

Review

# Towards an integral therapeutic protocol for Breast Cancer based upon the new H<sup>+</sup>-centered anticancer paradigm of the late post-Warburg era

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**Abstract:** A brand-new approach to the understanding of breast cancer (BC) is urgently needed. In this contribution, the etiology, pathogenesis, and treatment of this disease is approached from the new pH-centric anticancer paradigm. Only this Unitarian perspective based upon that the hydrogen ion (H<sup>+</sup>) dynamics of cancer, allows understanding and integrating the many dualisms, confusions, and paradoxes of the disease. The new H<sup>+</sup>-related wide range model can embrace under a unique frame of mind the many aspects of the disease and at the same time therapeutically interfere with most, if not with all, the hallmarks of cancer known to date. The pH-related armamentarium available for the treatment of BC here reviewed may be beneficial for all types and stages of the disease. In this vein, we have attempted a megasynthesis of traditional and new knowledge in the different areas of breast cancer research and treatment based upon the wide range approach afforded by the hydrogen ion dynamics of cancer. The concerted utilization of a pH-related drugs nowadays available for the treatment of breast cancer is advanced.

**Keywords:** Breast cancer etiopathogenesis; Breast cancer treatment; Hydrogen ion dynamics of cancer; pH-related paradigm; H<sup>+</sup>-related therapeutics of breast cancer.

## 1. Introduction

Breast cancer (BC) has become the second cause of mortality in women [1]. Rarely, BC kills a patient from local disease and its morbidity is mainly secondary to a progressive and relentless metastatic process [2,3]. The results of surgery, traditional chemotherapy and radiation are many times disappointing when not useless in advanced disease. Thus, a change towards a different perspective incorporating more effective and less toxic approaches to treatment is highly necessary. Outside the cancer research community dedicated to cancer metabolism, the new anticancer paradigm based upon the pH/(H<sup>+</sup>)/Proton dynamics still is a minority within the mainstream anticancer approaches. The model here described considers all aspects of malignancy under one single and integral perspective in order to embrace a wide array of apparently unrelated factors involved in the etiopathogenesis of BC [4]. This approach, based upon the cancer-selective and deregulated proton (H<sup>+</sup>) dynamics in cancer, allows reaching a new and deeper understanding of the intimate energetics of the acid-base dynamic nature of any malignant process, as well as of human neurodegenerative diseases (HNDDs), the latter as a beneficial side-effect of the H<sup>+</sup>-related outreaching paradigm [4-7].

This new and wide-ranged perspective is able to absorb within itself most areas of cancer research. As a consequence of the selective acid-base homeostatic disruption and energetic failure of cellular hydrogen ion ( $H^+$ ) dynamics, attempts to induce a significant intracellular acidification using proton transport and pump inhibitors (PTI and PPI), as well as other intracellular acidifiers and cancer proton reversal (CPR) agents of different origins and natures (repurposed drugs), are becoming an increasingly popular integral therapeutic strategy in cancer treatment [4,8]. The present contribution, from basic to translational to clinically-oriented, for the first time advances an integrated therapeutic approach describing the concerted and progressive utilization of a series of proton-related anti-cancer drugs that can be already used in bedside oncology in the treatment of BC. The new pH-based strategy allows to interfere with all the cancer metabolic hallmarks, from prevention to the treatment of advanced disease. Under this perspective our group has recently published two conceptual publications, one on the pH-related etiopathogenesis and treatment of brain tumors [9], and a second one on breast cancer [10].

### 1.1. Otto Warburg and pH today: the missing link.

One hundred years ago Otto Warburg considered the respiratory impairment of tumors and their aerobic glycolysis as the prime cause of cancer. This was later called the Warburg Effect. In one of his early studies Warburg and his coworkers looked at the effects of hydrogen ions, bicarbonate and glucose concentrations in anaerobic conditions. They observed that glycolysis increased up to 2-fold when cells were gassed with increasing  $CO_2$  - while maintaining pH at about 7.5 - and, on the other hand,  $CO_2$  gassing led to the acidification of the solutions, which resulted in reduced glycolysis [11]. In this publication, Warburg's interpretation of the role of pH was focused on a compensating effect of bicarbonate, as mimicking conditions in arterial and venous blood. Later, in a talk given at the Rockefeller Foundation, Warburg stated on glycolysis: "Special attention should be drawn to the remarkable influence of the bicarbonate..." [12]. Thus, Warburg was aware of that the pH was an important parameter in maintaining glycolysis in his culture system, but was he aware of its significance in cancer metabolism? It seems that he was never aware of this since he did not address the subject of the role of pH in glycolysis never again in his later work [13-15]. Instead, he discovered the factor responsible for hydrogen transferring capacity in respiration: the nucleotide NADP [16].

Very heated discussions followed in 1956, mainly between Otto Warburg and Sidney Weinhouse, on the role and meaning of glycolysis and its relationship to oxidative phosphorylation in the etiology of cancer [17]. Unfortunately, the pH/glycolysis/cancer relationships were completely absent from those discussions and disagreements. Since then, many different attempts and theories to explain the cause and role of the increased glycolysis of tumors have been and are still considered [18]. Nowadays, the historical limitations of past decades can be understood because the cause-effect relationships of  $pH_i$  elevations in stimulating glycolysis were first considered during Warburg's old age and mainly outside the cancer context [19-26]. Thus, Warburg had not a chance to understand and/or rightly interpret the complex etiopathogenic and metabolic relationships between  $pH_i/pH_e$ , aerobic and anaerobic glycolysis and/or the  $H^+$ -dynamics of cancer, the selective cancer proton reversal (CPR) or the concerted strategy of cancer cells and tissues. For him, those mysteries were still hiding in the future and very far from the way we understand them nowadays. Something that has been made possible only decades later, and thanks to the increasing knowledge of the role of proton extruders/and/or membrane cells-bound  $H^+$  transporters and pumps (PTs and PPs) in increasing  $pH_i$  and decreasing  $pH_e$  (CPR) in all cancer cells and tissues [4,9,27].

A few decades later, PET technology was going to bring a revival of interest in the old Warburg's genial work and theories: serendipity at work.

We know that during Warburg's life there were no real methods to determine  $pH_i$ . Thus, the conclusion that can be reached is that Warburg probably took for granted that the cytoplasm of cancer cells was acidic because of their high production of lactic acid, which nowadays we know that this is just the opposite of the real situation [13,28]. These are the reasons that fully justify the fact that Warburg could not be right on what he considered to be "the prime cause of cancer", namely: aerobic glycolysis. Nowadays, it all appears to indicate that the prime cause of cancer is not aerobic glycolysis of tumors and/or the respiratory impairment of cancer cells, as Warburg defended until his death, but all evidence seems to indicate that the prime cause of cancer is the main factor inducing aerobic glycolysis itself, namely, the selective intracellular alkalization of cells in all tumors and leukemias [4]. In the same vein, recent publications from at least three different groups have concluded that the Warburg phenomenon can be fully explained by the stimulatory effects of  $pH_i$  elevations on glycolysis [4,29-31].

It was not until half a century after Warburg's death that a microenvironmentally-based integrated strategy for cancer cells and tissues was first described [32]. At the same time, the dynamics of the hydrogen ion were advanced to act as the Unitarian multidimensional factor able to embrace under a new perspective the intimate relationships of cancer cells carbohydrate metabolism with intracellular acid-base changes [33].

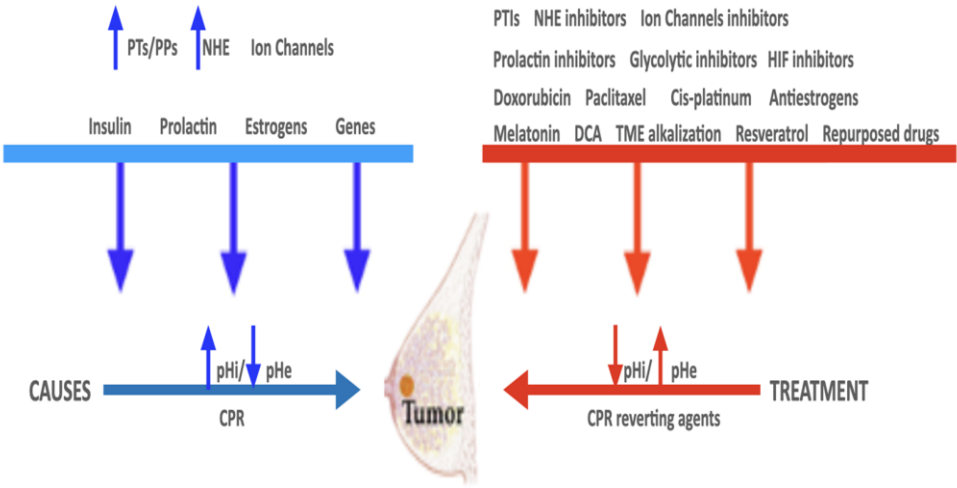
Finally, Otto Warburg once said, and that sentence became the founding motto of the International Society for Proton Dynamics of Cancer (ISPDC): "We can only cure what we can understand first" [6]. Since then, the  $H^+$ -centric paradigm has become the cutting-edge and main issue of the metabolic cancer research community. This has allowed understanding many aspects of the different areas of cancer research, mainly since transmembrane proton transporters (PTs) and its inhibitors (PTIs) increasingly came into play. So, one hundred years later, we still need to keep talking on the Warburg effect, in spite that appears that it can be fully explained by pH changes and cellular  $H^+$ -dynamics [4,18,27-31].

## **2. Breast cancer. pH-related etiology and pathogenesis. The basic approach.**

Most of the discoveries and therapeutic proposals of the new  $H^+$ -related paradigm have not yet entered mainstream bedside oncology, and, unfortunately, they still belong to the non-mainstream approach to cancer. In the meantime, the old, reductionist and almost exhausted anti-DNA model, still dominates most areas of research and treatment in basic and clinical oncology. In order to overcome some of these limitations, we have attempted to integrate the most important etiological and pathogenic factors of BC from the all-inclusive pH-related perspective (Figure 1).

CAUSES OF BREAST CANCER

INTEGRAL TREATMENT

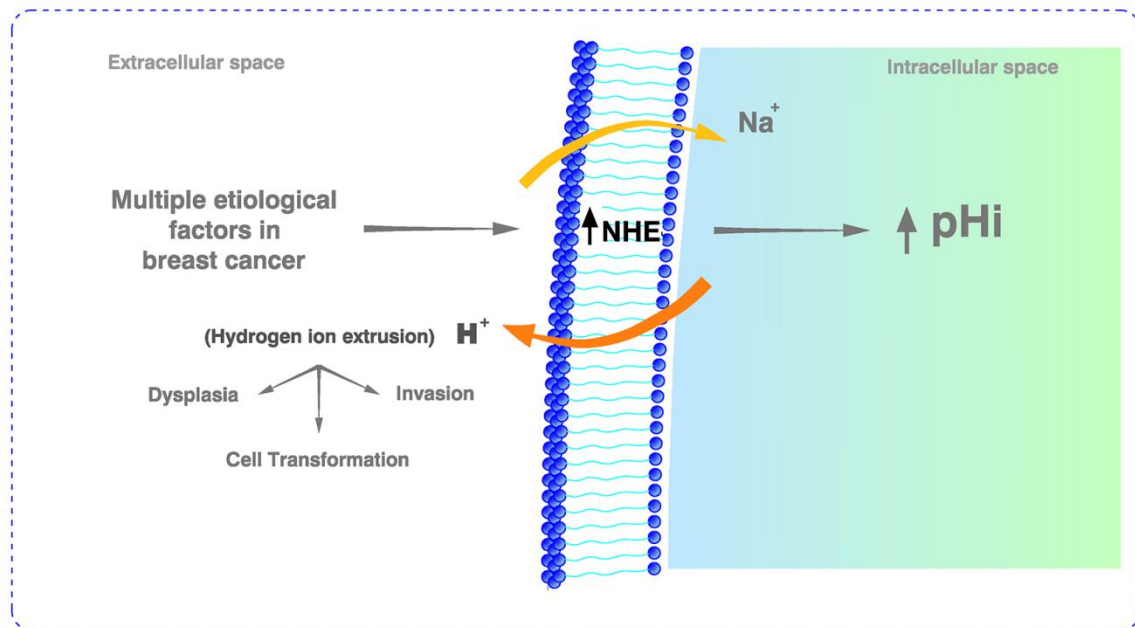


**Figure 1. pH-related causes and available treatments for breast cancer.** PTs: Proton transporters; PPs: Proton pumps; PTIs: proton transport inhibitors;PPIs: Proton pump inhibitors;NHE: Sodium - Hydrogen exchanger; HIF: Hypoxia Inducing factor; TME: Tumor microenvironment; DCA: Dichloroacetate.

In spite that all proton extruders are different, they all share the same or similar effects on the etiopathogenic deregulation of the pHi/pHe dynamics of cancer cells and tissues. These are:

**2.1. pH/NHE, H<sup>+</sup> extrusion and/or intracellular alkalization (CPR).**

H<sup>+</sup> extrusion from cells is induced by several membrane-bound proton transporters (PTs), pumps (PPs) and ion channels [4,34]. In cancer cells of all types and origins they manage to keep pHi normal to elevated under all hostile tumor microenvironmental (TME) conditions, like low O<sub>2</sub>, anoxia, lack of nutrients, low glucose levels and extracellular acidosis, mainly in order to protect themselves from a low pHi that would induce a cancer-selective therapeutic apoptosis. One of the most meaningful discoveries on BC etiology has been that H<sup>+</sup> efflux alone induces dysplasia and stimulates growth and invasion with oncogene RAS, while inhibiting it induces apoptosis in invasive BC cells [35]. Most importantly, a series of publications in this line have shown that the H<sup>+</sup> extrusion in BC cells, especially in triple-negative breast cancer (TNBC), is mainly mediated by NHE1 overexpression and H<sup>+</sup>-extrusion, NHE1 being the real actor that induces a high pHi-mediated carcinogenic effect on breast cells [36]. Furthermore, H<sup>+</sup> extrusion also is the main etiological mediator in the transition from ductal carcinoma *in situ* to invasive BC, where even the precancerous lesion already shows a higher than normal proton export rate [36-38] (Figure 2). Most recently, the intricate relationships of tumor pHi and pHe with ion channels and changes in membrane potential have been widely discussed and reviewed [39].



**Figure 2. H<sup>+</sup>-extrusion in the etiology of breast cancer.** Multiple etiological factors of different natures and origins are carcinogenic in breast cancer due to their positive regulation of NHE1 and/or intracellular alkalosis and/or extrusion of H<sup>+</sup>. This mechanism induces cell transformation and invasion (for further details, see text).

Furthermore, invasive BC cells show a more elevated pH<sub>i</sub> and a higher production and exportation rates of hydrogen ions to the TME than noninvasive cells [36,40]. Most recently, however, other channels, transporters and even certain aquaporins (AQP), mainly AQP1 and AQP3, as well as Cl<sup>-</sup> channels and a CA<sup>2+</sup> influx, have also been shown to be important in the initiation and progression of TNBC [41,42]. All these fundamental data clarify why and how NHE1, and its main consequences, H<sup>+</sup> extrusion and an elevated pH<sub>i</sub>, are involved in BC etiology, invasion, the metastatic process, as well as in multiple drug resistance (MDR) [35-38,43,44]. While a pathologically elevated pH<sub>i</sub> should be considered to be the main responsible factor of the BC-promoting activity, it secondarily induces a highly pathological and damaging extracellular/intratumoral TME with the final result of inducing cancer proton reversal (CPR). This selective and pathognomonic CPR has already become a highly differential hallmark of all cancer cells and tissues of all malignant tumors as compared to normality [45,46]. This makes CPR reversal the main therapeutic target of the entire pH and/or H<sup>+</sup>-centric paradigm [4].

The cohort of all these new discoveries in the cancer context now contributes to make it possible to apply them to the highly specific molecular, biochemical, and metabolic abnormalities in the etiology and pathogenesis of BC. NHE1, NBCn1, carbonic anhydrases (CAs) and monocarboxylate transporters (MCTs), mainly MCT4, are overexpressed in human BC, promoting the growth of at least triple-negative BC (TNBC) [47]. In this vein, NHE1 and NBCn1 drive cell cycle progression in human BC cells, while knocking them down reduces proliferation and tumor progression [48]. Finally, the activity of a significant number of carcinogenic and proangiogenic factors and oncogenes, as well as many other carcinogens, also upregulate NHE1.

## 2.2. Proton transporters (PTs), proton pumps (PPs) and growth factors (GFs).

NHE1 levels are higher in BC tissue than in normal breast tissue, and also in resistant BC cells than in sensitive cells, in a similar fashion that other PTs [4,9,43,47-63]. Besides NHE1 overexpression, carbonic anhydrases (CAs) also have an important role in the pathogenesis of BC, like V-ATPase proton pumps (PPs), the  $\text{Na}^+$ ,  $\text{HCO}_3^-$  cotransporter NBCn1, MCTs, hypoxia and HIF-1 [64]. A similar protumoral effect have certain oncogenes, gene mutations and products like *BRCA1* and *BRCA2*, apart from a dysfunctional p53 [65] and certain chemicals known to play a role in carcinogenesis [66,67]. All this myriad of factors belong to an already large list of mediating causes of cancer and BC cancer previously reported [9,10]. This large amount of data demonstrates that many different etiological factors of different natures and origins all act through pHi/pHe deregulation in the same direction, exerting a carcinogenic effect on BC pathogenesis.

### 2.3. Carbonic anhydrases (CAs).

Membrane-bound CAs, mainly the isoform CAIX, have an important role in the pathogenesis of BC as well as in other tumors, especially in hypoxic conditions [54]. Being induced by hypoxia and HIF1, CAIX overexpression is a sign of poor prognosis and promotes BC invasion and invasion in hypoxic microenvironments [68-71]. Furthermore, CAIX expression, as well as NHE activity, are associated with ER- tumors and a poor prognosis [10,72-74].

### 2.4. Monocarboxylate transporters (MCTs).

In the same line and with similar acid-base effects on cell homeostatic mechanisms than other PTs, MCTs induce: a) Further alkalization of the pHi of cancer cells; b) Worsening of the TME acidosis by removing lactic acid from the intracellular space [47], and c) Cell proliferation, migration, invasion, angiogenesis and survival [75]. Mainly the isoform MCT4, but also MCT1, are the most significant and their overexpression is associated with tumor cell aggressiveness and a significant worsening of prognosis either of BC or of other tumors [54,76,77].

### 2.5. The sodium-bicarbonate cotransporter (NBC1).

NBC1 has also been considered to be the main mechanism of  $\text{H}^+$  extrusion, pHi elevation and CPR in BC, being actively involved in both BC carcinogenesis and in metastatic disease [46,50,78]. Indeed, its inhibition decreases BC growth rates and increases survival in mice by maintaining a sufficiently high pHi compatible with the growth and survival of BC cells [50,79]. Also, NBC1 is synergistically associated with NHE1 and voltage-gated sodium channels like NaVi.5 [48,80,81], while targeting Na(v)1.5 sodium channels also diminishes invasion in metastatic BC [82].

### 2.6. Vacuolar ATPases (V-ATPase).

Since Peter Mitchell seminal description of the chemiosmotic hypothesis, this main energy-yielding mechanism dealing with electron transport and ATP synthesis in nature can also be considered as another acid-base mechanism induced by a  $\text{H}^+$  gradient across the mitochondrial membrane, a phenomenon dependent of ATPases [83]. From then on, it was going to elapse a long time until BC could also be considered a molecular, biochemical and metabolic disease of an intimate acid-base nature [10]. As it generally happens with PTs, V-ATPase proton pumps (PPs) are highly expressed in many tumors, apart from in BC, following the same rule of PTs, namely, that their upregulation is a sign of bad prognosis, facilitating faster cancer growth, tissue invasion, the metastatic process and chemoresistance (MDR), either in BC or other malignant tumors [84-86]. Also, the V-ATPases isoform a3 is selectively upregulated in BC cell invasion as compared to noninvasive cancer cells and normal breast tissue [84].



V-ATPase over-expression offers a growth advantage to cancer cells of any origin, disrupting pH homeostasis in the same direction that PTs, while inducing a more abnormal CPR; this is, further increasing pHi, decreasing TME pHe and at the same time acidifying endosomes and other intracellular organelles [62,87]. For all the above-mentioned reasons, V-ATPases have become a most significant target in any phase and subset of BC management. However, the main obstacle in treating cancer with V-ATPases inhibitors is that certain V-ATPases are ubiquitous in the human organism and, while they proved to be very active in *in vitro* conditions, they showed to be highly toxic for normal cells in *in vivo* conditions. Therefore drugs like Bafilomycin were abandoned as potential anti-cancer drugs [88].

## 2.7. Voltage-gated sodium channels (VGSC) and Ca<sup>++</sup> signalling.

Ion channels (ICs) are highly important membrane-bound additional factors in the etiopathogenesis of both cancer and human neurodegenerative diseases (HNDDs), pathologies that from an acid-base point of view dwell at both ends of a metabolic, biochemical and molecular spectrum [4-6]. In the cancer context, the most selective VSGs isoform is the NaV1.5-Na<sup>+</sup> channel, which is synergistically associated with NHE-1, both being overexpressed in BC and other tumors. Together they promote local growth through invadopodia formation and stimulation of the metastatic process in a similar way of what the other PTs and PPs do [80,81,89-93]. VGSC are expressed in highly metastatic cancer cells and are responsible for a sustained inward sodium current, H<sup>+</sup> extrusion, membrane depolarization, TME acidification and an increase in the degrees of CPR [41]. Through these mechanisms the invasiveness of cancer cells is enhanced by favoring the pH-dependent activity of acid proteases, cathepsins and pericellular tissue destruction [94]. ICs are especially important in the onset and progression of TNBC [95,96]. Besides ICs, Ca<sup>2+</sup> signalling induces a potent oncogenic drive in BC [97]. This uniporter channel promotes TNBC invasion and metastasis by favoring the Warburg effect [98].

2.8.

## Tumor microenvironmental (TME) acidosis.

Apart from cancer-specific intracellular alkalization, the protumoral effects of the acidification of the TME are the second main metabolic and molecular issue in cancer growth and dissemination, either in BC and/or other human malignant tumors [99]. Its damaging effects are several: a) Locally, stimulating tissue invasion and destruction, mainly by increasing the effects of invadopodia; b) Systematically, disrupting the immune defense mechanisms of the organism, in this way fostering uncontrolled tumor progression; and c) Increasing MDR to most chemotherapeutic agents. Many other factors of different natures contribute to the pathogenesis, growth and spread of BC through TME acidification, such as hormones, like estrogens, insulin, prolactin and sex steroids, growth factors like IGF1, EGF, VEGF and PDGF, as well as ion channels, cytokines and certain interleukins, apart from genetic abnormalities. Most of these factors, if not all, up-regulate NHE1 [85,100-125]. Recently, an issue covering the causes and consequences of tumor acidosis in cancer has been made available [106].

## 2.9. Estrogens.

Estrogens are important in the genesis of BC. They promote cellular proliferation while hindering apoptosis [72]. ER<sup>+</sup> cells are mainly associated with carbonic CA-XII while CA-IX is more frequently associated with ER<sup>-</sup> cells [126,127]. Besides BC, ER<sup>-</sup> cells are characterized not only by a high expression of NHE but also of hypoxia-inducible factor 1 (HIF-1) [56-58,68,128,129]. Therefore, ER<sup>+</sup> expression has

been used not only as a prognostic indicator but also as a factor to be taken into account in the choice of BC treatment, perhaps with the exception of inflammatory BC [130].

### **2.10. Insulin (INS) and insulin resistance.**

The tumor-stimulating properties of INS in BC are secondary to the fact that INS stimulates NHE1, rising pH<sub>i</sub> and increasing glycolysis [27,131,132]. High glucose loads, with or without insulin, also stimulate Na<sup>+</sup>/H<sup>+</sup> activity, cell cycle progression and activation of oncogene expression [133]. These effects are associated with BC carcinogenicity and progression [10], justifying the fact that hyperinsulinemia and obesity are protumoral factors that increase the incidence of BC [134-136]. On the contrary, antidiabetic drugs of the sulfonylurea family, known to stimulate the pancreatic secretion of INS, appear to have a negative impact on BC growth, also increasing BC risk [137-139]. Furthermore, the overexpression of INS and/or the IGF-1 gene are associated with a decrease in the length of life of women with BC, while their suppression increases life span and decreases tumorigenesis [27,91,131,132,134-136,140-146]. Hyperinsulinemia has also been considered an important factor in a wide array of human malignancies, while insulin inhibition has been proposed to decrease their growth [147,148]. Furthermore, recent studies have supported an association of the insulin/IGF axis with cancer recurrence, including BC and colorectal cancer [139,149].

### **2.11. Prolactin (PRL).**

The role of prolactin (PRL) in stimulating the growth of BC, even as an etiological factor, is well established. Indeed, PRL stimulates local growth and invasion of BC through NHE activation, in this way contributing to the metastatic process [150]. Recent studies have established that PRL signaling induces peripheral ruffle-targeted activation of NHE1 in BC cells [151]. Thus, PRL-mediated invasiveness of BC cells is NHE1 dependent, just like it happens with other hormones and growth factors (Figure 1). The development of BC also implies the association of PRL with other hormonal factors, like progesterone (PRG) and estrogens, whose chronic exposure also leads to hyperprolactinemia [152]. Furthermore, the interplay between PRL and progesterone in BC affects gene expression, producing a wide array of transcriptional regulators than those existing in the normal mammary gland. Finally, PRL, either coming from an increased circulating hormone or PRL produced by the mammary gland, have been found to induce BC in mice through the activation of the PRL receptor [153].

### **2.12. Genetic abnormalities.**

The Na<sup>+</sup>/H<sup>+</sup> exchanger isoform 1 (NHE1), as a fundamental factor in the etiology and pathogenesis of BC [35-38,43], is produced by the *APNH* gene located on chromosome 1p35-36, whose deletion is also related to the etiopathogenesis of different tumors [154]. Other genes have a role in BC metastasis, at least 133 as well as 113 migratory modulators of Hs578T and MDA-MB-231 cells, which predict BC progression and carry a bad prognosis [143]. Also, *BRCA1* and *BRCA2* are associated with familial breast and ovarian cancers [155]. The possibility that the BRCA carcinogenetic expression can also be secondary to NHE1 hyperactivity has been recently proposed [10].

### **2.13. MDR in breast cancer: pathogenetic mechanisms.**

Drug resistance of BC cells to drugs like doxorubicin (DOXO), paclitaxel and cis-platinum (CDDP) depends on pH regulation [156-158]. P-gp has been shown to need an H<sup>+</sup> gradient in order to function [159,160]. Initially, cell studies showed that resistance to DOXO and P-glycoprotein were directly related, drug resistance increasing with pH<sub>i</sub> elevations ranging from 1 at pH<sub>i</sub> 6.9 to more than 1000-fold at pH<sub>i</sub> 7.4 [161]. These important findings concluded that P-gp behaves as a proton (H<sup>+</sup>) extrusion pump [85]. A confirmation of this seminal information initially came from studies showing that the expression of P-gp leads to an elevation of pH<sub>i</sub> [119,162,163]. Besides, the levels of NHE1 are significantly higher in BC and other tumors when compared to adjacent normal tissues [164]. Also, there is an important role for V-ATPases in tumor invasion and chemoresistance in several cancers, including BC [62,165]. In summary, pH alterations have been shown to be behind the most fundamental aspects of MDR [85,113,166-168]. Finally, based upon the selective H<sup>+</sup>-dynamics of cancer, an integrated mechanism to explain MDR has



been developed [85,113,115,116,156,157,159,169]. Unfortunately, all this important perspective and knowledge has been completely obviated so far by traditional bedside oncology practice.

**3. Towards an etiology-based and H<sup>+</sup>-related integral treatment for breast cancer. The translational approach (Table 1)**

**3.1. Intracellular acidifiers (proton therapy). Na<sup>+</sup>/H<sup>+</sup> antiporter (NHE) and other proton transport inhibitors (PTI), old and new.**

The main therapeutic target of the pH-anticancer paradigm is addressed to the concerted inhibition of NHE1 and other PTs and PPs to selectively induce an intracellular acidification (IA) incompatible with the life of cancer cells [4,89,170-172] (Figure 1). This attempt should also lead towards the control and even inversion of the tumoral extracellular/microenvironmental acidification of cancer tissues (TME). Tumor cell proliferation is further abolished through the concerted inhibition of NHE1 and HCO<sub>3</sub><sup>-</sup>/Cl<sup>-</sup> exchangers [173]. Similarly, the simultaneous inhibition of NHE1 and H<sup>+</sup>-ATPases induces cancer cell apoptosis through a combination of synergisms that lower intracellular pH (“metabolic proton therapy”) together with TME alkalization (“metabolic antiproton therapy”) [4,10].

**3.2. On Amiloride (AM): past, present, and future.**

In 1961, mitotic stimulation was considered to be secondary to membrane potential aberrations and electrophysical abnormalities. However, not a single mention of pH was made at that time [174]. This effect later was interpreted as being secondary to an increase of the intracellular content of sodium, but not to any pH changes [175]. No matter that such conclusion survived the test of time [176], since the discovery of the Na<sup>+</sup>/H<sup>+</sup> antiporter (NHE) [177], the emphasis on cancer initiation and etiopathogenesis turned from Na<sup>+</sup> influx to its main consequence, namely, H<sup>+</sup> extrusion (Figure 2).

AM, a well-known diuretic and a weak and non-specific NHE inhibitor, has been commercially available for a long time and was the first Na<sup>+</sup>/H<sup>+</sup> antiporter inhibitor used as an anticancer drug [178]. Treatment with AM completely inhibits the formation of lung metastasis of BC in rats [179,180]. Also, AM has been repeatedly reported to have antitumoral, antiangiogenic and antimetastatic effects [181-183], decreasing VEGF expression and inducing tumor growth inhibition through a significant decrease in pHi, at least in gastric and leukemic cells [178,184]. The many anticancer effects of AM on basic cell behavior had also been fully described [185]. The case of a patient who went into a complete remission of metastatic ovarian cancer after being chronically treated with 15-30 mg/day of AM for one and a half years after mainstream chemotherapy had failed, was reported [186]. With all these data available, it becomes difficult to understand why AM and other more potent and selective NHE inhibitors (Table 1) have not been considered at all in BC treatment, from prevention, associated to traditional chemotherapy or as an antimetastatic agents. This can be secondary to two simple factors: a) AM is very cheap and b) It is not patentable. Also, a liposomal preparation of AM is commercially available. Finally, a wide array of these and other antiangiogenic drugs are known to inhibit NHE1 [144,187].

**Table 1. pH and/or H<sup>+</sup>-related options in the treatment of breast cancer.** BC: Breast cancer; NHE: Na<sup>+</sup>/H<sup>+</sup> antiporter; P-gp: P-glycoprotein; MDR: Multiple drug resistance; ER+: Estrogen positive cells; ER-: Estrogen negative cells; PTI: Proton transport inhibitors; PPI: Proton pump inhibitors. CAs: Carbonic anhydrases; TME: tumor microenvironment. (For further details, see text).

Drugs	Effects
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Amiloride (AM) (and/or liposomal amiloride)	AM is a non-specific and weak NHE inhibitor and cell acidifier. It also behaves as an antiangiogenic agent and has proved to be able to completely abrogate the metastatic process in transplanted BC in rats.
Acetazolamide (AZM)	AZM acidifies cells by inhibiting certain carbonic anhydrases (CAs). In BC is effective in reducing tumor invasion. For an increasing clinical effect AZM can be used together with NHE inhibitors.
Monocarboxylate transport (MCT) inhibitors	Quercetin is an MCT inhibitor and cell acidifier. Gastrointestinal absorption is limited. To overcome its scarce oral bioavailability a liposomal preparation is available.
V-ATPase inhibitors (PPI) (antiproton therapy)	PPI are occasionally used in the prevention of BC and in overcoming MDR. PPI also benefit from the extracellular acidity of tumors. Recent clinical studies support the utilization of PPI in BC and other solid tumors.
Doxorubicin (DOXO)	pHi elevations are directly related to increasing resistance to DOXO. P-gp also increases pHi, while P-gp inhibitors decreases DOXO resistance.
Paclitaxel	NHE1 inhibition improves the effect of Paclitaxel in triple-negative BC metastasis. Paclitaxel has also been shown to induce apoptosis in BC cells.
Cis-platinum (CDDP)	The first effect of CDDP consists in the induction of cellular acidification, inhibiting H <sup>+</sup> extrusion through NHE-1 downregulation. On the contrary, NHE-1 hyperactivity increases CDDP resistance by elevating pHi.
Antiestrogens	ER- BC cells correlate with a high expression of NHE activity and are also associated with CA-IX upregulation. Estrogens and CA-IX inhibition improve BC prognosis.
Melatonin (MT)	Because of the claimed antiestrogenic effects of MT it should be contemplated in the integral approach to BC therapy. MT decreases tumor aggressiveness and increases apoptosis in BC cell lines. MT also suppresses tumor aerobic metabolism (the Warburg effect) and decreases BC angiogenesis and metastasis.
Metformin (MET)	MET induces intracellular hyperacidification in tumor xenograft models. It has been reported to inhibit insulin and IGF-1, HIF-1 $\alpha$ , Warburg metabolism, gene expression, angiogenesis, cancer migration, invasion, and metastasis. It also decreases the side effects of DOXO. MET acts synergistically with chemotherapy and decreases its side-effects.

Treating HIF and tumor hypoxia	HIF activity promotes tumor cell survival and invasion. CAIX inhibitors have been reported to suppress BC growth and metastases by targeting tumor hypoxia and HIF. Different compounds and strategies have been tried to suppress HIF in BC research and treatment, so far without too much success.
Repurposed drugs	Because of their pH/related effects, drugs like Dichloroacetate, Phloretin, Lonidamine, Niclosamide, Docosahexaenoic acid, Salinomycin, Simvastatin and Resveratrol have been reported to be useful in the treatment of BC.
Cariporide (CP)	CP is a powerful NHE1 inhibitor that is barely available for clinical use in bedside oncology, although it can be purchased in a highly purified form from different sources. It induces apoptotic cells death in BC and other malignant tumors.
Compound 9t (C9t)	C9t is the most potent and selective NHE1 inhibitor. Besides, it is orally bioavailable, has low side-effects in mice and it presents a significantly improved safety profile over other NHE1 inhibitors. Unfortunately, it is not available for preclinical or clinical research, apparently because of the complicated method of synthesis and purification.
Phx-3	Phx-3 is a potent, selective, and non-toxic NHE1 inhibitor that has been shown to be highly effective in animal tumor models. It has also been used in Japan to treat gastrointestinal inflammatory disease.

3.3. Carbonic anhydrase (CA) inhibitors.

Carbonic anhydrase (CA) is a family of several isoforms of the metalloenzyme CA, such as the cytosolic CAII and the transmembrane CAIX/XII, which efficiently catalyze CO<sub>2</sub> hydration to bicarbonate and protons. By the coupling of these effects, a slightly alkaline intracellular pH is achieved (of around 7.2) at the same time that an acidic extracellular pH of the tumor is generated, with values as low as 6.5. Between the various CAs, CAIX and CAXII have been shown to have a prominent role in the regulation of tumor pH. Among them, CAIX has the most interesting features as a potential target of anti-cancer therapies [188]. Indeed, CAIX acidifies the TME under low O<sub>2</sub> conditions through HIF activity, promoting tumor cell survival and invasion in hypoxic microenvironments. In mice with BC treated with CAIX-specific inhibitors, there is a significant inhibition of tumor growth and metastatic formation, demonstrating that CAIX is fundamental for BC and should be used as a specific target in this disease along other PTI and PPI [4,10,69]. Interestingly, the combination of CAIX inhibitors and PPI has been shown to have synergistic antitumor effects [189].

Among the large number of sulfonamide, sulfamate, sulfamide, coumarin and CA IX/XII inhibitors reported to date, few compounds have been investigated in detail in animal tumor models, and only one of such derivatives, SLC-0111 (also known as WBI-5111) has progressed to clinical trials [190]. SLC-0111 also sensitizes cancer cells to conventional chemotherapy [191]. Interestingly, metastatic formation is inhibited in the T4 murine BC model by these novel CA inhibitors when used alone or with paclitaxel or doxorubicin [69].

Acetazolamide (AZM) is a CA pan-inhibitor and the only commercially available NHE inhibitor and intracellular acidifier [10,57,71]. In spite there are different prospective Phase I/II studies with other more selective and powerful CA inhibitors, either as anticancer drugs or associated to other more conventional treatments are under way. However, none of them has yet reached the clinical stage [56,129,164,191,192]. Since CAIX inhibition significantly reduces the invasion of BC cells, AZM represents a complementary drug that should be included in any integral treatment of BC, mainly in combination with other cellular acidifiers and PTI [56,58,68,70,71,129,164,192,193]. Finally, Topiramate also inhibits CAIV and induces pH<sub>i</sub> acidification, at least in glioblastoma multiforme [10,194].

### 3.4. Monocarboxylate transporter (MCT) inhibitors.

Quercetin (QUER) is a weak pan-monocarboxylate transporter (MCT) inhibitor and intracellular acidifier that is commercially available in many countries [195]. QUER causes tumor regression by increasing apoptosis [196]. Its main role is to inhibit lactate extrusion from cancer cells by downregulating MCT1 and MCT4, in this way inhibiting growth by decreasing TME acidosis in BC as well as in a wide array of other malignant tumors [52,54,75,197,198]. MCT inhibition in BC cells in different conditions has confirmed the potential of lactate transport inhibition in BC treatment, which it also significantly decreases *in vivo* tumor growth [75]. Until better and more specific MCT inhibitors are clinically available, QUER should be incorporated into the integral treatment of BC along with other PTI specialized in inhibiting H<sup>+</sup> extrusion from cancer cells [199]. Since gastrointestinal absorption of QUER is poor, the use of the liposomal drug form is advised [47,75,77,101,192,200,201]. Lonidamide is also a MCT inhibitor but is no longer available in bedside oncology [89,201].

### 3.5. Bicarbonate-dependent transport inhibitors (NBC1).

Since the expression of the electroneutral Na<sup>+</sup>, HCO<sub>3</sub><sup>-</sup>-cotransporter (SLC4A7, NBCn1) is upregulated in human BC and other malignancies, either in carcinogenesis or during the metastatic process, its inhibition becomes another therapeutic weapon that should be considered in BC treatment, also as an indirect TME alkalizer [202]. Unfortunately, there is not a NBC1 inhibitor available that could be used in bedside oncology, since the ones so far known, like Trifolcin, DIDS and Nigericin, even since the pioneering by the group of Tannock, have been known to be too toxic to treat human cancer [203,204]. Fortunately, inhibiting CAs with a CA-paninhibitor like AZM may also indirectly inhibit NBC1, at least partially [50]. Thus, any efforts to inhibit NBC1 should have an extra beneficial effect to be integrated in the concerted treatment of BC. In this regard, AZM, initially used to treat pain in advanced cancer patients, appears to have an antitumoral effect in the treatment of glioblastoma and in overcoming MDR, as well as in potentiating the effect of chemotherapy in other tumors [205-208]. Indeed, disrupting the Na<sup>+</sup>, HCO<sub>3</sub><sup>-</sup>-cotransporter NBCn1 decreases BC growth rates and increases survival in mice [50,79].

### 3.6. Proton pumps/ATPase inhibitors (PPI), TME alkalizers in cancer treatment, MDR, cancer pain and tumor immunity (antiproton therapy).

The clinical utilization of V-ATPase inhibitors of the omeprazole family (PPI) has an important therapeutic role in counteracting the highly pathological proton dynamics of BC and other tumors [10,87,209]. PPI are most effective in controlling the protumoral TME acidosis of tumors [34]. Recently, the use of anti-acidic drugs of the ATPase family as PPI has been successfully exploited as anticancer agents in both pre-clinical and clinical conditions [88]. Different studies also support a direct anti-tumor effect of PPI independently from cancer histology [10]. PPI are also useful, together with CA inhibitors, in downregulating exosome production, known to be involved in the progression of different human malignancies [210]. Furthermore,

another advantage of PPI is that they are prodrugs needing acidity for their full activation, thus lowering any side effects while being more effective in the TME acidified conditions of malignant tumors.

Other studies have used PPI, either as a single therapy or in combination with standard chemotherapy in humans with BC with overall positive results, also when used in overcoming of MDR [62,211,212]. BC patients receiving high PPI dosages obtained higher response rates and longer survivals [213]. Also, there is a significant increase in the survival of women who continue their PPI therapy after the completion of chemotherapy for BC [214]. On the other hand, women receiving PPI treatment for non-cancerous diseases have a reduced risk for developing BC [60,215]. Intermittent high dose PPI also improves MDR in metastatic BC [213]. Finally, V-ATPase inhibitors, along with other TME alkalizers, like acid-sensing ion channel 3, have been reported to improve lactic acid-mediated bone pain in metastatic disease in different human cancers [216-222].

TME acidity is known to blunt the immune defenses of the organism, which favors uncontrolled cancer progression and the metastatic process [102,108], since TME acidosis blocks T-cell activation [109]. Indeed, TME acidification has an essential role in the progression of inflammatory BC (IBC) [130], which makes TME a novel and fundamental therapeutic target in this most aggressive form of the disease. This therapeutic “antiproton therapy” should be continuously targeted in the chronic situation in BC in order to control, decrease and, if at all possible, revert TME acidity. To this end, large daily amounts of sodium bicarbonate plus DMSO (see section 5. 11 below) or other buffers have also been used in human cancer [220,221]. Thus, controlling TME acidity will correct T-cell dysfunction and allow improving the efficacy of any immunity-based anticancer therapies [104,105,110]. It is concluded that for all these reasons, namely: control of metastatic disease, pain therapy and immune failure, the TME has to be targeted in all types of BC cancer patients within an integrated program of treatment, even since the earliest stages [107,223]. This can be done directly through TME buffering, and indirectly using PPI and PTI in order to decrease lactate extrusion of cancer cells and collaborate in the induction of intracellular acidification (CPR reversal), which at the end is the main and fundamental target in pH-related cancer therapeutics [4,224]. However, some serious concerns have also been raised in recent times regarding the possible negative effect of the indiscriminate use of PPI on cancer mortality [225].

### **3.7. Voltage-gated sodium channels (VGSC) inhibitors.**

VGSC, mainly Na(v)1.5 sodium channels have become a relevant therapeutic target in cancer [146] since they promote cancer growth and invasion in BC [81,176,226]. Na(v)1.5 inhibition has been reported to increase survival in patients with BC [4,227]. Drugs like phenytoin, topiramate or ranolazine, as well as other repurposed drugs, can be used in decreasing invasion and metastases in BC by inhibiting Na(v)1.5 sodium channels. Thus, their utilization should be considered at least as complementary targets in any integral pH-related anticancer treatment [82]. The potential of ion channels in cancer has been extensively reviewed [228]. However, it becomes highly surprising that a clinical study of patients exposed to VGSC-inhibiting drugs have been associated with BC, bowel and prostate cancer patients [229].

## **4. Other pH-related available therapies in breast cancer treatment (Table 1).**

### **4.1 Cisplatin (CDDP) and pH/NHE.**

Cisplatin (CDDP) has been used in the treatment of BC and other malignancies for a long time [230-232]. From its first introduction in bedside oncology, different mechanisms of action for CDDP have been described [233,234]. Until most recently, an almost completely disregarded issue has been that CDDP significantly changes the pHi of cancer cells, inducing cytoplasmatic acidification through the inhibition of H<sup>+</sup> extrusion through NHE1 downregulation [232,233,235,236]. Indeed, this pHi lowering effect has been considered to be the first effect of CDDP on cancer cells [235]. Contrariwise, the activity of NHE-1 increases the resistance to CDDP by elevating pHi [232,233,235,236], this representing one more dualism of the pH-paradigm. Apart from inducing pHi acidification, CDDP shifts cells from glycolysis to oxidative metabolism. In this context, malignant cells either manage to maintain an alkaline pHi in order to survive and proliferate, or die [237].



#### 4.2. Doxorubicin (DOXO) and Paclitaxel.

Seminal studies showed that dynamic elevations of pH<sub>i</sub> induce a progressive increase in resistance to DOXO, at least in lung cancer cells, this resistance being suppressed by P-gp inhibitors. Contrariwise, P-gp increases pH<sub>i</sub> [161]. Furthermore, MDR is characterized by a selective reversal of the pH gradient (CPR) across all cancer cell membranes [4,9,85,156,157,161,163,168,192]. This allows understanding why the concerted inhibition of NHE1 plus CA inhibitors improves the efficacy of Paclitaxel by mediating in its induction of apoptosis in triple-negative BC cells and its metastases [36,38,44,128,156,168,192,230,232,238,239]. More recently, liposomal preparations and nanodrugs of DOXO and others compounds are trying to find a place in the treatment of BC and other tumors, and clinical trials with these methodologies are under way [240].

#### 4.3 Antiestrogens.

ER- cells show a higher expression of NHE1 activity than ER+ cells, while CA-IX also is more frequently associated with ER- cells than with ER+ [126,127]. ER-cells are also characterized by a higher expression of Hypoxia-inducible Factor (HIF) activity [10]. Thus, it can be understood that the selective inhibition of CA-IX improves the prognosis of BC and that NHE1 inhibition is therapeutically indicated at least in ER- tumors [193]. The role of Tamoxifen (TMX) and Letrozole (LTRZ) is well established in the treatment of BC (see section 5.5). Further connections among the pH paradigm and antiestrogens in BC have not been described, at least directly [2,72-74,126,127,193,241,242].

#### 4.4. Anti-insulin strategies and Metformin (MET).

Metformin (MET) has been introduced as an anticancer agent in BC bedside oncology. This antidiabetic drug has been shown to be an intracellular hyperacidifying agent in tumor models. It also functions as an anti-insulin factor, inhibiting INS and INS/IGF-1, while decreasing a wide array of other protumoral factors, like HIF-1 $\alpha$ , Warburg metabolism, gene expression, angiogenesis, cancer migration, invasion and metastasis. It has been used to target resistant cells in BC and has been even proposed to be a radio-sensitizer agent [243-263]. Also, antidiabetic agents, like Rosiglitazone and MET, show promising anticancer properties as INS-sensitizing agents [264-266], while sulphonylureas, because of their effects on stimulating INS release have been considered to be pro-tumorigenic [267]. Finally, INS inhibition has been proposed as a complementary treatment in a small series of patients with advanced cancer [147]. In spite that INS deprivation has not been proved to be an effective therapeutic measure, a low carbohydrate diet should always be contemplated in all BC patients in order to decrease the stimulatory effects of circulating INS on cancer growth, also because high glucose loads induce intracellular alkalinity and the Warburg Effect [268].

#### 4.5. Prolactin (PRL) inhibitors.

NHE1 inhibitors decrease PRL-induced BC invasion, while NHE1 activity is also decreased by the inhibition of Akt and/or ERK $\frac{1}{2}$ , factors that are known participants in growth hormone (GH) signaling pathways, another hormone not to be forgotten in BC [151]. Besides, other antagonists of PRL/PRL receptor interaction are used in the treatment of BC, either alone or with Tamoxifen (TMX) and/or Letrozole (LTRZ) [150]. Disrupting the effect of PRL and/or PRL receptor expression delays oncogene-induced BC [269]. Thus, PRL inhibitors like the dopaminergic agonists bromocriptine and cabergoline should be taken into account as part of the armamentarium of drugs in BC integral therapy, even as drug sensitizers [270].

#### 4.6. Melatonin (MT).

Melatonin (MT) has been postulated to be an antiestrogenic agent, so it should be strongly considered at least in the treatment of the same cohorts of BC patients that can benefit from antiestrogens [271,272]. In BC cell lines, treatment with MT decreases tumor aggressiveness and increases apoptosis [273]. MT plays a number of other different actions as an anti-cancer agent [274]. Among them, it regulates the expression of estrogen receptors, inhibits enzymes involved in the local synthesis of estrogens, activates the immune system and decreases angiogenesis by downregulating VEGF [271,275-277]. Finally, MT also inhibits other different angiogenic factors under hypoxic conditions [277].

MT has been reported to inhibit BC metastasis by maintaining a normal circadian expression of BMAL-1 in tumor hypoxia-induced acidosis [278]. Another positive effect described for MT in BC is that it decreases the expression of both the glucose transporter GLUT-1 and Ki-67 while increasing the expression

of the proapoptotic enzyme Caspase 3, therefore preventing the aggressive phenotype of BC cells under acidotic conditions [273]. MT also suppresses tumor aerobic metabolism (Warburg effect), inhibiting pathways that are key for the survival, growth and metastases of BC cells while decreasing resistance to anti-cancer drugs [272,279-281]. Finally, since ER+ BC frequently develops genetic or epigenetic-induced resistance to antiestrogens [282], the new MT-TMX conjugates may represent a further improvement in the treatment of BC in these situations [283].

#### 4.7. Repurposed drugs.

Dichloroacetate (DCA) is an anti-cancer agent that reverses the glycolytic phenotype in cancer cells by inhibiting pyruvate dehydrogenase kinase. Through this mechanism the growth of several BC cell lines was found to be inhibited by DCA. This drug also shows anti-proliferative properties and pro-apoptotic properties, and can be effective against highly metastatic disease *in vitro* and *in vivo* [284]. DCA also improves immune dysfunction in different tumors [285]. Other repurposed drugs that have been reported to be active in BC because of their pH-related acidifying effects, are DHA, Quercetin, Resveratrol, Phloretin, Lonidamine, Niclosamide, Docosahexaenoic acid (DHA), Simvastatin and the K<sup>+</sup> ionophore Salinomycin [286-294]. These and other repurposed drugs in cancer have been recently reviewed and proposed to show antiproliferative, pro-apoptotic and/or antimetastatic activity [295], either in BC or other tumors.

**4.8. Overcoming multiple drug resistance (MDR) in breast cancer: the integral approach.** NHE1 inhibition and/or cellular acidification down-regulate the MDR transporter [119,296,297]. Also, NHE is expressed in BC cells, mainly in RE- ones [298]. Thus, MDR and the CPR of cancer cells and tissues are related in a direct cause-effect relationship, two phenomena that cannot be separated from each other [85,113,115,116,156,157,159,169]. Since extracellular acidification also increases the activity of P-gp, in this way inducing MDR in different cancer cells and tissues [113,116,121], it becomes logical to associate PPI with PTL, not only to improve the effect of chemotherapy in metastatic BC, but also in the overcoming of MDR. The clinical use of such a combination is considered a fundamental therapeutic measure in any integrated clinical protocol in the treatment of BC [4,9,29,30,53,56,57,60-62,67,89,110,112,128,129,154,156,163,164,170,178-180,185-187,192,198,223,298-302]. The integral pH-related approach to MDR has shown that the therapeutic failure in inducing acidification of the cytoplasm and/or reverse CPR is the main factor underlying MDR. In addition to a therapeutic cellular acidification, there are other mechanisms to restore sensitivity to CDDP, like targeting V-ATPase, impairing endosomal function and inhibiting autophagy [303]. It is concluded that MDR is systematically characterized by an inversion of the pH gradient (CPR) across cancer cell membranes [4,9,85,156,157,161,163,168,192], one more time making CPR the main cancer-selective therapeutic target in any H<sup>+</sup>-related treatment of BC in bedside oncology.

#### 4.9. Proton therapy: Metabolic, radiotherapeutic, or both?

In previous sections (3.1; 3.2; 3.6), proton therapy (PRT) and antiproton therapy (APRT) have been considered in the pH-related metabolic treatment of cancer. Recently, PT has become the latest and more advanced method in radiotherapy (RPT), either in the oncology setting or in other clinical situations [304]. However, we are not aware that among the mediating effects on cells and tissues that have been described for RPT, any changes in hydrogen (H<sup>+</sup>) concentrations or pH-related physical dynamics of the radiated tissues have been described or even considered at all [305].

#### 4.10. H<sup>+</sup>-related autophagy in cancer: the coronavirus connection.

Autophagy has been extensively investigated in the treatment of cancer, however its role remains elusive [306]. However, after the formation of the initial autophagosome, it fuses with the other internal

vacuoles with non-specific roles in the digestion of unwanted material, which makes it difficult to distinguish autophagy from the other phagocytic processes. Thus, if there is an important role of autophagy in cancer, is still under discussion [307]. On the contrary, cell cannibalism and other cell-to-cell phenomena have proven to present an active role in cancer [307].

Among other repurposed drugs, the antimalarials chloroquine (CQ) and hydroxychloroquine (HC) have been studied in several clinical trials in oncology and suggested to benefit certain cancer patients, at least in glioblastoma multiforme. This effect has been blamed on their effect in inhibiting autophagy [308,309]. Like it happens in other pH-related cancer treatments, the acidic pH of the TME neutralizes the uptake of CQ by tumors [310]. Like in cancer, V-ATPase plays a significant role in the degree of activity of the malaria parasite; however, their interrelationships are very complex [311,312]. The interest of these associations resides in the fact that CK and HQ have been initially studied, however without success, in clinical trials in the COVID-19 pandemic [313] because they had been previously effective in other viral infections like SARS [314]. These data suggest that, both in COVID-19 and cancer, high dosages of V-ATPase inhibitors of the omeprazole family can act like other more powerful alkalizing agents like bleach and could be effective in overcoming resistance to CQ and/or HCQ in both cancer and COVID-19 infection.

#### **4.11. HIF inhibition.**

Tissue hypoxia on its own is an important factor in the etiology, physiopathology and development of different malignant tumors [185], mainly in scar tumors [185,315]. Besides, these prooncogenic situations can also be mediated by the hypoxia inducing factor (HIF), which involves the transcription of a wide array of genes, so allowing cancer cells to adapt, survive and grow in the most hostile hypoxic conditions [199], as well as inducing chemotherapy resistance [121,316]. During the last years, increasing efforts have been made to suppress HIF as an anticancer and antiangiogenic method to induce regressions in BC and other tumors [317,318]. To this end, a series of compounds and strategies were initially proposed and continue to be actively researched nowadays [197,257,260,277,319-322].

### **5. Towards a H<sup>+</sup>-related concerted utilization of clinically available drugs in the integral treatment of breast cancer. The clinical approach (Figure 1 and Table 1).**

**5.1 Amiloride (AM).** AM is the only NHE inhibitor commercially available nowadays. In cancer patients it has been used at dosages of 10 mg. three times a day, continuously during months to years. These dosages are well tolerated, however some degree of hyperkalemia occasionally ensues (K<sup>+</sup>: up to 6 mmol/L), as well as increases in BUN (up to 90 mg/dL). In those cases, AM is discontinued for two weeks and restarted at a lower dose [172,181,182,186]. No other side effects have been found after its chronic utilization in a wide array and number of cancer patients.

#### **5.2 Carbonic anhydrase (CA) inhibitors.**

Acetazolamide (AZM) is the only commercially available CA pan-inhibitor. It is used in the treatment of glaucoma and as a diuretic or in the treatment of epilepsy. Oral dosages for AZM range from 250 to 1000 mg/day. Like with Amiloride, it is important to have blood tests for K<sup>+</sup> and BUN every 3 to 4 weeks. AZM, as a CA pan-inhibitor and cell acidifier, represents a most promising drug in the treatment of BC, mainly in combination with NHE inhibitors. Although pre-clinical research has produced a list of potentially effective new CA inhibitors that are small molecules mostly directed against CA IX, there are not further information regarding dosages and effects [188]. Other CA-IX inhibitors, like SLC-0111, are indicated for hypoxic and acidic cancer cells that are chemotherapy-resistant. CA also increases BC cells response to Doxorubicin [191].

#### **5.3 V-ATPase inhibitors and/or proton pump inhibitors (PPI) (antiproton therapy).**

While many pre-clinical in vivo studies have shown the efficacy of PPIs as single anti-tumor agents, they have been exclusively used in combination with traditional chemotherapy. Based on pre-clinical investigations, the initial treatment protocols are based on three rules: (1) They should be done before chemotherapy, due to the evidence that it is needed to abrogate tumor acidity in order to allow other drugs to fully work; (2) High dosages, between 1.5 and 2.5 mg/kg/day of Lansoprazole or Pantoprazole, are recommended. Lately, it has been shown: (a) That Lansoprazole is the most active PPI; (b) That dosages change according to gender, i.e., 90 mg/day for men and 60 mg/day for women. And (3), that a continuous daily treatment is used for at least one year. However, an intermittent high dose of PPI also enhances the antitumor effects of chemotherapy in metastatic BC; however, intermittent high doses of PPI have been reported to enhance the antitumor effects of chemotherapy. [213]. All these conclusions have been supported by a retrospective analysis in women receiving PPI for non-cancer-related ailments (i.e. gastroprotective or anti-acidic treatments, Lansoprazole, 30 to 40 mg/day), showing that a gastroprotective dose is also adequate to protect from BC development [60,215].

#### 5.4 MCT inhibitors.

Quercetin (QUER), or Liposomal Quercetin, is the only commercially available MCT inhibitor. Oral doses of 3 grams a day of QUER are well tolerated in the long term. However, since the oral absorption QUER is very low, the use of a liposomal form (LQUER) of the drug is advisable. Tolerance is excellent at dosages of LQUER of 30 mg (concentration 1 mg/ml), three times a day.

#### 5.5 Cisplatin (CDDP), Paclitaxel (PCXL) and Doxorubicin (DOXO) (see Table 1).

Since many therapeutic protocols with different schedules and dosages of CDDP/PCTX, CDDP/DOXO or PCTK/DOXO have been available for a long time in the treatment of the different stages and subsets of BC, either as neoadjuvant therapy or in early stages or as treatment of advanced disease, no chemotherapy protocol will be considered here [323,324]. However this subject is outside the scope of this contribution, we are not aware that any of the many different chemotherapeutic regimes used in the treatment of BC has ever been associated with the pH-dysregulation known to be fundamental in the treatment of BC or any other malignant tumors.

#### 5.6 Antiestrogens.

About 70% of women with BC show estrogen receptor (ER) positive/HER2-negative tumor cells. In these subsets, Tamoxifen (TMX) has been widely used because it binds to ER impeding the tumor-promoting action of estrogens. Oral dosages of TMX range from 20 to 40 mg, administered in one or two doses a day during at least five years. However, several adverse effects have been reported for this drug; among them an increased incidence of uterine cancer, presumably associated with its estrogenic effects on these tissues [325]. Moreover, an increased risk of thromboembolism has been reported during the treatment with TMX or aromatase inhibitors [326].

Aromatase inhibitors lead to a decreased or absent production of estrogens by the adrenal glands. There are many aromatase inhibitors available, such as exemestane, anastrozole and letrozole, but none of them is free of toxicity; for instance, they produce osteoporosis or an increase in cholesterol levels [327]. Letrozole is used in postmenopausal women after five years of treatment with TMX at a daily dose of 2.5 p.o. Very recently, a phase II study conducted in Japan in 42 postmenopausal patients has investigated the efficacy and safety of the combination of palbociclib plus letrozole, concluding that this combination is effective in patients with ER+, EGFR- and advanced BC [328].

#### 5.7 Antiglycolytic drugs and insulin inhibitors.

Targeting glycolysis has represented a promising theoretical approach to the metabolic management of cancer for many years. The interruption of glycolysis would interrupt the cytoplasmic utilization of glucose by cancer cells, inhibiting cell growth and invasion, while activating the Krebs' cycle [329]. Drugs that decrease the cytoplasmic utilization of glucose include 2-Deoxyglucose, Lonidamine, 3-Bromopyruvate, Imatinib, Oxythiamine and Hydroxycitrate, as well as other drugs that restore mitochondrial function, like alpha-lipoic acid [329,330]. Also, glycolysis has been reported to be paradoxically inhibited by the administration of buffering agents like Sodium Bicarbonate or Potassium Citrate [331,332].

### **5.8 Prolactin inhibition in breast cancer.**

Despite the significant role that PRL plays in BC and its invasiveness, plasma levels of PRL are not usually analyzed in BC or PRL inhibitors used in its treatment. Dopaminergic agonists are used for PRL pituitary adenomas. In BC, perhaps the best option would be to administer a dose of bromocriptine able to decrease circulating PRL to undetectable levels. In situations in which PRL values are over the normal range, bromocriptine is given at oral doses beginning at 2.5 mg, three times/day, but in the case of BC it is likely that higher doses should be contemplated. Bromocriptine has been developed as a long-acting injectable presentation (Parlodel-LAR\*). Doses are in the range of 100 to 150 mg. i.m. every 4 weeks, but so far, its use is usually restricted to prolactinomas [333]. Cabergoline, a more recently discovered dopaminergic agonist, has the advantage of presenting longer-lasting dopamine agonist effects. In fact, a single oral dose of 0.5 mg. of cabergoline, leads to a marked fall in plasma PRL for at least seven days [334].

### **5.9 Melatonin in breast cancer treatment.**

In nurses or other female workers that work shifts the prevalence of BC is higher than in the normal population, a feature that appears to be secondary to disruption of the normal MT circadian rhythms [335,336]. Chronic treatment with MT is thought to have a preventive effect on BC incidence in these cases [337]. Indeed, the positive effects of MT on different cancers, particularly in BC, has been widely considered since 1992, when it was published that MT might be a natural oncostatic agent useful in BC cancer prevention [338]. Despite the dosages of commercial presentations of MT are very low, in the range of 1.9-10 mg, MT can be used at much higher dosages without showing any adverse side-effects. In fact, the toxicity of MT is very low, as many animal and human studies have demonstrated. In animals, an LD50 (lethal dose for 50% of the animals) could not be found, and very high doses, such as 800 mg/kg body weight did not produce any adverse effects [339]. Similarly, no side effects were observed in a Phase II clinical trial in which 1400 women were treated with 75 mg of MT daily at night, for four years [340]. Neither have we seen any adverse effect in a woman who took 50 mg of MT/daily during 9 years [341]. Moreover, 31 patients with Amyotrophic Lateral Sclerosis (ALS) were treated with rectal MT (300 mg/day) during 2 years without experiencing adverse effects from these high dosages [342]. Most recently, MT has been proposed as an antiglycolytic agent that inhibits Warburg-like metabolism and increases glucose oxidation [343].

Daily oral doses of MT in BC oscillate between 200 and 400 mg, every night. Locally, MT may also be used in the prevention of side effects of chemo/radiotherapy, such as oral mucositis and dermatitis. In the case of mucositis, MT is given as an oral gel, rinsing the mouth without swallowing it [344]. Also, a gel of MT can be applied in the zone to be radiated 15 minutes before each session to avoid the damaging effects of radiation to the skin [344,345].

### **5.10 Treating tumor hypoxia.**



Many HIF-1 inhibitors have been studied but no selective HIF-1 $\alpha$  inhibitor has been clinically approved. However, there are a few other drugs that can be used as a complementary treatment of some types of cancers. This subject has been extensively reviewed in recent years [346]. In this vein, CA inhibitors have been reported to suppress BC and other tumors growth and metastases by targeting hypoxia-induced CAIX [69,190,347].

#### **5.11 Resveratrol, 100 mg, capsules.**

Dosages: 100-1000 mg, t.i.d. permanently. Liposomes of Resveratrol are also available.

#### **5.12 Tumor microenvironment (TME) alkalization with Sodium Bicarbonate (BS) plus Dimethyl Sulfoxide (DMSO) (SB+DMSO) in cancer treatment (antiprotion therapy).**

Alkalization with SB alone has been shown to be effective in inhibiting metastases [107], while other methods of acid-base manipulation in the same direction have been reported to be clinically useful in treating intractable pain in cancer patients [348]. Most recently, systemic alkalization with small doses of SB has been reported to improve the effects of chemotherapy in pancreatic cancer [349]. Also recently, bone metastases from BC have been associated with TME acidification and lactic acid extrusion [124]. A mixture of dimethyl sulfoxide (DMSO) and sodium bicarbonate (SB) has been shown to be a safe and effective treatment of pain in advanced cancer patients [220-222,350]. It has also been reported that there is a prolongation of survival in advanced BC using SB plus DMSO [221,351]. Finally, the utilization of DMSO in humans has demonstrated its lack of toxicity when used for periods of up to 5 years [351]. No increase in Na<sup>+</sup>, salt retention or increase in blood pressure has been observed when the SB+DMSO mixture is used for months, or even years, and on a daily basis. However, Na<sup>+</sup>, K<sup>+</sup> and BUN should be checked at least monthly during treatment. Unexpectedly, alkalization of tumor pH and pHi with SB has shown cancer-promoting effects on BC tissues [352]. It is also paradoxical that the utilization of sodium bicarbonate, at least under certain circumstances, may lead to intracellular acidosis, this phenomenon being more evident at higher starting intracellular pHs [353].

Formulation of the SB+DMSO mixture:

34% DMSO (99'9% pharmaceutical quality 99'9% purity)

64% double-distilled water

2% SB.

Dosages: 10 cc, p.o, two to four times a day, on an empty stomach and separated from other medications. Only crystal bottles or high-density polyethylene (HDPE) should be used as containers, since DMSO can dissolve other kinds of plastic containers and become toxic to the patient. The simultaneous utilization of BS+DMSO along with any other chemotherapy protocol is also recommended.

#### **5.13 Repurposed drugs.**

Among a large list of repurposed drugs proposed for the treatment of BC and other tumors [4,88], Salinomycin has been shown to induce partial regressions of several pretreated cancers [294]. Furthermore, treatment with DHA has been shown to increase survival in BC patients with metastasis. The daily doses used in these clinical trials were in the range of 1.800mg DHA/day.

#### **5.14 Bicarbonate transporter inhibitors (NBC1).**

There is not a specific NBC1 inhibitor available for clinical utilization. However, knockdown of NBC1 has prolonged tumor-free survival and reduced cell proliferation in basic studies through a pHi-lowering effect [47]. Finally, the utilization of different ion channels and transporter inhibitors and antagonists has been recently considered in different attempts to downregulate NBC1 [41].

### **6. Powerful NHE inhibitors in the treatment of breast cancer (Table 1).**

**6.1 Cariporide.** Unfortunately, Cariporide is not usually available for human use.

## **6.2 Compound 9t (C9t).**

C9t (a 5-aryl-4-(4-(5-methyl-1H-imidazol-4-yl) piperidin-1-yl) pyrimidine analog), is perhaps the most promising anticancer drug of the pH-related anticancer armamentarium, but it is not available for either basic or clinical research. Recently, the patent holder (Bristol-Meyers-Squibb) released the patent for the entire world, with the exception of the United States until 2020 [298]. However the description of the process of synthesis was somewhat incomplete and so far all efforts to synthesize C9t in different countries have been unsuccessful (PATENT BRISTOL-MEYERS SQUIB WO 01 27107 A2, PCT/US00/27, 2001, US 6887870 B1; EP 1224183 B1) [354]. C9t has been shown to be 500-fold more potent against NHE1 than Cariporide. Besides, C9t is orally bioavailable, has low side effects in mice and presents an improved safety profile over other NHE1 inhibitors [298]. Compound 9t promises to act as a kind of "magic bullet-like" drug in a number of human malignancies.

## **6.3 Phx-3.**

Apparently, Phx-3 has been used in Japan for the treatment of inflammatory bowel disease [355].

## **7. Conclusions.**

In this contribution, the seminal acid-base aspects of cancer metabolism are considered under a fresh and integral perspective, starting with Otto Warburg's highly significant discoveries and running into the long post-Warburg era. Mainly thanks to the discovery of PET technology, Warburg theories were resurrected and, despite their historical limitations, have allowed a burst of a new interest in cancer carbohydrate metabolism along with its multiple basic to translational to clinical derivations. As a beneficial side effect to this growing evolution, a new pH-centric and/or H<sup>+</sup>-related paradigm was born and has rapidly evolved to give way to an entirely different perspective of the entire field of metabolic cancer research, far beyond the previous antiDNA paradigm of traditional oncology that has dominated cancer research and therapeutics during the last few decades.

From this new wide-range "acid-base" approach to cancer molecular biology, biochemistry, and metabolism, most of the etiological and pathogenetic factors of human cancer can now be interpreted through a single and Unitarian viewpoint. The cancer-specific combination of intracellular alkalization and its secondary extracellular acidification of all malignant tumors, which represents the mirror image of normality (acid inside/alkaline outside), conforms what it has been defined as cancer proton reversal (CPR). This reversal of intracellular/extracellular proton dynamics is induced by the expression and/or upregulation of membrane-bound proton transporters (PT) and (PP) pumps, whose concerted etiopathogenic role, apart from preventing the cancer-damaging cellular acidification by extruding H<sup>+</sup> from the cell by all possible means, creates a series of progressive and strategic dynamic abnormalities. Indeed, this is done from the onset of the malignant process to the end of it, which many times finish by killing the patient. For these reasons, PT and PP have become the targets of rapidly increasing therapeutic efforts in modern cancer research.

CPR itself has already become the primordial therapeutic target of all these efforts. The entire paradigm has grown to conclude that the concerted utilization of proton transport inhibitors (PTI) and proton pump inhibitors (PPI), when used in pharmacological dosages, could selectively decrease the pH<sub>i</sub> of cancer cells to apoptotic levels through a chain reaction-like mechanism, a concept that reminds the magic bullet dream of Paul Ehrlich theories. Also, a therapeutic alkalization of the tumor microenvironmental extracellular space (TME) appears to be a most practical and important measure that further contributes to the therapeutic reversal of CPR.

All these conceptual and practical advances, as well as the increasing basic and clinical experience in metabolic cancer research, is integrated in this contribution, which is specifically dedicated to the pH-related etiopathogenesis and treatment of breast cancer under the new and integral perspective afforded by the hydrogen ion (H<sup>+</sup>)-related anticancer paradigm.

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