What is claimed is:

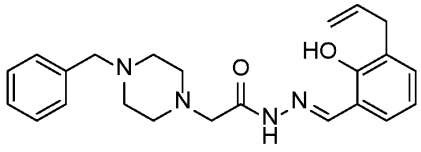
1. A composition comprising:

(a) a procaspase-3 activator;

(b) at least one second active agent, wherein the second active agent is a check-point inhibitor, cancer vaccine, metabolic modulator, macrophage inhibitor, or immune-stimulator or modulator; and

(c) optionally a pharmaceutically acceptable diluent, excipient, or carrier.

2. The composition of claim 1 wherein the procaspase-3 activator is PAC-1:



(PAC-1).

3. The composition of claim 1 wherein the second active agent has an effect in a cancer cell that induces apoptosis and PAC-1 enhances the effect of the second active agent by an amount greater than an additive effect, wherein PAC-1 primes the vulnerability of the cancer cell to the second active agent.

4. The composition of claim 1 wherein the second active agent modulates indoleamine-pyrrole 2,3-dioxygenase (IDO), adenosine A_{2A} receptor (A2AR), transforming growth factor beta (TGF-β), C-X-C chemokine receptor type 4 (CXCR-4), C-C chemokine receptor type 4 (CCR4), tumor necrosis factor receptor (CD27), interleukin-2 receptor subunit beta (CD122), death receptor 5 (DR5), inhibitors of apoptosis proteins (IAP), glutaminase, colony stimulating factor 1 receptor (CSF1R), toll-like receptors (TLRs), dendritic cells (DC), or a combination thereof.

5. The composition of claim 1 wherein the second active agent is ADXS11-001, ADXS31-142, AMP-224, AMP-514, atezolimumab, atezolizumab, avelumab, bevacizumab, cemiplimab, BLZ945, BMS-936559, BMS986016, BMS986156, BMS986205, CB839, CIMAvax, CMP001, CP870893, CPI-444, CRS207, CV301, DC vaccine, DNX2401, DS-8273a, durvalumab, epacadostat, FAZ053, FPA008, GDC0919, GSK3174998, GVAX, GWN323, IMCgp100,

IMP321, imprime PGG, indoximid, ipilimumab, JTX-2011, LAG525, LCL161, LK-301, LY2157299, LY2510924, LY3022855, MBG453, MEDI0562, MEDI0680, MEDI6469, MEDI9447, MGN1703, mogamulizumab, MOXR0916, neoantigen vaccine, NEO-PV-01, NIS793, nivolumab, NKTR-214, PBF509, PDR001, pembrolizumab, peptide vaccine, pexidartinib (PLX3397), PF-04518600, PF-3512676, REGN2810, REGN3767, RO7009789, SD101, talimogene laherparepvec, TPIV200/huFR-1, tremelimumab, TroVax, TSR022, ulocuplumab, urelumab, utomilumab, varlilumab, viagenpumatucel-L (HS-110), or a combination thereof.

6. The composition of claim 1 wherein the at least one second active agent is at least one check-point inhibitor that regulates an immune response via programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), tumor necrosis factor receptor superfamily-member 4 (TNFRSF4 or OX40), tumor necrosis factor receptor superfamily-member 9 (TNFRSF9 or 4-1BB), glucocorticoid-induced TNFR-related protein (GITR), inducible T-cell costimulator (ICOS), or a combination thereof.

7. The composition of claim 6 wherein the checkpoint inhibitor is anti-PD-1, anti-CTLA-4, or a combination thereof; wherein the anti-PD-1 is nivolumab or pembrolizumab, the anti-CTLA-4 is ipilimumab or tremelimumab, or a combination thereof.

8. The composition of claim 1 wherein the concentration of PAC-1 is about 0.1 μM to about 50 μM and the concentration of the second active agent is about 1 nM to about 100 μM.

9. The composition of claim 1 comprising a pharmaceutically acceptable diluent, excipient, or carrier, wherein a) the carrier comprises water, a buffer, a sugar, a cellulose, a cyclodextrin, dimethyl sulfoxide, polyethylene glycol, tocopherol, a liposome, a micelle, or a combination thereof, or b) the excipient comprises, a binder, a lubricant, a sorbent, a vehicle, a disintegrant, a preservative, or a combination thereof.

10. The composition of claim 1 wherein the composition selectively targets cancer cells, wherein the cancer cells are cells of bladder cancer, breast cancer, colon cancer, endometrial cancer, glioblastoma, leukemia, liver cancer, lung cancer, lymphoma, melanoma, meningioma, multiple myeloma, ovarian cancer, osteosarcoma, pancreatic cancer, prostate cancer, renal cancer, or thyroid cancer;

wherein the breast cancer is optionally triple negative breast cancer, lung cancer is optionally non-small cell lung cancer, and renal cancer is optionally metastatic renal cell carcinoma.

11. A method of inhibiting the growth or proliferation of cancer cells comprising contacting cancer cells with an effective amount of a composition of any one of claims 1-10, thereby inhibiting the growth or proliferation of the cancer cells.

12. The method of claim 11 wherein the growth or proliferation of the cancer cells is inhibited by suppressing mismatch-repair (MMR) proteins, or by caspase-3 activation mediated degradation of MutL homolog 1 (MLH1) proteins;

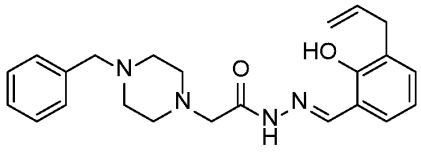
wherein DNA microsatellite instability (MSI) is induced.

13. A method of inducing apoptosis in a cancer cell comprising contacting the cancer cell with an effective amount of a composition of any one of claims 1-10, wherein apoptosis is induced by suppressing mismatch-repair (MMR) proteins in the cancer cell.

14. The method of claim 13 wherein the MMR proteins are MutL homolog 1 (MLH1) proteins, wherein degradation of MLH1 proteins, mediated by caspase-3 activation via the procaspase-3 activator, induces apoptosis in the cancer cell.

15. A method of treating a cancer comprising administering to a subject in need thereof, concurrently or sequentially, a therapeutically effective amount of a procaspase-3 activator and an effective amount of a second active agent, wherein the second active agent is an immunotherapeutic, wherein the effect of the immunotherapeutic is enhanced by the administration of the procaspase-3 activator.

16. The method of claim 15 wherein the procaspase-3 activator is PAC-1:



(PAC-1).

17. The method of claim 16 wherein the concentration of PAC-1 is about 0.1 μM to about 50 μM and the concentration of the second active agent is about 1 nM to about 100 μM.

18. The method of claim 16 wherein the concentration of PAC-1 is about 1 μM to about 10 μM and the concentration of the second active agent is about 1 nM to about 1 μM; or

wherein the total administered dose per day of PAC-1 is about 10 mg/kg to about 125 mg/kg and the daily total administered dose per day of the second active agent is about 1 mg/kg to about 100 mg/kg.

19. The method of claim 15 wherein the second active agent comprises a check-point inhibitor, cancer vaccine, metabolic modulator, macrophage inhibitor, immune-stimulator, or modulator; or a combination thereof.

20. The method of claim 15 wherein the second active agent is atezolimumab, avelumab, bevacizumab, BMS986016, BMS986156, CP870893, durvalumab, FAZ053, GSK3174998, GWN323, IMP321, ipilimumab, JTX-2011, LAG525, MBG453, MEDI0562, MEDI0680, MEDI6469, MOXR0916, nivolumab, PDR001, pembrolizumab, PF-04518600, REGN2810, REGN3767, RO7009789, tremelimumab, TSR022, urelumab, utomilumab, or a combination thereof.

21. The method of claim 15 wherein the immunotherapeutic is a check-point inhibitor, and the check-point inhibitor regulates an immune response via programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), tumor necrosis factor receptor superfamily-member 4 (TNFRSF4 or OX40), tumor necrosis factor receptor superfamily-member 9 (TNFRSF9 or 4-1BB), glucocorticoid-induced TNFR-related protein (GITR), inducible T-cell costimulator (ICOS), or a combination thereof.

22. The method of claim 15 wherein the procaspase-3 activator suppresses mismatch-repair (MMR) proteins;

wherein the MMR proteins comprise MutL homolog 1 (MLH1) proteins, and wherein degradation of MMR proteins, mediated by caspase-3 activation via the procaspase-3 activator, induces a deficiency in MMR proteins, DNA microsatellite instability (MSI), neoantigen expression, or a combination thereof, thereby enhancing the effect of the immunotherapeutic, and wherein the procaspase-3 activator increases tumor-infiltrating lymphocytes in the cancer.

23. The method of claim 15 wherein the cancer is bladder cancer, breast cancer, colon cancer, endometrial cancer, glioblastoma, leukemia, liver cancer, lung cancer, lymphoma, melanoma, meningioma, multiple myeloma, ovarian cancer, osteosarcoma, pancreatic cancer, prostate cancer, renal cancer, or thyroid cancer;

wherein the breast cancer is optionally triple negative breast cancer, lung cancer is optionally non-small cell lung cancer, and renal cancer is optionally metastatic renal cell carcinoma.

24. The method of any one of claims 15-23 wherein:

the compound PAC-1 and the second active agent are concurrently administered to the subject; or

the compound PAC-1 and the second active agent are sequentially administered to the subject, wherein the compound PAC-1 is administered to the subject before the second active agent or the compound PAC-1 is administered to the subject after the second active agent.

25. The method of any one of claims 15-23 wherein the compound PAC-1 and the second active agent are administered to the subject once daily (*q.d.*), twice a day (*b.i.d.*), three times a day (*t.i.d.*), or four times a day (*q.i.d.*), wherein the total administered dose per day of PAC-1 is about 1 mg/kg to about 150 mg/kg; or

each administered dose of PAC-1 is about 70 mg, about 175 mg, about 250 mg, about 375 mg, about 450 mg, about 500 mg, about 625 mg, about 750 mg, or about 1000 mg; or

each administered dose of PAC-1 is about 50 mg/m^2 to about 250 mg/m^2.

26. A method of treating a cancer comprising administering to a subject in need thereof, PAC-1 and an anti-PD-1 antibody wherein the PAC-1 is administered daily for 21 or more

consecutive days such that a total administered dose per day of the PAC-1 is about 100 mg/kg to about 125 mg/kg and the anti-PD-1 antibody is administered two times or four times over the 21 or more consecutive days, wherein a dose of the anti-PD-1 antibody is about 10 mg/kg and each of the dose of the anti-PD-1 antibody is administered on separate days.