NEOANTIGENS AND METHODS OF THEIR USE

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Application No. 62/316,530, filed March 31, 2016, U.S. Provisional Application No. 62/316,533, filed March 31, 2016, U.S. Provisional Application No. 62/316,547, filed March 31, 2016, U.S. Provisional Application No. 62/316,552, filed March 31, 2016, U.S. Provisional Application No. 62/316,567, filed April 1, 2016, and U.S. Provisional Application No. 62/316,571, filed April 1, 2016, each of which is incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The field of the present invention relates to immunotherapeutic peptides, nucleic acids encoding the peptides, peptide binding agents, and their use, for example, in the immunotherapy of cancer. In one aspect, the invention provides neoantigenic peptides, useful alone or in combination with other tumor-associated peptides, anti-cancer, or immunomodulatory agents to treat cancer.

BACKGROUND OF THE INVENTION

[0003] Tumor vaccines are typically composed of tumor antigens and immunostimulatory molecules (e.g., adjuvants, cytokines or TLR ligands) that work together to induce antigen-specific cytotoxic T cells (CTLs) that recognize and lyse tumor cells. Such vaccines contain either shared tissue restricted tumor antigens or a mixture of shared and patient-specific antigens in the form of whole tumor cell preparations. The shared tissue restricted tumor antigens are ideally immunogenic proteins with selective expression in tumors across many individuals and are commonly delivered to patients as synthetic peptides or recombinant proteins. In contrast, whole tumor cell preparations are delivered to patients as autologous irradiated cells, cell lysates, cell fusions, heat-shock protein preparations or total mRNA. Since whole tumor cells are isolated from the autologous patient, the cells may include patient-specific tumor antigens as well as shared tumor antigens. Finally, there is a third class of tumor antigens, neoantigens, that has rarely been used in vaccines, which consists of proteins with tumor-specific mutations (which can be patient-specific or shared) that result in altered amino acid sequences. Such mutated proteins are: (a) unique to the tumor cell as the mutation and it's corresponding protein are present only in the tumor; (b) avoid central tolerance and are therefore more likely to be immunogenic; (c) provide an excellent target for immune recognition including by both humoral and cellular immunity. However, the use of personalized neoantigens requires sequencing of each patient's genome and then production of a patient-specific neoantigen composition. Accordingly, there is still a need for developing additional cancer therapeutics.

BRIEF SUMMARY OF THE DISCLOSURE

[0003a] In one aspect, provided herein is a use of a pharmaceutical composition in the preparation of a medicament for treating cancer in a subject in need thereof, wherein the pharmaceutical composition comprises: (a) a recombinant or synthetic tumor-specific neoantigenic peptide; (b) a polynucleotide encoding the recombinant or synthetic tumor-specific neoantigenic peptide; (c) an antigen presenting cell expressing or loaded with the recombinant or synthetic tumor-specific neoantigenic peptide; or (d) a T cell having a T cell

receptor (TCR) that recognizes the recombinant or synthetic tumor-specific neoantigenic peptide; wherein the recombinant or synthetic tumor-specific neoantigenic peptide comprises a tumor-specific neoepitope comprising one or more contiguous mutant amino acids encoded by a frameshift, wherein the tumor-specific neoepitope is encoded by a GATA Binding Protein 3 (GATA3) gene of cancer cells of the subject or is expressed by cancer cells of the subject, and wherein the tumor-specific neoepitope is not expressed by non-cancer cells of the subject or is not encoded by a GATA3 gene of the non-cancer cells, wherein the recombinant or synthetic tumor-specific neoantigenic peptide is from 8 to 100 amino acids in length; and wherein: i. the subject expresses a major histocompatibility complex (MHC) encoded by an HLA B07:02 allele and the tumor-specific neoepitope is EPHLALQPL (SEQ ID NO: 529) or MFATLQRSSL (SEQ ID NO: 567); ii. the subject expresses a MHC encoded by an HLA B08:01 allele and the tumor-specific neoepitope is EPHLALQPL (SEQ ID NO: 529), FLKAESKIMF (SEQ ID NO: 536), IMKPKRDGYM (SEQ ID NO: 550), LHFCRSSIM (SEQ ID NO: 556), MFATLQRSSL (SEQ ID NO: 567) or YMFLKAESKI (SEQ ID NO: 598); iii. the subject expresses a MHC encoded by an HLA A24:02 allele and the tumor-specific neoepitope is MFLKAESKI (SEQ ID NO: 568) or YMFLKAESKI (SEQ ID NO: 598); iv. the subject expresses a MHC encoded by an HLA A02:01 allele and the tumor-specific neoepitope is VLPEPHLAL (SEQ ID NO: 594); and/or the subject expresses a MHC encoded by an HLA A03:01 allele and the tumor-specific neoepitope is VLWTTPPLQH (SEQ ID NO: 1430).

[0003b] In one aspect, provided herein is a pharmaceutical composition as defined in the use as described herein.

[0003c] In one aspect, provided herein is a recombinant T cell receptor (TCR) capable of binding at least one recombinant or synthetic tumor-specific neoantigenic peptide as defined in the use as descrbied herein in an MHC-peptide complex comprising the at least one recombinant or synthetic tumor-specific neoantigenic peptide.

[0003d] In one aspect, provided herein is a pharmaceutical composition as defined in the use as described herein, wherein the neoantigenic peptide is from 8 to 50 amino acids in length.

[0004] Provided herein is an isolated neoantigenic peptide comprising a tumor-specific neoepitope, wherein the isolated neoantigenic peptide is not a native polypeptide, wherein the neoepitope comprises at least 8 contiguous amino acids

of an amino acid sequence represented by: AxByCz, wherein each A and C represents an amino acid corresponding to the native polypeptide, y is at least 1 and B represents an amino acid substitution or insert of the native polypeptide, x + y + z is at least 8, the at least 8 contiguous amino acids comprises By, and the native polypeptide is encoded by a gene selected from the group consisting of: (a) ABL1, wherein AxByCz is (i) VADGLITTLHYPAPKRNKPTVYGVSPNYDKWEMERTDITMKHKLGGGQYGKVYEGVWKKYSLTV AVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVC, (ii) VADGLITTLHYPAPKRNKPTVYGVSPNYDKWEMERTDITMKHKLGGGQYGVVYEGVWKKYSLTV AVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVC, (iii) LLGVCTREPPFYIITEFMTYGNLLDYLRECNRQEVNAVVLLYMATQISSATEYLEKKNFIHRDLAARN CLVGENHLVKVADFGLSRLMTGDTYTAHAGAKF, (iv) SLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVCTREPPFYIIIEFMTYGNLLDYLRECNR QEVNAVVLLYMATQISSAMEYLEKKNFIHRDLA, or (v) STVADGLITTLHYPAPKRNKPTVYGVSPNYDKWEMERTDITMKHKLGGGQHGEVYEGVWKKYSLT VAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLG; (b) ALK, wherein AxByCz is (i) SSLAMLDLLHVARDIACGCQYLEENHFIHRDIAARNCLLTCPGPGRVAKIADFGMARDIYRASYYRK GGCAMLPVKWMPPEAFMEGIFTSKTDTWSFGVLL, or (ii) QVAVKTLPEVCSEQDELDFLMEALIISKFNHQNIVRCIGVSLQSLPRFILMELMAGGDLKSFLRETRPR PSQPSSLAMLDLLHVARDIACGCQYLEENHFI; (c) BRAF, wherein AxByCz is MIKLIDIARQTAQGMDYLHAKSIIHRDLKSNNIFLHEDLTVKIGDFGLATEKSRWSGSHQFEQLSGSIL WMAPEVIRMQDKNPYSFQSDVYAFGIVLYELM; (d) BTK, wherein AxByCz is MIKEGSMSEDEFIEEAKVMMNLSHEKLVQLYGVCTKQRPIFIITEYMANGSLLNYLREMRHRFQTQQ LLEMCKDVCEAMEYLESKQFLHRDLAARNCLVND; (e) EEF1B2, wherein AxByCz is MGFGDLKSPAGLQVLNDYLADKSYIEGYVPSQADVAVFEAVSGPPPADLCHALRWYNHIKSYEKEK ASLPGVKKALGKYGPADVEDTTGSGAT; (f) EGFR, wherein AxByCz is (i) SLNITSLGLRSLKEISDGDVIISGNKNLCYANTINWKKLFGTSGQKTKIIRNRGENSCKATGQVCHALC SPEGCWGPEPRDCVSCRNVSRGRECVDKCNLL, or (ii) IPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTVQLIMQLMPFGCLLDYVREHKD NIGSQYLLNWCVQIAKGMNYLEDRRLVHRDLAA; (g) ERBB3, wherein AxByCz is ERCEVVMGNLEIVLTGHNADLSFLQWIREVTGYVLVAMNEFSTLPLPNLRMVRGTQVYDGKFAIFV MLNYNTNSSHALRQLRLTQLTEILSGGVYIEKNDK; (h) ESR1, wherein AxByCz is (i) HLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYGLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGEA, (ii) NQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVCLKSIILLNSGVYTFLPSTLKSLEEKDHIHRVLD KITDTLIHLMAKAGLTLQQQHQRLAQLLLILSH, (iii)

IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLCDLLLEMLDAHRLHAP
TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE, (iv)
IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLNDLLLEMLDAHRLHAP
TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE, or (v)
IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLSDLLLEMLDAHRLHAP
TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE; (i) FGFR3, wherein AxByCz is
HRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERCPHRPILQAGLPANQTA
VLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVG; (j) FRG1B, wherein AxByCz is
AVKLSDSRIALKSGYGKYLGINSDELVGHSDAIGPREQWEPVFQNGKMALSASNSCFIRCNEAGDIEA
KSKTAGEEEMIKIRSCAEKETKKKDDIPEEDKG; (k) HER2, wherein AxByCz is
GSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGLGSPYVSRLLGICLTSTV
QLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCM; (l) IDH1, wherein AxByCz is (i)
RVEEFKLKQMWKSPNGTIRNILGGTVFREAIICKNIPRLVSGWVKPIIIGHHAYGDQYRATDFVVPGP
GKVEITYTPSDGTQKVTYLVHNFEEGGGVAMGM, (ii)
RVEEFKLKQMWKSPNGTIRNILGGTVFREAIICKNIPRLVSGWVKPIIIGCHAYGDQYRATDFVVPGPG
KVEITYTPSDGTQKVTYLVHNFEEGGGVAMGM, (iii)
RVEEFKLKQMWKSPNGTIRNILGGTVFREAIICKNIPRLVSGWVKPIIIGGHAYGDQYRATDFVVPGP
GKVEITYTPSDGTQKVTYLVHNFEEGGGVAMGM, or (iv)
RVEEFKLKQMWKSPNGTIRNILGGTVFREAIICKNIPRLVSGWVKPIIIGSHAYGDQYRATDFVVPGPG
KVEITYTPSDGTQKVTYLVHNFEEGGGVAMGM; (m) KIT, wherein AxByCz is (i)
VEATAYGLIKSDAAMTVAVKMLKPSAHLTEREALMSELKVLSYLGNHMNIANLLGACTIGGPTLVIT
EYCCYGDLLNFLRRKRDSFICSKQEDHAEAALYK, or (ii)
VEATAYGLIKSDAAMTVAVKMLKPSAHLTEREALMSELKVLSYLGNHMNIANLLGACTIGGPTLVIT
EYCCYGDLLNFLRRKRDSFICSKQEDHAEAALYK; (n) MEK, wherein AxByCz is (i)
ISELGAGNGGVVFKVSHKPSGLVMARKLIHLEIKPAIRNQIIRELQVLHESNSPYIVGFYGAFYSDGEIS
ICMEHMDGGSLDQVLKKAGRIPEQILGKVSI, or (ii)
LGAGNGGVVFKVSHKPSGLVMARKLIHLEIKPAIRNQIIRELQVLHECNSLYIVGFYGAFYSDGEISIC
MEHMDGGSLDQVLKKAGRIPEQILGKVSIAVI; (o) MYC, wherein AxByCz is (i)
MPLNVSFTNRNYDLDYDSVQPYFYCDEEENFYQQQQQSDLQPPAPSEDIWKKFELLPTPPLSPSRRSG
LCSPSYVAVTPFSLRGDNDGG, (ii)
FTNRNYDLDYDSVQPYFYCDEEENFYQQQQQSELQPPAPSEDIWKKFELLSTPPLSPSRRSGLCSPSY
VAVTPFSLRGDNDGGGGSFSTADQLEMVTELLG, or (iii)
TNRNYDLDYDSVQPYFYCDEEENFYQQQQQSELQPPAPSEDIWKKFELLPIPPLSPSRRSGLCSPSYVA
VTPFSLRGDNDGGGGSFSTADQLEMVTELLGG; (p) PDGFRa, wherein AxByCz is
VAVKMLKPTARSSEKQALMSELKIMTHLGPHLNIVNLLGACTKSGPIYIIIEYCFYGDLVNYLHKNRD

SFLSHHPEKPKKELDIFGLNPADESTRSYVILS; (q) PIK3CA, wherein AxByCz is (i) IEEHANWSVSREAGFSYSHAGLSNRLARDNELRENDKEQLKAISTRDPLSKITEQEKDFLWSHRHYC VTIPEILPKLLLSVKWNSRDEVAQMYCLVKDWPP, (ii) HANWSVSREAGFSYSHAGLSNRLARDNELRENDKEQLKAISTRDPLSEITKQEKDFLWSHRHYCVTI PEILPKLLLSVKWNSRDEVAQMYCLVKDWPPIKP, or (iii) LFINLFSMMLGSGMPELQSFDDIAYIRKTLALDKTEQEALEYFMKQMNDARHGGWTTKMDWIFHTI KQHALN; (r) POLE, wherein AxByCz is QRGGVITDEEETSKKIADQLDNIVDMREYDVPYHIRLSIDIETTKLPLKFRDAETDQIMMISYMIDGQG YLITNREIVSEDIEDFEFTPKPEYEGPFCVFN; (s) PTEN, wherein AxByCz is KFNCRVAQYPFEDHNPPQLELIKPFCEDLDQWLSEDDNHVAAIHCKAGKGQTGVMICAYLLHRGKF LKAQEALDFYGEVRTRDKKGVTIPSQRRYVYYYSY; (t) RAC1, wherein AxByCz is MQAIKCVVVGDGAVGKTCLLISYTTNAFSGEYIPTVFDNYSANVMVDGKPVNLGLWDTAGQEDYD RLRPLSYPQTVGET; and (u) TP53, wherein AxByCz is (i) IRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNSSCMGSMNRRPILTIITLEDSSG NLLGRNSFEVRVCACPGRDRRTEEENLRKKGEP, (ii) TYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRHCPHHERCSDSDGLAP PQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEV, (iii) EGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNSSCMGGMNQRPILTIITLEDSSGNLL GRNSFEVRVCACPGRDRRTEEENLRKKGEPHHE, (iv) EGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNSSCMGGMNWRPILTIITLEDSSGNLL GRNSFEVRVCACPGRDRRTEEENLRKKGEPHHE, or (v) PEVGSDCTTIHYNYMCNSSCMGGMNRRPILTIITLEDSSGNLLGRNSFEVCVCACPGRDRRTEEENLR KKGEPHHELPPGSTKRALPNNTSSSPQPKKKPL.

[0005] In examples, the native polypeptide is encoded by the EGFR, ERBB3 or FGFR3 gene and at least one By is expressed extracellularly.

[0006] Provided herein is an isolated neoantigenic peptide comprising a tumor-specific neoepitope, wherein the isolated neoantigenic peptide is not a native polypeptide, wherein the neoepitope comprises at least 8 contiguous amino acids of an amino acid sequence represented by: AxByCz, wherein each A is an amino acid corresponding to the native polypeptide; By is absent; each C is an amino acid encoded by a frameshift of a sequence encoding the native polypeptide; x + y + z is at least 8; the at least 8 contiguous amino acids comprises at least one Cz; and the native polypeptide is encoded by a gene selected from the group consisting of: (a) APC, wherein Cz is (i) AKFQQCHSTLEPNPADCRVLVYLQNQPGTKLLNFLQERNLPPKVVLRHPKVHLNTMFRRPHSCLAD VLLSVHLIVLRVVRLPAPFRVNHAVEW, (ii) APVIFQIALDKPCHQAEVKHLHHLLKQLKPSEKYLKIKHLLLKRERVDLSKLQ, or (iii)

MLQFRGSRFFQMLILYYILPRKVLQMDFLVHPA; (b) ARID1A, wherein Cz is (i)
ALGPHSRISCLPTQTRGCILLAATPRSSSSSSSNDMIPMAISSPPKAPLLAAPSPASRLQCINSNSRITSGQ
WMAHMALLPSGTKGRCTACHTALGRGSLSSSSCPQPSPSLPASNKLPSLPLSKMYTTSMAMPILPLPQ
LLLSADQQAAPRTNFHSSLAETVSLHPLAPMPSKTCHHK, (ii)
AHQGFPAAKESRVIQLSLLSLLIPPLTCLASEALPRPLLALPPVLLSLAQDHSRLLQCQATRCHLGHPV
ASRTASCILP, (iii)
PILAATGTSVRTAARTWVPRAAIRVPDPAAVPDDHAGPGAECHGRPLLYTADSSLWTTRPQRVWST
GPDSILQPAKSSPSAAAATLLPATTVPDPSCPTFVSAAATVSTTTAPVLSASILPAAIPASTSAVPGSIPL
PAVDDTAAPPEPAPLLTATGSVSLPAAATSAASTLDALPAGCVSSAPVSAVPANCLFPAALPSTAGAIS
RFIWVSGILSPLNDLQ, (iv)
PCRAGRRVPWAASLIHSRFLLMDNKAPAGMVNRARLHITTSKVLTLSSSSHPTPSNHRPRPLMPNLRI
SSSHSLNHHSSSPLSLHTPSSHPSLHISSPRLHTPPSSRRHSSTPRASPPTHSHRLSLLTSSSNLSSQHPRR
SPSRLRILSPSLSSPSKLPIPSSASLHRRSYLKIHLGLRHPQPPQ, (v)
RTNPTVRMRPHCVPFWTGRILLPSAASVCPIPFEACHLCQAMTLRCPNTQGCCSSWAS, or (vi)
TNQALPKIEVICRGTPRCPSTVPPSPAQPYLRVSLPEDRYTQAWAPTSRTPWGAMVPRGVSMAHKVA
TPGSQTIMPCPMPTTPVQAWLEA; (c) β2M, wherein Cz is (i)
RMERELKKWSIQTCLSARTGLSISCTTLNSPPLKKMSMPAV, or (ii)
LCSRYSLFLAWRLSSVLQRFRFTHVIQQRMESQIS; (d) CDH1, wherein Cz is (i)
RSACVTVKGPLASVGRHSLSKQDCKFLPFWGFLEEFLLC, (ii)
IQWGTTTAPRPIRPPFLESKQNCSHFPTPLLASEDRRETGLFLPSAAQKMKKAHFLKTWFRSNPTKTK
KARFSTASLAKELTHPLLVSLLLKEKQDG, (iii)
PTDPFLGLRLGLHLQKVFHQSHAEYSGAPPPPPAPSGLRFWNPSRIAHISQLLSWPQKTEERLGYSSHQ
LPRK, (iv) FCCSCCFFGGERWSKSPYCPQRMTPGTTFITMMKKEAEKRTRTLT, or (v)
WRRNCKAPVSLRKSVQTPARSSPARPDRTRRLPSLGVPGQPWALGAAASRRCCCCCRSPLGSARSRS
PATLALTPRATRSRCPGATWREAASWAE; (e) GATA3, wherein Cz is (i)
PGRPLQTHVLPEPHLALQPLQPHADHAHADAPAIQPVLWTTPPLQHGHRHGLEPCSMLTGPPARVPA
VPFDLHFCRSSIMKPKRDGYMFLKAESKIMFATLQRSSLWCLCSNH; or (ii)
PRPRRCTRHPACPLDHTTPPAWSPPWVRALLDAHRAPSESPCSPFRLAFLQEQYHEA; (f) MLL2,
wherein Cz is
TRRCHCCPHLRSHPCPHHLRNHPRPHHLRHHACHHHLRNCPHPHFLRHCTCPGRWRNRPSLRRLRSL
LCLPHLNHHLFLHWRSRPCLHRKSHPHLLHLRRLYPHHLKHRPCPHHLKNLLCPRHLRNCPLPRHLK
HLACLHHLRSHPCPLHLKSHPCLHHRRHLVCSHHLKSLLCPLHLRSLPFPHHLRHHACPHHLRTRLCP
HHLKNHLCPPHLRYRAYPPCLWCHACLHRLRNLPCPHRLRSLPRPLHLRLHASPHHLRTPPHPHHLR
THLLPHHRRTRSCPCRWRSHPCCHYLRSRNSAPGPRGRTCHPGLRSRTCPPGLRSHTYLRRLRSHTCP
PSLRSHAYALCLRSHTCPPRLRDHICPLSLRNCTCPPRLRSRTCLLCLRSHACPPNLRNHTCPPSLRSHA

CPPGLRNRICPLSLRSHPCPLGLKSPLRSQANALHLRSCPCSLPLGNHPYLPCLESQPCLSLGNHLCPLC PRSCRCPHLGSHPCRLS; (g) PTEN, wherein Cz is (i) SWKGTNWCNDMCIFITSGQIFKGTRGPRFLWGSKDQRQKGSNYSQSEALCVLL, (ii) KRTKCFTFG, (iii) PIFIQTLLLWDFLQKDLKAYTGTILMM, (iv) QKMILTKQIKTKPTDTFLQILR, (v) GFWIQSIKTITRYTIFVLKDIMTPPNLIAELHNILLKTITHHS, (vi) NYSNVQWRNLQSSVCGLPAKGEDIFLQFRTHTTGRQVHVL, or (vii) YQSRVLPQTEQDAKKGQNVSLLGKYILHTRTRGNLRKSRKWKSM; (h) TP53, wherein Cz is (i) SSQNARGCSPRGPCTSSSYTGGPCTSPLLAPVIFCPFPENLPGQLRFPSGLLAFWDSQVCDLHVLPCPQ QDVLPTGQDLPCAAVG, (ii) GAAPTMSAAQIAMVWPLLSILSEWKEICVWSIWMTETLFDIVWWCPMSRLRLALTVPPSTTTTCVTV PAWAA, (iii) TGGPSSPSSHWKTPVVIYWDGTALRCVFVPVLGETGAQRKRISARKGSLTTSCPQGALSEHCPTTPAP LPSQRRNHWMENISPFRSVGVSASRCSES, (iv) FHTPARHPRPRHGHLQAVTAHDGGCEALPPP, (v) CCPRTILNNGSLKTQVQMKLPECQRLLPPWPLHQQLLHRRPLHQPPPGPCHLLSLPRKPTRAATVSV WASCILGQPSL, (vi) VRKHFQTYGNYFLKTTFCPPCRPKQWMI, or (vii) LARTPLPSTRCFANWPRPALCSCGLIPHPRPAPASAPWPSTSSHST; or (i) VHL wherein Cz is (i) ELQETGHRQVALRRSGRPPKCAERPGAADTGAHCTSTDGRLKISVETYTVSSQLLMVLMSLDLDTGL VPSLVSKCLILRVK, (ii) KSDASRLSGA, (iii) RTAYFCQYHTASVYSERAMPPGCPEPSQA, (iv) TRASPPRSSSAIAVRASCCPYGSTSTASRSPTQRCRLARAAASTATEVTFGSSEMQGHTMGFWLTKLN YLCHLSMLTDSLFLPISHCQCIL, (v) SSLRITGDWTSSGRSTKIWKTTQMCRKTWSG, or (vi) RRRRGGVGRRGVRPGRVRPGGTGRRGGDGGRAAAARAALGELARALPGHLLQSQSARRAARMAQ LRRRAAALPNAAAWHGPPHPQLPRSPLALQRCRDTRWASG; (j) ACVR2A, wherein AxByCz is (i) GVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKRQP, or (ii) GVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKTALKYIFVAVRAICVM KSFLIFRRWKSHSPLQIQLHLSHPITTSCSIPWCHLC; (k) C15ORF40, wherein AxByCz is TAEAVNVAIAAPPSEGEANAELCRYLSKVLELRKSDVVLDKVGLALFFFFFETKSCSVAQAGVQWRS LGSLQPPPPGFKLFSCLSFLSSWDYRRMPPCLANFCIFNRDGVSPCWSGWS; (l) CNOT1, wherein AxByCz is (i) LSVIIFFFVYIWHWALPLILNNHHICLMSSIILDCNSVRQSIMSVCFFFFSVIFSTRCLTDSRYPNICWFK, or (ii) LSVIIFFFVYIWHWALPLILNNHHICLMSSIILDCNSVRQSIMSVCFFFFCYILNTMFDR; (m) EIF2B3, wherein AxByCz or Cz is VLVLSCDLITDVALHEVVDLFRAYDASLAMLMRKGQDSIEPVPGQKGKKKQWSSVTSLEWTAQERG CSSWLMKQTWMKSWSLRDPSYRSILEYVSTRVLWMPTSTV; (n) EPHB2, wherein AxByCz or Cz is SIQVMRAQMNQIQSVEGQPLARRPRATGRTKRCQPRDVTKKTCNSNDGKKREWEKRKQILGGGGK YKEYFLKRILIRKAMTVLAGDKKGLGRFMRCVQSETKAVSLQLPLGR; (o) ESRP1, wherein AxByCz

is (i) LDFLGEFATDIRTHGVHMVLNHQGRPSGDAFIQMKSADRAFMAAQKCHKKKHEGQIC, or (ii) LDFLGEFATDIRTHGVHMVLNHQGRPSGDAFIQMKSADRAFMAAQKCHKKT; (p) FAM11B, wherein AxByCz is GALCKDGRFRSDIGEFEWKLKEGHKKIYGKQSMVDEVSGKVLEMDISKKKHYNRKISIKKLNRMKV PLMKLITRV; (q) GBP3, wherein AxByCz is RERAQLLEEQEKTLTSKLQEQARVLKERCQGESTQLQNEIQKLQKTLKKKPRDICRIS; (r) JAK1, wherein AxByCz is (i) VNTLKEGKRLPCPPNCPDEVYQLMRKCWEFQPSNRTSFQNLIEGFEALLKTSN or (ii) CRPVTPSCKELADLMTRCMNYDPNQRPFFRAIMRDINKLEEQNPDIVSEKNQQLKWTPHILKSAS; (s) LMAN1, wherein AxByCz is (i) DDHDVLSFLTFQLTEPGKEPPTPDKEISEKEKEKYQEEFEHFQQELDKKKRGIPEGPPRPPRAACGGNI, or (ii) DDHDVLSFLTFQLTEPGKEPPTPDKEISEKEKEKYQEEFEHFQQELDKKKRNSRRATPTSKGSLRRKY LRV; (t) MSH3, wherein AxByCz is (i) TKSTLIGEDVNPLIKLDDAVNVDEIMTDTSTSYLLCISENKENVRDKKKGQHFYWHCGSAACHRRGC V, or (ii) LYTKSTLIGEDVNPLIKLDDAVNVDEIMTDTSTSYLLCISENKENVRDKKRATFLLALWECSLPQARL CLIVSRTLLLVQS; (u) NDUFC2, wherein AxByCz is (i) LPPPKLTDPRLLYIGFLGYCSGLIDNLIRRRPIATAGLHRQLLYITAFFFCWILSCKT, or (ii) SLPPPKLTDPRLLYIGFLGYCSGLIDNLIRRRPIATAGLHRQLLYITAFFLLDIIL; (v) RBM27, wherein AxByCz is NQSGGAGEDCQIFSTPGHPKMIYSSSNLKTPSKLCSGSKSHDVQEVLKKKTGSNEVTTRYEEKKTGSV RKANRMPKDVNIQVRKKQKHETRRKSKYNEDFERAWREDLTIKR; (w) RPL22, wherein AxByCz is (i) MAPVKKLVVKGGKKKEASSEVHS, or (ii) MAPVKKLVVKGGKKRSKF; (x) SEC31A, wherein AxByCz is (i) MPSHQGAEQQQQQHHVFISQVVTEKEFLSRSDQLQQAVQSQGFINYCQKKN, or (ii) MPSHQGAEQQQQQHHVFISQVVTEKEFLSRSDQLQQAVQSQGFINYCQKKLMLLRLNLRKMCGPF; (y) SEC63, wherein AxByCz is (i) AEVFEKEQSICAAEEQPAEDGQGETNKNRTKGGWQQKSKGPKKTAKSKKKETFKKKTYTCAITTVK ATETKAGKWSRWE, or (ii) MAEVFEKEQSICAAEEQPAEDGQGETNKNRTKGGWQQKSKGPKKTAKSKKRNL; (z) SLC35F5, wherein AxByCz is NIMEIRQLPSSHALEAKLSRMSYPVKEQESILKTVGKLTATQVAKISFFFALCGFWQICHIKKHFQTHK LL; (aa) SMAP1, wherein AxByCz is (i) YEKKKYYDKNAIAITNISSSDAPLQPLVSSPSLQAAVDKNKLEKEKEKKKGREKERKGARKAGKTTY S, or (ii)

KYEKKKYYDKNAIAITNISSSDAPLQPLVSSPSLQAAVDKNKLEKEKEKKRKRKREKRSQKSRQNHL QLKSCRRKISNWSLKKVPALKKLRSPLWIF; (bb) TFAM, wherein AxByCz is (i) IYQDAYRAEWQVYKEEISRFKEQLTPSQIMSLEKEIMDKHLKRKAMTKKKRVNTAWKTKKTSFSL, or (ii) IYQDAYRAEWQVYKEEISRFKEQLTPSQIMSLEKEIMDKHLKRKAMTKKKS; (cc) TGFBR2, wherein AxByCz is (i) KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKAW, or (ii) EKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKSLVRLSSCVPVALMSAM TTSSSQKNITPAILTCC; (dd) THAP5, wherein AxByCz is VPSKYQFLCSDHFTPDSLDIRWGIRYLKQTAVPTIFSLPEDNQGKDPSKKNPRRKTWKMRKKYAQKP SQKNHLY; (ee) TTK, wherein AxByCz is GTTEEMKYVLGQLVGLNSPNSILKAAKTLYEHYSGGESHNSSSSKTFEKKGEKNDLQLFVMSDTTYK IYWTVILLNPCGNLHLKTTSL; and (ff) XPOT, wherein AxByCz is QQLIRETLISWLQAQMLNPQPEKTFIRNKAAQVFALLFVTEYLTKWPKFFLTFSQ.

[0007] Provided herein is an isolated neoantigenic peptide comprising a tumor-specific neoepitope, wherein the isolated neoantigenic peptide is not a native polypeptide, wherein the neoepitope comprises at least 8 contiguous amino acids of an amino acid sequence represented by: AxByCz, wherein each A is an amino acid corresponding to a first native polypeptide; each C is an amino acid corresponding to a second native polypeptide, or a cryptic exon or exon of a splice variant of the first native polypeptide, each B is an amino acid that is not an amino acid corresponding to the first native polypeptide, the second native polypeptide, or the cryptic exon of the first native polypeptide, and x + y + z is at least 8, wherein y is absent and the at least 8 contiguous amino acids comprises at least one Ax and at least one Cz, or y is at least 1 and the at least 8 contiguous amino acids comprises at least one By, wherein: (a) the first native polypeptide is encoded by a BCR gene, the second native polypeptide is encoded by an ABL gene, and (i) y is 0, and AxByCz is ERAEWRENIREQQKKCFRSFSLTSVELQMLTNSCVKLQTVHSIPLTINKEEALQRPVASDFEPQGLSEA ARWNSKENLLAGPSENDPNLFVALYDFVASG, or (ii) y is 1, and AxByCz is ELQMLTNSCVKLQTVHSIPLTINKEDDESPGLYGFLNVIVHSATGFKQSSKALQRPVASDFEPQGLSE AARWNSKENLLAGPSENDPNLFVALYDFVASGD; (b) the first native polypeptide is encoded by a C11orf95 gene, the second native polypeptide is encoded by an RELA gene, y is 1, and AxByCz is ISNSWDAHLGLGACGEAEGLGVQGAEEEEEEEEEEEEEGAGVPACPPKGPELFPLIFPAEPAQASGPY VEIIEQPKQRGMRFRYKCEGRSAGSIPGERSTD; (c) the first native polypeptide is encoded by a CBFB gene and the second native polypeptide is encoded by an MYH11 gene, y is 0, and AxByCz is LQRLDGMGCLEFDEERAQQEDALAQQAFEEARRRTREFEDRDRSHREEMEVHELEKSKRALETQME EMKTQLEELEDELQATEDAKLRLEVNMQALKGQF; (d) the first native polypeptide is encoded by a CD74 gene and the second native polypeptide is encoded by an ROS1 gene, y is 0, and AxByCz is KGSFPENLRHLKNTMETIDWKVFESWMHHWLLFEMSRHSLEQKPTDAPPKAGVPNKPGIPKLLEGS

KNSIQWEKAEDNGCRITYYILEIRKSTSNNLQNQ; (e) the first native polypeptide is encoded by an EGFR gene and the second native polypeptide is encoded by (i) an SEPT14 gene, y is 0, and AxByCz is LPQPPICTIDVYMIMVKCWMIDADSRPKFRELIIEFSKMARDPQRYLVIQLQDKFEHLKMIQQEEIRKL EEEKKQLEGEIIDFYKMKAASEALQTQLSTD; or (ii) an EGFR gene, y is 1, and AxByCz is MRPSGTAGAALLALLAALCPASRALEEKKGNYVVTDHGSCVRACGADSYEMEEDGVRKCKKCEGP CRKVCNGIGIGEFKD; (f) the first native polypeptide is encoded by a EML4 gene, the second native polypeptide is encoded by an ALK gene, y is 1, and AxByCz is SWENSDDSRNKLSKIPSTPKLIPKVTKTADKHKDVIINQAKMSTREKNSQVYRRKHQELQAMQMEL QSPEYKLSKLRTSTIMTDYNPNYCFAGKTSSISDL (g) the first native polypeptide is encoded by a FGFR3 gene, the second native polypeptide is encoded by an TACC3 gene, y is 0, and AxByCz is EGHRMDKPANCTHDLYMIMRECWHAAPSQRPTFKQLVEDLDRVLTVTSTDVKATQEENRELRSRCE ELHGKNLELGKIMDRFEEVVYQAMEEVQKQKELS, (h) the first native polypeptide is encoded by a NAB gene, the second native polypeptide is encoded by an STAT6 gene, y is at least 1, and AxByCz is RDNTLLLRRVELFSLSRQVARESTYLSSLKGSRLHPEELGGPPLKKLKQEATSKSQIMSLWGLVSKMP PEKVQRLYVDFPQHLRHLLGDWLESQPWEFLVGSDAFCC; (i) the second native polypeptide is encoded by an ERG, y is 0, and (i) the first native polypeptide is encoded by a NDRG1 gene, and AxByCz is MSREMQDVDLAEVKPLVEKGETITGLLQEFDVQEALSVVSEDQSLFECAYGTPHLAKTEMTASSSSD YGQTSKMSPRVPQQDW or (ii) the first native polypeptide is encoded by a TMPRSS2 gene, and AxByCz is MALNSEALSVVSEDQSLFECAYGTPHLAKTEMTASSSSDYGQTSKMSPRVPQQDW; (j) the first native polypeptide is encoded by a PML gene, the second native polypeptide is encoded by an RARA gene, y is 1, and AxByCz is (i) VLDMHGFLRQALCRLRQEEPQSLQAAVRTDGFDEFKVRLQDLSSCITQGKAIETQSSSSEEIVPSPPSP PPLPRIYKPCFVCQDKSSGYHYGVSACEGCKG, or (ii) RSSPEQPRPSTSKAVSPPHLDGPPSPRSPVIGSEVFLPNSNHVASGAGEAAIETQSSSSEEIVPSPPSPPPL PRIYKPCFVCQDKSSGYHYGVSACEGCKG; (k) the first native polypeptide is encoded by a RUNX1 gene, the second native polypeptide is encoded by an CBFA2T1 (RUNX1T1) gene, y is 1, and AxByCz is VARFNDLRFVGRSGRGKSFTLTITVFTNPPQVATYHRAIKITVDGPREPRNRTEKHSTMPDSPVDVKT QSRLTPPTMPPPPTTQGAPRTSSFTPTTLTNGT; (l) the first native polypeptide is encoded by a AR-v7 gene, the cryptic exon or the exon of a splice variant is encoded by the AR-v7 gene, y is 0, and AxByCz is SCKVFFKRAAEGKQKYLCASRNDCTIDKFRRKNCPSCRLRKCYEAGMTLGEKFRVGNCKHLKMTRP .

[0008] Provided herein is an isolated neoantigenic peptide comprising a tumor-specific neoepitope, wherein the isolated neoantigenic peptide is not a native polypeptide, wherein the neoepitope comprises at least 8 contiguous amino acids of an amino acid sequence represented by: AxByCz wherein each A is an amino acid corresponding to a first native polypeptide; each B is an amino acid that is not an amino acid corresponding to

the first native polypeptide or the second native polypeptide, each C is an amino acid encoded by a frameshift of a sequence encoding a second native polypeptide; x + y + z is at least 8, wherein y is absent and the at least 8 contiguous amino acids comprises at least one Cz, or y is at least 1 and the at least 8 contiguous amino acids comprises at least one By and/or at least one Cz; and (a) the first native polypeptide is encoded by an AC011997.1 gene, the second native polypeptide is encoded by a LRRC69 gene, y is 1, and AxByCz is MAGAPPPASLPPCSLISDCCASNQRDSVGVGPSEPGNNIKICNESASRK (b) the first native polypeptide is encoded by an EEF1DP3 gene, the second native polypeptide is encoded by a FRY gene, y is 1, and AxByCz is HGWRPFLPVRARSRWNRRLDVTVANGRSWKYGWSLLRVPQVNGIQVLNVSLKSSSNVISY, (c) the first native polypeptide is encoded by a MAD1L1 gene, the second native polypeptide is encoded by a MAFK gene, y is 0, and AxByCz is RLKEVFQTKIQEFRKACYTLTGYQIDITTENQYRLTSLYAEHPGDCLIFKLRVPGSSVLVTVPGL, or (d) the first native polypeptide is encoded by a PPP1R1B gene, the second native polypeptide is encoded by a STARD3 gene, y is 1, and AxByCz is AEVLKVIRQSAGQKTTCGQGLEGPWERPPPLDESERDGGSEDQVEDPALSALLLRPRPPRPEVGAHQ DEQAAQGADPRLGAQPACRGLPGLLTVPQPEPLLAPPSAA.

[0009] In examples, the isolated neoantigenic peptide comprises a sequence according to Table 1. In examples, x + y + z is at most 500, at most 250, at most 150, at most 125, or at most 100 In examples, x + y + z is at least 8, at least 50, at least 100, at least 200, or at least 300. In examples, z is at most 500, at most 250, at most 150, at most 125, or at most 100. In examples, z is at least 8, at least 50, at least 100, at least 200, or at least 300. In examples, the isolated neoantigenic peptide is from about 8 to about 500 amino acids in length. In examples, the isolated neoantigenic peptide is from about 8 to about 100 amino acids in length. In examples, the isolated neoantigenic peptide is from about 8 to about 50 amino acids in length. In examples, the isolated neoantigenic peptide is from about 15 to about 35 amino acids in length. In examples, the isolated neoantigenic peptide is from about 8 and about 15 amino acids in length. In examples, the isolated neoantigenic peptide is from about 8 and about 11 amino acids in length. In examples, the isolated neoantigenic peptide is 9 or 10 amino acids in length. In examples, the isolated neoantigenic peptide binds major histocompatibility complex (MHC) class I. In examples, the isolated neoantigenic peptide binds MHC class I with a binding affinity of about 500 nM or less. In examples, the isolated neoantigenic peptide binds MHC class I with a binding affinity of about 250 nM or less. In examples, the isolated neoantigenic peptide binds MHC class I with a binding affinity of about 50 nM or less. In examples, the isolated neoantigenic peptide is from about 8 and about 30 amino acids in length. In examples, the isolated neoantigenic peptide is from about 8 to about 25 amino acids in length. In examples, the isolated neoantigenic peptide is from about 15 to about 24 amino acids in length. In examples, the isolated neoantigenic peptide is from about 9 to about 15 amino acids in length. In examples, the isolated neoantigenic peptide binds MHC class II. In examples, the

isolated neoantigenic peptide binds MHC class II with a binding affinity of 1000 nM or less. In examples, the isolated neoantigenic peptide binds MHC class I with a binding affinity of about 500 nM or less. In examples, the isolated neoantigenic peptide further comprises flanking amino acids. In examples, the flanking amino acids are not native flanking amino acids In examples, the isolated neoantigenic peptide has a total length of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, at least 100, at least 150, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, or at least 500 amino acids. In examples, the isolated neoantigenic peptide has a total length of at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, at most 20, at most 21, at most 22, at most 23, at most 24, at most 25, at most 26, at most 27, at most 28, at most 29, at most 30, at most 40, at most 50, at most 60, at most 70, at most 80, at most 90, at most 100, at most 150, at most 200, at most 250, at most 300, at most 350, at most 400, at most 450, or at most 500 amino acids. In examples, the isolated neoantigenic peptide is a first neoantigenic peptide linked to at least a second neoantigenic peptide. In examples, the isolated neoantigenic peptide is linked to the at least second neoantigenic peptide by a poly-glycine or poly-serine linker. In examples, the second neoantigenic peptide binds MHC class I or class II with a binding affinity of less than about 1000 nM. In examples, the second neoantigenic peptide binds MHC class I or class II with a binding affinity of less than about 500 nM. In examples, isolated neoantigenic peptide and the second neoantigenic peptide bind to human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, or -DR. In examples, the isolated neoantigenic peptide binds a class I HLA and the second neoantigenic peptide binds a class II HLA. In examples, the isolated neoantigenic peptide binds a class II HLA and the second neoantigenic peptide binds a class I HLA. In examples, the isolated neoantigenic peptide further comprises a modification which increases in vivo half-life, cellular targeting, antigen uptake, antigen processing, MHC affinity, MHC stability, antigen presentation, or a combination thereof. In examples, the modification is conjugation to a carrier protein, conjugation to a ligand, conjugation to an antibody, PEGylation, polysialylation HESylation, recombinant PEG mimetics, Fc fusion, albumin fusion, nanoparticle attachment, nanoparticulate encapsulation, cholesterol fusion, iron fusion, acylation, amidation, glycosylation, side chain oxidation, phosphorylation, biotinylation, the addition of a surface active material, the addition of amino acid mimetics, or the addition of unnatural amino acids. In examples, the isolated neoantigenic peptide further comprises a modification which increases cellular targeting to antigen presenting cells. In examples, the antigen presenting cells are dendritic cells. In examples, the dendritic cells are targeted using DEC205, XCR1, CD197, CD80, CD86, CD123, CD209, CD273, CD283, CD289, CD184, CD85h, CD85j, CD85k, CD85d, CD85g, CD85a, CD141, CD11c, CD83, TSLP receptor, Clec9a, or CD1a marker. In examples, the dendritic cells are targeted using the CD141, DEC205, Clec9a, or XCR1 marker. In examples, the dendritic cells are autologous cells. In examples, one or more of the dendritic cells are bound to a T cell. In examples,

the T cell is an autologous T cell. In examples, the isolated neoantigenic peptide is not a isolated neoantigenic peptide listed in Table 2. In examples, the isolated neoantigenic peptide is linked to at least one additional neoantigenic peptide listed in Table 1 or 2.

[0010] Provided herein is an in vivo delivery system comprising an isolated neoantigenic peptide described herein. In examples, the delivery system includes cell-penetrating peptides, nanoparticulate encapsulation, virus like particles, liposomes, or any combination thereof. In examples, the cell-penetrating peptide is TAT peptide, herpes simplex virus VP22, transportan, Antp, or any combination thereof.

[0011] Provided herein is a cell comprising an isolated neoantigenic peptide described herein. In examples, the cell is an antigen presenting cell. In examples, the cell is a dendritic cell. In examples, the cell is an autologous cell. In examples, the cell is bound to a T cell. In examples, the T cell is an autologous T cell.

[0012] Provided herein is a composition comprising an isolated neoantigenic peptide described herein.

[0013] In examples, the composition comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, or at least 100 of the isolated neoantigenic peptides comprising a tumor-specific neoepitope according to Table 1 or 2. In examples, the composition comprises from about 2 to about 20 neoantigenic peptides, or from about 2 to about 30 neoantigenic peptides. In examples, the neoantigen is specific for an individual subject's tumor. In examples, the composition further comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, or at least 100 additional neoantigenic peptides. In examples, the composition comprises from about 4 to about 20 additional neoantigenic peptides, from about 4 to about 30 additional neoantigenic peptides. In examples, at least onof the additional neoantigenic peptides is specific for an individual subject's tumor. In examples, the subject specific neoantigenic peptide is selected by identifying sequence differences between the genome, exome, and/or transcriptome of the subject's tumor sample and the genome, exome, and/or transcriptome of a non-tumor sample. In examples, the samples are fresh or formalin-fixed paraffin embedded tumor tissues, freshly isolated cells, or circulating tumor cells. In examples, the sequence differences are determined by Next Generation Sequencing.

[0014] Provided herein is an isolated polynucleotide encoding an isolated neoantigenic peptide described herein. In examples, the polynucleotide is DNA. In examples, the polynucleotide is RNA. In examples, the RNA is a self-amplifying RNA. In examples, the RNA is modified to increase stability, increase cellular targeting, increase translation efficiency, adjuvanticity, cytosol accessibility, and/or decrease cytotoxicity. In examples, the modification is conjugation to a carrier protein, conjugation to a ligand, conjugation to an

antibody, codon optimization, increased GC-content, incorporation of modified nucleosides, incorporation of 5'-cap or cap analog, and/or incorporation of an unmasked poly-A sequence.

[0015] Provided herein is a cell comprising the polynucleotide described herein.

[0016] Provided herein is a vector comprising the polynucleotide described herein. In examples, the polynucleotide is operably linked to a promoter. In examples, the vector is a self-amplifying RNA replicon, plasmid, phage, transposon, cosmid, virus, or virion. In examples, the vector is derived from an adeno-associated virus, herpesvirus, lentivirus, or a pseudotype thereof.

[0017] Provided herein is an in vivo delivery system comprising the isolated polynucleotide described herein. In examples, the delivery system includes spherical nucleic acids, viruses, virus-like particles, plasmids, bacterial plasmids, or nanoparticles.

[0018] Provided herein is a cell comprising a vector or delivery system described herein. In examples, the cell is an antigen presenting cell. In examples, the cell is a dendritic cell. In examples, the cell is an immature dendritic cell.

[0019] Provided herein is a composition comprising at least one polynucleotide described herein. In examples, the composition comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, or at least 100 of the isolated polynucleotides. In examples, the composition comprises from about 2 and about 20 of the isolated polynucleotides, or from about 2 to about 30 of the isolated polynucleotides. In examples, the neoantigenic peptides are encoded by a vector comprising one or more of the the isolated polynucleotides. In examples, the composition further comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, or at least 100 additional neoantigenic polynucleotides encoding for additional neoantigenic peptides. In examples, one or more of the additional neoantigenic peptides are encoded by a vector comprising one or more of the additional neoantigenic polynucleotides. In examples, the composition comprises from about 4 to about 20 additional neoantigenic polynucleotides, or from about 4 to about 30 additional neoantigenic polynucleotides. In examples, the isolated polynucleotides and the additional neoantigenic polynucleotides are linked. In examples, the polynucleotides are linked using nucleic acids that encode a poly-glycine or poly-serine linker. In examples, at least one of the additional neoantigenic peptide is specific for an individual subject 's tumor. In examples, the subject specific neoantigenic peptide is selected by identifying sequence differences between the genome, exome, and/or transcriptome of the subject’s tumor sample and the genome, exome, and/or transcriptome of a non-tumor sample. In examples, the samples are fresh or formalin-fixed

paraffin embedded tumor tissues, freshly isolated cells, or circulating tumor cells. In examples, the sequence differences are determined by Next Generation Sequencing.

[0020] Provided herein is a T cell receptor (TCR) capable of binding at least one neoantigenic peptide described herein or an MHC-peptide complex comprising at least one neoantigenic peptide described herein. The In examples, the MHC of the MHC-peptide is MHC class I or class II. In examples, TCR is a bispecific TCR further comprising a domain comprising an antibody or antibody fragment capable of binding an antigen. In examples, the antigen is a T cell-specific antigen. In examples, the antigen is CD3. In examples, the antibody or antibody fragment is an anti-CD3 scFv.

[0021] Provided herein is a chimeric antigen receptor comprising: (i) a T cell activation molecule; (ii) a transmembrane region; and (iii) an antigen recognition moiety capable of binding at least one neoantigenic peptide described hereinor an MHC-peptide complex comprising at least one neoantigenic peptide described herein. In examples, CD3-zeta is the T cell activation molecule. In examples, the chimeric antigen receptor further comprises at least one costimulatory signaling domain. The In examples, the signaling domain is CD28, 4-1BB, ICOS, OX40, ITAM, or Fc epsilon RI-gamma. In examples, the antigen recognition moiety is capable of binding the isolated neoantigenic peptide in the context of MHC class I or class II. In examples, the CD3-zeta, CD28, CTLA-4, ICOS, BTLA, KIR, LAG3, CD137, OX40, CD27, CD40L, Tim-3, A2aR, or PD-1 transmembrane region. In examples, the neoantigenic peptide is located in the extracellular domain of a tumor associated polypeptide. In examples, the MHC of the MHC-peptide is MHC class I or class II.

[0022] Provided herein is a T cell comprising the T cell receptor or chimeric antigen receptor described herein, optionally wherein the T cell is a helper or cytotoxic T cell. In examples, the T cell is a T cell of a subject.

[0023] Provided herein is a T cell comprising a T cell receptor (TCR) capable of binding at least one neoantigenic peptide described herein or an MHC-peptide complex comprising at least one neoantigenic peptide described herein, wherein the T cell is a T cell isolated from a population of T cells from a subject that has been incubated with antigen presenting cells and one or more of the at least one neoantigenic peptide described herein for a sufficient time to activate the T cells. In examples, the T cell is a CD8+ T cell, a helper T cell or cytotoxic T cell. In examples, the population of T cells from a subject is a population of CD8+ T cells from the subject. In examples, the one or more of the at least one neoantigenic peptide described herein is a subject-specific neoantigenic peptide. In examples, the subject-specific neoantigenic peptide has a different tumor neo-epitope that is an epitope specific to a tumor of the subject. In examples, the subject-specific neoantigenic peptide is an expression product of a tumor-specific non-silent mutation that is not present in a non-tumor sample of the subject. In examples, the subject-specific neoantigenic peptide binds to a HLA protein of the subject. In examples, the subject-specific neoantigenic peptide binds to a HLA protein of the subject with an IC50 less than 500 nM. In examples, the activated CD8+ T cells are separated from the antigen presenting cells. In examples, the antigen presenting cells are dendritic cells or CD40L-expanded B

cells. In examples, the antigen presenting cells are non-transformed cells. In examples, the antigen presenting cells are non-infected cells. In examples, the antigen presenting cells are autologous. In examples, the antigen presenting cells have been treated to strip endogenous MHC-associated peptides from their surface. In examples, the treatment to strip the endogenous MHC-associated peptides comprises culturing the cells at about 26°C. In examples, the treatment to strip the endogenous MHC-associated peptides comprises treating the cells with a mild acid solution. In examples, the antigen presenting cells have been pulsed with at least one neoantigenic peptide described herein. In examples, pulsing comprises incubating the antigen presenting cells in the presence of at least about 2 μg/ml of each of the at least one neoantigenic peptide described herein. In examples, ratio of isolated T cells to antigen presenting cells is between about 30:1 and 300:1. In examples, the incubating the isolated population of T cells is in the presence of IL-2 and IL-7. In examples, the MHC of the MHC-peptide is MHC class I or class II.

[0024] Provided herein is a method for activating tumor specific T cells comprising: isolating a population of T cells from a subject; and incubating the isolated population of T cells with antigen presenting cells and at least one neoantigenic peptide described herein for a sufficient time to activate the T cells. In examples, the T cell is a CD8+ T cell, a helper T cell or cytotoxic T cell. In examples, the population of T cells from a subject is a population of CD8+ T cells from the subject. In examples, the one or more of the at least one neoantigenic peptide described herein is a subject-specific neoantigenic peptide. In examples, the subject-specific neoantigenic peptide has a different tumor neo-epitope that is an epitope specific to a tumor of the subject. In examples, the subject-specific neoantigenic peptide is an expression product of a tumor-specific non-silent mutation that is not present in a non-tumor sample of the subject. In examples, the subject-specific neoantigenic peptide binds to a HLA protein of the subject. In examples, the subject-specific neoantigenic peptide binds to a HLA protein of the subject with an IC50 less than 500 nM. In examples, the method further comprises separating the activated T cells from the antigen presenting cells. In examples, the method further comprises testing the activated T cells for evidence of reactivity against at least one of neoantigenic peptide of described herein. In examples, the antigen presenting cells are dendritic cells or CD40L-expanded B cells. In examples, the antigen presenting cells are non-transformed cells. In examples, the antigen presenting cells are non-infected cells. In examples, the antigen presenting cells are autologous. In examples, the antigen presenting cells have been treated to strip endogenous MHC-associated peptides from their surface. In examples, the treatment to strip the endogenous MHC-associated peptides comprises culturing the cells at about 26°C. In examples, the treatment to strip the endogenous MHC-associated peptides comprises treating the cells with a mild acid solution. In examples, the antigen presenting cells have been pulsed with at least one neoantigenic peptide described herein. In examples, pulsing comprises incubating the antigen presenting cells in the presence of at least about 2 μg/ml of each of at least one neoantigenic peptide described herein. In examples, ratio of isolated T cells to antigen presenting cells is between about 30:1 and 300:1. In examples,

the incubating the isolated population of T cells is in the presence of IL-2 and IL-7. In examples, the MHC of the MHC-peptide is MHC class I or class II.

[0025] Provided herein is a composition comprising activated tumor specific T cells produced by a method described herein.

[0026] Provided herein is a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of activated tumor specific T cell described herein, or produced by a method described herein. In examples, the administering comprises administering from about 10^6 to 10^{12}, from about 10^8 to 10^{11}, or from about 10^9 to 10^{10} of the activated tumor specific T cells.

[0027] Provided herein is a nucleic acid comprising a promoter operably linked to a polynucleotide encoding the T cell receptor described herein. In examples, the TCR is capable of binding the at least one neoantigenic peptide in the context of major histocompatibility complex (MHC) class I or class II.

[0028] Provided herein is a nucleic acid comprising a promoter operably linked to a polynucleotide encoding the chimeric antigen receptor described herein. In examples, the antigen recognition moiety is capable of binding the at least one neoantigenic peptide in the context of major histocompatibility complex (MHC) class I or class II. In examples, the neoantigenic peptide is located in the extracellular domain of a tumor associated polypeptide. In examples, the nucleic acid comprises the CD3-zeta, CD28, CTLA-4, ICOS, BTLA, KIR, LAG3, CD137, OX40, CD27, CD40L, Tim-3, A2aR, or PD-1 transmembrane region.

[0029] Provided herein is an antibody or antibody fragment capable of binding at least one neoantigenic peptide described herein or an MHC-peptide complex comprising at least one neoantigenic peptide described herein, optionally wherein the antibody fragment is a bi-specific T cell engager (BiTE). In examples, the antibody or antibody fragment binds to an extracellular portion of the at least one neoantigenic peptide. In examples, the native polypeptide is encoded by a gene selected from the group consisting of: β2M, wherein Cz is RMERELKKWSIQTCLSARTGLSISCTTLNSPPLKKMSMPAV, or LCSRYSLFLAWRLSSVLQRFRFTHVIQQRMESQIS; EGFR, wherein AxByCz is IPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTVQLIMQLMPFGCLLDYVREHKD NIGSQYLLNWCVQIAKGMNYLEDRRLVHRDLAA; BTK, wherein AxByCz is MIKEGSMSEDEFIEEAKVMMNLSHEKLVQLYGVCTKQRPIFIITEYMANGSLLNYLREMRHRFQTQQ LLEMCKDVCEAMEYLESKQFLHRDLAARNCLVND; or ESR1, wherein AxByCz is HLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYGLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGEA, NQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVCLKSIILLNSGVYTFLPSTLKSLEEKDHIHRVLD KITDTLIHLMAKAGLTLQQQHQRLAQLLLILSH, IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLCDLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE, IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLNDLLLEMLDAHRLHAP

TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE, or IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLSDLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE; or HER2, wherein AxByCz is GSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGLGSPYVSRLLGICLTSTV QLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCM. In examples, the antibody or antibody fragment is a bispecific antibody or antibody fragment. In examples, one antigen binding domain of the bispecific antibody or antibody fragment is an anti-CD3 binding domain.

[0030] Provided herein is a modified cell transfected or transduced with a nucleic acid described herein. In examples, the modified cell is a T cell, tumor infiltrating lymphocyte, NK-T cell, TCR-expressing cell, CD4+ T cell, CD8+ T cell, or NK cell.

[0031] Provided herein is a composition comprising the T cell receptor or chimeric antigen receptor described herein.

[0032] Provided herein is a composition comprising autologous subject T cells containing the T cell receptor or chimeric antigen receptor described herein. In examples, the composition further comprises an immune checkpoint inhibitor. In examples, the composition further comprises at least two immune checkpoint inhibitors. In examples, each of the immune checkpoint inhibitors inhibits a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands or a combination thereof. In examples, each of the immune checkpoint inhibitors interacts with a ligand of a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands or a combination thereof. In examples, the T cells are PD-1 and/or CTLA4 knockout T cells, optionally,wherein the PD-1 and/or CTLA4 knockout T cells are created using a CRISPR system. In examples, the composition further comprises an immune modulator or adjuvant. In examples, the immune modulator is a co-stimulatory ligand, a TNF ligand, an Ig superfamily ligand, CD28, CD80, CD86, ICOS, CD40L, OX40, CD27, GITR, CD30, DR3, CD69, or 4-1BB. In examples, the immune modulator is at least one cancer cell or cancer cell extract. In examples, the cancer cell is autologous to the subject in need of the composition. In examples, the cancer cell has undergone lysis or been exposed to UV radiation. In examples, the composition further comprises an adjuvant. In examples, the adjuvant is selected from the group consisting of: Poly(I:C), Poly-ICLC, STING agonist, 1018 ISS, aluminium salts, Amplivax, AS15, BCG, CP-870,893, CpG7909, CyaA, dSLIM, GM-CSF, IC30, IC31, Imiquimod, ImuFact IMP321, IS Patch, ISS, ISCOMATRIX, JuvImmune, LipoVac, MF59, monophosphoryl lipid A, Montanide IMS 1312 VG, Montanide ISA 206 VG, Montanide ISA 50 V2, Montanide ISA 51 VG, OK-432, OM-174, OM-197-MP-EC, ISA-TLR2 agonist, ONTAK, PepTel®. vector system, PLG microparticles, resiquimod, SRL172, virosomes and other virus-like particles, YF-17D, VEGF trap, R848, beta-glucan, Pam3Cys, Pam3CSK4, acrylic or methacrylic polymers, copolymers

of maleic anhydride, and QS21 stimulon. In examples, the composition induces a humoral response when administered to a subject. In examples, the composition induces a T helper cell type 1 when administered to a subject.

[0033] Provided herein is a method of inhibiting growth of a tumor cell expressing a tumor-specific neoepitope, comprising contacting the tumor cell with the peptide, polynucleotide, delivery system, vector, composition, antibody, or cells described herein.

[0034] Provided herein is a method of prophylaxis of a subject, comprising contacting a cell of the subject with the peptide, polynucleotide, delivery system, vector, composition, antibody, or cells described herein. In examples, the native polypeptide is encoded by a gene selected from the group consisting of: β2M, wherein Cz is RMERELKKWSIQTCLSARTGLSISCTTLNSPPLKKMSMPAV, or LCSRYSLFLAWRLSSVLQRFRFTHVIQQRMESQIS; EGFR, wherein AxByCz is IPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTVQLIMQLMPFGCLLDYVREHKD NIGSQYLLNWCVQIAKGMNYLEDRRLVHRDLAA; BTK, wherein AxByCz is MIKEGSMSEDEFIEEAKVMMNLSHEKLVQLYGVCTKQRPIFIITEYMANGSLLNYLREMRHRFQTQQ LLEMCKDVCEAMEYLESKQFLHRDLAARNCLVND; or ESR1, wherein AxByCz is HLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLYGLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGEA, NQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVCLKSIILLNSGVYTFLPSTLKSLEEKDHIHRVLD KITDTLIHLMAKAGLTLQQQHQRLAQLLLILSH, IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLCDLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE, IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLNDLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE, or IHLMAKAGLTLQQQHQRLAQLLLILSHIRHMSNKGMEHLYSMKCKNVVPLSDLLLEMLDAHRLHAP TSRGGASVEETDQSHLATAGSTSSHSLQKYYITGE; and HER2, wherein AxByCz is GSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGLGSPYVSRLLGICLTSTV QLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCM.

[0035] Provided herein is a method of treating cancer or initiating, enhancing, or prolonging an anti-tumor response in a subject in need thereof comprising administering to the subject the peptide, polynucleotide, vector, composition, antibody, or cells described herein. In examples, the subject is a human. In examples, the subject has cancer. In examples, the cancer is selected from the group consisting of urogenital, gynecological, lung, gastrointestinal, head and neck cancer, malignant glioblastoma, malignant mesothelioma, non-metastatic or metastatic breast cancer, malignant melanoma, Merkel Cell Carcinoma or bone and soft tissue sarcomas, haematologic neoplasias, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndrome and acute lymphoblastic leukemia, non-small cell lung cancer (NSCLC), breast

cancer, metastatic colorectal cancers, hormone sensitive or hormone refractory prostate cancer, colorectal cancer, ovarian cancer, hepatocellular cancer, renal cell cancer, pancreatic cancer, gastric cancer, oesophageal cancers, hepatocellular cancers, cholangiocellular cancers, head and neck squamous cell cancer soft tissue sarcoma, and small cell lung cancer. In examples, the peptide, polynucleotide, vector, composition, antibody, or cells described herein is for use in treating a corresponding cancer according to Table 1 or Table 2. In examples, the peptide, polynucleotide, vector, composition, antibody, or cells described herein is for use in treating a subject with an HLA type that is a corresponding HLA type according to Table 1 or Table 2. In examples, the subject has undergone surgical removal of the tumor. In examples, the peptide, polynucleotide, vector, composition, or cells is administered via intravenous, intraperitoneal, intratumoral, intradermal, or subcutaneous administration. In examples, the peptide, polynucleotide, vector, composition, or cells is administered into an anatomic site that drains into a lymph node basin. In examples, administration is into multiple lymph node basins. In examples, administration is by a subcutaneous or intradermal route. In examples, peptide is administered. In examples, administration is intratumorally. In examples, polynucleotide, optionally RNA, is administered. In examples, the polynucleotide is administered intravenously. In examples, the cell is a T cell or dendritic cell. In examples, the peptide or polynucleotide comprises an antigen presenting cell targeting moiety. In examples, the cell is an autologous cell. In examples, the method further comprises administering at least one immune checkpoint inhibitor to the subject. In examples, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In examples, the checkpoint inhibitor is selected from the group consisting of a monoclonal antibody, a humanized antibody, a fully human antibody and a fusion protein or a combination thereof In examples, the checkpoint inhibitors is a PD-1 antibody or a PD-L1 antibody. In examples, the checkpoint inhibitor is selected from the group consisting of ipilimumab, tremelimumab, nivolumab, avelumab, durvalumab, atezolizumab, pembrolizumab, and any combination thereof. In examples, the checkpoint inhibitor inhibits a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands, and any combination thereof. In examples, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands or a combination thereof. In examples, two or more checkpoint inhibitors are administered. In examples, at least one of the two or more checkpoint inhibitors is a PD-1 antibody or a PD-L1 antibody. In examples, at least one of the two or more checkpoint inhibitors is selected from the group consisting of ipilimumab, tremelimumab, nivolumab, avelumab, durvalumab, atezolizumab, and pembrolizumab. In examples, the checkpoint inhibitor and the composition are administered simultaneously or sequentially in any order. In examples, the peptide, polynucleotide, vector, composition, or cells is administered prior to the checkpoint inhibitor. In examples, the peptide, polynucleotide, vector, composition, or cells is administered after the

checkpoint inhibitor. In examples, administration of the checkpoint inhibitor is continued throughout neoantigen peptide, polynucleotide, vector, composition, or cell therapy. In examples, the neoantigen peptide, polynucleotide, vector, composition, or cell therapy is administered to subjects that only partially respond or do not respond to checkpoint inhibitor therapy. In examples, the composition is administered intravenously or subcutaneously. In examples, the checkpoint inhibitor is administered intravenously or subcutaneously. In examples, the checkpoint inhibitor is administered subcutaneously within about 2 cm of the site of administration of the composition. In examples, the composition is administered into the same draining lymph node as the checkpoint inhibitor. In examples, the method further comprises administering an additional therapeutic agent to the subject either prior to, simultaneously with, or after treatment with the peptide, polynucleotide, vector, composition, or cells. In examples, the additional agent is a chemotherapeutic agent, an immunomodulatory drug, an immune metabolism modifying drug, a targeted therapy, radiation an anti-angiogenesis agent, or an agent that reduces immune-suppression. In examples, the chemotherapeutic agent is an alkylating agent, a topoisomerase inhibitor, an anti-metabolite, or an anti-mitotic agent. In examples, the additional agent is an anti-glucocorticoid induced tumor necrosis factor family receptor (GITR) agonistic antibody or antibody fragment, ibrutinib, docetaxeol, cisplatin, a CD40 agonistic antibody or antibody fragment, an IDO inhibitor, or cyclophosphamide. In examples, the method elicits a CD4+ T cell immune response or a CD8+ T cell immune response. In examples, the method elicits a CD4+ T cell immune response and a CD8+ T cell immune response.

[0036] Provided herein is a method for stimulating an immune response in a subject, comprising administering an effective amount of modified cells or composition described herein. In examples, the immune response is cytotoxic and/or humoral immune response. In examples, the method stimulates a T cell-mediated immune response in a subject. In examples, the T cell-mediated immune response is directed against a target cell. In examples, the target cell is a tumor cell. In examples, the modified cells are transfected or transduced in vivo. In examples, the modified cells are transfected or transduced ex vivo. In examples, the modified cells are autologous subject T cells. In examples, the autologous subject T cells are obtained from a subject that has received a neoantigen peptide or nucleic acid vaccine. In examples, the neoantigen peptide or nucleic acid vaccine comprises at least one personalized neoantigen. In examples, the neoantigen peptide or nucleic acid vaccine comprises at least one additional neoantigenic peptide listed in Table 1 or 2. In examples, the subject received a chemotherapeutic agent, an immunomodulatory drug, an immune metabolism modifying drug, targeted therapy or radiation prior to and/or during receipt of the neoantigen peptide or nucleic acid vaccine. In examples, the subject receives treatment with at least one checkpoint inhibitor. In examples, the autologous T cells are obtained from a subject that has already received at least one round of T cell therapy containing a neoantigen. In examples, the method further comprises adoptive T cell therapy. In examples, the adoptive T cell therapy comprises autologous T cells. In examples, the autologous T cells are targeted against tumor antigens. In examples, the adoptive T cell therapy further

comprises allogenic T cells. In examples, the allogenic T cells are targeted against tumor antigens. In examples, the adoptive T cell therapy is administered before the checkpoint inhibitor, after the checkpoint inhibitor, or simultaneously eith the checkpoint inhibitor.

[0037] Provided herein is a method for evaluating the efficacy of any of the cells described herein, comprising: (i) measuring the number or concentration of target cells in a first sample obtained from the subject before administering the modified cell, (ii) measuring the number concentration of target cells in a second sample obtained from the subject after administration of the modified cell, and (iii) determining an increase or decrease of the number or concentration of target cells in the second sample compared to the number or concentration of target cells in the first sample. In examples, treatment efficacy is determined by monitoring a clinical outcome; an increase, enhancement or prolongation of anti-tumor activity by T cells; an increase in the number of anti-tumor T cells or activated T cells as compared with the number prior to treatment; B cell activity; CD4+ T cell activity; or a combination thereof. In examples, treatment efficacy is determined by monitoring a biomarker. In examples, the biomarker is selected from the group consisting of CEA, Her-2/neu, bladder tumor antigen, thyroglobulin, alpha-fetoprotein, PSA, CA 125, CA19.9, CA 15.3, leptin, prolactin, osteopontin, IGF-II, CD98, fascin, sPIgR, 14-3-3 eta, troponin I, circulating tumor cell RNA or DNA, and b-type natriuretic peptide. In examples, clinical outcome is selected from the group consisting of tumor regression; tumor shrinkage; tumor necrosis; anti-tumor response by the immune system; tumor expansion, recurrence or spread; or a combination thereof. In examples, the treatment effect is predicted by presence of T cells or by presence of a gene signature indicating T cell inflammation or a combination thereof.

[0038] Provided herein is a method of treating cancer or initiating, enhancing, or prolonging an anti-tumor response in a subject in need thereof comprising administering to the subject: the peptide, polynucleotide, vector, composition, antibody, or cells described herein; and at least one checkpoint inhibitor. In examples, the method further comprises administration of an immunomodulator or adjuvant. In examples, the immunomodulator or adjuvant is selected from the group consisting of Poly(I:C), Poly-ICLC, STING agonist, 1018 ISS, aluminium salts, Amplivax, AS15, BCG, CP-870,893, CpG7909, CyaA, dSLIM, GM-CSF, IC30, IC31, Imiquimod, ImuFact IMP321, IS Patch, ISS, ISCOMATRIX, JuvImmune, LipoVac, MF59, monophosphoryl lipid A, Montanide IMS 1312 VG, Montanide ISA 206 VG, Montanide ISA 50 V2, Montanide ISA 51 VG, OK-432, OM-174, OM-197-MP-EC, ISA-TLR2 agonist, ONTAK, PepTel® vector system, PLG microparticles, resiquimod, SRL172, virosomes and other virus-like particles, YF-17D, VEGF trap, R848, beta-glucan, Pam3Cys, Pam3CSK4, acrylic or methacrylic polymers, copolymers of maleic anhydride, and QS21 stimulon. a co-stimulatory ligand, a TNF ligand, an Ig superfamily ligand, CD28, CD80, CD86, ICOS, CD40L, OX40, CD27, GITR, CD30, DR3, CD69, or 4-1BB. In examples, the immunomodulator or adjuvant is Poly-ICLC. In examples, the checkpoint inhibitor is an anti-PDl antibody or antibody fragment. In examples, the anti-PDl antibody or antibody fragment is nivolumab or pembolizumab. In examples, the checkpoint inhibitor is an anti-PD-L1 antibody or antibody fragment. In examples, the anti-

PD-L1 antibody or antibody fragmentis avelumab, durvalumab or atezolizumab. In examples, the checkpoint inhibitor is an anti-CTLA4 antibody or antibody fragment. In examples, the anti-CTLA4 antibody is ipilimumab or tremelimumab. In examples, the method comprises administering both an anti-PD1 antibody and an anti-CTLA4 antibody. In examples, administration of the checkpoint inhibitor is initiated before initiation of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In examples, administration of the checkpoint inhibitor is initiated after initiation of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In examples, administration of the checkpoint inhibitor is initiated simultaneously with the initiation of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In examples, the peptide, polynucleotide, vector, composition, antibody, or cell is administered intravenously or subcutaneously. In examples, the checkpoint inhibitor is administered intravenously or subcutaneously. In examples, the checkpoint inhibitor is administered subcutaneously within about 2 cm of the site of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In examples, the peptide, polynucleotide, vector, composition, antibody, or cell is administered into the same draining lymph node as the checkpoint inhibitor.

[0039] Provided herein is a kit comprising the peptide, polynucleotide, vector, composition, antibody, cells, or composition described herein. In examples, the cancer is selected from the group consisting of: adrenal, bladder, breast, cervical, colorectal, glioblasoma, head and neck, kidney chromophobe, kidney clear cell, kidney papillary, liver, lung adenocarcinoma, lung squamous, ovarian, pancreatic, melanoma, stomach, uterine corpus endometrial,and uterine carcinosarcoma. In examples, the cancer is selected from the group consisting of: prostate cancer, bladder, lung squamous, NSCLC, breast, head and neck, lung adenocarcinoma, GBM, Glioma, CML, AML, supretentorial ependyomas, acute promyelocytic leukemia, solitary fibrous tumors, and crizotinib resistant cancer. In examples, the cancer is selected from the group consisting of: CRC, head and neck, stomach, lung squamous, lung adenocarcinoma, Prostate, Bladder. stomach, renal cell carcinoma, and uterine. In examples, the cancer is selected from the group consisting of: melanoma, lung squamous, DLBCL, uterine, head and neck, uterine, liver, and CRC. In examples, the cancer is selected from the group consisting of: lymphoid cancer; Burkitt lymphoma, neuroblastoma, prostate adenocarcinoma, colorectal adenocarcinoma; Uterine/Endometrium Adenocarcinoma; MSI+; endometrium serous carcinoma; endometrium carcinosarcoma-malignant mesodermal mixed tumour; glioma; astrocytoma; GBM, acute myeloid leukaemia associated with MDS; chronic lymphocytic leukaemia-small lymphocytic lymphoma; myelodysplastic syndrome; acute myeloid leukaemia; luminal NS carcinoma of breast; chronic myeloid leukaemia; ductal carcinoma of pancreas; chronic myelomonocytic leukaemia; myelofibrosis; myelodysplastic syndrome; prostate adenocarcinoma; essential thrombocythaemia; and medullomyoblastoma. In examples, the cancer is selected from the group consisting of: colorectal, uterine, endometrial, and stomach. In examples, the cancer is selected from the group consisting of: cervical, head and neck, anal, stomach, Burkitt's lymphoma, and nasopharyngeal carcinoma. In examples, the cancer is selected from the group consisting of: bladder,

colorectal, and stomach. In examples, the cancer is selected from the group consisting of: lung, CRC, melanoma, breast, NSCLC, and CLL. In examples, the subject is a partial or non-responder to checkpoint inhibitor therapy. In examples, the cancer is selected from the group consisting of: bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), breast cancer, cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), chronic lymphocytic leukaemia (CLL), colorectal cancer (CRC), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), Prostate Cancer, skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), thyroid adenocarcinoma (THCA), and uterine corpus endometrioid carcinoma (UCEC). In examples, the cancer is selected from the group consisting of: colorectal cancer, uterine cancer, endometrium cancer, stomach cancer, and Lynch syndrome. In examples, the cancer is an MSI+ cancer.

[0040] The present disclosure is directed to an isolated neoantigenic peptide comprising a tumor-specific neoepitope defined in Table 1, wherein the isolated neoantigenic peptide is not a native polypeptide. The present disclosure is also directed to an isolated neoantigenic peptide which comprises a tumor-specific neoepitope and is defined in Table 1.

[0041] In some examples, the isolated neoantigenic peptide is between about 8 to about 50 amino acids in length. In another example, the isolated neoantigenic peptide is between about 15 to about 35 amino acids in length. In another example, the isolated neoantigenic peptide is about 15 amino acids or less in length. In another example, the isolated neoantigenic peptide is between about 8 and about 11 amino acids in length. In another example, the isolated neoantigenic peptide is 9 or 10 amino acids in length. In another example, the isolated neoantigenic peptide binds major histocompatibility complex (MHC) class I. In another example, the isolated neoantigenic peptide binds MHC class I with a binding affinity of less than about 500 nM.

[0042] In some examples, the isolated neoantigenic peptide is about 30 amino acids or less in length. In another example, the isolated neoantigenic peptide is between about 6 and about 25 amino acids in length. In another example, the isolated neoantigenic peptide is between about 15 and about 24 amino acids in length. In another example, the isolated neoantigenic peptide is between about 9 and about 15 amino acids in length. In another example, the isolated neoantigenic peptide binds MHC class II. In another example, the isolated neoantigenic peptide binds MHC class II with a binding affinity of less than about 1000 nM.

[0043] In some examples, the isolated neoantigenic peptide further comprises flanking amino acids. In another example, the flanking amino acids are not native flanking amino acids. In another example, the isolated neoantigenic peptide is linked to at least a second neoantigenic peptide. In another example, the peptides are linked using a poly-glycine or poly-serine linker. In another example, the second neoantigenic peptide binds MHC class I or class II with a binding affinity of less than about 1000 nM. In another example, the second neoantigenic peptide binds MHC class I or class II with a binding affinity of less than about 500

nM. In another example, both of the neoepitopes bind to human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, or -DR. In another example, the isolated neoantigenic peptide binds a class I HLA and the second neoantigenic peptide binds a class II HLA. In another example, the isolated neoantigenic peptide binds a class II HLA and the second neoantigenic peptide binds a class I HLA.

[0044] In some examples, the isolated neoantigenic peptide further comprises modifications which increase in vivo half-life, cellular targeting, antigen uptake, antigen processing, MHC affinity, MHC stability, or antigen presentation. In another example, the modification is conjugation to a carrier protein, conjugation to a ligand, conjugation to an antibody, PEGylation, polysialylation HESylation, recombinant PEG mimetics, Fc fusion, albumin fusion, nanoparticle attachment, nanoparticulate encapsulation, cholesterol fusion, iron fusion, acylation, amidation, glycosylation, side chain oxidation, phosphorylation, biotinylation, the addition of a surface active material, the addition of amino acid mimetics, or the addition of unnatural amino acids. In another example, the cells that are targeted are antigen presenting cells. In another example, the antigen presenting cells are dendritic cells. In another example, the dendritic cells are targeted using DEC205, XCR1, CD197, CD80, CD86, CD123, CD209, CD273, CD283, CD289, CD184, CD85h, CD85j, CD85k, CD85d, CD85g, CD85a, CD141, CD11c, CD83, TSLP receptor, Clec9a or CD1a marker. In another example, the dendritic cells are targeted using the CD141, DEC205, or XCR1 marker.

[0045] In some examples, the disclosure provides an in vivo delivery system comprising an isolated neoantigenic peptide described herein. In another example, the delivery system includes cell-penetrating peptides, nanoparticulate encapsulation, virus like particles, or liposomes. In another example, the cell-penetrating peptide is TAT peptide, herpes simplex virus VP22, transportan, or Antp.

[0046] In some examples, the disclosure is directed to a cell comprising an isolated neoantigenic peptide described herein. In another example, the cell is an antigen presenting cell. In another example, the cell is a dendritic cell.

[0047] In some examples, the disclosure is directed to a composition comprising an isolated neoantigenic peptide described herein. In another example, the composition comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or at least 30 of the isolated neoantigenic peptides comprising a tumor-specific neoepitope defined in Table 1 or 2. In another example, the composition comprises between 2 and 20 neoantigenic peptides. In another example, the composition further comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25, at least 26, at least 27, at least 28, at least 29, or at least 30 additional neoantigenic peptides. In another example, the composition comprises between about 4 and about 20 additional neoantigenic peptides. In another example, the additional neoantigenic peptide is specific

for an individual patient's tumor. In another example, the patient specific neoantigenic peptide is selected by identifying sequence differences between the genome, exome, and/or transcriptome of the patient's tumor sample and the genome, exome, and/or transcriptome of a non-tumor sample. In another example, the samples are fresh or formalin-fixed paraffin embedded tumor tissues, freshly isolated cells, or circulating tumor cells. In another example, the sequence differences are determined by Next Generation Sequencing.

[0048] In some examples, the disclosure is directed to an isolated polynucleotide encoding an isolated neoantigenic peptide described herein. In another example, the isolated polynucleotide is RNA, optionally a self-amplifying RNA. In another example, the RNA is modified to increase stability, increase cellular targeting, increase translation efficiency, adjuvanticity, cytosol accessibility, and/or decrease cytotoxicity. In another example, the modification is conjugation to a carrier protein, conjugation to a ligand, conjugation to an antibody, codon optimization, increased GC-content, incorporation of modified nucleosides, incorporation of 5'-cap or cap analog, and/or incorporation of an unmasked poly-A sequence.

[0049] In some examples, the disclosure is directed to a cell comprising a polynucleotide described herein.

[0050] In some examples, the disclosure is directed to a vector comprising a polynucleotide described herein. In another example, the polynucleotide is operably linked to a promoter. In another example, the vector comprises a self-amplifying RNA replicon, plasmid, phage, transposon, cosmid, virus, or virion. In another example, the vector is an adeno-associated virus, herpesvirus, lentivirus, or pseudotypes thereof.

[0051] In some examples, the disclosure is directed to an in vivo delivery system comprising an isolated polynucleotide described herein. In another example, the delivery system includes spherical nucleic acids, viruses, virus-like particles, plasmids, bacterial plasmids, or nanoparticles.

[0052] In some examples, the disclosure is directed to a cell comprising a vector or delivery system described herein. In another example, the cell is an antigen presenting cell. In another example, the cell is a dendritic cell. In another example, the cell is an immature dendritic cell.

[0053] In some examples, the disclosure is directed to a composition comprising at least one polynucleotide described herein. In another example, the composition comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or at least 30 of the isolated polynucleotides. In another example, the composition comprises between about 2 and about 20 polynucleotides that encode neoantigenic peptides. In another example, the composition further comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or at least 30 additional neoantigenic polynucleotides encoding for additional neoantigenic peptides. In some examples, the composition comprises between about 4 and about 20 additional neoantigenic polynucleotides. In some examples, the isolated

polynucleotides and the additional neoantigenic polynucleotides are linked. In some examples, the polynucleotides are linked using nucleic acids that encode a poly-glycine or poly-serine linker. In some examples, at least one of the additional neoantigenic peptide is specific for an individual patient's tumor. In some examples, the patient specific neoantigenic peptide is selected by identifying sequence differences between the genome, exome, and/or transcriptome of the patient's tumor sample and the genome, exome, and/or transcriptome of a non-tumor sample. In some examples, the samples are fresh or formalin-fixed paraffin embedded tumor tissues, freshly isolated cells, or circulating tumor cells. In some examples, the sequence differences are determined by Next Generation Sequencing.

[0054] In some examples, the disclosure is directed to a T cell receptor (TCR) capable of binding at least one neoantigenic peptide described herein. In some examples, the TCR is capable of binding the isolated neoantigenic peptide in the context of MHC class I or class II.

[0055] In some examples, the disclosure is directed to a chimeric antigen receptor comprising: (i) a T cell activation molecule; (ii) a transmembrane region; and (iii) an antigen recognition moiety capable of binding an isolated neoantigenic peptide described herein. In some examples, the chimeric antigen receptor contains CD3-zeta as the T cell activation molecule. In some examples, the chimeric antigen receptor further comprises at least one costimulatory signaling domain. In some examples, the signaling domain is CD28, 4-1BB, ICOS, OX40, ITAM, or Fc epsilon RI-gamma. In some examples, the antigen recognition moiety is capable of binding the isolated neoantigenic peptide in the context of MHC class I or class II. In some examples, the chimeric antigen receptor comprises the CD3-zeta, CD28, CTLA-4, ICOS, BTLA, KIR, LAG3, CD137, OX40, CD27, CD40L, Tim-3, A2aR, or PD-1 transmembrane region. In some examples, the tumor-specific epitope is located in the extracellular domain of a tumor associated polypeptide.

[0056] In some examples, the disclosure is directed to a T cell comprising the T cell receptor or chimeric antigen receptor described herein. In some examples, the T cell is a helper or cytotoxic T cell.

[0057] In some examples, the disclosure is directed to a nucleic acid comprising a promoter operably linked to a polynucleotide encoding a T cell receptor described herein. In some examples, the TCR is capable of binding the at least one neoantigenic peptide in the context of major histocompatibility complex (MHC) class I or class II. In another example, the nucleic acid comprises a promoter operably linked to a polynucleotide encoding a chimeric antigen receptor described herein. In another example, the antigen recognition moiety is capable of binding the at least one neoantigenic peptide in the context of major histocompatibility complex (MHC) class I or class II. In some examples, the tumor-specific epitope is located in the extracellular domain of a tumor associated polypeptide. In some examples, the nucleic acid comprises the CD3-zeta, CD28, CTLA-4, ICOS, BTLA, KIR, LAG3, CD137, OX40, CD27, CD40L, Tim-3, A2aR, or PD-1 transmembrane region.

[0058] In some examples, the disclosure is directed to an antibody capable of binding at least one neoantigenic peptide described herein.

[0059] In some examples, the disclosure is directed to a modified cell transfected or transduced with a nucleic acid described herein. In some examples, the modified cell is a T cell, tumor infiltrating lymphocyte, NK-T cell, TCR-expressing cell, $CD4^+$ T cell, $CD8^+$ T cell, or NK cell.

[0060] In some examples, the disclosure is directed to a composition comprising a T cell receptor or chimeric antigen receptor described herein. In some examples, the composition comprises autologous patient T cells containing a T cell receptor or chimeric antigen receptor. In some examples, the composition further comprises an immune checkpoint inhibitor. In some examples, the composition further comprises at least two immune checkpoint inhibitors. In some examples, each of the immune checkpoint inhibitors inhibits a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands or a combination thereof. In some examples, each of the immune checkpoint inhibitors interacts with a ligand of a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands or a combination thereof.

[0061] In some examples, the composition further comprises an immune modulator or adjuvant. In another example, the immune modulator is a co-stimulatory ligand, a TNF ligand, an Ig superfamily ligand, CD28, CD80, CD86, ICOS, CD40L, OX40, CD27, GITR, CD30, DR3, CD69, or 4-1BB. In another example, the immune modulator is at least one cancer cell or cancer cell extract. In another example, the cancer cell is autologous to the subject in need of the composition. In another example, the cancer cell has undergone lysis or been exposed to UV radiation. In another example, the adjuvant induces a humoral when administered to a subject. In another example, the adjuvant induces a T helper cell type 1 when administered to a subject.

[0062] In some examples, the disclosure is directed to a method of inhibiting growth of a tumor cell expressing a tumor-specific neoepitope described herein, comprising contacting the tumor cell with the peptide, polynucleotide, delivery system, vector, composition, antibody, or cells of the disclosure.

[0063] In some examples, the disclosure is directed to a method of treating cancer or initiating, enhancing, or prolonging an anti-tumor response in a subject in need thereof comprising administering to the subject the peptide, polynucleotide, vector, composition, antibody, or cells described herein.

[0064] In some examples, the cancer is selected from adrenal, bladder, breast, cervical, colorectal, glioblasoma, head and neck, kidney chromophobe, kidney clear cell, kidney papillary, liver, lung adeno, lung squamous, ovarian, pancreatic, melanoma, stomach, uterine corpus endometrial,and uterine carcinosarcoma.

[0065] In some examples, the cancer is selected from the group of: prostate cancer, bladder, lung squamous, NSCLC, breast, head and neck, lung adenocarcinoma, GBM, Glioma, CML, AML, supretentorial ependyomas, acute promyelocytic leukemia, solitary fibrous tumors, and crizotinib resistant cancer.

[0066] In some examples, the cancer is selected from the group consisting of CRC, head and neck, stomach, lung squamous, lung adeno., Prostate, Bladder. stomach, renal cell carcinoma, and uterine.

[0067] In some examples, the cancer is selected from the group consisting of melanoma, lung squamous, DLBCL, uterine, head and neck, uterine, liver, and CRC.

[0068] In some examples, the cancer is selected from the group consisting of lymphoid cancer; Burkitt lymphoma, neuroblastoma, prostate adenocarcinoma, colorectal adenocarcinoma; Uterine/Endometrium Adenocarcinoma; MSI^+; endometrium serous carcinoma; endometrium carcinosarcoma-malignant mesodermal mixed tumour; glioma; astrocytoma; GBM, acute myeloid leukaemia associated with MDS; chronic lymphocytic leukaemia-small lymphocytic lymphoma; myelodysplastic syndrome; acute myeloid leukaemia; luminal NS carcinoma of breast; chronic myeloid leukaemia; ductal carcinoma of pancreas; chronic myelomonocytic leukaemia; myelofibrosis; myelodysplastic syndrome; prostate adenocarcinoma; essential thrombocythaemia; and medullomyoblastoma..

[0069] In some examples, the cancer is selected from the group consisting of colorectal, uterine, endometrial, and stomach.

[0070] In some examples, the cancer is selected from the group consisting of cervical, head and neck, anal, stomach, Burkitt's lymphoma, and nasopharyngeal carcinoma.

[0071] In some examples, the cancer is selected from the group consisting of bladder, colorectal, and stomach.

[0072] In some examples, the cancer is selected from the group consisting of lung, CRC, melanoma, breast, NSCLC, and CLL.

[0073] In some examples, the cancer is selected from the group consisting of adrenocortical carcinoma (ACC), acute promyelocytic leukemia, acute myeloid leukemia (AML), AML associated with myelodysplastic syndromes (MDS), anal cancer, astrocytoma, bladder cancer, bladder urothelial carcinoma (BLCA), breast cancer, breast invasive carcinoma (BRCA), Burkitt's Lymphoma, castration-resistant prostate cancer, cervical cancer, cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), chronic lymphocytic leukaemia-small lymphocytic lymphoma, chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), chronic myelomonocytic leukaemia, colorectal adenocarcinoma, colorectal cancer (CRC), Crizotinib resistant non-small cell lung cancer (NSCLC), diffuse large B-cell lymphoma (DLBCL), ductal carcinoma of pancreas, endometrium carcinosarcoma-malignant mesodermal mixed tumour, endometrium serous carcinoma, essential thrombocythaemia, glioblastoma multiforme (GBM), Glioma, head and neck cancer, head and neck squamous cell carcinoma (HNSC), invasive lobular carcinoma (ILC) LumA breast cancer, kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), acute myeloid leukemia (LAML), liver hepatocellular carcinoma (LIHC), liver cancer, lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), Luminal NS carcinoma of breast, lung cancer, lymphoid cancer, medullomyoblastoma, melanoma, microsatellite instability $(MSI)^+$ colorectal cancer (CRC), MSI^+ endometrioid carcinoma, MSI^+ stomach cancer, MSI^+ uterine/endometrium cancer, myelodysplastic syndrome, myelofibrosis, nasopharyngeal carcinoma, neuroblastoma, non-small cell lung

cancer (NSCLC), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), prostate cancer, renal cell carcinoma, skin cutaneous melanoma (SKCM), solitary fibrous tumors, stomach adenocarcinoma (STAD), stomach cancer, supretentorial ependyomas, thyroid adenocarcinoma (THCA), uterine corpus endometrioid carcinoma (UCEC), or uterine carcinosarcoma (UCS), uterine cancer, and uterine/endometrium adenocarcinoma.

[0074] In some examples, the cancer is selected from the group consisting of bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), breast cancer, cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), chronic lymphocytic leukaemia (CLL), colorectal cancer (CRC), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), Prostate Cancer, skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), thyroid adenocarcinoma (THCA), and uterine corpus endometrioid carcinoma (UCEC).

[0075] In some examples, the subject is a human. In another example, the subject has cancer. In another example, the cancer is selected from the group consisting of urogenital, gynecological, lung, gastrointestinal, head and neck cancer, malignant glioblastoma, malignant mesothelioma, non-metastatic or metastatic breast cancer, malignant melanoma, Merkel Cell Carcinoma or bone and soft tissue sarcomas, haematologic neoplasias, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndrome and acute lymphoblastic leukemia, non-small cell lung cancer (NSCLC), breast cancer, metastatic colorectal cancers, hormone sensitive or hormone refractory prostate cancer, colorectal cancer, ovarian cancer, hepatocellular cancer, renal cell cancer, pancreatic cancer, gastric cancer, oesophageal cancers, hepatocellular cancers, cholangiocellular cancers, head and neck squamous cell cancer soft tissue sarcoma, and small cell lung cancer. In another example, the subject has undergone surgical removal of the tumor. In another example, the peptide, polynucleotide, vector, composition, or cells is administered via intravenous, intraperitoneal, intratumoral, intradermal, or subcutaneous administration. In another example, the peptide, polynucleotide, vector, composition, or cells is administered into an anatomic site that drains into a lymph node basin. In another example, the administration is into multiple lymph node basins. In another example, the administration is by a subcutaneous or intradermal route.

[0076] In some examples of the method, a peptide is administered. In another example, the administration is intratumorally. In another example of the method, a polynucleotide, optionally RNA, is administered. In another example, the polynucleotide is administered intravenously. In some examples of the method, a cell is administered. In another example, the cell is a T cell or dendritic cell. In another example, the peptide or polynucleotide comprises an antigen presenting cell targeting moiety.

[0077] In another example of the method, at least one immune checkpoint inhibitor is also administered to the subject. In another example, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In

another example, the checkpoint inhibitor is selected from the group consisting of a monoclonal antibody, a humanized antibody, a fully human antibody and a fusion protein or a combination thereof. In another example, the checkpoint inhibitor inhibits a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands or a combination thereof. In another example, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from the group consisting of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, and B-7 family ligands or a combination thereof. In another example, two or more checkpoint inhibitors are administered. In another example, the checkpoint inhibitors are: (i) ipilimumab or tremelimumab, and (ii) nivolumab. In another example, the checkpoint inhibitor and the composition are administered simultaneously or sequentially in any order. In another example, a neoantigenic peptide, polynucleotide, vector, composition, or cells is administered prior to the checkpoint inhibitor. In another example, a peptide, polynucleotide, vector, composition, or cells is administered after the checkpoint inhibitor. In another example, the checkpoint inhibitor is continued throughout neoantigen peptide, polynucleotide, vector, composition, or cell therapy. In another example, the neoantigen peptide, polynucleotide, vector, composition, or cell therapy is administered to subjects that only partially respond or do not respond to checkpoint inhibitor therapy. In another example, the composition is administered intravenously or subcutaneously. In another example, the checkpoint inhibitor is administered intravenously or subcutaneously. In another example, the checkpoint inhibitor is administered subcutaneously within about 2 cm of the site of administration of the composition. In another example, the composition is administered into the same draining lymph node as the checkpoint inhibitor.

[0078] In some examples of the method, an additional agent is administered. In another example, the agent is a chemotherapeutic agent, an immunomodulatory drug, an immune metabolism modifying drug, a targeted therapy, radiation an anti-angiogenesis agent, or an agent that reduces immune-suppression. In another example, the chemotherapeutic agent is an alkylating agent, a topoisomerase inhibitor, an anti-metabolite, or an anti-mitotic agent. In another example, the additional agent is an anti-glucocorticoid induced tumor necrosis factor family receptor (GITR) agonistic antibody or antibody fragment, ibrutinib, docetaxeol, cisplatin, or cyclophosphamide. In another example, the administration elicits a $CD4^+$ T cell immune response. In another example, the administration elicits a $CD4^+$ T cell immune response and a $CD8^+$ T cell immune response.

[0079] In some examples, the disclosure is directed to a method for stimulating an immune response in a subject, comprising administering an effective amount of modified cells or composition described herein. In another example, the immune response is cytotoxic and/or humoral immune response. In another example, the method stimulates a T cell-mediated immune response in a subject. In another example, the T cell-mediated immune response is directed against a target cell. In another example, the target cell is a tumor cell. In another

example, the modified cells are transfected or transduced in vivo. In another example, the modified cells are transfected or transduced ex vivo. In another example, the modified cells are autologous patient T cells. In another example, the autologous patient T cells are obtained from a patient that has received a neoantigen peptide or nucleic acid vaccine. In another example, the neoantigen peptide or nucleic acid vaccine comprises at least one personalized neoantigen. In another example, the neoantigen peptide or nucleic acid vaccine comprises at least one additional neoantigenic peptide described herein. In another example, the patient received a chemotherapeutic agent, an immunomodulatory drug, an immune metabolism modifying drug, targeted therapy or radiation prior to and/or during receipt of the neoantigen peptide or nucleic acid vaccine. In another example, the patient receives treatment with at least one checkpoint inhibitor. In another example, the autologous T cells are obtained from a patient that has already received at least one round of T cell therapy containing a neoantigen. In another example, the method further comprises adoptive T cell therapy. In another example, the adoptive T cell therapy comprises autologous T cells. In another example, the autologous T cells are targeted against tumor antigens. In another example, the adoptive T cell therapy further comprises allogenic T cells. In another example, the allogenic T cells are targeted against tumor antigens. In another example, the adoptive T cell therapy is administered before the checkpoint inhibitor.

[0080] In some examples, the disclosure is directed to a method for evaluating the efficacy of treatment comprising: (i) measuring the number or concentration of target cells in a first sample obtained from the subject before administering the modified cell, (ii) measuring the number concentration of target cells in a second sample obtained from the subject after administration of the modified cell, and (iii) determining an increase or decrease of the number or concentration of target cells in the second sample compared to the number or concentration of target cells in the first sample. In another example, the treatment efficacy is determined by monitoring a clinical outcome; an increase, enhancement or prolongation of anti-tumor activity by T cells; an increase in the number of anti-tumor T cells or activated T cells as compared with the number prior to treatment; B cell activity; CD4 T cell activity; or a combination thereof. In another example, the treatment efficacy is determined by monitoring a biomarker. In another example, the biomarker is selected from the group consisting of CEA, Her-2/neu, bladder tumor antigen, thyroglobulin, alpha-fetoprotein, PSA, CA 125, CA19.9, CA 15.3, leptin, prolactin, osteopontin, IGF-II, CD98, fascin, sPIgR, 14-3-3 eta, troponin I, and b-type natriuretic peptide. In another example, the clinical outcome is selected from the group consisting of tumor regression; tumor shrinkage; tumor necrosis; anti-tumor response by the immune system; tumor expansion, recurrence or spread; or a combination thereof. In another example, the treatment effect is predicted by presence of T cells or by presence of a gene signature indicating T cell inflammation or a combination thereof.

[0081] In some examples, the disclosure is directed to a method of treating cancer or initiating, enhancing, or prolonging an anti-tumor response in a subject in need thereof comprising administering to the subject: (a) the peptide, polynucleotide, vector, composition, antibody, or cells described herein; and (b) at least one

checkpoint inhibitor. In another example, the method further comprises administration of an immunomodulator or adjuvant. In another example, the immunomodulator or adjuvant is selected from the group consisting of Poly(I:C), Poly-ICLC, STING agonist, 1018 ISS, aluminium salts, Amplivax, AS15, BCG, CP-870,893, CpG7909, CyaA, dSLIM, GM-CSF, IC30, IC31, Imiquimod, ImuFact IMP321, IS Patch, ISS, ISCOMATRIX, JuvImmune, LipoVac, MF59, monophosphoryl lipid A, Montanide IMS 1312 VG, Montanide ISA 206 VG, Montanide ISA 50 V2, Montanide ISA 51 VG, OK-432, OM-174, OM-197-MP-EC, ISA-TLR2 agonist, ONTAK, PepTel® vector system, PLG microparticles, resiquimod, SRL172, virosomes and other virus-like particles, YF-17D, VEGF trap, R848, beta-glucan, Pam3Cys, Pam3CSK4, acrylic or methacrylic polymers, copolymers of maleic anhydride, and QS21 stimulon. a co-stimulatory ligand, a TNF ligand, an Ig superfamily ligand, CD28, CD80, CD86, ICOS, CD40L, OX40, CD27, GITR, CD30, DR3, CD69, or 4-1BB. In another example, the immunomodulator or adjuvant is Poly-ICLC. In another example, the checkpoint inhibitor is an anti-PDl antibody or antibody fragment. In another example, the inhibitor of the PD-1 pathway is nivolumab. In another example, the checkpoint inhibitor is an anti-CTLA4 antibody or antibody fragment. In another example, the anti-CTLA4 antibody is ipilimumab or tremelimumab. In another example, the method comprises administering both an anti-PD1 antibody and an anti-CTLA4 antibody. In another example, the administration of the checkpoint inhibitor is initiated before initiation of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In another example, the administration of the checkpoint inhibitor is initiated after initiation of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In another example, the administration of the checkpoint inhibitor is initiated simultaneously with the initiation of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In another example, the peptide, polynucleotide, vector, composition, antibody, or cell is administered intravenously or subcutaneously. In another example, the checkpoint inhibitor is administered intravenously or subcutaneously. In another example, the checkpoint inhibitor is administered subcutaneously within about 2 cm of the site of administration of the peptide, polynucleotide, vector, composition, antibody, or cell. In another example, the peptide, polynucleotide, vector, composition, antibody, or cell is administered into the same draining lymph node as the checkpoint inhibitor.

[0082] In some examples of the therapeutic methods, the additional therapeutic agent is for example, a chemotherapeutic or biotherapeutic agent, radiation, or immunotherapy. Any suitable therapeutic treatment for a particular cancer may be administered. Examples of chemotherapeutic and biotherapeutic agents include, but are not limited to, an angiogenesis inhibitor, such ashydroxy angiostatin K l-3, DL-a-Difluoromethy!-oroithine, endostatiii, fumagillin, genistein, minocycline, staurosporine, and thalidomide; a DNA intercaitor/cross-linker, such as Bleomycin, Carboplatin, Carrmistme, Chlorambucil, Cyclophosphamide, cis-Diammineplat nurn(D) dichloride (Cispiatin), Melphalan, Mitoxantrone, and Oxaliplatin; a DNA synthesis inhibitor, such as (±)-Amethopterin (Methotrexate), 3-Amino-1,2,4-beiizotriazine 1,4-dioxide, Aminopterin, Cytosine β-D-arabinofuraiioside, 5-Fmoro-5'~ deoxyuridine, 5-Fhsorouracil, Ganciclovir, Hydroxyurea, and

Mitomycin C; a DNA-RNA transcription regulator, such as Aetinomycin D, Dau orubicin, Doxorubicin, Homoharringtonine, and Idarubicin; an oη/.γηκ; inhibitor, such as S(-i-)-Camptothecm, Curcumin, (-)-Deguelm, 5,6-Dichiorobenzimidazole 1 -β-D-ribofuranoside, Etoposide, Formestane, Fostriecin, Hispidin, 2-Immo-l-imidazoli-dineacetic acid (Cyclocreatine), Mevmolin, Trichostatin A, Tyrphostin AG 34, and Tyrphostin AG 879; a gene regulator, such as 5-Aza-2'-deoxycytidine, 5-Azacytidine, Cholecalciferol (Vitamin D3), 4-Hydroxytamoxifen, Melatonin, Mifepristone, Raloxifene, all trans-Retinal (Vitamin A aldehyde), Retinoic acid all trans (Vitamin A acid), 9-cis-Retinoic Acid, 13-cis-Retinoic acid, Retinol (Vitamin A), Tamoxifen, and Troglitazone; a microtubule inhibitor, such as Colchicine, docetaxel, Dolastatirs 15, Nocodazole, Paclitaxel, Podophyl!otoxin, Rhizoxin, Vinblastine, Vi cristine, Vindesiiie, and Vinorelbine (Navelbine); and an unclassified therapeutic agent, such as 17-(Allyiamino)-l 7-demethoxygeIdanamycin, 4-Amino-l,8-naphthalimide, Apigenin, Brefeldin A, Cimetidine, Dichioromethylene-diphosphonic acid, Leuprolide (Leuprorelin), Luteinizing Hormone-Releasing Hormone, Pifithrin-a, Rapamycin, Sex hormone-binding globulin, Thapsigargin, and Urinary trypsin inhibitor fragment (Bikunin). The therapeutic agent may be altretamine, amifostine, asparaginase, capecitabine, cladribine, cisapride, cyiarahirse, dacarbazine (DT1C), dactinomycin, dronabinol, epoetin alpha, “filgrastim, fludarabine, gemcitabine, granisetron, ifosfamide, irinotecan, lansoprazole, levamisole, leucovorin, megestrol, mesna, metoclopramide, mitotane, omeprazole, ondansetron, pilocarpine, prochloroperazine, or topotecan hydrochloride. The therapeutic agent may be a monoclonal antibody such as rituximab (Rituxan®), alemtuzumab (Campath®), Bevacizumab (Avastin®), Cetuximab (Erbitux®), panitumumab (Vectibix®), and trastuzumab (Herceptin®), Vemurafenib (Zelboraf®) imatinib mesylate (Gleevec®), erlotinib (Tarceva®), gefitinib (Iressa®), Vismodegib (Erivedge™), 90Y-ibritumomab tiuxetan, 1311-tosit.umomab, ado-trastuzumab emtansine, lapatinib (Tykerb®), pertuzumab (Perjeta™), ado-trastuzumab emtansine (adcyla™), regorafenib (Stivarga®), sunitinib (Sutent®), Denosumab (Xgeva®), sorafenib (Nexavar®), pazopanib (Votrient®), axitinib (Inita®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif®), ofatumumab (Arzerra®), obinutuzumab (Gazyva™), ibrutinib (Imbruvica™), idelalisib (Zydelig®), crizotinib (Xalkori®), erlotinib (Tarceva®), afatimb dimaleate (Giiotrif®), ceritinib (LDK378/Zykadia), Tositumomab and 1311-tositumomab (Bexxar®), ibritumomab tiuxetan (Zevalin®), brentuximab vedotin (Adcetris®), bortezomib (Velcade®), siltuximab (Sylvant™), trametinib (ekinist®), dabrafenib (Tafmlar®), pembrolizimiab (Keytruda®), carfilzomib (Kyprolis®), Ramucirumab (Cyramza™), Cabozantinib (Cometriq™), vandetanib (Caprelsa®), Optionally, the therapeutic agent is a neoantigen. The therapeutic agent may be a cytokine such as interferons (INFs), interlcukins (ILs), or hematopoietic growth factors. The therapeutic agent may be INF-

α, IL-2, Aldesleukin, IL-2, Erythropoietin, Granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor. The therapeutic agent may be a targeted therapy such as toremifene (Fareston®), fulvestrant (Faslodex®), anastrozole (Arimidex®), exemestane (Aromasin®), letrozole (Femara®), ziv-aflibercept (Zaltrap®), Aiitretinoin (Panretin®), temsirolimus (Torisel®), Tretinoin (Vesanoid®), denileukin diftitox (Ontak®), vorinostat (Zoiinza®), romidepsin (Istodax®), bexarotene (Targretin®), pralatrexate (Foiotyn®), !enaliomide (Revlimid®), belinostat (Beleodaq™), lenaliomide (Revlimid®), pomalidomide (Pomalyst®), Cabazitaxel (Jevtana®), enzaluiamide (Xtandi®), abiraterone acetate (Zytiga®), radium 223 chloride (Xofigo®), or everolimus (Afiniior®). Aditionally, the therapeutic agent may be an epigenetic targeted drug such as HDAC inhibitors, kinase inhibitors, DNA methyltransferase inhibitors, histone demethylase inhibitors, or histone methylation inhibitors. The epigenetic drugs may be Azacitidine (Vidaza), Decitabine (Dacogen), Vorinostat (Zoiinza), Romidepsin (Istodax), or Ruxolitinib (Jakafi). For prostate cancer treatment, a preferred chemotherapeutic agent with which anti- CTLA-4 can be combined is paclitaxel (TAXOL).

[0083] In some examples, the disclosure is directed to a kit comprising any neoantigen therapeutic described herein.

[0084] Where examples of the disclosure are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but also each member of the group individually and all possible subgroups of the main group, and also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

INCORPORATION BY REFERENCE

[0085] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference in their entirety for all purposes, to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. For example, all publications and patents mentioned herein are incorporated herein by reference in their entirety for the purpose of describing and disclosing the kits, compositions, and methodologies that are described in the publications, which might be used in connection with the methods, kits, and compositions described herein. The documents discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors described herein are not entitled to antedate such disclosure by virtue of prior invention or for any other reason.

BRIEF DESDCRIPTION OF THE DRAWINGS

[0086] **Figure 1** depicts and exemplary graph of 562 peptides with predicted affinity for select HLA Class I molecule between 1 nM and 100,000 nM (plotted on x-axis) that were synthesized. Actual affinity (IC_{50} (nM)) was measured as described (y-axis). Thick vertical and horizontal lines denote 500 nM cutoff between weak and very weak predicted and observed binders, respectively. Diagonal dotted line depicts line-of-best fit (Graphpad Prism) with R^2 of 0.45.

[0087] **Figure 2** depicts and exemplary graph of 275 peptides from Figure 1 that were tested for stability ($T_{1/2}$; hrs) on their respective HLA Class I molecules. Peptides were binned according to observed affinity from Figure 1. Median and interquartile range is shown for each bin.

[0088] **Figure 3A** depicts and exemplary graph of HLA-A02:01$^+$ T cells co-cultured with monocyte-derived dendritic cells loaded with TMPRSS2::ERG fusion neoepitope (ALNSEALSV; HLA-A02:01) for 10 days. CD8$^+$ T cells were analyzed for antigen-specificity for TMPRSS2::ERG fusion neoepitope using multimers (initial: BV421 and PE).

[0089] **Figure 3B** depicts and exemplary graph of HLA-A02:01$^+$ T cells co-cultured with monocyte-derived dendritic cells loaded with TMPRSS2::ERG fusion neoepitope (ALNSEALSV; HLA-A02:01) for 10 days. CD8$^+$ T cells were analyzed for antigen-specificity for TMPRSS2::ERG fusion neoepitope using multimers (validation: APC and BUV396).

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical composition in the preparation of a medicament for treating cancer in a subject in need thereof, wherein the pharmaceutical composition comprises:

(a) a recombinant or synthetic tumor-specific neoantigenic peptide;

(b) a polynucleotide encoding the recombinant or synthetic tumor-specific neoantigenic peptide;

(c) an antigen presenting cell expressing or loaded with the recombinant or synthetic tumor-specific neoantigenic peptide; or

(d) a T cell having a T cell receptor (TCR) that recognizes the recombinant or synthetic tumor-specific neoantigenic peptide;

wherein the recombinant or synthetic tumor-specific neoantigenic peptide comprises a tumor-specific neoepitope comprising one or more contiguous mutant amino acids encoded by a frameshift, wherein the tumor-specific neoepitope is encoded by a GATA Binding Protein 3 (GATA3) gene of cancer cells of the subject or is expressed by cancer cells of the subject, and wherein the tumor-specific neoepitope is not expressed by non-cancer cells of the subject or is not encoded by a GATA3 gene of the non-cancer cells,

wherein the recombinant or synthetic tumor-specific neoantigenic peptide is from 8 to 100 amino acids in length; and

wherein:

i. the subject expresses a major histocompatibility complex (MHC) encoded by an HLA B07:02 allele and the tumor-specific neoepitope is EPHLALQPL (SEQ ID NO: 529) or MFATLQRSSL (SEQ ID NO: 567);

ii. the subject expresses a MHC encoded by an HLA B08:01 allele and the tumor-specific neoepitope is EPHLALQPL (SEQ ID NO: 529), FLKAESKIMF (SEQ ID NO: 536), IMKPKRDGYM (SEQ ID NO: 550), LHFCRSSIM (SEQ ID NO: 556), MFATLQRSSL (SEQ ID NO: 567) or YMFLKAESKI (SEQ ID NO: 598);

iii. the subject expresses a MHC encoded by an HLA A24:02 allele and the tumor-specific neoepitope is MFLKAESKI (SEQ ID NO: 568) or YMFLKAESKI (SEQ ID NO: 598);

iv. the subject expresses a MHC encoded by an HLA A02:01 allele and the tumor-specific neoepitope is VLPEPHLAL (SEQ ID NO: 594); and/or

v. the subject expresses a MHC encoded by an HLA A03:01 allele and the tumor-specific neoepitope is VLWTTPPLQH (SEQ ID NO: 1430).

2. The use of claim 1, wherein the tumor-specific neoepitope binds to a MHC class I molecule with a binding affinity of 500 nM or less.

3. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of VLWTTPPLQH (SEQ ID NO: 1430) and the subject expresses a MHC molecule encoded by a A03:01 HLA allele.

4. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of EPHLALQPL (SEQ ID NO: 529) and the subject expresses a MHC molecule encoded by a B07:02 or B08:01 HLA allele.

5. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of FLKAESKIMF (SEQ ID NO: 536) and the subject expresses a MHC molecule encoded by a B08:01 HLA allele.

6. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of IMKPKRDGYM (SEQ ID NO: 550) and the subject expresses a MHC molecule encoded by a B08:01 HLA allele.

7. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of LHFCRSSIM (SEQ ID NO: 556) and the subject expresses a MHC molecule encoded by a B08:01 HLA allele.

8. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of MFATLQRSSL (SEQ ID NO: 567) and the subject expresses a MHC molecule encoded by a B07:02 or B08:01 HLA allele.

9. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of MFLKAESKI (SEQ ID NO: 568) and the subject expresses a MHC molecule encoded by a A24:02 HLA allele.

10. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of VLPEPHLAL (SEQ ID NO: 594) and the subject expresses a MHC molecule encoded by a A02.01 HLA allele.

11. The use of claims 1 or 2, wherein the tumor-specific neoepitope has a sequence of YMFLKAESKI (SEQ ID NO: 598) and the subject expresses a MHC molecule encoded by a A24:02 or B08:01 HLA allele.

12. The use of any one of claims 1-11, wherein the cancer is breast cancer.
13. The use of claim 12, wherein the breast cancer is selected from the group consisting of metastatic breast cancer, breast invasive carcinoma, luminal non-squamous (NS) carcinoma of breast, HER-2-positive breast cancer and microsatellite instability (MSI+) breast cancer.
14. The use of any one of claims 1-13, wherein the pharmaceutical composition and an immune checkpoint inhibitor is to be administered to the subject.
15. The use of any one of claims 1-14, wherein the recombinant or synthetic tumor-specific neoantigenic peptide is to be administered to the subject in combination with letrozole.
16. The use of any one of claims 1-14, wherein the recombinant or synthetic tumor-specific neoantigenic peptide is to be administered to the subject in combination with fulvestrant.
17. The use of any one of claims 1-16, wherein the polynucleotide encoding the recombinant or synthetic tumor-specific neoantigenic peptide is DNA.
18. The use of any one of claims 1-16, wherein the polynucleotide encoding the recombinant or synthetic tumor-specific neoantigenic peptide is a messenger RNA (mRNA).
19. The use of any one of claims 1-18, wherein the polynucleotide encoding the recombinant or synthetic tumor-specific neoantigenic peptide is comprised in a vector.
20. The use of any one of claims 1-19, wherein the recombinant or synthetic tumor-specific neoantigenic peptide is greater than 10 amino acids in length.
21. The use of claim 20, wherein the recombinant or synthetic tumor-specific neoantigenic peptide is processed endogenously.
22. The use of claim 21, wherein the recombinant or synthetic tumor-specific neoantigenic peptide sequence comprises one or more alterations to improve a likelihood for efficient proteasomal processing of the peptide.
23. A pharmaceutical composition as defined in the use of any one of claims 1-22.
24. A recombinant T cell receptor (TCR) capable of binding at least one recombinant or synthetic tumor-specific neoantigenic peptide as defined in the use of any one of claims 1-22 in an MHC-peptide complex comprising the at least one recombinant or synthetic tumor-specific neoantigenic peptide.
25. The recombinant TCR of claim 24, wherein the MHC of the MHC-peptide complex is MHC class I or class II.

26. The recombinant TCR of claim 24 or 25, wherein the TCR is a chimeric antigen receptor, comprising: i) a T cell activation molecule; (ii) a transmembrane region; and (iii) an antigen recognition moiety capable of binding the at least one recombinant or synthetic tumor-specific neoantigenic peptide.

27. The chimeric antigen receptor of claim 26, wherein the T cell activation molecule is a CD3 binding antibody or fragment thereof.

28. A pharmaceutical composition as defined in the use of any one of claims 1-22, wherein the neoantigenic peptide is from 8 to 50 amino acids in length.