rapid and robust upregulation of numerous inflammatory mediators, including cytokines, chemokines and interferons. Co-incident with the expression of these genes is the migration of DCs to draining lymph nodes (dLN) and the upregulation of factors important for T cell activation, such as MHC and co-stimulatory molecules. Thus, the process of PRR signaling leads to a shift in DC activities from a non-stimulatory (naïve) state to an "activated" state (K. Inaba, *et al*. *J. Exp. Med*., vol. 191, no. 6, pp. 927–36, Mar. 2000 I. Mellman and R. M. Steinman, *Cell*, vol. 106, no. 3, pp. 255–8, Aug. 2001).

SUMMARY

There is a need to diversify current approaches to cancer immunotherapy. Accordingly, described herein are methods of inducing or enhancing an adaptive immune response to a cancer in a subject and methods of treating cancer in a subject. In one aspect, the present disclosure provides a use of (i) a Toll-Like Receptor (TLR) ligand; (ii) a non-canonical inflammasome-activating lipid; and (iii) a cancer immunogen in the manufacture of a medicament for combination therapy to induce or enhance an adaptive immune response to a cancer in a subject. In another aspect, the present disclosure provides a use of (i) a Toll-Like Receptor (TLR) ligand; (ii) a non-canonical inflammasome-activating lipid and (iii) a cancer immunogen in the manufacture of a medicament for combination therapy to treat cancer in a subject. In some examples, the methods hyperactivate dendritic cells (DCs), which induce T helper type I (TH1) and cytotoxic T lymphocyte (CTL) responses in the absence of TH2 immunity. Hyperactivating stimuli drive T cell responses that protect against tumors that are sensitive or resistant to PD-1 inhibition. These protective responses depend on inflammasomes in DCs and can be generated using tumor lysates as immunogens.

Thus, provided herein are methods of inducing or enhancing an adaptive immune response to a cancer in a subject that comprise administering an effective amount of (i) a Toll-Like Receptor (TLR) ligand;, (ii) a non-canonical inflammasome-activating lipid,; and (iii) an cancer immunogen to the subject.

Also provided herein are methods of treating cancer in a subject that comprise administering an effective amount of (i) a Toll-Like Receptor (TLR) a TLR ligand;, (ii) a non-canonical inflammasome-activating lipid, and (iii) a cancern immunogen to the subject.

In some examples of the methods described herein, the cancer immunogen is an infectious agent immunogen, wherein an infection with the infectious agent is associated with development of cancer.

In some examples of the methods described herein, the cancer immunogen is from a cancer immunogen cell.

In some examples of the methods described herein, the cancer immunogen is or comprises whole tumor cell lysate.

In some examples of the methods described herein, the TLR ligand is selected from a TLR1 ligand, a TLR2 ligand, a TLR3 ligand, a TLR4 ligand, a TLR5 ligand, a TLR6 ligand, a TLR7 ligand, a TLR8 ligand, a TLR9 ligand, a TLR10 ligand, a TLR11 ligand, a TLR12 ligand, a TLR13 ligand, and combinations thereof.

In some examples of the methods described herein, the TLR ligand is a TLR4 ligand.

In some examples of the methods described herein, the TLR4 ligand is selected from monophosphoryl lipid A (MPLA), lipopolysaccharide (LPS), or combinations thereof.

In some examples of the methods described herein, the non-canonical inflammasome-activating lipid comprises a species of oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (oxPAPC).

In some examples of the methods described herein, the non-canonical inflammasome-activating lipid comprises 2-[[(2R)-2-[(E)-7-carboxy-5-hydroxyhept-6-enoyl]oxy-3-hexadecanoyloxypropoxy]-hydroxyphosphoryl]oxyethyl-trimethylazanium (**HOdiA-PC**), [(2R)-2-[(E)-7-carboxy-5-oxohept-6-enoyl]oxy-3-hexadecanoyloxypropyl] 2-(trimethylazaniumyl)ethyl phosphate (**KOdiA-PC**), 1-palmitoyl-2-(5-hydroxy-8-oxo-octenoyl)-sn-glycero-3-phosphorylcholine (**HOOA-PC**), 2-[[(2R)-2-[(E)-5,8-dioxooct-6-enoyl]oxy-3-hexadecanoyloxypropoxy]-hydroxyphosphoryl]oxyethyl-trimethylazanium (**KOOA-PC**), [(2R)-3-hexadecanoyloxy-2-(5-oxopentanoyloxy)propyl] 2-(trimethylazaniumyl)ethyl phosphate (**POVPC**), [(2R)-2-(4-carboxybutanoyloxy)-3-hexadecanoyloxypropyl] 2-(trimethylazaniumyl)ethyl phosphate (**PGPC**), [(2R)-3-hexadecanoyloxy-2-[4-[3-[(E)-[2-[(Z)-oct-2-enyl]-5-oxocyclopent-3-en-1-ylidene]methyl]oxiran-2-yl]butanoyloxy]propyl] 2-(trimethylazaniumyl)ethyl phosphate (**PECPC**), [(2R)-3-hexadecanoyloxy-2-[4-[3-[(E)-[3-hydroxy-2-[(Z)-oct-2-enyl]-5-oxocyclopentylidene]methyl]oxiran-2-yl]butanoyloxy]propyl] 2-(trimethylazaniumyl)ethyl phosphate (**PEIPC**), or a combination thereof.

In some examples of the methods described herein, the non-canonical inflammasome-activating lipid comprises [(2R)-2-(4-carboxybutanoyloxy)-3-hexadecanoyloxypropyl] 2-(trimethylazaniumyl)ethyl phosphate (**PGPC**).

In some examples of the methods described herein, the subject is a mammal.

In some examples of the methods described herein, the subject is a human.

In some examples of the methods described herein, the TLR ligand, oxPAPC species, and cancer immunogen are administered as part of a pharmaceutical composition.

In some examples of the methods described herein, the immune response is a prophylactic immune response.

In some examples of the methods described herein, the immune response is a therapeutic immune response.

In some examples of the methods described herein, the adaptive immune response comprises T-cell activation.

In some examples of the methods described herein, the method further comprises treating the subject with one or more therapeutic interventions.

In some examples of the methods described herein, the TLR ligand, oxPAPC species, and cancer immunogen, and one or more therapeutic interventions are co-administered or sequentially administered.

In some examples of the methods described herein, the one or more therapeutic interventions comprises: radiation, chemotherapy, surgery, therapeutic antibodies, immunomodulatory agents, proteasome inhibitors, pan-deacetylase (DAC) inhibitors, histone deacetylase (HDAC) inhibitors, checkpoint inhibitors, adoptive cell therapies, vaccines or combinations thereof.

In some examples of the methods described herein, the adoptive cell therapies comprise: CAR-T cell therapy, CAR- NK cell therapy, T cells, dendritic cells or combinations thereof.Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

What is claimed:

1. Use of (i) a Toll-Like Receptor (TLR) ligand; (ii) a non-canonical inflammasome-activating lipid; and (iii) a cancer immunogen in the manufacture of a medicament for combination therapy to induce or enhance an adaptive immune response to a cancer in a subject.

2. Use of (i) a Toll-Like Receptor (TLR) ligand; (ii) a non-canonical inflammasome-activating lipid and (iii) a cancer immunogen in the manufacture of a medicament for combination therapy to treat cancer in a subject.

3. The use of claim 1 or claim 2, wherein the cancer immunogen is an infectious agent immunogen, wherein an infection with the infectious agent is associated with development of cancer.

4. The use of claim 1 or 2, wherein the cancer immunogen is from a cancer cell.

5. The use of claim 4, wherein the cancer immunogen is or comprises whole tumor cell lysate.

6. The use of any one of claims 1–5, wherein the TLR ligand is selected from a TLR1 ligand, a TLR2 ligand, a TLR3 ligand, a TLR4 ligand, a TLR5 ligand, a TLR6 ligand, a TLR7 ligand, a TLR8 ligand, a TLR9 ligand, a TLR10 ligand, a TLR11 ligand, a TLR12 ligand, a TLR13 ligand, and combinations thereof.

7. The use of any one of claims 1–5, wherein the TLR ligand is a TLR4 ligand.

8. The use of claim 7, wherein the TLR4 ligand is selected from monophosphoryl lipid A (MPLA), lipopolysaccharide (LPS), or combinations thereof.

9. The use of any one of claims 1–8, wherein the non-canonical inflammasome-activating lipid comprises a species of oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine (oxPAPC).

10. The use of any one of claims 1–8, wherein the non-canonical inflammasome-activating lipid comprises 2-[[(2R)-2-[(E)-7-carboxy-5-hydroxyhept-6-enoyl]oxy-3-hexadecanoyloxypropoxy]-hydroxyphosphoryl]oxyethyl-trimethylazanium (**HOdiA-PC**), [(2R)-2-[(E)-7-carboxy-5-oxohept-6-enoyl]oxy-3-hexadecanoyloxypropyl] 2-(trimethylazaniumyl)ethyl phosphate (**KOdiA-PC**), 1-palmitoyl-2-(5-hydroxy-8-oxo-octenoyl)-*sn*-glycero-3-phosphorylcholine (**HOOA-PC**), 2-[[(2R)-2-[(E)-5,8-dioxooct-6-enoyl]oxy-3-hexadecanoyloxypropoxy]-hydroxyphosphoryl]oxyethyl-trimethylazanium (**KOOA-PC**), [(2R)-3-hexadecanoyloxy-2-(5-oxopentanoyloxy)propyl] 2-(trimethylazaniumyl)ethyl phosphate (**POVPC**), [(2R)-2-(4-carboxybutanoyloxy)-3-hexadecanoyloxypropyl] 2-(trimethylazaniumyl)ethyl phosphate (**PGPC**), [(2R)-3-hexadecanoyloxy-2-[4-[3-[(E)-[2-[(Z)-oct-2-enyl]-5-oxocyclopent-3-en-1-ylidene]methyl]oxiran-2-yl]butanoyloxy]propyl] 2-(trimethylazaniumyl)ethyl phosphate (**PECPC**), [(2R)-3-hexadecanoyloxy-2-[4-[3-[(E)-[3-hydroxy-2-[(Z)-oct-2-enyl]-5-oxocyclopentylidene]methyl]oxiran-2-yl]butanoyloxy]propyl] 2-(trimethylazaniumyl)ethyl phosphate (**PEIPC**), or a combination thereof.

11. The use of any one of claims 1–8, wherein the non-canonical inflammasome-activating lipid comprises [(2R)-2-(4-carboxybutanoyloxy)-3-hexadecanoyloxypropyl] 2-(trimethylazaniumyl)ethyl phosphate (**PGPC**).

12. The use of any one of claims 1–11, wherein the subject is a mammal.

13. The use of claim 12, wherein the subject is a human.

14. The use of any one of claims 1–13, wherein the TLR ligand, oxPAPC species, and cancer immunogen are to be administered as part of a pharmaceutical composition.

15. The use of any one of claims 1–14, wherein the immune response is a prophylactic immune response.

16. The use of any one of claims 1–15, wherein the immune response is a therapeutic immune response.

17. The use of any one of claims 1–16, wherein the adaptive immune response comprises T-cell activation.

18. The use of any one of claims 1–17 further comprising one or more therapeutic interventions.

19. The use of any one of claims 1–18, wherein the TLR ligand, oxPAPC species, and cancer immunogen, and one or more therapeutic interventions are to be co-administered or to be sequentially administered.

20. The use of claim 18 or claim 19, wherein the one or more therapeutic interventions comprises: radiation, chemotherapy, surgery, therapeutic antibodies, immunomodulatory agents, proteasome inhibitors, pan-deacetylase (DAC) inhibitors, histone deacetylase (HDAC) inhibitors, checkpoint inhibitors, adoptive cell therapies, vaccines or combinations thereof.

21. The use of claim 20, wherein the adoptive cell therapies comprise: CAR-T cell therapy, CAR- NK cell therapy, T cells, dendritic cells or combinations thereof.