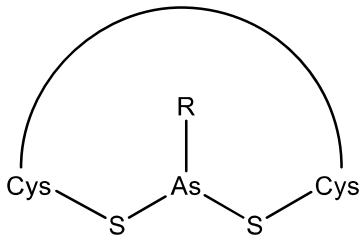
preventing cell replication. Additionally arsenic accumulation within the cell nucleus results in DNA fragmentation.

[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.

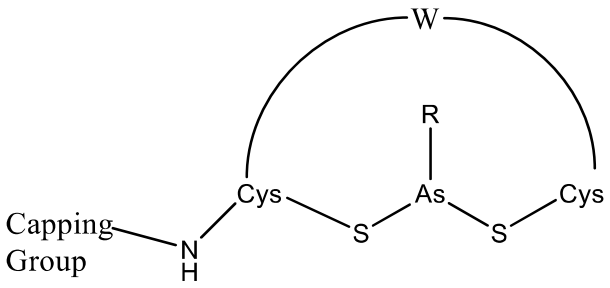
[0006] Unfortunately, ATO induces toxic side effects which can limit the dose of the anti-cancer drug that can be administered in treatment of APL and other cancers. This can lead to incomplete tumour response, the development of adverse cardiac events, drug resistance, discontinuation of treatment and, 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; 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; and wherein in formula I and II 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. CVNHPAFAC;
11. CRGDRGPDC;
12. CRGDKTTNC;
13. CRGDHAGDC;
14. CLSYYPSYC;
15. CTPSPPFSHC;
16. CPHSKPCLC;
17. CSDSWHYWC;

18. CSDWQHPWC;
19. CSDYNHHWC;
20. CSDGQHYWC;
21. CYDSWHYWC;
22. CFDGNHIWC;
23. CTDFPRSFC;
24. CTQDRQHPC;
25. CLSRYLDQC;
26. CGNSNPKSC;
27. CPHNLTKLC ; and

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

[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

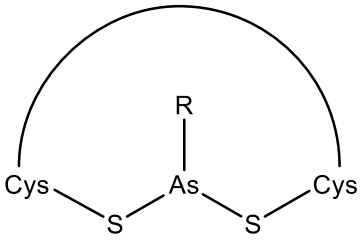
arsenic between two cysteines which generates the cyclised tumour homing peptide.

[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.

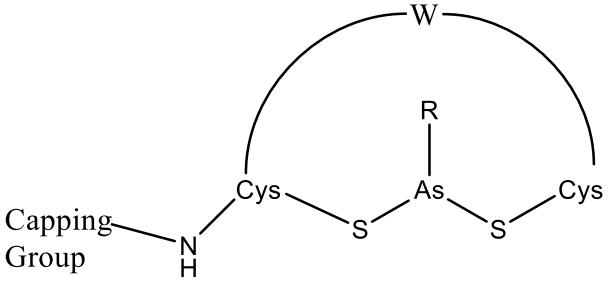
CLAIMS

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

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;

and

wherein in formula I and II 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. CVNHPAFAC;
11. CRGDRGPDC;
12. CRGDKTTNC;
13. CRGDHAGDC;
14. CLSYYPSYC;
15. CTPSPPFSHC;
16. CPHSKPCLC;
17. CSDSWHYWC;
18. CSDWQHPWC;
19. CSDYNHHWC;
20. CSDGQHYWC;
21. CYDSWHYWC;
22. CFDGNHIWC;
23. CTDFPRSFC;
24. CTQDRQHPC;
25. CLSRYLDQC;
26. CGNSNPKSC;
27. CPHNLTKLC ; and

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

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 anti-cancer agent has the structure of formula I.

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

7. A pharmaceutical composition comprising an anti-cancer agent of any one of claims 1 to 6 and a pharmaceutically acceptable carrier, diluent and/or excipient.

8. Use of the anti-cancer agent of any one of claims 1 to 6 or the pharmaceutical composition of claim 7 in the manufacture of a medicament for treating cancer in a patient.

9. The use of claim 8, wherein the cancer is a haematological malignancy or a solid tumour.

10. The use of claim 8 or claim 9, wherein the cancer is selected from a leukemia, multiple myeloma, and a lymphoma.

11. The use of any one of claims 8 to 10, 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.

12. The use of claim 8, wherein the cancer 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).

13. The use of any one of claims 8 to 12, wherein the anti-cancer agent is to be administered in combination with one or more of an immunotherapeutic, monoclonal antibody, chemotherapeutic, radioprotectant and radiotherapeutic.

14. A process for producing the anti-cancer agent of any one of claims 1 to 6, 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.

15. The process of claim 14 wherein the arsenic compound is an oxide of arsenic.

16. The process of claim 14 or claim 15, wherein the arsenic compound further comprises an alkyl, hydroxyl or aryl group bonded to the arsenic.

17. The process of any one of claims 14 to 16, further comprising the step (a)(i) of modifying a selected tumour homing peptide to present two cysteine residues.

18. An anti-cancer agent when produced by the process of any one of claims 14 to 17.