CLAIMS

What is claimed is:

1. Use of an effective amount of a PEGylated H-NOX protein in the manufacture of a medicament for treating cancer in an individual, wherein the PEGylated H-NOX protein is to be administered in combination with immunotherapy, wherein the PEGylated H-NOX protein is a trimeric H-NOX protein comprising three monomers, wherein the monomers comprise an H-NOX domain and a trimerization domain, wherein the H-NOX domain is a *Thermoanaaerobacter tengcongensis* H-NOX domain set forth in SEQ ID NO:2 comprising an L144F suibstitution, and wherein the immunotherapy is an anti-CTLA-4 therapy, an anti-PD-1 therapy, an anti-PD-L1 therapy, a dual PD-1/CTLA-4 blockade therapy, or a dual PD-1/PD-L1 blockade therapy.

2. The use of claim 1, wherein the cancer is brain cancer, glioblastoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, melanoma, lung cancer, uterine cancer, ovarian cancer, colorectal cancer, anal cancer, liver cancer, hepatocellular carcinoma, stomach cancer, testicular cancer, endometrial cancer, cervical cancer, Hodgkin's Disease, non-Hodgkin's lymphoma, esophageal cancer, intestinal cancer, thyroid cancer, adrenal cancer, bladder cancer, kidney cancer, breast cancer, multiple myeloma, sarcoma, or squamous cell cancer.

3. The use of any of claims 1 or 2, wherein the individual is a human.

4. The use of any one of claims 1-3, wherein the H-NOX protein is to be administered by intravenous, intra-arterial, intratumoral, intravesicular, inhalation, intraperitoneal, intrapulmonary, intramuscular, subcutaneous, intra-tracheal, transmucosal, intraocular, intrathecal, or transdermal administration.

5. The use of any one of claims 1-4, wherein administration of the H-NOX protein is to be repeated.

6. The use of any one of claims 1-5, wherein the H-NOX protein is to be administered as a bolus and/or by infusion.

7. The use of any one of claims 1-6, wherein the H-NOX protein is to be administered in combination with radiation therapy.

8. The use of claim 7, wherein the radiation therapy is to be administered to the individual 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours after the H-NOX protein is administered.

9. The use of any one of claims 1-6, wherein the H-NOX protein is to be administered in combination with chemotherapy or immunotherapy.

10. The use of claim 9, wherein the administration of the H-NOX protein and/or the administration of the immunotherapy is to be repeated.

11. The use of claim 1-10, wherein the H-NOX domain is covalently linked to the polymerization domain.

12. The use of claim 1, wherein the trimeric H-NOX protein comprises one or more trimerization domains.

13. The use of claim 12, wherein the trimerization domain is a foldon domain.

14. The use of claim 13, wherein the foldon domain comprises the amino acid sequence of SEQ ID NO:4.

15. The use of any one of claims 1-14, wherein the O_2 dissociation constant of the H-NOX protein is within 2 orders of magnitude of that of hemoglobin, and wherein:

a) the NO reactivity of the H-NOX protein is at least 10-fold lower than that of hemoglobin.

b) the O_2 dissociation constant of the polymeric H-NOX protein is between about 1 nM and about 1000 nM at 20 °C;

c) the O_2 dissociation constant of the H-NOX protein is between about 1 μM and about 10 μM at 20 °C;

d) the O_2 dissociation constant of the H-NOX protein is between about 10 μM and about 50 μM at 20 °C;

e) the NO reactivity of the H-NOX protein is less than about 700 s^{-1} at 20 °C;

f) the NO reactivity of the H-NOX protein is at least 100-fold lower or at least 1000-fold lower than that of hemoglobin;

g) the k_{off} for oxygen of the H-NOX protein is less than or equal to about 0.65 s^{-1}at 20 °C, or between about 0.21 $s^{-1}$and about 0.65 s^{-1} at 20 °C, or between about 1.35 $s^{-1}$and about 2.9 s^{-1} at 20 °C. or;

h) the rate of heme autoxidation of the H-NOX protein is less than about 1 h^{-1}at 37 °C.

16. The use of any one of claims 1-15, wherein the H-NOX protein is in a pharmaceutical composition.

17. The use of claim 16, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

18. A kit for modulating tumor immunity in an individual comprising an O_2 carrier protein for the use of any one of claims 1-17.

19. The kit of claim 18, wherein the kit further comprises one or more of a vial, a vessel, an ampule, a bottle, a jars, or flexible packaging.