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(54) Title: USE OF MYELOPEROXIDASE (MPO) INHIBITORS FOR THE TREATMENT OF CHEMORESISTANT ACUTE MYELOID LEUKEMIA (AML)

(57) Abstract: Chemotherapy commonly alters cellular redox balance and increases the oxidative state. Recent studies have reported that chemoresistant cells have an increased reactive oxygen species (ROS) content in hematological malignancies. Here the inventors demonstrate that chemoresistant acute myeloid leukemia (AML) cells have a decreased level of mitochondrial and cytosolic ROS associated with an overexpression of myeloperoxidase (MPO), a heme protein that converts chloride and hydrogen peroxide to hypochlorous acid (HOC1). They also show that high MPO-expressing AML cells are less sensitive to AraC *in vitro* and *in vivo*. Targeting MPO expression and enzyme activity sensitizes to AraC treatment by triggering sustained oxidative stress in the high MPO expressing AML cells. Thus the present invention relates to use of myeloperoxidase (MPO) inhibitors for the treatment of chemoresistant acute myeloid leukemia (AML).



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USE OF MYELOPEROXIDASE (MPO) INHIBITORS FOR THE TREATMENT OF CHEMORESISTANT ACUTE MYELOID LEUKEMIA (AML)

5 **FIELD OF THE INVENTION:**

The present invention relates to use of myeloperoxidase (MPO) inhibitors for the treatment of chemoresistant acute myeloid leukemia (AML).

BACKGROUND OF THE INVENTION:

Acute myeloid leukemia (AML) is the most common adult leukemia. It is characterized
10 by clonal expansion of immature myeloblasts and initiates from rare leukemic stem cells (LSCs). Despite a high rate of complete remission after conventional induction chemotherapy, the overall survival is still poor for these patients, especially in elderly patients. Recent innovative therapies that are FDA-approved or under clinical development, target either particular genetic features such as PML-RARa, FLT3-ITD and IDH mutations or specific
15 cellular dependency processes such as BCL2 overexpression and epigenetic modifications (Döhner et al. 2015; Lagadinou et al. 2013; Sánchez-Mendoza & Rego 2017; Reiter et al. 2018; Cruijnsen et al. 2014; Tsai et al. 2012). However these new therapies did not necessarily eradicate the therapeutic resistance in these patients. Furthermore, recent studies have shown mechanisms of acquired resistance to these molecularly targeted drugs in AML (Garcia and Stone, 2017;
20 Hospital et al 2017; Intlekofer et al. 2018).

Energy metabolism and redox homeostasis are well-appreciated hallmarks of carcinogenesis and play crucial roles in response to chemotherapy in cancer cells. Several reports emphasize that targeting these features could abolish the tumorogenesis and sensitize resistant cells to chemotherapy (DeBerardinis et al. 2008; Deberardinis et al. 2008; Vander
25 Heiden & DeBerardinis 2017; Galluzzi et al. 2014; Glasauer & Chandel 2014; Hamanaka et al. 2013; DeBerardinis & Chandel 2016; Hosseini et al. 2014; Hosseini et al. 2017). In the same vein, others and we have recently shown that chemoresistant leukemic cells present an elevated oxidative phosphorylation (OxPHOS) with imbalance of redox homeostasis (Lee et al. 2017; Farge et al. 2017). Moreover, targeting the mitochondrial oxidative metabolism with OxPHOS
30 inhibitors rewires the metabolism toward glycolysis and sensitizes the resistant cells to AraC in acute myeloid leukemia (AML) (Farge et al. 2017; Bosc et al. 2017).

SUMMARY OF THE INVENTION:

The present invention relates to use of myeloperoxidase (MPO) inhibitors for the treatment of chemoresistant acute myeloid leukemia (AML). In particular, the present invention is defined by the claims.

DETAILED DESCRIPTION OF THE INVENTION:

5 Chemotherapy commonly alters cellular redox balance and increases the oxidative state. Recent studies have reported that chemoresistant cells have an increased reactive oxygen species (ROS) content in hematological malignancies. Here the inventors demonstrate that chemoresistant acute myeloid leukemia (AML) cells have a decreased level of mitochondrial and cytosolic ROS associated with an overexpression of myeloperoxidase (MPO), a heme
10 protein that converts chloride and hydrogen peroxide to hypochlorous acid (HOCl). They also show that high MPO-expressing AML cells are less sensitive to AraC *in vitro* and *in vivo*. Moreover, high MPO AML cell lines produce a higher level of HOCL and exhibit an increased rate of mitochondrial oxygen consumption when compared to low MPO expressing AML cells. Targeting MPO expression and enzyme activity sensitizes to AraC treatment by triggering
15 sustained oxidative stress in the high MPO expressing AML cells. This results from superoxide accumulation in mitochondria that impairs oxidative phosphorylation and energetic metabolism and drives apoptotic death and selective eradication of chemoresistant AML cells *in vitro* and *in vivo*.

 Accordingly, one object of the present invention relates to a method of treating
20 chemoresistant acute myeloid leukemia (AML) in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one myeloperoxidase (MPO) inhibitor.

 As used herein, the term "acute myeloid leukemia" or "acute myelogenous leukemia" ("AML") refers to a cancer of the myeloid line of blood cells, characterized by the rapid growth
25 of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.

 As used herein; the term "chemoresistant acute myeloid leukemia" refers to the clinical situation in a patient suffering from acute myeloid leukemia when the proliferation of cancer cells cannot be prevented or inhibited by means of a chemotherapeutic agent or a combination
30 of chemotherapeutic agents usually used to treat AML, at an acceptable dose to the patient. The leukemia can be intrinsically resistant prior to chemotherapy, or resistance may be acquired during treatment of leukemia that is initially sensitive to chemotherapy.

 As used herein, the term "chemotherapeutic agent" refers to any chemical agent with therapeutic usefulness in the treatment of cancer. Chemotherapeutic agents as used herein

encompass both chemical and biological agents. These agents function to inhibit a cellular activity upon which the cancer cell depends for continued survival. Categories of chemotherapeutic agents include alkylating/alkaloid agents, antimetabolites, hormones or hormone analogs, and miscellaneous antineoplastic drugs. Most if not all of these drugs are directly toxic to cancer cells and do not require immune stimulation. Suitable chemotherapeutic agents are described, for example, in Slapak and Kufe, Principles of Cancer Therapy, Chapter 86 in Harrison's Principles of Internal medicine, 14th edition; Perry et al., Chemotherapeutic, Ch 17 in Abeloff, Clinical Oncology 2nd ed., 2000 ChurchillLivingstone, Inc.; Baltzer L. and Berkery R. (eds): Oncology Pocket Guide to Chemotherapeutic, 2nd ed. St. Louis, Mosby-Year Book, 1995; Fischer D. S., Knobf M. F., Durivage HJ. (eds): The Cancer Chemotherapeutic Handbook, 4th ed. St. Louis, Mosby-Year Handbook. In some embodiments the chemotherapeutic agent is cytarabine (cytosine arabinoside, Ara-C, Cytosar-U), quizartinib (AC220), sorafenib (BAY 43-9006), lestaurtinib (CEP-701), midostaurin (PKC412), carboplatin, carmustine, chlorambucil, dacarbazine, ifosfamide, lomustine, mechlorethamine, procarbazine, pentostatin, (2'deoxycoformycin), etoposide, teniposide, topotecan, vinblastine, vincristine, paclitaxel, dexamethasone, methylprednisolone, prednisone, all- trans retinoic acid, arsenic trioxide, interferon-alpha, rituximab (Rituxan®), gemtuzumab ozogamicin, imatinib mesylate, Cytosar-U), melphalan, busulfan (Myleran®), thiotepa, bleomycin, platinum (cisplatin), cyclophosphamide, Cytosan®), daunorubicin, doxorubicin, idarubicin, mitoxantrone, 5-azacytidine, cladribine, fludarabine, hydroxyurea, 6-mercaptopurine, methotrexate, 6-thioguanine, or any combination thereof. In some embodiments, the leukemia is resistant to a combination of daunorubicin, or idarubicin plus cytarabine (AraC).

As used herein, the term "treatment" or "treat" refer to both prophylactic or preventive treatment as well as curative or disease modifying treatment, including treatment of patient at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and includes suppression of clinical relapse. The treatment may be administered to a patient having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay the onset of, reduce the severity of, or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a patient beyond that expected in the absence of such treatment. By "therapeutic regimen" is meant the pattern of treatment of an illness, e.g., the pattern of dosing used during therapy. A therapeutic regimen may include an induction regimen and a maintenance regimen. The phrase "induction regimen" or "induction period" refers to a therapeutic regimen (or the portion of a therapeutic regimen) that is used for

the initial treatment of a disease. The general goal of an induction regimen is to provide a high level of drug to a patient during the initial period of a treatment regimen. An induction regimen may employ (in part or in whole) a "loading regimen", which may include administering a greater dose of the drug than a physician would employ during a maintenance regimen, administering a drug more frequently than a physician would administer the drug during a maintenance regimen, or both. The phrase "maintenance regimen" or "maintenance period" refers to a therapeutic regimen (or the portion of a therapeutic regimen) that is used for the maintenance of a patient during treatment of an illness, e.g., to keep the patient in remission for long periods of time (months or years). A maintenance regimen may employ continuous therapy (e.g., administering a drug at a regular intervals, e.g., weekly, monthly, yearly, etc.) or intermittent therapy (e.g., interrupted treatment, intermittent treatment, treatment at relapse, or treatment upon achievement of a particular predetermined criteria [e.g., pain, disease manifestation, etc.]).

The method of the present invention is particularly suitable for preventing relapse of a patient suffering from AML who was treated with chemotherapy (e.g. AraC). As used herein, the term "relapse" refers to the return of cancer after a period of improvement in which no cancer could be detected. Thus, the method of the present invention is particularly useful to prevent relapse after putatively successful treatment with chemotherapy (e.g. AraC).

A further object of the present invention relates to a method of treating AML in a subject in need thereof comprising administering to the subject a therapeutically effective combination comprising at least one chemotherapeutic agent and an MPO inhibitor.

As used herein, the term "combination" is intended to refer to all forms of administration that provide a first drug together with a further (second, third...) drug. The drugs may be administered simultaneously, separate or sequential and in any order. Drugs administered in combination have biological activity in the subject to which the drugs are delivered. Within the context of the invention, a combination thus comprises at least two different drugs, and wherein one drug is at least one chemotherapeutic agent and wherein the other drug is at least one MPO inhibitor.

As used herein the term "Myeloperoxidase" or MPO has its general meaning in the art and refers to a heme-containing enzyme. The enzyme uses hydrogen peroxide to oxidize chloride to hypochlorous acid. Other halides and pseudohalides (like thiocyanate) are also physiological substrates to MPO.

As used herein, a "MPO inhibitor" refers to any compound natural or not which is capable of inhibiting the activity of MPO, in particular MPO kinase activity. MPO inhibitors

are well known in the art. The term encompasses any MPO inhibitor that is currently known in the art or that will be identified in the future, and includes any chemical entity that, upon administration to a patient, results in inhibition or down-regulation of a biological activity associated with activation of the MPO. The term also encompasses inhibitor of expression. The MPO inhibition of the compounds may be determined using various methods well known in the art.

Examples of compounds that can be used as MPO-inhibitors are compounds described in WO 2006/062465, WO 2006/062465, WO 2003/089430, WO 2003/089430, or WO 2003/089430.

In some embodiments, the MPO inhibitor of the present invention is selected from the group consisting of:

- 1-butyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-isobutyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(pyridin-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2-fluoro-benzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[2-(2-methoxyethoxy)-3-propoxybenzyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(6-ethoxy-pyridin-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-piperidin-3-ylmethyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-butyl-4-thioxo-1,3,4,5-tetrahydro-2H-pyrrolo[3,2-d]pyrimidin-2-one;
- 1-(2-isopropoxyethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2-methoxy-2-methylpropyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2-ethoxy-2-methylpropyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(piperidin-4-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(1-methylpiperidin-3-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;

- 1-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2-methoxybenzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 5 - 1-(3-methoxybenzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2,4-dimethoxybenzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(3-chloropyridin-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 10 - 1-{[3-(2-ethoxyethoxy)pyridin-2-yl]methyl}-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(6-oxo-1,6-dihydropyridin-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 15 - 1-(1H-indol-3-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(1H-benzimidazol-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(5-chloro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 20 - 1-[(5-fluoro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(1H-indol-6-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 25 - 1-(1H-indol-5-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(5-fluoro-1H-indol-3-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(1H-imidazol-5-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 30 - 1-(1H-imidazol-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(5-chloro-1H-benzimidazol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;

- 1-[(4,5-dimethyl-1H-benzimidazol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 7-bromo-1-isobutyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one; and
- 5 - 1-(3-chlorophenyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-c]pyrimidin-4-one.
- 1,3-diisobutyl-8-methyl-6-thioxanthine;
- 1,3-dibutyl-8-methyl-6-thioxanthine;
- 3-isobutyl-1,8-dimethyl-6-thioxanthine;
- 3-(2-methylbutyl)-6-thioxanthine;
- 10 - 3-isobutyl-8-methyl-6-thioxanthine;
- 3-isobutyl-2-thioxanthine;
- 3-isobutyl-2,6-dithioxanthine;
- 3-isobutyl-8-methyl-2-thioxanthine;
- 3-isobutyl-7-methyl-2-thioxanthine;
- 15 - 3-cyclohexylmethyl-2-thioxanthine;
- 3-(3-methoxypropyl)-2-thioxanthine;
- 3-cyclopropylmethyl-2-thioxanthine;
- 3-isobutyl-1-methyl-2-thioxanthine;
- 3-(2-tetrahydrofuryl-methyl)-2-thioxanthine;
- 20 - 3-(2-methoxy-ethyl)-2-thioxanthine;
- 3-(3-(1-morpholinyl)-propyl)-2-thioxanthine;
- 3-(2-furyl-methyl)-2-thioxanthine;
- 3-(4-methoxybenzyl)-2-thioxanthine;
- 3-(4-fluorobenzyl)-2-thioxanthine;
- 25 - 3-phenethyl-2-thioxanthine;
- (+)-3-(2-tetrahydrofuryl-methyl)-2-thioxanthine;
- (-)-3-(2-tetrahydrofuryl-methyl)-2-thioxanthine; and
- 3-n-butyl-2-thioxanthine.
- 3-(pyridin-2-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 30 - 3-(pyridin-3-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(pyridin-4-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{[3-ethoxy-4-(2-ethoxyethoxy)pyridin-2-yl]methyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;

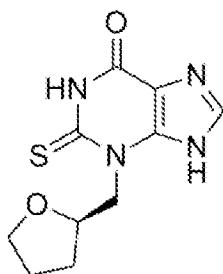
- 3-[(5-fluoro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(5-fluoro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 5 - 3-[(2-butyl-4-chloro-1H-imidazol-5-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(1H-benzimidazol-2-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[1-(1H-benzimidazol-2-yl)ethyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 10 - 3-[(5-chloro-1H-indol-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one
- 3-[(4-fluoro-1H-indol-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-(1H-Benzimidazol-2-yl)ethyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 15 - 3-(1H-Pyrazol-3-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(5-Methylpyrazin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(3-Isopropylisoxazol-5-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 20 - 3-[(4-Methyl-1,2,5-oxadiazol-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(6-Butoxypyridin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(4-Butoxypyridin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(3-Butoxypyridin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 25 - 3-[2-(Pyridin-2-ylmethoxy)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(3,5-Dimethylisoxazol-4-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(1-Methyl-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 30 - 3-(2-Phenyl-2-pyridin-2-ylethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(Quinolin-4-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(6-Phenoxypyridin-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;

- 3-{2-[(Quinolin-4-ylmethyl)amino]ethyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-[(1-Methyl-1H-indol-3-yl)methyl]amino)ethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 5 - 3-{2-[Methyl(quinolin-4-ylmethyl)amino]ethyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-Aminopropyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-{2-[(Pyridin-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 10 - 3-{2-[(Pyridin-3-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[(Pyridin-4-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 15 - 3-(2-[(6-Chloropyridin-3-yl)methyl]amino)propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-[2-({[6-(Trifluoromethyl)pyridin-3-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-(2-[(4,6-Dichloropyrimidin-5-yl)methyl]amino)propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 20 - 3-[2-({[2-(Dimethylamino)pyrimidin-5-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[(Quinolin-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 25 - 3-{2-[(Quinolin-3-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-[(1-tert-Butyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl]amino)propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[1-(1,1-Dioxidotetrahydro-3-thienyl)-3,5-dimethyl-1H-pyrazol-4-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 30 - 3-{2-[(1H-Benzoimidazol-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[1-(Phenylsulfonyl)-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;

- 3-{2-[(1-[(4-methylphenyl)sulfonyl]-1H-pyrrol-2-yl)methyl]amino}propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-(2-{[(1-methyl-1H-pyrrol-2-yl)methyl]amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 5 - 3-[2-({[1-(4-sec-Butylphenyl)-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[1-(3-Methoxyphenyl)-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[2,5-Dimethyl-1-(1,3-thiazol-2-yl)-1H-pyrrol-3-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 10 - 3-[2-({[4-(3-Chlorobenzoyl)-1-methyl-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[(1H-Imidazol-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 15 - 3-(2-{[(1-Methyl-1H-imidazol-2-yl)methyl]amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-{[(4-Bromo-1-methyl-1H-imidazol-5-yl)methyl]amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-{[(1-Methyl-1H-indol-3-yl)methyl]amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 20 - 2-Thioxo-3-{2-[(1H-1,2,3-triazol-5-ylmethyl)amino]propyl}-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[1-(Benzyloxy)-1H-imidazol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 25 - 3-(2-{[(6-Bromo-2-methylimidazo[1,2-a]pyridin-3-yl)methyl]amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[(1-[2-(2-Methoxyphenoxy)ethyl]-1H-pyrrol-2-yl)methyl]amino}propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]pyridine-2-carboxamide;
- 30 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]nicotinamide;
- N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]isonicotinamide;

- N-[1-methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]-1,8-naphthyridine-2-carboxamide;
- N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]quinoline-2-carboxamide;
- 5 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]pyrimidine-2-carboxamide; and
- N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]-1H-imidazole-2-carboxamide trifluoroacetate.

In some embodiment, the MPO inhibitor is AZD5904 which has the formula of:



10 In some embodiments, the MPO inhibitor is an inhibitor of MPO expression. An “inhibitor of expression” refers to a natural or synthetic compound that has a biological effect to inhibit the expression of a gene. In a preferred embodiment of the invention, said inhibitor of gene expression is a siRNA, an antisense oligonucleotide or a ribozyme. For example, anti-
15 sense oligonucleotides, including anti-sense RNA molecules and anti-sense DNA molecules, would act to directly block the translation of MPO mRNA by binding thereto and thus preventing protein translation or increasing mRNA degradation, thus decreasing the level of MPO, and thus activity, in a cell. For example, antisense oligonucleotides of at least about 15
20 bases and complementary to unique regions of the mRNA transcript sequence encoding MPO can be synthesized, e.g., by conventional phosphodiester techniques. Methods for using antisense techniques for specifically inhibiting gene expression of genes whose sequence is known are well known in the art (e.g. see U.S. Pat. Nos. 6,566,135; 6,566,131; 6,365,354; 6,410,323; 6,107,091; 6,046,321; and 5,981,732). Small inhibitory RNAs (siRNAs) can also
25 function as inhibitors of expression for use in the present invention. MPO gene expression can be reduced by contacting a subject or cell with a small double stranded RNA (dsRNA), or a vector or construct causing the production of a small double stranded RNA, such that MPO gene expression is specifically inhibited (i.e. RNA interference or RNAi). Antisense oligonucleotides, siRNAs, shRNAs and ribozymes of the invention may be delivered in vivo alone or in association with a vector. In its broadest sense, a "vector" is any vehicle capable of

facilitating the transfer of the antisense oligonucleotide, siRNA, shRNA or ribozyme nucleic acid to the cells and typically cells expressing MPO. Typically, the vector transports the nucleic acid to cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In general, the vectors useful in the invention include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources that have been manipulated by the insertion or incorporation of the antisense oligonucleotide, siRNA, shRNA or ribozyme nucleic acid sequences. Viral vectors are a preferred type of vector and include, but are not limited to nucleic acid sequences from the following viruses: retrovirus, such as moloney murine leukemia virus, harvey murine sarcoma virus, murine mammary tumor virus, and rous sarcoma virus; adenovirus, adeno-associated virus; SV40-type viruses; polyoma viruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known to the art.

By a "therapeutically effective amount" of the inhibitor as above described is meant a sufficient amount to provide a therapeutic effect. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed, the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific polypeptide employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. However, the daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per adult per day. Typically, the compositions contain 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 mg of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from 1 mg to about 100 mg of the active ingredient. An effective amount of the drug is ordinarily supplied at a dosage level from 0.0002 mg/kg to about 20 mg/kg of body weight per day, especially from about 0.001 mg/kg to 7 mg/kg of body weight per day.

Typically, the inhibitor of the present invention is combined with pharmaceutically acceptable excipients, and optionally sustained-release matrices, such as biodegradable polymers, to form pharmaceutical compositions. "Pharmaceutically" or "pharmaceutically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to a mammal, especially a human, as appropriate. A pharmaceutically acceptable carrier or excipient refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Typically, the pharmaceutical compositions contain vehicles, which are pharmaceutically acceptable for a formulation capable of being injected. These may be in particular isotonic, sterile, saline solutions (monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride and the like or mixtures of such salts), or dry, especially freeze-dried compositions which upon addition, depending on the case, of sterilized water or physiological saline, permit the constitution of injectable solutions. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. Sterile injectable solutions are prepared by incorporating the inhibitor at the required amount in the appropriate solvent with several of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The invention will be further illustrated by the following figures and examples. However, these examples and figures should not be interpreted in any way as limiting the scope of the present invention.

FIGURES:

Figures 1A and B show that downregulation of MPO by shMPO and/or ABAH sensitized cells to AraC as shown by lower EC_{50} for AraC in shMPO-transduced cells compared to shCtrl-transduced cells.

EXAMPLE:**Results*****In vivo* response to cytarabine is correlated with ROS generation capacity and MPO expression**

5 Redox homeostasis is a key regulator of the chemotherapeutic response in cancer cells and increased ROS levels are often observed in drug resistant cells, suggesting greater capacity to regulate ROS production and to survive in presence of a higher ROS level. To determine whether this specific redox capacity and ROS levels are already pre-existing features that persist through cytarabine (AraC) we have determined cytosolic and mitochondrial reactive oxygen
10 species (ROS as measured by CMH2DCF-DA and MitoSox, respectively) levels in cells from AML patients and cell lines in accordance with their response to AraC *in vivo* in twenty patient-derived xenograft (PDX) and two cell line-derived xenograft (CLDX) models. Thus, AML patients and cell lines that are high responders to AraC *in vivo*, had higher cytosolic and mitochondrial ROS level in response to AraC compared to vehicle than low responders (**data**
15 **not shown**), suggesting that ROS generation capacity in AML cells might determine the outcome of response to AraC. Next, gene set enrichment analysis indicated that ROS metabolic process gene signature (96 genes from GO database) was enriched in AML cells at diagnosis of patients that are low responders to AraC *in vivo* (GSE97393) and in human viable residual AML blasts purified from bone marrow of NSG mice treated with AraC (GSE97631) (**data not**
20 **shown**). This suggests that lower ROS levels in residual AML cells post-AraC is associated to genes implicated in ROS metabolism and High OxPHOS activity in pre-existing AML cells, as we previously described for the latter.

Datamining analyses of upregulated genes in both AraC-resistant AML blasts and in low responder patients revealed enrichment in genes involved in biological pathways such as
25 cellular proliferation, immune response and response to oxidative stress (**data not shown**). Focusing on genes implicated in ROS metabolism, we found that 27 genes upregulated in AraC residual cells *in vivo* and 11 genes upregulated at diagnosis in patients with a low response to AraC (**data not shown**). Comparing these two specific ROS gene signatures with curated GO ROS gene signature, Venn diagram showed only one common upregulated gene implicated in
30 response to oxidative stress as MPO (**data not shown**). Next we confirmed that MPO expression was significantly higher in AML patients and cell lines (4) that are low responder *in vivo* compared to high responder (**data not shown**). While its RNA expression was heterogeneous in AML, it was also higher in both complex and normal karyotypes compared normal hematopoietic stem cells (cohort BloodPool; **data not shown**). Surprisingly, expression

of MPO was negatively correlated to NPM1 mutation that is considered as a favorable prognosis in AML (**data not shown**) and to M5 subgroup (**data not shown**). Taking advantage of the MPO expression heterogeneity in AML patients, we have generated gene signatures from 3 independent publicly accessible cohorts (TCGA, Verhaak and Metzeler) of patients with the highest MPO expression compared to the lowest MPO expression (hereinafter called MPO gene signature including 485 genes, 101 genes and 111 genes, respectively) (**data not shown**). A GSEA analysis showed that this specific MPO gene set is enriched in both patients with lower response to AraC *in vivo* and AraC treated residual cells *in vivo* (**data not shown**). Altogether, these results indicate that resistance to AraC is positively associated to high MPO expression in AML cells.

Enhanced MPO expression and activity increases resistance to cytarabine and sensitizes to ABAH in AML

Previous studies have demonstrated that MPO play a crucial role in inducing oxidative stress-mediated apoptosis in AML cells (Nakazato et al. 2007; Kim et al. 2010). Nakazato and colleagues reported that the H₂O₂/MPO/halide system are key mediators of apoptosis induced by polyphenol, (–)-epigallocatechin-3-gallate(EGCG) in AML cells(Nakazato et al. 2007). They have proposed that EGCG and other ROS-generating agents may serve as an enhancer of chemotherapy via MPO-mediated production of ROS in myeloid leukemic cells (Nakazato et al. 2007). In another study Kim and others (Kim et al. 2010) have demonstrated that AML cells having an elevated level of MPO are more sensitive to Parthenolide (PTL). They have suggested that MPO level is critical determinant of PTL-induced apoptosis in leukemia cells and PTL can be combined with common antileukemia drugs to overcome chemoresistance and enhance therapeutic responses. However the role of MPO in AML chemoresistance is not clearly known.

Therefore, we examined herein whether high MPO expressing cells are more resistant to AraC and more vulnerable to MPO inhibitors. For this end, we first assessed the expression, gene set enrichment, and the activity of MPO in four diverse AML cell lines. AML cell lines with higher MPO protein expression level (**data not shown**) were enriched in MPO gene signatures generated from TCGA, Verhaak and Metzeler databases, respectively (**data not shown**). Moreover high MPO cell lines had also an elevated level of MPO activity (**data not shown**) as treatment of AML cells with 4-AminoBenzoic Acid Hydrazide (ABAH), an irreversible and specific inhibitor of MPO activity resulted in significant reduction of MPO activity in higher MPO-expressing AML cell lines (**data not shown**). Similarly, higher MPO-

expressing AML cells were more sensitive to ABAH compared to low MPO-expressing cells *in vitro* (**data not shown**).

To test our hypothesis, we selected two AML cell lines with 2 different levels of MPO expression e.g. MOLM-14 (as high MPO cell line) and U937 (as a low MPO cell line). Taking advantage of our *in vivo* CLDX and PDX assay, we injected low and high MPO-expressing AML cell lines in adult NSG mice, we treated xenografted mice with PBS or AraC, we then dissected BM and sorted viable human AML blasts to assess EC₅₀ for AraC and ABAH (**data not shown**). EC₅₀ for AraC was significantly increased upon both PBS- and AraC-treatment *in vivo* in High MPO-expressing MOLM14 cells compared to low MPO-expressing U937 cells (**data not shown**). Of note, EC₅₀ for MPO inhibitor (ABAH) was significantly decreased upon both PBS- and AraC-treatment *in vivo* in High MPO-expressing MOLM14 cells compared to low MPO-expressing U937 cells (**data not shown**). Consistent with these results, we found that EC₅₀ for ABAH of sorted human AML cells from PBS- or AraC-treated (n=6) PDX models was significantly reduced in AraC-residual cells compared to PBS-treated cells (**data not shown**). Similarly and based on the fluorescence of the redox dye R19-S, we sorted and purified human AML cell subpopulations with High vs. Low HOCL content from *in vitro* MOLM14 and CLDX models *in vivo* (**data not shown**) and revealed that subfractionated AML cells with High HOCL content (e.g. High ABAH-sensitive MPO activity; **data not shown**) were more resistant to AraC and more sensitive to ABAH compared to subfractionated AML cells with Low HOCL content *in vivo* and *in vitro* (**data not shown**). These data strongly suggest that MPO upregulation or increase in HOCL content contribute to resistance to AraC in AML cells.

Elevated MPO expression is associated with alterations in both ROS metabolism and energetic balance in AML

ROS homeostasis and ROS signaling play a crucial role in response to treatment in AML patients (Hole et al. 2011; Laganidou et al., 2013; Farge et al., 2017). In particular, ROS have been known as critical mediators of genotoxics-induced cell death for long even though their cellular effectors are still ill-defined (Matés et al. 2012). In this context, we have also shown a novel role for ROS in AML response to chemotherapeutic drugs (Bossis et al. 2014). As MPO is one of the key (but underestimated/understudied) components of ROS metabolism (**data not shown**), we were next wondered whether and how MPO would impact ROS metabolism in AML *in vitro* and *in vivo*. Cytosolic ROS level is significantly increased in residual AML cells from chemoresistant MOLM14 CLDX models upon AraC chemotherapy *in vivo* (Fig. 3B). On the contrary, mitochondrial ROS (mtROS) was increased in chemosensitive U937 and not in

MOLM14 CLDX *in vivo* (Fig. 3C). Importantly, HOCL content was elevated upon AraC in High MPO-expressing MOLM-14 cells *in vivo* (**data not shown**).

Under physiological conditions, mitochondrial ROS (mtROS) production and detoxification process are tightly balanced. Impairment of this equilibrium enables mtROS to induce a diverse array of signaling networks such as intracellular signaling associated with metabolic switch toward “Warburg effect”, inflammation, differentiation, cellular damage and cell death (Okon & Zou 2015; Sabharwal & Schumacker 2014; Liemburg-Apers et al. 2015; Wang et al. 2018). Interestingly, recent studies indicated that elevated level of mtROS could be considered as hallmark of mitochondrial dysfunction (Liemburg-Apers et al. 2015; Galvan et al. 2017) and as previously reported mitochondrial targeting selectively sensitizes resistant cells to chemotherapy (Fu et al. 2017; Farge, Saland, de Toni, et al. 2017). Consistent with these studies Lagadino et al. characterized oxidative state of leukemia stem cells (LSCs) and suggested mitochondria as the primary site of oxidative metabolism in LSC-enriched populations. Accordingly these studies emphasize the role of mitochondria in resistance to chemotherapy. Here, we wondered whether MPO might influence mitochondrial and OXPHOS metabolism in AML. First our GSEA illustrated an enrichment of High OXPHOS signature in High MPO population obtained from several databases (**data not shown**). To confirm this transcriptomic work, we measured oxygen consumption rates in four different AML cell lines in presence of ABAH by Seahorse analyzer (**data not shown**). We showed that *in vitro* ABAH treatment significantly reduced basal and ATP-linked OCR in high MPO cell lines compared to Low MPO cell lines (**data not shown**). Of note, *in vitro* ABAH treatment significantly increased proton leak and mito ROS in high MPO cell lines compared to Low MPO cell lines (**data not shown**). Similarly, purified human AML cell subpopulations with High vs. Low HOCL content from MOLM14 cells *in vitro* and *in vivo* consume a higher level of oxygen rather than Low subfractionated AML cells (**data not shown**).

Altogether, these results suggest that elevated level of MPO is associated with a higher OXPHOS gene phenotype and activities that is previously correlated to resistance to AraC. We also emphasized that while AML cells with high HOCL content have an increased mitochondrial oxygen consumption, the inhibition of MPO activity leads to mitochondrial respiration impairment through the induction of proton leak and excessive mtROS production.

MPO Inhibition Enhances Response to cytarabine in AML

As previous work (Farge et al, Lee et al; Kun et al) showed that highly OXPHOS cells are resistant to chemotherapies, we asked how inhibition of MPO sensitizes AML cells to AraC by blocking/inhibiting mitochondrial energetic and oxidative metabolisms. Furthermore

persistent ROS stress may induce adaptive responses, enabling cancer cells to survive with high levels of ROS. Affecting (up or down) these excessive ROS levels can therefore render cancer cells highly susceptible to apoptosis through alterations of both energetic and ROS metabolisms. Recent publications have, however, shown that the leukemic phenotype correlates with elevated ROS levels. In particular, one of them has demonstrated that AML cells are more susceptible to oxidative stress than normal cells because of their deregulated mitochondrial metabolism, suggesting that pharmacological interventions aiming at altering ROS levels might reveal a selective anti-leukemic strategy (Sriskanthadevan et al. 2015). Further supporting this idea, parthenolide or piperlongumine, two naturally occurring ROS inducer, and arsenic was shown to preferentially target the poorly abundant AML Stem Cells (LSCs), which both (i) are responsible for patient relapse due to their intrinsic poor sensitivity to chemotherapeutic drugs and (ii) display deregulated redox metabolism (Guzman et al. 2005; Eleni D. Lagadinou et al. 2013; Pei et al. 2013). To answer this question, U937 and Molm14 were treated *in vitro* with PBS, AraC, ABAH and combination of ABAH and AraC for 24h. While, no significant change in HOCl level was observed in U937, HOCL level was significantly increased in Molm14 upon treatment with AraC. AraC-mediated increased HOCL was restored in the presence of ABAH (**data not shown**). ROS measurement showed that mtROS level was significantly elevated following monotherapy with ABAH and combination therapy in high MPO cell line (**data not shown**). Basal respiration and the ratio of OCR/ECAR were diminished in Molm14 after treatment by ABAH and under combination therapy (**data not shown**). Altogether, combination therapy in Molm14 resulted in decreased MPO activity, increased mtROS and decreased OXPHOS,.

To further analyze the role of MPO in the resistance to AraC, we employed a shRNA technology to reduce gene expression of MPO. A remarkable reduction of HOCL content even in the presence of AraC was observed in shMPO-transduced Molm14 cells (**data not shown**). Measurement of ROS confirmed that MPO downregulation was associated to overproduction of mtROS (**data not shown**).

Depletion of MPO decreased OCR/ECAR ratio emphasizing that MPO has an impact on OXPHOS metabolism (**data not shown**). Knocking down MPO by specific shRNA have also a significant effect on expression of several genes involved in DNA repair such as H2A histone family, member X (H2AX) and 8-Oxoguanine DNA Glycosylase (OGG1), an enzyme involving in repair of oxidative damages. The mRNA expression of H2AX and OGG1 were significantly upregulated in shMPO-transduced cells treated with AraC (**data not shown**).

A remarkable increase in protein level of ATM and phosphorylated H2AX was seen in shCTL- and shMPO-transduced cells treated with AraC compare to cells treated with PBS (**data not shown**). Finally, a significant increase in MMP loss and a significant decreased viability was found when shMPO-transduced cells were subjected to AraC (**data not shown**).

***In Vivo* Inhibition of MPO Therapeutically sensitizes Resistance cells to Arac**

Given the observations outlined above, we sought to confirm the role of MPO *in vivo*. We injected MPO-depleted and mock AML cells to adult NSG mice and the mice were treated with AraC. MPO mRNA expression was significantly reduced in human shMPO-transduced cells in both untreated and treated cells with AraC (**data not shown**). Measurement of HOCL level showed a remarkable decrease in HOCL level in human depleted-MPO blasts following AraC therapy (**data not shown**).

As expected, mtROS level was significantly increased in human MPO-depleted cells upon AraC (**data not shown**). We observed a decrease of mitochondrial oxygen consumption rate in human MPO-KO sorted AML cells upon chemotherapy (**data not shown**). Increased OGG1 level in human MPO-KO cells upon AraC treatment suggest an increased oxidative damages in these cells (**data not shown**). In agreement, loss of mitochondrial membrane potential and a significant reduction in viability were observed in shMPO-treated with AraC (**data not shown**). MPO primes AML differentiation(Kim et al. 2012) and elevated level of differentiation correlate positively to high OXPHOS status(Farge, Saland, de Toni, et al. 2017). Accordingly we evaluated expression of CD11b as marker of differentiation in human blasts and the results showed that AraC therapy significantly reduce the differentiation rate in MPO-depleted cells (**data not shown**). As shown in **Figures 1A and B**, downregulation of MPO by shMPO and/or ABAH sensitized cells to AraC as shown by lower EC₅₀ for AraC in shMPO-transduced cells compared to shCtrl-transduced cells.

Discussion:

In summary, our previous study demonstrated that AraC treatment leads to increased OXPHOS metabolism and ROS generation in residual AML cells (Farge, Saland, Toni, et al. 2017). In this study, we showed that MPO level negatively associated to mtROS generation. Hence high responders AML cells with a lower level of MPO (U937) produce a large amount of mtROS under treatment with AraC. On the contrary, low responder cell lines (Molm 14) had high MPO and low mtROS level. Using *in vivo* and *in vitro* models, we showed that depletion or inhibition of MPO in these cells sensitize them to AraC treatment through affecting mitochondrial redox balance and mitochondrial metabolism, resulting finally in their eradication by apoptosis. Overall, MPO in addition to be biomarker of inflammation and

differentiation could be considered as biomarker of OXPHOS metabolism and chemoresistance AML cells to AraC. Regarding the role of MPO in several pathways, this enzyme could be considered as a potential therapeutic target to overcome chemoresistance in AML cells.

REFERENCES:

- 5 Throughout this application, various references describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference into the present disclosure.

CLAIMS:

1. A method of treating chemoresistant acute myeloid leukemia (AML) in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one myeloperoxidase (MPO) inhibitor.
- 5 2. The method of claim 1 wherein the leukemia is resistant to a chemotherapeutic agent selected from the group consisting of cytarabine (cytosine arabinoside, Ara-C, Cytosar-U), quizartinib (AC220), sorafenib (BAY 43-9006), lestaurtinib (CEP-701), midostaurin (PKC412), carboplatin, carmustine, chlorambucil, dacarbazine, ifosfamide, lomustine, mechlorethamine, procarbazine, pentostatin, (2'deoxycoformycin),
10 etoposide, teniposide, topotecan, vinblastine, vincristine, paclitaxel, dexamethasone, methylprednisolone, prednisone, all- trans retinoic acid, arsenic trioxide, interferon-alpha, rituximab (Rituxan®), gemtuzumab ozogamicin, imatinib mesylate, Cytosar-U, melphalan, busulfan (Myleran®), thiotepea, bleomycin, platinum (cisplatin), cyclophosphamide, Cytoxan®., daunorubicin, doxorubicin, idarubicin, mitoxantrone,
15 5-azacytidine, cladribine, fludarabine, hydroxyurea, 6-mercaptopurine, methotrexate, 6-thioguanine, or any combination thereof.
3. The method of claim 1 wherein the leukemia is resistant to a combination of daunorubicin, or idarubicin plus cytarabine (AraC).
4. The method of claim 1 wherein the MPO inhibitor is selected from the group consisting
20 of:
 - 1-butyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
 - 1-isobutyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
 - 1-(pyridin-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
 - 1-(2-fluoro-benzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
 - 25 - 1-[2-(2-methoxyethoxy)-3-propoxybenzyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
 - 1-(6-ethoxy-pyridin-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;

- 1-piperidin-3-ylmethyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-butyl-4-thioxo-1,3,4,5-tetrahydro-2H-pyrrolo[3,2-d]pyrimidin-2-one;
- 1-(2-isopropoxyethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2-methoxy-2-methylpropyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2-ethoxy-2-methylpropyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(piperidin-4-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(1-methylpiperidin-3-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2-methoxybenzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(3-methoxybenzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(2,4-dimethoxybenzyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(3-chloropyridin-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-{[3-(2-ethoxyethoxy)pyridin-2-yl]methyl}-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(6-oxo-1,6-dihydropyridin-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(1H-indol-3-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(1H-benzimidazol-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;

- 1-[(5-chloro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(5-fluoro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 5 - 1-(1H-indol-6-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(1H-indol-5-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(5-fluoro-1H-indol-3-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-(1H-imidazol-5-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 10 - 1-(1H-imidazol-2-ylmethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 1-[(5-chloro-1H-benzimidazol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 15 - 1-[(4,5-dimethyl-1H-benzimidazol-2-yl)methyl]-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one;
- 7-bromo-1-isobutyl-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one; and
- 1-(3-chlorophenyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-c]pyrimidin-4-one.
- 1,3-diisobutyl-8-methyl-6-thioxanthine;
- 20 - 1,3-dibutyl-8-methyl-6-thioxanthine;
- 3-isobutyl-1,8-dimethyl-6-thioxanthine;
- 3-(2-methylbutyl)-6-thioxanthine;
- 3-isobutyl-8-methyl-6-thioxanthine;
- 3-isobutyl-2-thioxanthine;

- 3-isobutyl-2,6-dithioxanthine;
- 3-isobutyl-8-methyl-2-thioxanthine;
- 3-isobutyl-7-methyl-2-thioxanthine;
- 3-cyclohexylmethyl-2-thioxanthine;
- 5 - 3-(3-methoxypropyl)-2-thioxanthine;
- 3-cyclopropylmethyl-2-thioxanthine;
- 3-isobutyl-1-methyl-2-thioxanthine;
- 3-(2-tetrahydrofuryl-methyl)-2-thioxanthine;
- 3-(2-methoxy-ethyl)-2-thioxanthine;
- 10 - 3-(3-(1-morpholinyl)-propyl)-2-thioxanthine;
- 3-(2-furyl-methyl)-2-thioxanthine;
- 3-(4-methoxybenzyl)-2-thioxanthine;
- 3-(4-fluorobenzyl)-2-thioxanthine;
- 3-phenethyl-2-thioxanthine;
- 15 - (+)-3-(2-tetrahydrofuryl-methyl)-2-thioxanthine;
- (?) -3-(2-tetrahydrofuryl-methyl)-2-thioxanthine; and
- 3-n-butyl-2-thioxanthine.
- 3-(pyridin-2-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(pyridin-3-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 20 - 3-(pyridin-4-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{[3-ethoxy-4-(2-ethoxyethoxy)pyridin-2-yl]methyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;

- 3-[(5-fluoro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(5-fluoro-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(2-butyl-4-chloro-1H-imidazol-5-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 5 - 3-(1H-benzimidazol-2-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[1-(1H-benzimidazol-2-yl)ethyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(5-chloro-1H-indol-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one
- 3-[(4-fluoro-1H-indol-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-(1H-Benzimidazol-2-yl)ethyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 10 - 3-(1H-Pyrazol-3-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(5-Methylpyrazin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(3-Isopropylisoxazol-5-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(4-Methyl-1,2,5-oxadiazol-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 15 - 3-[(6-Butoxypyridin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(4-Butoxypyridin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(3-Butoxypyridin-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-(Pyridin-2-ylmethoxy)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[(3,5-Dimethylisoxazol-4-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 20 - 3-[(1-Methyl-1H-indol-2-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-Phenyl-2-pyridin-2-ylethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(Quinolin-4-ylmethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;

- 3-[(6-Phenoxypyridin-3-yl)methyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[(Quinolin-4-ylmethyl)amino]ethyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-{[(1-Methyl-1H-indol-3-yl)methyl]amino}ethyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[Methyl(quinolin-4-ylmethyl)amino]ethyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-Aminopropyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-{2-[(Pyridin-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-{2-[(Pyridin-3-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[(Pyridin-4-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-{[(6-Chloropyridin-3-yl)methyl]amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-[2-({[6-(Trifluoromethyl)pyridin-3-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-(2-{[(4,6-Dichloropyrimidin-5-yl)methyl]amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[2-(Dimethylamino)pyrimidin-5-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-{2-[(Quinolin-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-{2-[(Quinolin-3-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;

- 3-(2-{{(1-tert-Butyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl}amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[1-(1,1-Dioxidotetrahydro-3-thienyl)-3,5-dimethyl-1H-pyrazol-4-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 5 - 3-{2-[(1H-Benzimidazol-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[1-(Phenylsulfonyl)-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 3-{2-[(1-[(4-methylphenyl)sulfonyl]-1H-pyrrol-2-yl)methyl]amino}propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one trifluoroacetate;
- 10 - 3-(2-{{(1-methyl-1H-pyrrol-2-yl)methyl}amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[1-(4-sec-Butylphenyl)-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 15 - 3-[2-({[1-(3-Methoxyphenyl)-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[2,5-Dimethyl-1-(1,3-thiazol-2-yl)-1H-pyrrol-3-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-[2-({[4-(3-Chlorobenzoyl)-1-methyl-1H-pyrrol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 20 - 3-{2-[(1H-Imidazol-2-ylmethyl)amino]propyl}-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 3-(2-{{(1-Methyl-1H-imidazol-2-yl)methyl}amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
- 25 - 3-(2-{{(4-Bromo-1-methyl-1H-imidazol-5-yl)methyl}amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;

- 3-(2-{{(1-Methyl-1H-indol-3-yl)methyl}amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
 - 2-Thioxo-3-{2-[(1H-1,2,3-triazol-5-ylmethyl)amino]propyl}-1,2,3,7-tetrahydro-6H-purin-6-one;
 - 5 - 3-[2-({[1-(Benzyloxy)-1H-imidazol-2-yl]methyl}amino)propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
 - 3-(2-{{(6-Bromo-2-methylimidazo[1,2-a]pyridin-3-yl)methyl}amino}propyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
 - 10 - 3-{2-[(1-[2-(2-Methoxyphenoxy)ethyl]-1H-pyrrol-2-yl)methyl]amino}propyl]-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one;
 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]pyridine-2-carboxamide;
 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]nicotinamide;
 - 15 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)-ethyl]isonicotinamide;
 - N-[1-methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]-1,8-naphthyridine-2-carboxamide;
 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]quinoline-2-carboxamide;
 - 20 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]pyrimidine-2-carboxamide; and
 - N-[1-Methyl-2-(6-oxo-2-thioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)ethyl]-1H-imidazole-2-carboxamide trifluoroacetate.
5. The method of claim 1 wherein the MPO inhibitor is AZD5904
- 25 6. The method of claim 1 wherein the MPO inhibitor is an inhibitor of MPO expression such as siRNA or an antisense oligonucleotide.

7. Use of a MPO inhibitor for preventing relapse of a patient suffering from AML who was treated with chemotherapy.
8. A method of treating AML in a subject in need thereof comprising administering to the subject a therapeutically effective combination comprising at least one chemotherapeutic agent and an MPO inhibitor.

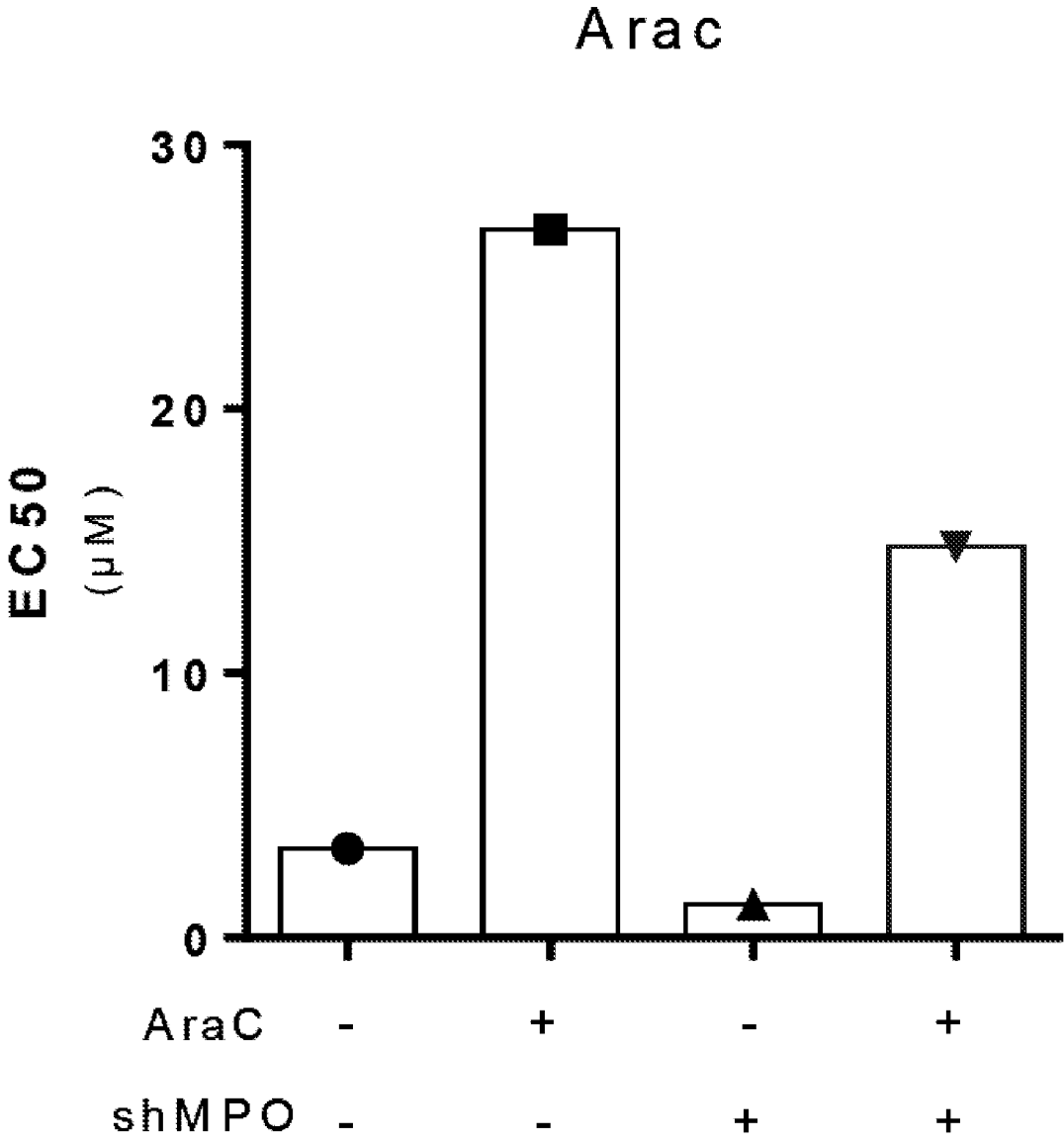
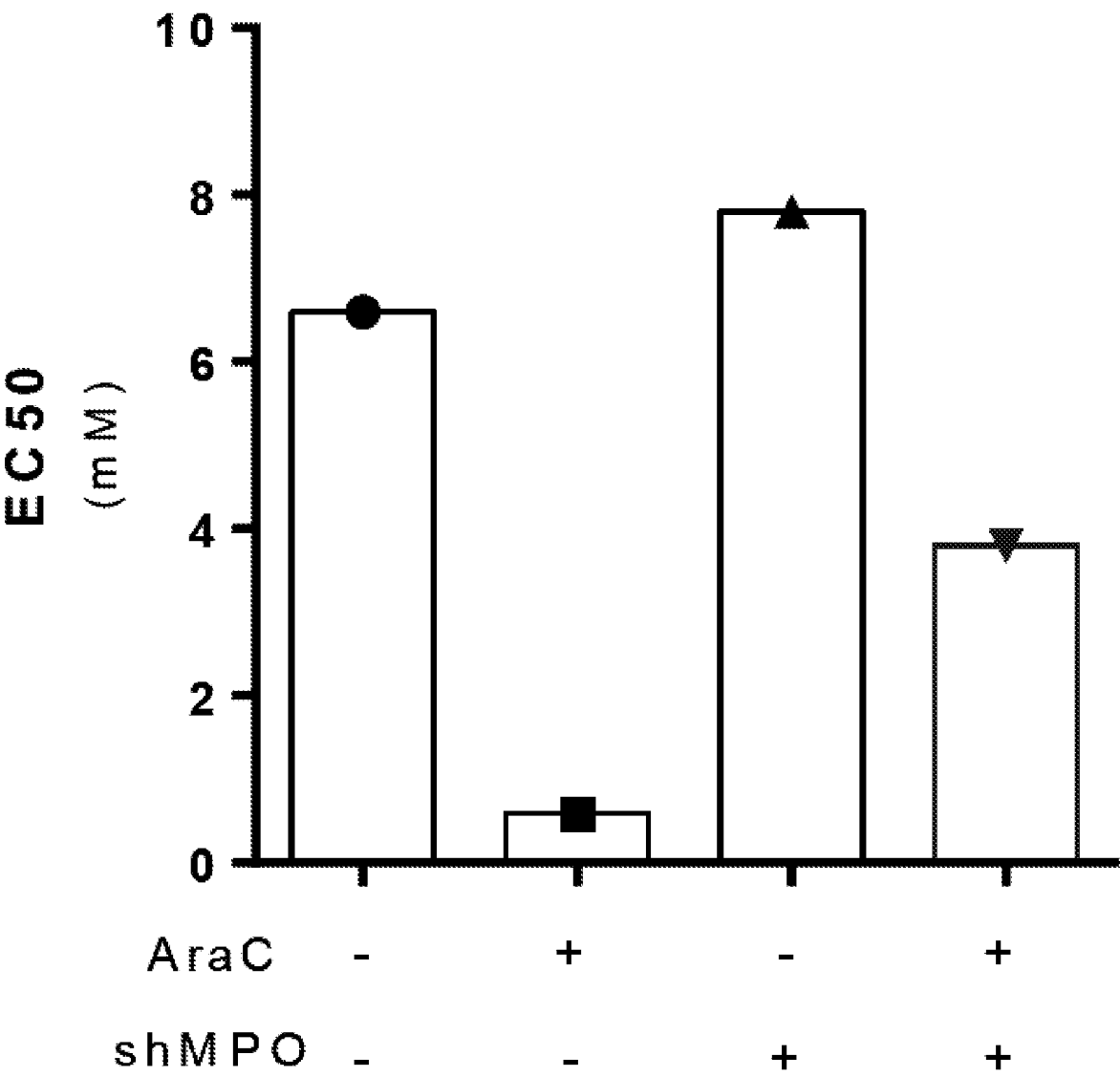


Figure 1A



Figures 1B

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/001013

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K45/06 A61K31/16 A61K31/7068 A61P35/02 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHLAIFER DANIEL ET AL: "Potential strategies for circumventing myeloperoxidase-catalyzed degradation of vinca alkaloids", LEUKEMIA, MACMILLAN PRESS LTD, US, vol. 8, no. 4, 1 January 1994 (1994-01-01), pages 668-671, XP009511793, ISSN: 0887-6924 page 670, column 1 ----- -/--	1,2,6-8
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
4 April 2019	11/04/2019	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Büttner, Ulf	

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/001013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHLAIFER DANIEL ET AL: "Antisense inhibition of myeloperoxidase increases the sensitivity of the HL-60 cell line to vincristine", LEUKEMIA, MACMILLAN PRESS LTD, US, vol. 8, no. 2, 1 January 1994 (1994-01-01) , pages 289-291, XP009511794, ISSN: 0887-6924	1,2,6-8
A	page 291, last paragraph -----	3-5
X	ASGHARI MOHAMMAD HOSSEIN ET AL: "Does the use of melatonin overcome drug resistance in cancer chemotherapy?", LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 196, 31 January 2018 (2018-01-31), pages 143-155, XP085351308, ISSN: 0024-3205, DOI: 10.1016/J.LFS.2018.01.024	1-3,7,8
A	page 670, last paragraph -----	4
X	WO 2015/009879 A1 (HAMNER INST [US]) 22 January 2015 (2015-01-22) figure 5 examples -----	1-3,7,8
X	A L SAMUELS ET AL: "A pre-clinical model of resistance to induction therapy in pediatric acute lymphoblastic leukemia", BLOOD CANCER JOURNAL, vol. 4, no. 8, 1 August 2014 (2014-08-01), pages e232-e232, XP055567964, DOI: 10.1038/bcj.2014.52 table 2 -----	1-3,7,8
A	HUANG JIANSHEG ET AL: "Ordered cleavage of myeloperoxidase ester bonds releases active site heme leading to inactivation of myeloperoxidase by benzoic acid hydrazide analogs", ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 548, 13 March 2014 (2014-03-13), pages 74-85, XP028844574, ISSN: 0003-9861, DOI: 10.1016/J.ABB.2014.02.014 page 76, column 1, paragraph 2 ----- -/--	1-8

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/001013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Y SAWAYAMA ET AL: "Expression of myeloperoxidase enhances the chemosensitivity of leukemia cells through the generation of reactive oxygen species and the nitration of protein", LEUKEMIA., vol. 22, no. 5, 1 May 2008 (2008-05-01), pages 956-964, XP055567337, US ISSN: 0887-6924, DOI: 10.1038/leu.2008.8 page 962, last paragraph -----	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2018/001013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015009879	A1	22-01-2015	NONE
