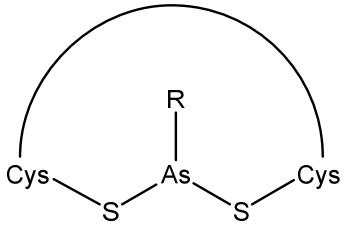
preventing cell replication. Additionally arsenic accumulation within the cell nucleus results in DNA fragmentation.

[0005] Acute promyelocytic leukemia (APL) is an aggressive form of leukemia that can cause mortality within three months, if left untreated. One of the most effective current treatments for APL is ATO which successfully cures 85% of patients who have relapsed following other therapies. ATO was approved in late 2015 for first line APL combination therapy. It exhibits multifaceted behaviour which is beneficial for overcoming resistance; as such it has invoked considerable interest for treatment of a range of other cancers, particularly haematological malignancies.

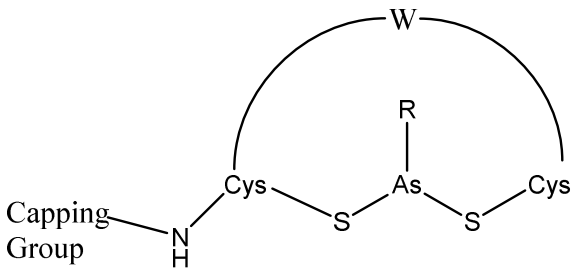
[0006] Unfortunately, ATO induces toxic side effects which can limit the dose of the anti-cancer drug that can be administered in treatment of APL and other cancers. This can lead to incomplete tumour response, the development of adverse cardiac events, drug resistance, discontinuation of treatment and, ultimately, the progression of the disease. The underlying cause of the toxic side effects stems from the fact that arsenic-containing anti-cancer drugs, such as ATO, indiscriminately kill both cancerous and healthy cells.

SUMMARY

[0006a] In one aspect, the present disclosure refers to an anti-cancer agent comprising a cyclised tumour homing peptide having an arsenic atom bonded to two cysteine residues; and wherein the anti-cancer agent has a structure as shown in formula I or formula II:



formula I



formula II

wherein, in formula I: the sulfur atoms shown and to which the arsenic is bonded are the thiol sulfurs of the respective cysteine residues; the cysteine residues in formula I are separated by less than 20 amino acid residues represented by the curved line; and R is a stabilising group selected from the group consisting of hydroxyl, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_1 to C_6 alkoxy, aryl, cycloalkyl, heterocyclic, and short chain peptides, each of which groups may be substituted or unsubstituted; wherein, in formula II: the atoms and groups are as described for formula I; the capping group is formed from an amino reactive compound; and W is between 2 to 20 amino acid residues.

[0006b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising an anti-cancer agent as disclosed herein and a pharmaceutically acceptable carrier, diluent and/or excipient.

[0006c] In another aspect, the present disclosure refers to a use of the anti-cancer agent as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a patient.

[0006d] In another aspect, the present disclosure refers to a process for producing the anti-cancer agent as disclosed herein, including the steps of: (a) contacting a tumour homing peptide comprising two cysteine residues with an arsenic compound; and (b) allowing the arsenic to become bound to each of the two cysteine residues to form a cyclised tumour homing peptide comprising a bound arsenic atom; to thereby produce the anti-cancer agent.

[0006e] In another aspect, the present disclosure refers to an anti-cancer agent when produced by the process as disclosed herein.

[0007] According to a first example of the disclosure, there is provided an anti-cancer agent comprising a cyclised tumour homing peptide having an arsenic atom bonded to two cysteine residues.

[0008] Suitably, the arsenic atom bonded to the two cysteine residues allows the tumour homing peptide to be cyclic. That is, it is the bridging of the arsenic between two cysteines which generates the cyclised tumour homing peptide.

[0009] In one example, the two arsenic-bonded cysteine residues of the tumour homing peptide are separated, one from the other, by less than 20 amino acid residues.

[0010] In certain examples, the two arsenic-bonded cysteine residues of the tumour homing peptide are separated by less than 18 amino acid residues, or less than 16 amino acid residues, or less than 15 amino acid residues, or less than 14 amino acid residues.

[0011] In examples, prior to cyclisation to form the anti-cancer agent, the two cysteine residues which bind the arsenic atom are the respective N-terminal and C-terminal peptide residues of the tumour homing peptide.

[0012] If not naturally present on the tumour homing peptide, the two cysteine residues which bind the arsenic atom can be added onto the tumour homing peptide to thereby form the respective N-terminal and C-terminal peptide residues.

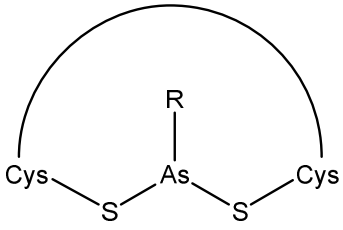
[0013] The N-terminal cysteine may comprise a capping group bonded to its terminal amino nitrogen.

[0014] In an example, the anti-cancer agent further comprises a stabilising group bonded to the arsenic atom.

[0015] Suitably, the stabilising group is selected from the group consisting of hydroxyl, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, aryl, cycloalkyl and heterocyclic.

[0016] In examples, the tumour homing peptide comprises at least one arginine and/or lysine residue.

[0017] In one example, the anti-cancer agent has a structure as shown in formula I:



formula I

wherein, the sulfur atoms to which the arsenic is bonded are the thiyl sulfurs of the respective cysteine residues;

the cysteine residues in formula I are separated by less than 20 amino acid residues represented by the curved line; and

R is a stabilising group selected from the group consisting of hydroxyl, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_1 to C_6 alkoxy, aryl, cycloalkyl, glutathiyl and heterocyclic, each of which groups may be substituted or unsubstituted.

[0018] According to a second example of the disclosure, there is provided a pharmaceutical composition comprising an anti-cancer agent of the first example and a pharmaceutically acceptable carrier, diluent and/or excipient.

[0019] According to a third example of the disclosure there is provided a method of treating a cancer in a patient including the step of administering an anti-cancer agent of the first example or the pharmaceutical composition of the second example to the patient, to thereby treat the cancer.

[0020] A fourth example of the disclosure resides in an anti-cancer agent of the first example for use in treating a cancer in a patient.

[0021] A fifth example of the disclosure resides in the use of an anti-cancer agent of the first example in the manufacture of a medicament for the treatment of a cancer.

[0022] In relation to the third to fifth examples, in one example the cancer is a haematological malignancy or a solid tumour.

[0023] According to a sixth example of the disclosure there is provided a process for producing an anti-cancer agent including the steps of:

(a) contacting a tumour homing peptide comprising two cysteine residues with an arsenic compound; and

(b) allowing the arsenic to become bound to each of the two cysteine residues to form a cyclised tumour homing peptide comprising a bound arsenic atom;

to thereby produce the anti-cancer agent.

[0024] The anti-cancer agent may be as described for the first example.

[0025] The arsenic compound may be an oxide of arsenic.

[0026] In one example, the arsenic compound may comprise an alkyl, hydroxyl or aryl group bonded to arsenic.

[0027] In one example, the process may comprise the step (a)(i) of modifying a selected tumour homing peptide to present two cysteine residues.

[0028] A seventh example of the disclosure resides in an anti-cancer agent when produced by the process of the sixth example.

[0029] An eighth example of the disclosure resides in a method of delivering a therapeutically effective amount of arsenic to a patient including the step of administering to the patient an appropriate amount of the anti-cancer agent of the first example or the pharmaceutical composition of the second example, to thereby deliver the therapeutically effective amount of arsenic.

[0030] The method of the eighth example may include any of the examples described for the first example.

[0031] A ninth example of the disclosure resides in a method of diagnosing a cancer including the steps of:

(i) administering an anti-cancer agent of the first example comprising at least one radiolabelled atom, to a patient;

(ii) allowing the anti-cancer agent to become localised to the cancer; and

(iii) detecting the presence of the at least one radiolabelled atom of the anti-cancer agent,

to thereby diagnose the cancer.

[0032] The various features and examples of the present disclosure, referred to in individual sections above apply, as appropriate, to other sections, *mutatis mutandis*. Consequently, features specified in one section may be combined with features specified in other sections as appropriate.

[0033] Further features and advantages of the present disclosure will become apparent from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

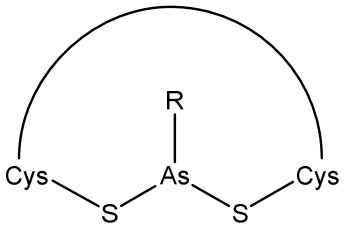
[0034] In order that the invention may be readily understood and put into practical effect, preferred embodiments will now be described by way of example with reference to the accompanying figures wherein:

[0035] FIG 1A shows the positive ion ESI-mass spectrum for LHP with peaks at m/z 407.4 and m/z 610.5 assigned $[LHP + 3H^+]^{3+}$ and $[LHP + 2H^+]^{2+,}$ respectively; FIG 1B depicts the ESI-MS results for the 8 h reactions of AsI_3 and LHP in (a) phosphate buffer (pH 8) and (b) triethylamine (pH 8) with peaks at m/z 431.4 and m/z 646.8 assigned $[HyAs(LHP) + 3H^+]^{3+}$ and $[HyAs(LHP) + 2H^+]^{2+,}$ respectively, confirming the production of the desired product, HyAs(LHP). Ions at m/z 407.6, m/z 610.5, and m/z 628.8 are assigned to the free peptide, $[LHP + 3H^+]^{3+}$, $[LHP + 2H^+]^{2+}$, and $[LHP.2H_2O + 2H^+]^{2+}$, respectively. The ion at m/z 837.9 is identified as $[HyAs(LHP)_2 + 3H^+]^{3+}$; FIG 1C is the ESI-MS result for the reaction of MMA(V) and LHP in phosphate buffer (pH 8) following 16 h incubation at 37 ^{0}C. Ions at *m/z* 437.1 $[MeAs(LHP) + 3H^+]^{3+}$, *m/z* 444.8 $[MeAs(LHP) + Na^+ + 2H^+]^{3+}$, *m/z* 655.1 $[MeAs(LHP) + 2H^+]^{2+}$, and *m/z* 666.4 $[MeAs(LHP) + Na^+ + H^+]^{2+}$, confirming the production of the desired product, MeAs(LHP). The free peptide ions occur at *m/z* 407.6 $[LHP + 3H^+]^{3+}$, * = *m/z* 414.9 $[LHP + Na^+ + 2H^+]^{3+}$, *m/z* 610.5 $[LHP + 2H^+]^{2+}$, *m/z* 629.6 $[LHP + Na^+ + H^+]^{2+}$; FIG 1D shows the ESI-MS results for the products from the reaction of PAO and LHP in phosphate buffer (pH 8) following 4 h incubation at 37 ^{0}C with ions at *m/z* 457.6 $[PhAs(LHP) + 3H^+]^{3+}$ and *m/z* 685.5 [PhAs(LHP) +

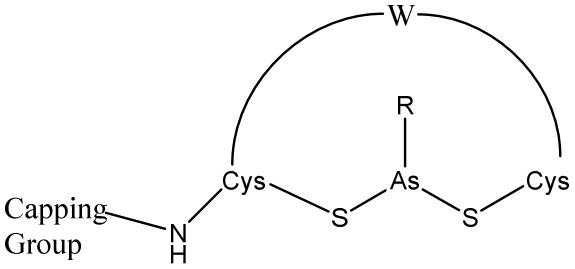
CLAIMS

1. An anti-cancer agent comprising a cyclised tumour homing peptide having an arsenic atom bonded to two cysteine residues; and

wherein the anti-cancer agent has a structure as shown in formula I or formula II:



formula I



formula II

wherein, in formula I:

the sulfur atoms shown and to which the arsenic is bonded are the thiol sulfurs of the respective cysteine residues;

the cysteine residues in formula I are separated by less than 20 amino acid residues represented by the curved line; and

R is a stabilising group selected from the group consisting of hydroxyl, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_1 to C_6 alkoxy, aryl, cycloalkyl, heterocyclic, and short chain peptides, each of which groups may be substituted or unsubstituted;

wherein, in formula II:

the atoms and groups are as described for formula I;

the capping group is formed from an amino reactive compound; and

W is between 2 to 20 amino acid residues.

2. The anti-cancer agent of claim 1, wherein the capping group is an alkanoyl group which may be optionally substituted.

3. The anti-cancer agent of claim 1, wherein the capping group is an acetyl group.

4. The anti-cancer agent of any one of the preceding claims, wherein R is selected from the group consisting of hydroxyl, C_1 to C_6 alkyl, and aryl.

5. The anti-cancer agent of any one of the preceding claims wherein the tumour homing peptide comprises at least one arginine and/or lysine residue.

6. The anti-cancer agent of any one of the preceding claims, wherein the anti-cancer agent has the structure of formula I.

7. The anti-cancer agent of any one of claims 1 to 5, wherein the anti-cancer agent has the structure of formula II.

8. The anti-cancer agent of any one of the preceding claims, wherein the tumour homing peptide to which the arsenic atom is bonded between two cysteine residues is selected from the group consisting of:

1. CAYHRLRRC;
2. CDCRGDCFC;
3. CPIEDRPMC;
4. CNRRTKAGC;
5. CGTKRKC;
6. CRGDGWC;
7. CVSNPRWKC;
8. CHVLWSTRC;
9. CLDGGRPKC;
10. GCSVSSVGALCTHV;
11. CRGDGWC;
12. CDCRGDCFC;

13. CVNHPAFAC;
14. CRGDRGPDC;
15. CRGDKTTNC;
16. CRGDHAGDC;
17. CLSYYPSYC;
18. CTPSPPFSHC;
19. CPHSKPCLC;
20. CSDSWHYWC;
21. CSDWQHPWC;
22. CSDYNHHWC;
23. CSDGQHYWC;
24. CYDSWHYWC;
25. CFDGNHIWC;
26. CTDFPRSFC;
27. CTQDRQHPC;
28. CLSRYLDQC;
29. CRGDCF;
30. CGNSNPKSC;
31. CPHNLTKLC ; and

wherein the arsenic atom, when in the formed anti-cancer agent, is bonded to and bridged between two of the cysteine residues of the above peptide sequences.

9. A pharmaceutical composition comprising an anti-cancer agent of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, diluent and/or excipient.

10. Use of the anti-cancer agent of any one of claims 1 to 8 or the pharmaceutical composition of claim 9 in the manufacture of a medicament for treating cancer in a patient.

11. The use of claim 10, wherein the cancer is a haematological malignancy or a solid tumour.

12. The use of claim 10 or claim 11, wherein the cancer is selected from a leukemia, multiple myeloma, and a lymphoma.

13. The use of any one of claims 10 to 12, wherein the cancer is selected from the group consisting of squamous cell carcinoma, basal cell carcinoma, melanoma, tumours of the epithelial lining of glands or ducts, adenocarcinoma, papillary carcinoma, papillary adenocarcinoma,

tumours of the liver and biliary tract, hepatocellular carcinoma, tumours of the gastrointestinal tract, squamous cell carcinoma of the oesophagus, adenocarcinoma of the oesophagus, colorectal carcinoma (colon cancer), gastric carcinoma (stomach cancer), tumours of the respiratory tract, bronchogenic carcinoma, small cell carcinoma, large cell carcinoma, tumours of the urogenital tract, transitional cell carcinomas of the bladder, squamous cell carcinoma of the bladder, carcinoma of the prostate, carcinoma of the cervix, blood cells and related cells (leukemias), acute and chronic lymphocytic leukemia, polycythemia vera, cancers of lymphoid tissue, malignant lymphomas including Hodgkin's lymphoma and non-Hodgkin's lymphoma, follicular lymphoma, diffuse lymphoma, small lymphocytic lymphoma, large cell lymphoma, lymphoblastic lymphoma, multiple myeloma, tumours of connective tissue, cancers of bone osteosarcoma, tumours of the nervous system, neuroblastoma, retinoblastoma, glioblastoma, oligodendroglioma, tumours associated with oncogenic viruses, Burkitts lymphoma, b cell lymphoma's in immuno-comprised individuals, nasopharyngeal carcinoma, esophagus and gastroesophageal cancers, epidermal squamous cell cancers, pancreatic islet tumours, breast carcinoma, lung cancer, colorectal cancer, retinoblastoma, hepatic cancer, pancreatic cancer, brain cancer, mesothelioma and hepatitis b virus hepatocellular carcinoma.

14. The use of any one of claim 10 to claim 12, wherein, when the cancer is a leukemia, it is selected from the group consisting of chronic myeloid leukemia, t-cell lymphoma, myelodysplastic syndrome, colon cancer, pancreatic cancer, brain cancer, mesothelioma and acute promyelocytic leukemia (APL).

15. The use of any one of claims 10 to 14, wherein the anti-cancer agent is to be administered in combination with one or more of an immunotherapeutic, monoclonal antibody, chemotherapeutic, radioprotectant and radiotherapeutic.

16. A process for producing the anti-cancer agent of any one of claims 1 to 8, including the steps of:

    (a) contacting a tumour homing peptide comprising two cysteine residues with an arsenic compound; and

    (b) allowing the arsenic to become bound to each of the two cysteine residues to form a cyclised tumour homing peptide comprising a bound arsenic atom;

    to thereby produce the anti-cancer agent.

17. The process of claim 16 wherein the arsenic compound is an oxide of arsenic.

18. The process of claim 16 or claim 17, wherein the arsenic compound further comprises an alkyl, hydroxyl or aryl group bonded to the arsenic.

19. The process of any one of claims 16 to 18, further comprising the step (a)(i) of modifying a selected tumour homing peptide to present two cysteine residues.

20. An anti-cancer agent when produced by the process of any one of claims 16 to 19.