: 16), UniProt Acc. No. F2WTK5 (simian adenovirus serotype 49; SEQ ID NO: 17), UniProt Acc. No. A0A0A1EWW1 (rhesus adenovirus serotype 51; SEQ ID NO: 18), UniProt Acc. No. A0A0A1EWX7 (rhesus adenovirus serotype 52; SEQ ID NO: 19), and UniProt Acc. No. A0A0A1EWZ7 (rhesus adenovirus serotype 53; SEQ ID NO: 20).

The amino acid sequences of the above penton bases are as follows (the respective UniProt Acc. No. is indicated in brackets):

10 Human Adenovirus Serotype 3 poenton base hAd3 (Q2Y0H9); SEQ ID NO: 1:

MRRRAVLGGA VVYPEGPPPS YESVMQQQAA MIQPPLEAPF VPPRYLAPTE
 GRNSIRYSEL SPLYDTHKLY LVDNKSADIA SLNYQNDHSN FLTTVVQNND
 15 FTPTEASTQT INFDERSRWG GQLKTIMHTN MPNVNEYMFS NKFKARVMVS
 RKAPEGVTVN DTYDHKEDIL KYEWFEFILP EGNFSATMTI DLMNNAIIDN
 20 YLEIGRQNGV LESDIGVKFD TRNFRLGWDP ETKLIMPGVY TYEAFHPDIV
 LLPGCGVDFT ESRLSNLLGI RKRHPFQEGF KIMYEDLEGG NIPALLDVTA
 YEESKKDTHH ETTTLAVAAE TSEDDITRG DTYITEKQKR EAAAAEVKKE
 25 LKIQPLEKDS KRSYNVLED KINTAYRSWY LSNYGNPEK GIRSWTLLTT
 SDVTCGAEQV YWSLPDMMQD PVTFRSTRQV NNYPVVGAEI MPVFSKSFYN
 30 EQAVYSQQLR QATSLTHVFN RFPENQILIR PPAPTITTVS ENVPALTDHG
 TLPLRSSIRG VQRVTVTGAR RRTCPYVYKA LGIVAPRVLS SRTF

hAd2 (P03276); SEQ ID NO: 2:

35 MQRAAMYEEG PPSYESVVS AAPVAAALGS PFDAPLDPPF VPPRYLRPTG
 GRNSIRYSEL APLFDTHRVY LVDNKSTDVA SLNYQNDHSN FLTTVIQNND
 40 YSPGEASTQT INLDDRSHWG GDLKTHLHTN MPNVNEFMFT NKFKARVMVS
 RSLTKDKQVE LKYEWEFTL PEGNYSETMT IDLMNNAIVE HYLKVGRQNG
 VLESDIGVKF DTRNFRLGFD PVTGLVMPGV YTNEAFHPDI ILLPGCGVDF
 45 THSRLSNLLG IRKRQPFQEG FRITYDDLEG GNIPALLDVD AYQASLKDDT
 EQGGDGAGGG NNSGSGAEEN SNAAAAAMQP VEDMNDHAIR GDTFATRAEE
 50 KRAEAEAAAE AAAPAAQPEV EKPQKKPVIV PLTEDSKKRS YNLISNDSTF
 TQYRSWYLA NYGDPQTGIR SWTLLCTPDV TCGSEQVYWS LPDMMQDPVT
 FRSTSQISNF PVVGAELLPV HSKSFYNDQA VYSQLIRQFT SLTHVFNRFV
 55 ENQILARPPA PTITTVSENV PALTDHGTLV LRNSIGGVQR VTITDARRRT

CPYVYKALGI VSPRVLSSRT F

hAd4 (Q2KSF3); SEQ ID NO: 3:

5
MMRRAYPEGP PPSYESVMQQ AMAAAAIQP PLEAPYVPPR YLAPTEGRNS
IRYSELTPLY DTTRLYLVDN KSADIASLNY QNDHSNFLT T VVQNNDFTP
10 EASTQTINFD ERSRWGGQLK TIMHTNMPNV NQFMYSNKFK ARVMVSRKTP
NGVTVGDN YD GSQDELKYEW VEFELPEGNF SVTMTIDLMN NAIIDNYLAV
15 GRQNGVLESD IGVKFDTRNF RLGWDPVTEL VM PGVYTNEA FHPDIVLLPG
CGVDFTESRL SNLLGIRKRQ PFQEGFQIMY EDLDGGNIPA LLDVEAYEKS
KEESVAAATT AVATASTEVR DDNFASAAV AAVKADETKS KIVIQPVEKD
20 SKERSYNVLS DKKNTAYRSW YLAYNYGDRD KGVRSWTLT TSDVTCGVEQ
VYWSLPDMMQ DPVTFRSTHQ VSNYPVVGAE LLPVYSKSF NEQAVYSQQ
25 RAFTSLTHVF NRPENQILV RPPAPTITTV SENVPALTDH GTLPLRSSIR
GVQRVTVTDA RRRTCPYVYK ALGIVAPRVL SSRTF

hAd5 (P12538); SEQ ID NO: 4:

30 MRRAAMYEEG PPSYESVVS AAPVAAALGS PFDAPLDPPF VPPRYLRPTG
GRNSIRYSEL APLFDTRVY LVDNKSTDVA SLNYQNDHSN FLTTVIQNN
35 YSPGEASTQT INLDDRSHWG GDLKTLHTN MPNVNEFMFT NKFKARVMVS
RLPTKDNQVE LKYEWVEFTL PEGNYSETMT IDLMNNAIVE HYLKVGRQNG
VLESDIGVKF DTRNFR LGFD PVTGLVMPGV YTNEAFHPDI ILLPGCGVDF
40 THSRLSNLLG IRKRQPFQEG FRITYDDLEG GNIPALLDVD AYQASLKDDT
EQGGGGAGGS NSSGSGAEEN SNAAAAAMQP VEDMNDHAIR GDTFATRAEE
45 KRAEAEAAAE AAAPAAQPEV EKPQKKPVIK PLTEDSKKRS YNLISNDSTF
TQYRSWYLAY NYGDPQTGIR SWTLLCTPDV TCGSEQVYWS LPDMMQDPVT
FRSTRQISNF PVVGAELLPV HSKSFYNDQA VYSQLIRQFT SLTHVFNRF
50 ENQILARPPA PTITTVSENV PALTDHGTLR LRNSIGGVQR VTITDARRRT
CPYVYKALGI VSPRVLSSRT F

55 hAd7 (Q9JFT6); SEQ ID NO: 5:

MMRRAVLGGA MVYPEGPPPS YESVMQQQAA MIQPPLEAPF VPPRYLAPTE
GRNSIRYSEL SPLYDTTKLY LVDNKSADIA SLNYQNDHSN FLTTVVQNN
60 FTPTEASTQT INFDESRWG GQLKTIMHTN MPNVNEYMFS NKFKARVMVS

5 RKAPEGVIVN DTYDHKEDIL KYEWFETLTP EGNFSATMTI DLMNNAIDN
 YLEIGRQNGV LESDIGVKFD TRNFRLGWD P ETKLIMPGVY TYEAFHPDIV
 10 LLPGCGVDFT ESRLSNLLGI RKRHPFQEGF KIMYEDLEGG NIPALLDVTA
 YEESKKDTTT ETTTLAVAE TSEDDNITRG DTYITEKQKR EAAAAEVKKE
 LKIQPLEKDS KRSYINVLED KINTAYRSWY LSYNYGNPEK GIRSWTLLTT
 SDVTCGAEQV YWSLPDMMQD PVTFRSTRQV NNYPVVGAE MPVFSKSFYN
 15 EQAVYSQQLR QATSLTHVFN RFPENQILIR PPAPTITTVS ENVPALTDHG
 TLPLRSSIRG VQRVTVDAR RRTCPYVYKA LGIVAPRVLS SRTF

hAd11 (D2DM93); SEQ ID NO: 6:

20 MRRVVLGGAV VYPEGPPPSY ESVMQQQATA VMQSPLEAPF VPPRYLAPTE
 GRNSIRYSEL APQYDTTRYLY LVDNKSADIA SLNYQNDHSN FLTTVVQNND
 25 FTPTEASTQT INFDERSRWG GQLKTIMHTN MPNVNEYMFS NNFKARVMVS
 RKPPEGA AVG DTYDHKQDIL EYEWFEFTLP EGNFSVTMTI DLMNNAIDN
 YLKVGRQNGV LESDIGVKFD TRNFRLGWD P ETKLIMPGVY TYEAFHPDIV
 30 LLPGCGVDFT ESRLSNLLGI RKKQPFQEGF KILYEDLEGG NIPALLDVDA
 YENSKKEQKA KIEAAAEAKA NIVASDSTRV ANAGEVRGDN FAPTPVPTAE
 SLLADVSGGT DVKLTIQPVE KDSKNRSYNV LEDKINTAYR SWYLSYNYGD
 35 PEKGVRSWTL LTTSDVTCGA EQVWSLPDM MQDPVTFRST RQVSNYPVVG
 AELMPVFSKS FYNEQAVYSQ QLRQSTSLTH VFNRFPENQI LIRPPAPTIT
 40 TVSENVALT DHGTLPLRSS IRGVQRVTVT DARRRTPYV YKALGIVAPR
 VLSSRTF

hAd12 (P36716); SEQ ID NO: 7:

45 MRRAVELQTV AFPETPPPSY ETVM AAAPPY VPPRYLGPT E GRNSIRYSEL
 SPLYDTTRYLY LVDNKSSDIA SLNYQNDHSN FLTTVVQNND YSPIEAGTQT
 50 INFDERSRWG GDLKTILHTN MPNVNDFMFT TKFKARVMVA RKTNNEGQTI
 LEYEWAEFVL PEGNYSETMT IDLMNNAIIE HYLRVGRQHG VLESDIGVKF
 DTRNFRLGWD PETQLVTPGV YTNEAFHPDI VLLPGCGVDF TESRLSNILG
 55 IRKRQPFQEG FVIMYEHLEG GNIPALLDVK KYENSLQDQN TVRGDNFIAL
 NKAARIEPVE TDPKGRSYNL LPDKKNTKYR SWYLAYNYGD PEKGVRSWTL
 60 LTTDPVTGGS EQVWSLPDM MQDPVTFRSS RQVSNYPVVA AELLPVHAKS

FYNEQAVYSQ LIRQSTALTR VFNRFPENQI LVRPPAATIT TVSENVALT
DHGTLPLRSS ISGVQRTIT DARRRTPYV YKALGIVSPR VLSSRTF

5 hAd17 (F1DT65); SEQ ID NO: 8:

MRRAVVSSSP PPSYESVMAQ ATLEVFPVPP RYMAPTEGRN SIRYSELAPL
YDTRVYLVLD NKSADIASLN YQNDHSNFLT TVVQNNDFTP AEASTQTINF
10 DERSRWGGDL KTIHTNMPN VNEYMFTSKF KARVMVARKH PQGVEATDLS
KDILEYEWFE FTLPEGNFSE TMTIDLMNNA ILENYLQVGR QNGVLESDIG
15 VKFDSRNFKL GWDPVTKLVM PGVYTYEAFH PDVLLPGCG VDFTESRLSN
LLGIRKKQPF QEGFRIMYED LEGGNIPALL DVPKYLESKK KLEEALENAA
KANGPARGDS SVSREVEKAA EKELVIEPIK QDDSKRSYNL IEGTMDTLR
20 SWYLSYTYGD PEKGVSQWTL LTPDVTGCG EQVWVSLPDL MQDPVTFRST
QQVSNYPVVG AELMPFRAKS FYNDLAVYSQ LIRSYTSLTH VFNRFDPNQI
25 LCRPPAPTIT TVSENVALT DHGTLPLRSS IRGVQRTVT DARRRTPYV
YKALGIVAPR VLSSRTF

30 hAd25 (M0QUK0); SEQ ID NO: 9:

MRRAVVSSSP PPSYESVMAQ ATLEVFPVPP RYMAPTEGRN SIRYSELAPQ
YDTRVYLVLD NKSADIASLN YQNDHSNFLT TVVQNNDFTP AEASTQTINF
35 DERSRWGGDL KTIHTNMPN VNEYMFTSKF KARVMVARKH PENVDKTDLS
QDKLEYEWFE FTLPEGNFSE TMTIDLMNNA ILENYLQVGR QNGVLESDIG
40 VKFDSRNFKL GWDPVTKLVM PGVYTYEAFH PDVLLPGCG VDFTESRLSN
LLGIRKKQPF QEGFRIMYED LEGGNIPALL DTKKYLDISK ELEDAAKEAA
KQQGDGAVTR GDTHLTVAQE KAAEKELVIV PIEKDESNRS YNLIKDTHDT
45 MYRSWYLSYT YGDPEKGVQS WTLTTPDVT CGAEQVYWSL PDLMDPVT
RSTQQVSNYP VVGAELMPFR AKSFYNDLAV YSQLIRSYTS LTHVFNRFPD
50 NQILCRPPAP TITTVSENV ALT DHGTLPL RSSIRGVQRV TVTDARRRTC
PYVYKALGIV APRVLSSRTF

55 hAd35 (Q7T941); SEQ ID NO: 10:

MRRVVLGGAV VYPEGPPPSY ESVMQQQAT AVMQSPLEAP FVPPRYLAPT
EGRNSIRYSE LAPQYDTRL YLVDNKSADI ASLNYQNDHS NFLTTVVQNN
60 DFTPTASTQ TINFDESRW GGQLKTIMHT NMPNVNEYMF SNKFKARVMV

SRKPPDGA AV GDTYDHKQDI LEYEWFEFTL PEGNFSVTMT IDLMNNAIID
 NYLKVG RQNG VLES DIGVKF DTRNFKLGWD PETKLIMPGV YTYEAFHPDI
 5 VLLPGCGVDF TESRLSNLLG IRKKQPFQEG FKILYEDLEG GNIPALLDVD
 AYENSKKEQK AKIEAATAAA EAKANIVASD STRVANAGEV RGDNFAPTPV
 10 PTAESLLADV SEGTDVKLTI QPVEKDSKNR SYNVEDKIN TAYRSWYLSY
 NYGDPEKGVR SWTLLTSDV TCGAEQVYWS LPDMMKDPVT FRSTRQVSNY
 PVVGAELMPV FSKSFYNEQA VYSQQLRQST SLTHVFNRF ENQILIRPPA
 15 PTITTVSENV PALTDHGTLP LRSSIRGVQR VTVTDARRRT CPYVYKALGI
 VAPRVLSSRT F

20 hAd37 (Q912J1); SEQ ID NO: 11

MRRAVVSSSP PPSYESVMAQ ATLEVFPFVPP RYMAPTEGRN SIRYSELAPL
 YDTRVYLVD NKSADIASLN YQNDHSNFLT TVVQNNDFTP AEASTQTINF
 25 DERSRWGGDL KTILHTNMPN VNEYMFTSKF KARVMVARKK AEGADANDRS
 KDILEYQWFE FTLPEGNFSE TMTIDLMNNA ILENYLQVGR QNGVLES DIG
 30 VKFDSRNFKL GWDVPVKLVMPGVYTYEAFH PDVLLPGCG VDFTESRLSN
 LLGIRKKQPF QEGFRIMYED LVGGNIPALL NVKEYLKDKE EAGKADANTI
 KAQNDAVPRG DNYASAAEAK AAGKEIELKA ILKDDSDRSY NVIEGTTDTL
 35 YRSWYLSYTY GDPEKGVQSW TLLTTPDVTC GAEQVYWSLP DLMQDPVTFR
 STQQVS NYPV VGAELMPFRA KSFYNDLAVY SQLIRSYTSL THVFNRF PDN
 40 QILCRPPAPT ITTVSENVPA LTDHGTLP LR SSIRGVQRVT VTDARRRTCP
 YVYKALGIVA PRVLSSRTF

45 hAd41 (F8WQN4); SEQ ID NO: 12:

MRRAVGVPPV MAYAEGPPPS YESVMGSADS PATLEALYVP PRYLGPTEGR
 NSIRYSELAP LYDTRVYLV DNKSADIASL NYQNDHSNFQ TTVVQNNDF
 50 PAEAGTQTIN FDESRWGAD LKTILRTNMP NINEFMSTNK FKARLMVEKK
 NKETGLPRYE WFEFTLPEGN YSETMTIDLM NNAIVDNYLE VGRQNGVLES
 DIGVKFDTRN FRLGWDVPVK LVMPGVYTNE AFHPDIVLLP GCGVDFTQSR
 55 LSNLLGIRKR LPFQEGFQIM YEDLEGGNIP ALLDVTKYEA SIQKAKEEGK
 EIGDDTFATR PQDLVIEPVA KDSKNRSYNL LPNDQNNTAY RSWFLAYNYG
 60 DPNKGVQSWT LLTTADVTCG SQQVYWSLPD MMQDPVTFRP STQVS NYPV
 GVLLPVHAK SFYNEQAVYS QLIRQSTALT HVFNRF PENQ ILVRPPAPTI

TTVSENPAL TDHGTLP LRS SISGVQRVTI TDARRRTCPY VHKALGIVAP
KVLSSRTF

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Gorilla Adenovirus Penton Base gorAd (E5L3Q9); SEQ ID NO: 13:

MMRRAVLGGA VVYPEGPPPS YESVMQQQAA AVMQPSLEAP FVP PRYLAPT
10 EGRNSIRYSE LAPQYDTRL YLVDNKSADI ASLNYQNDHS NFLTTVVQNN
DFTPTEASTQ TINFDESRW GGQLKTIMHT NMPNVNEYMF SNKFARVMV
15 SREASKIDSE KNDRSKDTLK YEWFEFTLPE GNFSATMTID LMNNAIIDNY
LAVGRQNGVL QSDIGVKFDT RNFR LGWDPV TKLVMPGVYT YEAFHPDIVL
LPDCGVDFTE SRLSNLLGIR KRHPFQEGFK IMYEDLEGGN IPALLDVAEY
20 ESKSKEIASS TTTTAVTTVA RNVADTSVEA VAVAVVDTIK AENDSAVRGD
NFQSKNDMKA SEEVTVVPVS PPTVTETETK EPTIKPLEKD TKDRSYNVIS
GTNDTAYRSW YLAYNYGDPE KGVRSWTLT TSDVTCGAEQ VYWSLPDMMQ
25 DPVTFRSTRQ VSNYPVVGAE LMPVFSKSFY NEQAVYSQQL RQTSLTHIF
DRFPENQILI RPPAPTITTV SENVPALTDH GTLPLRSSIR GVQRVTVTDA
30 RRRTCPYVYK ALGIVAPRVL SSRTF

Cimpanzee Adenovirus Penton Base chimpAd (G9G849); SEQ ID NO: 14:

35 MMRRAYPEGP PPSYESVMQQ AAAAAAAMQP PLEAPYVPPR YLAPTEGRNS
IRYSELAPLY DTTRLYLVDN KSADIASLNY QNDHSNFLTT VVQNNDFPTPT
EASTQTINF D ERSRWGGQLK TIMHTNMPNV NEFMYSNKFK ARVMVSRKTP
40 NGVTVDGSQ DILEYEWVEF ELPEGNFSVT MTIDL MNNAI IDNYLAVGRQ
NGVLESDIGV KFDTRNFRLG WDPVTEL VMP GVTNEAFHP DIVLLPGCGV
45 DFTE SRLSNL LGIRKRQPFQ EGFQIMYEDL EGNIPALLD VDAYEKSKEE
SAAAATAAVA TASTEVRGDN FASPAAVAAA EAAETESKIV IQPVEKDSKD
RSYNVLPDKI NTAYRSWYLA YNYGDPEKGV RSWTLT TSD VTCGVEQVYW
50 SLPDMMQDPV TFRSTRQVSN YPVVGAELLP VYSKSFNEQ AVYSQQLRAF
TSLTHVFNRF PENQILVRPP APTITTVSEN VPALTDHGT LPLRSSIRGVQ
55 RVTVTDARRR TCPYVYKALG IVAPRVLSSR TF

Simian Adenovirus Serotype 18 Penton Base, sAd18 (H8PFZ9); SEQ ID NO: 15:

60 MRAVGVPV MAYAEGPPPS YETVMGAADS PATLEALYVP PRYLGPTTEGR

NSIRYSELAP LYDTTRVYLV DNKSADIASL NYQNDHSNFL TTVVQNNDF
 PVEAGTQTIN FDESRWGGD LKTI LR TNMP NINEFMSTNK FRARLMVEKV
 5 NKETNAPRYE WFEFTLPEGN YSETMTIDLM NNAIVDNYLE VGRQNGVLES
 DIGVKFDTRN FRLGWDPVTK LVMPGVYTNE AFHPDIVLLP GCGVDFTQSR
 10 LSNLLGIRKR MPFQAGFQIM YEDLEGGNIP ALLDVAKYEA SIQKAREQQQ
 EIRGDNFTVI PRDVEIVPVE KDSKDRSYNL LPGDQNTAY RSWFLAYNYG
 DPEKGVRSWT LLTTTDTVTCG SQQVWVSLPD MMQDPVTFRP SSQVS NYPVV
 15 GVLLPVHAK SFYNEQAVYS QLIRQSTALT HVFNRF PENQ ILVRPPAPTI
 TTVSENPAL TDHGTLPLRS SISGVQRVTI TDARRRTCPY VHKALGIVAP
 KVLSSRTF

20 **sAd20 (F6KSU4); SEQ ID NO: 16:**

MRRAVAIPSA AVALGPPPSY ESVMASANLQ APLENPYVPP RYLEPTGGRN
 25 SIRYSELTP L YDTTRLYLVD NKSADIATLN YQNDHSNFLT SVVQNSDYTP
 AEASTQTINL DDRSRWGGDL KTI LHTNMPN VNEFMFTNSF RAKLMVAHET
 NKDPVYKWVE LTLPEGNFSE TMTIDLMNNA IVDHYLAVGR QNGVKESEIG
 30 VKFDTRNFRL GWDPQTELVM PGVYTNEAFH PDVLLPGCG VDFTYSRLSN
 LLGIRKRMPF QEGFQIMYED LVGGNIPALL DVPAYEASIT TVAAKEVRGD
 35 NFEAAAAAAA TGAQPQAA PV VRPVTQDSKG RSYNIITGTN NTAYRSWYLA
 YNYGDPEKGV RSWTLLTTPD VTCGSEQVYW SMPDMYVDPV TFRSSQQVSS
 YPVVGAELLP IHSKSFYNEQ AVYSQLIRQQ TALTHVFNR F PENQILVRPP
 40 APTITTVSEN VPALTDHGTL PLQNSIRGVQ RVTITDARR TCPYVYKALG
 IVAPRVLSSR TF

45 **sAd49 (F2WTK5); SEQ ID NO: 17:**

MRRAVPAAAI PATVAYADPP PSYESVMAGV PATLEAPYVP PRYLGPTEGR
 50 NSIRYSELAP LYDTTRVYLV DNKSADIASL NYQNDHSNFL TTVVQNNDF
 PVEAGTQTIN FDESRWGGQ LKTI LHTNMP NVNEFMFTNS FRAKVMVSRK
 55 QNEEGQTELE YEWVEFVLPE GNYSETMTLD LMNNAIVDHY LLVGRQNGVL
 ESDIGVKFDT RNFR LGWDPV TKLVMPGVYT NEAFHPDVVL LPGCGVDFTQ
 SRLSNLLGIR KRQPFQEGFR IMYEDLEGGN IPALLNVKAY EDSIAAAMRK
 60 HNLPLRGDVF AVQPQEIVIQ PVEKD GKERS YNLLPDDKNN TAYRSWYLA

NYGDPLKGVR SWTLLTTPDV TCGSEQVYWS LPDLMQDPVT FRPSSQVSNY
 PVVGAELLPL QAKSFYNEQA VYSQLIRQST ALTHVFNRFP ENQILVRPPA
 5 ATITTVSENV PALTDHGTLP LRSSISGVQR VTITDARRRT CPYVYKALGI
 VAPRVLSSRT F

10 **Rhesus Adenovirus Serotype 51 Penton Base, rhAd51 (A0A0A1EWW1); SEQ ID NO: 18:**

MRAVRVTPA AYEGPPPSYE SVMGSANVPA TLEAPYVPPR YLGPTTEGRNS
 IRYSELAPLY DTTKVYLVDN KSADIASLNY QNDHSNFLT T VVQNNDFTP
 15 EAGTQTINFD ERSRWGGQLK TILHTNMPNI NEFMSTNKFR AKLMVEKSNA
 ETRQPRYEFW EFTIPEGNYS ETMTIDLMNN AIVDNYLQVG RQNGVLES
 20 GVKFDTRNFR LGWDPVTKLV MPGVYTNEAF HPDIVLLPGC GVDFTQSRLS
 NLLGIRKRRP FQEGFQIMYE DLEGGNIPAL LDVSKYEASI QRAKAEGREI
 RGDTFAVAPQ DLEIVPLTKD SKDRSYNIIN NTTDTLYRSW FLAYNYGDPE
 25 KGVRSWTILT TTDVTCGSQQ VYWSLPDMMQ DPVTFRPSTQ VSNFPVVGTE
 LLPVHAKSFY NEQAVYSQLI RQSTALTHVF NRPENQILV RPPAPTITTV
 30 SENVPALTDH GTLPLRSSIS GVQRTITDA RRRTCPYVYK ALGVVAPKVL
 SSRTF

35 **rhAd52 (A0A0A1EWX7); SEQ ID NO: 19:**

MRAVRVTPA AYEGPPPSYE SVMGSANVPA TLEAPYVPPR YLGPTTEGRNS
 IRYSELAPLY DTTKVYLVDN KSADIASLNY QNDHSNFLT T VVQNNDFTP
 40 EAGTQTINFD ERSRWGGQLK TILHTNMPNI NEFMSTNKFR ARLMVKKVEN
 QPPEYEFWFEF TIPEGNYSET MTIDLMNNAI VDNYLQVGRQ NGVLES
 45 KFDTRNFRLG WDPVTKLVMP GVYTNEAFHP DIVLLPGCGV DFTQSRLSNL
 LGIRKRRPFQ EGFQIMYEDL EGGNIPALLD VTKYEQSVQR AKAEGREIRG
 DTFVSPQDL VIEPLEHDSK NRSYNLLPNK TDTAYRSWFL AYNYGDPK
 50 VRSWTILTTT DVTCSQQVY WSLPDMMQDP VTFRPSTQVS NFPVVGTELL
 PVHAKSFYNE QAVYSQLIRQ STALTHVFNR FPENQILVRP PAPTITTVSE
 55 NVPALTDHGT LPLRSSISGV QRTITDARR RTCPYVYKAL GVVAPKVLSS
 RTF

60 **rhAd53 (A0A0A1EWZ7); SEQ ID NO: NO 20:**

MRAVRVTPA VYAEPPPSY ESVMGSANVP ATLEAPYVPP RYLGPTTEGRN

SIRYSELAPL YDTTKVYLVD NKSADIASLN YQNDHSNFLT TVVQNNDFTP
 TEAGTQTINF DERSRWGGQL KTIHTNMPN INEFMSTNKF RARLMVEKTS
 5 GQPPKYEWFE FTIPEGNYSE TMTIDLMNNA IVDNYLQVGR QNGVLES DIG
 VKFDTRNFRL GWDPVTKLVM PGVYTNEAFH PDIVLLPGCG VDFTQSRLSN
 10 LLGIRKRRPF QEGFQIMYED LEGGNIPGLL DVPAYEQLQ QAQEEGRVTR
 GDTFATAPNE VVIKPLLKDS KDRSYNIITD TDTLYRSWF LAYNYGDPEN
 GVRSWTILTT TDVTCGSQQV YWSLPDMMQD PVTFRPSTQV SNFPVVGTEL
 15 LPVHAKSFYN EQAVYSQLIR QSTALTHVFN RFPENQILVR PPAPTITTVS
 ENVPALTDHG TLPLRSSISG VQRVITIDAR RRTCPYVYKA LGVVAPKVLS
 SRTF
 20

The polypeptide of the present invention is not confined to those known specific sequences for amino acid stretches A, B, and C forming the multimerization jellyroll fold domain of the above-referenced adenovirus sub- und serotypes, respectively. Amino acid segments A, B, and C can also have similar amino acid sequences to the sequences of known adenovirus penton base protomers as long as the sequences of A, B, and C are such that the resulting polypeptide adopts the jellyroll fold and assembles into pentameric complexes (also denoted "penton proteins") twelve of which in turn self-assemble to form a dodecameric supercomplex (the VLP of the invention) under appropriate conditions as further outlined below. Typically, such similar sequences of segments A, B and C share an amino acid sequence identity of at least 85 %, more preferred at least 90 %, even more preferred 95 %, particularly preferred at least 98 %, most preferred at least 99 %, with the respective amino acid sequence of a known adenovirus penton base, preferably those of SEQ ID NOs: 1 to 20, more preferably amino acid stretches A, B and C as provided in below Tables 1 to 3.

35 As used herein, amino acid sequences are stated from N to C terminal using the single letter code of IUPAC, if not otherwise specifically indicated.

According to a preferred embodiment of the invention, amino acid stretch A has the following consensus sequence (SEQ ID NO: 21):

40 (U)₁₋₄₇ PTX₁GRNSIRY SX₂X₃X₄PX₅X₆DTT X₇X₈YLVDNKSA DIASLNYQND
 HSNFX₅TTVX₉Q NNDX₁₀X₁₁PX₁₂EAX₁₃ TQTINX₁₄DX₁₅RS RWGX₁₆X₁₇LKTIX₁₈
 X₁₉TZ₁Z₂Z₃Z₄Z₅Z₆Z₇Z₈ Z₉Z₁₀Z₁₁Z₁₂Z₁₃Z₁₄Z₁₅

wherein:		amino acid stretch A ends on the C-terminal side before Z ₁ at residue T or at an amino acid from Z ₁ to Z ₁₅
	U	is any or no amino acid
5	X ₁	is E or G
	X ₂	is E or S
	X ₃	is L or V
	X ₄	is A or S
	X ₅	is L or Q
10	X ₆	is Y or E
	X ₇	is R or K
	X ₈	is V or L
	X ₉	is V or I
	X ₁₀	is F or Y
15	X ₁₁	is T or S
	X ₁₂	is A or T or I or G
	X ₁₃	is S or G
	X ₁₄	is F or L
	X ₁₅	is E or D
20	X ₁₆	is A or G
	X ₁₇	is D or Q
	X ₁₈	is L or M
	X ₁₉	is H or R
25	Z ₁	, if present, is N
	Z ₂	, if present, is M
	Z ₃	, if present, is P
	Z ₄	, if present, is N
	Z ₅	, if present, is V or I
30	Z ₆	, if present, is N
	Z ₇	, if present, is E or D
	Z ₈	, if present, is Y or F
	Z ₉	, if present, is M
	Z ₁₀	, if present, is F or S or Y
35	Z ₁₁	, if present, is T or S
	Z ₁₂	, if present, is S or N
	Z ₁₃	, if present, is K
	Z ₁₄	, if present, is F
	Z ₁₆	, if present, is K

More preferred amino acid sequences of segment A of the polypeptide according to the invention are outlined in the following Table 1:

5 Tab. 1: Preferred sequences for segment A of general formula (I)

Sequence based on penton base protomer of	Sequence according to UniProt Acc. No.	SEQ ID NO:	N-terminal amino acid selected from positions	C-terminal amino acid selected from positions
hAd3	Q2Y0H9	1	1 to 48	129 to 144
hAd2	P03276	2	1 to 48	129 to 144
hAd4	Q2KSF3	3	1 to 44	125 to 140
hAd5	P12538	4	1 to 48	129 to 144
hAd7	Q9JFT6	5	1 to 48	129 to 144
hAd11	D2DM93	6	1 to 48	129 to 144
hAd12	P36716	7	1 to 38	119 to 134
hAd17	F1DT65	8	1 to 35	116 to 131
hAd25	M0QUK0	9	1 to 43	124 to 139
hAd35	Q7T941	10	1 to 49	130 to 145
hAd37	Q912J1	11	1 to 35	116 to 131
hAd41	F8WQN4	12	1 to 46	127 to 142
gorAd	E5L3Q9	13	1 to 49	130 to 145
ChimpAd	G9G849	14	1 to 44	125 to 140
sAd18	H8PFZ9	15	1 to 46	127 to 142
sAd20	F6KSU4	16	1 to 45	126 to 141
sAd49	F2WTK5	17	1 to 48	127 to 142
rhAd51	A0A0A1EWW1	18	1 to 43	124 to 139
rhAd52	A0A0A1EWX7	19	1 to 43	124 to 139
rhAd53	A0A0A1EWZ7	20	1 to 44	125 to 140

According to a further preferred embodiment of the invention, amino acid stretch B of above general formula (I) has the following sequence (SEQ ID NO: 22):

10 $Z_{17}Z_{18}Z_{19}Z_{20}Z_{21}Z_{22}Z_{23}Z_{24}Z_{25}Z_{26}Z_{27}QVYWSLPDX_{20}MX_{21}DPVTFRST$
 $X_{22}QX_{23}X_{24}NX_{25}PVVGX_{26}ELZ_{28}Z_{29}Z_{30}$

wherein: amino acid stretch B begins on the N-terminal side at an amino acid from Z_{17} to Z_{27} or at amino acid Q after Z_{27} ;

- amino acid stretch B ends on the C-terminal side before Z₂₈ at amino acid L or at an amino acid from Z₂₈ to Z₃₀:
- 5 Z₁₇ , if present, is L or S
- Z₁₈ , if present, is T or P or C
- Z₁₉ , if present, is T or P
- Z₂₀ , if present, is P or S or A or R
- Z₂₁ , if present, is N or D
- Z₂₂ , if present, is G or V
- Z₂₃ , if present, is H or T
- 10 Z₂₄ , if present, is C
- Z₂₅ , if present, is G
- Z₂₆ , if present, is A or V or S
- Z₂₇ , if present, is E or Q
- X₂₀ is L or M
- 15 X₂₁ is Q or K
- X₂₂ is Q or R or S
- X₂₃ is V or I
- X₂₄ is S or N
- X₂₅ is Y or F
- 20 X₂₆ is A or V
- Z₂₈ , if present, is M or L
- Z₂₉ , if present, is P
- Z₃₀ , if present, is V or F

- 25 More preferred amino acid sequences of segment B of the polypeptide according to the invention are outlined in the following Table 2:

Tab. 2: Preferred sequences for segment B of general formula (I)

Sequence based on penton base protomer of	Sequence according to UniProt Acc. No.	SEQ ID NO:	N-terminal amino acid selected from positions	C-terminal amino acid selected from positions
hAd3	Q2Y0H9	1	398 to 409	440 to 443
hAd2	P03276	2	425 to 436	467 to 470
hAd4	Q2KSF3	3	379 to 390	421 to 444
hAd5	P12538	4	425 to 436	467 to 470
hAd7	Q9JFT6	5	398 to 409	440 to 443

hAd11	D2DM93	6	415 to 426	457 to 460
hAd12	P36716	7	351 to 362	393 to 397
hAd17	F1DT65	8	370 to 381	413 to 416
hAd25	M0QUK0	9	388 to 399	440 to 443
hAd35	Q7T941	10	445 to 456	497 to 500
hAd37	Q912J1	11	372 to 383	414 to 417
hAd41	F8WQN4	12	362 to 373	404 to 407
gorAd	E5L3Q9	13	416 to 427	458 to 461
ChimpAd	G9G849	14	372 to 383	420 to 423
sAd18	H8PFZ9	15	353 to 364	395 to 398
sAd20	F6KSU4	16	358 to 369	400 to 403
sAd49	F2WTK5	17	356 to 367	398 to 401
rhAd51	A0A0A1EWW1	18	352 to 363	394 to 397
rhAd52	A0A0A1EWX7	19	350 to 361	392 to 395
rhAd53	A0A0A1EWZ7	20	351 to 362	393 to 396

According to a further preferred embodiment of the invention, segment C of above general formula (I) has the following sequence (SEQ ID NO: 23):

5 Z₃₁Z₃₂Z₃₃ALTDHGT LPLRSSIX₂₇GV QRVTX₂₈TDARR RTCPYVYKA LGIVX₃₀PX₃₁VLS
SRTF

wherein: amino acid stretch C begins on the N-terminal side at an amino acid from Z₃₁
to Z₃₃ or at amino acid A after Z₃₃;

10 Z₃₁ , if present, is N
Z₃₂ , if present, is V
Z₃₃ , if present, is P
X₂₇ is R or S or G
X₂₈ is V or I
15 X₂₉ is Y or H
X₃₀ is A or S
X₃₁ is R or K

20 More preferred amino acid sequences of segment C of the polypeptide according to the
invention are outlined in the following Table 3:

Tab. 3: Preferred sequences for segment C of general formula (I)

Sequence based on penton base protomer of	Sequence according to UniProt Acc. No.	SEQ ID NO:	N-terminal amino acid selected from positions	C-terminal amino acid position
hAd3	Q2Y0H9	1	492 to 495	544
hAd2	P03276	2	519 to 522	571
hAd4	Q2KSF3	3	466 to 469	535
hAd5	P12538	4	492 to 495	571
hAd7	Q9JFT6	5	465 to 468	544
hAd11	D2DM93	6	482 to 485	561
hAd12	P36716	7	419 to 422	497
hAd17	F1DT65	8	438 to 441	517
hAd25	M0QUK0	9	455 to 458	534
hAd35	Q7T941	10	522 to 525	561
hAd37	Q912J1	11	439 to 442	519
hAd41	F8WQN4	12	439 to 432	508
gorAd	E5L3Q9	13	483 to 486	875
ChimpAd	G9G849	14	445 to 458	532
sAd18	H8PFZ9	15	420 to 423	508
sAd20	F6KSU4	16	425 to 428	512
sAd49	F2WTK5	17	423 to 426	511
rhAd51	A0A0A1EWW1	18	419 to 422	505
rhAd52	A0A0A1EWX7	19	417 to 420	503
rhAd53	A0A0A1EWZ7	20	418 to 421	504

Particularly preferred polypeptides of the invention are based on the jellyroll fold domain of the penton base protomer of hAd3. In particular, polypeptides are preferred wherein amino acid stretch A has an amino acid sequence starting at a position selected from amino acids 1 to 48, most preferred amino acid position 1, until an amino acid position selected from positions 129 to 144, most preferred amino acid position 132, amino acid stretch B has an amino acid sequence starting at a position selected from position 398 to 409, most preferred amino acid position 407, until a position selected from positions 440 to 443, most preferred amino acid position 442, and amino acid stretch C has an amino acid sequence starting at a position selected from position 492 to 495, most preferred amino acid position 493, until amino acid position 544, wherein amino acid positions refer to the sequence laid down in UniProt Acc. No. QY0H9 (SEQ ID NO: 1).

The linking segments L₁ and L₂ of the polypeptide according to the invention may be selected from oligopeptide linkers such as oligopeptides having 4 to 10 amino acids, preferably having amino acids G and S. A preferred example is GGGS (SEQ ID 24). Another example is a linker composed of G and S and having multiple GGS repeats such as 2, 3, 4, 5
5 or more GGS repeats. A particularly preferred linker of this type is GGSGGS (SEQ ID NO: 25).

In other preferred embodiments, L₁ is a polypeptide sequence comprising an RGD loop of an adenovirus penton base having a different serotype compared to the serotype of the
10 adenovirus(es) from which said amino acid stretches A, B and C are derived and/or L₂ is a polypeptide sequence comprising a variable loop of an adenovirus penton base having a different serotype compared to the serotype of the adenovirus from which said amino acid stretches A, B and C are derived.

In further embodiments of the invention L₁ is an RGD loop and L₂ is a, preferably non-adenoviral oligopeptide of preferably 4 to 20 amino acids, more preferably 4 to 10 amino acids, particularly preferred an oligopeptide linker composed of G and S as defined above. In similar embodiments, L₂ is or comprises a variable loop, and L₁ is an oligopeptide linker as defined before. It is also envisaged according to the invention that L₂ is or comprises an RGD
15 loop and L₁ is an oligopeptide linker, and it is also contemplated that L₁ is a variable loop and L₂ is an oligopeptide linker.

In other preferred embodiments, as mentioned before, the L₁ and L₂, respectively sequences may be selected from crown domain sequences of penton base proteins from an adenovirus
25 other than the adenovirus from which the multimerization domain is derived. Generally, the combination of the crown-multimerization domain chimera is not restricted. Preferred chimeras are selected from combinations of the crown and multimerization domains as outlined above. The crown domains, optionally, and preferably, including non-adenoviral sequences inserted in an RGD loop and/or a variable loop of the respective crown domain,
30 are more preferably as disclosed in WO 2017/167988 A1.

It is thereby understood that crown domains of adenovirus penton bases are typically made up of two amino acid stretches: the so-called big fragment and small fragment. The big fragment of the crown domain is located more N-terminally in the amino acid sequence of the
35 respective adenovirus penton base protein whereas the small fragment of the crown domain is located more C-terminally. According to the invention it is preferred when the big fragment (containing the RGD loop as mentioned above) corresponds to L₁ of general formula (I), and

it is further preferred that the small fragment (containing the variable loop) corresponds to L₂ of general formula (I). According to certain embodiments of the invention, the big and small fragment stem from the same adenovirus penton base. According to other embodiments of the invention, the big fragment and the small fragment stem from different adenovirus penton bases, or that only one of the big and small fragments stem from an adenovirus penton base protein different from the adenovirus from which the multimerization domain, i.e. amino stretches A, B and C) is derived from.

Preferred crown domains for use in the chimeric constructs of the invention include the crown domains selected from the group consisting of from the group consisting of penton bases of human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53).

Preferred amino acid sequences of the above-indicated adenovirus penton bases used for the crown domain are laid down in generally accessible databases such as UniProt and UniProtE, and especially preferred sequences referred to herein for the above-mentioned adenovirus subtypes are laid down in UniProt Acc. No. Q2Y0H9 (human adenovirus serotype 3; SEQ ID NO: 1), UniProt Acc. No. P03276 (human adenovirus serotype 2; SEQ ID NO: 2), UniProt Acc. No. Q2KSF3 (human adenovirus serotype 4; SEQ ID NO: 3), UniProt Acc. No. P12538 (human adenovirus serotype 5; SEQ ID NO: 4), UniProt Acc. No. Q9JFT6 (human adenovirus serotype 7; SEQ ID NO: 5), UniProt Acc. No. D2DM93 (human adenovirus serotype 11; SEQ ID NO: 6), UniProt Acc. No. P36716 (human adenovirus serotype 12; SEQ ID NO: 7), UniProt Acc. No. F1DT65 (human adenovirus serotype 17; SEQ ID NO: 8), UniProt Acc. No. M0QUK0 (human adenovirus serotype 25; SEQ ID NO: 9), UniProt Acc. No. Q7T941 (human adenovirus serotype 35; SEQ ID NO: 10), UniProt Acc. No. Q912J1 (human adenovirus serotype 37; SEQ ID NO: 11), UniProt Acc. No. F8WQN4 (human adenovirus serotype 41; SEQ ID NO: 12), UniProt Acc. No. E5L3Q9 (gorilla adenovirus; SEQ ID NO: 13), UniProt Acc. No. G9G849 (chimpanzee adenovirus; SEQ ID NO: 14), UniProt Acc. No. H8PFZ9 (simian adenovirus serotype 18; SEQ ID NO: 15), UniProt Acc. No. F6KSU4 (simian adenovirus serotype 20; SEQ ID NO: 16), UniProt Acc. No. F2WTK5

(simian adenovirus serotype 49; SEQ ID NO: 17), UniProt Acc. No. A0A0A1EWW1 (rhesus adenovirus serotype 51; SEQ ID NO: 18), UniProt Acc. No. A0A0A1EWX7 (rhesus adenovirus serotype 52; SEQ ID NO: 19), and UniProt Acc. No. A0A0A1EWZ7 (rhesus adenovirus serotype 53; SEQ ID NO: 20).

5

Most preferred sequences of big fragments of crown domains for use in the chimeric constructs of the invention are outlined in the following Table 4:

Table 4: Preferred sequences for big fragment of crown domains for use in chimeric constructs

10

Sequence based on penton base protomer of	Sequence according to UniProt Acc. No.	SEQ ID NO:	N-terminal amino acid selected from positions	C-terminal amino acid selected from positions
hAd3	Q2Y0H9	1	130 to 145	397 to 408
hAd2	P03276	2	130 to 145	424 to 435
hAd4	Q2KSF3	3	126 to 141	378 to 389
hAd5	P12538	4	130 to 145	424 to 435
hAd7	Q9JFT6	5	130 to 145	397 to 408
hAd11	D2DM93	6	130 to 145	414 to 425
hAd12	P36716	7	120 to 135	350 to 361
hAd17	F1DT65	8	117 to 132	369 to 380
hAd25	M0QUK0	9	125 to 140	387 to 398
hAd35	Q7T941	10	131 to 146	444 to 455
hAd37	Q912J1	11	117 to 132	371 to 382
hAd41	F8WQN4	12	128 to 143	361 to 373
gorAd	E5L3Q9	13	131 to 146	415 to 427
ChimpAd	G9G849	14	126 to 141	371 to 382
sAd18	H8PFZ9	15	128 to 143	352 to 363
sAd20	F6KSU4	16	127 to 142	357 to 368
sAd49	F2WTK5	17	128 to 143	355 to 366
rhAd51	A0A0A1EWW1	18	125 to 140	351 to 362
rhAd52	A0A0A1EWX7	19	125 to 140	349 to 360
rhAd53	A0A0A1EWZ7	20	126 to 141	350 to 361

Most preferred sequences of big fragments of crown domains for use in the chimeric constructs of the invention are outlined in the following Table 5:

Table 5: Preferred sequences for big fragment of crown domains for use in chimeric constructs

Sequence based on penton base protomer of	Sequence according to UniProt Acc. No.	SEQ ID NO:	N-terminal amino acid selected from positions	C-terminal amino acid selected from positions
hAd3	Q2Y0H9	1	441 to 444	491 to 494
hAd2	P03276	2	468 to 471	518 to 521
hAd4	Q2KSF3	3	422 to 445	465 to 468
hAd5	P12538	4	468 to 471	491 to 494
hAd7	Q9JFT6	5	441 to 444	464 to 467
hAd11	D2DM93	6	458 to 461	481 to 484
hAd12	P36716	7	394 to 398	418 to 421
hAd17	F1DT65	8	414 to 417	438 to 441
hAd25	M0QUK0	9	441 to 444	454 to 457
hAd35	Q7T941	10	498 to 501	521 to 524
hAd37	Q912J1	11	415 to 418	438 to 441
hAd41	F8WQN4	12	405 to 408	438 to 441
gorAd	E5L3Q9	13	459 to 462	482 to 485
ChimpAd	G9G849	14	421 to 424	444 to 457
sAd18	H8PFZ9	15	396 to 399	419 to 422
sAd20	F6KSU4	16	401 to 404	424 to 427
sAd49	F2WTK5	17	399 to 402	422 to 425
rhAd51	A0A0A1EWW1	18	395 to 398	418 to 421
rhAd52	A0A0A1EWX7	19	393 to 396	416 to 419
rhAd53	A0A0A1EWZ7	20	394 to 397	417 to 420

- 5 A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 2 (hAd2) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12),
- 10 human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus

serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

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A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 3 (hAd3) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 4 (hAd4) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 5 (hAd5) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 7

(hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian
5 adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

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A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 7 (hAd7) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5
15 (hAd5), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus
20 serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

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A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 11 (hAd11) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5
30 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype
35 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 12 (hAd12) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus
5 serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian
10 adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

15 A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 17 (hAd17) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5
20 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus
25 serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

30 A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 25 (hAd25) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11),
35 human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian

adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 35 (hAd35) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 37 (hAd37) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of human adenovirus serotype 41 (hAd41) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus

serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of gorilla adenovirus (gorAd) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of chimpanzee adenovirus (ChimpAd) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect

to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of
5 simian adenovirus serotype 18 (sAd18) is combined with a crown domain of an adenovirus
penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus
serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5
(hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11),
human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human
10 adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus
serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd),
chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 20 (sAd20), simian
adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus
adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect
15 to specific sequences for the multimerization and the crown domain selected for this
combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of
simian adenovirus serotype 20 (sAd20) is combined with a crown domain of an adenovirus
20 penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus
serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5
(hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11),
human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human
adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus
25 serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd),
chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian
adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus
adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect
to specific sequences for the multimerization and the crown domain selected for this
30 combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of
simian adenovirus serotype 49 (sAd49) is combined with a crown domain of an adenovirus
penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus
35 serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5
(hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11),
human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human

adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), rhesus adenovirus serotype 51 (rhAd51), rhesus
5 adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of
10 rhesus adenovirus serotype 51 (rhAd51) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human
15 adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific
20 sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.

A preferred embodiment of the invention is a chimera in which a multimerization domain of rhesus adenovirus serotype 52 (rhAd52) is combined with a crown domain of an adenovirus
25 penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus
30 serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is
35 referred to the specific examples according to Tables 1 to 5.

- A preferred embodiment of the invention is a chimera in which a multimerization domain of rhesus adenovirus serotype 53 (rhAd53) is combined with a crown domain of an adenovirus penton base selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 3 (hAd3), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd41), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), and rhesus adenovirus serotype 52 (rhAd52). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.
- A particularly preferred crown domain for providing chimeras of the invention is the crown domain of the penton base protein of human adenovirus serotype 3 (hAd3). For preferred sequences as regards the amino acid positions of SEQ ID NO: 1 it is referred to Table 4 (big fragment) and Table 5 (small fragment).
- In even more preferred chimeras of the invention, the crown domain of the penton base protein of human adenovirus serotype 3 (hAd3) is combined with a multimerization domain of a penton base protein of an adenovirus selected from human adenovirus serotype 2 (hAd2), human adenovirus serotype 4 (hAd4), human adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35 (hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41), gorilla adenovirus (gorAd), chimpanzee adenovirus (ChimpAd), simian adenovirus serotype 18 (sAd18), simian adenovirus serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51 (rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53 (rhAd53). With respect to specific sequences for the multimerization and the crown domain selected for this combination it is referred to the specific examples according to Tables 1 to 5.
- A particularly preferred crown domain for providing chimeras of the invention is the crown domain of the penton base of chimpanzee adenovirus (ChimpAd). For preferred sequences

as regards the amino acid positions of SEQ ID NO: 14 it is referred to Table 4 (big fragment) and Table 5 (small fragment).

In even more preferred chimeras of the invention, the crown domain of the penton base
5 protein of chimpanzee adenovirus (ChimpAd) is combined with a multimerization domain of a
penton base protein of an adenovirus selected from human adenovirus serotype 3 (hAd3),
human adenovirus serotype 2 (hAd2), human adenovirus serotype 4 (hAd4), human
adenovirus serotype 5 (hAd5), human adenovirus serotype 7 (hAd7), human adenovirus
serotype 11 (hAd11), human adenovirus serotype 12 (hAd12), human adenovirus serotype
10 17 (hAd17), human adenovirus serotype 25 (hAd25), human adenovirus serotype 35
(hAd35), human adenovirus serotype 37 (hAd37), human adenovirus serotype 41 (hAd41),
gorilla adenovirus (gorAd), simian adenovirus serotype 18 (sAd18), simian adenovirus
serotype 20 (sAd20), simian adenovirus serotype 49 (sAd49), rhesus adenovirus serotype 51
(rhAd51), rhesus adenovirus serotype 52 (rhAd52), and rhesus adenovirus serotype 53
15 (rhAd53). With respect to specific sequences for the multimerization and the crown domain
selected for this combination it is referred to the specific examples according to Tables 1 to
5.

As already outlined above, it is one premier embodiment of the invention to include an
20 antigen, more particularly an antigen of an infectious agent such as a virus, bacterium or
other pathogen, or a tumour or cancer antigen, into one or both of L₁ and L₂. With respect to
preferable sites of inclusion of antigens in RGD loops and/or variable loops of adenoviral
crown domains, it is *expressis verbis* referred to WO 2017/167988 A1. As used herein, the
term "antigen" refers a structure recognized by molecules of the immune response, e.g.
25 antibodies, T cell receptors (TCRs) etc.

Antigens of infectious agents include, but are not limited to, e.g. viral infectious agents, such
as HIV, hepatitis viruses such as hepatitis A virus, hepatitis B virus or hepatitis C virus,
herpes virus, varicella zoster virus, rubella virus, yellow fever virus, dengue fever virus,
30 flaviviruses (e.g. Zika virus), influenza viruses, Marburg disease virus, Ebola viruses and
arboviruses such as Chikungunya virus. Antigens of bacterial infectious agents include, but
are not limited to, antigens of e.g. *Legionella*, *Helicobacter*, *Vibrio*, infectious *E. coli* strains,
Staphylococci, *Salmonella* and *Streptococci*. Antigens of infectious protozoan pathogens
include, but are not limited to, antigens of *Plasmodium*, *Trypanosoma*, *Leishmania* and
35 *Toxoplasma*. Further examples of antigens of pathogenic agents include antigens of fungal
pathogens such as antigens of *Cryptococcus neoformans*, *Histoplasma capsulatum*,
Coccidioides immitis, *Blastomyces dermatitidis* and *Candida albicans*.

Specific examples of tumor antigens which can be used according to the invention include, but not limited to 707-AP, AFP, ART-4, BAGE, beta-catenin/m, Bcr-abl, CAMEL, CAP-1, CASP-8, CDC27/m, CDK4/m, CEA, CT, Cyp-B, DAM, ELF2M, ETV6-AML1, G250, GAGE, GnT-V, Gp100, HAGE, HER-2/neu, HLA-A*0201-R170I, HPV-E7, HSP70-2M, HAST-2, hTERT (or hTRT), iCE, KIAA0205, LAGE, LDLR/FUT, MAGE, MART-1/Melan-A, MC1R, myosin/m, MUC1, MUM-1, -2, -3, NA88-A, NY-ESO-1, p190 minor bcr-abl, Pml/RAR.alpha., PRAME, PSA, PSM, RAGE, RU1 or RU2, SAGE, SART-1 or SART-3, TEL/AML1, TPI/m, TRP-1, TRP-2, TRP-2/INT2 and WT1.

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Especially in the context of antigens included into the inventive polypeptides as L₁ and/or L₂, but also with respect to any protein-protein interaction such as receptor-ligand binding, it is possible to include a selection and/or evolutionary process for providing target binding-optimized sequences such as optimized antigens to exert an improved immune response thereto. A preferred process is ribosome display as outlined in detail in Schaffitzel et al. (2001) in: Protein-Protein Interactions, A Molecular Cloning Manual: In vitro selection and evolution of protein-ligand interaction by ribosome display (Golemis E., ed.), pages 535-567, Cold Spring Harbor Laboratory Press, New York. The ribosome display protocol has the advantage of being carried out completely *in vitro* at all steps of the selection process.

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Further possible selection processes are also known in the art and include phage display (Smith (1985) Science 228, 1315-1317; Winter et al. (1994) Annu. Rev. Immunol. 12, 433-455), yeast two-hybrid systems (Fields and Song (1989) Nature 340, 245-246; Chien et al. (1983) Proc. Natl. Acad. Sci. U.S.A. 88, 9578-9582), and cell surface display methods (Georgiu et al. (1993) Trends Biotechnol. 11, 6-10; Boder and Wittrup (1997) Nat. Biotechnol. 15, 553-557).

20

The ribosome display process can basically be used in two ways for optimization of antigens or other amino acid sequences involved in targeting a specific molecule by use of the polypeptides of the invention. Either, an antigen (or other binder) sequence can be selected first from an initial library of polypeptides sequences that can be as large as 10¹⁴ individual sequences, more typically 10⁹ to 10¹⁰ sequences, optionally employing evolutionary procedures as described in detail in Schaffitzel et al. (2001), *supra*. After selection of the optimized antigen sequences, the nucleotide sequence encoding it is cloned into an appropriate vector of the invention such that a polypeptide is expressed where the optimized antigen is included in or represents L₁ and/or L₂ according to formula (I) above.

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- According to an alternative embodiment of this aspect of the invention, a library of potential antigen encoding sequences is directly cloned into a nucleic acid of the invention such that each sequence encodes a polypeptide which is a part of or is, respectively, one or both of L_1 and L_2 as defined in formula (I), *supra*. The inventive polypeptides comprising an initial library
- 5 of antigen sequences (or, in other embodiments, other binder sequences) are than expressed *in vitro* and selection of optimized antigen (or other binder) sequences is carried out according to the ribosome display methodology as outlined in detail in Schaffitzel et al. (2001), *supra*.
- 10 A further embodiment of polypeptides of the invention relates to polypeptides where L_1 and/or L_2 are or are coupled to, respectively, antibody sequences or parts of antibodies such as antibody fragments. In this context of the invention the term "antibody" is an immunoglobulin specifically binding to an antigen.
- 15 The term "antibody fragment" refers to a part of an antibody which retains the ability of the complete antibody to specifically bind to an antigen. Examples of antibody fragments include, but are not limited to, Fab fragments, Fab' fragments, $F(ab')_2$ fragments, heavy chain antibodies, single-domain antibodies (sdAb), scFv fragments, fragment variables (Fv), VH domains, VL domains, nanobodies, IgNARs (immunoglobulin new antigen receptors), di-
- 20 scFv, bispecific T-cell engagers (BITEs), dual affinity re-targeting (DART) molecules, triple bodies, diabodies, a single-chain antibody and the like.
- A "diabody" is a fusion protein or a bivalent antibody which can bind different antigens. A diabody is composed of two single protein chains (typically two scFv fragments) each
- 25 comprising variable fragments of an antibody. Diabodies therefore comprise two antigen-binding sites and can, thus, target the same (monospecific diabody) or different antigens (bispecific diabody).
- The term "single domain antibody" as used in the context of the present invention refers to
- 30 antibody fragments consisting of a single, monomeric variable domain of an antibody. Simply, they only comprise the monomeric heavy chain variable regions of heavy chain antibodies produced by camelids or cartilaginous fish. Due to their different origins they are also referred to VHH or VNAR (variable new antigen receptor)-fragments. Alternatively, single-domain antibodies can be obtained by monomerization of variable domains of
- 35 conventional mouse or human antibodies by the use of genetic engineering. They show a molecular mass of approximately 12-15 kDa and thus, are the smallest antibody fragments capable of antigen recognition. Further examples include nanobodies or nanoantibodies.

Antigen-binding entities useful in the context of the invention also include "antibody mimetic" which expression as used herein refers to compounds which specifically bind antigens similar to an antibody, but which compounds are structurally unrelated to antibodies. Usually, antibody mimetics are artificial peptides or proteins with a molar mass of about 3 to 20 kDa which comprise one, two or more exposed domains specifically binding to an antigen. Examples include inter alia the LACI-D1 (lipoprotein- associated coagulation inhibitor); affilins, e.g. human- γ B crystalline or human ubiquitin; cystatin; Sac7D from *Sulfolobus acidocaldarius*; lipocalin and anticalins derived from lipocalins; DARPins (designed ankyrin repeat domains); SH3 domain of Fyn; Kunits domain of protease inhibitors; monobodies, e.g. the 10th type III domain of fibronectin; adnectins: knottins (cysteine knot miniproteins); atrimers; evibodies, e.g. CTLA4-based binders, affibodies, e.g. three-helix bundle from Z-domain of protein A from *Staphylococcus aureus*; Trans-bodies, e.g. human transferrin; tetranectins, e.g. monomeric or trimeric human C-type lectin domain; microbodies, e.g. trypsin-inhibitor-II; affilins; armadillo repeat proteins. Nucleic acids and small molecules are sometimes considered antibody mimetics as well (aptamers), but not artificial antibodies, antibody fragments and fusion proteins composed from these. Common advantages over antibodies are better solubility, tissue penetration, stability towards heat and enzymes, and comparatively low production costs.

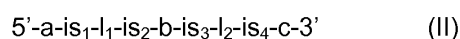
As native penton base proteins do, the polypeptides of the invention assemble into pentameric complexes, 12 of which in turn assemble into virus-like particles (VLPs) in a buffer solution of preferably pH about 5.0 to about 8.0. Preferred examples are buffer conditions at or near physiological conditions such as PBS, pH 7.4, or TBS or TBS-T pH 7.2 to 7.6. Under such conditions, the polypeptides of the invention form VLPs at a temperature of about from about 20 to about 42 °C. The present invention is also directed to such pentameric complexes and VLPs.

Further subject matter of the invention is a nucleic acid coding for the polypeptide as defined herein.

According to the present invention, the terms "nucleic acid" and "polynucleotide" are used interchangeably and refer to DNA, RNA or species containing one or more nucleotide analogues. Preferred nucleic acids or polynucleotides according to the present invention are DNA, most preferred double-stranded (ds) DNA. Nucleotide sequences of the present disclosure are shown from 5' to 3', and the IUPAC single letter code for bases is used, if not otherwise used as indicated.

Another embodiment relates to a nucleic acid prepared for insertion of the versatile segments L_1 and L_2 as defined in general formula (1). That is, this embodiment of the nucleic acid encodes segments A, B and C, but has insertion sites between the segments coding for A
 5 and B, and between the segments encoding B and C.

Thus, this embodiment can be represented by the following general formula (II):



10 wherein

- a is a nucleotide sequence encoding A of general formula (I);
- b is a nucleotide sequence encoding B of general formula (I);
- c is a nucleotide sequence encoding C of general formula (I); and
- l_1, l_2 is each a nucleotide sequence;
- 15 is_1 to is_4 are each independently a nucleotide sequence comprising at least one insertion site.

An insertion site in the context of this embodiment of the invention is preferably a recognition sequence of a restriction enzyme or of a homing endonuclease. More preferably, the is_1 to is_4 are each different insertion sites, more particularly each is_1 to is_4 is a recognition sequence of different restriction enzymes. A preferred embodiment of the nucleic acid prepared for insertion of nucleotide sequences coding for L_1 and L_2 has a nucleotide sequence wherein is_1 comprises an EcoRI site, is_2 comprises a RsrII site, is_3 comprises a SacI site, and is_4 comprises a XbaI site.

25

Restriction enzyme sites are generally well-known to the skilled person. Preferred examples are as defined above, but restriction sites can be selected from a wide variety and guidance can be found at the various manufacturers of restriction enzymes such as New England Biolabs, Inc., Ipswich, MA, USA.

30

Examples of such homing endonuclease (HE) sites include, but are not limited to, recognition sequences of PI-SceI, I-CeuI, I-PpoI, I-HmuI, I-CreI, I-DmoI, PI-PfuI and I-MsoI, PI-PspI, I-SceI, other LAGLIDAG group members and variants thereof, SegH and Hef or other GIY-YIG homing endonucleases, I-ApeII, I-AniI, Cytochrome b mRNA maturase bl3, PI-TfiI and PI-TfuII, PI-ThyI and others; see Stoddard B.L. (2005) Q. Rev. Biophys. 38, 49-95.
 35 Corresponding enzymes are commercially available, e. g. from New England Biolabs Inc., Ipswich, MA, USA.

In preferred embodiments of the present invention, the above-defined nucleic acid additionally comprises at least one site for integration of the nucleic acid into a vector or host cell. The integration site may allow for a transient or genomic incorporation.

5

With respect to the integration into a vector, in particular into a plasmid or virus, the integration site is preferably compatible for integration of the nucleic acid into an adenovirus, adeno-associated virus (AAV), autonomous parvovirus, herpes simplex virus (HSV), retrovirus, rhadinovirus, Epstein-Barr virus, lentivirus, semliki forest virus or baculovirus.

10

Particularly preferred integration sites that may be incorporated into the nucleic acid of the present invention can be selected from the transposon element of Tn7, λ -integrase specific attachment sites and site-specific recombinases (SSRs), in particular LoxP site or FLP recombinase specific recombination (FRT) site. Further preferred mechanisms for integration of the nucleic acid according to the invention are specific homologous recombination sequences such as lef2-603/Orf1629.

15

In further preferred embodiments of the present invention, the nucleic acid as described herein additionally contains one or more resistance markers for selecting against otherwise toxic substances. Preferred examples of resistance markers useful in the context of the present invention include, but are not limited to, antibiotics such as ampicillin, chloramphenicol, gentamycin, spectinomycin, and kanamycin resistance markers.

20

The nucleic acid of the present invention may also contain one or more ribosome binding site(s) (RBS)

25

Further subject-matter of the present invention relates to a vector comprising a nucleic acid as defined above.

Preferred vectors of the present invention are plasmids, expression vectors, transfer vectors, more preferred eukaryotic gene transfer vectors, transient or viral vector-mediated gene transfer vectors. Other vectors according to the invention are viruses such as adenovirus vectors, adeno-associated virus (AAV) vectors, autonomous parvovirus vectors, herpes simplex virus (HSV) vectors, retrovirus vectors, rhadinovirus vectors, Epstein-Barr virus vectors, lentivirus vectors, semliki forest virus vectors and baculovirus vectors.

30
35

Baculovirus vectors suitable for integrating a nucleic acid according to the invention (e.g. present on a suitable plasmid such as a transfer vector) are also subject matter of the present invention and preferably contain site-specific integration sites such as a Tn7 attachment site (which may be embedded in a lacZ gene for blue/white screening of productive integration) and/or a LoxP site. Further preferred baculovirus according to the invention contain (alternative to or in addition to the above-described integration sites) a gene for expressing a substance toxic for host flanked by sequences for homologous recombination. An example for a gene for expressing a toxic substance is the diphtheria toxin A gene. A preferred pair of sequences for homologous recombination is e.g. Isf2-603/Orf1629. The baculovirus can also contain further marker gene(s) as described above, including also fluorescent markers such as GFP, YFP and so on. Specific examples of corresponding baculovirus are, for example disclosed in WO 2010/100278 A1.

Further applicable vectors for use in the invention are disclosed in WO 2005/085456 A1.

Vectors useful in prokaryotic host cells comprise, preferably besides the above-exemplified marker genes (one or more thereof), an origin of replication (ori). Examples are BR322, ColE1, and conditional origins of replication such as OriV and R6Ky, the latter being a preferred conditional origin of replication which makes the propagation of the vector of the present application dependent on the *pir* gene in a prokaryotic host. OriV makes the propagation of the vector of the present application dependent on the *trfA* gene in a prokaryotic host.

Furthermore, the present invention is directed to a host cell containing the nucleic acid of the invention and/or the vector of the present invention.

The host cells may be prokaryotic or eukaryotic. Eukaryotic host cells may for example be mammalian cells, preferably human cells. Examples of human host cells include, but are not limited to, HeLa, Huh7, HEK293, HepG2, KATO-III, IMR32, MT-2, pancreatic β -cells, keratinocytes, bone-marrow fibroblasts, CHP212, primary neural cells, W12, SK-N-MC, Saos-2, WI38, primary hepatocytes, FLC4, 143TK, DLD-1, embryonic lung fibroblasts, primary foreskin fibroblasts, MRC5, and MG63 cells. Further preferred host cells of the present invention are porcine cells, preferably CPK, FS-13, PK-15 cells, bovine cells, preferably MDB, BT cells, bovine cells, such as FLL-YFT cells. Other eukaryotic cells useful in the context of the present invention are *C. elegans* cells. Further eukaryotic cells include yeast cells such as *S. cerevisiae*, *S. pombe*, *C. albicans* and *P. pastoris*. Furthermore, the present invention is directed to insect cells as host cells which include cells

from *S. frugiperda*, more preferably Sf9, Sf21, Express Sf+, High Five H5 cells, and cells from *D. melanogaster*, particularly S2 Schneider cells. Further host cells include *Dictyostelium discoideum* cells and cells from parasites such as *Leishmania spec.*

- 5 Prokaryotic hosts according to the present invention include bacteria, in particular *E. coli* such as commercially available strains like TOP10, DH5 α , HB101, BL21(DE3) etc.

10 The person skilled in the art is readily able to select appropriate vector construct/host cell pairs for appropriate propagation and/or transfer of the nucleic acid elements according to the present invention into a suitable host. Specific methods for introducing appropriate vector elements and vectors into appropriate host cells are equally known to the art and methods can be found in the latest edition of Ausubel et al. (ed.) Current Protocols In Molecular Biology, John Wiley & Sons, New York, USA.

15 In preferred embodiments of the present invention, the vector as defined above additionally comprises a site for site specific recombinases (SSRs), preferably one or more LoxP sites for Cre-lox specific recombination. In further preferred embodiments, the vector according to the present invention comprises a transposon element, preferably a Tn7 attachment site.

20 It is further preferred that the attachment site as defined above is located within a marker gene. This arrangement makes it feasible to select for successfully integrated sequences into the attachment site by transposition. According to preferred embodiments, such a marker gene is selected from luciferase, β -GAL, CAT, fluorescent encoding protein genes, preferably GFP, BFP, YFP, CFP and their variants, and the lacZ α gene.

25 Furthermore, the present invention is directed to a host cell containing the nucleic acid of the invention and/or the vector of the present invention.

30 The host cells may be prokaryotic or eukaryotic. Eukaryotic host cells may for example be mammalian cells, preferably human cells. Examples of human host cells include, but are not limited to, HeLa, Huh7, HEK293, HepG2, KATO-III, IMR32, MT-2, pancreatic β -cells, keratinocytes, bone-marrow fibroblasts, CHP212, primary neural cells, W12, SK-N-MC, Saos-2, WI38, primary hepatocytes, FLC4, 143TK, DLD-1, embryonic lung fibroblasts, primary foreskin fibroblasts, MRC5, and MG63 cells. Further preferred host cells of the present invention are porcine cells, preferably CPK, FS-13, PK-15 cells, bovine cells, preferably MDB, BT cells, bovine cells, such as FLL-YFT cells. Other eukaryotic cells useful in the context of the present invention are *C. elegans* cells. Further eukaryotic cells

include yeast cells such as *S. cerevisiae*, *S. pombe*, *C. albicans* and *P. pastoris*.

Furthermore, the present invention is directed to insect cells as host cells which include cells from *S. frugiperda*, more preferably Sf9, Sf21, Express Sf+, High Five H5 cells, and cells from *D. melanogaster*, particularly S2 Schneider cells. Further host cells include

5 *Dictyostelium discoideum* cells and cells from parasites such as *Leishmania spec.*

Prokaryotic hosts according to the present invention include bacteria, in particular *E. coli* such as commercially available strains like TOP10, DH5 α , HB101, BL21(DE3) etc.

10 The person skilled in the art is readily able to select appropriate vector construct/host cell pairs for appropriate propagation and/or transfer of the nucleic acid elements according to the present invention into a suitable host. Specific methods for introducing appropriate vector elements and vectors into appropriate host cells are equally known to the art and methods can be found in the latest edition of Ausubel et al. (ed.) Current Protocols In Molecular
15 Biology, John Wiley & Sons, New York, USA.

The present invention also provides the polypeptide, the nucleic acid encoding such a polypeptide, the vector containing a polypeptide-encoding nucleic acid, the host cell comprising such a vector as well as the VLP as defined above for use as a medicament, in
20 particular for use in the treatment and/or prevention of an infectious disease, an immune disease, tumour or cancer.

Therefore, the present invention is also directed to pharmaceutical compositions comprising a polypeptide as defined herein, a nucleic acid encoding such a polypeptide, a vector
25 containing a polypeptide-encoding nucleic, a host cell comprising such a vector or a VLP as described above together with at least one pharmaceutically acceptable carrier, excipient and/or diluent.

Generally, the preparation of pharmaceutical compositions in the context of the present
30 invention, their dosages and their routes of administration are known to the skilled person, and guidance can be found in the latest edition of Remington's Pharmaceutical Sciences (Mack publishing Co., Eastern, PA, USA).

The pharmaceutical compositions of the invention contain a therapeutically effective amount
35 of the active ingredient as outlined above. The therapeutically effective amount depends on the active ingredient and in particular on the route of administration. The pharmaceutical composition according to the invention will preferably be applied by parenteral administration,

in particular by infusion such as intravenous, intraarterial or intraosseous infusion, or by injection, e.g. intravenous, intraarterial, intraperitoneal, intramuscular, intradermal, subcutaneous or intrathecal injection. In the case of anti-tumor therapy, the pharmaceutical composition such as a pharmaceutical composition containing VLPs according to the
5 invention, can also be administered by intra-tumoral injection.

Inventive solutions for injection or infusion typically contain VLPs of the invention in water or an aqueous buffer solution, preferably an isotonic buffer at physiological pH. Liquid pharmaceutical compositions of the invention may contain further ingredients such as
10 pharmaceutically acceptable stabilizers, suspending aids, emulsifiers and the likes. Further ingredients of the pharmaceutical composition of the invention are adjuvants, in particular in the context of application of the constructs of the invention for vaccination purposes.

Further subject matter of the invention are methods of treatment making use of the beneficial
15 properties of the polypeptides, nucleic acids, host cells, vectors and/or VLPs of the invention. In a preferred embodiment, the invention provides a method for the prevention and/or treatment of an infectious disease comprising the step of administering to a subject, preferably a human, a therapeutically effective amount of the pharmaceutical composition as defined above, wherein the pharmaceutical composition comprises VLPs of the invention
20 containing antigens (particularly comprised in L₁ and/or L₂ of the inventive polypeptide as defined above) of the infective agent causing the infectious disease. Another embodiment is a method for preventing and/or treating a tumor or cancer disease the step of administering a therapeutically effective amount of the pharmaceutical composition as defined above to a subject, preferably a human, wherein the pharmaceutical composition comprises VLPs of the
25 invention containing one or more tumour antigens (particularly comprised in L₁ and/or L₂ of the inventive polypeptide as defined above).

The present invention is further directed to a method for producing the polypeptide as described herein comprising the step of cultivating the recombinant host cell in a suitable
30 medium, wherein the host cell comprises a vector which comprises a nucleic encoding the polypeptide, under conditions allowing the expression of said polypeptide.

Preferably, the method for producing the polypeptide of the invention further comprises the step of recovering the expressed polypeptide from the host cells and/or the medium. Even
35 more preferred, the method also comprises the step of purifying the recovered polypeptide by purification means known in the art such as centrifugation, gel chromatography, affinity chromatography etc.

The invention also provides a method for producing the VLP as defined herein comprising the step of incubating a solution of the polypeptide under conditions allowing the assembly of the polypeptide into a VLP as outlined before. The proper formation of VLPs can be tested by
5 inspecting a sample solution with an electron microscope.

The Figures show:

Fig. 1: **(A)** Dodecahedra formed by base proteins of certain Adenovirus serotypes represent
10 a versatile scaffold. **(B)** They comprise 60 copies of the adenovirus base protein which can be split into a crown domain (in orange) and a multimerization domain (in blue). Within the multimerization domain, the termini generated by splitting can be reconnected by short oligopeptide linkers yielding contiguous polypeptide chains. Both the N and C-termini of the
15 base protein are contained in the multimerization domain.

Fig. 2: shows a schematical overview of the jellyroll fold domain of a preferred embodiment of the inventive polypeptide based on the penton base protomer of hAd3.

Fig. 3: : The Adenovirus base protein is shown schematically on the extreme left. The crown
20 domain (see Fig. 1) is colored in yellow, the multimerization domain is colored in blue. The N and C-termini of the base protein are contained in the multimerization domain, which mediates penton and dodecahedron formation. Removal of the crown domain yields an autonomous multimerization domain which, in place of formerly the crown domain, now contains oligopeptides, polypeptides, proteins or protein complexes as shown schematically
25 towards from middle to right. The multimerization domains now give rise to virus-like particles presenting these entities on their surface. Naturally, crown domains and engineered crown domains derived from a range of Adenovirus serotypes can also be fitted on out multimerization domain scaffold, including engineered crown domains containing heterologous peptide and polypeptide sequences.

30
Fig. 4: Adenovirus derived dodecahedral display platform (ADDomer) is shown in a schematic fashion. The original particle is shown on the left. The base protein is formed by the multimerization domain (blue) and the crown domain (yellow). 60 base proteins form a virus-like particle (VLP). ADDomers displaying (instead of the crown domain) multiple copies
35 of oligopeptides, polypeptides and protein domains, proteins or protein complexes are shown on the right. Color coding is as in Fig. 3.

Fig. 5: Schematic representation of vector pACEBac_VAJB-CHIK.

The present invention is further illustrated by the following non-limiting example:

5 EXAMPLE

A nucleic acid with the sequence denoted DNasegVAJB-CHIK (SEQ ID NO: 26; flanked by BamHI site at the 5' end and by a HindIII site at the 3' end; see underlined sequence below) was synthesized by a commercial supplier:

```

10  ggatccatgaggagacgagccgtgctaggcggagcgggtggtgtatccggaggggtcctcc
    tcctttcttacgagagcgtgatgcagcaacaggcggcgatgatacagccccactggagg
    ctcccttcgtacccccacggtacctggcgcctacggaagggagaaaacagcattcgttac
    tcggagctgtcgccctgtacgataaccaccaagttgtatctggtggacaacaagtcggc
15  ggacatcgccctccctgaactatcagaacgaccacagcaacttcctgaccacgggtggtgc
    agaacaatgactttacccccacggaggctagcaccacagaccatcaactttgacgagcgg
    tcgcatggggcggtcagctgaagaccatcatgcacaccaacatgcccgagggtgaaaa
    cctgtattttcagagcaccaaagataactttaacgtgtataaagcgaccgcgccgtatc
    tggcgcatggaggtgcagagcaggtctactggtcgctccctgacatgatgcaagacca
20  gtcaccttcgctccacaagacaagtcacaactaccagtggtgggtgcagagcttat
    gcccggtggaagcggaggtagcgttcctgctctcacagatcacgggacctgcccgttac
    gcagcagtatccggggagtcagcgcgtgaccgttactgacgccagacgccgcacctgt
    ccctacgtttacaaggccctgggcatagtcgcgccgcgcgttctttcaagccgcacttt
    ctgataagctt

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25

The construct was cloned into transfer plasmid pACEBac (Geneva Biotech, Geneva, Switzerland) using cleavage sites BamHI and HindIII, giving rise to the construct pACEBac_VAJB-CHIK (SEQ ID NO: 27):

```

30  accggttgacttgggtcaactgtcagaccaagtttactcatatatacttttagattgatt
    taaaacttcatttttaatttaaaaggatctaggtgaagatcctttttgataatctcatg
    accaaaatcccttaacgtgagttttcgttccactgagcgtcagaccccgtagaaaagat
    caaaggatcttcttgagatccttttttctgcgcgtaatctgctgcttgcaaacaaaaa
    aaccaccgctaccagcgggtggtttgtttgccggatcaagagctaccaactctttttccg
35  aaggttaactggcttcagcagagcgcagataccaaatactgttcttctagtgtagccgta
    gttaggccaccacttcaagaactctgtagcaccgcctacatacctcgctctgctaattcc
    tgttaccagtggctgctgccagtggcgataagtcgtgtcttaccgggttggaactcaaga
    cgatagttaccggataaaggcgcagcggctcgggctgaacgggggggttcgtgcacacagcc
    cagcttgagcgaacgacctacaccgaactgagatacctacagcgtgagctatgagaaa
40  gcgccacgcttcccgaagggagaaaaggcggacaggtatccggtaagcggcaggggtcgga

```

acaggagagcgacgagggagcttccaggggaaacgcctgggtatctttatagtcctgt
cgggtttcgccacctctgacttgagcgctgatttttggatgctcgtcagggggcgga
gcctatggaaaaacgccagcaacgcggcctttttacggttcctggccttttgctggcct
tttgctcacatgttctttcctgcggttatccctgattgacttgggtcgtctcttctgtg
5 gatgcgagatgccctgctgaagcgggtgtgggcggacaataaagtcttaactgaaca
aaatagatctaaactatgacaataaagtcttaactagacagaatagttgtaactgaa
atcagtcacgattatgctgtgaaaaagcatactggacttttgttatggctaaagcaaact
cttcattttctgaagtgc aaattgcccgctgtattaaagagggcggtggccaagggcat
gtaaagactatattcgcggttgtgacaatttaccgaacaactccgcgccgggaagc
10 cgatctcggttgaacgaattgttaggtggcggtacttgggtcgatatcaaagtgcac
acttcttcccgatgcccactttgtatagagagccactgcgggatcgtcaccgtaatc
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tgagcgcggtggcaatgccctgcctccggtgctcgcggagactgcgagatcatagata
tagatctcactacgcggctgctcaaacttgggcagaacgtaagccgcgagagcgccaac
15 aaccgcttcttggtcgaaggcagcaagcgcgatgaatgtcttactacggagcaagttcc
cgaggtaatcgaggtccggctgatgttgggagtaggtggctacgtctccgaactcacga
ccgaaaagatcaagagcagcccgcatggatttgacttgggtcagggccgagcctacatgt
gcgaatgatgcccatacttgagccactaactttgttttagggcgactgccctgctgcg
taacatcggttctgctgctgctaacatcggttctgctccataacatcaaacatcgaccac
20 ggcgtaacgcgcttctgctgcttggatgcccgaggcatagactgtacaaaaaacagtcac
aacaagccatgaaaaccgccactgcgcggttaccacgcgtgcgttcggtcaaggttctg
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gcagcagcgaagtcgccataacttcgtatagcatacattatacgaagttatctgtaact
25 ataacggtcctaaggtagcgagtttaaacactagtatcgattcgcgacctactccggaa
tattaatagatcatggagataattaaaatgataaccatctcgcaataaataagtattt
tactgttttcgtaacagttttgtaataaaaaaacctataaatattccggattattcata
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30 atacagccccactggaggtcccttcgtacccccacggtacctggcgccctacggaagg
gagaaacagcattcgttactcggagctgtcgcacctgtacgataccaccaagttgtatc
tggtggacaacaagtcggcgacatcgccctcctgaactatcagaacgaccacagcaac
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catcaactttgacgagcggctcgcgatggggcggtcagctgaagaccatcatgcacacca
35 acatgcccGGAGGTgaaaacctgtattttcagagcaccaaagataactttaacgtgtat
aaagcgacccgcccTatctggcgcatGGAGGTGcagagcaggtctactggctcgtccc
tgacatgatgcaagaccacgtcaccttccgctccacaagacaagtcaacaactaccag
tggtgggtgcagagcttatgcccGGTGAagcggAggtagcgttccctgctctcacagat
cacgggacccctgccgttacgcagcagtatccggggagtcagcgcgtgaccgttactga
40 cgccagacgcgcacctgtccctacgtttacaaggccctgggcatagtcgcgcgcgcg
ttctttcaagccgcactttctgataagcttccatcaactttgacgagcggctcgcgatgg
ggcggtcagctgaagaccatcatgcacaccaacatgcccacgtgaacgagtacatgtt
cagcaacaagttcaaggcgaggagcttgtcgagaagtactagaggatcataatcagcc
ataccacattttagaggttttacttgccttaaaaaacctcccacacctccccctgaac
45 ctgaaacataaaatgaatgcaattgttgttgttaacttgtttattgcagcttataatgg
ttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttactgcatt
ctagttgtgggtttgtccaaactcatcaatgtatcttatcatgtctggatctgatcactg
cttgagcctagaagatccggctgctaacaaagcccgaaggaagctgagttggctgctg
ccaccgctgagcaataactatcataacccttaggtatacccatctaattggaaccaga
50 taagtgaatctagttccaaactattttgtcatttttaattttcgtattagcttacgac
gctacaccacagttcccatctattttgtcactcttccctaaataatccttaaaaactcca
tttccacccctccagttcccaactattttgtccgcccaca

DNA sequencing was used to verify the proper insertion. The open reading frame encodes the protein VAJB-CHIK (SEQ ID NO: 28) which contains the major neutralizing epitope from Chikungunya virus STKDNFNVYKATRPYLAH (SEQ ID NO: 29) in loop L1.

5

VAJB-CHIK (SEQ ID NO: 28):

```

MRRRAVLGGA VVYPEGPPPS YESVMQQQAA MIQPPLEAPF VPPRYLAPTE
GRNSIRYSEL SPLYDTTKLY LVDNKSADIA SLNYQNDHSN FLTTVVQNND
10 FTPTEASTQT INFDESRWG GQLKTIMHTN MPGGENLYFQ STKDNFNVYK
ATRPYLAHGG AEQVYWSLPD MMQDPVTFRS TRQVNNYPVV GAELMPGGSG
GSPALTDHG TLPLRSSIRG VQRVTVDAR RRTCPYVYKA LGIVAPRVLS
SRTF

```

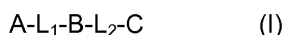
15 pACEBac_VAJB-CHIK was then used to transform DH10EMBacY cells (Geneva Biotech, Geneva, Switzerland) harbouring the baculoviral genome EMBacY as an artificial chromosome (described in Fitzgerald DJ et al. Nat Methods. 2006 Dec;3(12):1021-32 PMID: 17117155). Composite baculovirus with the expression cassette for VAJB1 integrated by Tn7 transposition in the DH10EMBacY cells was then identified by blue/white screening, and
20 recombinant baculovirus generated as described (ibid). *Spodoptera frugiperda* line 21 (Sf21) insect cell cultures were infected with baculovirus thus generated as described by Fitzgerald et al. (2006) Nat Methods, *supra* .

Large-scale (100ml-500ml) expression was carried out in *Trichoplusia ni* Hi5 cells in shaker
25 flasks and recombinant protein expression followed by measuring yellow fluorescent protein (YFP) fluorescence as described (Fitzgerald DJ et al. Nat Methods. 2006 Dec;3(12):1021-32 PMID: 17117155). When YFP fluorescence reached a plateau (normally after 72 hours after proliferation arrest in the cell culture, see Fitzgerald et al, Nat Methods 2006), insect cell cultures were harvested and cells pelleted by centrifugation (4000g, 10min). Cells were
30 frozen in liquid nitrogen and stored at -80 degrees Celsius.

For protein preparation, cells were lysed by freeze-thawing in phosphate buffered saline (PBS) containing whole protease inhibitor cocktail (Roche Ltd). Protein was purified by loading on a sucrose gradient from 15% to 40% w/v sucrose and ultracentrifugation overnight
35 at 100.000 g. The gradient was harvested and protein content identified by means of denaturing polyacrylamide gel electrophoresis (SDS-PAGE) followed by Commassie Brilliant Blue staining. The fractions containing VAJB1 were pooled and dialysed against PBS (or HEPES 10mM, pH 7.4, 50mM NaCl). A second purification step was performed on 5ml HiQ column (BioRAD) using a linear gradient from 50mM to 500mM NaCl. Pentamer and
40 Dodecamer formation was verified by negative stain (uranyl acetate) electron microscopy.

Claims

1. A polypeptide having the structure of formula (I)



5 wherein

A is an N-terminal amino acid stretch of an adenovirus penton base protein;

B is an amino acid stretch of an adenovirus penton base protein;

C is a C-terminal amino acid stretch of an adenovirus penton base;

10 wherein B is an amino acid stretch located between A and C in the sequence of said adenovirus penton base;

wherein A, B and C form the jellyroll fold domain of said adenovirus penton base protein;

L_1 and L_2 are independently from one another selected from the group consisting of an oligopeptide, a polypeptide, a protein, and a protein complex;

15 wherein said oligopeptide, polypeptide, protein and protein complex, respectively, are either essentially non-adenoviral or, if adenoviral, are from an adenovirus having a different serotype compared to the serotype of the adenovirus from which said amino acid stretches A, B and C are derived.

20 2. The polypeptide of claim 1, wherein amino acid stretch A comprises beta sheets 1, 2 and 3 of the jellyroll fold domain of said adenovirus.

3. The polypeptide of claim 1 or 2, wherein amino acid stretch B comprises beta sheets 4 and 5 of the jellyroll fold domain of said adenovirus.

25

4. The polypeptide according to any one of the preceding claims, wherein amino acid stretch C comprises beta sheets 6, 7 and 8 of the jellyroll fold domain of adenovirus.

30

5. The polypeptide according to any one of the preceding claims, wherein amino acid stretches A, B, and C have an amino acid sequence each independently selected from the group consisting of penton bases of human adenovirus serotype 2, human adenovirus serotype 3, human adenovirus serotype 4, human adenovirus serotype 5,

human adenovirus serotype 7, human adenovirus serotype 11, human adenovirus serotype 12, human adenovirus serotype 17, human adenovirus serotype 25, human adenovirus serotype 35, human adenovirus serotype 37, human adenovirus serotype 41, gorilla adenovirus, chimpanzee adenovirus, simian adenovirus serotype 18,
 5 simian adenovirus serotype 20, simian adenovirus serotype 49, rhesus adenovirus serotype 51, rhesus adenovirus serotype 52, and rhesus adenovirus serotype 53.

6. The polypeptide of claim 5, wherein amino acid stretch A has the following consensus sequence (SEQ ID NO: 21):

10

(U)₁₋₄₇ PTX₁GRNSIRY SX₂X₃X₄PX₅X₆DTT X₇X₃YLVDNKSA DIASLNYQND
 HSNFX₅TTVX₉Q NNDX₁₀X₁₁PX₁₂EAX₁₃ TQTINX₁₄DX₁₅RS RWGX₁₆X₁₇LKTIX₁₈
 X₁₉TZ₁Z₂Z₃Z₄Z₅Z₆Z₇Z₈ Z₉Z₁₀Z₁₁Z₁₂Z₁₃Z₁₄Z₁₅

15 wherein: amino acid stretch A ends on the C-terminal side before Z₁ at residue T or at an amino acid from Z₁ to Z₁₅

U is any or no amino acid

X₁ is E or G

X₂ is E or S

20 X₃ is L or V

X₄ is A or S

X₅ is L or Q

X₆ is Y or E

X₇ is R or K

25 X₈ is V or L

X₉ is V or I

X₁₀ is F or Y

X₁₁ is T or S

X₁₂ is A or T or I or G

30 X₁₃ is S or G

X₁₄ is F or L

X₁₅ is E or D

X₁₆ is A or G

X₁₇ is D or Q

35 X₁₈ is L or M

X₁₉ is H or R

Z₁ , if present, is N

- 5 Z₂ , if present, is M
 Z₃ , if present, is P
 Z₄ , if present, is N
 Z₅ , if present, is V or I
 Z₆ , if present, is N
 Z₇ , if present, is E or D
 Z₈ , if present, is Y or F
 Z₉ , if present, is M
 Z₁₀ , if present, is F or S or Y
 10 Z₁₁ , if present, is T or S
 Z₁₂ , if present, is S or N
 Z₁₃ , if present, is K
 Z₁₄ , if present, is F
 Z₁₆ , if present, is K

15

7. The polypeptide of claim 6, wherein amino acid stretch A is selected from the group consisting of the following sequences:
- from an amino acid selected from positions 1 to 48, to an amino acid selected from positions 129 to 144 of UniProt Acc. No. Q2Y0H9;
- 20 from an amino acid selected from positions 1 to 48, to an amino acid selected from positions 129 to 144 of UniProt Acc. No. P03276;
- from an amino acid selected from positions 1 to 44, to an amino acid selected from positions 125 to 140 of UniProt Acc. No. Q2KSF3;
- from an amino acid selected from positions 1 to 48, to an amino acid selected from positions 129 to 144 of UniProt Acc. No. P12538;
- 25 from an amino acid selected from positions 1 to 48, to an amino acid selected from positions 129 to 144 of UniProt Acc. No. Q9JFT6;
- from an amino acid selected from positions 1 to 48, to an amino acid selected from positions 129 to 144 of UniProt Acc. No. D2DM93;
- 30 from an amino acid selected from positions 1 to 38, to an amino acid selected from positions 119 to 134 of UniProt Acc. No. P36716;
- from an amino acid selected from positions 1 to 35, to an amino acid selected from positions 116 to 131 of UniProt Acc. No. F1DT65;
- from an amino acid selected from positions 1 to 43, to an amino acid selected from positions 124 to 139 of UniProt Acc. No. M0QUK0;
- 35 from an amino acid selected from positions 1 to 49, to an amino acid selected from positions 130 to 145 of UniProt Acc. No. Q7T941;

- from an amino acid selected from positions 1 to 35, to an amino acid selected from positions 116 to 131 of UniProt Acc. No. Q912J1;
 from an amino acid selected from positions 1 to 46, to an amino acid selected from positions 127 to 142 of UniProt Acc. No. F8WQN4;
 5 from an amino acid selected from positions 1 to 49, to an amino acid selected from positions 130 to 145 of UniProt Acc. No. E5L3Q9;
 from an amino acid selected from positions 1 to 44, to an amino acid selected from positions 125 to 140 of UniProt Acc. No. G9G849;
 from an amino acid selected from positions 1 to 46, to an amino acid selected from positions 127 to 142 of UniProt Acc. No. H8PFZ9;
 10 from an amino acid selected from positions 1 to 45, to an amino acid selected from positions 126 to 141 of UniProt Acc. No. F6KSU4;
 from an amino acid selected from positions 1 to 46, to an amino acid selected from positions 127 to 142 of UniProt Acc. No. F2WTK5;
 15 from an amino acid selected from positions 1 to 43, to an amino acid selected from positions 124 to 139 of UniProt Acc. No. A0A0A1EWW1;
 from an amino acid selected from positions 1 to 43, to an amino acid selected from positions 124 to 139 of UniProt Acc. No. A0A0A1EWX7; and
 from an amino acid selected from positions 1 to 44, to an amino acid selected from positions 125 to 140 of UniProt Acc. No. A0A0A1EWZ7.
 20

8. The polypeptide according to any one of claims 5 to 7, wherein amino acid stretch B of above general formula (I) has the following sequence (SEQ ID NO: 22):

25 $Z_{17}Z_{18}Z_{19}Z_{20}Z_{21}Z_{22}Z_{23}Z_{24}Z_{25}Z_{26}Z_{27}QVYWSLPDX_{20}MX_{21}DPVTFRST$
 $X_{22}QX_{23}X_{24}NX_{25}PVVGX_{26}ELZ_{28}Z_{29}Z_{30}$

- wherein: amino acid stretch B begins on the N-terminal side at an amino acid from Z_{17} to Z_{27} or at amino acid Q after Z_{27} ;
 30 amino acid stretch B ends on the C-terminal side before Z_{28} at amino acid L or at an amino acid from Z_{28} to Z_{30} ;

- Z_{17} , if present, is L or S
 Z_{18} , if present, is T or P or C
 Z_{19} , if present, is T or P
 35 Z_{20} , if present, is P or S or A or R
 Z_{21} , if present, is N or D
 Z_{22} , if present, is G or V
 Z_{23} , if present, is H or T

	Z ₂₄	, if present, is C
	Z ₂₅	, if present, is G
	Z ₂₆	, if present, is A or V or S
	Z ₂₇	, if present, is E or Q
5	X ₂₀	is L or M
	X ₂₁	is Q or K
	X ₂₂	is Q or R or S
	X ₂₃	is V or I
	X ₂₄	is S or N
10	X ₂₅	is Y or F
	X ₂₆	is A or V
	Z ₂₈	, if present, is M or L
	Z ₂₉	, if present, is P
	Z ₃₀	, if present, is V or F

15

9. The polypeptide of claim 8, wherein amino acid stretch B is selected from the group consisting of the following sequences:
- from an amino acid selected from positions 398 to 409, to an amino acid selected from positions 440 to 443 of UniProt Acc. No. Q2Y0H9;
- 20 from an amino acid selected from positions 425 to 436, to an amino acid selected from positions 467 to 470 of UniProt Acc. No. P03276;
- from an amino acid selected from positions 379 to 390, to an amino acid selected from positions 421 to 444 of UniProt Acc. No. Q2KSF3;
- from an amino acid selected from positions 425 to 436, to an amino acid selected from positions 467 to 470 of UniProt Acc. No. P12538;
- 25 from an amino acid selected from positions 398 to 409, to an amino acid selected from positions 440 to 443 of UniProt Acc. No. Q9JFT6;
- from an amino acid selected from positions 415 to 426, to an amino acid selected from positions 457 to 460 of UniProt Acc. No. D2DM93;
- 30 from an amino acid selected from positions 351 to 362, to an amino acid selected from positions 393 to 397 of UniProt Acc. No. P36716;
- from an amino acid selected from positions 370 to 381, to an amino acid selected from positions 413 to 416 of UniProt Acc. No. F1DT65;
- from an amino acid selected from positions 388 to 399, to an amino acid selected from positions 440 to 443 of UniProt Acc. No. M0QUK0;
- 35 from an amino acid selected from positions 445 to 456, to an amino acid selected from positions 497 to 500 of UniProt Acc. No. Q7T941;

- from an amino acid selected from positions 372 to 383, to an amino acid selected from positions 414 to 417 of UniProt Acc. No. Q912J1;
 from an amino acid selected from positions 362 to 373, to an amino acid selected from positions 404 to 407 of [Please insert UniProt Acc. No. F8WQN4;
 5 from an amino acid selected from positions 416 to 427, to an amino acid selected from positions 458 to 461 of UniProt Acc. No. E5L3Q9;
 from an amino acid selected from positions 372 to 383, to an amino acid selected from positions 420 to 423 of UniProt Acc. No. G9G849;
 from an amino acid selected from positions 353 to 364, to an amino acid selected from positions 395 to 398 of UniProt Acc. No. H8PFZ9;
 10 from an amino acid selected from positions 358 to 369, to an amino acid selected from positions 400 to 403 of UniProt Acc. No. F6KSU4;
 from an amino acid selected from positions 356 to 367, to an amino acid selected from positions 398 to 401 of UniProt Acc. No. F2WTK5;
 15 from an amino acid selected from positions 352 to 363, to an amino acid selected from positions 394 to 397 of UniProt Acc. No. A0A0A1EWW1;
 from an amino acid selected from positions 350 to 361, to an amino acid selected from positions 392 to 395 of UniProt Acc. No. A0A0A1EWX7; and
 from an amino acid selected from positions 351 to 362, to an amino acid selected from positions 393 to 396 of UniProt Acc. No. A0A0A1EWZ7.
 20
10. The polypeptide according to any one of claims 5 to 9, wherein amino acid stretch C of above general formula (I) has the following sequence (SEQ ID NO: 23):

25 $Z_{31}Z_{32}Z_{33}$ ALTDHGT LPLRSSIX₂₇GV QRVTX₂₈TDARR RTCPYVYKA
 LGIVX₃₀PX₃₁VLS SRTF

- wherein: amino acid stretch C begins on the N-terminal side at an amino acid from Z_{31} to Z_{33} or at amino acid A after Z_{33} ;
- 30 Z_{31} , if present, is N
 Z_{32} , if present, is V
 Z_{33} , if present, is P
 X_{27} is R or S or G
 X_{28} is V or I
 35 X_{29} is Y or H
 X_{30} is A or S
 X_{31} is R or K

11. The polypeptide of claim 10, wherein the amino acid stretch C is selected from the group consisting of the following sequences:
- 5 from an amino acid selected from positions 492 to 495, to the C-terminal amino acid of UniProt Acc. No. Q2Y0H9;
- from an amino acid selected from positions 519 to 522, to the C-terminal amino acid of UniProt Acc. No. P03276;
- from an amino acid selected from positions 466 to 469, to the C-terminal amino acid of UniProt Acc. No. Q2KSF3;
- 10 from an amino acid selected from positions 492 to 495, to the C-terminal amino acid of UniProt Acc. No. P12538;
- from an amino acid selected from positions 465 to 468, to the C-terminal amino acid of UniProt Acc. No. Q9JFT6;
- from an amino acid selected from positions 482 to 485, to the C-terminal amino acid of UniProt Acc. No. D2DM93;
- 15 from an amino acid selected from positions 419 to 422, to the C-terminal amino acid of UniProt Acc. No. P36716;
- from an amino acid selected from positions 438 to 441, to the C-terminal amino acid of [Please insert UniProt Acc. No. F1DT65;
- 20 from an amino acid selected from positions 455 to 458, to the C-terminal amino acid of UniProt Acc. No. M0QUK0;
- from an amino acid selected from positions 522 to 525, to the C-terminal amino acid of UniProt Acc. No. Q7T941;
- from an amino acid selected from positions 439 to 442, to the C-terminal amino acid of UniProt Acc. No. Q912J1;
- 25 from an amino acid selected from positions 429 to 432, to the C-terminal amino acid of UniProt Acc. No. F8WQN4;
- from an amino acid selected from positions 483 to 486, to the C-terminal amino acid of UniProt Acc. No. E5L3Q9;
- 30 from an amino acid selected from positions 445 to 448, to the C-terminal amino acid of UniProt Acc. No. G9G849;
- from an amino acid selected from positions 420 to 423, to the C-terminal amino acid of UniProt Acc. No. H8PFZ9;
- from an amino acid selected from positions 425 to 428, to the C-terminal amino acid of UniProt Acc. No. F6KSU4;
- 35 from an amino acid selected from positions 423 to 426, to the C-terminal amino acid of UniProt Acc. No. F2WTK5;

- from an amino acid selected from positions 419 to 422, to the C-terminal amino acid of UniProt Acc. No. A0A0A1EWW1;
from an amino acid selected from positions 417 to 420, to the C-terminal amino acid of UniProt Acc. No. A0A0A1EWX7; and
5 from an amino acid selected from positions 418 to 421, to the C-terminal amino acid of UniProt Acc. No. A0A0A1EWZ7.
12. The polypeptide according to any one of the preceding claims wherein amino acid stretch A has the sequence of positions 1 to 132 of UniProt Acc. No. Q2Y0H9, amino acid stretch B has the sequence of positions 407 to 442 of UniProt Acc. No. Q2Y0H9, and amino acid stretch C has the sequence of positions 493 to 544 of UniProt Acc. No. Q2Y0H9.
13. The polypeptide according to any one of the preceding claims wherein L_1 and/or L_2 is an oligopeptide having a sequence of 4 to 40 amino acids being selected from amino acids G and S.
14. The polypeptide of claim 13 wherein L_1 and/or L_2 is independently selected from the group consisting of GGGS (SEQ ID NO: 24) and GGSGGS (SEQ ID NO: 25).
15. The polypeptide according to any one of claims 1 to 12 wherein L_1 is an adenoviral sequence comprising an RGD loop of an adenovirus penton base having a different serotype compared to the serotype of the adenovirus(es) from which said amino acid stretches A, B and C are derived and/or L_2 is an adenoviral sequence comprising a variable loop of an adenovirus penton base having a different serotype compared to the serotype of the adenovirus from which said amino acid stretches A, B and C are derived.
16. The polypeptide of claim 15 wherein L_1 is a big fragment of a crown domain of an adenovirus penton base having a different serotype compared to the serotype of the adenovirus(es) from which said amino acid stretches A, B and C are derived and L_2 is a small fragment of a crown domain of an adenovirus penton base having a different serotype compared to the serotype of the adenovirus(es) from which said amino acid stretches A, B and C are derived.
17. The polypeptide of claim 16 wherein the big and the small fragment are derived from a penton base protein of the same adenovirus.

18. The polypeptide of claim 16 wherein the big and the small fragment are derived from a penton base protein of different adenoviruses.
- 5 19. The polypeptide according to any one of claims 15 to 18 wherein one or more non-adenoviral sequences are inserted into the RGD loop and/or variable loop.
20. The polypeptide according to any one of the preceding claims wherein L₁ and/or L₂ comprise an antigen.
- 10 21. The polypeptide of claim 20 wherein the antigen is selected from the group consisting of an antigen of an infectious agent and a tumour antigen.
22. The polypeptide according to any one of the preceding claims wherein a nucleic acid, a drug, label and/or binding partner of a biological binding pair is/are coupled to L₁ and/or L₂.
- 15 23. A nucleic acid encoding the polypeptide according to any one of the preceding claims.
- 20 24. A nucleic acid comprising a sequence having the following general formula (II)
- $$5'-a-is_1-l_1-is_2-b-is_3-l_2-is_4-c-3' \quad (II)$$
- wherein
- 25 a is a nucleotide sequence encoding A of general formula (I);
- b is a nucleotide sequence encoding B of general formula (I);
- c is a nucleotide sequence encoding C of general formula (I);
- l₁, l₂ are each a nucleotide sequence; and
- is₁ to is₄ are each independently a nucleotide sequence comprising at least one
- 30 insertion site.
25. The nucleic acid of claim 24 wherein is₁ to is₄ are selected from the group consisting of recognition sequences of restriction enzymes, and recognition sequences of homing endonucleases.
- 35 26. The nucleic acid of claim 25 wherein is₁ comprises an EcoRI site, is₂ comprises a RsrII site, is₃ comprises a SacI site, and is₄ comprises a XbaI site.

27. A vector comprising a nucleic acid according to any one of claims 23 to 26.
28. The vector of claim 27 comprising a nucleic claim according to any one of claims 23
5 to 26 within an expression cassette.
29. A recombinant host cell comprising the nucleic acid according to any one of claims 23 to 26 or the vector of claim 27 or 28.
- 10 30. A pentameric complex of the polypeptide according to any one of claims 1 to 22.
31. A virus-like particle (VLP) comprising 12 pentameric complexes of claim 30.
32. The polypeptide according to any one of claims 1 to 22, the nucleic acid of claim 23,
15 the vector of claim 27 or 28, the host cell of claim 29, or the VLP of claim 31 for use as a medicament.
33. A pharmaceutical composition comprising the polypeptide according to any one of
20 claims 1 to 22, the nucleic acid of claim 23, the vector of claim 27 or 28, the host cell of claim 29, or the VLP of claim 31 together with at least one pharmaceutically acceptable carrier, excipient and/or diluent.
34. A method for producing the polypeptide according to any one of claims 1 to 22
25 comprising the step of cultivating the recombinant host cell of claim 29, wherein the host cell comprises a vector of claim 28 which comprises a nucleic of claim 23, under conditions allowing the expression of said polypeptide.
35. A method for producing the VLP of claim 31 comprising the step of incubating a
30 solution of the polypeptide according to any one of claims 1 to 22 under conditions allowing the assembly of the polypeptide into a VLP.
36. The polypeptide according to any one of claims 1 to 22, the nucleic acid of claim 23,
the vector of claim 27 or 28, the host cell of claim 29, or the VLP of claim 31 for use
35 in the treatment and/or prevention of an infectious disease, an immune disease, tumour or cancer.