highly specific targeting is the limited availability of truly tumor-restricted antigens. Accordingly, new methods of treating neoplasia are urgently required.

Summary of the Invention

[0004a] In one aspect, provided herein is a T cell, the T cell comprising: a) a chimeric antigen receptor (CAR) that binds to a first antigen with a dissociation constant (K_d) of 1×10^{-8} M or more; and, b) a chimeric co-stimulating receptor (CCR) that binds to a second antigen; wherein binding of the CAR to the first antigen is capable of delivering an activation signal to the T-cell, and wherein binding of the CCR to the second antigen is capable of delivering a costimulatory signal to the T cell but does not alone deliver an activation signal to the T cell.

[0004b] In another aspect, provided herein is use of a pharmaceutical composition in the manufacture of a medicament for the treatment of tumors, wherein the pharmaceutical composition comprises the T cell as described herein and a pharmaceutically acceptable excipient.

[0004c] In another aspect, provided herein is use of the T cell as described herein in the manufacture of a medicament for inducing tumor cell death, and/or treating or preventing tumors in an individual organism.

[0004d] In another aspect, provided herein is the production method of a T cell as described herein comprising introducing into the T cell a first nucleic acid molecule that encodes a CAR and a second nucleic acid molecule that encodes a CCR.

[0004e] In another aspect, provided herein is a kit comprising the T cell as described herein.

[0004f] In another aspect, provided herein is a vector, the vector comprising a) a first polynucleotide that encodes a chimeric antigen receptor (CAR) that binds to a first antigen with a dissociation constant (K_d) of 1×10^{-8} M or more; and, b) a second polynucleotide that encodes a chimeric co-stimulating receptor (CCR); wherein binding of the CAR to the first antigen is capable of delivering an activation signal to the T cell comprising the vector and, wherein binding of the CCR to the second antigen is capable of delivering a costimulatory signal to the T cell but does not alone deliver an activation signal to the T cell.

[0004g] In another aspect, provided herein is a T cell comprising the vector as described herein.

[0004h] In another aspect, provided herein is a pharmaceutical composition comprising the T cell as described herein and a pharmaceutically acceptable excipient for use in therapy.

[0004i] In another aspect, provided herein is the T cell as described herein for use in therapy.

[0005] The present invention generally provides immunoresponsive cells, including T cells and Natural Killer (NK) cells, expressing an antigen binding receptor (e.g., CAR or TCR) having immune cell activating actvity and a chimeric co-stimulating receptor (CCR), and methods of use therefore for the treatment of neoplasia, infectious disease, and other pathologies.

[0006] In one aspect, the invention provides an isolated immunoresponsive cell having an antigen recognizing receptor that binds a first antigen with low affinity, where the binding activates the immunoresponsive cell, and a chimeric co stimulating receptor (CCR) that binds a second antigen and stimulates the immunoresponsive cell.

[0007] In another aspect, the invention provides a method of inducing tumor cell death in a subject, the method comprising administering an effective amount of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen with low affinity, where the binding activates the immunoresponsive cell, and a chimeric co-stimulating receptor (CCR) that binds a second antigen and stimulates the immunoresponsive cell, thereby inducing tumor cell death in the subject.

[0008] In still another aspect, the invention provides a method of treating or preventing a neoplasia in a subject, the method comprising administering an effective amount of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen with low affinity, where the binding activates the immunoresponsive cell, and a chimeric co-stimulating receptor (CCR) that binds a second antigen and stimulates the immunoresponsive cell, thereby treating or preventing a neoplasia in the subject.

[0009] In yet another aspect, the invention provides a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a T cell