[0006] Covalent modification of histones is a fundamental mechanism of control of gene expression, and one of the major epigenetic mechanisms at play in eukaryotic cells (Kouzarides, *Cell*, *128*, 693-705 (2007)). Because distinct transcriptional states define fundamental cellular processes, such as cell type specification, lineage commitment, cell activation and cell death, their aberrant regulation is at the core of a range of diseases (Medzhitov *et al.*, *Nat. Rev. Immunol.*, *9*, 692-703 (2009); Portela *et al.*, *Nat. Biotech.*, 28, 1057-1068 (2010)). A fundamental component of the epigenetic control of gene expression is the interpretation of histone modifications by proteins that harbor specialized motifs that bind to such modifications. Among them, bromodomains have evolved to bind to acetylated histones and by so doing they represent fundamental links between chromatin structure and gene transcription (Fillipakoppoulos *et al.*, *Cell*, *149*, 214-231 (2012)).

[0007] Bromodomains, which are approximately 110 amino acids long, are found in a large number of chromatin-associated proteins and have been identified in approximately 70 human proteins, often adjacent to other protein motifs (Jeanmougin F., et al., *Trends Biochem. Sci.,* 1997, *22*, 5, 151-153; and Tamkun J.W., et al., *Cell*, 1992, *7*, 3, 561-572). Interactions between bromodomains and modified histones may be an important mechanism underlying chromatin structural changes and gene regulation. Bromodomain-containing proteins have been implicated in disease processes including cancer, inflammation and viral replication. *See, e.g.*, Prinjha *et al.*, *Trends Pharm. Sci.*, 33(3):146-153 (2012) and Muller *et al.*, *Expert Rev.*, 13(29):1-20 (September 2011).

[0008] Cell-type specificity and proper tissue functionality requires the tight control of distinct transcriptional programs that are intimately influenced by their environment. Alterations to this transcriptional homeostasis are directly associated with numerous disease states, most notably cancer, immuno-inflammation, neurological disorders, and metabolic diseases. Bromodomains reside within key chromatin modifying complexes that serve to control distinctive disease-associated transcriptional pathways. This is highlighted by the observation that mutations in bromodomain-containing proteins are linked to cancer, as well as immune and neurologic dysfunction. Hence, the selective inhibition of bromodomains across the family creates varied opportunities as novel therapeutic agents in human dysfunction.

[0009] There is a need for treatments for cancer, immunological disorders, and other bromodomain related diseases.

SUMMARY

[00010] In one example, there is disclosed the use of a CBP/EP300 bromodomain inhibitor in the manufacture of a medicament for treating or delaying progression of cancer in an individual. In one example, there is disclosed a method for treating cancer in an animal comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor to the animal. In one aspect, the present invention refers to the use of a CBP/EP300 bromodomain inhibitor compound in the manufacture of a medicament for treating or delaying progression of cancer in an individual or for enhancing immune function in an individual having cancer; wherein the individual is human.

[00011] In one example, there is disclosed a method for treating or delaying progression of cancer in an individual comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor to the individual.

[00012] In one example, there is disclosed the use of a CBP/EP300 bromodomain inhibitor in the manufacture of a medicament for enhancing immune function in an individual having cancer, the use comprising an effective amount of a CBP/EP300 bromodomain inhibitor to be administered to the individual. In one example, there is disclosed a method of enhancing immune function in an individual having cancer comprising administering an effective amount of a CBP/EP300 bromodomain inhibitor.

[00013] In certain examples, CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the CBP/EP300 bromodomain inhibitor.

[00014] In certain examples, the number of CD8 T cells is elevated relative to prior to administration of the CBP/EP300 bromodomain inhibitor.

[00015] In certain examples, the CD8 T cell is an antigen-specific CD8 T cell.

[00016] In certain examples, the cancer has elevated levels of T-cell infiltration.

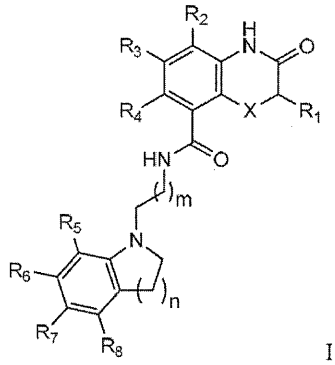
[00017] In certain examples, the cancer is associated with increased intratumoral Treg cell density.

[00018] In certain examples, the cancer is selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer (NSCLC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer, and Wilms' tumor.

We claim:

1. Use of a CBP/EP300 bromodomain inhibitor compound in the manufacture of a medicament for treating or delaying progression of cancer in an individual or for enhancing immune function in an individual having cancer; wherein the individual is human.

2. The use of claim 1, wherein the CBP/EP300 bromodomain inhibitor compound is a compound of Formula I:



I

wherein:

X is NH or O;

m is 1 or 2;

n is 1 or 2;

R_1 is independently selected from the group consisting of substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, substituted or unsubstituted C_2–$_6$alkynyl and substituted or unsubstituted C_3–6carbocyclyl;

R_2 is independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, and substituted or unsubstituted C_2–$_6$alkynyl;

R_3 independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, and substituted or unsubstituted C_2–$_6$alkynyl;

R_4 independently selected from the group consisting of hydrogen, halogen, substitutedor unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, and substituted or unsubstituted C_2–$_6$alkynyl;

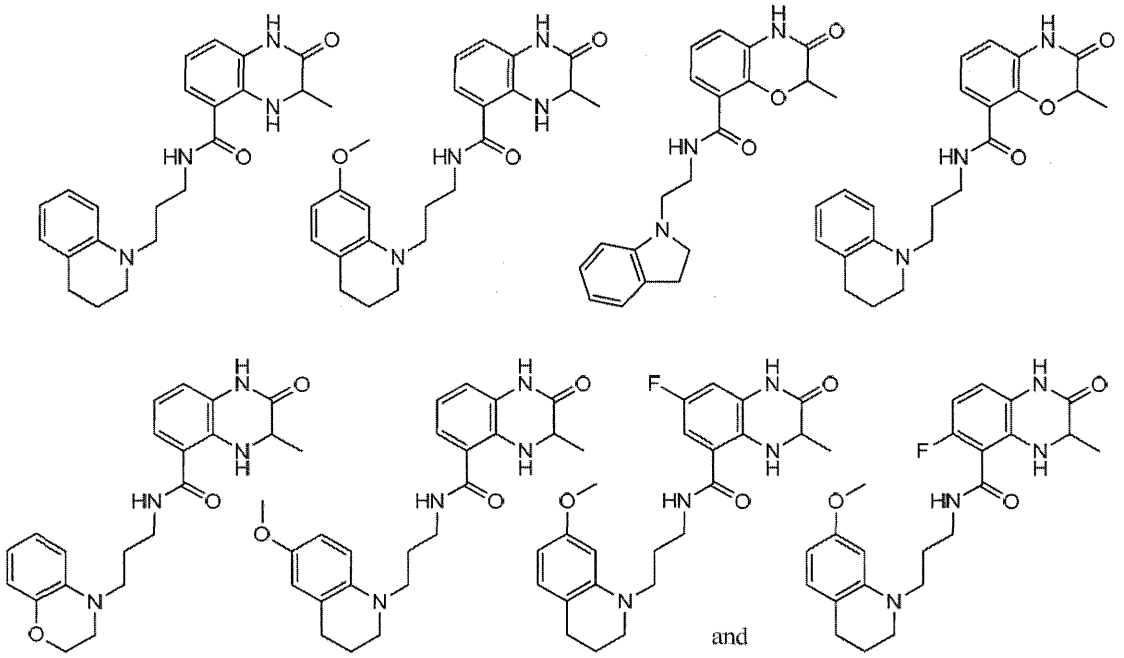
R_5 independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, substituted or unsubstituted C_2–$_6$alkynyl, and OC_1-C_6 alkyl;

R_6 independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, substituted or unsubstituted C_2–$_6$alkynyl, and OC_1-C_6 alkyl;

R_7 independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, substituted or unsubstituted C_2–$_6$alkynyl, and OC_1-C_6 alkyl; and

R_8 independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2–$_6$alkenyl, substituted or unsubstituted C_2–$_6$alkynyl, and OC_1-C_6 alkyl; or a pharmaceutically acceptable salt or solvate thereof.

3. The use of claim 1 or 2, wherein the compound is selected from:



4. The use of claim 1 to 3, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the CBP/EP300 bromodomain inhibitor.

5. The use of claim 4, wherein the number of CD8 T cells is elevated relative to prior to administration of the CBP/EP300 bromodomain inhibitor.

6. The use of any one of claims 4-5, wherein the CD8 T cell is an antigen-specific CD8 T cell.

7. The use of any one of claims 1-6, wherein the cancer has elevated levels of T-cell infiltration.

8. The use of any one of claims 1-7, wherein the cancer is associated with increased intratumoral Treg cell density.

9. The use of any one of claims 1-8, wherein the cancer is selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic

leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer (NSCLC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer, and Wilms' tumor.

10. The use of any one of claims 1-9, wherein the cancer is melanoma, NSCLC, renal, ovarian, colon, pancreatic, hepatocellular, or breast cancer.

11. The use of any one of claims 1-10, wherein the cancer is NSCLC, ovarian, pancreatic, hepatocellular, or breast cancer.

12. The use of any one of claims 1-9, wherein the cancer is melanoma, NSCLC, or renal cell carcinoma.

13. The use of any one of claims 1-12, wherein the CBP/EP300 bromodomain inhibitor inhibits CBP.

14. The use of any one of claims 1-12, wherein the CBP/EP300 bromodomain inhibitor inhibits EP300.