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REVIEW ARTICLE

Repositioning of proton pump inhibitors in cancer therapy

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Abstract Drug repositioning, as a smart way to exploit new molecular targets of a known drug, has been gaining increasing attention in the discovery of anti-cancer drugs. Proton pump inhibitors (PPIs) as benzimidazole derivatives, which are essentially H^+–K^+-ATPases inhibitors, are commonly used in the treatment of acid-related diseases such as gastric ulcer. In recent years, exploring the new application of PPIs in anti-cancer field has become a hot research topic. Interestingly, cancer cells display an alkaline intracellular pH and an acidic extracellular pH. The extracellular acidity of tumors can be corrected by PPIs that are selectively activated in an acid milieu. It is generally believed that PPIs might provoke disruption of pH homeostasis by targeting V-ATPase on cancer cells, which is the theoretical basis for PPIs to play an anti-cancer role. Numerous studies have shown specialized effects of the PPIs on tumor cell growth, metastasis, chemoresistance, and autophagy. PPIs may really represent new anti-cancer drugs due to better safety and tolerance, the potential selectivity in targeting tumor acidity, and the ability to inhibit mechanism pivotal for cancer homeostasis. In this review, we focus on the new therapeutic applications of PPIs in multiple cancers, explaining the rationale behind this approach and providing practical evidence.

Keywords Proton pump inhibitors (PPIs) · Cancer · V-ATPase · Acidic microenvironment

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Introduction

Malignant tumors have emerged as the leading cause of patients' death worldwide. Accordingly, tumor-related studies have always been at the forefront of medical science. In spite of significant advances in the molecular basis of tumors, it is difficult to bring new drugs from preclinical screening to clinical trials for their high development costs and low success rates. Drug repurposing is the process of exploiting new indications for the existing drugs or biologics [1]. The advantage of drug repositioning is that these types of drugs are probably to enter clinical trials faster and less expensively, due to previously verified pharmacokinetic, toxicology, and safety data. New drugs for malignant tumors may be found by drug repositioning. Thus, interests in this strategy have been growing rapidly in recent years. For example, aspirin, the oldest non-steroidal anti-inflammatory drug (NSAID), has been shown to benefit on multiple aspects of cancer chemoprevention, by reducing both incidence and mortality [2], and metastasis in patients already diagnosed with cancer [3]. Besides, there are other examples of repositioned drugs in oncology, such as metformin, thalidomide, digoxin, disulfiram, itraconazole, and so on [4].

Among non-oncological drugs, the antacid drugs proton pump inhibitors (PPIs), commonly available and low cost, are one promising example that could be repurposed. PPIs as benzimidazole derivatives which are essentially H^+–K^+-ATPases inhibitors, are currently used in the treatment of acid-related diseases such as gastric ulcer. Commonly, the PPIs family includes omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, and ilaprazole. Particularly, ilaprazole (also known as IY-81149), the latest PPI, was synthesized by Il-Yang (South Korea) and presently developed by Livzon Pharmaceutical Group Inc. (China), and has been approved by the State Food and Drug Administration of

China (license ID: CN 1121714A) [5, 6]. Recently, encouraging reports on the application of PPIs in cancer therapy have sprung up. The enhancement of chemotherapeutic effects as well as inhibition of proliferation and induction of apoptosis by PPIs has been reported as early as 1999 [7–9].

Unlike the traditional cytotoxic agents, PPIs exert antitumor effects by targeting the tumor microenvironment. Tumor microenvironment is characterized by acidification and hypoxia, which is induced by the chronic imbalance of cellular homeostasis occurring in tumor cells [10]. The acidic extracellular environment favors tissue damage, activation of destructive enzymes in the extracellular matrix (ECM), and the increased metastatic potential as well as the acquisition of multidrug resistance (MDR) cell phenotypes. Actually, the abnormal pH gradient between the extracellular environment and the cell cytoplasm is regulated by different ion/proton pump systems including the vacuolar-H^+-ATPase (V-ATPase), whose expression and activity are enhanced in tumors [11, 12]. For this reason, targeting tumor pH homeostasis is being considered as a valid and feasible strategy against cancer. The application of specific inhibitors of V-ATPase might promise the inhibition on the survival of tumor cells, the reduction of tumor metastasis, and the reversal of chemoresistance by decreasing the acidity of tumor microenvironment. It is generally believed that PPIs might provoke the disruption of pH homeostasis by targeting V-ATPase on tumor cells, which is the theoretical basis for PPIs to play an anti-cancer role [8, 13, 14]. Besides V-ATPase, scientists have made a breakthrough in exploiting other molecular mechanisms by which PPIs can induce varied anti-tumor activities. In this review, we focus on the new therapeutic applications of PPIs in multiple cancers, explaining the rationale behind this approach and providing practical evidence.

The acidic microenvironment of tumors

The evolvement of tumor microenvironment

The tumor microenvironment evolves and adjusts its functions to satisfy the compelling need of tumor cells to survive and grow. For instance, cancer cells that are eager for energy take up much more glucose than normal cells mainly through aerobic glycolysis, converting most incoming glucose to lactate even under normal oxygen concentrations, which is the so-called "Warburg effect" [10]. Such an altered metabolic pattern results in an elevated production of lactate and proton accumulation intracellularly. To maintain the intracellular pH (pHi), tumor cells have evolved various powerful mechanisms to counteract cytosolic acidification and discharge accumulated protons out of the cells, including Na^+/H^+ exchangers (NHE), carbonic anhydrases, H^+-linked monocarboxylate transporters (MCT) and proton pumps like V-ATPase. Consequently, tumors have an alkaline pHi (7.2–7.4) and lower extracellular pH (pHe) (6.5–7.1), which is a salient feature of tumor microenvironment. In the meantime, the V-ATPase also alters the pH gradient between the cytoplasm (alkaline) and the lumen of intracellular vesicles (very acidic) [11, 15].

The relationship between acidic microenvironment and tumors

The acidic microenvironment induces the selection of tumor cells which can survive these extreme conditions, leading to a more aggressive phenotype of tumors. Thus, the acidity has been shown to play a key role in resistance to chemotherapy [16], proliferation, metastasis [17], and immune escape of tumor cells [18]. In addition to activating NF-κB and a number of genes such as p53, p21, as well as Bax, Cyclins, and HSPs which are known to promote malignant progression [19], acidic environment suppresses radiation-induced apoptosis, and prolonged radiation-induced G2 arrest in cancer cells, which results in DNA damage repair [20, 21]. The metastatic potential of tumor cells is believed to be regulated by the interactions between tumor cells and ECM [22]. The low pHe triggers the secretion and activation of proteolytic enzymes including MMP-2, MMP-9, tissue serine proteases, adamalysin-related membrane proteases, cysteine proteinases cathepsins, and gelatinases, resulting in degradation and remodeling of ECM and thus promotion of tumor invasion and metastasis [17]. The up-regulation of pro-angiogenic factors such as VEGF and IL-8 also contributes to the metastasis process [19].

Tumor acidity also provides favorable conditions for the development of chemoresistance. Weakly basic drugs, like doxorubicin and vinblastine, can be protonated in acidic extracellular environment, leading to ion-trapping, which retards the uptake of these drugs. Once inside tumor cells, basic drugs will be sequestrated in acidic organelles, such as endosomes or lysosomal-like vesicles, and subsequently, their elimination is carried out through increased activity of the secretory pathway, thereby limiting drug available for their molecular targets (usually DNA) [23]. Besides, the low pHe induces an increased activity of drug efflux pumps P-glycoprotein (P-gp), which is closely associated with MDR of tumors. As a consequence, there remains a lower concentration of chemotherapeutic drugs in tumor cells and thus reduced cytotoxic efficacy [24]. More interestingly, tumor acidity was found to negatively regulate tumor-specific effector T cells and might, indeed, contribute to the dysfunction of anti-tumor immunity. Thus, the acidity itself representing a mechanism of immune escape can be overcome by drugs targeting pH-regulatory pathways, like PPIs,

which increase the clinical potential of T cell-based cancer immunotherapy [18].

Involvement of V-ATPase in malignancy of tumors

Among various mechanisms that regulate the tumor microenvironment, V-ATPase is especially significant, because it can be inhibited by PPIs [12]. The V-ATPase is a multisubunit complex consisting of a cytoplasmic domain V_1 (made of subunit A, B, C, D, E, F, G, and H) where ATP is hydrolyzed and a transmembrane domain V_0 (made of subunit a, c, c′, c″, and d) responsible for proton translocation. In addition to the expression on the membrane of many intracellular compartments, including endosomes, lysosomes, and secretory vesicles, V-ATPase also functionally locates at the plasma membrane of certain cells, including tumor cells, renal intercalated cells, osteoclasts, and macrophages, and is involved in processes such as receptor-mediated endocytosis, intracellular trafficking, acidification of endosomes, bone degradation, and control of cytoplasmic pH [25].

In tumor cells, the extrusion of protons by V-ATPase causes intracellular alkalinization and extracellular acidification which are important mechanisms favoring tumor growth, metastasis, and chemoresistance. Inhibition of V-ATPase via molecular silencing suppressed the growth and metastasis of human hepatocellular carcinoma xenografts by the decrease of proton extrusion and the downregulation of MMPs and gelatinase activity, which resulted in blocking ECM degradation and remodeling [26]. Bafilomycin, a common V-ATPase inhibitor, could delay tumor growth by inducing the expression of hypoxia-inducible factor-1α (HIF-1α), p21 as well as cell-cycle arrest [27], and promote apoptosis via lysosomal dysfunction and caspase-3 activation in a cytochrome c-independent manner [28]. Compared to normal cells, V-ATPase is overexpressed and more active in tumor cells, especially in metastatic cells, which is positively correlated to their invasion and metastasis [29, 30]. In fact, lowly metastatic breast cancer cells preferentially use the ubiquitous Na^+/H^+ exchanger and HCO_3^--based-H^+-transporting mechanisms, whereas highly metastatic cells use plasma membrane V-ATPase [29]. Thus, different uses of ion exchangers may help to distinguish tumor cells with different metastatic behaviors. Furthermore, V-ATPase has been suggested to play a role in the acquisition of the MDR phenotype by increased expression in chemoresistant cancer cells, which can be induced by chemotherapeutics [31, 32]. The protonation, sequestration, and secretion model indicates that intracellular drug distribution can be affected by intracellular pH and lysosomal pH. Increased lysosomal pH via inhibition of V-ATPase contributes to the accumulation of anti-cancer drugs in nuclei and sensitizes tumor cells to the basic chemotherapeutic agents like doxorubicin, 5-fluorouracil, and vincristine [33].

More interestingly, the low lysosomal pH stimulates the activity of a battery of resident hydrolases responsible for the degradation of various non-selective and selective cargos delivered by autophagic processes. However, the role of V-ATPase in membrane dynamics, which is required for the uptake of autophagic cargo, is far from fully understood [34]. Recently, it was found that bafilomycin disrupted autophagic flux independently of its effect on V-ATPase-mediated acidification but dependently of Ca-P60A/SERCA-mediated autophagosome–lysosome fusion [35]. Of note, V-ATPase has been unexpectedly shown to be a key regulator in various steps of endocytotic/recycling pathways. In the Wnt/β-catenin pathway, the endosomal acidic environment, provided by V-ATPase, may influence LRP6 endocytosis, phosphorylation, and β-catenin activation [36]. The V-ATPase is also required for physiological as well as pathological activation of the Notch receptor [37]. Archazolid, another V-ATPase inhibitor, leaded to a delayed recycling of the EGFR [38]. Furthermore, archazolid was shown to overcome trastuzumab resistance in breast cancer by retaining human epidermal growth factor receptor 2 (HER2) in dysfunctional vesicles of the recycling pathway and consequently abrogates HER2-signaling [39].

Altogether, V-ATPase may represent a promising target molecule or biomarker for cancer treatment. Molecular silencing and pharmacologic inhibitors of the V-ATPase exhibit desirable anti-cancer action, but such approaches may result in severe toxicity and be unfeasible and problematic [40]. In contrast, PPIs as potential V-ATPase inhibitors are expected to make contributions and progresses in clinical anti-cancer application with the safety data and convenient administration.

Anti-cancer activity of PPIs

Since the introduction of omeprazole in 1989, PPIs have steadily become the mainstays in treatment of acid-related disorders due to consistent patient tolerance, excellent safety, and superior acid suppressing capability. They are prodrugs requiring protonation for functional activation in acidic environment, accumulating selectively in acidic gastric luminal space, and ultimately inhibiting acid secretion by covalent binding with cysteine residues in α-subunit of H^+/K^+-ATPase [41]. Besides targeting the gastric proton pump, PPIs have also been shown to inhibit the V-ATPase. The initial evidence demonstrated that omeprazole bound to the cysteine residue near the nucleotide-binding domain in the subunit A, resulting in the inactivation of V-ATPase in adrenal chromaffin granules [13]. Thus, treatment with PPIs can provoke disruption of pH homeostasis in cancer

cells and exert anti-cancer effects. In addition, some studies have provided evidence for the interaction of PPIs with P-gp. PPIs inhibited P-gp-mediated digoxin efflux in Caco-2 cells [42], suggesting that PPIs might act as P-gp substrates and inhibitors. This effect of PPIs is likely to contribute to reversing MDR of tumors. Indeed, mechanisms underlying PPIs' anti-tumor activity are far from being entirely known and appear to be related to specific cancer types. Then, we will describe diverse biological effects of PPIs on different types of tumors.

Digestive system cancers

Gastric cancer

Gastric cancer remains a major health burden across the globe with an estimated 951,600 new gastric cancer cases and 723,100 deaths occurred in 2012, making it the fifth most common malignancy worldwide and the third leading cause of cancer-related deaths worldwide [43]. Early studies have shown that PPIs selectively induced in vivo and in vitro apoptotic cell death in gastric cancer [44–46]. The selective anti-cancer activity of PPIs might be related to the high expression of H^+/K^+-ATPase in cytoplasmic membrane of gastric cancer cells, which is helpful to maintain the survival of cancer cells in acidic tumor microenvironment. Therefore, gastric cancer cells were more tolerant to low pH condition than normal gastric mucosal cells that lost viability at pH below 5.9, suggesting the potential selectivity of PPIs in targeting tumor acidity [44]. Yeo et al. [44] have reported that pantoprazole induced apoptosis and decreased the cell survival rate in gastric cancer cells via p38 activation and down-regulation of p-ERK 1/2, respectively. In addition, PPI-induced apoptosis in gastric cancer cells was dependent on the activation of caspase cascade via the mitochondrial apoptotic pathway [46]. By contrast, normal gastric mucosal cells showed less sensitivity to PPI profiting from the protective effect of anti-apoptotic regulators HSP27 and HSP70 [44]. Pantoprazole also suppressed tumor growth by inhibiting HIF-1α expression and its translocation into nucleus to interact with HIF-1β in human gastric adenocarcinoma cells [47]. Moreover, pantoprazole could act as the inhibitor of the human M2 isoform of pyruvate kinase (PKM2), a key enzyme that regulates aerobic glycolysis, which is critical for rapid growth of gastric cancer cells [48]. As inhibitors of V-ATPase, PPIs had anti-proliferative, pro-apoptotic, and anti-invasive effects on gastric cancer cells through down-regulation of phospho-LRP6, β-catenin in Wnt/β-catenin signaling pathway and its target proliferation gene c-Myc, and the cell-cycle gene cyclin D1 [49]. Notably, the relationship between PPI and Wnt/β-catenin signal pathway was reported using an adriamycin-resistant gastric cancer cell model (SGC7901/ADR) coupled with enhanced migratory and invasive capability and typical epithelial-to-mesenchymal transition (EMT) phenotype, as well as strong activation of Wnt/β-catenin signaling pathway compared with parental sensitive cells [50]. Results showed that pantoprazole treatment significantly suppressed the migration and invasion via inhibiting the expression of Akt, GSK-3β, and β-catenin in SGC7901/ADR cells. Also EMT phenotype was reversed by pantoprazole, accompanied by alteration of EMT markers, such as activation of E-cadherin and concurrent inhibition of N-cadherin, Vimentin, and Snail proteins. More importantly, pantoprazole could improve the poor responsiveness of gastric tumor to the conventional chemotherapy agents which was associated with PPI-mediated decrease of the V-ATPase expression in cancer cells, resulting in the acidification of pHi and alkalinization of pHe. Reversed pH gradient not only enhanced cytotoxic effects of anti-tumor drugs such as adriamycin but also increased ADR level intracellularly [51]. Meanwhile, the V-ATPase/mTOR/HIF-1α/P-gp and MRP1 signaling pathway were down-regulated after pantoprazole administration [14]. However, the mutual relationship between any two of those proteins in the signaling pathway has not been confirmed. Another mechanism underlying PPI-induced cytotoxicity and sensitivity to cisplatin in gastric cancer cells is partially related to the inhibition of the secretion of pro-inflammatory cytokine IL-6 and the suppression of STAT3. The downstream targets of STAT3, c-Myc, cyclin D1, and Bcl-2 were also down-regulated [52].

Colorectal cancer

Colorectal cancer is the third most common cancer in males and the second in females, with an estimated 1.4 million cases and 693,900 deaths occurring in 2012 [43]. PPIs may have a chemopreventive effect on colorectal carcinogenesis by reducing inflammation. Daily injections of omeprazole (10 mg/kg) reduced the development of colorectal tumors in a mice model of colitis-induced carcinogenesis, likely based on the ability to inhibit the level of pro-inflammatory molecules such as NO, TBA-RS, IL-6, TNF-α, and the expressions of iNOS and COX-2 [53]. Decreased expressions of MMPs were also observed in omeprazole-treated mice, in accordance with significant decreases in the number of β-catenin-accumulated crypts. Notably, the chemopreventive actions of PPIs were independent of gastric acid suppression. Besides, administration of dietary omeprazole significantly inhibited chemically induced colon carcinogenesis in rats by inducing Cdk inhibitor p21 and suppressing the expression of cyclin A, survivin, and anti-apoptotic proteins Bcl-2 and Bcl-xL [54]. More interestingly, pantoprazole was found to effectively inhibited the growth of colon tumor both in vitro and in vivo by inhibiting TOPK activities and the downstream signaling molecule phospho-histone H_3. T cell-originated protein kinase (TOPK), which belongs to

MAPKK family, is highly activated in human colon cancer cells and promotes tumorigenesis and progression. The inhibition of TOPK could benefit 30–40% of colorectal cancer patients, which might represent a new avenue of investigation for targeted therapy [55]. The observation offered an alternative therapy for colorectal cancer by targeting TOPK with pantoprazole, or at least pantoprazole is a good lead compound for designing novel TOPK inhibitors [56].

Esophageal cancer

Esophageal cancer is one of the most fatal malignancies in the world with an estimated 455,800 new cases and 400,200 deaths occurred in 2012 worldwide [43]. Cisplatin- and 5-FU-based chemotherapy in combination with irradiation has become standard treatment for esophageal cancer patients. However, the resistance of tumors to anti-cancer drugs is a major obstacle to overcome in the non-surgical anti-cancer treatment of esophageal cancer. Encouraging results have been reported that esomeprazole could inhibit tumor cell survival, metastatic potential, and enhance the sensitivity towards cisplatin or 5-FU in esophageal cancer cell lines. Interestingly, esomeprazole did not lead to intracellular acidification, suggesting that the acid inhibitory effect was not the main action of PPI in esophageal cancer cell lines, while the expression of a number of resistance-relevant miRNAs has been regulated by PPI. Specifically, miR-141 and miR-200b were significantly up-regulated, whereas miR-376a was down-regulated after esomeprazole treatment in esophageal tumor cells [57]. Besides, PPIs have potential clinical use as chemoprevention agents, for example, rabeprazole protected against the development of esophageal cancer in a clinically relevant surgical rat reflux model [58]. Moreover, epidemiologic studies have shown that the long-term use of PPIs had close association with lower rates of dysplasia and esophageal adenocarcinoma in patients with Barrett's esophagus [59]. However, whether the suppression of dysplasia and adenocarcinoma depends on the anti-acid action of PPIs or not still remains to be elucidated.

Pancreatic cancer

Based on GLOBOCAN estimates, a total of 330,400 pancreatic cancer patients would die in 2012 worldwide, ranking the seventh leading cause of cancer death in men and women [43]. Relief of adverse events induced by chemotherapy is an important issue for pancreatic cancer patients, especially those with a poor prognosis. PPIs could be a potential preventive measure for chemotherapy-induced gastroesophageal reflux disease (GERD) in pancreatic cancer patients [60]. In addition, omeprazole acted as a chemosensitizer and anti-cancer agent by modulating autophagy in pancreatic cancer cells [61]. Morphologically, the accumulation of phagophores and early autophagosomes reflected not only autophagy induction but also a disturbance of the lysosomal transport system after omeprazole treatment. Omeprazole led to a dose-dependent elevation of both the LC3-I and the LC3-II fractions in pancreatic cancer cells which pointed to both strong autophagy induction and impaired turnover. A modulation of the lysosomal transport system was proved by the expression of LAMP-1, Cathepsin-D, and β-COP in lysosome- and Golgi complex containing cell fractions. However, either the autophagy itself or its role in overcoming chemoresistance remained controversial. Though omeprazole has been detected intracellularly, it did not cause a consistent change in the intralysosomal pH value of pancreatic cancer cells, revealing that there were other mechanisms for anti-tumor effects of PPI besides of V-ATPase inhibition and lysosomal pH elevation. By in silico screening of an FDA-approved drug database, PPIs were identified as effective inhibitors of the thioesterase (TE) domain of human fatty acid synthase (FASN) [62]. FASN is up-regulated in many cancers, which plays an essential role in cancer cell survival, drug resistance, and poor prognosis [63]. PPIs directly bound to the active site and inhibited FASN TE with an activity ranking of omeprazole > pantoprazole > lansoprazole > rabeprazole. Thus, cancer cell subtypes with higher FASN activity were likely more sensitive to PPIs inhibition of survival. In clinic, the quasimesenchymal pancreatic ductal adenocarcinoma (QM-PDA) is the most aggressive type of pancreatic tumors with the lowest rates of patient survival. However, omeprazole could inhibit the invasion of QM-PDA cells through a non-genomic aryl hydrocarbon receptor (AHR) pathway that did not involve ligand-induced nuclear uptake of the AHR [64], which was potentially important for QM-PDA therapy.

Breast cancer

Breast cancer is the most frequently diagnosed cancer and the most prominent cause of cancer death in women globally, with an estimated 1.67 million cases (25% of all cancers) and 521,900 deaths in 2012 worldwide [43]. As compared to other forms of breast cancer, triple negative breast cancer (estrogen, progesterone, and HER2-negative) has a more aggressive clinical course, tendency towards visceral metastases, and significantly lower survival rate with limited treatment options [65]. Encouraging results have been reported that combined treatment of triple negative breast cancer (TNBC) cells with esomeprazole increased their sensitivity to doxorubicin. Nevertheless, response of TNBC cells to esomeprazole could be mediated by gastric type proton pump (H^+/K^+ ATPase) which was contrary to the previous beliefs that gastric type proton pump expression was restricted to parietal cells of the stomach epithelia. Inhibition of H^+/K^+-ATPase caused a build-up of protons inside the

cells, lowering the intracellular pH, which decreased breast cancer cell growth and survival [66]. More evidence indicated that PPIs had an anti-neoplastic effect in human breast cancer cells through its ability to suppress the V-ATPase activity, leading to cytosolic acidification, and lysosomal and endosomal alkalinization [67, 68]. Raised endosomal pH inhibited endosomal sequestration of doxorubicin in breast cancer cells, which explained the fact that PPIs pretreatment enhanced the distribution and cytotoxicity of doxorubicin in breast cancer cells both in vitro and in vivo [68, 69]. Thus, improving tumor microenvironment could be important in future development of new breast cancer treatments. Meanwhile, lansoprazole induced a large amount of intracellular ROS accumulation, proposing that ROS played a critical role in PPI-induced cell death in breast cancer cells [67]. In addition, omeprazole may have potential clinical applications for inhibition of breast cancer metastasis due to its AHR agonist activity [70]. The anti-metastatic effect of omeprazole was linked to decreased expression of MMP-9 and AHR-dependent suppression of the pro-metastatic gene CXCR4.

Genital system cancers

Ovarian cancer

Epithelial ovarian cancer (EOC) is the leading cause of death among all gynecological cancers and the 5-year survival rate is dismal at 11% for patients with stage IV and 23–41% for patients with stage III EOC. Paclitaxel is commonly used in the first-line chemotherapy after primary cytoreductive surgery in ovarian cancer patients [71]. The data from The Cancer Genome Atlas (TCGA) have shown that higher expression of V-ATPase mRNA was significantly coupled with poor survival in ovarian cancer patients. Inhibition of V-ATPase expression by siRNA or omeprazole significantly increased the cytotoxicity of paclitaxel in paclitaxel-resistant EOC cells. Moreover, combination treatment of omeprazole and paclitaxel obviously decreased the total tumor weight compared with paclitaxel monotherapy in a chemoresistant EOC animal model and a patient-derived xenograft model of clear cell carcinoma with relatively high expression of V-ATPase [72]. These findings suggest V-ATPase as a candidate target molecule or biomarker for cancer treatment and provide a potential role for PPI as a chemosensitizer in EOC.

Prostate cancer

Prostate cancer is the most frequently diagnosed cancer among men in developed countries where about two-thirds of all prostate cancer cases occur among just 17% of the global male population in 2012 [43]. One of the key management strategies for prostate cancer is to overcome chemotherapy resistance. Pantoprazole has been shown to increase the cytotoxicity of docetaxel in human prostate cancer both in vitro and in vivo by inhibiting docetaxel-induced autophagy [73]. High levels of autophagy have been associated with resistance to chemotherapy, presumably because autophagy facilitates survival of stressed or damaged cells through recycling of cellular breakdown products [74]. Pantoprazole appeared to inhibit autophagy through a similar mechanism to the specific lysosomal V-ATPase inhibitor bafilomycin A1 which disrupts lysosomal pH regulation and thus prevent autolysosome formation and degradation of captured cytoplasmic content. In addition, pretreatment with pantoprazole increased docetaxel-induced expression of γH2AX and cleaved caspase-3, and decreased Ki67 in tumor sections, which are biomarkers in relation to functional blood vessels of PC3 xenografts. Knockdown of Beclin-1 or Atg7 increased pantoprazole-induced cytotoxicity of docetaxel, whereas the toxicity was not increased further by pantoprazole in the double knockdown cell line with absent autophagy [73]. Therefore, PPIs as inhibitors of autophagy might be considered for prostate cancer treatments combined with chemotherapy drugs and radiotherapy.

Melanoma

Melanoma is the leading cause of death from skin disease, requiring timely diagnosis and management [75]. Metastatic melanoma is associated with poor prognosis and still limited therapeutic options. An innovative treatment approach for this disease is represented by targeting acidosis, which can be implemented by PPIs inhibiting the V-H^+-ATPase activity and disturbing tumor pH gradients with major consequences on drug retention and traffic of acidic vesicles in melanoma cells [8]. Systemic esomeprazole administration dramatically prolonged survival time of melanoma-bearing animals, without any signs of systemic toxicity [30]. Indeed, the anti-tumor effects of PPIs were pH-dependent against human melanoma [30, 76]. Lansoprazole pretreatment for 24 h significantly increased the therapeutic effects of paclitaxel against human metastatic melanoma cells, exclusively when cultured in unbuffered condition, conceivably due to the reduced pH mimicking the spontaneous acidification of tumors [76]. The acidity played opposite roles in inducing an increase of the PPI activity and a decrease in paclitaxel effect. Actually, the fact that a low extracellular pH caused higher resistance to paclitaxel has ever been proved in breast cancer cell line MCF-7 [16]. An additional effect of PPI treatment on human melanoma cell lines is the autophagy modulation. Melanoma cells treated with esomeprazole rapidly accumulated autophagosomes and LC3-II protein within few hours, at the same time reducing the autophagic flux. Moreover, esomeprazole treatment caused a consistent inhibition on the mTOR signaling pathway with reduced phosphorylation of p70-S6K and 4-EBP1. Inhibition of

autophagy by knockdown of Atg5 and Beclin-1 or by bafilomycin A treatment significantly enhanced the cytotoxicity of esomeprazole, strongly indicating that autophagy may represent an adaptive survival mechanism of melanoma cells in response to PPI insult. Following by autophagy, esomeprazole induced apoptosis of melanoma cells through a caspase-dependent pathway involving cytosolic acidification and the accumulation of ROS derived from mitochondrial dysfunctions and NADPH oxidase [77]. Although belonging to the same family, PPIs have shown different anti-tumor efficacy in metastatic melanoma cells. Among them, lansoprazole revealed the highest efficacy both in vitro and in vivo, maintaining its efficacy over time even upon drug removal from the cell culture medium confirming the validity of pulse administration in clinical conditions [78].

Lymphoma

Lymphoma is the third most common childhood malignancy, accounting for approximately 15% of cancers diagnosed in children (0–14 years of age) [79]. Despite good response rates obtained from poly-chemotherapies, a relevant proportion of lymphoma patients are not cured for some reasons including chemoresistance, relapses, severe toxicity, and secondary malignancies. Fortunately, PPIs have shown varied anti-tumor effects in lymphoma. Omeprazole induced apoptosis in human lymphoblastic T cells by upregulating both caspases and lysosomal cysteine protease [80]. Moreover, omeprazole and esomeprazole induced apoptosis of human B cell lymphoma cells through the alteration of pH gradients regulation as well as ROS production, enhancement of lysosomal membrane permeabilization, and MMP. Despite the presence of active caspases in PPI-treated cells, the pan-caspase inhibitor z-VAD-fmk had no effect on PPI-induced apoptosis, suggesting that activated caspases were not instrumental in the pro-apoptotic effect of PPI on human B cell lymphoma cells [81]. Obviously, the in vivo effectiveness of PPI depended on the ability of tumor cells to acidify their environment, allowing first the drug to target tumor cells and then to be activated in situ. Pantoprazole has shown a significant retardation of tumor progression on a murine model of a transplantable Dalton's T cell lymphoma (DL) via the reversal of acidosis in tumor microenvironment to a neutral pH, which was due to the inhibition on the function of V-ATPase and another pH regulator MCT-1 in tumor cells. The down-regulation of HIF-1α genes, Bcl-2, Hsp70, GLUT-1, SOCS-5, and CD62L proteins along with an augmentation on the expression of PUMA genes, p53, and CAD proteins were observed in tumor cells after PPI treatment. Besides, the neutralization of pH following pantoprazole administration was conducive for the host's anti-tumor immune responses because of the elevation in the levels of IL-6 and IFN-γ along with an inhibition on IL-10, IL-4, and TGF-β in the ascitic fluid of pantoprazole-administered tumor-bearing mice [82]. These evidences suggest that the regulation of cellular pH may represent a suitable target for novel anti-tumor strategies and indicate the potential use of PPIs as anti-neoplastic agents towards lymphoma.

Leukemia

Leukemia is a malignant disorder resulting in impairment of blood cell production and unrestrained proliferation of immature blood cells. In 2017, 62,130 new leukemia cases and 24,500 cancer deaths are projected to occur in the United States [83]. As early as 1999, omeprazole has been shown to exert a significant potentiating effect to hypericin-mediated cytotoxicity by reducing the intracellular pH in human leukemic HL-60 cell line [7]. Besides, at low dose (13 μM), either omeprazole or esomeprazole pretreatment significantly increased the sensitivity of the pre-B acute lymphoblastic leukemia (ALL) cells to the cytotoxicity induced by vinblastine, a commonly used chemotherapeutic agent in the treatment of ALL. In addition, bone-marrow-derived leukemic blasts cells isolated from patients with ALL were remarkably sensitive to the dose-dependent apoptosis-inducing effects of omeprazole [81]. Tyrosine kinase inhibitors (TKIs), imatinib, and nilotinib are currently approved for the treatment of newly diagnosed chronic phase chronic myeloid leukemia (CP-CML) patients. It has been found that the intracellular concentration of nilotinib was significantly increased accompanying with a concomitant decrease in IC_{50} in the presence of pantoprazole which was capable of blocking ABCB1-mediated nilotinib efflux, while there was no significant effect for imatinib [84]. This result was consistent with the findings of Yin et al. [85]. These findings provided support for the clinical observation of enhanced response rates in CP-CML patients treated with nilotinib and PPIs. Moreover, PPIs can greatly prevent patients from TKI-induced gastrointestinal side effects.

Myeloma

Multiple myeloma (MM) is the second most common hematological malignancy and responsive to a limited number of therapeutic options [86]. Recent studies found that either lansoprazole or omeprazole showed direct cytotoxicity against human myeloma cell lines in buffered medium at pH 6.5, an acidic condition that approximated the pH values observed in tumors and allowed a full activation of PPIs [87]. Notably, omeprazole had less cytotoxicity than lansoprazole. Moreover, most of the myeloma cells died of an apoptotic-like cell death rather than necrosis after the exposure to lansoprazole, while preincubation with the pan-caspase inhibitor z-VAD-fmk had no significant effect on lansoprazole-induced cytotoxicity of MM cells. This

suggested that activated caspases were not instrumental for lansoprazole-induced apoptosis in human myeloma cell lines, indicating that a different pathway might be responsible for the cytotoxicity of lansoprazole.

Osteosarcoma

Osteosarcoma is a rare tumor with an overall incidence of 0.2/100,000 new cases/year. It is more frequently diagnosed in adolescents and young adults where it accounts for >10% of all solid cancers [88]. The most effective drugs used for treatment of osteosarcoma include cisplatin, doxorubicin, and methotrexate. However, resistance towards these chemotherapeutic agents is responsible for the failure of the osteosarcoma treatment [89]. Ferrari et al. [90] presented preclinical and clinical data to evaluate the activity of esomeprazole as chemosensitizer against human osteosarcoma. The fact that pretreatment of esomeprazole for 24 h significantly increased the activity of cisplatin in osteosarcoma both in vitro and in vivo, as well as credible clinical trial data, strongly supported the use of PPI as adjunct treatment for osteosarcoma patients.

Clinical investigations

PPIs have been met with outstanding success in preclinical studies both in vitro and in vivo. Several clinical trials have been performed and others are currently underway. For instance, studies observed the use of esomeprazole as chemosensitizer in neoadjuvant chemotherapy for the treatment of osteosarcoma [90] and as combination treatment with doublet TP regimen (docetaxel and cisplatin) in metastatic breast cancer (Clinical Trials. gov Identifier: NCT01069081) [91]. It has been shown that pretreatment of cancer patients with esomeprazole prior to chemotherapy was effective and PPI administration had no additional toxicity in patients. Recently, a phase I study demonstrated that administration of high-dose pantoprazole prior to doxorubicin was feasible in patients with advanced solid tumors (NCT01163903) [92]. Patients with advanced solid tumors ($n = 24$) received doxorubicin 60 mg/m^2 and escalating doses of pantoprazole (80, 160, 240, and 360 mg) administered intravenously prior to doxorubicin. Dose-level 4 (pantoprazole 360 mg) was considered to exceed the maximum tolerated dose. The median maximum serum concentration after injection of pantoprazole 240 mg was 84.3 μM, which was close to the concentration shown previously to enhance doxorubicin activity in human tumor xenografts. Fatigue, neutropenia, and leukopenia were the most common treatment-related adverse events, similar to those that were expected following treatment with doxorubicin alone. Repeated intravenous administration of pantoprazole 240 mg did not pose any apparent additional safety risk when coupled with doxorubicin. Therefore, the recommended phase II dose of pantoprazole, 240 mg, would be evaluated in combination with docetaxel in patients with castration-resistant prostate cancer (NCT01748500). In this trial, autophagy markers would be detected using IHC for LC3B, ATG5, and p62 as well as ERG to evaluate pharmacokinetic interactions of pantoprazole with docetaxel (http://clinicaltrials.gov/). More recently, a phase II study evaluating the effectiveness of combination of rabeprazole with capecitabine at metronomic dosage of 1500 mg/die (mCAP) as salvage treatment for patients with advanced gastrointestinal tumors was performed in Italy [93]. Positive results suggested that combination of mCAP and PPI was likely to present therapeutic hope for patients who cannot resort to more standard treatments. In addition, based on the preliminary laboratory investigations showing that PPIs effectively inhibited human FASN [62], a phase II clinical trial known as "Inhibiting Fatty Acid Synthase to Improve Efficacy of Neoadjuvant Chemotherapy" (NCT02595372) is under planning and currently recruiting participants.

There are also two phase I/II studies in companion animals with spontaneously occurring tumors to evaluate the feasibility of modulating the acidic tumor microenvironment by PPIs [94, 95]. Results were very positive as the treatment with PPIs resulted in the down staging of tumors for the vast majority of the animals, suggesting that alkalinization of advanced cancer patients will probably become an adopted strategy in veterinary oncology due to its low cost, better tumor control, and limited toxicity. However, very little is known as to whether cancers in animals share the same pathological characteristics with that in human regarding tumor microenvironment.

Perspectives and conclusions

This review has pointed out the novel anti-tumor effects of gastric PPIs, and extended the clinical application as anticancer agents by targeting V-ATPase or other molecular targets on cancer cells (Figs. 1, 2). Still, several issues remain controversial. First, to date, the revealed molecular mechanisms underlying anti-cancer effects of PPIs are far from conclusive. PPIs were found to have impact on the pathways that were actually involved in the effect of tumor acidity, including Wnt/β-catenin, mTOR, HIF-1α, P-gp, and MAPK subfamily (p38 and ERK). In the meantime, PPIs could also interact with acidity-unrelated proteins such as PKM2, TOPK, AHR, and FASN. The V-ATPase is recognized as the novel target of PPIs, which has been confirmed in various tumors. Other molecular targets are limited to certain tumors and need further studies and exploration. Second, it is known that PPIs are prodrugs requiring activation in acidic environment. However, PPIs were also effective in vitro when a

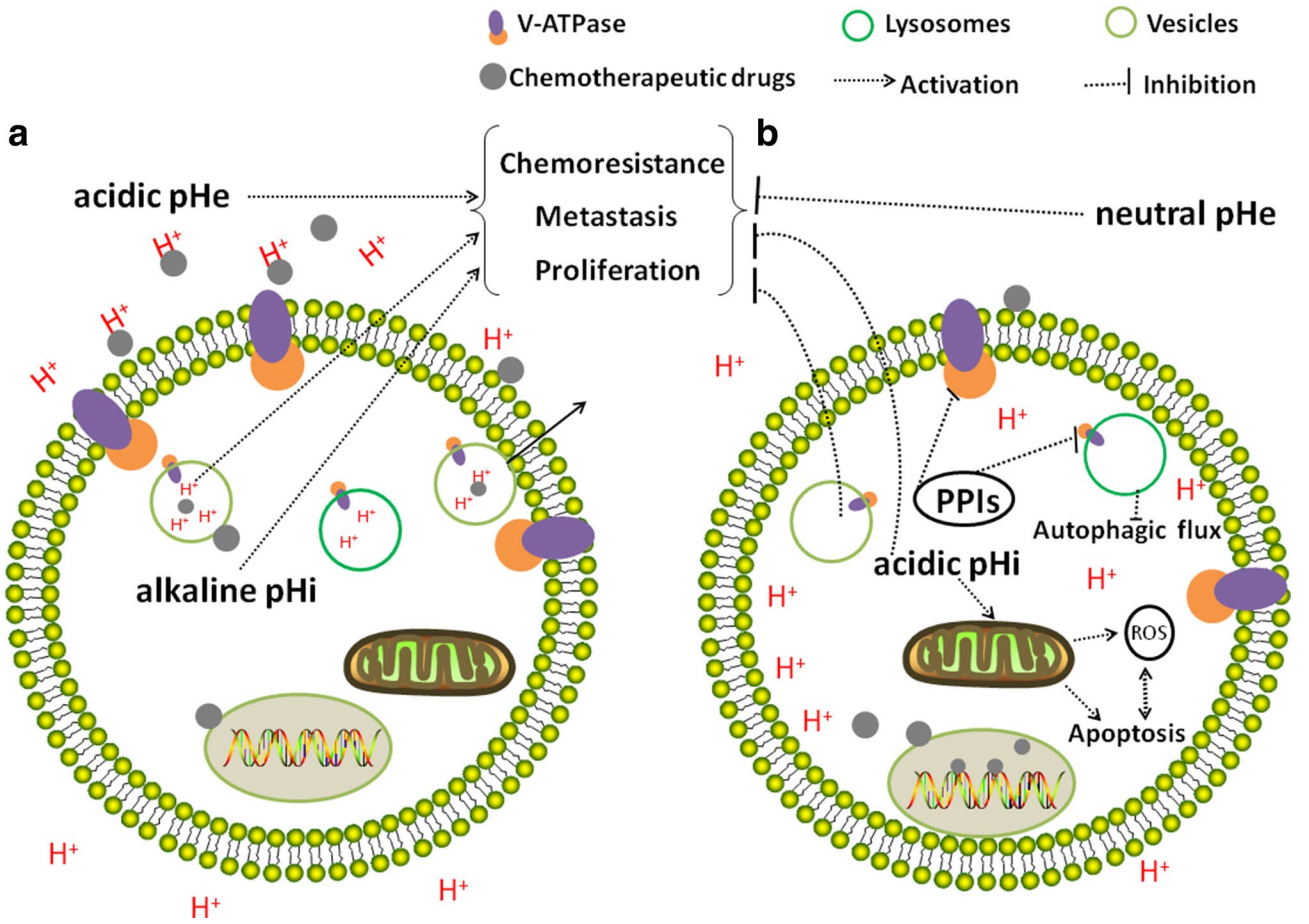

Fig. 1 Molecular mechanism of PPIs targeting V-ATPase on the plasma membrane and acidic organelle membranes of cancer cells. **a** In cancer cells, the extrusion of protons by V-ATPase causes intracellular alkalinization and extracellular acidification, which are important mechanisms favoring proliferation, metastasis, and chemoresistance of cancer cells. **b** PPIs treatment might provoke disruption of pH homeostasis by inhibiting the activity of V-ATPase, thus depriving them of malignant behaviors. Besides, PPI-induced intracellular acidification contributes to the accumulation of ROS and pro-apoptosis through mitochondrial dysfunction in cancer cells. The disturbance of the lysosomal pH regulation by PPIs leads to reduced autophagic flux

"physiological" pH of the medium (7.4) was used [47, 57, 61, 70]. This indicated that some other targets might exist for PPIs in tumor cells besides activating in acidic intracellular compartments. Third, the required concentration of PPIs in vitro for anti-cancer purpose was higher than that in the clinical treatment of acid-related diseases. This gastroprotective dose of PPIs would probably be insufficient to elicit anti-tumor effects in vitro. Actually, most in vitro studies did not consider some microenvironmental factors that may affect drug distribution in solid tumors. It is believed that PPIs may achieve higher local concentrations at tumor site. Moreover, patients with advanced solid tumors have shown good tolerability when treated with PPIs at relatively high doses of up to 240 mg [92]. Fourth, drug interactions in pharmacokinetics must be considered when combining PPIs with anti-cancer drugs. Omeprazole are primarily metabolized by cytochrome P450 (CYP450) enzymes with high affinity. It has, therefore, been suggested that omeprazole might enhance the effect of anti-cancer agents which are also metabolized by CYP enzymes. However, until now, it has not been found that PPIs alter the pharmacokinetics and toxicities of anti-cancer agents. Therefore, the synergy between PPIs and anti-cancer drugs is based on pharmacodynamics rather than pharmacokinetics. Fifth, while belonging to the same family of generic drugs, PPIs show different anti-tumor effects. Prior studies have described that lansoprazole has shown higher anti-tumor effect, compared to other PPIs [67, 78]. However, the conclusion should be taken with caution in view of both the physiochemistry of different PPIs such as pKa values and the pathological characteristics of various tumors. Last but not least, despite being overall safe drugs, several long-term adverse effects are associated with PPIs, particularly regarding the possibly higher risk of gastric cancer caused by PPIs. Some case reports suggested that the long-term use of PPIs could promote the development of gastric pre-malignant lesions with a potentially increased

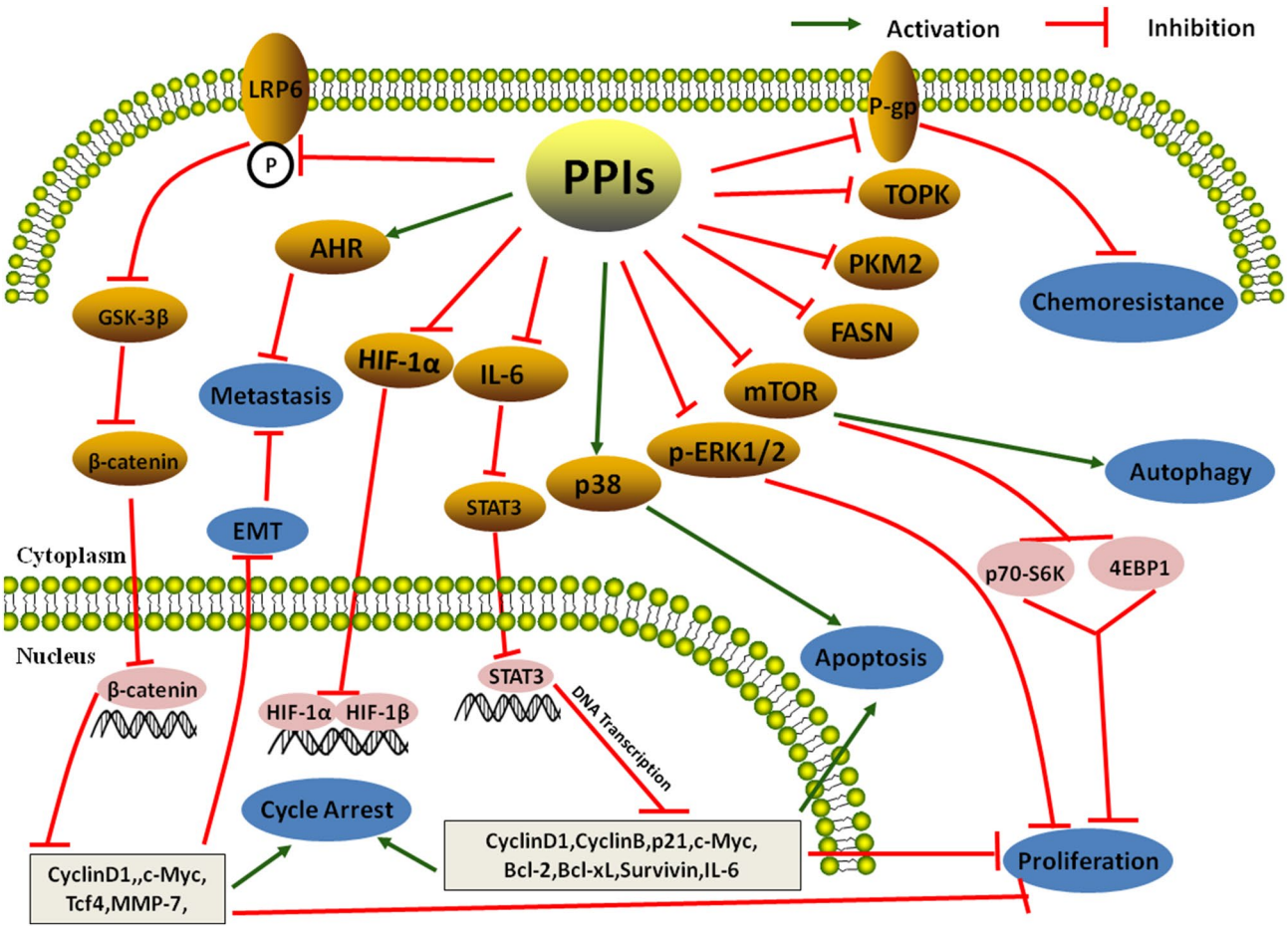

Fig. 2 PPIs regulate some intracellular signaling pathways which are associated with their anti-cancer effects. *TOPK* T cell-originated protein kinase, *PKM2* M2 isoform of pyruvate kinase, *FASN* fatty acid synthase, *HIF-1α* hypoxia-inducible factor-1α, *AHR* aryl hydrocarbon receptor, *EMT* epithelial-to-mesenchymal transition

incidence of gastric cancer [96–98]. Nevertheless, the value of such studies was limited by patient selection and other possible biases (due to patient characteristics and contemporary use of other drugs).

In summary, PPIs may be repositioned as new anti-cancer drugs for at least three important features: (1) the potential selectivity in targeting tumor acidity where they can be converted to the active drugs, (2) the ability to inhibit mechanism pivotal for cancer homeostasis, and (3) the known pharmacokinetics, toxicology, and safety profiles. Nevertheless, more preclinical and clinical trials are needed to provide more precise molecular mode of action for targeted therapies of PPIs in cancer, and to conform the compatibility of drugs, efficacy, and adverse events.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Tobinick EL (2009) The value of drug repositioning in the current pharmaceutical market. Drug News Perspect 22(2):119–125. doi:10.1358/dnp.2009.22.2.1303818
2. Rothwell PM, Price JF, Fowkes FG et al (2012) Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 379(9826):1602–1612. doi:10.1016/S0140-6736(11)61720-0
3. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z (2012) Effect of daily aspirin on risk of cancer metastasis: a study

of incident cancers during randomised controlled trials. Lancet 379(9826):1591–1601. doi:10.1016/S0140-6736(12)60209-8
4. Wurth R, Thellung S, Bajetto A, Mazzanti M, Florio T, Barbieri F (2016) Drug-repositioning opportunities for cancer therapy: novel molecular targets for known compounds. Drug Discov Today 21(1):190–199. doi:10.1016/j.drudis.2015.09.017
5. Kwon D, Chae JB, Park CW et al (2001) Effects of IY-81149, a newly developed proton pump inhibitor, on gastric acid secretion in vitro and in vivo. Arzneimittelforschung 51(3):204–213. doi:10.1055/s-0031-1300026
6. Ji XQ, Du JF, Chen G, Chen G, Yu B (2014) Efficacy of ilaprazole in the treatment of duodenal ulcers: a meta-analysis. World J Gastroenterol 20(17):5119–5123. doi:10.3748/wjg.v20.i17.5119
7. Mirossay L, Mirossay A, Kocisova E, Radvakova I, Miskovsky P, Mojzis J (1999) Hypericin-induced phototoxicity of human leukemic cell line HL-60 is potentiated by omeprazole, an inhibitor of H^+K^+-ATPase and 5′-(N, N-dimethyl)-amiloride, an inhibitor of Na^+/H^+ exchanger. Physiol Res 48(2):135–141
8. Luciani F, Spada M, De Milito A et al (2004) Effect of proton pump inhibitor pretreatment on resistance of solid tumors to cytotoxic drugs. J Natl Cancer Inst 96(22):1702–1713. doi:10.1093/jnci/djh305
9. Breedveld P, Zelcer N, Pluim D et al (2004) Mechanism of the pharmacokinetic interaction between methotrexate and benzimidazoles: potential role for breast cancer resistance protein in clinical drug–drug interactions. Cancer Res 64(16):5804–5811. doi:10.1158/0008-5472.CAN-03-4062
10. Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 324(5930):1029–1033. doi:10.1126/science.1160809
11. Neri D, Supuran CT (2011) Interfering with pH regulation in tumors as a therapeutic strategy. Nat Rev Drug Discov 10(10):767–777. doi:10.1038/nrd3554
12. Fais S, De Milito A, You H, Qin W (2007) Targeting vacuolar H^+-ATPases as a new strategy against cancer. Cancer Res 67(22):10627–10630. doi:10.1158/0008-5472.CAN-07-1805
13. Moriyama Y, Patel V, Ueda I, Futai M (1993) Evidence for a common binding site for omeprazole and N-ethylmaleimide in subunit A of chromaffin granule vacuolar-type H(+)-ATPase. Biochem Biophys Res Commun 196(2):699–706. doi:10.1006/bbrc.1993.2306
14. Chen M, Huang SL, Zhang XQ, Zhang B, Zhu H, Yang VW, Zou XP (2012) Reversal effects of pantoprazole on multidrug resistance in human gastric adenocarcinoma cells by down-regulating the V-ATPases/mTOR/HIF-1α/P-gp and MRP1 signaling pathway in vitro and in vivo. J Cell Biochem 113(7):2474–2487. doi:10.1002/jcb.24122
15. Spugnini EP, Citro G, Fais S (2010) Proton pump inhibitors as anti vacuolar-ATPases drugs: a novel anticancer strategy. J Exp Clin Cancer Res 29:44. doi:10.1186/1756-9966-29-44
16. Tavares-Valente D, Baltazar F, Moreira R, Queiros O (2013) Cancer cell bioenergetics and pH regulation influence breast cancer cell resistance to paclitaxel and doxorubicin. J Bioenerg Biomembr 45(5):467–475. doi:10.1007/s10863-013-9519-7
17. Abaza M, Luqmani YA (2013) The influence of pH and hypoxia on tumor metastasis. Expert Rev Anticancer Ther 13(10):1229–1242. doi:10.1586/14737140.2013.843455
18. Bellone M, Calcinotto A, Filipazzi P, De Milito A, Fais S, Rivoltini L (2013) The acidity of the tumor microenvironment is a mechanism of immune escape that can be overcome by proton pump inhibitors. Oncoimmunology 2(1):e22058. doi:10.4161/onci.22058
19. Song CW, Griffin R, Park HJ (2006) Influence of tumor pH on therapeutic response. In Teicher BA (ed) Cancer drug discovery and development: cancer drug resistance. Humana Press, Totowa, NJ, pp 21–42. doi:10.1007/978-1-59745-035-5_2
20. Park H, Lyons JC, Griffin RJ, Lim BU, Song CW (2000) Apoptosis and cell cycle progression in an acidic environment after irradiation. Radiat Res 153(3):295–304. doi:10.1038/sj.cdd.4400702
21. Park HJ, Lee SH, Chung H et al (2003) Influence of environmental pH on G2-phase arrest caused by ionizing radiation. Radiat Res 159(1):86–93. doi:10.1667/0033-7587(2003)159[0086:IOEPOG]2.0.CO;2
22. Lunt SJ, Chaudary N, Hill RP (2009) The tumor microenvironment and metastatic disease. Clin Exp Metastasis 26(1):19–34. doi:10.1007/s10585-008-9182-2
23. De Milito A, Fais S (2005) Tumor acidity, chemoresistance and proton pump inhibitors. Future Oncol 1(6):779–786. doi:10.2217/14796694.1.6.779
24. Thews O, Gassner B, Kelleher DK, Schwerdt G, Gekle M (2006) Impact of extracellular acidity on the activity of P-glycoprotein and the cytotoxicity of chemotherapeutic drugs. Neoplasia 8(2):143–152. doi:10.1593/neo.05697
25. Nishi T, Forgac M (2002) The vacuolar (H^+)-ATPases—nature's most versatile proton pumps. Nat Rev Mol Cell Biol 3(2):94–103. doi:10.1038/nrm729
26. Lu X, Qin W, Li J et al (2005) The growth and metastasis of human hepatocellular carcinoma xenografts are inhibited by small interfering RNA targeting to the subunit ATP6L of proton pump. Cancer Res 65(15):6843–6849. doi:10.1158/0008-5472.CAN-04-3822
27. Lim JH, Park JW, Kim MS, Park SK, Johnson RS, Chun YS (2006) Bafilomycin induces the p21-mediated growth inhibition of cancer cells under hypoxic conditions by expressing hypoxia-inducible factor-1α. Mol Pharmacol 70(6):1856–1865. doi:10.1124/mol.106.028076
28. Nakashima S, Hiraku Y, Tada-Oikawa S et al (2003) Vacuolar H^+-ATPase inhibitor induces apoptosis via lysosomal dysfunction in the human gastric cancer cell line MKN-1. J Biochem 134(3):359–364. doi:10.1093/jb/mvg153
29. Sennoune SR, Bakunts K, Martinez GM, Chua-Tuan JL, Kebir Y, Attaya MN, Martinez-Zaguilan R (2004) Vacuolar H^+-ATPase in human breast cancer cells with distinct metastatic potential: distribution and functional activity. Am J Physiol Cell Physiol 286(6):C1443–C1452. doi:10.1152/ajpcell.00407.2003
30. De Milito A, Canese R, Marino ML et al (2010) pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity. Int J Cancer 127(1):207–219. doi:10.1002/ijc.25009
31. Perez-Sayans M, Somoza-Martin JM, Barros-Angueira F, Diz PG, Rey JM, Garcia-Garcia A (2010) Multidrug resistance in oral squamous cell carcinoma: the role of vacuolar ATPases. Cancer Lett 295(2):135–143. doi:10.1016/j.canlet.2010.03.019
32. Murakami T, Shibuya I, Ise T et al (2001) Elevated expression of vacuolar proton pump genes and cellular pH in cisplatin resistance. Int J Cancer 93(6):869–874. doi:10.1002/ijc.1418
33. You H, Jin J, Shu H et al (2009) Small interfering RNA targeting the subunit ATP6L of proton pump V-ATPase overcomes chemoresistance of breast cancer cells. Cancer Lett 280(1):110–119. doi:10.1016/j.canlet.2009.02.023
34. Mijaljica D, Prescott M, Devenish RJ (2011) V-ATPase engagement in autophagic processes. Autophagy 7(6):666–668. doi:10.4161/auto.7.6.15812
35. Mauvezin C, Neufeld TP (2015) Bafilomycin A1 disrupts autophagic flux by inhibiting both V-ATPase-dependent acidification and Ca-P60A/SERCA-dependent autophagosome-lysosome fusion. Autophagy 11(8):1437–1438. doi:10.1080/15548627.2015.1066957
36. Cruciat CM, Ohkawara B, Acebron SP, Karaulanov E, Reinhard C, Ingelfinger D, Boutros M, Niehrs C (2010) Requirement of prorenin receptor and vacuolar H^+-ATPase-mediated acidification for Wnt signaling. Science 327(5964):459–463. doi:10.1126/science.1179802

37. Vaccari T, Duchi S, Cortese K, Tacchetti C, Bilder D (2010) The vacuolar ATPase is required for physiological as well as pathological activation of the Notch receptor. Development 137(11):1825–1832. doi:10.1242/dev.045484
38. Wiedmann RM, von Schwarzenberg K, Palamidessi A et al (2012) The V-ATPase-inhibitor archazolid abrogates tumor metastasis via inhibition of endocytic activation of the Rho-GTPase Rac1. Cancer Res 72(22):5976–5987. doi:10.1158/0008-5472.CAN-12-1772
39. von Schwarzenberg K, Lajtos T, Simon L, Muller R, Vereb G, Vollmar AM (2014) V-ATPase inhibition overcomes trastuzumab resistance in breast cancer. Mol Oncol 8(1):9–19. doi:10.1016/j.molonc.2013.08.011
40. Perez-Sayans M, Somoza-Martin JM, Barros-Angueira F, Rey JM, Garcia-Garcia A (2009) V-ATPase inhibitors and implication in cancer treatment. Cancer Treat Rev 35(8):707–713. doi:10.1016/j.ctrv.2009.08.003
41. Sachs G, Shin JM, Howden CW (2006) Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 23(Suppl 2):2–8. doi:10.1111/j.1365-2036.2006.02943.x
42. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF (2001) Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol 364(6):551–557. doi:10.1007/s00210-001-0489-7
43. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65(2):87–108. doi:10.3322/caac.21262
44. Yeo M, Kim DK, Kim YB, Oh TY, Lee JE, Cho SW, Kim HC, Hahm KB (2004) Selective induction of apoptosis with proton pump inhibitor in gastric cancer cells. Clin Cancer Res 10(24):8687–8696. doi:10.1158/1078-0432.CCR-04-1065
45. Gu M, Zhang Y, Zhou X, Ma H, Yao H, Ji F (2014) Rabeprazole exhibits antiproliferative effects on human gastric cancer cell lines. Oncol Lett 8(4):1739–1744. doi:10.3892/ol.2014.2354
46. Yeo M, Kim DK, Park HJ, Cho SW, Cheong JY, Lee KJ (2008) Retraction: blockage of intracellular proton extrusion with proton pump inhibitor induces apoptosis in gastric cancer. Cancer Sci 99(1):185. doi:10.1111/j.1349-7006.2007.00642.x
47. Shen Y, Wu Y, Chen M, Shen W, Huang S, Zhang L, Zou X (2012) Effects of pantoprazole as a HIF-1α inhibitor on human gastric adenocarcinoma sgc-7901 cells. Neoplasma 59(2):142–149. doi:10.4149/neo_2012_019
48. Shen Y, Chen M, Huang S, Zou X (2016) Pantoprazole inhibits human gastric adenocarcinoma SGC-7901 cells by downregulating the expression of pyruvate kinase M2. Oncol Lett 11(1):717–722. doi:10.3892/ol.2015.3912
49. Shen W, Zou X, Chen M, Shen Y, Huang S, Guo H, Zhang L, Liu P (2013) Effect of pantoprazole on human gastric adenocarcinoma SGC7901 cells through regulation of phosphor-LRP6 expression in Wnt/β-catenin signaling. Oncol Rep 30(2):851–855. doi:10.3892/or.2013.2524
50. Zhang B, Yang Y, Shi X et al (2015) Proton pump inhibitor pantoprazole abrogates adriamycin-resistant gastric cancer cell invasiveness via suppression of Akt/GSK-β/β-catenin signaling and epithelial-mesenchymal transition. Cancer Lett 356(2):704–712. doi:10.1016/j.canlet.2014.10.016
51. Chen M, Zou X, Luo H, Cao J, Zhang X, Zhang B, Liu W (2009) Effects and mechanisms of proton pump inhibitors as a novel chemosensitizer on human gastric adenocarcinoma (SGC7901) cells. Cell Biol Int 33(9):1008–1019. doi:10.1016/j.cellbi.2009.05.004
52. Huang S, Chen M, Ding X, Zhang X, Zou X (2013) Proton pump inhibitor selectively suppresses proliferation and restores the chemosensitivity of gastric cancer cells by inhibiting STAT3 signaling pathway. Int Immunopharmacol 17(3):585–592. doi:10.1016/j.intimp.2013.07.021
53. Kim YJ, Lee JS, Hong KS, Chung JW, Kim JH, Hahm KB (2010) Novel application of proton pump inhibitor for the prevention of colitis-induced colorectal carcinogenesis beyond acid suppression. Cancer Prev Res (Phila) 3(8):963–974. doi:10.1158/1940-6207.CAPR-10-0033
54. Patlolla JM, Zhang Y, Li Q, Steele VE, Rao CV (2012) Anti-carcinogenic properties of omeprazole against human colon cancer cells and azoxymethane-induced colonic aberrant crypt foci formation in rats. Int J Oncol 40(1):170–175. doi:10.3892/ijo.2011.1214
55. Zlobec I, Molinari F, Kovac M et al (2010) Prognostic and predictive value of TOPK stratified by KRAS and BRAF gene alterations in sporadic, hereditary and metastatic colorectal cancer patients. Br J Cancer 102(1):151–161. doi:10.1038/sj.bjc.6605452
56. Zeng X, Liu L, Zheng M et al (2016) Pantoprazole, an FDA-approved proton-pump inhibitor, suppresses colorectal cancer growth by targeting T-cell-originated protein kinase. Oncotarget 7(16):22460–22473. doi:10.18632/oncotarget.7984
57. Lindner K, Borchardt C, Schopp M, Burgers A, Stock C, Hussey DJ, Haier J, Hummel R (2014) Proton pump inhibitors (PPIs) impact on tumour cell survival, metastatic potential and chemotherapy resistance, and affect expression of resistance-relevant miRNAs in esophageal cancer. J Exp Clin Cancer Res 33:73. doi:10.1186/s13046-014-0073-x
58. Miyashita T, Shah FA, Marti GP et al (2011) Rabeprazole impedes the development of reflux-induced esophageal cancer in a surgical rat model. Dig Dis Sci 56(5):1309–1314. doi:10.1007/s10620-010-1465-1
59. El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE (2004) Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. Am J Gastroenterol 99(10):1877–1883. doi:10.1111/j.1572-0241.2004.30228.x
60. Uwagawa T, Misawa T, Iida T, Sakamoto T, Gocho T, Wakiyama S, Hirohara S, Yanaga K (2010) Proton-pump inhibitor as palliative care for chemotherapy-induced gastroesophageal reflux disease in pancreatic cancer patients. J Palliat Med 13(7):815–818. doi:10.1089/jpm.2009.0404
61. Udelnow A, Kreyes A, Ellinger S et al (2011) Omeprazole inhibits proliferation and modulates autophagy in pancreatic cancer cells. PLoS One 6(5):e20143. doi:10.1371/journal.pone.0020143
62. Fako VE, Wu X, Pflug B, Liu JY, Zhang JT (2015) Repositioning proton pump inhibitors as anticancer drugs by targeting the thioesterase domain of human fatty acid synthase. J Med Chem 58(2):778–784. doi:10.1021/jm501543u
63. Alo PL, Amini M, Piro F et al (2007) Immnunohistochemical expression and prognostic significance of fatty acid synthase in pancreatic carcinoma. Anticancer Res 27(4B):2523–2527
64. Jin UH, Kim SB, Safe S (2015) Omeprazole inhibits pancreatic cancer cell invasion through a nongenomic aryl hydrocarbon receptor pathway. Chem Res Toxicol 28(5):907–918. doi:10.1021/tx5005198
65. Dent R, Trudeau M, Pritchard KI et al (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 13(15 Pt 1):4429–4434. doi:10.1158/1078-0432.CCR-06-3045
66. Goh W, Sleptsova-Freidrich I, Petrovic N (2014) Use of proton pump inhibitors as adjunct treatment for triple-negative breast cancers. An introductory study. J Pharm Pharm Sci 17(3):439–446
67. Zhang S, Wang Y, Li SJ (2014) Lansoprazole induces apoptosis of breast cancer cells through inhibition of intracellular proton extrusion. Biochem Biophys Res Commun 448(4):424–429. doi:10.1016/j.bbrc.2014.04.127
68. Yu M, Lee C, Wang M, Tannock IF (2015) Influence of the proton pump inhibitor lansoprazole on distribution and activity of doxorubicin in solid tumors. Cancer Sci 106(10):1438–1447. doi:10.1111/cas.12756
69. Patel KJ, Lee C, Tan Q, Tannock IF (2013) Use of the proton pump inhibitor pantoprazole to modify the distribution and activity of

doxorubicin: a potential strategy to improve the therapy of solid tumors. Clin Cancer Res 19(24):6766–6776. doi:10.1158/1078-0432.CCR-13-0128
70. Jin UH, Lee SO, Pfent C, Safe S (2014) The aryl hydrocarbon receptor ligand omeprazole inhibits breast cancer cell invasion and metastasis. BMC Cancer 14:498. doi:10.1186/1471-2407-14-498
71. Matsuo K, Lin YG, Roman LD, Sood AK (2010) Overcoming platinum resistance in ovarian carcinoma. Expert Opin Investig Drugs 19(11):1339–1354. doi:10.1517/13543784.2010.515585
72. Lee YY, Jeon HK, Hong JE et al (2015) Proton pump inhibitors enhance the effects of cytotoxic agents in chemoresistant epithelial ovarian carcinoma. Oncotarget 6(33):35040–35050. doi:10.18632/oncotarget.5319
73. Tan Q, Joshua AM, Saggar JK et al (2015) Effect of pantoprazole to enhance activity of docetaxel against human tumour xenografts by inhibiting autophagy. Br J Cancer 112(5):832–840. doi:10.1038/bjc.2015.17
74. Yang ZJ, Chee CE, Huang S, Sinicrope FA (2011) The role of autophagy in cancer: therapeutic implications. Mol Cancer Ther 10(9):1533–1541. doi:10.1158/1535-7163.MCT-11-0047
75. Karavan M, Compton N, Knezevich S, Raugi G, Kodama S, Taylor L, Reiber GE (2014) Teledermatology in the diagnosis of melanoma. J Telemed Telecare 20(1):18–23. doi:10.1177/1357633X13517354
76. Azzarito T, Venturi G, Cesolini A, Fais S (2015) Lansoprazole induces sensitivity to suboptimal doses of paclitaxel in human melanoma. Cancer Lett 356(2 Pt B):697–703. doi:10.1016/j.Canlet.2014.10.017
77. Marino ML, Fais S, Djavaheri-Mergny M et al (2010) Proton pump inhibition induces autophagy as a survival mechanism following oxidative stress in human melanoma cells. Cell Death Dis 1:e87. doi:10.1038/cddis.2010.67
78. Lugini L, Federici C, Borghi M, Azzarito T, Marino ML, Cesolini A, Spugnini EP, Fais S (2016) Proton pump inhibitors while belonging to the same family of generic drugs show different antitumor effect. J Enzyme Inhib Med Chem 31(4):538–545. doi:10.3109/14756366.2015.1046062
79. Marcotte EL, Ritz B, Cockburn M, Clarke CA, Heck JE (2014) Birth characteristics and risk of lymphoma in young children. Cancer Epidemiol 38(1):48–55. doi:10.1016/j.canep.2013.11.005
80. Scaringi L, Cornacchione P, Ayroldi E, Corazzi L, Capodicasa E, Rossi R, Marconi P (2004) Omeprazole induces apoptosis in jurkat cells. Int J Immunopathol Pharmacol 17(3):331–342. doi:10.1177/039463200401700313
81. De Milito A, Iessi E, Logozzi M et al (2007) Proton pump inhibitors induce apoptosis of human B-cell tumors through a caspase-independent mechanism involving reactive oxygen species. Cancer Res 67(11):5408–5417. doi:10.1158/0008-5472.CAN-06-4095
82. Vishvakarma NK, Singh SM (2011) Mechanisms of tumor growth retardation by modulation of pH regulation in the tumor-microenvironment of a murine T cell lymphoma. Biomed Pharmacother 65(1):27–39. doi:10.1016/j.biopha.2010.06.012
83. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67(1):7–30. doi:10.3322/caac.21387
84. White DL, Eadie LN, Saunders VA, Hiwase DK, Hughes TP (2013) Proton pump inhibitors significantly increase the intracellular concentration of nilotinib, but not imatinib in target CML cells. Leukemia 27(5):1201–1204. doi:10.1038/leu.2012.295
85. Yin OQ, Giles FJ, Baccarani M et al (2012) Concurrent use of proton pump inhibitors or H2 blockers did not adversely affect nilotinib efficacy in patients with chronic myeloid leukemia. Cancer Chemother Pharmacol 70(2):345–350. doi:10.1007/s00280-012-1881-3
86. Dimopoulos MA, San-Miguel JF, Anderson KC (2011) Emerging therapies for the treatment of relapsed or refractory multiple myeloma. Eur J Haematol 86(1):1–15. doi:10.1111/j.1600-0609.2010.01542.x
87. Canitano A, Iessi E, Spugnini EP, Federici C, Fais S (2016) Proton pump inhibitors induce a caspase-independent antitumor effect against human multiple myeloma. Cancer Lett 376(2):278–283. doi:10.1016/j.canlet.2016.04.015
88. Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, Casali PG (2013) Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer 49(3):684–695. doi:10.1016/j.ejca.2012.09.011
89. Marina N, Gebhardt M, Teot L, Gorlick R (2004) Biology and therapeutic advances for pediatric osteosarcoma. Oncologist 9(4):422–441. doi:10.1634/theoncologist.9-4-422
90. Ferrari S, Perut F, Fagioli F et al (2013) Proton pump inhibitor chemosensitization in human osteosarcoma: from the bench to the patients' bed. J Transl Med 11:268. doi:10.1186/1479-5876-11-268
91. Wang BY, Zhang J, Wang JL et al (2015) Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. J Exp Clin Cancer Res 34:85. doi:10.1186/s13046-015-0194-x
92. Brana I, Ocana A, Chen EX et al (2014) A phase I trial of pantoprazole in combination with doxorubicin in patients with advanced solid tumors: evaluation of pharmacokinetics of both drugs and tissue penetration of doxorubicin. Invest New Drugs 32(6):1269–1277. doi:10.1007/s10637-014-0159-5
93. Marchetti P, Milano A, D'Antonio C, Romiti A, Falcone R, Roberto M, Fais S (2016) Association between proton pump inhibitors and metronomic capecitabine as salvage treatment for patients with advanced gastrointestinal tumors: a randomized phase II trial. Clin Colorectal Cancer 15(4):377–380. doi:10.1016/j.clcc.2016.06.005
94. Spugnini EP, Baldi A, Buglioni S et al (2011) Lansoprazole as a rescue agent in chemoresistant tumors: a phase I/II study in companion animals with spontaneously occurring tumors. J Transl Med 9:221. doi:10.1186/1479-5876-9-221
95. Spugnini EP, Buglioni S, Carocci F, Francesco M, Vincenzi B, Fanciulli M, Fais S (2014) High dose lansoprazole combined with metronomic chemotherapy: a phase I/II study in companion animals with spontaneously occurring tumors. J Transl Med 12:225. doi:10.1186/s12967-014-0225-y
96. Attila T, Santharam R, Blom D, Komorowski R, Koch TR (2005) Multifocal gastric carcinoid tumor in a patient with pernicious anemia receiving lansoprazole. Dig Dis Sci 50(3):509–513. doi:10.1007/s10620-005-2466-3
97. Jianu CS, Lange OJ, Viset T et al (2012) Gastric neuroendocrine carcinoma after long-term use of proton pump inhibitor. Scand J Gastroenterol 47(1):64–67. doi:10.3109/00365521.2011.627444
98. Ko Y, Tang J, Sanagapalli S, Kim BS, Leong RW (2016) Safety of proton pump inhibitors and risk of gastric cancers: review of literature and pathophysiological mechanisms. Expert Opin Drug Saf 15(1):53–63. doi:10.1517/14740338.2016.1118050