involving stimulation of an immune response, such as targeted T cell therapies. Accordingly, novel therapeutic strategies for treating neoplasia are urgently required.

SUMMARY

In one aspect, the present disclosure refers to an immunoresponsive cell comprising:

1) a chimeric antigen receptor (CAR) that binds to ROR1 and comprises an intracellular signaling domain of a CD3ζ polypeptide and an intracellular signaling domain of a co-stimulatory receptor; and

2) a nucleic acid encoding a recombinant CD40L,

wherein the immunoresponsive cell is selected from the group consisting of T cells, Natural Killer cells, cytotoxic T cells, regulatory T cells, and combinations thereof.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising an effective amount of an immunoresponsive cell as described herein and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure refers to a kit for treating a neoplasm, the kit comprising an immunoresponsive cell comprising: a) a chimeric antigen receptor (CAR) that binds to ROR1 and comprises an intracellular signaling domain of a CD3ζ polypeptide and an intracellular signaling domain of a co-stimulatory receptor; and b) a nucleic acid encoding a recombinant CD40L, wherein the immunoresponsive cell is selected from the group consisting of T cells, Natural Killer cells, cytotoxic T cells, regulatory T cells, and combinations thereof.

The present disclosure generally provides immunoresponsive cells (e.g., T cells, Natural Killer (NK) cells, cytotoxic T lymphocytes (CTLs), and regulatory T cells), expressing an antigen binding receptor (e.g., CAR or TCR) having immune cell activating activity and a single-chain variable fragment (scFv) that binds an antigen having immunosuppressive activity (e.g., CD47, PD-1, CTLA-4, and ligands thereof), thereby reducing or eliminating the immunosuppressive activity of the antigen.

The disclosure further provides immunoresponsive cells (e.g., T cells, Natural Killer (NK) cells, cytotoxic T lymphocytes (CTLs), and regulatory T cells), expressing an antigen binding receptor (e.g., CAR or TCR) having immune cell activating activity and a single-chain variable fragment (scFv) that binds an antigen having immunostimulatory or proinflammatory activity (e.g., CD28, OX-40, 4-1BB,

CD40 and ligands thereof), thereby enhancing the immunostimulatory activity of the antigen.

The disclosure further provides immunoresponsive cells (e.g., T cells, Natural Killer (NK) cells, cytotoxic T lymphocytes (CTLs), and regulatory T cells), expressing an antigen binding receptor (e.g., CAR or TCR) having immune cell activating activity and CD40L, for example, exogenous CD40L (CD40L that has been introduced directly or indirectly into the cell (for example, via a vector of naked nucleic acid comprising a nucleic acid sequence encoding CD40L), as compared to endogenous CD40L arising in the cell itself), thereby enhancing the immunostimulatory activity of the antigen.

Accordingly, the disclosure provides methods of using such immunoresponsive cells for the treatment of neoplasia, infectious disease, and other pathologies.

In one example, the disclosure provides an isolated immunoresponsive cell having an antigen recognizing receptor that binds an antigen, where the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity.

In another example, the disclosure provides a method of treating or preventing neoplasia in a subject, the method comprising administering, to the subject, an

What is claimed is:

1. An immunoresponsive cell comprising:

1) a chimeric antigen receptor (CAR) that binds to ROR1 and comprises an intracellular signaling domain of a CD3ζ polypeptide and an intracellular signaling domain of a co-stimulatory receptor; and

2) a nucleic acid encoding a recombinant CD40L,

wherein the immunoresponsive cell is selected from the group consisting of T cells, Natural Killer cells, cytotoxic T cells, regulatory T cells, and combinations thereof.

2. The immunoresponsive cell of claim 1, wherein the nucleic acid is comprised in a vector.

3. The immunoresponsive cell of claim 2, wherein the vector is a viral vector.

4. The immunoresponsive cell of claim 3, wherein the viral vector is a retroviral vector.

5. The immunoresponsive cell of claim 1, wherein the immunoresponsive cell is a T cell.

6. The immunoresponsive cell of claim 1, wherein the recombinant CD40L enhances an immune response of the immunoresponsive cell.

7. The immunoresponsive cell of claim 1, wherein the co-stimulatory receptor is CD28, 4-1BB, or OX-40.

8. The immunoresponsive cell of claim 1, wherein the co-stimulatory receptor is CD28.

9. A pharmaceutical composition comprising an effective amount of an immunoresponsive cell of claim 1 and a pharmaceutically acceptable excipient.

10. The pharmaceutical composition of claim 9, wherein said composition is for treating a neoplasm and the immunoresponsive cell is a T cell.

11. A kit for treating a neoplasm, the kit comprising an immunoresponsive cell comprising: a) a chimeric antigen receptor (CAR) that binds to ROR1 and comprises an intracellular signaling domain of a CD3ζ polypeptide and an intracellular signaling domain

of a co-stimulatory receptor; and b) a nucleic acid encoding a recombinant CD40L, wherein the immunoresponsive cell is selected from the group consisting of T cells, Natural Killer cells, cytotoxic T cells, regulatory T cells, and combinations thereof.

12. The kit of claim 11, wherein the kit further comprises written instructions for using said cell for the treatment of a subject having a neoplasm.

13. The kit of claim 11, wherein the co-stimulatory receptor is CD28, 4-1BB, or OX40.

14. The kit of claim 11, wherein the co-stimulatory receptor is CD28.