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C2AZ as Treatment Adjunct - A Review

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Abstract

This paper is a technical note showing how the established pharmacodynamic actions of four non-oncology drugs happen to inhibit several established pathophysiological mechanisms active in driving or facilitating breast cancers' growth. The resulting four repurposed drug regimen, C2AZ, uses the analgesic drug celecoxib; the antifungal drug clotrimazole; a drug used to treat rheumatoid arthritis, auranofin; and a drug used to treat asthma, zileuton. All four have a large database showing that they inhibit one or more growth driving pathways of breast cancer. The four drugs of C2AZ have been well tolerated in general medical practice and no drug-drug interaction is predictable. All four are old, cheap, generic drugs. They are predicted to be growth retarding rather than directly cytotoxic so C2AZ would best be studied in an adjunctive role.

Keywords: Auranofin; Breast cancer; Celecoxib; Clotrimazole; Nrf2; Zileuton

Abbreviations: COX: Cyclooxygenase; KCa3.1: Intermediate-conductance Ca++ activated K+ channel; 5-LO: 5-lipoxygenase; Nrf2: NF-E2-related factor 2

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Introduction

This paper presents the rationale for addition of an antifungal drug, clotrimazole, an analgesic drug, celecoxib, an anti-rheumatoid arthritis drug, auranofin, and an anti-asthma drug that inhibits 5-lipoxygenase (5-LO), zileuton - the C2AZ Regimen - as adjunctive treatment of breast cancer. As things now stand (as of Summer 2020), breast cancer, once it has metastasized, is incurable. The four drugs of C2AZ have been well tolerated when used individually in general medical practice and, surprisingly, all have robust preclinical database supporting their adjunctive use in treating breast cancer. They have never been used clinically for breast cancer.

Nests of metastatic breast cancer cells can remain quiescent for years, then for as yet to be identified reasons, they exit the dormant state, start dividing, actively growing, and further metastasizing [1-3]. One could infer that dormant breast cancer nidi are actually the predominant breast cancer form from the fact that punctilious autopsy of middle-aged women dying from non-cancer causes, 18% had occult *in situ* breast cancer as did elderly women dying of non-cancer causes [4]. It is the aim of C2AZ to increase the chance of breast cancer cell nests to remain dormant. Details follow:

Literature Review

High dose celecoxib

Celecoxib is an analgesic drug, generically available and widely used in low doses for treating pain. It is a selective cyclooxygenase-2 (COX-2) inhibitor that also inhibits several isoforms of carbonic anhydrase. 99% of metastatic breast cancers grossly overexpress COX-2 [5]. Although COX-2 has commonly been called "... a ubiquitous driver of mammary carcinogenesis..." [5]. This must be understood as one driver among many cross-covering drivers.

The role of COX-2 and its eicosanoid prostaglandin product PGE2 in breast cancer growth and its associated immunosuppression has been the subject of several recent reviews [5-10]. People dying of metastatic breast cancer had grossly elevated RNA transcripts levels of both 5-LO and COX-2 [11]. Note the particular value of combined inhibition of PGE2 formation by COX-2 inhibition with simultaneous leukotriene synthesis inhibition during breast cancer treatment [9,12-16]. C2AZ aims to achieve this by combining high dose celecoxib with zileuton (vide infra). Giving a leukotriene inhibitor with any COX inhibitor when treating cancer is important to obviate shunting from COX inhibition to increased leukotriene synthesis [15,16].

Celecoxib inhibits CA IX with a Ki of ~ 16 nM, comparable to the

traditional, clinically used, archetypal, nonselective carbonic anhydrase inhibitor acetazolamide, that has Ki variously reported as 5 to 25 nM [17-21]. Celecoxib's plasma concentration-time curve is dose proportional between 200 and 800 mg, Tmax is 2 to 4 hours, T1/2 is 11 hours, Cmax after an 800 mg dose is ~ 2.9 ± 0.4 mg/L. Celecoxib is 98% albumin bound. Celecoxib is metabolised primarily by hepatic CYP2C9 [22]. IC 50 is 15 ± 1 µg/L for COX-1 and 0.04 ± 0.01 µg/L for COX-2 giving a selectivity ratio, COX-1: COX-2 of 375 [22]. Although celecoxib is a sulfonamide, allergic reactions in people who are sulfonamide allergic are not common. A curiosity of COX-2 is, that while it is traditionally termed an inducible isoform and COX-1 the constitutive form, COX-2 is constitutively expressed in the human brain and renal macula densa and adjacent cortical thick ascending limb [23].

In searching for drugs that might augment auranofin's selective cytotoxicity to cancer cells, a high-throughput drug screening identified celecoxib [24]. The combination generated greater oxidative stress than either alone did mitochondrial hexokinase inhibition with catastrophic decrease in intracellular ATP without seeming to impair non-malignant tissue function or vitality [24]. Celecoxib together with auranofin (vide infra) are particularly effective in increasing damaging intracellular ROS to which cancer cells are more sensitive than non-malignant cells [24,25]. In short, inhibition of carbonic anhydrase and COX-2 with high dose celecoxib is eminently worth trying in metastatic breast cancer.

Clotrimazole

Clotrimazole is a broad-spectrum antifungal drug, most commonly used today as oral troches to treat mucositis, or topical 1% cream to treat tinea corporis, pedis, or intercruralis. Clotrimazole has excellent oral bioavailability. Since the potential advantages of adding clotrimazole to current treatments of GB in 2010 [26], much new data on the general cancer-growth inhibiting effects of clotrimazole has accrued. Clotrimazole inhibited proliferation of human breast cancer cell lines MCF-7, MDA-MB-231 and T47D [27-29].

Clotrimazole and KCa3.1

The outer cell membrane intermediate-conductance Ca^{++} activated K^{+} channel (KCa3.1) is inhibited by clotrimazole in an intermediate nM range [30-32]. Well-functioning KCa3.1 channels drive breast cancer growth and KCa3.1 inhibition impairs breast cancer cells' growth [33-37].

KCa3.1 opening triggers or induces the secretion of IL-1beta, an effect blocked by clotrimazole [38]. IL-1beta also promotes is growth in breast cancers and contributes to the characteristic local immunosuppression [39-44]. IL-1beta also enhances or induces a shift towards glycolysis via glycerol-3-phosphate dehydrogenase phosphorylation [45].

Phosphofructokinase inhibition and inhibiting glycolysis: Potential for reversing Warburg effect

Clotrimazole directly inhibits function of a key glycolytic enzyme - phosphofructokinase [46-50]. Part of glycolysis, aerobic or anaerobic - occurs free in the cytosol, but partly occurs where the enzymes mediating the steps are held in cytosol but on an actin filament scaffolding. Clotrimazole untethers these, predominantly phosphofructokinase, resulting in its inhibition [28,51,52]. Clotrimazole decreases glycolysis in other cancer model systems with consequent retardation of growth. Direct inhibition of breast cancer growth by clotrimazole has been demonstrated [48,53].

The Warburg effect of increased aerobic glycolysis has been widely demonstrated in the common cancers and specifically in breast cancer [54-60]. This makes phosphofructokinase a particularly attractive target for inhibition in that phosphofructokinase is a rate limiting enzyme in aerobic (and anaerobic) glycolysis.

It is precisely the cancer stem cell subpopulation that is particularly associated with increased glycolysis and relative radio resistance. Indeed, when forced to switch from reliance upon glycolysis by clotrimazole inhibition of phosphofructokinase, stem-like features of glioblastoma are reduced [61]. We can expect the same in breast cancer [62-64]. Whether or not clotrimazole could be similarly helpful in human patients remains to be formally evaluated. In short, inhibition of KCa3.1 and phosphofructokinase with clotrimazole is eminently worth trying in metastatic breast cancer.

Auranofin

Auranofin is an inhibitor of cathepsin B and thioredoxin reductase [65,66]. It is FDA/EMA approved and marketed since the 1980s to treat rheumatoid arthritis [67,68]. Auranofin is now seeing a renaissance as treatment adjunct in several cancers, including breast cancer, by virtue of its inhibition of thioredoxin reductase [69-76]. Thioredoxin reductase recharges [reduces] oxidized 12 kDa thioredoxin, a process essential to coping with mitochondrial reactive oxygen species (ROS). Thioredoxin donates reducing equivalents (electrons) to oxidized metabolic intermediates using an intermolecular cysteine thiol-disulfide exchange.

BRCA1 protein is part of a multimeric protein complex that repairs double strand DNA breaks. Mutations in *BRCA1* predispose women to breast and ovarian cancer. Breast cancer cells with mutated *BRCA1* are more sensitive to auranofin [77]. Auranofin was effective in reducing triple-negative breast cancer growth in *in vitro* and in xenograft models at auranofin levels that did not affect non-transformed breast cell viability [78,79]. Similar results from auranofin were seen in estrogen-progesterone receptor expressing breast cancer [80,81].

NRF2 is one of the main transcription factor regulators of the antioxidant responses. p53 is often mutated in breast cancer [82]. Thioredoxin is a mutant p53-activated NRF2 target with pro-survival and pro-migratory functions in breast cancer cells under oxidative stress [83].

Nrf2 is a transcription factor of genes coding for antioxidant proteins. NRF2 is kept in cytosol by Kelch like-ECH-associated protein 1 (KEAP1) and Cullin 3, [84]. Kept in cytosol, Nrf2 tends to be degraded quickly. Unbound Nrf2 translocates to nucleus where it triggers transcription of its antioxidant target genes. Nrf2 is a transcriptional regulator that targets heme oxygenase-1 (HMOX1), ferritin (FTH) genes, and that coding for thioredoxin (TXRD1). NRF2-driven metabolic reprogramming promotes

breast cancer cells' exit from dormancy [85]. Human breast cancers overexpress Nrf2 and patient survival is shorter in those with higher Nrf2 expression, longer in those with lesser Nrf2 expression [86,87]. Higher Nrf2 expression facilitates tumor neoangiogenesis as well [88].

Although there are doubtless a coalition of intracellular forces that together give rise to a cancer cells' dormant state, Nrf2 is one, a consequence of which we might be able to inhibit. Auranofin inhibits thioredoxin reductase, thereby reversing a core effect of Nrf2 [24,78,79,89,90]. Thioredoxin and thioredoxin reductase tend to be elevated in a variety of the common lethal cancers [91]. Auranofin in high nanomolar concentration increased radiation induced cell death in MDA-MB-231 breast cancer cells [92].

Thioredoxin and thioredoxin reductase is located in both cytoplasmic and nuclear compartments of breast cancer cells [93]. Breast cancers with higher thioredoxin levels are more resistant to docetaxel [94]. By immunohistochemistry on 224 breast cancers, high expression of cytoplasmic peroxiredoxin-I was a negative prognostic sign [95]. Thioredoxin 1 is increased in breast cancer tissue and in-patient sera even in those with stage 1 disease [96,97]. In short, inhibiting thioredoxin reductase with auranofin is eminently worth trying in metastatic breast cancer.

Zileuton

Zileuton is an inhibitor of 5-LO, inhibiting formation of 5-LO products - leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4. It is marketed and FDA/EMA approved to treat asthma [98,99]. Zileuton and inhibition of 5-LO decreases growth in a wide variety of cancers in preclinical study [100-110]. There has been no reported clinical study of zileuton in any cancer. Let C2AZ be the first.

5-LO sits at the branchpoint in the metabolism of arachidonate to leukotriene synthesis from prostaglandin synthesis [111]. 5-LO by itself is inactive. It requires 5-lipoxygenase activating protein (FLAP). FLAP is elevated in breast cancer tissue and degree of elevation was inversely correlated with survival [111].

Human breast cancers overexpress 5-LO [112,113]. Serum levels of 5-LO are elevated in breast cancer patients [114]. Untreated breast cancer cell lines synthesize large amounts of leukotriene LTB4 [115]. Insulin-like growth factor 1 stimulated growth and leukotriene synthesis in breast cancer cell line MCF-7 [116]. *In vitro* growth of human breast cancer cell line MDA-MB-231 was inhibited by non-marketed 5-LO inhibitors [117].

Human breast cancer exhibits a strong predilection for metastasis to bone. A nidus of bone resorption is required for that process to occur. In experimental models of breast cancer-mediated bone resorption, 5-LO inhibition inhibited that process [118,119].

5-LO product LTB4 stimulated breast cancer growth by a positive feedback loop with fatty acid synthase [120]. Agonism at the LTB4 receptor mediated paclitaxel resistance in MCF-7 breast cancer [121]. Expression of BLT2, a LTB4 receptor, is upregulated in human breast cancer cells, suggesting an autocrine growth loop mediating aggressiveness [122-124]. Higher breast cancer tissue expression of BLT2 is associated with shorter survival [123]. This work also indicated that survival under high ROS load was partly dependent on LTB4-BTL2 signaling, leading to the conclusion in the current paper on C2AZ, that zileuton plus auranofin would be a particularly felicitous combination.

Serum alanine aminotransferase (ALT) must be monitored during zileuton treatment as this reflects occasional liver injury with zileuton. ALT elevations usually resolve upon zileuton discontinuation. Standard zileuton dosing in asthma would be two 600 mg extended-release tablets twice daily within one hour of morning and evening meals [125].

In a murine breast cancer study, zileuton decreased metastasis and circulating breast cancer cells [126]. Leukotrienes are instrumental in new vessel formation associated with breast cancer growth [127]. 5-LO products, specifically LTB_4 contribute to the immunosuppression and Treg generation in breast cancer [128]. Neutrophils are active in 5-LO leukotriene generation that facilitate establishment of breast cancer metastases [129]. In short, inhibiting 5-LO with zileuton is eminently worth trying in metastatic breast cancer.

Discussion

Two genes are synthetic lethal if mutation of either gene alone is compatible with viability but mutation of both leads to death. The inverse corollary would be our principle of multiple cross-covering growth drive pathways in cancers generally, and in breast cancer specifically. We therefore believe a polypharmacy approach will be needed for long-term control of breast cancer. Adjunctive use of C2AZ during breast cancer treatment is a step in that direction.

The combination of celecoxib and zileuton has been used and shown to be effective in inhibiting growth in a variety of animal cancer models [130-133]. Note also that no untoward interactions were seen when using simultaneous celecoxib and zileuton in these cancer models.

C2AZ regimen is not without risks. The unknown risks of combining the all C2AZ drugs together are partly mitigated by absence of any predictable risk of the combination beyond additive liver irritation potential. Patients must take zileuton 600 mg every 6 hours and 4% develop elevated hepatic transaminases [134]. Although these elevations were reversible, this means monitoring of liver function will be required.

Two leukotriene receptor blockers are approved for use in humans in treating asthma - zafirlukast and montelukast [135-137]. They block receptors for cysteinyl leukotrienes LTC4, LTD4, and LTE4 and so might be substituted for zileuton in jurisdictions where zileuton is not marketed or in case of transaminase elevations with zileuton. Both zafirlukast and montelukast inhibited *in vitro* viability of breast cancer cell line MDA MB-231, with concentrations near those clinically achievable [138].

Conclusion

Given that metastatic breast cancer is incurable (as of Summer 2020) an adjunctive four drug protocol, C2AZ, was designed to

keep the small paucicellular metastases dormant. C2AZ uses the documented attributes of four drugs repurposed to treat breast cancer. How these three drugs constructively intersect with and inhibit the relevant known growth-driving aspects of breast cancer was reviewed in this paper. In short, the projected safety of the C2AZ regimen, it is eminently worth trying in metastatic breast cancer.

Declarations

Ethics approval and consent to participate

No human or animal subjects were used in this work.

Consent for publication

The sole author, REK, consents for publication.

Availability of data and materials

All data has been presented in the manuscript.

Competing interests

The author has no competing interest.

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This was unfunded research.

Authors' contributions

REK is the sole author.

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References

1 De Angelis ML, Francescangeli F, Zeuner A (2019) Breast cancer stem cells as drivers of tumor chemoresistance, dormancy and relapse: New challenges and therapeutic opportunities. Cancers (Basel) 11: 1569.

2 Demicheli R (2001) Tumour dormancy: Findings and hypotheses from clinical research on breast cancer. Semin Cancer Biol 11: 297-306.

3 Ferrer AI, Trinidad JR, Sandiford O, Etchegaray JP, Rameshwar P (2020) Epigenetic dynamics in cancer stem cell dormancy. Cancer Metastasis Rev 39: 721-738.

4 Nielsen M (1989) Autopsy studies of the occurrence of cancerous, atypical and benign epithelial lesions in the female breast. APMIS Suppl 10: 1-56.

5 Harris RE, Casto BC, Harris ZM (2014) Cyclooxygenase-2 and the inflammogenesis of breast cancer. World J Clin Oncol 5: 677-692.

6 Ching MM, Reader J, Fulton AM (2020) Eicosanoids in Cancer: Prostaglandin E2 Receptor 4 in Cancer Therapeutics and Immunotherapy. Front Pharmacol 11: 819-824.

7 Cai Y, Yousef A, Grandis JR, Johnson DE (2020) NSAID therapy for PIK3CA-Altered colorectal, breast, and head and neck cancer. Adv Biol Regul 75: 100653.

8 Lala PK, Nandi P, Majumder M (2018) Roles of prostaglandins in tumor-associated lymphangiogenesis with special reference to breast cancer. Cancer Metastasis Rev 37: 369-384.

9 Gautam S, Roy S, Ansari MN, Saeedan AS, Saraf SA, et al. (2017) DuCLOX-2/5 inhibition: A promising target for cancer chemoprevention. Breast Cancer 24: 180-190.

10 Regulski M, Regulska K, Prukała W, Piotrowska H, Stanisz B, et al. (2016) COX-2 inhibitors: a novel strategy in the management of breast cancer. Drug Discov Today 21: 598-615.

11 Jiang WG, Douglas-Jones A, Mansel RE (2003) Levels of expression of lipoxygenases and cyclooxygenase-2 in human breast cancer. Prostaglandins Leukot Essent Fatty Acids 69: 275-281.

12 Ranjbar MM, Assadolahi V, Yazdani M, Nikaein D, Rashidieh B (2016) Virtual Dual inhibition of COX-2 / 5-LOX enzymes based on binding properties of alpha-amyrins, the anti-inflammatory compound as a promising anti-cancer drug. EXCLI J 15: 238-245.

13 Orlando UD, Garona J, Ripoll GV, Maloberti PM, Solano ÁR, et al. (2012) The functional interaction between Acyl-CoA synthetase 4, 5-lipooxygenase and cyclooxygenase-2 controls tumor growth: A novel therapeutic target. PLoS One 7: e40794.

14 Kennedy BM, Harris RE (2018) Cyclooxygenase and lipoxygenase gene expression in the inflammogenesis of breast cancer. Inflammopharmacology s10787.

15 Kast RE (2003) Tenofovir, COX inhibitors and zileuton during cancer immunotherapies: up-regulated TNF-alpha increases antigen driven lymphocyte proliferation. Mol Immunol 40: 297-303.

16 Ganesh R, Marks DJ, Sales K, Winslet MC, Seifalian AM (2012) Cyclooxygenase/lipoxygenase shunting lowers the anti-cancer effect of cyclooxygenase-2 inhibition in colorectal cancer cells. World J Surg Oncol 10: 200.

17 Nocentini A, Moi D, Deplano A, Osman SM, AlOthman ZA, et al. (2019) Sulfonamide/sulfamate switch with a series of piperazinylureido derivatives: Synthesis, kinetic and *in silico* evaluation as carbonic anhydrase isoforms I, II, IV, and IX inhibitors. Eur J Med Chem 186: 111896.

18 Sethi KK, Vullo D, Verma SM, Tanç M, Carta F, et al. (2013) Carbonic anhydrase inhibitors: synthesis and inhibition of the human carbonic anhydrase isoforms I, II, VII, IX and XII with benzene sulfonamides incorporating 4,5,6,7-tetrabromophthalimide moiety. Bioorg Med Chem 21: 5973-5982.

19 Dogne JM, Thiry A, Pratico D, Masereel B, Supuran CT (2007) Dual carbonic anhydrase--cyclooxygenase-2 inhibitors. Curr Top Med Chem 7: 885-891.

20 Weber A, Casini A, Heine A, Kuhn D, Supuran CT, et al. (2004) Unexpected nanomolar inhibition of carbonic anhydrase by COX-2-selective celecoxib: new pharmacological opportunities due to related binding site recognition. J Med Chem 47: 550-557.

21 De Luca L, Mancuso F, Ferro S, Buemi MR, Angeli A, et al. (2018) Inhibitory effects and structural insights for a novel series of coumarin-based compounds that selectively target human CA IX and CA XII carbonic anhydrases. Eur J Med Chem 143: 276-282.

22 Davies NM, McLachlan AJ, Day RO, Williams KM (2000) Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclooxygenase-2 inhibitor. Clin Pharmacokinet 38: 225-242.

23 de Vries EF, van Waarde A, Buursma AR, Vaalburg W (2003) Synthesis and in vivo evaluation of 18F-desbromo-DuP-697 as a PET tracer for cyclooxygenase-2 expression. J Nucl Med 44: 1700-1706.

24 Han Y, Chen P, Zhang Y, Lu W, Ding W, et al. (2019) Synergy between Auranofin and Celecoxib against Colon Cancer In Vitro and In Vivo through a Novel Redox-Mediated Mechanism. Cancers (Basel) 11: 9.

25 Ralph SJ, Nozuhur S, ALHulais RA, Rodríguez-Enríquez S, Moreno-Sánchez R (2019) Repurposing drugs as pro-oxidant redox modifiers to eliminate cancer stem cells and improve the treatment of advanced stage cancers. Med Res Rev 39: 2397-2426.

26 Kast RE (2010) Profound blockage of CXCR4 signaling at multiple points using the synergy between plerixafor, mirtazapine, and clotrimazole as a new glioblastoma treatment adjunct. Turk Neurosurg 20: 425-429.

27 Bae SH, Park JH, Choi HG, Kim H, Kim SH (2018) Imidazole Antifungal Drugs Inhibit the Cell Proliferation and Invasion of Human Breast Cancer Cells. Biomol Ther (Seoul) 26: 494-502.

28 Meira DD, Marinho-Carvalho MM, Teixeira CA, Veiga VF, Da Poian AT, et al. (2005) Clotrimazole decreases human breast cancer cells viability through alterations in cytoskeleton-associated glycolytic enzymes. Mol Genet Metab 84: 354-362.

29 Motawi TM, Sadik NA, Fahim SA, Shouman SA (2015) Combination of imatinib and clotrimazole enhances cell growth inhibition in T47D breast cancer cells. Chem Biol Interact 233: 147-156.

30 Lee BS, Devor DC, Hamilton KL (2017) Modulation of Retrograde Trafficking of KCa3.1 in a Polarized Epithelium. Front Physiol 8: 489.

31 Grössinger EM, Weiss L, Zierler S, Rebhandl S, Krenn PW, et al. (2014) Targeting proliferation of chronic lymphocytic leukemia (CLL) cells through KCa3.1 blockade. Leukemia 28: 954-958.

32 Zhang P, Yang X, Yin Q, Yi J, Shen W, et al. (2016) Inhibition of SK4 Potassium Channels Suppresses Cell Proliferation, Migration and the Epithelial-Mesenchymal Transition in Triple-Negative Breast Cancer Cells. PLoS One 11: e0154471.

33 Faouzi M, Chopin V, Ahidouch A, Ouadid-Ahidouch H (2010) Intermediate Ca2+-sensitive K+ channels are necessary for prolactin-induced proliferation in breast cancer cells. J Membr Biol 234: 47-56.

34 Faouzi M, Hague F, Geerts D, Ay AS, Potier-Cartereau M, et al. (2016) Functional cooperation between KCa3.1 and TRPC1 channels in human breast cancer: Role in cell proliferation and patient prognosis. Oncotarget 7: 36419-36435.

35 Mohr CJ, Gross D, Sezgin EC, Steudel FA, Ruth P, et al. (2019) K+Ca++3.1 Channels Confer Radioresistance to Breast Cancer Cells. Cancers (Basel) 11: 1285.

36 Ohya S, Kanatsuka S, Hatano N, Kito H, Matsui A, et al. (2016) Downregulation of the Ca++-activated K+ channel KC a3.1 by histone deacetylase inhibition in human breast cancer cells. Pharmacol Res Perspect 4: e00228.

37 Steudel FA, Mohr CJ, Stegen B, Nguyen HY, Barnert A, et al. (2017) SK4 channels modulate Ca++ signalling and cell cycle progression in murine breast cancer. Mol Oncol 11: 1172-1188.

38 Schroeder ME, Russo S, Costa C, Hori J, Tiscornia I, et al. (2017) Pro-inflammatory Ca++-activated K+ channels are inhibited by hydroxychloroquine. Sci Rep 7: 1892.

39 Kaplanov I, Carmi Y, Kornetsky R, Shemesh A, Shurin GV, et al. (2019) Blocking IL-1β reverses the immunosuppression in mouse breast cancer and synergizes with anti-PD-1 for tumor abrogation. Proc Natl Acad Sci USA 116: 1361-1369.

40 Tulotta C, Ottewell P (2018) The role of IL-1B in breast cancer bone metastasis. Endocr Relat Cancer 25: R421-R434.

41 Rutter JL, Benbow U, Coon CI, Brinckerhoff CE (1997) Cell-type specific regulation of human interstitial collagenase-1 gene expression by interleukin-1 beta (IL-1 beta) in human fibroblasts and BC-8701 breast cancer cells. J Cell Biochem 66: 322-236.

42 Hou Z, Falcone DJ, Subbaramaiah K, Dannenberg AJ (2011) Macrophages induce COX-2 expression in breast cancer cells: role of IL-1β autoamplification. Carcinogenesis 32: 695-702.

43 Guo B, Fu S, Zhang J, Liu B, Li Z (2016) Targeting inflammasome/IL-1 pathways for cancer immunotherapy. Sci Rep 6: 36107.

44 Jeon M, Han J, Nam SJ, Lee JE, Kim S (2016) Elevated IL-1β expression induces invasiveness of triple negative breast cancer cells and is suppressed by zerumbone. Chem Biol Interact 258: 126-233.

45 Lu J, Xu Z, Duan H, Ji H, Zhen Z, et al. (2020) Tumor-associated macrophage interleukin-β promotes glycerol-3-phosphate dehydrogenase activation, glycolysis and tumorigenesis in glioma cells. Cancer Sci 111: 1979-1990.

46 Zancan P, Rosas AO, Marcondes MC, Marinho-Carvalho MM, Sola-Penna M (2007) Clotrimazole inhibits and modulates heterologous association of the key glycolytic enzyme 6-phosphofructo-1-kinase. Biochem Pharmacol 73: 1520-1527.

47 Coelho RG, Calaça Ide C, Celestrini Dde M, Correia AH, Costa MA, et al. (2011) Clotrimazole disrupts glycolysis in human breast cancer without affecting non-tumoral tissues. Mol Genet Metab 103: 394-398.

48 Furtado CM, Marcondes MC, Carvalho RS, Sola-Penna M, Zancan P (2015) Phosphatidylinositol-3-kinase as a putative target for anticancer action of clotrimazole. Int J Biochem Cell Biol 62: 132-141.

49 Marcondes MC, Sola-Penna M, Zancan P (2010) Clotrimazole potentiates the inhibitory effects of ATP on the key glycolytic enzyme 6-phosphofructo-1-kinase. Arch Biochem Biophys 497: 62-67.

50 Marcondes MC, Fernandes AC, Itabaiana I Jr, De Souza RO, Sola-Penna M, et al. (2015) Nanomicellar Formulation of Clotrimazole Improves Its Antitumor Action toward Human Breast Cancer Cells. PLoS One 10: e0130555.

51 Penso J, Beitner R (2002) Clotrimazole decreases glycolysis and the viability of lung carcinoma and colon adenocarcinoma cells. Eur J Pharmacol 451: 227-235.

52 Glass-Marmor L, Beitner R (1997) Detachment of glycolytic enzymes from cytoskeleton of melanoma cells induced by calmodulin antagonists. Eur J Pharmacol 328: 241-248.

53 Furtado CM, Marcondes MC, Sola-Penna M, De Souza ML, Zancan P (2012) Clotrimazole preferentially inhibits human breast cancer cell proliferation, viability and glycolysis. PLoS One 7: e30462.

54 Niu W, Luo Y, Wang X, Zhou Y, Li H, et al. (2018) BRD7 inhibits the Warburg effect and tumor progression through inactivation of HIF1α/LDHA axis in breast cancer. Cell Death Dis 9: 519.

55 Luo P, Zhang C, Liao F, Chen L, Liu Z, et al. (2019) Transcriptional positive cofactor 4 promotes breast cancer proliferation and metastasis through c-Myc mediated Warburg effect. Cell Commun Signal 17: 36.

56 Hart PC, Mao M, de Abreu AL, Ansenberger-Fricano K, Ekoue DN, et al. (2015) MnSOD upregulation sustains the Warburg effect via mitochondrial ROS and AMPK-dependent signalling in cancer. Nat Commun 6: 6053.

57 Luis C, Duarte F, Faria I, Jarak I, Oliveira PF, et al. (2019) Warburg Effect Inversion: Adiposity shifts central primary metabolism in MCF-7 breast cancer cells. Life Sci 223: 38-46.

58 Willmann L, Schlimpert M, Halbach S, Erbes T, Stickeler E, et al. (2015) Metabolic profiling of breast cancer: Differences in central metabolism between subtypes of breast cancer cell lines. J Chromatogr B Analyt Technol Biomed Life Sci 1000: 95-104.

59 Ayyasamy V, Owens KM, Desouki MM, Liang P, Bakin A, et al. (2011) Cellular model of Warburg effect identifies tumor promoting function of UCP2 in breast cancer and its suppression by genipin. PLoS One 6: e24792.

60 Isidoro A, Casado E, Redondo A, Acebo P, Espinosa E, et al. (2005) Breast carcinomas fulfill the Warburg hypothesis and provide metabolic markers of cancer prognosis. Carcinogenesis 26: 2095-2104.

61 Zhou K, Yao YL, He ZC, Chen C, Zhang XN, et al. (2018) VDAC2 interacts with PFKP to regulate glucose metabolism and phenotypic reprogramming of glioma stem cells. Cell Death Dis 9: 988.

62 Shiraishi T, Verdone JE, Huang J, Kahlert UD, Hernandez JR, et al. (2015) Glycolysis is the primary bioenergetic pathway for cell motility and cytoskeletal remodeling in human prostate and breast cancer cells. Oncotarget 6: 130-143.

63 Ciavardelli D, Rossi C, Barcaroli D, Volpe S, Consalvo A, et al. (2014) Breast cancer stem cells rely on fermentative glycolysis and are sensitive to 2-deoxyglucose treatment. Cell Death Dis 5: e1336.

64 Peng F, Wang JH, Fan WJ, Meng YT, Li MM, et al. (2018) Glycolysis gatekeeper PDK1 reprograms breast cancer stem cells under hypoxia. Oncogene 37: 1062-1074.

65 Papaioannou M, Mylonas I, Kast RE, Brüning A (2013) Disulfiram/copper causes redox-related proteotoxicity and concomitant heat shock response in ovarian cancer cells that is augmented by auranofin-mediated thioredoxin inhibition. Oncoscience 1: 21-29.

66 Kast RE (2010) Glioblastoma invasion, cathepsin B, and the potential for both to be inhibited by auranofin, an old anti-rheumatoid arthritis drug. Cent Eur Neurosurg 71: 139-142.

67 Davis P (1984) Auranofin. Clin Rheum Dis 10: 369-383.

68 Gottlieb NL (1986) Pharmacology of auranofin: overview and update. Scand J Rheumatol Suppl 63: 19-28.

69 Kast RE, Karpel-Massler G, Halatsch ME (2014) CUSP9* treatment protocol for recurrent glioblastoma: aprepitant, artesunate, auranofin, captopril, celecoxib, disulfiram, itraconazole, ritonavir, sertraline augmenting continuous low dose temozolomide. Oncotarget 5: 8052-8082.

70 Kast RE, Boockvar JA, Brüning A, Cappello F, Chang WW, et al. (2013) A conceptually new treatment approach for relapsed glioblastoma: coordinated undermining of survival paths with nine repurposed drugs (CUSP9) by the International Initiative for Accelerated Improvement of Glioblastoma Care. Oncotarget 4: 502-530.

71 Onodera T, Momose I, Kawada M (2019) Potential Anticancer Activity of Auranofin. Chem Pharm Bull (Tokyo) 67: 186-191.

72 Ye DJ, Kwon YJ, Baek HS, Cho E, Kwon TU, et al. (2019) Combination treatment with auranofin and nutlin-3a induces synergistic cytotoxicity in breast cancer cells. J Toxicol Environ Health 82: 626-637.

73 Li H, Hu J, Wu S, Wang L, Cao X, et al. (2016) Auranofin mediated inhibition of PI3K/AKT/mTOR axis and anticancer activity in non-small cell lung cancer cells. Oncotarget 7: 3548-3558.

74 Hou GX, Liu PP, Zhang S, Yang M, Liao J, et al. (2018) Elimination of stem-like cancer cell side population by auranofin through modulation of ROS and glycolysis. Cell Death Dis 9: 89.

75 Hu J, Zhang H, Cao M, Wang L, Wu S, et al. (2018) Auranofin Enhances Ibrutinib's Anticancer Activity in EGFR-Mutant Lung Adenocarcinoma. Mol Cancer Ther 17: 2156-2163.

76 Liu N, Guo Z, Xia X, Liao Y, Zhang F, et al. (2019) Auranofin lethality to prostate cancer includes inhibition of proteasomal deubiquitinases and disrupted androgen receptor signaling. Eur J Pharmacol 846: 1-11.

77 Oommen D, Yiannakis D, Jha AN (2016) BRCA1 deficiency increases the sensitivity of ovarian cancer cells to auranofin. Mutat Res 785: 8-15.

78 Chepikova OE, Malin D, Strekalova E, Lukasheva EV, Zamyatnin AA Jr, et al. (2020) Lysine oxidase exposes a dependency on the thioredoxin antioxidant pathway in triple-negative breast cancer cells. Breast Cancer Res Treat 183: 549-564.

79 Raninga PV, Lee AC, Sinha D, Shih YY, Mittal D, et al. (2020) Therapeutic cooperation between auranofin, a thioredoxin reductase inhibitor and anti-PD-L1 antibody for treatment of triple-negative breast cancer. Int J Cancer 146: 123-136.

80 Lee JE, Kwon YJ, Baek HS, Ye DJ, Cho E, et al. (2017) Synergistic induction of apoptosis by combination treatment with mesupron and auranofin in human breast cancer cells. Arch Pharm Res 40: 746-759.

81 Liu C, Liu Z, Li M, Li X, Wong YS, et al. (2013) Enhancement of auranofin-induced apoptosis in MCF-7 human breast cells by selenocystine, a synergistic inhibitor of thioredoxin reductase. PLoS One 8: e53945.

82 Fortuno C, James PA, Spurdle AB (2018) Current review of TP53 pathogenic germline variants in breast cancer patients outside Li-Fraumeni syndrome. Hum Mutat 39: 1764-1773.

83 Lisek K, Campaner E, Ciani Y, Walerych D, Del Sal G (2018) Mutant p53 tunes the NRF2-dependent antioxidant response to support survival of cancer cells. Oncotarget 9: 20508-20523.

84 Itoh K, Wakabayashi N, Katoh Y, Ishii T, Igarashi K, et al. (1999) Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino terminal Neh2 domain. Genes Dev 13: 76-86.

85 Fox DB, Garcia NMG, McKinney BJ, Lupo R, Noteware LC, et al. (2020) NRF2 activation promotes the recurrence of dormant tumour cells through regulation of redox and nucleotide metabolism. Nat Metab 2: 318-334.

86 Simplicio-Revoredo CM, de Oliveira Pereira R, de Almeida Melo M, Lopes-Costa PV, de Tarso Moura-Borges P, et al. (2020) Expression of Nrf2 and NF-κB transcription factors in breast cancer and breast fibroadenoma: Insights for a new therapeutic approach. Oncotarget 11: 1629-1636.

87 Wu X, Liu C, Li Z, Gai C, Ding D, et al. (2020) Regulation of GSK3β/Nrf2 signaling pathway modulated erastin-induced ferroptosis in breast cancer. Mol Cell Biochem 473: 217-228.

88 Zhou S, Ye W, Zhang M, Liang J (2012) The effects of nrf2 on tumor angiogenesis: a review of the possible mechanisms of action. Crit Rev Eukaryot Gene Expr 22: 149-160.

89 Liu X, Zhang Y, Lu W, Han Y, Yang J, et al. (2020) Mitochondrial TXNRD3 confers drug resistance via redox-mediated mechanism and is a potential therapeutic target in vivo. Redox Biol 36: 101652.

90 Clapper E, Wang S, Raninga PV, Di Trapani G, Tonissen KF (2020) Cross-talk between Bcr-abl and the Thioredoxin System in Chronic

Myeloid Leukaemia: Implications for CML Treatment. Antioxidants (Basel) 9: 207.

91 Lincoln DT, Ali Emadi EM, Tonissen KF, Clarke FM (2003) The thioredoxin-thioredoxin reductase system: over-expression in human cancer. Anticancer Res 23: 2425-2433.

92 Rodman SN, Spence JM, Ronnfeldt TJ, Zhu Y, Solst SR, et al. (2016) Enhancement of Radiation Response in Breast Cancer Stem Cells by Inhibition of Thioredoxin and Glutathione-Dependent Metabolism. Radiat Res 186: 385-395.

93 Turunen N, Karihtala P, Mantyniemi A, Sormunen R, Holmgren A, et al. (2004) Thioredoxin is associated with proliferation, p53 expression and negative estrogen and progesterone receptor status in breast carcinoma. APMIS 112: 123-132.

94 Kim SJ, Miyoshi Y, Taguchi T, Tamaki Y, Nakamura H, et al. (2005) High thioredoxin expression is associated with resistance to docetaxel in primary breast cancer. Clin Cancer Res 11: 8425-8430.

95 Woolston CM, Storr SJ, Ellis IO, Morgan DA, Martin SG (2011) Expression of thioredoxin system and related peroxiredoxin proteins is associated with clinical outcome in radiotherapy treated early stage breast cancer. Radiother Oncol 100: 308-313.

96 Cha MK, Suh KH, Kim IH (2009) Overexpression of peroxiredoxin I and thioredoxin1 in human breast carcinoma. J Exp Clin Cancer Res 28: 93.

97 Park BJ, Cha MK, Kim IH. Thioredoxin 1 as a serum marker for breast cancer and its use in combination with CEA or CA15-3 for improving the sensitivity of breast cancer diagnoses. BMC Res Notes 7: 7.

98 Carter GW, Young PR, Albert DH, Bouska J, Dyer R, et al. (1991) 5-lipoxygenase inhibitory activity of zileuton. J Pharmacol Exp Ther 256: 929-937.

99 Rubin P, Dubé L, Braeckman R, Swanson L, Hansen R, et al. (1991) Pharmacokinetics, safety, and ability to diminish leukotriene synthesis by zileuton, an inhibitor of 5-lipoxygenase. Agents Actions Suppl 35: 103-116.

100 Yoshimura R, Matsuyama M, Tsuchida K, Kawahito Y, Sano H, et al. (2003) Expression of lipoxygenase in human bladder carcinoma and growth inhibition by its inhibitors. J Urol 170: 1994-1999.

101 Sarveswaran S, Chakraborty D, Chitale D, Sears R, Ghosh J (2015) Inhibition of 5-lipoxygenase selectively triggers disruption of c-Myc signaling in prostate cancer cells. J Biol Chem 290: 4994-5006.

102 Matsuyama M, Yoshimura R, Mitsuhashi M, Hase T, Tsuchida K, et al. (2004) Expression of lipoxygenase in human prostate cancer and growth reduction by its inhibitors. Int J Oncol 24: 821-827.

103 Hussey HJ, Tisdale MJ (1996) Inhibition of tumour growth by lipoxygenase inhibitors. Br J Cancer 74: 683-687.

104 Hayashi T, Nishiyama K, Shirahama T (2006) Inhibition of 5-lipoxygenase pathway suppresses the growth of bladder cancer cells. Int J Urol 13: 1086-1091.

105 Zhou GX, Ding XL, Wu SB, Zhang HF, Cao W, et al. (2015) Inhibition of 5-lipoxygenase triggers apoptosis in pancreatic cancer cells. Oncol Rep 33: 661-668.

106 Chang J, Tang N, Fang Q, Zhu K, Liu L, et al. (2019) Inhibition of COX-2 and 5-LOX regulates the progression of colorectal cancer by promoting PTEN and suppressing PI3K/AKT pathway. Biochem Biophys Res Commun 517: 1-7.

107 Avis I, Hong SH, Martinez A, Moody T, Choi YH, et al. (2001) Five-lipoxygenase inhibitors can mediate apoptosis in human breast cancer cell lines through complex eicosanoid interactions. FASEB J 15: 2007-2009.

108 Lee PP, Ip MM (1992) Regulation of proliferation of rat mammary tumor cells by inhibitors of cyclooxygenase and lipoxygenase. Prostaglandins Leukot Essent Fatty Acids 45: 21-31.

109 Meng Z, Cao R, Yang Z, Liu T, Wang Y, et al. (2013) Inhibitor of 5-lipoxygenase, zileuton, suppresses prostate cancer metastasis by upregulating E-cadherin and paxillin. Urology 82: 1452.

110 Xu XM, Deng JJ, Yuan GJ, Yang F, Guo HT, et al. (2011) 5-Lipoxygenase contributes to the progression of hepatocellular carcinoma. Mol Med Rep 4: 1195-1200.

111 Jiang WG, Douglas-Jones AG, Mansel RE (2007) Aberrant expression of 5-lipoxygenase-activating protein (5-LOXAP) has prognostic and survival significance in patients with breast cancer. Prostaglandins Leukot Essent Fatty Acids 74: 125-134.

112 Kim JH, Hubbard NE, Ziboh V, Erickson KL (2005) Attenuation of breast tumor cell growth by conjugated linoleic acid via inhibition of 5-lipoxygenase activating protein. Biochim Biophys Acta 1736: 244-250.

113 Costa H, Touma J, Davoudi B, Benard M, Sauer T, et al. (2019) Human cytomegalovirus infection is correlated with enhanced cyclooxygenase-2 and 5-lipoxygenase protein expression in breast cancer. J Cancer Res Clin Oncol 145: 2083-2095.

114 Kumar R, Singh AK, Kumar M, Shekhar S, Rai N, et al. (2016) Serum 5-LOX: a progressive protein marker for breast cancer and new approach for therapeutic target. Carcinogenesis 37: 912-927.

115 Przylipiak A, Hafner J, Przylipiak J, Köhn FM, Runnebaum B, et al. (1998) Influence of 5-lipoxygenase on in vitro growth of human mammary carcinoma cell line MCF-7. Gynecol Obstet Invest 46: 61-64.

116 Avis IM, Jett M, Boyle T, Vos MD, Moody T, et al. (1996) Growth control of lung cancer by interruption of 5-lipoxygenase-mediated growth factor signaling. J Clin Invest 97: 806-813.

117 Earashi M, Noguchi M, Kinoshita K, Tanaka M (1995) Effects of eicosanoid synthesis inhibitors on the in vitro growth and prostaglandin E and leukotriene B secretion of a human breast cancer cell line. Oncology 52: 150-155.

118 Tumber A, Morgan HM, Meikle MC, Hill PA (2001) Human breast-cancer cells stimulate the fusion, migration and resorptive activity of osteoclasts in bone explants. Int J Cancer 91: 665-672.

119 Garcia C, Boyce B, Gilles J, Dallas M, Qiao M, et al. (1996) Leukotriene B4 stimulates bone resorption both in vitro and in vivo. J Bone Miner Res 11: 1619–1627.

120 Hu N, Li Y, Zhao Y, Wang Q, You JC, et al. (2011) A novel positive feedback loop involving FASN/p-ERK1/2/5-LOX/LTB4/FASN sustains high growth of breast cancer cells. Acta Pharmacol Sin 32: 921-929.

121 Kim H, Park GS, Lee JE, Kim JH (2013) A leukotriene B4 receptor-2 is associated with paclitaxel resistance in MCF-7/DOX breast cancer cells. Br J Cancer 109: 351-359.

122 Kim H, Choi JA, Park GS, Kim JH (2012) BLT2 up-regulates interleukin-8 production and promotes the invasiveness of breast cancer cells. PLoS One 7: e49186.

123 Park J, Jang JH, Park GS, Chung Y, You HJ, et al. (2018) BLT2, a leukotriene B4 receptor 2, as a novel prognostic biomarker of triple-negative breast cancer. BMB Rep 51: 373-377.

124 Choi JA, Lee JW, Kim H, Kim EY, Seo JM, et al. (2010) Pro-survival of estrogen receptor-negative breast cancer cells is regulated by a BLT2-reactive oxygen species-linked signaling pathway. Carcinogenesis 31: 543-551.

125 Bouchette D, Preuss CV (2020) Zileuton. Treasure Island (FL): Stat Pearls Publishing.

126 Gener P, Montero S, Xandri-Monje H, Díaz-Riascos ZV, Rafael D, et al. (2020) Zileuton loaded in polymer micelles effectively reduce breast cancer circulating tumor cells and intratumoral cancer stem cells. Nanomedicine 24: 102106.

127 Kim TY, Kim J, Choo HY, Kwon HJ (2016) Inhibition of 5-lipoxygenase suppresses vascular endothelial growth factor-induced angiogenesis in endothelial cells. Biochem Biophys Res Commun 478: 1117-1122.

128 Wejksza K, Lee-Chang C, Bodogai M, Bonzo J, Gonzalez FJ, et al. (2013) Cancer-produced metabolites of 5-lipoxygenase induce tumor-evoked regulatory B cells via peroxisome proliferator-activated receptor α. J Immunol 190: 2575-2584.

129 Wculek SK, Malanchi I (2015) Neutrophils support lung colonization of metastasis-initiating breast cancer cells. Nature 528: 413-417.

130 Gregor JI, Kilian M, Heukamp I, Kiewert C, Kristiansen G, et al. (2005) Effects of selective COX-2 and 5-LOX inhibition on prostaglandin and leukotriene synthesis in ductal pancreatic cancer in Syrian hamster. Prostaglandins Leukot Essent Fatty Acids 73: 89-97.

131 Wenger FA, Kilian M, Bisevac M, Khodadayan C, von Seebach M, et al. (2002) Effects of Celebrex and Zyflo on liver metastasis and lipid peroxidation in pancreatic cancer in Syrian hamsters. Clin Exp Metastasis 19: 681-687.

132 Wenger FA, Kilian M, Achucarro P, Heinicken D, Schimke I, et al. (2002) Effects of Celebrex and Zyflo on BOP-induced pancreatic cancer in Syrian hamsters. Pancreatology 2: 54-60.

133 Chen X, Wang S, Wu N, Sood S, Wang P, et al. (2004) Overexpression of 5-lipoxygenase in rat and human esophageal adenocarcinoma and inhibitory effects of zileuton and celecoxib on carcinogenesis. Clin Cancer Res 10: 6703-6709.

134 Israel E, Cohn J, Dubé L, Drazen JM (1996) Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma: A randomized controlled trial (Zileuton Clinical Trial Group). JAMA 275: 931-936.

135 Dunn CJ, Goa KL (2001) Zafirlukast: an update of its pharmacology and therapeutic efficacy in asthma. Drugs 61: 285-315.

136 Hoxha M, Rovati GE, Cavanillas AB (2017) The leukotriene receptor antagonist montelukast and its possible role in the cardiovascular field. Eur J Clin Pharmacol 73: 799-809.

137 McMillan RM (2001) Leukotrienes in respiratory disease. Paediatr Respir Rev 2: 238-244.

138 Suknuntha K, Yubolphan R, Krueaprasertkul K, Srihirun S, Sibmooh N, et al. (2018) Leukotriene Receptor Antagonists Inhibit Mitogenic Activity in Triple Negative Breast Cancer Cells. Asian Pac J Cancer Prev 19: 833-837.