

CELL IMMUNOTHERAPY FOR THE TREATMENT OF CANCER

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 63/001,275, filed March 28, 2020, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] Embodiments of the disclosure concern at least the fields of cell biology, molecular biology, immunology, and medicine.

BACKGROUND

[0003] Glioblastoma (GBM) is an aggressive malignancy with a poor prognosis. After recurrence, there is no standard therapy, and survival is less than 9 months. Results from three first-in-man chimeric antigen receptor (CAR) T-cell trials targeting IL13R α 2 (Brown *et al.*, 2016), Her2/CMV (Ahmed *et al.*, 2010), and EGFRvIII (O'Rourke *et al.*, 2017) were recently reported with disappointing clinical results.

[0004] There is currently a critical need to advance cellular therapies against GBM, as well as other solid tumors, especially with the great responses they proved in leukemia and lymphoma. The present disclosure provides solutions to long-felt needs of advancing cellular therapy against cancers, including at least glioblastoma.

BRIEF SUMMARY

[0005] Embodiment Examples of the disclosure include methods and compositions related to cell therapies for a medical condition. The cell therapies encompass immune effector cells or other cells for administration to an individual in need thereof. In specific embodiment examples, the cells are enhanced in activity compared to other cell therapies because the cells comprise one or more exogenously provided interleukins (IL) and optionally comprise one or more other heterologous gene products, such as one or more engineered receptors. The cells may be exposed externally to one or more cytokines (such as in culture) and/or they may be transfected to express a heterologous cytokine (as opposed to the endogenous cytokines expressed from the genome of the cell), including from one or more vectors. The disclosure encompasses immunotherapy with *ex vivo*-expanded and activated natural killer (NK) cells in combination with exogenous cytokines (for example, IL-2, IL-12, IL-21, IL-18, IL-15, IL-7) or NK cells engineered to secrete

or express membrane-bound or tethered cytokines (for example, IL-2, IL-12, IL-21, IL-18, IL-15, IL-7) on their surface for the treatment of glioblastoma (GBM) and other cancers. Prior to delivery, the cells may have been exposed under suitable conditions to an effective amount of IL-2, IL-12, IL-21, IL-18, IL-15, and/or IL-7 in culture. In particular embodimentexamples, the cells comprise one or more exogenously provided interleukins that are not IL-15, although in alternative embodimentexamples the cells comprise exogenously provided IL-15.

[0005a] In one aspect, the present disclosure refers to a composition comprising natural killer (NK) cells, said NK cells comprising one or more exogenously provided interleukins (IL), wherein the IL is not IL-15, and wherein the NK cell comprises one or more engineered receptors.

[0006] In specific embodimentexamples, the disclosure encompasses methods of treating glioblastoma using adoptive cell therapy comprising NK cells. In particular aspectexamples, the NK cells are effective particularly against glioblastoma stem cells, and the disclosure provides methods and compositions for enhancing NK cells against glioblastoma cells of any kind, including glioblastoma cells. The disclosure encompasses methods of killing glioblastoma stem cells in an individual with glioblastoma comprising administering to the individual an effective amount of NK cells engineered to express one or more exogenously provided IL and/or that have been cultured in the presence of one or more IL. In some embodimentexamples, the glioblastoma stem cells are killed by NK cells that express one or more engineered receptors, and the engineered receptors may or may not target one or more antigens that are expressed on glioblastoma stem cells. In certain cases, glioblastoma stem cells are killed by NK cells that have been engineered to express one or more engineered receptors, that have been engineered to express one or more exogenous cytokines, and/or that have been cultured in the presence of one or more IL.

[0007] EmbodimentExample of the disclosure include compositions comprising immune effector cells of any kind including natural killer (NK) cells, said cells comprising one or more exogenously provided IL, optionally wherein the IL is not IL-15, and wherein the cell comprises one or more engineered receptors. In particular embodimentexamples, the IL is selected from the group consisting of IL-12, IL-21, IL-2, IL-15, IL-18, IL-7, and a combination thereof. In specific cases, the IL is IL-12, IL-21, or both. In any embodimentexample of the disclosure, the IL may be secreted, tethered, or membrane bound in the cell. As used herein, “exogenously provided” may be further defined as being expressed from a vector in the cells and/or wherein the cells are externally exposed to the one or more IL.

[0008] In particular embodimentexamples, engineered receptors utilized in cells of the disclosure are engineered antigen receptors, such as a chimeric antigen receptor (CAR) or a T cell receptor (TCR). The antigen may be a cancer antigen, including a solid tumor antigen, or it may be an

antigen associated with a pathogen. In cases wherein the antigen is a cancer antigen, specific examples include an antigen selected from the group consisting of 5T4, 8H9, $\alpha_v\beta_6$ integrin, BCMA, B7-H3, B7-H6, CAIX, CA9, CD5, CD19, CD20, CD22, CD30, CD33, CD38, CD44, CD44v6, CD44v7/8, CD70, CD123, CD138, CD171, CEA, CSPG4, CS1, CLL1, CD99, DLL3, EGFR, EGFR family including ErbB2 (HER2), EGFRvIII, EGP2, EGP40, , ERBB3, ERBB4, ErbB3/4, EPCAM, EphA2, EpCAM, FAP, FBP, fetal AchR, FR α , GD2, GD3, Glypican-3 (GPC3), HLA-A1+MAGE1, HLA-A1+NY-ESO-1, IL-11R α , IL-13R α 2, Lambda, Lewis-Y, L1CAM, Kappa, KDR, MCSP, Mesothelin, Muc1, Muc16, NCAM, NKG2D Ligands, NY-ESO-1, PRAME, PSC1, PSCA, PSMA, ROR1, SP17, Survivin, TAG72, TEMs, HMW-MAA, VEGFR2, and a combination thereof. In some embodiment examples, the engineered receptor is a cytokine receptor, chemokine receptor, or homing receptor, or a cell may have a combination of these.

[0009] In particular embodiment example, the cells of the disclosure are cells, including NK cells, that comprise a suicide gene. In some cases, the cell is reduced or inhibited in expression of one or more of endogenous genes selected from the group consisting of TDAG8, NKG2A, SIGLEC-7, LAG3, TIM3, CISH, FOXO1, TGFB β 2, TIGIT, CD96, ADORA2, NR3C1, PD1, PDL-1, PDL-2, CD47, SIRPA, SHIP1, ADAM17, RPS6, 4EBP1, CD25, CD40, IL21R, ICAM1, CD95, CD80, CD86, IL10R, CD5, CD7, and a combination thereof.

[0010] Embodiment Examples of the disclosure include populations of any cells encompassed herein. In one aspect, the present disclosure refers to a population of cells comprising any one of the compositions disclosed herein, comprised in a suitable medium.

[0011] In one aspect, the present disclosure refers to use of any one of the compositions disclosed herein in the manufacture of a medicament for treating cancer in an individual. In one embodiment example, there are methods of treating cancer in an individual, comprising the step of administering a therapeutically effective amount of any of the compositions encompassed herein. In some cases, the cancer cells in the individual have increased expression of NK ligands, such as MICA/B, ULBP1, ULBP2/5, ULBP3, B7-H6, CD112, CD155, HLA-ABC, HLA-DR, HLA-3, or a combination thereof. The engineered NK cells may express one or more engineered antigen receptors that target one or more of these NK ligands, or that may target other targets. The compositions may be provided to the individual intracranially, by injection, intravenously, intraarterially, intraperitoneally, intratracheally, intratumorally, intramuscularly, endoscopically, intralesionally, intracranially, percutaneously, subcutaneously, regionally, by perfusion, in a tumor microenvironment, or a combination thereof.

[0012] For cancer treatments, the cancer may be a solid tumor or is not a solid tumor. The cancer may be of the lung, brain, breast, blood, skin, pancreas, liver, colon, head and neck, kidney, thyroid, stomach, spleen, gallbladder, bone, ovary, testes, endometrium, prostate, rectum, anus, cervix, or is hematological. In specific cases, the cancer is glioblastoma.

[0013] In treatment method embodimentexamples of the disclosure, the individual may be a mammal, such as a human, dog, cat, horse, cow, sheep, pig, or rodent. The individual may be administered one or more additional cancer therapies, including surgery, radiation, chemotherapy, hormone therapy, immunotherapy, or a combination thereof. In some embodimentexamples, any method of the disclosure further comprises the step of diagnosing cancer in the individual. In some embodimentexamples, any method of the disclosure further comprises the step of generating the cells. Any cells utilized herein may be autologous or allogeneic with respect to the individual.

[0014] The foregoing has outlined rather broadly the features and technical advantages of the present disclosure in order that the detailed description that follows may be better understood. Additional features and advantages will be described hereinafter which form the subject of the claims herein. It should be appreciated by those skilled in the art that the conception and specific embodimentexamples disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present designs. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope as set forth in the appended claims. The novel features which are believed to be characteristic of the designs disclosed herein, both as to the organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] For a more complete understanding of the present disclosure, reference is now made to the following descriptions taken in conjunction with the accompanying drawing, in which: