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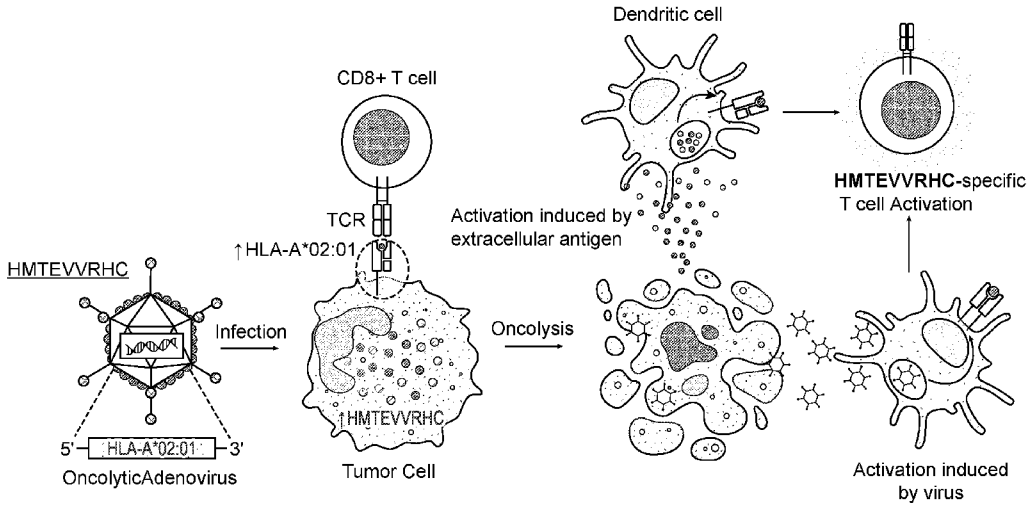


FIG. 3

(57) Abstract: Provided herein are recombinant adenoviruses comprising: (a) a modified E1 coding region; (b) an inactive E3 coding region; (c) a HLA-A*02:01 open reading frame; and (d) an immunopeptide sequence present in a capsid protein encoding region, wherein the immunopeptide sequence comprises a p53-derived immunopeptide.

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RECOMBINANT ONCOLYTIC ADENOVIRUS FOR CANCER THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 63/451,960, filed on March 14, 2023. The disclosure of the prior application is considered part of the disclosure of this application and is incorporated herein by reference in its entirety.

SEQUENCE LISTING

This application contains a Sequence Listing that has been submitted electronically as an ASCII text file named "44807-0451WO1_SL_ST26.xml". The ASCII text file, created on March 12, 2024, is 81,934 bytes in size. The material in the ASCII text file is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

The present disclosure relates to compositions and methods that employ a recombinant oncolytic adenovirus to specifically treat cancers that have p53-mutant tumor cells.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under grant GM135485 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Cancer cells harbor clonal mutations that cause them to produce unique proteins which are not present in normal cells. These cancer-associated proteins, known as neoantigens, can trigger anti-cancer immune responses. A general goal of cancer immunotherapy is to enhance such responses so that the immune system can eliminate neoantigen-expressing cancer cells.

SUMMARY

Provided herein are recombinant adenoviruses comprising: (a) a modified E1 coding region; (b) an inactive E3 coding region; (c) an HLA-A*02:01 open reading frame; and (d) an immunopeptide sequence present in a capsid protein encoding region, wherein the immunopeptide sequence comprises a p53-derived immunopeptide.

In some embodiments, the recombinant adenovirus is an adenovirus serotype 5. In some embodiments, the modified E1 coding region comprises a deletion of an E1B-55K gene and prevents virus-mediated degradation of p53. In some embodiments, the inactive E3 coding region comprises a deletion of an E3-19K gene. In some embodiments, the HLA-A*02:01 open reading frame replaces the E3-19K gene. In some embodiments, the capsid protein encoding region comprises a pIX domain. In some embodiments, the capsid protein encoding region comprises a hexon domain.

In some embodiments, the immunopeptide sequence comprises SEQ ID NO: 1. In some embodiments, the HLA-A*02:01 open reading frame comprises SEQ ID NO: 3. In some embodiments, the recombinant adenovirus further comprises an engineered fiber domain. In some embodiments, the engineered fiber domain comprises SEQ ID NO: 7. In some embodiments, the recombinant adenovirus comprises SEQ ID NO: 9.

Also provided herein are cells comprising any one of the recombinant adenoviruses described herein.

Also provided herein are pharmaceutical compositions comprising any one of the recombinant adenoviruses; or any one of the cells described herein; and a pharmaceutically acceptable carrier.

Also provided herein are methods of increasing surface density of an immunopeptide on a cell, the method comprising delivering any one of the recombinant adenoviruses described herein into the cell under conditions sufficient for replication of the recombinant adenovirus vector in the cell. In some embodiments, the immunopeptide sequence comprises a p53 immunopeptide. In some embodiments, the immunopeptide sequence comprises SEQ ID NO: 1.

Also provided herein are methods of treating a cancer in a subject, the method comprising administering a pharmaceutically effective amount of any one of the pharmaceutical compositions described herein, wherein the cancer comprises a p53 mutation. In some embodiments, the p53

mutation comprises a p53R175H mutation. In some embodiments, the cancer is an ovary cancer, colorectum cancer, esophagus cancer, head and neck cancer, larynx cancer, lung cancer, skin cancer, pancreas cancer, stomach cancer, liver cancer, brain cancer, bladder cancer, breast cancer, uterus cancer, soft tissue cancer, lymph node cancer, prostate cancer, bone cancer, endocrine gland cancer, or cervix cancer.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows an exemplary schematic of an oncolytic virus ("AN-01") that is a replication-competent derivative of human adenovirus serotype 5 (HAd5) as described herein.

FIGs. 2A-2B show exemplary schematics of a platform for the assembly of personalized oncolytic adenoviruses (OAds) that increase the presentation of specified neoantigens. **FIG. 2A** shows an exemplary schematic illustration of the 36 kb human adenovirus 5 (HAdV5) genome showing the programmable elements of this system. A method known as AdenoBuilder permits the assembly of full-length viral genomes from 5-7 plasmid inserts that span the linear genome. These viral segments can each be customized, and then assembled in a large variety of combinations. **FIG. 2B** shows a patient-specific HLA expression cassette is inserted in place of the viral E3-19K gene. Tumor-associated neoantigen peptide sequences, structurally compatible with the selected HLA protein, are inserted into the hypervariable regions of the hexon gene. The non-essential capsid protein pIX is also a site for insertion of heterologous antigens as fusion proteins. A modified fiber gene can expand viral tropism to include cell types that poorly express the adenovirus receptor,

CAR. Cancer specific viral replication can be enhanced by engineering deletions that eliminate expression of the viral E1B-55K. E1A, and/or E4ORF1 genes.

FIG. 3 shows an exemplary schematic of proof-of-concept studies employing a model neoantigen derived from the p53 R175H mutant protein. Recent studies have shown that an immunopeptide (HMTEVVRHC) that contains the most common p53 mutation (R175H) is presented in complex with HLA-A*02:01 (HLA-A2). A prototype replication-competent OAd that encodes this specific HLA protein and expresses hexon-incorporated HMTEVVRHC is used to increase the abundance of this immune complex.

FIG. 4 shows expression of exogenous HLA-A2 on the cell surface following infection by a replication-competent adenovirus. A549 lung carcinoma cells with a CRISPR-mediated deletion of the endogenous HLA gene cluster (HLA-KO) were infected with an OAd that expresses an HLA-A2 transgene cassette positioned within the deleted viral E3 region (as illustrated in **FIG. 2**). Following infection, this OAd restored total HLA expression to levels that were similar to those endogenously expressed by unmodified A549. Cell surface expression of endogenous HLA proteins and exogenous HLA-2 was similarly increased by the addition of interferon γ (right panel).

FIG. 5 shows enhanced cell surface expression of HLA-A2 following infection by a replication-competent OAd. A panel of HLA-A2-positive, p53 R175H-mutant cells was treated with increasing amounts of an HLA-A2-expressing OAd. The abundance of HLA-A2 was measurably increased in TYKNU and KLE cells, in which endogenous levels of HLA-A2 expression are relatively low. Each of these cell lines harbors the common TP53 R175H mutation.

FIGs. 6A-6B show T cell activation by endogenous and exogenous pHLA-A2/R175H peptide complexes. The indicated cell types were co-cultured with stimulated PBMCs. T cell activation was assessed by quantification of interferon-γ by ELISA. **FIG. 6A** shows a bispecific antibody (H2-SCDB) links the endogenous pHLA-A2/ HMTEVVRHC complex and T cell CD3 and thereby triggers T cell activation in unmodified KMS26 cells, which harbor the p53 R175H mutation. T cell activation is absent in p53-knockout derivatives of KMS26, demonstrating that T cell activation is indeed antigen-specific. **FIG. 6B** shows A549 lung carcinoma cells lacking the HLA gene cluster (HLA-KO) and harboring a knock-in of the p53 R175H mutation were infected with the OAd that expresses HLA-A2, across a range of MOI. There was no T cell activation in

the absence of virus. In infected cells, the level of T cell activation could be significantly increased by immunopeptide loading, suggesting that the abundance of HMTEVVRHC was limiting.

DETAILED DESCRIPTION

Neoantigens are presented to neighboring immune cells in a multistep process that involves degradation of the mutant protein by the proteasome and the binding of the resultant peptides to the class 1 major histocompatibility complex (MHC class 1). The bound peptide/MHC-1 complexes localize to the cell surface where they can engage T cells via the T cell receptor. This critical interaction allows the adaptive immune system to recognize the abnormal proteins uniquely produced by tumors and to initiate robust cytotoxic responses that ultimately prevent disease progression.

The ability of a cancer cell to display any given neoantigen is highly dependent on the genetic makeup of the individual, a phenomenon known as antigen restriction. The MHC class 1 complex is composed of several proteins, including the human leukocyte antigen (HLA) proteins which directly bind the neoantigen-derived peptide. The human HLA genes are highly polymorphic and, accordingly, there is considerable variability in the HLA proteins that are expressed in the human population. Because of a variety of structural constraints, HLA proteins differ in the types of peptides they are able to bind and present on the cell surface. For this reason, a given cancer-associated neoantigen may be effectively displayed by one patient, whereas the identical neoantigen arising in the tumor of a different patient may fail to be displayed. This failure occurs when the HLA proteins expressed in an individual lack the ability to bind a neoantigen-associated peptide. Antigen presentation thus requires structural compatibility between the neoantigen and the HLA proteins present.

In some embodiments, a method described herein involves co-expression, by a single adenovirus vector, of both a desired neoantigen and an HLA protein that can bind to that neoantigen and which is also expressed endogenously by the patient. Engineered so as to express a public neoantigen, recurrently found in a subset of cancer patients, and its cognate HLA protein, such a virus would represent a personalized therapeutic for use in a defined patient population. In concept, bespoke therapeutic vectors could be designed for individual patients, based on the unique neoantigens produced by their cancers.

One important neoantigen, present at high frequency in many types of cancer, is TP53 (tumor protein p53, commonly referred to as p53). TP53 was among the first tumor suppressor genes to be identified and is inactivated in the majority of human tumors. Mutations in TP53 most commonly occur as single-nucleotide variants at positions that cluster in the DNA-binding domain. Some of the recurrent mutations that occur within this broad domain occur more frequently than might be expected if such mutations arose entirely by chance; these are known as "hot spot" mutations.

Proteins encoded by the common mutant TP53 alleles are expressed at elevated levels. These overexpressed proteins, unique to tumor cells, are potentially immunogenic and therefore represent an attractive target for immunotherapies.

Recent studies have shown that the most common TP53 mutant, known as R175H, is processed to produce an immunopeptide that can be displayed on the cell surface. Display of this p53 mutant-derived peptide, HMTEVVRHC, is restricted. An HLA allele known as A*02:01 produces a protein that can bind this peptide and present it to T cells. The HLA allele A*02:01 is present in more than 40% of the US Caucasian population.

Antigen presentation is not essential for cell survival, and many tumors lose this capability. Thus, a significant obstacle to the effective presentation of the HMTEVVRHC peptide derived from the overexpressed p53 R175H protein is the general loss of the antigen presentation machinery that occurs during tumorigenesis. Accordingly, many tumor cells exhibit low levels of HLA expression compared to normal cells. Expression of a heterologous HLA allele from a virus is one approach for enhancing antigen presentation in tumor tissue. The rescue of antigen presentation by transgenic HLA expression would be predicted to be broadly beneficial, even in patients who naturally harbor an HLA allele that is structurally compatible with the neoantigen of interest.

In some embodiments, a minigene encoding interferon-γ can be engineered into the virus downstream of the HLA open reading frame and expressed from a bicistronic transcript. Interferon-γ is a potent immunomodulator. In some embodiments, exogenous interferon-γ strongly stimulates the antigen presentation machinery and thereby increases the expression of HLA proteins on the cell surface. The expression of transgenic interferon-γ would thus further stimulate presentation of the desired neoantigen(s).

In some embodiments, a replication-competent recombinant oncolytic virus (e.g., "AN-01") can be designed to specifically treat cancers that harbor the p53 "hot spot" point mutation R175H. This virus would express the HLA allele A*02:01, thereby increasing the surface presentation of HMTEVVRHC. Cancer cells infected by this virus would overexpress A*02:01 and thereby increase display of the HMTEVVRHC peptide arising from endogenous p53 R175H mutant protein. In addition, integration of the HMTEVVRHC coding sequence into the engineered viral capsid would increase the intracellular abundance of this peptide upon capsid degradation, further enhancing its density at the cell surface. By increasing the display of HMTEVVRHC on the surface of infected cells, AN-01 would enhance T cell responses against this neoantigen expressed by infected as well as non-infected cancer cells.

Unmodified adenoviruses have a well-known ability to degrade p53 protein. However, viruses engineered with mutations that prevent the expression of the viral protein E1B-55K lack this ability. Such viruses have shown a tendency to preferentially replicate in some cells that are p53-deficient. A viral modification that prevents the expression of E1B-55K would therefore be expected to preserve high levels of p53 R175H expression, and would potentially increase the replication of AN-01 in some tumor cells that harbor the loss-of-function p53 R175H mutation.

In concept, a therapeutic virus such as AN-01 could be used to increase T cell responses against any tumor that harbors the TP53 R175H mutation and which arises in a patient with the HLA-A*02:01 haplotype. Because HLA expression is generally reduced in cancers, heterologous expression of an A*02:01 transgene could provide beneficial anticancer effects in individuals that have the HLA A*02:01 allelotype.

Strategies to treat p53-mutant tumors are currently lacking. Targeted therapies have mostly been developed to target oncogenes rather than tumor suppressor genes due to the fact that oncogenic proteins are activated by mutations or amplifications, while the proteins encoded by tumor suppressor genes are already inactivated, and reactivation is extremely difficult or impossible, depending on the nature of the alteration.

In some embodiments, described herein are methods in which a modified replication-competent adenovirus vector is used to express a neoantigen as well as an a structurally compatible HLA protein, wherein a method could be applied to any desired neoantigen target for which an HLA binding partner has been identified. In some embodiments, the methods can use a recombinant adenovirus as a therapeutic for p53-mutant tumors.

Provided herein are recombinant adenoviruses that include (a) a modified E1 coding region; (b) an inactive E3 coding region; (c) an HLA-A*02:01 open reading frame; and (d) an immunopeptide sequence present in a capsid protein encoding region, wherein the immunopeptide sequence comprises a p53 immunopeptide. Also provided herein are methods of increasing surface density of a specified immunopeptide on a cell, wherein a method includes introducing any one of the recombinant adenoviruses described herein into the cell under conditions sufficient for replication of the recombinant adenovirus vector in the cell. Also provided herein are methods of treating a cancer in a subject, wherein a method includes administering a pharmaceutically effective amount of any one of the pharmaceutical compositions described herein, wherein the cancer comprises a p53 mutation.

Various non-limiting aspects of these methods are described herein, and can be used in any combination without limitation. Additional aspects of various components of the methods described herein are known in the art.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

As used herein, the term "about", when used herein in reference to a value, refers to a value that is similar, in context to the referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by "about" in that context. For example, in some embodiments, the term "about" may encompass a range of values that are within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value.

As used herein, the term "administration" typically refers to the administration of a composition to a subject or system to achieve delivery of an agent that is, or is included in, the composition. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be ocular, oral, parenteral, etc. In some particular embodiments, administration may be bronchial (e.g., by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, transdermal, etc.), enteral, intra-arterial, intra-venous, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, intracisternal, within a specific organ (e.g., intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical,

tracheal (e.g., by intratracheal instillation), vaginal, vitreal, etc. In some embodiments, administration may involve only a single dose. In some embodiments, administration may involve application of a fixed number of doses. In some embodiments, administration may involve dosing that is intermittent (e.g., a plurality of doses separated in time) and/or periodic (e.g., individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (e.g., perfusion) for at least a selected period of time.

As used herein, the terms "cancer", "malignancy", "neoplasm", "tumor", and "carcinoma", refer to cells that exhibit relatively abnormal, uncontrolled, and/or autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In some embodiments, a tumor may be or comprise cells that are precancerous (e.g., benign), malignant, pre-metastatic, metastatic, and/or non-metastatic. The present disclosure specifically identifies certain cancers to which its teachings may be particularly relevant. In some embodiments, a relevant cancer may be characterized by a solid tumor. In some embodiments, a relevant cancer may be characterized by a hematologic tumor. In general, examples of different types of cancers known in the art include, for example, hematopoietic cancers including leukemias, lymphomas (Hodgkin's and non-Hodgkin's), myelomas and myeloproliferative disorders; sarcomas, melanomas, adenomas, carcinomas of solid tissue, squamous cell carcinomas of the mouth, throat, larynx, and lung, liver cancer, genitourinary cancers such as prostate, cervical, bladder, uterine, and endometrial cancer and renal cell carcinomas, bone cancer, pancreatic cancer, skin cancer, cutaneous or intraocular melanoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, head and neck cancers, breast cancer, gastro-intestinal cancers and nervous system cancers, benign lesions such as papillomas, and the like.

As used herein, a "cell" can refer to either a prokaryotic or eukaryotic cell, optionally obtained from a subject or a commercially available source.

As used herein, "delivering", "gene delivery", "gene transfer", "transducing" can refer to the introduction of an exogenous polynucleotide into a host cell, irrespective of the method used for the introduction. Such methods include a variety of well-known techniques such as vector-mediated gene transfer (e.g., viral infection/transfection, or various other protein-based or lipid-based gene delivery complexes) as well as techniques facilitating the delivery of "naked" polynucleotides (e.g., electroporation, "gene gun" delivery and various other techniques used for the introduction of polynucleotides). The introduced polynucleotide may be stably or transiently

maintained in the host cell. Stable maintenance typically requires that the introduced polynucleotide either contains an origin of replication compatible with the host cell or integrates into a replicon of the host cell such as an extrachromosomal replicon (e.g., a plasmid) or a nuclear or mitochondrial chromosome.

In some embodiments, a polynucleotide can be inserted into a host cell by a gene delivery molecule. Examples of gene delivery molecules can include, but are not limited to, liposomes, micelles biocompatible polymers, including natural polymers and synthetic polymers; lipoproteins; polypeptides; polysaccharides; lipopolysaccharides; artificial viral envelopes; metal particles; and bacteria, or viruses, such as baculovirus, adenovirus and retrovirus, bacteriophage, cosmid, plasmid, fungal vectors and other recombination vehicles typically used in the art which have been described for expression in a variety of eukaryotic and prokaryotic hosts, and may be used for gene therapy as well as for simple protein expression.

As used herein, the term "encode" as it is applied to nucleic acid sequences refers to a polynucleotide which is said to "encode" a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, can be transcribed and/or translated to produce the mRNA for the polypeptide and/or a fragment thereof. The antisense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

As used herein, the term "engineered" refers to the aspect of having been manipulated by the hand of man. For example, a polypeptide is considered to be "engineered" when the polypeptide sequence is manipulated by the hand of man. For example, in some embodiments, an engineered polypeptide comprises a sequence that includes one or more amino acid mutations, deletions and/or insertions that have been introduced by the hand of man into a reference polypeptide sequence. In some embodiments, an engineered polypeptide includes a polypeptide that has been fused (i.e., covalently linked) to one or more additional polypeptides by the hand of man, to form a fusion polypeptide that would not naturally occur *in vivo*. Comparably, a cell or organism is considered to be "engineered" if it has been manipulated so that its genetic information is altered (*e.g.*, new genetic material not previously present has been introduced, for example by transformation, mating, somatic hybridization, transfection, transduction, or other mechanism, or previously present genetic material is altered or removed, for example by substitution or deletion mutation, or by mating protocols). As is common practice and is understood by those in the art,

derivatives and/or progeny of an engineered polypeptide or cell are typically still referred to as "engineered" even though the actual manipulation was performed on a prior entity.

As used herein, the term "exogenous" refers to any material introduced from or originating from outside a cell, a tissue or an organism that is not produced by or does not originate from the same cell, tissue, or organism in which it is being introduced.

As used herein, the term "expression" refers to the process by which polynucleotides are transcribed into mRNA and/or the process by which the transcribed mRNA is subsequently translated into peptides, polypeptides, or proteins. In some embodiments, if the polynucleotide is derived from genomic DNA, expression may include splicing of the mRNA in a eukaryotic cell. The expression level of a gene may be determined by measuring the amount of mRNA or protein in a cell or tissue sample; further, the expression level of multiple genes can be determined to establish an expression profile for a particular sample.

As used herein, "nucleic acid" is used to include any compound and/or substance that comprise a polymer of nucleotides. In some embodiments, a polymer of nucleotides can be referred to as a polynucleotide. Exemplary nucleic acids or polynucleotides can include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β-D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 2'-amino-α-LNA having a 2'-amino functionalization) or hybrids thereof. Naturally-occurring nucleic acids generally have a deoxyribose sugar (e.g., found in deoxyribonucleic acid (DNA)) or a ribose sugar (e.g., found in ribonucleic acid (RNA)).

A nucleic acid can contain nucleotides having any of a variety of analogs of these sugar moieties that are known in the art. A deoxyribonucleic acid (DNA) can have one or more bases selected from the group consisting of adenine (A), thymine (T), cytosine (C), or guanine (G), and a ribonucleic acid (RNA) can have one or more bases selected from the group consisting of uracil (U), adenine (A), cytosine (C), or guanine (G).

In some embodiments, the term "nucleic acid" refers to a deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), or a combination thereof, in either a single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleotides. Unless

otherwise indicated, a particular nucleic acid sequence also implicitly encompasses complementary sequences as well as the sequence explicitly indicated. In some embodiments of any of the isolated nucleic acids described herein, the isolated nucleic acid is DNA. In some embodiments of any of the isolated nucleic acids described herein, the isolated nucleic acid is RNA.

Modifications can be introduced into a nucleotide sequence by standard techniques known in the art, such as site-directed mutagenesis and polymerase chain reaction (PCR)-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., arginine, lysine and histidine), acidic side chains (e.g., aspartic acid and glutamic acid), uncharged polar side chains (e.g., asparagine, cysteine, glutamine, glycine, serine, threonine, tyrosine, and tryptophan), nonpolar side chains (e.g., alanine, isoleucine, leucine, methionine, phenylalanine, proline, and valine), beta-branched side chains (e.g., isoleucine, threonine, and valine), and aromatic side chains (e.g., histidine, phenylalanine, tryptophan, and tyrosine), and aromatic side chains (e.g., histidine, phenylalanine, tryptophan, and tyrosine).

As used herein, the term "nucleotides" and "nt" are used interchangeably herein to generally refer to biological molecules that comprise nucleic acids. Nucleotides can have moieties that contain the known purine and pyrimidine bases. Nucleotides may have other heterocyclic bases that have been modified. Such modifications include, e.g., methylated purines or pyrimidines, acylated purines or pyrimidines, alkylated riboses, or other heterocycles. In some embodiments, nucleic acid modifications can also include a blocking modification comprising a 3' end modification (e.g., a 3' dideoxy C (3'ddC), 3'ddG, 3'ddA, 3'ddT, 3' inverted dT, 3' C3 spacer, 3' amino, 3' biotinylation, or 3' phosphorylation). The terms "polynucleotides," "nucleic acid," and "oligonucleotides" can be used interchangeably, and refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence,

isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise non-naturally occurring sequences. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component.

As used herein, the term "recombinant" refers to polypeptides that are designed, engineered, prepared, expressed, created, manufactured, and/or or isolated by recombinant means, such as polypeptides expressed using a recombinant expression vector transfected into a host cell; polypeptides isolated from a recombinant, combinatorial human polypeptide library; polypeptides isolated from an animal (e.g., a mouse, rabbit, sheep, fish, etc.) that is transgenic for or otherwise has been manipulated to express a gene or genes, or gene components that encode and/or direct expression of the polypeptide or one or more component(s), portion(s), element(s), or domain(s) thereof; and/or polypeptides prepared, expressed, created or isolated by any other means that involves splicing or ligating selected nucleic acid sequence elements to one another, chemically synthesizing selected sequence elements, and/or otherwise generating a nucleic acid that encodes and/or directs expression of the polypeptide or one or more component(s), portion(s), element(s), or domain(s) thereof. In some embodiments, one or more of such selected sequence elements is found in nature. In some embodiments, one or more of such selected sequence elements is designed *in silico*. In some embodiments, one or more such selected sequence elements results from mutagenesis (e.g., *in vivo* or *in vitro*) of a known sequence element, e.g., from a natural or synthetic source such as, for example, in the germline of a source organism of interest (e.g., of a human, a mouse, etc.).

As used herein, the term "subject" refers an organism, typically a mammal (e.g., a human). In some embodiments, a subject is suffering from a relevant disease, disorder, or condition. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject displays one or more signs or symptoms or characteristics of a disease, disorder, or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is someone with one or more features characteristic of susceptibility to or risk of a disease, disorder, or

condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

As used herein, the term "treating" means a reduction in the number, frequency, severity, or duration of one or more (e.g., two, three, four, five, or six) symptoms of a disease or disorder in a subject (e.g., any of the subjects described herein), and/or results in a decrease in the development and/or worsening of one or more symptoms of a disease or disorder in a subject.

As used herein, a "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "*plasmid*", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "*expression vectors*." Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose.

Recombinant Adenovirus

As used herein, a "recombinant adenovirus" can refer to an adenoviral vector used to deliver genetic material into a cell, wherein the adenoviral vector includes a non-enveloped double-stranded DNA vector. In some embodiments, an adenoviral vector has a packaging capacity of about 35 kb. The recombinant adenovirus can be used to deliver a gene of interest into

a eukaryotic cell where the gene of interest is subsequently expressed. In some embodiments, there can be two phases of adenovirus transcription, an early and late phase, which occur before and after replication, respectively. In some embodiments, the recombinant adenovirus can have early-transcribed regions that include E1, E2, E3, and E4 regions. In some embodiments, an E1 region can include E1A and E1B genes that are involved in replication of the recombinant adenovirus. In some embodiments, an E2 region encodes protein that provide the machinery of viral DNA replication and transcription of genes. In some embodiments, an E3 region encodes protein that are involved in modulating the immune response of infected cells. In some embodiments, an E4 region encodes protein that are involved in the metabolism of viral mRNA and provide functions that promote viral DNA replication and shut-off host protein synthesis.

Recombinant adenoviruses can be species-specific and generated from different serotypes (e.g., 51 human serotypes and 27 simian serotypes), wherein human serotypes are divided into six subgroups (e.g., subgroups A-F) based on sequence homology and their ability to agglutinate red blood cells. In some embodiments, the recombinant adenovirus can be a human adenovirus serotype A, B, C, D, E, or F. In some embodiments, the recombinant adenovirus can be a human adenovirus serotype C. In some embodiments, the recombinant adenovirus can be a human adenovirus serotype 1, 2, 5, or 6. In some embodiments, the recombinant adenovirus can be a human adenovirus serotype 5.

Provided herein are recombinant adenoviruses that include (a) a modified E1 coding region; (b) an inactive E3 coding region; (c) a HLA-A*02:01 open reading frame; and (d) an immunopeptide sequence present in a capsid protein encoding region, wherein the immunopeptide sequence comprises a p53 immunopeptide.

In some embodiments, a recombinant adenovirus can be engineered to facilitate enhanced replication in p53-mutant tumor cells, and to increase the presentation of an immunopeptide by a human leukocyte antigen-A (HLA-A) on the surface of a cell. As used herein, an "immunopeptide" can refer to a human leukocyte antigen (HLA) peptide, which is a peptide presented to the immune system on the surface of specific molecules (e.g., Major Histocompatibility Complexes (MHC)). An immunopeptide can be an antigen fragment of about 8-25 amino acids that are loaded intracellularly onto MHC complexes before transportation to the cell surface for T cell inspection. In some embodiments, the immunopeptide can include about 8 to about 24 (e.g., about 8 to about 20, about 8 to about 18, about 8 to about 16, about 8 to about 14, about 8 to about 12, about 8 to

about 10, about 10 to about 24, about 10 to about 20, about 10 to about 18, about 10 to about 16, about 10 to about 14, about 10 to about 12, about 12 to about 24, about 12 to about 20, about 12 to about 18, about 12 to about 16, about 12 to about 14, about 14 to about 24, about 14 to about 20, about 14 to about 18, about 14 to about 16, about 16 to about 24, about 16 to about 20, about 16 to about 18, about 18 to about 24, about 18 to about 20, or about 20 to about 24) amino acids.

In some embodiments, the immunopeptide comprises a tumor-specific neoantigen. In some embodiments, the immunopeptide comprises a HLA-restricted neoantigen. In some embodiments, the immunopeptide comprises a p53-derived immunopeptide. In some embodiments, the immunopeptide comprises a p53 R175H immunopeptide. In some embodiments, the p53 R175H immunopeptide comprises HMTEVVRHC (**SEQ ID NO: 1**). In some embodiments, the p53 R175H immunopeptide comprises IYKQSQHMTEVVRRCPHHERCSDSDG (**SEQ ID NO: 10**).

In some embodiments, the recombinant adenovirus can include an E1 region (e.g., a modified E1 region), an E3 region (e.g., a modified E3 region), and/or a capsid protein encoding region (e.g., a modified capsid protein encoding region). In some embodiments, the recombinant adenovirus can include a plurality of capsid protein encoding regions. In some embodiments, the plurality of capsid protein encoding regions can include a pIX domain, a hexon domain, and/or a fiber domain.

In some embodiments, the recombinant adenovirus can include an inactivated E1 region, wherein the inactivated E1 region comprises an inactivating mutation (e.g., nonsense mutation, insertion, deletion, or point mutation). In some embodiments, the inactivated E1 region can include a deletion mutation. In some embodiments, the inactivated E1 region includes a deletion of an E1B-55K gene. Adenovirus E1B-55K forms part of the p53 degradation complex, and a deletion of this gene can cause increased levels of p53 protein following infection. In some embodiments, the elimination of E1B-55K can result in defective nuclear export of viral transcripts and reduced production of viral proteins, wherein the elimination of E1B-55K expression should further enhance the specificity for replication in tumor cells.

In some embodiments, the recombinant adenovirus can include an inactivated E3 region, wherein the inactivated E3 region comprises an inactivating mutation (e.g., nonsense mutation, insertion, deletion, and/or point mutation). In some embodiments, the inactivated E3 region can include a deletion mutation. In some embodiments, the inactivated E3 region includes a deletion of an E3-19K gene. Adenovirus E3-19K is a multifunctional protein that allows the wild type virus

to escape immune recognition, wherein E3-19K promotes immune escape, in part, by sequestering MHC Class 1 proteins in the endoplasmic reticulum (ER). In some embodiments, replacing E3-19K with HLA-A can result in relieving the functional sequestration of MHC Class 1 while increasing the overall expression of a HLA-A protein. In some embodiments, the HLA-A protein can specifically bind to the HMTEVVRHC peptide.

In some embodiments, the recombinant adenovirus can include a HLA-A*02:01 open reading frame. As used herein, a "HLA-A*02:01" refers to a restriction element for peptide presentation to T cells in disease and cancer, wherein a HLA-A*02:01 open reading frame can regulate translation of cancer associated transcripts and encode HLA-presented immunogenic tumor antigens. In some embodiments, the HLA-A*02:01 open reading frame can be inserted into the E3 region of the recombinant adenovirus. In some embodiments, the HLA-A*02:01 open reading frame is placed downstream of an active viral promoter element and upstream of a transcription terminator. In some embodiments, the HLA-A*02:01 open reading frame can replace the E3-19K gene of the recombinant adenovirus. In some embodiments, the HLA-A*02:01 open reading frame replaces the E3-19K gene so that its expression is controlled by endogenous adenoviral elements. In some embodiments, the HLA-A*02:01 open reading frame comprises **SEQ ID NO: 3**.

In some embodiments, the recombinant adenovirus can include an immunopeptide sequence present in a capsid protein encoding region. As used herein, a "capsid protein" can refer to a protein shell of a virus that encloses its genetic material. The capsid shell of an adenovirus comprises multiple copies of three major capsid proteins (e.g., hexon, penton base, and fiber) and four minor/cement proteins (e.g., IIIa, VI, VIII, and IX, alternatively referred to as pIIIa, pVI, pVIII and pIX). Since adenoviruses are not enveloped by membranes, their capsid proteins are directly recognized by the innate and adaptive immune systems, and displaying an immunopeptide (e.g., a p53 immunopeptide) on the surface of the recombinant adenovirus can stimulate an increased level of B cell and/or T cell immunity. In some embodiments, following the internalization of the recombinant adenovirus into a cell and the subsequent processing of the viral proteins in the ER, the immunopeptide could be generated upon the degradation of the modified capsid protein and therefore be available for display in complex with transgenic HLA-A*02:01.

In some embodiments, the capsid protein encoding region can include a pIX domain, wherein the pIX domain includes the immunopeptide sequence. In some embodiments, the capsid

encoding region can include a hexon domain, wherein the hexon domain includes the immunopeptide sequence. In some embodiments, the recombinant adenovirus includes an immunopeptide sequence inserted into a capsid protein encoding region. In some embodiments, the recombinant adenovirus includes the immunopeptide sequence inserted into one or more capsid protein encoding regions.

In some embodiments, the targeted neoantigen coding sequence HMTEVVRHC is incorporated in-frame with the coding region for the capsid protein pIX. In some embodiments, the targeted neoantigen coding sequence HMTEVVRHC is incorporated in-frame with the coding sequence for adenovirus 5 hexon capsid protein. In some embodiments, the targeted neoantigen coding sequence HMTEVVRHC is incorporated into a hexon capsid protein derived from other adenovirus serotypes or serotype hybrids.

In some embodiments, the recombinant adenovirus further comprises an engineered fiber domain. In some embodiments, the recombinant adenovirus specifically recognizes a coxsackievirus and adenovirus receptor (CAR) to infect a cell. In some embodiments, the recombinant adenovirus specifically recognizes the CAR receptor by a fiber protein. In some embodiments, the fiber protein includes a structure at the c-terminal end of the fiber known as a knob region. In some embodiments, to extend the infectivity of the recombinant adenovirus, the fiber domain can be engineered to include fiber proteins from an adenovirus type 5 and adenovirus type 35. In some embodiments, the engineered fiber domain can include the knob region from an adenovirus type 35. In some embodiments, the engineered fiber domain comprises **SEQ ID NO: 7**.

In some embodiments, the recombinant adenovirus includes a sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to **SEQ ID NO: 9**. In some embodiments, the recombinant adenovirus includes a sequence comprising **SEQ ID NO: 9**.

Pharmaceutical Compositions and Therapeutic Applications

In some embodiments, the present disclosure provides cells comprising any one of the recombinant adenoviruses described herein. In some embodiments, the present disclosure also provides pharmaceutical compositions comprising any one of the recombinant adenoviruses; or any one of the cells described herein; and a pharmaceutically acceptable carrier.

As used herein, the term "pharmaceutical composition" refers to a composition in which an active agent is formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, a pharmaceutical composition can include a buffer, a diluent, solubilizer, emulsifier, preservative, adjuvant, an excipient, or any combination thereof. In some embodiments, a composition, if desired, can also contain one or more additional therapeutically active substances. In some embodiments, the composition is suitable for administration to a human or animal subject. In some embodiments, the active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population.

Also provided herein are methods of increasing surface density of an immunopeptide on a cell, the method including delivering any one of the recombinant adenoviruses described herein into the cell under conditions sufficient for replication of the recombinant adenovirus in the cell. In some embodiments, the immunopeptide comprises a p53 immunopeptide. In some embodiments, the immunopeptide comprises a p53 R175H immunopeptide. In some embodiments, the p53 R175H immunopeptide comprises HMTEVVRHC (**SEQ ID NO: 1**). In some embodiments, the p53 R175H immunopeptide comprises IYKQSQHMTEVVRRCPHHERCSDSDG (**SEQ ID NO: 10**).

Also provided herein are methods of treating a cancer in a subject, the method including administering a pharmaceutically effective amount of any one of the pharmaceutical compositions described herein, wherein the cancer comprises a p53 mutation. In some embodiments, the p53 mutation comprises a p53R175H mutation.

As used herein, the term "pharmaceutically effective amount" means an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, and/or condition in accordance with a therapeutic dosing regimen, to treat the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence and/or severity of, stabilizes one or more characteristics of, and/or delays onset of, one or more symptoms of the disease, disorder, and/or condition. Those of ordinary skill in the art will appreciate that the term "pharmaceutically effective amount" does not in fact require successful treatment be achieved in a particular individual. Rather, a pharmaceutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. For example, in some

embodiments, term "pharmaceutically effective amount", refers to an amount which, when administered to an individual in need thereof in the context of inventive therapy, will block, stabilize, attenuate, or reverse a cancer-supportive process occurring in said individual, or will enhance or increase a cancer-suppressive process in said individual. In the context of cancer treatment, a "pharmaceutically effective amount" is an amount which, when administered to an individual diagnosed with a cancer, will prevent, stabilize, inhibit, or reduce the further development of cancer in the individual. A particularly preferred "pharmaceutically effective amount" of a composition described herein reverses (in a therapeutic treatment) the development of a malignancy or helps achieve or prolong remission of a malignancy. A pharmaceutically effective amount administered to an individual to treat a cancer in that individual may be the same or different from a pharmaceutically effective amount administered to promote remission or inhibit metastasis. As with most cancer therapies, the therapeutic methods described herein are not to be interpreted as, restricted to, or otherwise limited to a "cure" for cancer; rather the methods of treatment are directed to the use of the described compositions to "treat" a cancer, i.e., to effect a desirable or beneficial change in the health of an individual who has cancer. Such benefits are recognized by skilled healthcare providers in the field of oncology and include, but are not limited to, a stabilization of patient condition, a decrease in tumor size (tumor regression), an improvement in vital functions (e.g., improved function of cancerous tissues or organs), a decrease or inhibition of further metastasis, a decrease in opportunistic infections, an increased survivability, a decrease in pain, improved motor function, improved cognitive function, improved feeling of energy (vitality, decreased malaise), improved feeling of well-being, restoration of normal appetite, restoration of healthy weight gain, and combinations thereof. In addition, regression of a particular tumor in an individual (e.g., as the result of treatments described herein) may also be assessed by taking samples of cancer cells from the site of a tumor (e.g., over the course of treatment) and testing the cancer cells for the level of metabolic and signaling markers to monitor the status of the cancer cells to verify at the molecular level the regression of the cancer cells to a less malignant phenotype. Those of ordinary skill in the art will appreciate that, in some embodiments, a pharmaceutically effective amount may be formulated and/or administered in a single dose. In some embodiments, a pharmaceutically effective amount may be formulated and/or administered in a plurality of doses, for example, as part of a dosing regimen.

In some embodiments, the cancer is an ovary cancer, colorectum cancer, esophagus cancer, head and neck cancer, larynx cancer, lung cancer, skin cancer, pancreas cancer, stomach cancer, liver cancer, brain cancer, bladder cancer, breast cancer, uterus cancer, soft tissue cancer, lymph node cancer, prostate cancer, bone cancer, endocrine gland cancer, or cervix cancer.

EXAMPLES

The disclosure is further described in the following examples, which do not limit the scope of the disclosure described in the claims.

Example 1 – Increasing surface density of p53R175H immunopeptide on a p53 mutant tumor cell.

Viruses that contain the aforementioned features are assembled in a modular fashion from synthetic components using a platform known as AdenoBuilder [Jang et al., STAR Protoc. 2022 Jan 20;3(1):101123, PMC8783202]. Briefly, Adenobuilder is comprised of a set of plasmids with inserts that span the wild type Adenovirus serotype 5 (Ad5) genome. This assembly platform permits individual features to be introduced into any region of the virus by standard plasmid cloning methods. In addition, multiple genetic elements can be introduced into single virus in a single assembly step. For AN-01, the HLA cassette is introduced into the viral E3 region, which is contained in a plasmid known as pAd5-B6. The HMTEVVRHC coding sequence will be alternatively introduced in-frame with the viral pIX gene (located in plasmid pAd5-B2) or into hypervariable regions of the hexon gene (located in plasmid pAd5-B5). Next, the inserts of these plasmids, together with the remaining, unmodified regions of the viral genome harbored in other AdenoBuilder plasmids, are excised by restriction digestion and assembled in vitro. The resulting synthetic genomes are directly introduced into the packaging cell line HEK293 to produce infectious virus.

SEQ ID NO: 1 – p53 R175H immunopeptide

HMTEVVRHC

SEQ ID NO: 2 - Human adenovirus 5, complete genome, unmodified

CATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAGGGGGTGG
AGTTTGTGACGTGGCGCGGGGCGTGGGAACGGGGCGGGTGACGTAGTAGTGTGGCG
GAAGTGTGATGTTGCAAGTGTGGCGGAACACATGTAAGCGACGGATGTGGCAAAAG

TGACGTTTTTGGTGTGCGCCGGTGTACACAGGAAGTGACAATTTTCGCGCGGTTTTA
GGCGGATGTTGTAGTAAATTTGGGCGTAACCGAGTAAGATTTGGCCATTTTCGCGGG
AAAACTGAATAAGAGGAAGTGAAATCTGAATAATTTTGTGTTACTCATAGCGCGTA
ATATTTGTCTAGGGCCGCGGGGACTTTGACCGTTTACGTGGAGACTCGCCCAGGTGT
TTTTCTCAGGTGTTTTCCGCGTTCCGGGTCAAAGTTGGCGTTTTATTATTATAGTCAG
CTGACGTGTAGTGTATTTATACCCGGTGAGTTCCTCAAGAGGCCACTCTTGAGTGCC
AGCGAGTAGAGTTTTCTCCTCCGAGCCGCTCCGACACCGGGACTGAAAATGAGACA
TATTATCTGCCACGGAGGTGTTATTACCGAAGAAATGGCCGCCAGTCTTTTGGACCA
GCTGATCGAAGAGGTACTGGCTGATAATCTTCCACCTCCTAGCCATTTTGAACCACC
TACCCTTCACGAACTGTATGATTTAGACGTGACGGCCCCCGAAGATCCCAACGAGG
AGGCGGTTTCGCAGATTTTTCCCGACTCTGTAATGTTGGCGGTGCAGGAAGGGATTG
ACTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCCTCACCTTTCCCGGCA
GCCCGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCCAAACCTTGTACC
GGAGGTGATCGATCTTACCTGCCACGAGGCTGGCTTTCCACCCAGTGACGACGAGG
ATGAAGAGGGTGAGGAGTTTGTGTTAGATTATGTGGAGCACCCCGGGCACGGTTGC
AGGTCTTGTCATTATCACCGGAGGAATACGGGGGACCCAGATATTATGTGTTCGCTT
TGCTATATGAGGACCTGTGGCATGTTTGTCTACAGTAAGTGAAAATTATGGGCAGTG
GGTGATAGAGTGGTGGGTTTGGTGTGGTAATTTTTTTTTTAATTTTTACAGTTTTGTG
GTTTAAAGAATTTTGTATTGTGATTTTTTTAAAAGGTCCTGTGTCTGAACCTGAGCCT
GAGCCCGAGCCAGAACCGGAGCCTGCAAGACCTACCCGCCGTCCTAAAATGGCGCC
TGCTATCCTGAGACGCCCGACATCACCTGTGTCTAGAGAATGCAATAGTAGTACGGA
TAGCTGTGACTCCGGTCCTTCTAACACACCTCCTGAGATACACCCGGTGGTCCCGCT
GTGCCCCATTAAACCAGTTGCCGTGAGAGTTGGTGGGCGTCGCCAGGCTGTGGAATG
TATCGAGGACTTGCTTAACGAGCCTGGGCAACCTTTGGACTTGAGCTGTAAACGCCC
CAGGCCATAAGGTGTAAACCTGTGATTGCGTGTGTGGTTAACGCCTTTGTTTGCTGA
ATGAGTTGATGTAAGTTTAATAAAGGGTGAGATAATGTTTAACTTGCATGGCGTGTT
AAATGGGGCGGGGCTTAAAGGGTATATAATGCGCCGTGGGCTAATCTTGGTTACATC
TGACCTCATGGAGGCTTGGGAGTGTTTGGAAGATTTTTCTGCTGTGCGTAACTTGCT
GGAACAGAGCTCTAACAGTACCTCTTGGTTTTGGAGGTTTCTGTGGGGCTCATCCCA
GGCAAAGTTAGTCTGCAGAATTAAGGAGGATTACAAGTGGGAATTTGAAGAGCTTT
TGAAATCCTGTGGTGAGCTGTTTGATTCTTTGAATCTGGGTCACCAGGCGCTTTTCCA
AGAGAAGGTCATCAAGACTTTGGATTTTTCCACACCGGGGCGCGCTGCGGCTGCTGT
TGCTTTTTTGAGTTTTATAAAGGATAAATGGAGCGAAGAAACCCATCTGAGCGGGGG
GTACCTGCTGGATTTTCTGGCCATGCATCTGTGGAGAGCGGTTGTGAGACACAAGAA
TCGCCTGCTACTGTTGTCTTCCGTCCGCCCGGCGATAATACCGACGGAGGAGCAGCA
GCAGCAGCAGGAGGAAGCCAGGCGGCGGCGGCAGGAGCAGAGCCCATGGAACCCG
AGAGCCGGCCTGGACCCTCGGGAATGAATGTTGTACAGGTGGCTGAACTGTATCCA
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GGCTGCAGCCAGGGGATGATTTTGAGGAGGCTATTAGGGTATATGCAAAGGTGGCA
CTTAGGCCAGATTGCAAGTACAAGATCAGCAAACTTGTAAATATCAGGAATTGTTGC
TACATTTCTGGGAACGGGGCCGAGGTGGAGATAGATACGGAGGATAGGGTGGCCTT
TAGATGTAGCATGATAAATATGTGGCCGGGGGTGCTTGGCATGGACGGGGTGGTTA
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CAACCTTATCCTACACGGTGTAAGCTTCTATGGGTTTAACAATACCTGTGTGGAAGC
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GTGTCGCCCCAAAAGCAGGGCTTCAATTAAGAAATGCCTCTTTGAAAGGTGTACCTT
GGGTATCCTGTCTGAGGGTAACTCCAGGGTGCGCCACAATGTGGCCTCCGACTGTGG
TTGCTTCATGCTAGTGAAAAGCGTGGCTGTGATTAAGCATAACATGGTATGTGGCAA
CTGCGAGGACAGGGCCTCTCAGATGCTGACCTGCTCGGACGGCAACTGTCACCTGCT
GAAGACCATTCACGTAGCCAGCCACTCTCGCAAGGCCTGGCCAGTGTTTGAGCATA
ACATACTGACCCGCTGTTCCTTGCATTTGGGTAACAGGAGGGGGGTGTTCCTACCTT
ACCAATGCAATTTGAGTCACACTAAGATATTGCTTGAGCCCGAGAGCATGTCCAAGG
TGAACCTGAACGGGGTGTTTGACATGACCATGAAGATCTGGAAGGTGCTGAGGTAC
GATGAGACCCGCACCAGGTGCAGACCCTGCGAGTGTGGCGGTAAACATATTAGGAA
CCAGCCTGTGATGCTGGATGTGACCGAGGAGCTGAGGCCCGATCACTTGGTGCTGGC
CTGCACCCGCGCTGAGTTTGGCTCTAGCGATGAAGATACAGATTGAGGTACTGAAAT
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CAGCCGCTGCAGCCACCGCCCGCGGGATTGTGACTGACTTTGCTTTCCTGAGCCCGC
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TGGCACAATTGGATTCTTTGACCCGGGAACTTAATGTCGTTTCTCAGCAGCTGTTGG
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GGGTCCTGTGTATTTTTTCCAGGACGTGGTAAAGGTGACTCTGGATGTTCAGATACA
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GGGTGGTGTTGTAGATGATCCAGTCGTAGCAGGAGCGCTGGGCGTGGTGCCTAAAA
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AAGCGGTTAAGCTGGGATGGGTGCATACGTGGGGATATGAGATGCATCTTGGACTG
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ACCACCAGCACAGTGTATCCGGTGCACTTGGGAAATTTGTCATGTAGCTTAGAAGGA
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TCCATAATGATGGCAATGGGCCCACGGGCGGCGGCCTGGGCGAAGATATTTCTGGG
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GCGCGGGCGGAGGGTGCCAGACTGCGGTATAATGGTTCCATCCGGCCCAGGGGCGT
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GAAAGCAGGTTCCTGAGCAGCTGCGACTTACCGCAGCCGGTGGGCCCGTAAATCAC
ACCTATTACCGGGTGCAACTGGTAGTTAAGAGAGCTGCAGCTGCCGTCATCCCTGAG
CAGGGGGGCCACTTCGTTAAGCATGTCCCTGACTCGCATGTTTTCCCTGACCAAATC
CGCCAGAAGGCGCTCGCCGCCCAGCGATAGCAGTTCTTGCAAGGAAGCAAAGTTTT
TCAACGGTTTGAGACCGTCCGCCGTAGGCATGCTTTTGAGCGTTTGACCAAGCAGTT
CCAGGCGGTCCCACAGCTCGGTCACCTGCTCTACGGCATCTCGATCCAGCATATCTC
CTCGTTTCGCGGGTTGGGGCGGCTTTCGCTGTACGGCAGTAGTCGGTGCTCGTCCAG
ACGGGCCAGGGTCATGTCTTTCCACGGGCGCAGGGTCCTCGTCAGCGTAGTCTGGGT
CACGGTGAAGGGGTGCGCTCCGGGCTGCGCGCTGGCCAGGGTGCGCTTGAGGCTGG

TCCTGCTGGTGCTGAAGCGCTGCCGGTCTTCGCCCTGCGCGTCGGCCAGGTAGCATT
TGACCATGGTGTCATAGTCCAGCCCCTCCGCGGCGTGGCCCTTGGCGCGCAGCTTGC
CCTTGGAGGAGGCGCCGCACGAGGGGCAGTGCAGACTTTTGAGGGCGTAGAGCTTG
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SEQ ID NO: 3 - HLA-A*02:01

ATGGCCGTCATGGCGCCCCGAACCCTCGTCCTGCTACTCTCGGGGGCTCTGGCCCTG
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GATAGAAAAGGAGGGAGCTACTCTCAGGCTGCAAGCAGTGACAGTGCCCAGGGCTC
TGATGTGTCTCTCACAGCTTGTAAAGTGTGA

SEQ ID NO: 4 - C-terminal addition to pIX orf to display mutant P53 R175H peptide HMTEVVRHC (amino acid)

KQSQHMTEVVRHCPHHE

SEQ ID NO: 5 - C-terminal addition to pIX orf to display mutant P53 R175H peptide HMTEVVRHC (nucleic acid)

AAGCAGTCACAGCACATGACGGAGGTTGTGAGGCACTGCCCCCACCATGAG

SEQ ID NO: 6 - 30 spacer

TCGAGATCCCAACCTATCTGAGCGAAGATGAACTGAAAGCCGCCGAAGCCGCCTTC
AAACGCCACAACCCAACCGCGGAAGCAGTCACAGCACATGACGGAGGTTGTGAGGC
ACTGCCCCCACCATGAG

SEQ ID NO: 7 - Ad5/35 hybrid fiber (Ad5 base-Ad35 shaft-Ad35 knob) (amino acid)

MKRARPSEDTFNPVYPYDTETGPPTVPFLTPPFVSPNGFQESPPGVLTLKCLTPLTTTGGS
LQLKVGGGLTVDDTDGTLQENIRATAPITKNNHSVELSIGNGLETQNNKLCAKLGNGLK
FNNGDICIKDSINTLWTGINPPPNCQIVENTNTNDGKLTLVLVKNGGLVNGYVSLVGVSD
TVNQMFTQKTANIQLRLYFDSSGNLLTEESDLKIPLKNKSSTATSETVASSKAFMPSTTA
YPFNTTTRDSENYIHGICYYMTSYDRSLFPLNISIMLNSRMISSNVAYAIQFEWNLNASES
PESNIATLTTSPFFFSYITEDDN

SEQ ID NO: 8 - Ad5/35 hybrid fiber (Ad5 base-Ad35 shaft-Ad35 knob) (nucleic acid)

ATGAAGCGCGCAAGACCGTCTGAAGATACCTTCAACCCCGTGTATCCATATGACAC
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TTTCAAGAGAGTCCCCCTGGAGTTCTTACTTTAAAATGTTTAACCCCACTAACAACC
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SEQ ID NO: 9 - AN-01 replication-competent oncolytic virus

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CATCGTAGTCATGCTCATGCAGATAAAGGCAGGTAAGCTCCGGAACCACCACAGAA
AAAGACACCATTTTTCTCTCAAACATGTCTGCGGGTTTCTGCATAAACACAAAATAA
AATAACAAAAAAACATTTAAACATTAGAAGCCTGTCTTACAACAGGAAAAACAACC
CTTATAAGCATAAGACGGACTACGGCCATGCCGGCGTGACCGTAAAAAAACTGGTC
ACCGTGATTAAAAAGCACCACCGACAGCTCCTCGGTCATGTCCGGAGTCATAATGTA
AGACTCGGTAAACACATCAGGTTGATTCACATCGGTCAGTGCTAAAAAGCGACCGA

AATAGCCCGGGGGAATACATACCCGCAGGCGTAGAGACAACATTACAGCCCCCATA
GGAGGTATAACAAAATTAATAGGAGAGAAAAACACATAAACACCTGAAAAACCCTC
CTGCCTAGGCAAAATAGCACCCTCCCGCTCCAGAACAACATACAGCGCTTCCACAG
CGGCAGCCATAACAGTCAGCCTTACCAGTAAAAAAGAAAACCTATTAAAAAAACAC
CACTCGACACGGCACCAGCTCAATCAGTCACAGTGTAAAAAAGGGCCAAGTGCAGA
GCGAGTATATATAGGACTAAAAAATGACGTAACGGTTAAAGTCCACAAAAAACACC
CAGAAAACCGCACGCGAACCTACGCCCAGAAACGAAAGCCAAAAAACCCCACAACT
TCCTCAAATCGTCACTTCCGTTTTCCCACGTTACGTAACTTCCCATTTTAAGAAAACT
ACAATTCCCAACACATACAAGTTACTCCGCCCTAAAACCTACGTCACCCGCCCCGTT
CCCACGCCCCGCGCCACGTCACAAACTCCACCCCCTCATTATCATATTGGCTTCAAT
CCAAAATAAGGTATATTATTGATGATG

SEQ ID NO: 10 - p53 R175H immunopeptide

IYKQSQHMTEVVRRCPHHERCSDSDG

Example 2 - Development of replication-competent oncolytic adenoviruses (OAds)

A platform, as described herein, is designed for the rapid assembly and packaging of bespoke OAds that simultaneously boost the *in vivo* expression of tumor-specific neoantigens along with compatible, patient-specific HLA proteins. The specified neoantigen(s) and the corresponding HLA protein are co-expressed from a single personalized virus. By boosting the presentation of tumor-specific immunopeptide/HLA complexes on infected cells after *in vivo* administration, these viruses are designed to stimulate the expansion of cytotoxic CD8+ T cells and reactivate memory helper T cells, which can then mediate highly specific anti-tumor effects.

Adenoviruses are highly immunogenic. This property is extensively exploited in the generation of replication-incompetent adenovirus-based vaccines. The natural immunogenicity of adenoviruses also contributes to the anti-tumor effects of replication-competent OAds, which trigger antigen release upon cell lysis. In some embodiments, incorporating tumor-derived neoantigens and compatible HLA genes into the next-generation OAds may provoke more robust and specific anti-tumor responses.

Personalized viruses can be rapidly assembled from plasmid modules via an *in vitro* assembly system called AdenoBuilder (**FIG. 2**). In this system, plasmid inserts that span the human Adenovirus serotype 5 (HAdV5) genome are assembled enzymatically. Because this synthetic genome assembly platform is modular, it is straightforward to combine premade elements, such as high-frequency HLA transgenes, and tumor-derived antigen sequences, into customized viruses. For the assembly of personalized OAds, peptide neoantigens can be encoded into permissive sites

in the capsid proteins hexon or pIX and thereby expressed at high levels after infection as viral-fusion proteins. Arrays of antigenic protein sequences as well as immune enhancers, such as platelet-derived growth factor (PDGF) or epidermal growth factor (EGF), can also be expressed as traditional transgenes in tandem with the HLA protein from bicistronic transgene cassettes.

Another important feature that are introduced into the OAds are specific deletions that are known to allow them to replicate selectively in cancer cells. For example, viruses with deletions in E1A, E1B and E4ORF1 are defective for a variety of functions. Cancer cells in effect complement these defects and permit robust replication.

Initial proof-of-concept studies were focused on a so-called "public" neoantigen, *i.e.* one that is present in many tumors. A particularly widespread neoantigen, present at high frequency in many types of cancer, is TP53 (tumor protein p53, commonly referred to as p53). Proteins encoded by common mutant TP53 alleles are generally expressed at elevated levels. These overexpressed proteins, unique to tumor cells, are potentially immunogenic and therefore represent an attractive target for immunotherapies.

Recent studies have shown that the most common TP53 mutant, known as R175H, is processed to produce an immunopeptide that can be displayed on the cell surface (**FIG. 3**). Display of this p53 mutant-derived peptide, HMTEVVRHC, is restricted to HLA- A*02:01. The HLA allele A*02:01 is present in more than 40% of the US Caucasian population.

A replication-competent recombinant oncolytic virus prototype was designed for the treatment of cancers that harbor the p53 "hot spot" point mutation R175H. This virus expresses the HLA allele A*02:01, thereby increasing the surface presentation of HMTEVVRHC. Studies (**FIG. 4**) have shown that cancer cells infected by this virus overexpress A*02:01 and thereby increase display of the HMTEVVRHC peptide arising from endogenous p53 R175H mutant protein. Incorporation of the HMTEVVRHC coding sequence into the engineered viral capsid substantially increases the intracellular abundance of this peptide upon capsid degradation, further enhancing its density at the cell surface (**FIG. 5**). In vitro experiments (**FIG. 6**) demonstrate that this virus effectively enhances the display of HMTEVVRHC on the surface of infected cells and facilitates antigen-specific T cell activation.

WHAT IS CLAIMED IS:

1. A recombinant adenovirus comprising:
   (a) a modified E1 coding region;
   (b) an inactive E3 coding region;
   (c) a HLA-A*02:01 open reading frame; and
   (d) an immunopeptide sequence present in a capsid protein encoding region,
   wherein the immunopeptide sequence comprises a p53-derived immunopeptide.

2. The recombinant adenovirus vector of claim 2, wherein the recombinant adenovirus is an adenovirus serotype 5.

3. The recombinant adenovirus of claim 1 or 2, wherein the modified E1 coding region comprises a deletion of an E1B-55K gene and prevents virus-mediated degradation of p53.

4. The recombinant adenovirus of any one of claims 1-3, wherein the inactive E3 coding region comprises a deletion of an E3-19K gene.

5. The recombinant adenovirus of claim 4, wherein the HLA-A*02:01 open reading frame replaces the E3-19K gene.

6. The recombinant adenovirus of any one of claims 1-5, wherein the capsid protein encoding region comprises a pIX domain.

7. The recombinant adenovirus of any one of claims 1-6, wherein the capsid protein encoding region comprises a hexon domain.

8. The recombinant adenovirus of any one of claims 1-7, wherein the immunopeptide sequence comprises SEQ ID NO: 1.

9. The recombinant adenovirus of any one of claims 1-8, wherein the HLA-A*02:01 open reading frame comprises SEQ ID NO: 3.

10. The recombinant adenovirus of any one of claims 1-9, further comprising an engineered fiber domain.

11. The recombinant adenovirus of claim 10, wherein the engineered fiber domain comprises SEQ ID NO: 7.

12. The recombinant adenovirus of any one of claims 1-11, wherein the recombinant adenovirus comprises SEQ ID NO: 9.

13. A cell comprising the recombinant adenovirus of any one of claims 1-12.

14. A pharmaceutical composition comprising the recombinant adenovirus of any one of claims 1-12; or the cell of claim 13; and a pharmaceutically acceptable carrier.

15. A method of increasing surface density of an immunopeptide on a cell, the method comprising delivering the recombinant adenovirus of any one of claims 1-12 into the cell under conditions sufficient for replication of the recombinant adenovirus vector in the cell.

16. The method of claim 15, wherein the immunopeptide sequence comprises a p53 immunopeptide.

17. The method of claim 15 or 16, wherein the immunopeptide sequence comprises SEQ ID NO: 1.

18. A method of treating a cancer in a subject, the method comprising administering a pharmaceutically effective amount of the pharmaceutical composition of claim 14, wherein the cancer comprises a p53 mutation.

19. The method of claim 18, wherein the p53 mutation comprises a p53R175H mutation.

20. The method of claim 18 or 19, wherein the cancer is an ovary cancer, colorectum cancer, esophagus cancer, head and neck cancer, larynx cancer, lung cancer, skin cancer, pancreas cancer, stomach cancer, liver cancer, brain cancer, bladder cancer, breast cancer, uterus cancer, soft tissue cancer, lymph node cancer, prostate cancer, bone cancer, endocrine gland cancer, or cervix cancer.

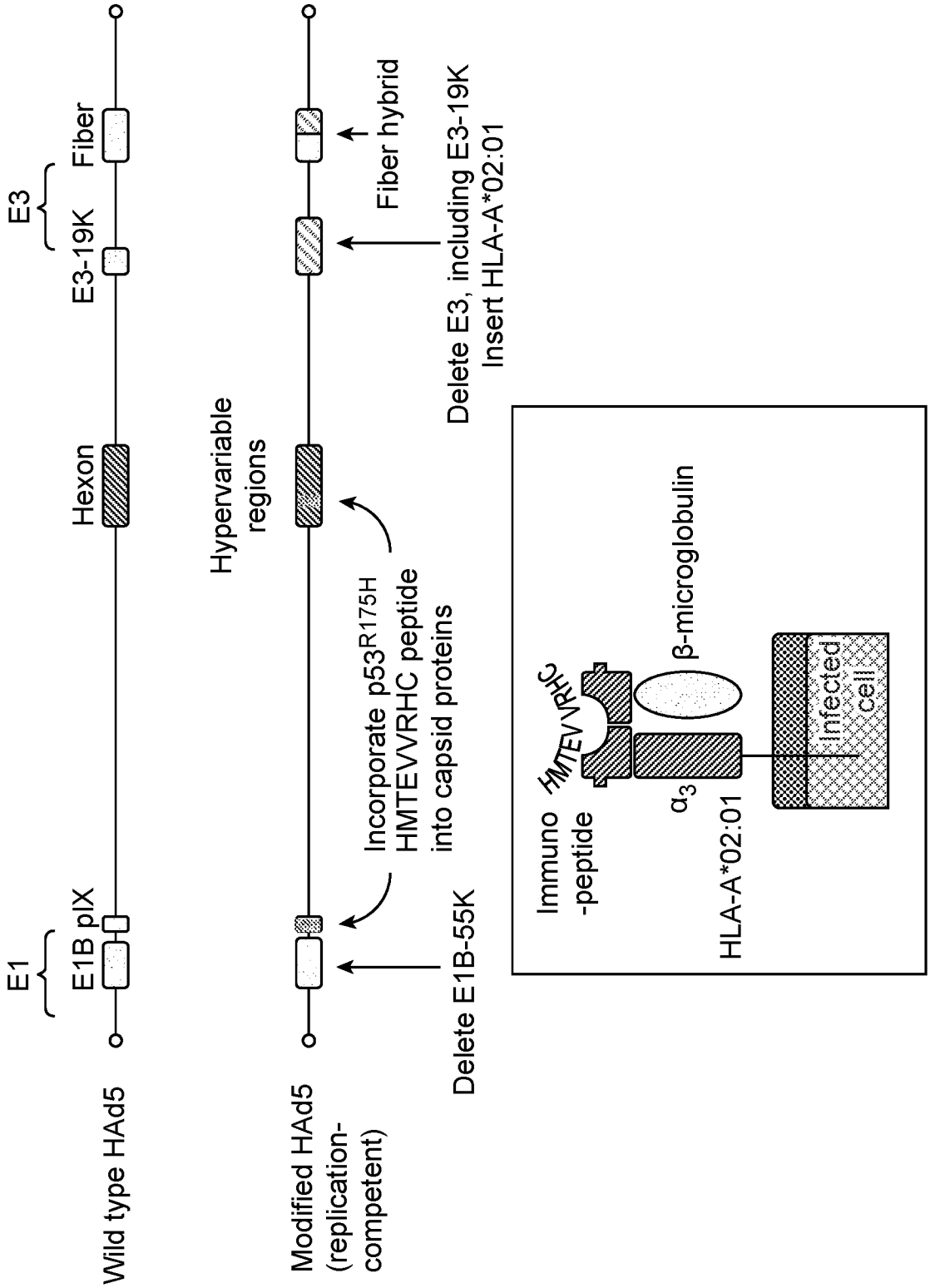

E1
E1B pIX
E3
E3-19K
Fiber
Hexon
Hypervariable regions
Wild type HAd5
Modified HAd5 (replication-competent)
Incorporate p53R175H HMTEVVRHC peptide into capsid proteins
Delete E1B-55K
Delete E3, including E3-19K
Insert HLA-A*02:01
Fiber hybrid
Immuno -peptide
HMTEVVRHC
β-microglobulin
α3
HLA-A*02:01
Infected cell

FIG. 1

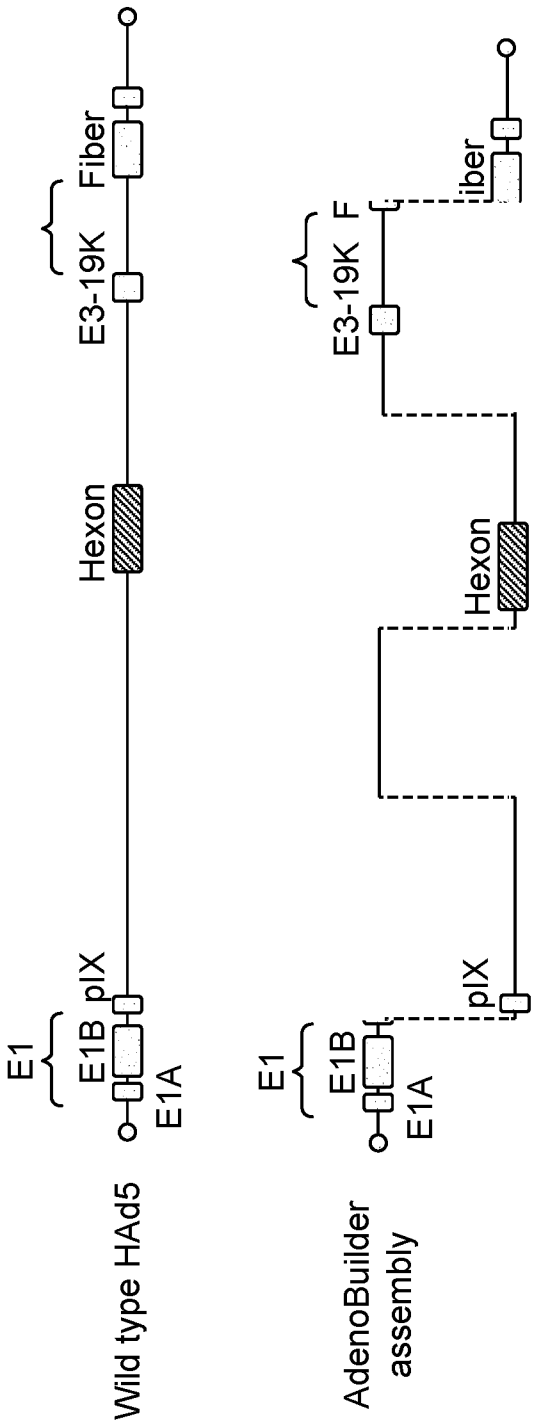

E1
E1B
pIX
E1A
Hexon
E3-19K
Fiber
Wild type HAd5
AdenoBuilder assembly
Replace hypervariable regions
pIX fusion
Incorporate antigenic peptide(s) into capsid proteins
Delete E3, including E3-19K
Insert patient-specific HLA
OAd modifications boost expression of peptide/HLA complexes
E1B-55K Δ
E4ORF1 Δ
Fiber hybrid
26-bp E1A Δ
Additional OAd Modifications permit preferential replication in cancer cells

FIG. 2A

FIG. 2B

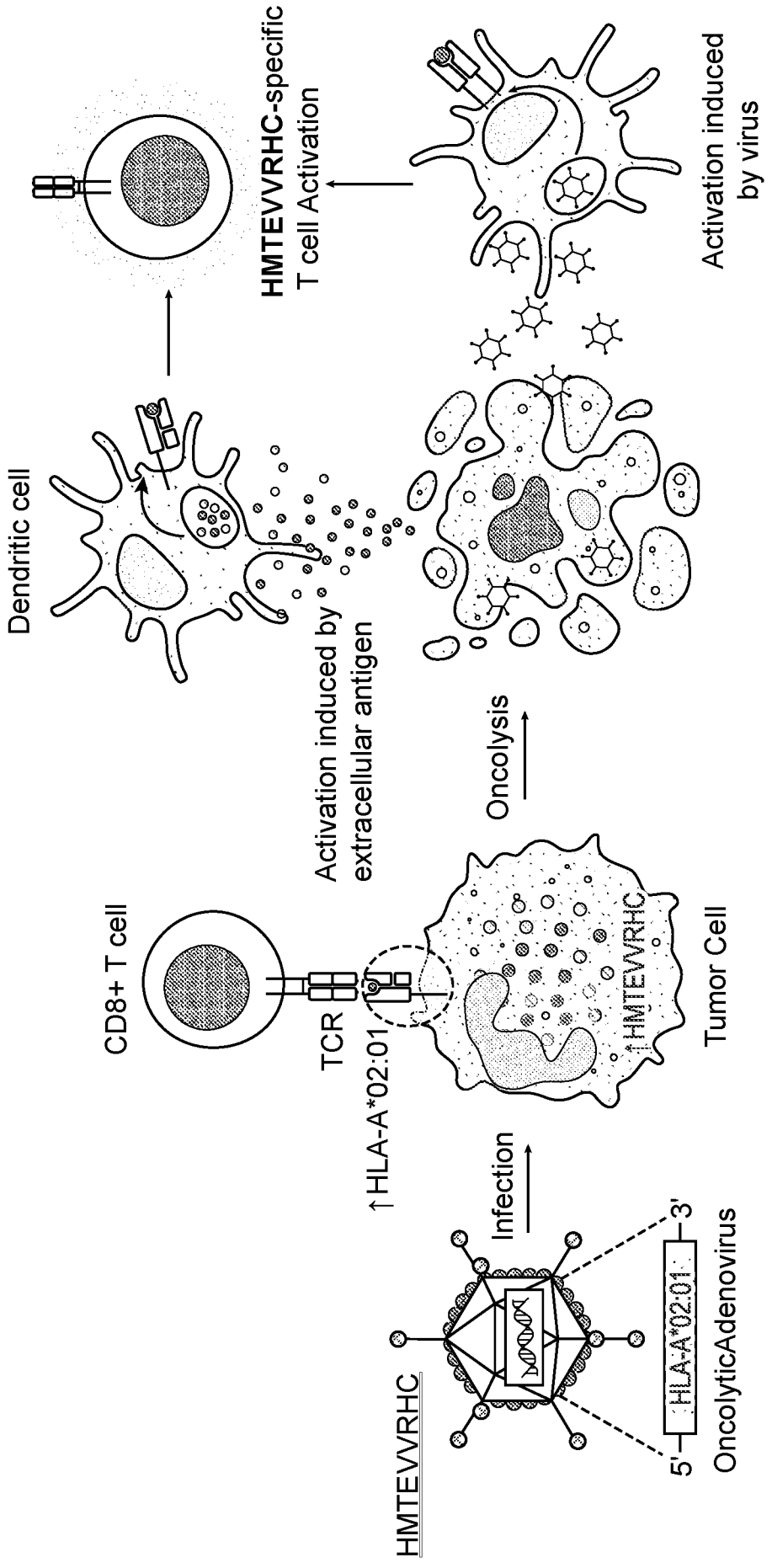

HMTEVVRHC
Infection
OncolyticAdenovirus
5'
HLA-A*02:01
3'
↑HLA-A*02:01
TCR
CD8+ T cell
Oncolysis
↑HMTEVVRHC
Tumor Cell
Activation induced by extracellular antigen
Dendritic cell
HMTEVVRHC-specific T cell Activation
Activation induced by virus

FIG. 3

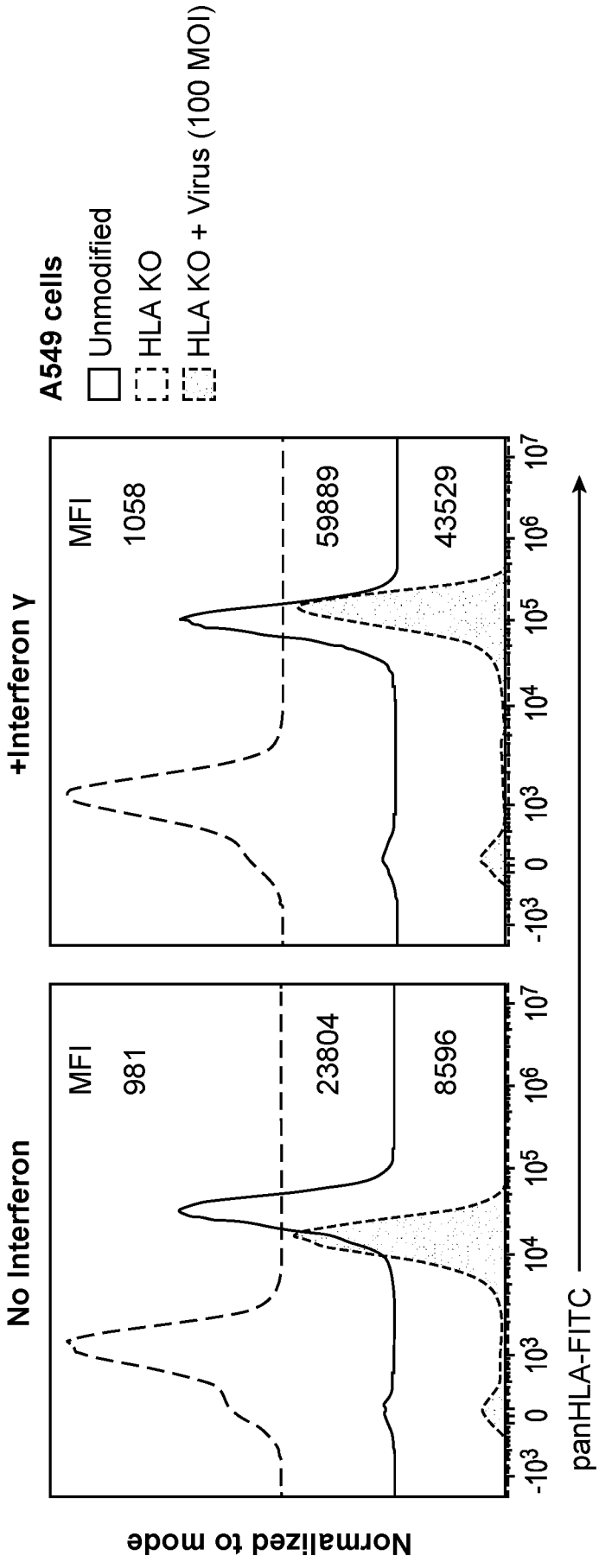

A549 cells
Unmodified
HLA KO
HLA KO + Virus (100 MOI)
+Interferon γ
No Interferon
MFI
1058
59889
43529
MFI
981
23804
8596
-10³ 0 10³ 10⁴ 10⁵ 10⁶ 10⁷
panHLA-FITC
Normalized to mode

FIG. 4

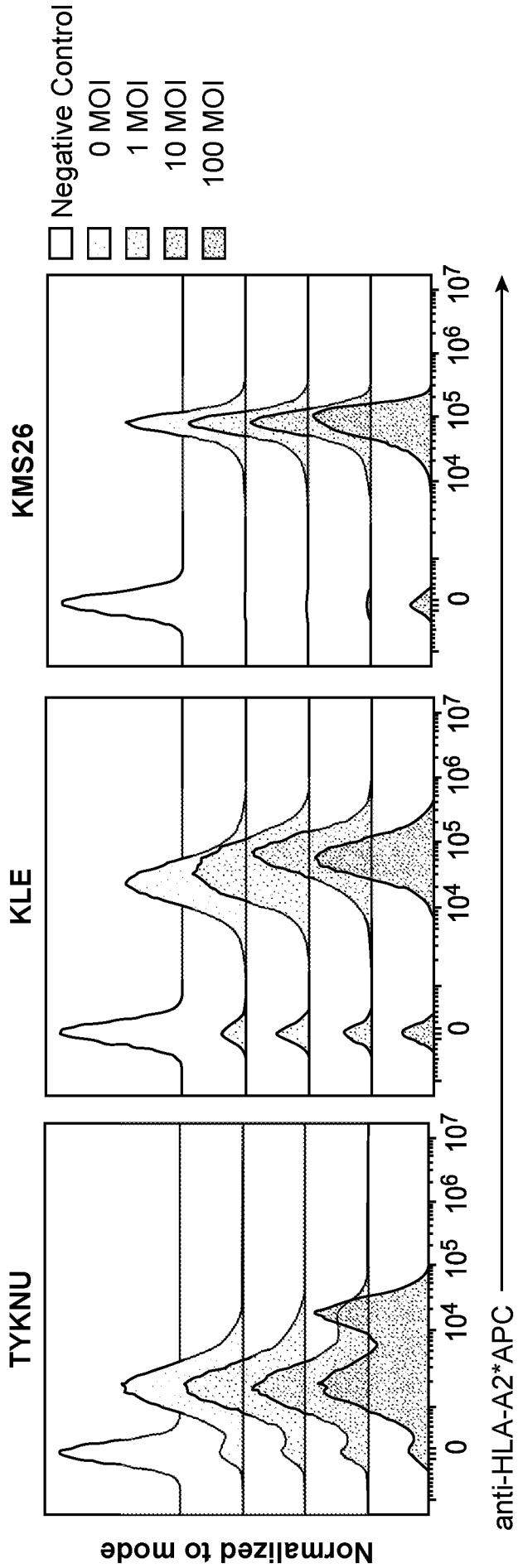

Negative Control
0 MOI
1 MOI
10 MOI
100 MOI
KMS26
KLE
TYKNU
0
10^4
10^5
10^6
10^7
anti-HLA-A2*APC
Normalized to mode

FIG. 5

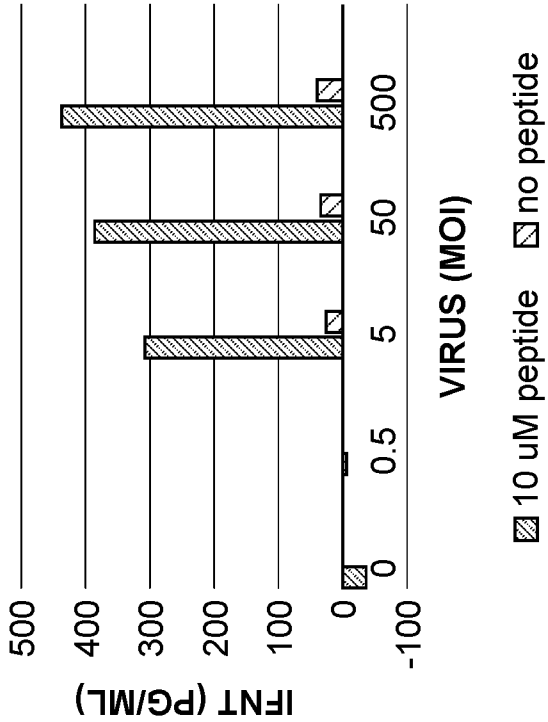

IFNT (PG/ML)
500
400
300
200
100
0
-100
0
0.5
5
50
500
VIRUS (MOI)
10 uM peptide
no peptide

FIG. 6B

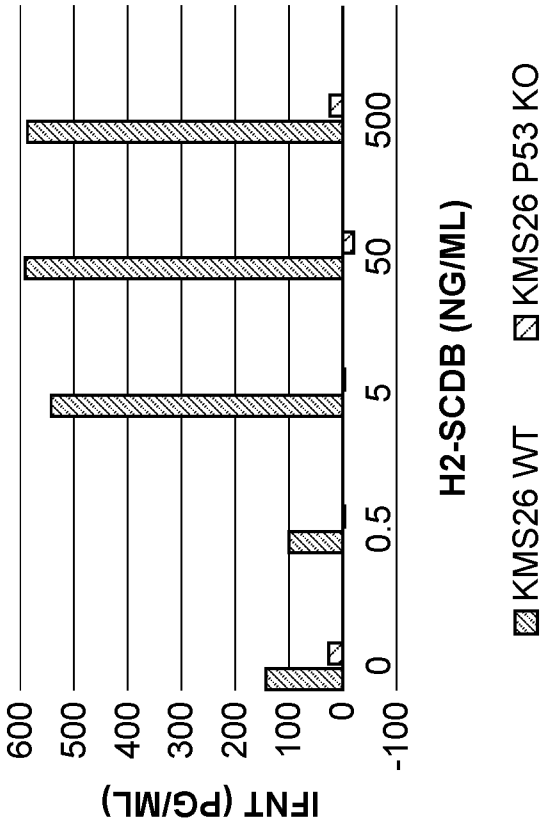

IFNT (PG/ML)
600
500
400
300
200
100
0
-100
0
0.5
5
50
500
H2-SCDB (NG/ML)
KMS26 WT
KMS26 P53 KO

FIG. 6A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/019670

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 35/12*** (2024.01); *A61K 48/00* (2024.01); ***A61P 35/00*** (2024.01); *C07K 14/725* (2024.01); ***C12N 15/861*** (2024.01); *C12N 5/10* (2024.01); ***C12N 7/04*** (2024.01); *C12P 21/00* (2024.01)

CPC: ***C12N 15/861; A61K 35/12; A61K 39/4632; A61P 35/00; C12N 7/04;*** *A61K 48/00; C07K 14/7051; C12N 5/10; C12P 21/00*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 8,974,777 B2 (CASCALLO PIQUERAS et al.) 10 March 2015 (10.03.2015) entire document	1-3
A	HSIUE et al. Targeting a neoantigen derived from a common TP53 mutation. Science, 5 March 2021, Vol. 371, eabc8697, Pgs. 1-14. entire document	1-3
A	US 7,785,887 B2 (SHEN et al.) 31 August 2010 (31.08.2010) entire document	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 May 2024 (07.05.2024)	**16 May 2024 (16.05.2024)**

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US **Commissioner for Patents** **P.O. Box 1450, Alexandria, VA 22313-1450**	**MATOS** **TAINA**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/019670

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☑ forming part of the international application as filed.
   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

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

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/019670

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☑ Claims Nos.: **4-20**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).