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(54) Title: INORGANIC SELENIUM FOR TREATMENT OF BENIGN TUMORS

(57) Abstract: The invention relates to the use of selenate or its pharmaceutically acceptable salts, in nutritional or supranutritional amounts, in methods and compositions for inhibiting the growth of benign tumor cells and treating or preventing benign tumors, particularly benign tumors in which the Akt signaling pathway is activated or in which Bcl 2 levels are elevated. Methods of preventing malignant conversion of benign tumors and benign tumor cells to malignant tumors or malignant tumor cells is also described.

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“INORGANIC SELENIUM FOR TREATMENT OF BENIGN TUMORS”

FIELD OF THE INVENTION

[0001] This invention relates generally to the use of selenate or its pharmaceutically acceptable salts, especially in supranutritional amounts, in methods and compositions for inhibiting the growth or proliferation of benign tumor cells. The present invention also relates to the use of selenate or a pharmaceutically acceptable salt thereof in combination with at least one other therapy for treating or preventing benign tumors or for inhibiting the growth or proliferation of benign tumor cells. In certain embodiments, the methods of the invention are useful for treating or preventing benign tumors, especially benign tumors in which the Akt signaling pathway is activated or benign tumors in which Bcl-2 levels are elevated. Additionally, the present invention relates to the use of selenate or a pharmaceutically acceptable salt thereof for preventing malignant conversion of benign tumor cells or benign tumors to malignant tumor cells or malignant tumors.

BACKGROUND OF THE INVENTION

[0002] Although many benign tumors are asymptomatic and harmless, some benign tumors occur in positions that cause symptoms such as pain and in the brain or spine symptoms such as loss of mobility, loss of sight etc. Some benign tumors may cause clinical symptoms that are bothersome to a patient, for example, lower urinary tract symptoms (LUTS) resulting from benign prostatic hyperplasia. Some benign tumors may grow to a size that causes damage to tissues, organs or nerves in its vicinity, whilst others may cause serious illness or death if they occur near vital organs or press against vital organs. Some 13,000 deaths per year in the US are attributed to benign tumors and many more benign tumors require treatment. Furthermore, some benign tumors are known to have a high propensity to undergo malignant conversion to produce malignant or cancerous tumors.

[0003] There has been much interest in the use of selenium compounds as cancer-preventive agents. Studies spanning the last 20 years have documented their cancer-preventive action in tumors of the mammary gland (Ip, C. 1981, *Cancer Res.* 41:4386-4390), colon (Reddy *et al.* 1981, *Cancer Res.* 47:5901-5904), lung and prostate (Clark *et al.* 1996, *Jama* 276:1957-1963). Both phase II and III clinical trials for prostate cancer prevention using an organic selenomethionine are currently underway (Nelson *et al.* 1999, *Semin. Urol. Oncol.*, 17(2):91-6).

[0004] Selenium compounds used in chemoprevention studies can broadly be classified into inorganic and organic selenium forms. The typical form of inorganic selenium, sodium selenite, (Na_2SeO_3) is relatively toxic, causing single- and double-strand break DNA

damage, whilst the typical organic selenium entity, selenomethionine (SeMet) is relatively non-toxic and non-DNA-damaging (Lu *et al.* 1995, *Biochem. Pharmacol.* 50(2):213-9; Sinha *et al.* 1996, *Cancer Lett.* 107(2):277-84; Stewart *et al.* 1999, *Free Radic. Biol. Med.* 26(1-2):42-8).

5 [0005] Organic selenomethionine, the major constituent of dietary selenium, is incorporated into cellular selenoproteins, such as thioredoxin reductase and glutathione peroxidase *via* a series of complex intermediates (Allan *et al.* 1999, *Annu. Rev. Nutr.* 19:1-16). Since these selenocysteine-containing selenoenzymes, such as the antioxidant glutathione peroxidase and the redox-regulatory thioredoxins, are involved in cellular responses to
10 mutagenic oxidative stress, it has long been proposed that supranutritional levels of selenium intake boosts anticarcinogenic cellular activity by promoting a cellular reducing environment (Allan *et al.* 1999, *supra*).

 [0006] It is, however, becoming increasingly clear that the nature of the anti-tumorigenic action of selenium compounds is dependent on the chemical form in which the
15 element is administered (Ip, C. 1998, *J. Nutr.* 128:1845-1854). Organic selenium in the form of methylseleninic acid induces G1 arrest, as well as DNA fragmentation and caspase mediated cleavage of PARP, which are two markers of apoptosis, in DU145 prostate cancer cells (Jiang *et al.* 2001, *Cancer Res.* 61:3062-3070).

 [0007] In contrast, selenite induces S-phase arrest and apoptotic DNA
20 fragmentation, which is independent of caspase function (Jiang *et al.* 2002, *Mol. Cancer Ther.* 1:1059-1066). Differences have also been reported for the inorganic selenium compounds, with selenite and selenate inhibiting lymphocyte growth *via* different mechanisms (Spyrou *et al.* 1996, *Cancer Res.* 56:4407-4412). These differences may be explained in part by variations in metabolism and bioavailability between *in vitro* cell culture and *in vivo* studies (Dong *et al.*
25 2003, *Cancer Res.* 63:52-59).

 [0008] The role of the PI3K/Akt pathway in uncontrolled cell proliferation is increasingly recognized. Akt is a serine/threonine kinase that is activated in response to membrane receptor stimulated PI3K phosphorylation. Akt, in turn, regulates the activity of several proteins involved in the control of apoptosis, including the Forkhead (FKHR)
30 transcription factors, Bad, Caspase 9, GSK-3 β and mTOR (Vivanco, I. and Sawyers, C.L. 2002, *Nat. Rev. Cancer* 2:289-501). Akt overactivity may occur in benign tumors resulting in lack of apoptosis. Furthermore, higher than normal levels of Bcl-2 proteins may occur in benign tumors, including those that may be susceptible to malignant conversion.

 [0009] Radiotherapy resistance in tumor cells has also been linked with
35 upregulation of the PI3K/Akt pathway (Soderlund *et al.* 2005, *Int. J. Oncol.*, 26:25-32; Zhan *et al.* 2004, *Histol. Histopathol.*, 19:915-923; Tanno *et al.* 2004, *Cancer Res.*, 64:3486-3490; Li *et*

al. 2004, *Oncogene*, 23:4594-4602; McKenna *et al.*, 2003, *Genes Chromosomes Cancer*, 28:330-338; Liang *et al.* 2003, *Mol. Cancer Ther.* 2:353-360).

[0010] Interest in the clinical use of selenium-containing compounds as a chemopreventive agent has become widespread following the publication of Clark *et al.* (1996, *supra*). These results have spurred a number of human clinical trials using supranutritional selenomethionine as a chemopreventive agent for prostate cancer (Meuillet *et al.* 2004, *J. Cell Biochem.* 91:443-458).

[0011] However, it has been noted that there are marked differences in tumor progression *in vivo*, depending upon the selenium compound administered. For instance, inorganic sodium selenate significantly reduces tumor progression in comparison to organic selenomethionine, methylselenocysteine or selenized yeast (Corcoran *et al.* 2004, *J. Urol.*, 171:907-910). In addition, certain selenium compounds, such as sodium selenite have been found to be toxic to cells when used at certain doses (Jiang *et al.* 2002, *supra*).

SUMMARY OF THE INVENTION

[0012] The present invention is predicated in part on the discovery that a specific type of inorganic selenium compound, namely selenate, significantly inhibits benign tumor cell proliferation, especially when used at high or supranutritional amounts, as compared to other selenium compounds. It has also been found that selenate and its pharmaceutically acceptable salts have an inhibitory effect on benign tumor cells, especially those in which the Akt signaling pathway is activated or those in which Bcl-2 activity is elevated, and have a strong synergistic inhibitory effect on benign tumor cell growth when used in combination with at least one of a cytostatic agent, a cytotoxic agent and a radiotherapy that is optionally administered with a radiosensitizing agent. Further, it has been found that selenate and its pharmaceutically acceptable salts have an inhibitory effect on malignant conversion of benign tumor cells to malignant tumor cells.

[0013] Accordingly, in one aspect, the present invention provides methods for inhibiting the growth or proliferation of benign tumor cells. These methods generally comprise exposing the benign tumor cells to an effective amount of selenate or a pharmaceutically acceptable salt thereof. In some embodiments, the benign tumor cells are tumor cells in which the Akt-signaling pathway is activated. The activation of the Akt signaling pathway involves activation of at least one member selected from Akt, mTOR, GSK-3 β and FKHR. In illustrative examples of this type, the activation of the Akt signaling pathway involves phosphorylation of Akt (e.g., phosphorylation of the Thr 308 and Ser 473 residues of Akt). In other embodiments, the activation of the Akt signaling pathway involves inactivation of PTEN. In some embodiments, the Akt signaling pathway is over-activated. In some embodiments, the benign tumor cells have an abnormally increased Bcl-2 activity. In some embodiments, the amount of selenate or its pharmaceutically acceptable salt, to which the tumor cells are exposed, is a nutritional amount. In other embodiments, the amount is a supranutritional amount. Suitably, the tumor cells are selected from benign adenoma tumor cells, angiofibroma tumor cells, hemangioma tumor cells, leiomyoma tumor cells (fibroid), benign chorangioma tumor cells, cystadenoma tumor cells, dermoid tumor cells, desmoid tumor cells, fibroadenoma tumor cells, fibroma tumor cells, benign ganglioneuroma tumor cells, lipoma tumor cells, meningioma tumor cells, myxoma tumor cells, neurofibroma tumor cells, nevus tumor cells, osteochondroma tumor cells, pheochromocytoma tumor cells, polyposis tumor cells, schwannoma tumor cells, benign teratoma tumor cells, benign thymoma tumor cells and Brenner tumor cells. In specific embodiments, the tumor cells are prostatic intraepithelial neoplasia (PIN) tumor cells, benign prostatic hyperplastic (hypertrophic) tumor cells, ductal carcinoma in situ (DCIS) tumor cells, meningioma tumor cells or benign colonic tumor cells (colon polyps).

[0014] In another aspect, the present invention provides methods for preventing malignant conversion of a benign tumor cell to a malignant tumor cell. These methods generally comprise administering to the subject a therapeutically effective amount of selenate or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount is a nutritional amount. In other embodiments, the therapeutically effective amount is a supranutritional amount. In specific embodiments, the benign tumor cell is a benign colonic or rectal tumor cell, a high grade prostatic intraepithelial neoplasia tumor cell, an atypical small acinar proliferative tumor cell or a ductal carcinoma in situ (DCIS) tumor cell.

[0015] In a further aspect, the present invention provides a use of selenate or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a benign tumor.

[0016] In still a further aspect, the present invention provides a use of selenate or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing malignant conversion of benign tumors to malignant tumors.

[0017] In some embodiments of the methods and uses broadly described above, the selenate or its pharmaceutically acceptable salt is administered in combination with at least one of a cytostatic agent, a cytotoxic agent or a radiotherapy that is optionally administered with a radiosensitizing agent. In other embodiments, the selenate is formulated in a composition with at least one cytostatic agent or cytotoxic agent. In still other embodiments, the selenate is formulated in a composition with a radiosensitizing agent for use in combination with radiotherapy.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: graphically represents the growth inhibitory (cytostatic) effect of sodium selenate at 25 μ M, 50 μ M and 100 μ M on prostate stromal cells with time.

Figure 2: graphically represents the growth inhibitory effect of sodium selenate at 25 μ M, 50 μ M and 100 μ M on the proliferation of prostate stromal cells at 4 days (A), 11 days (B) and 18 days (C).

DETAILED DESCRIPTION OF THE INVENTION

1. *Definitions*

[0018] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are described. For the purposes of the present invention, the following terms are defined below.

[0019] The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0020] As used herein, the term "about" refers to a quantity, level, value, dimension, size, or amount that varies by as much as 30%, 20%, or 10% to a reference quantity, level, value, dimension, size, or amount.

[0021] As used herein, the term "Akt signaling pathway activation-inhibiting amount" in the context of treating or preventing a benign tumor or inhibiting the growth of benign tumor cells is meant the administration of an amount or series of doses of selenate, which is effective in antagonizing the Akt signaling pathway, including preventing or reducing activation of Akt by preventing or reducing the expression of Akt or an upstream member of the pathway, or by reducing the level or functional activity of an expression product of the *Akt* gene or of an upstream gene member of the pathway, or by preventing or reducing phosphorylation of Akt. The amount will vary depending on the health and physical condition of the individual to be treated, the taxonomic group of the individual to be treated, the formulation of the composition, the assessment of the medical situation, and other relevant factors. It is expected that the amount will fall within a relatively broad range that can be determined by routine trials. In specific embodiments, an Akt signaling pathway activation-inhibiting amount is a nutritional or supranutritional amount of selenate.

[0022] As used herein, the term "Bcl-2 activity-reducing amount" in the context of treating or preventing a benign tumor or inhibiting the growth of benign tumor cells is meant the administration of an amount or series of doses of selenate, which is effective in reducing the levels of Bcl-2 activity in benign tumor cells or benign tumors, including downregulating Bcl-2 transcription and modulation of activity of Bcl-2. The amount will vary depending on the health and physical condition of the individual to be treated, the taxonomic group of the individual to be treated, the formulation of the composition, the assessment of the medical situation, and other relevant factors. It is expected that the amount will fall within a relatively broad range that

can be determined by routine trials. In specific embodiments, a Bcl-2 activity-reducing amount is a nutritional or supranutritional amount of selenate.

[0023] By "benign tumor in which Bcl-2 activity is elevated" is meant a benign tumor which has levels of Bcl-2 protein that are above levels found in normal cells. Normal
5 levels of Bcl-2 protein found in normal cells are very low and generally not detectable. Benign tumors in which Bcl-2 activity is elevated may undergo malignant conversion to malignant tumors in which Bcl-2 activity is elevated. Examples of such benign tumors include colonic polyps and DCIS which may convert to colon cancer or breast cancer respectively.

[0024] As used herein, the term "benign tumor" refers to abnormal growth or
10 proliferation cells in a localised manner. Benign tumors do not invade surrounding tissue or metastasize to other organs. Benign tumors may be asymptomatic, and discovered, for example, by screening, or they may be symptomatic and require treatment. Benign tumors although causing no immediate threat to the subject, may grow and press on other tissues or organs resulting in symptoms of the tumor, for example a meningioma in the brain may grow to a size
15 where it damages the brain or causes malfunction in the brain. In some cases, a benign tumor may undergo malignant conversion to give a malignant tumor or cancer. Illustrative examples of benign tumors include, but are not limited to benign adenomas, angiofibromas, hemangiomas, leiomyomas, benign chorangiomas, cystadenomas, dermoid tumors, desmoid tumors, fibroadenomas, fibromas, benign ganglioneuromas, lipomas, meningiomas, myxomas,
20 neurofibromas, nevus tumors, osteochondromas, pheochromocytomas, polyps such as colonic polyps, schwannomas, benign teratomas, benign thyomas and Brenner tumors. Other types of benign tumors include prostatic intraepithelial neoplasia, benign prostatic hyperplastic (hypertrophic) tumors and ductal carcinoma in situ.

[0025] The phrases "benign tumor in which the Akt pathway is over-activated,"
25 "benign tumor in which Akt is over-activated" and the like refer to a benign tumor in which not only Akt is overexpressed, but the kinase activity of Akt is positively enhanced by phosphorylation of the Thr 308 and Ser 473 residues. Akt is often over-activated in drug-resistant or refractory tumors. Examples of benign tumors in which Akt is over-activated or constitutively activated include, but are not limited to, prostatic intraepithelial neoplasia and
30 breast ductal carcinoma in situ.

[0026] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0027] As used herein the term "cytostatic agent" refers to a substance that can inhibit cell proliferation or cell division without necessarily killing the cell. Suitably, the cytostatic agent inhibits the proliferation of tumor cells.

5 [0028] The term "cytotoxic agent" or "cytotoxic therapy" as used herein refers to a substance or therapy that is harmful to cells and ultimately causes cell death. In some embodiments, the cytotoxic agent harms rapidly dividing cells such as tumor cells and causes tumor cell death, especially tumor cell death while not causing damage to or causing less damage to non-tumor cells. An example of a cytotoxic therapy is radiotherapy.

10 [0029] As used herein the terms "drug resistant" and "refractory" refer to a tumor cell which is unresponsive or partially unresponsive to treatments normally used to treat the cancer or kill the tumor cell.

[0030] As used herein the term "in combination with" refers to the treatment of cancer or exposure of a tumor cell to at least two agents such that their effects on the tumor cell occur, at least in part, over the same time period. Administration of at least two agents may
15 occur simultaneously in a single composition, or each agent may be simultaneously or sequentially administered in separate compositions.

[0031] The phrase "inhibiting growth of tumor cells" is taken to mean that tumor cell growth is ceased or reduced and cell proliferation or cell division is ceased or reduced. This is also known as cytostasis. The growth of tumor cells can be measured in terms of weight or
20 volume or cell number or cellular metabolic activity, i.e. MTT assay.

[0032] The term "malignant conversion" as used herein refers to the conversion of benign tumors or benign tumor cells into malignant tumors or malignant tumor cells. Once malignant conversion has occurred, the tumor or tumor cells may invade other tissues or metastasize to other organs or tissues, and the subject has a cancerous tumor. Examples of
25 benign tumors that undergo malignant conversion include colonic polyps and DCIS which may be converted to colon cancer or breast cancer respectively.

[0033] As used herein, the term "nutritional amount" includes an amount of selenium that provides an average daily intake. In the US, the average daily intake is 80-120 µg/day.

30 [0034] By "pharmaceutically acceptable carrier" it is meant a solid or liquid filler, diluent or encapsulating substance that may be safely used in topical, local or systemic administration.

[0035] The term "pharmaceutically acceptable salt" as used herein in relation to selenate refers to metal ion salts which are toxicologically safe for human and animal
35 administration. For example, suitable metal ion salts of selenate include, but are not limited to,

sodium, potassium, lithium, magnesium, calcium, iron, nickel, zinc, ammonium and alkylammonium salts. A preferred salt of selenate is the sodium salt, Na_2SeO_4 .

[0036] The term "radiotherapy" as used herein refers to the treatment or exposure of a tumor or tumor cells to high energy radiation. The effectiveness of radiotherapy may be enhanced by selenate or its pharmaceutically acceptable salt. Furthermore, radiotherapy may be further enhanced by administration of radiosensitizing agent. Illustrative examples of radiosensitizing agents include but are not limited to efaproxiral, etanidazole, flusol, misonidazole, nimorazole, temoporfin and tirapazamine.

[0037] The terms "subject" or "individual" or "patient", used interchangeably herein, refer to any subject, particularly a vertebrate subject and more particularly a mammalian subject, for whom prophylaxis or treatment is desired. Suitable vertebrate animals that fall within the scope of the invention include, but are not limited to, primates, avians, livestock animals (e.g., pigs, sheep, cows, horses, donkeys), laboratory test animals (e.g., rabbits, mice, rats, guinea pigs, hamsters), companion animals (e.g., cats and dogs) and captive wild animals (e.g., foxes, deer, dingoes). A preferred subject is a human in need of treatment or prophylaxis of a benign tumor or may be at risk of a benign tumor undergoing malignant conversion to a malignant tumor. However, it will be understood that the aforementioned terms do not imply that symptoms are present.

[0038] The term "supranutritional" as used herein, refers to an amount which is greater than the amount considered as a nutritional requirement. The average daily intake of selenium in the US is 80-120 $\mu\text{g}/\text{day}$. A supranutritional amount of selenium provides selenium to a subject at above the recommended daily allowance. For example, a supranutritional amount of selenium may be 3 $\mu\text{g}/\text{kg}$ to 20 mg/kg per day, 0.015 mg/kg to 20 mg/kg , 0.15 mg/kg to 20.0 mg/kg , 0.1 mg/kg to 14 mg/kg , 0.1 mg/kg to 13 mg/kg , 0.1 mg/kg to 12 mg/kg , 0.1 mg/kg to 10 mg/kg , 0.1 mg/kg to 9 mg/kg , 0.1 mg/kg to 8 mg/kg , 0.1 mg/kg to 7 mg/kg , 0.1 mg/kg to 6 mg/kg , 0.15 mg/kg to 5 mg/kg , 0.15 mg/kg to 4 mg/kg , 0.15 mg/kg to 3 mg/kg , 0.15 mg/kg to 2 mg/kg , 0.15 mg/kg to 1 mg/kg , especially 0.07 mg/kg to 6.5 mg/kg or 0.1 mg/kg to 14 mg/kg or 0.15 mg/kg to 5 mg/kg per day, and more especially 0.07 mg/kg to 2 mg/kg per day.

[0039] As used herein, the term "effective amount" in the context of treating or preventing a benign tumor or inhibiting the growth of benign tumor cells is meant the administration of an amount of selenate or a pharmaceutically acceptable salt thereof, either in a single dose or as part of a series of doses, that is effective for inhibiting the growth and/or proliferation of benign tumor cells or for causing benign tumor cell death or for preventing metastatic conversion of a benign tumor to a malignant tumor. The effective amount will vary depending on the health and physical condition of the individual to be treated, the taxonomic group of the individual to be treated, and the formulation of the composition, the assessment of

the medical situations and other relevant factors. It is expected that the amount will fall within a relatively broad range that can be determined through routine trials. In specific embodiments, an effective amount is a nutritional or supranutritional amount. In some embodiments, an effective amount is an Akt-signaling pathway activation inhibiting amount or a Bcl-2 activity-reducing amount.

2: *Methods for inhibiting tumor cell growth and proliferation and for preventing malignant conversion*

[0040] The present invention is predicated in part on the determination that selenate, as opposed to other forms of selenium such as selenite, is effective in inhibiting the growth or proliferation of benign tumor cells, especially those in which the Akt signaling pathway is activated or in which Bcl-2 activity is elevated. Accordingly, in one aspect, the present invention provides methods for inhibiting the growth or proliferation of benign tumor cells, wherein the methods generally comprise exposing the tumor cells to an effective amount, such as an Akt signaling pathway activation-inhibiting amount or a Bcl-2 activity-reducing amount of selenate or a pharmaceutically acceptable salt thereof. In some embodiments of the invention, the amount of selenate or its pharmaceutically acceptable salt thereof is a nutritional amount. In other embodiments, the amount of selenate or its pharmaceutically acceptable salt is a supranutritional amount, which is generally from about 0.015 mg/kg to 20.0 mg/kg, usually from about 0.07 mg/kg to 6.5 mg/kg or 0.1 mg/kg to 14 mg/kg or from about 0.15 mg/kg to 5 mg/kg, especially 0.07 mg/kg to 2 mg/kg per day.

[0041] The present invention can be used effectively against various types of tumor cells. Illustrative examples of benign tumors that may be treated or prevented include, but are not limited to benign adenomas, angiofibromas, hemangiomas, leiomyomas, benign chorangiomas, cystadenomas, dermoid tumors, desmoid tumors, fibroadenomas, fibromas, benign ganglioneuromas, lipomas, meningiomas, myxomas, neurofibromas, nevus tumors, osteochondromas, pheochromocytomas, polyps, schwannomas, benign teratomas, benign thyomas and Brenner tumors. In some embodiments, the tumor is a prostatic intraepithelial neoplasia, colonic polyps, atypical small acinar proliferative tumor cells, benign prostatic hyperplastic (hypertrophic) tumor cells (benign prostatic hyperplasia) or a ductal carcinoma in situ. In a related aspect, the invention provides methods for treating or preventing a benign tumor in which Akt is activated, wherein the methods generally comprise administering to a subject in need thereof an Akt signaling pathway activation-inhibiting amount of selenate or a pharmaceutically acceptable salt thereof. In a further related aspect, the invention provides methods for treating or preventing a benign tumor in which Bcl-2 activity is elevated, wherein the methods generally comprise administering to a subject in need thereof a Bcl-2 activity-reducing amount of selenate or a pharmaceutically acceptable salt thereof. In some

embodiments, the amount of selenate or pharmaceutically acceptable salt thereof is a nutritional amount. In other embodiments, the amount is a supranutritional amount as broadly defined above.

5 [0042] In some embodiments, the tumor cell is drug resistant. In some embodiments, the tumor cell has an overactive Akt pathway.

[0043] In certain embodiments, the selenate or its pharmaceutically acceptable salt is administered in combination with at least one cytostatic agent or cytotoxic agent. Non-limiting examples of cytostatic agents are selected from: (1) kinase inhibitors, illustrative examples of which include Iressa®, Gleevec, Tarceva™, (Erlotinib HCl), BAY-43-9006, 10 inhibitors of the split kinase domain receptor tyrosine kinase subgroup (e.g., PTK787/ZK 222584 and SU11248); (2) receptor kinase targeted antibodies, which include, but are not limited to, Trastuzumab (Herceptin®), Cetuximab (Erbix®), Bevacizumab (Avastin™), Rituximab (ritusan®), Pertuzumab (Omnitarg™); (3) mTOR pathway inhibitors, illustrative examples of which include rapamycin and CCI-778; (4) Apo2L/Trail, anti-angiogenic agents 15 such as but not limited to endostatin, combrestatin, angiostatin, thrombospondin and vascular endothelial growth inhibitor (VEGI); (5) antineoplastic immunotherapy vaccines, representative examples of which include activated T-cells, non-specific immune boosting agents (i.e., interferons, interleukins); (6) hormonal antineoplastic agents, non-limiting examples of which include Nilutamide, Cyproterone acetate, Anastrozole, Exemestane, Tamoxifen, Raloxifene, 20 Bicalutamide, Aminoglutethimide, Leuporelin acetate, Toremifene citrate, Letrozole, Flutamide, Megestrol acetate and Goserelin acetate; (7) gonadal hormones such as but not limited to Cyproterone acetate and Medoxyprogesterone acetate; (8) antimetabolites, illustrative examples of which include Cytarabine, Fluorouracil, Gemcitabine, Topotecan, Hydroxyurea, Thioguanine, Methotrexate, Colaspase, Raltitrexed and Capicitabine; (9) anabolic agents, such 25 as but not limited to, Nandrolone; (10) adrenal steroid hormones, illustrative examples of which include Methylprednisolone acetate, Dexamethasone, Hydrocortisone, Prednisolone and Prednisone.

[0044] The methods of the present invention may be employed in combination with other known treatments for benign tumors, for instance but not limited to, surgery, 30 chemotherapy and radiotherapy. In some embodiments, the selenate or its pharmaceutically acceptable salt is used in combination with radiotherapies, such as but not limited to, conformal external beam radiotherapy (50-100 Grey given as fractions over 4-8 weeks), either single shot or fractionated, high dose rate brachytherapy, permanent interstitial brachytherapy, systemic radio-isotopes (e.g., Strontium 89). In some embodiments the radiotherapy may be administered 35 in combination with a radiosensitizing agent. Illustrative examples of radiosensitizing agents include but are not limited to efaproxiral, etanidazole, fluosol, misonidazole, nimorazole,

temoporfin and tirapazamine. In other embodiments, selenate or its pharmaceutically acceptable salt is used in combination with a tumorectomy.

[0045] In some embodiments, the cytostatic agent is a nucleic acid molecule, suitably an antisense or siRNA recombinant nucleic acid molecule. In other embodiments, the cytostatic agent is a peptide or polypeptide. In still other embodiments, the cytostatic agent is small molecule. The cytostatic agent may be a cytotoxic agent that is suitably modified to enhance uptake or delivery of the agent. Non-limiting examples of such modified cytotoxic agents include, but are not limited to, pegylated or albumin-labelled cytotoxic drugs.

[0046] In embodiments where the benign tumor is benign prostatic hypertrophy (benign prostatic hyperplasia) or prostatic intraepithelial neoplasia, the selenate or pharmaceutically acceptable salt thereof may be administered in combination with 5-alpha reductase inhibitors such as finasteride or dutasteride; alpha adrenergic receptor blockers such as terazosin (Hytrin), doxazosin (cardura), alfuzosin, tamsulosin (flomax) and Prazosin (Minipress); selective estrogen receptor modulators (SERMs) such as toremifene citrate (Acapodene), tamoxifen and raloxifen; selective androgen receptor modulators (SARMs) such as prostarine; or phytotherapeutics such as those derived from the American dwarf palm tree (saw palmetto or *Serenoa repens*), African plum tree (*Pygeum africanum*), pumpkin seeds, rye pollen extracts, South African star grass roots, stinging nettle roots and the purple cone flower.

[0047] In embodiments where the benign tumor is colonic polyps, the selenate or pharmaceutically acceptable salt thereof may be administered in combination with non steroidal anti inflammatory drugs such as aspirin, ibuprofen, naproxene; or Cox-2 inhibitors such as sulindac, celocoxib (celebrex), refocoxib (vioxx) and lumiracoxib.

[0048] In embodiments where the benign tumor is ductal carcinoma in situ the selenate or pharmaceutically acceptable salt thereof may be administered in combination with selective estrogen receptor modulators such as tamoxifen, raloxifen and toremifene citrate.

[0049] In embodiments where the benign tumor is meningioma, the selenate or pharmaceutically acceptable salt thereof may be administered in combination with progesterone receptor antagonists such as mifepristone; immune modulating agents such as interferon; chemotherapy such as hydroxyurea and external beam radiation.

[0050] Certain embodiments of the present invention are directed to methods for treating or preventing a benign tumor in a subject, which methods generally comprise administering to the subject a therapeutically effective amount of selenate or a pharmaceutically acceptable salt thereof. To practice these methods, the person managing the subject can determine the effective dosage form of selenate or its pharmaceutically acceptable salts for the particular condition and circumstances of the subject. A therapeutically effective amount of

selenate is one that is effective for the treatment or prevention of the benign tumor, including the prevention of incurring a symptom (e.g., proliferation of tumor cells), holding in check such symptoms, and/or treating existing symptoms associated with the tumor (e.g., pain, tenderness, headaches, menstrual irregularity, urinary retention, cosmetic effect, shortness of breath, altered bowel habit, malena, haematemesis, focal neurological deficit). In some embodiments, the therapeutically effective amount is a nutritional amount. In other embodiments, the amount is a supranutritional amount of selenate or its pharmaceutically acceptable salt. In specific embodiments, the selenate is suitably in the form of the salt, sodium selenate (Na_2SeO_4).

[0051] Modes of administration, amounts of selenate administered, and selenate formulations, for use in the methods of the present invention, are discussed below. The tumor to be treated may be determined by measuring one or more diagnostic parameters indicative of the course of the disease, compared to a suitable control. In the case of a human subject, a "suitable control" may be the individual before treatment, or may be a human (e.g., an age-matched or similar control) treated with a placebo. In accordance with the present invention, the treatment or prevention of a benign tumor includes and encompasses without limitation: (i) preventing a benign tumor in a subject who may be predisposed to the benign tumor but has not yet been diagnosed with the benign tumor and, accordingly, the treatment constitutes prophylactic treatment for the benign tumor; (ii) inhibiting tumorigenesis, i.e., arresting the development of the benign tumor; (iii) relieving symptoms resulting from the benign tumor; or (iv) preventing malignant conversion of a benign tumor.

[0052] The methods of the present invention are suitable for treating an individual who has been diagnosed with a benign tumor, who is suspected of having a benign tumor, who is known to be susceptible and who is considered likely to develop a benign tumor, who is considered likely to develop a recurrence of a previously treated benign tumor, or who has a benign tumor which may undergo malignant conversion to a malignant tumor.

[0053] In specific embodiments of the above methods, the benign tumor is a high grade prostatic intraepithelial neoplasia (HGPIN), colonic polyp or ductal carcinoma in situ (DCIS) that may undergo malignant conversion to prostate cancer, colon cancer or breast cancer respectively. In other embodiments, the tumor to be treated may be a meningioma.

[0054] Exemplary subjects for treatment with the methods of the invention are vertebrates, especially mammals. In certain embodiments, the subject is selected from the group consisting of humans, sheep, cattle, horses, bovine, pigs, dogs and cats. A preferred subject is a human.

[0055] The selenate or pharmaceutically acceptable salt may be formulated by following any number of techniques known in the art of drug delivery. Selenate or its pharmaceutically acceptable salts may of course be administered by a number of means keeping

in mind that all formulations are not suitable for every route of administration. Selenate or its pharmaceutically acceptable salts can be administered in solid or liquid form. The application may be oral, rectal, nasal, topical (including buccal and sublingual), or by inhalation. Selenate or its pharmaceutically acceptable salts may be administered together with conventional
5 pharmaceutical acceptable adjuvant, carriers and/or diluents.

[0056] The solid forms of application comprise tablets, capsules, powders, pills, pastilles, suppositories and granular forms of administration. They may also include carriers or additives, such as flavors, dyes, diluents, softeners, binders, preservatives, lasting agents and/or enclosing materials. Liquid forms of administration include solutions, suspensions and
10 emulsions. These may also be offered together with the above-mentioned additives.

[0057] Solutions and suspensions of selenate or pharmaceutically acceptable salt thereof, assuming a suitable viscosity for ease of use, may be injected. Suspensions too viscous for injection may be implanted using devices designed for such purposes, if necessary. Sustained release forms are generally administered *via* parenteral or enteric means. Parenteral
15 administration is another route of administration of the selenate or a pharmaceutically acceptable salt thereof used to practice the invention. "Parenteral" includes formulations suitable for injection and for nasal, vaginal, rectal, and buccal administration.

[0058] The administration of selenate or its pharmaceutically acceptable salts may involve an oral prolonged dose formulation. Oral dose formulations are preferably administered
20 once daily to three times daily in the form of a sustained release capsule or tablet, or alternatively as an aqueous based solution. Selenate or its pharmaceutically acceptable salt may be administered intravenously either daily, continuously, once a week or three times a week.

[0059] The administration of selenate or its pharmaceutically acceptable salts may include daily administration, preferably once daily in the form of a sustained release capsule or
25 tablet, or once daily as an aqueous solution.

[0060] Combinations of selenate or its pharmaceutically acceptable salt and at least one cytostatic agent or a cytotoxic agent or a radiosensitizing agent may be administered in solid or liquid form in a single formulation or composition or in separate formulations or compositions. In some embodiments, the selenate or its pharmaceutically acceptable salt and the
30 cytostatic agent(s) or cytotoxic agent(s) or radiosensitizing agent(s) are administered orally as a single tablet or capsule or separate tablets or capsules. In other embodiments, the selenate or its pharmaceutically acceptable salt and the cytostatic agent(s) or cytotoxic agent(s) or radiosensitizing agent(s), are administered intravenously in a single composition or separate compositions.

[0061] The present invention also provides pharmaceutical compositions for treating or preventing a benign tumor or preventing a benign tumor undergoing malignant conversion, generally comprising a supranutritional amount, suitably from about 0.5 mg to about 1.0 g of selenate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. In some embodiments, the selenate or its pharmaceutically acceptable salt is in an amount of about 5.0 mg to about 700 mg or 5 mg to 450 mg. In illustrative examples, the selenate or its pharmaceutically acceptable salt is an amount of about 0.07 mg to 6.5 mg, 5 mg to 450 mg or 7.5 mg to 250 mg, especially 50 mg to 200 mg, for example, 50 mg to 100 mg or 100 mg to 150 mg for a single or divided daily dose. The pharmaceutical composition may be for treating a benign tumor in which Akt is activated or over-activated or a benign tumor in which Bcl-2 activity is elevated.

[0062] In some embodiments, the pharmaceutical compositions further comprise at least one cytostatic agent or cytotoxic agent. In other embodiments, the pharmaceutical compositions may further comprise a radiosensitizing agent for use with radiotherapy. In other embodiments, the pharmaceutical composition may further comprise a second agent that is suitable for treating a benign tumor, such as 5- α -reductase inhibitors, α -adrenergic receptor blockers, selective estrogen receptor modulators, selective androgen receptor modulators, phytotherapeutics, anti-inflammatory drugs, Cox-2 inhibitors, progesterone receptor antagonists, immune modulating agents or chemotherapy.

[0063] The pharmaceutical composition of the present invention may include any additional components that are non-immunogenic and biocompatible with selenate, as well as capable of bioabsorption, biodegradation, elimination as an intact molecule. The formulation may be supplied in a ready-to-use form or may be supplied as a sterile powder or liquid requiring vehicle addition prior to administration. If sterility is desired, the formulation may be made under sterile conditions, the individual components of the mixture may be sterile, or the formulation may be sterile filtered prior to use. Such a solution can also contain appropriate pharmaceutically acceptable carriers, such as but not limited to buffers, salts, excipients, preservatives, etc.

[0064] In some embodiments, sustained release oral formulations are used for administering selenate or its pharmaceutically acceptable salt in the methods of the invention. These formulations generally comprise selenate or its pharmaceutically acceptable salt having decreased solubility in order to delay absorption into the bloodstream. In addition, these formulations may include other components, agents, carriers, etc., which may also serve to delay absorption of the selenate or its pharmaceutically acceptable salt. Microencapsulation, polymeric entrapment systems, and osmotic pumps, which may or may not be bioerodible, may

also be used to allow delayed or controlled diffusion of the selenate or a pharmaceutically acceptable salt thereof from a capsule or matrix.

[0065] The selenate or its pharmaceutically acceptable salts can be used solus or as part of another agent. Accordingly, the present invention also contemplates an agent that
5 comprises selenate or a pharmaceutically acceptable salt thereof for the treatment of a benign tumor, especially one in which Akt is activated or in which Bcl-2 activity is elevated, or for the prevention of malignant conversion of a benign tumor to a malignant tumor.

[0066] In order that the nature of the present invention may be more clearly
understood and put into practical effect, particular preferred embodiments thereof will now be
10 described with reference to the following non-limited examples.

EXAMPLES

EXAMPLE 1

Isolation of primary benign tumor cell lines

5 [0067] Primary meningioma tissue samples will be obtained from the Royal Melbourne Hospital under a protocol approved by the Institutional Review Board. Primary cultures of meningiomas will be established according to established protocols (Friend KE, Radinsky R, McCutcheon IE. Growth hormone receptor expression and function in meningiomas: effect of a specific receptor antagonist. *J Neurosurg* 1999; 91:93-9).

10 [0068] Briefly, tumor tissue will be collected at the time of resection from patients with benign, or atypical, meningioma as determined by neuropathologic review using WHO 2000 criteria. Tumor fragments will be immediately transferred to the laboratory for further processing, carefully minced into small pieces, and treated with 0.4% trypsin/EDTA to dissociate the cells. The cells will be washed with PBS supplemented with 200 units/mL penicillin and 200 µg/mL streptomycin and transferred to 100-mm² tissue culture dishes
15 containing DMEM supplemented with 10% FCS, 100 units/mL penicillin, and 100 µg/mL streptomycin. The cells will be grown in humidified incubators at 37°C with 5% CO₂ for 5 days, with periodic medium changes and then allowed to reach confluence. Low-passage cells (<7 passages) will used for proliferation experiments.

EXAMPLE 2

Cell proliferation assays

Benign tumor growth curve

25 [0069] Benign meningioma tumor growth curves will be analysed by allowing 2 x 10⁵ tumor cells. The cells will be allowed to attach overnight in culture dishes. After 16 hours the medium will be changed to include sodium selenate in the presence of serum at the indicated concentrations and allowed to grow until specified time points. Supernatants and cells will then be harvested, combined and viable cells assessed by Trypan Blue exclusion assay. Experiments will be performed in triplicate.

MTT Growth Assay

30 [0070] MTT Growth Assays will be performed by plating 1 x 10³ meningioma tumor cells per well in a 96 well plate and allowing the cells to attach overnight. At 16 hours the medium will be replaced with fresh media containing sodium selenate (5-250 µM). For
35 experiments determining the additional effect of PI3K inhibition on sodium selenate growth

inhibition, LY294002 (Promega, Madison, WI, USA) will be added at a concentration of 10-50 μ M with the sodium selenate. The controls for this experiment will then receive an equal volume of LY294002 diluent (DMSO). MTT growth assays will then be performed according to the manufacturer's protocol (Sigma). Experiments will be performed in triplicate.

5

EXAMPLE 3

The effect of sodium selenate on the growth/proliferation or survival of benign tumor cells.

Primary human prostate stromal cell lines as a model for human benign prostatic hyperplasia (BPH)

10 MATERIALS AND METHODS

[0071] **Cell Culture.** The prostate stromal (PrS) cell line was obtained from Cambrex Bio Science (Walkersville, MC, USA, www.cambrex.com) and was routinely cultured in Stromal Cell Medium BulletKit (Clonetics SCGM BulletKit, CC-3205) purchased from Cambrex. Complete growth medium was prepared from the BulletKit containing stromal cell
15 basal medium supplemented with 0.1% human fibroblast growth factor B, 0.1% insulin, 5% fetal bovine serum and 0.1% gentamicin sulphate amphotericin-B according to supplier specification. Cells were cultured at 37°C in 5% CO₂.

[0072] ***In Vitro* – growth proliferation study.** 4 x 10³ PrS cells were plated per well in a Falcon 6-well plate and were allowed to attach overnight at 5%CO₂/ 37°C in complete
20 growth medium. The medium was replaced with fresh complete growth medium containing various concentration of sodium selenate (25, 50 and 100 μ M) and were allowed to grow until specified time points (day 4, 11 and 18). Cells were trypsinised according to supplier specification and viable cells were assessed by trypan blue exclusion assay at the specified time points indicated above. Experiments were performed in triplicate per selenate treatment dose.

25 [0073] **Statistical analysis.** Data are presented as mean $\pm$ SEM, unless otherwise indicated. Differences between treatment groups were analyzed using Fisher's least significant difference test with significance assumed at p<0.01, ANOVA. All statistical analysis was performed using STATGRAPHICS statistical software (Virginia, USA).

[0074] The results are shown in Table 1 and Figures 1 and 2.

Table 1. Growth inhibitory (cytostatic) effect of sodium selenate on prostate stromal cell growth over time.

Treatment Groups	No. of days in culture	No. of viable cells (mean)
Complete growth medium (control)	1	40000.0
25 μ M Selenate	1	40000.0
50 μ M Selenate	1	40000.0
100 μ M Selenate	1	40000.0
Complete growth medium (control)	4	44666.7
25 μ M Selenate	4	48000.0
50 μ M Selenate	4	15666.7
100 μ M Selenate	4	11666.7
Complete growth medium (control)	11	163333.0
25 μ M Selenate	11	61333.3
50 μ M Selenate	11	19333.3
100 μ M Selenate	11	4000.0
Complete growth medium (control)	18	480000.0
25 μ M Selenate	18	81333.3
50 μ M Selenate	18	7666.7
100 μ M Selenate	18	2962.7

5 [0075] The results show that 25 μ M selenate effectively impedes prostate stromal cell growth after 11 days in culture. Higher concentrations of selenate, 50 μ M and 100 μ M are very effective at controlling prostate stromal cell growth.

 [0076] The disclosure of every patent, patent application, and publication cited herein is hereby incorporated herein by reference in its entirety.

10 [0077] The citation of any reference herein should not be construed as an admission that such reference is available as "Prior Art" to the instant application.

 [0078] Throughout the specification the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. Those of skill in the art will therefore appreciate that, in light of the instant disclosure, various modifications and changes can be made in the particular
15 embodiments exemplified without departing from the scope of the present invention. All such modifications and changes are intended to be included within the scope of the appended claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of inhibiting the growth or proliferation of benign tumor cells comprising exposing the benign tumor cells to an effective amount of selenate or a pharmaceutically acceptable salt thereof.

5 2. A method according to claim 1, wherein the benign tumor cells are tumor cells in which the Akt-signaling pathway is activated or over-activated.

3. A method according to claim 1, wherein the benign tumor cells have abnormally increased Bcl-2 activity.

4. A method according to claim 1, wherein the benign tumor cells are selected
10 from benign adenoma tumor cells, angiofibroma tumor cells, hemangioma tumor cells, leiomyoma tumor cells (fibroid), benign chorangioma tumor cells, cystadenoma tumor cells, dermoid tumor cells, desmoid tumor cells, fibroadenoma tumor cells, fibroma tumor cells, benign ganglioneuroma tumor cells, lipoma tumor cells, meningioma tumor cells, myxoma tumor cells, neurofibroma tumor cells, nevus tumor cells, osteochondroma tumor cells,
15 pheochromocytoma tumor cells, polyposis tumor cells, schwannoma tumor cells, benign teratoma tumor cells, benign thymoma tumor cells and Brenner tumor cells.

5. A method according to claim 1, wherein the benign tumor cells are selected from prostatic intraepithelial neoplasia (PIN) tumor cells, benign prostatic hyperplastic (hypertrophic) tumor cells, ductal carcinoma in situ (DCIS) tumor cells, meningioma tumor
20 cells or benign colonic tumor cells (colon polyps).

6. A method of treating or preventing a benign tumor in a subject comprising administering to the subject an effective amount of selenate or a pharmaceutically acceptable salt thereof.

7. A method according to claim 6, wherein the effective amount of selenate or a
25 pharmaceutically acceptable salt thereof is a nutritional amount.

8. A method according to claim 6, wherein the effective amount of selenate or a pharmaceutically acceptable salt thereof is a supranutritional amount.

9. A method according to claim 6, wherein the benign tumor is selected from benign adenomas, angiofibromas, hemangiomas, leiomyomas, benign chorangiomas, cystadenomas, dermoid tumors, desmoid tumors, fibroadenomas, fibromas, benign
30 ganglioneuromas, lipomas, meningiomas, myxomas, neurofibromas, nevus tumors, osteochondromas, pheochromocytomas, polyps, schwannomas, benign teratomas, benign thyomas and Brenner tumors.

10. A method according to claim 6, wherein the benign tumor is selected from
35 prostatic intraepithelial neoplasia, colonic polyps, atypical small acinar proliferative tumor cells, benign prostatic hyperplastic (hypertrophic) tumor cells or a ductal carcinoma in situ.

11. A method according to claim 6, further comprising administration in combination with another known treatment for benign tumors.

12. A method according to claim 11, wherein the other known treatments for benign tumors are selected from surgery, radiotherapy and chemotherapy.

5 13. A method according to claim 6, further comprising administering at least one cytotoxic or cytostatic agent or a radiosensitizing agent or a second agent used to treat benign tumors.

10 14. A method according to claim 13, wherein the cytostatic agent is selected from kinase inhibitors, receptor kinase targeted antibodies, mTOR pathway inhibitors, Apo2L/Trail antiangiogenic agents, antineoplastic immunotherapy vaccines, hormonal antineoplastic agents, gonadal hormones, antimetabolites, anabolic agents, adrenal steroid hormones and microtubule-stabilizing agents.

15 15. A method according to claim 13, wherein the radiosensitizing agent is selected from efaproxiral, etanidazole, flusol, misonidazole, nimorazole, temoporfin and tirapazamine.

16. A method according to claim 13, wherein the second agent used to treat benign tumors is selected from 5- α -reductase inhibitors, α -adrenergic receptor blockers, selective estrogen receptor modulators, selective androgen receptor modulators, phytotherapeutics, non-steroidal anti-inflammatory drugs, Cox-2 inhibitors, progesterone receptor antagonists, immune modulating agents and chemotherapy.

20 17. A method of preventing benign tumor cells or a benign tumor undergoing malignant conversion to malignant tumor cells or a malignant tumor in a subject, comprising administering to the subject an effective amount of selenate or a pharmaceutically acceptable salt thereof.

25 18. A method according to claim 17, wherein the effective amount of selenate or a pharmaceutically acceptable salt thereof is a nutritional amount.

19. A method according to claim 17, wherein the effective amount of selenate or a pharmaceutically acceptable salt thereof is a supranutritional amount.

30 20. A method according to claim 17, wherein the benign tumor cells are benign colonic or rectal tumor cells, high grade prostatic intraepithelial neoplasia tumor cells, atypical small acinar proliferative tumor cells or ductal carcinoma in situ tumor cells.

21. A method according to claim 17, wherein the benign tumor is a high grade prostatic intraepithelial neoplasia, a colonic polyp or a ductal carcinoma in situ.

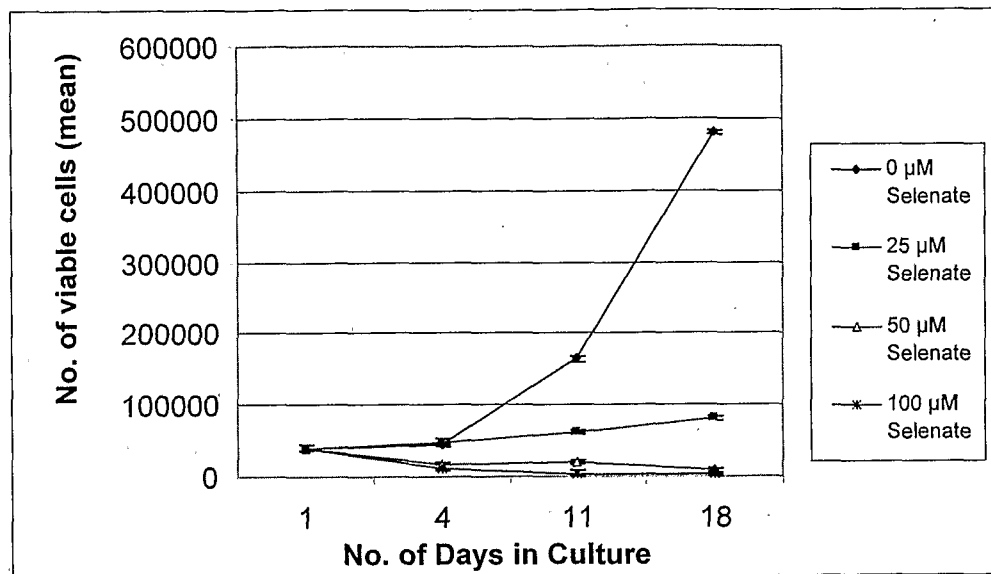
35 22. A pharmaceutical composition comprising selenate or a pharmaceutically acceptable salt thereof and at least one of a cytostatic agent, a cytotoxic agent, a radiosensitizing agent or a second agent used to treat benign tumors and a pharmaceutically acceptable carrier.

23. Use of selenate or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a benign tumor.

24. Use of selenate or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing benign tumor cells or a benign tumor undergoing malignant conversion to malignant tumor cells or a malignant tumor.

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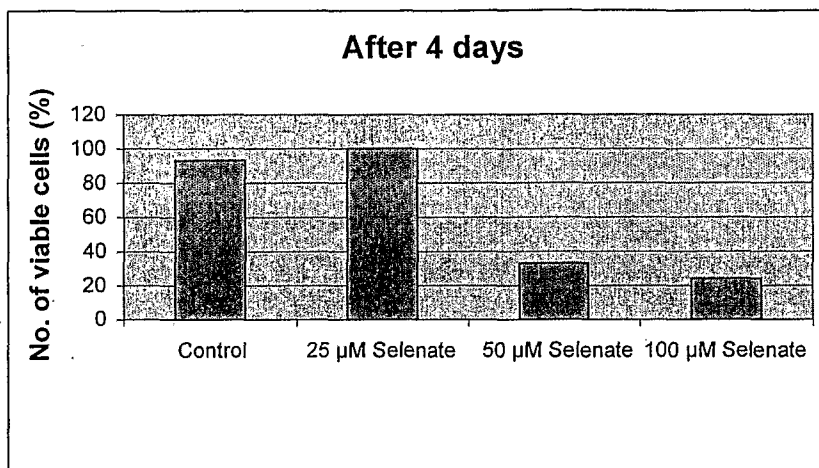
FIGURE 1



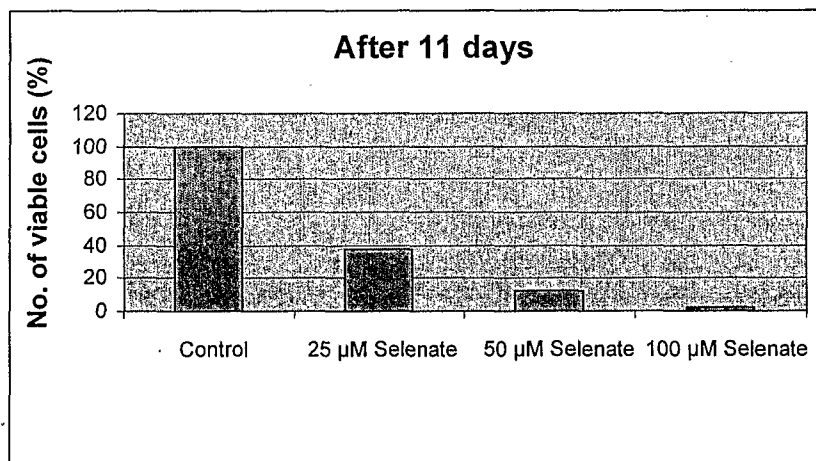
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FIGURE 2

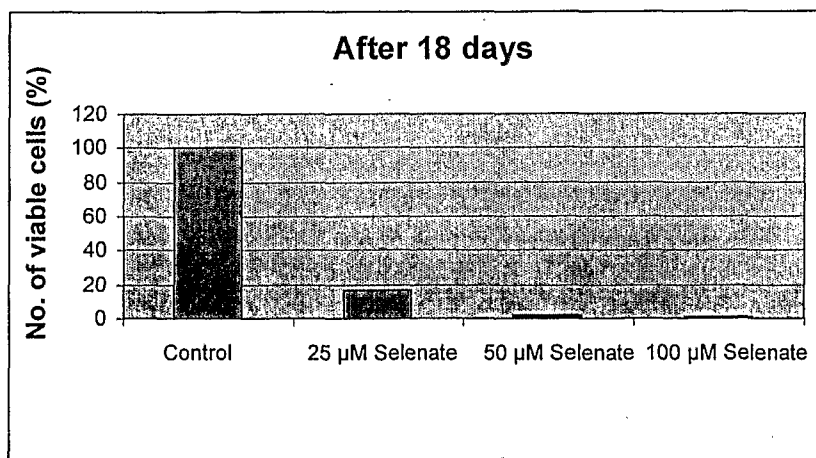
A



5 B



C



INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2007/000393

A. CLASSIFICATION OF SUBJECT MATTER		
Int. Cl.		
A61K 33/04 (2006.01) A61P 35/00 (2006.01)		
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)		
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)		
WPIDS and Medline. Keywords: selenate, cancer, tumour, tumor, neoplasm, benign and related terms.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2005/115472 A2 (Abbott Laboratories), 8 December 2005 see page 9 line 31, page 13 line 5 to page 14 line 25, page 27 line 16 to page 30 line 25, page 31 line 4 to page 34 line 30.	1-4, 6-9, 11-14, 17-19, 22-24
Y	see page 9 line 31, page 13 line 5 to page 14 line 25, page 27 line 16 to page 30 line 25, page 31 line 4 to page 34 line 30.	1-24
X	DAVIS, C.D. ET AL The Chemical Form of Selenium Influences 3,2'-Dimethyl-4-aminobiphenyl-DNA Adduct Formation in Rat Colon. Journal of Nutrition, 1999, volume 129, pages 63-69 see abstract and page 63, right hand column, 2 nd paragraph.	6-10, 17-21, 23-24
Y	see abstract and page 63, right hand column, 2 nd paragraph.	1-24
☒ Further documents are listed in the continuation of Box C ☒ See patent family annex		
* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 08 May 2007		Date of mailing of the international search report 11 MAY 2007
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929		Authorized officer Steven Chew AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : (02) 6283 2248

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2007/000393

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2005/048925 A2 (The Board of Trustees of the Leland Stanford Junior University), 2 June 2005 see claim 1 and paragraphs 0025, 0044, 0049, 0051, 0070 and 0080.	11-16, 22
Y	CLARK, L.C. ET AL Plasma Selenium Concentration Predicts the Prevalence of Colorectal Adenomatous Polyps. Cancer Epidemiology, Biomarkers and Prevention, January/February 1993, volume 2, pages 41-46 (see abstract)	1-24
P,X	WO2006/032074 A1 (University of Melbourne), 30 March 2006 (see whole document)	1-24
A	WO2001/054688 A1 (Merck and Co Inc.), 2 August 2001	
A	CORCORAN, N.M. ET AL Inorganic Selenium Retards Progression of Experimental Hormone Refractory Prostate Cancer. Journal of Urology, February 2004, volume 171, pages 907-910	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2007/000393

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
WO	2005115472	CA	2564592	US	2006034944		
WO	2005048925						
WO	2006032074	AU	2005287854				
WO	0154688	AU	36533/01	CA	2396593	EP	1253921
		US	6486204	US	2001047022		
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.							
END OF ANNEX							