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Does Baking Soda Function as a Magic Bullet for Patients With Cancer? A Mini Review

Mengyuan Yang, PhD[1], Xian Zhong, MD[1], and Ying Yuan, PhD[1]

Abstract

Sodium bicarbonate, commonly known as baking soda, is widely used in the clinic as an antacid for treating gastric hyperacidity, among other conditions. Chao et al have reported a clinical trial about targeting intratumor lactic acidosis–transarterial chemoembolization. Based on conventional transarterial chemoembolization, the authors added a 5% sodium bicarbonate solution to cytotoxic drugs, resulting in a high local control rate. The explanation for the antitumor effects of sodium bicarbonate is related to acidosis in the tumor microenvironment. In this review, we summarize the findings from studies administering sodium bicarbonate alone or in combination with other anticancer therapies as cancer treatments, and discuss methods for safe and effective use of sodium bicarbonate in the clinic.

Keywords

sodium bicarbonate, tumor microenvironment, TILA-TACE, animal experiments, review

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Introduction

Transarterial chemoembolization (TACE) is widely employed for the local control of hepatocellular carcinoma (HCC) lesions, which are too large to be surgically resected.[1] By inserting a catheter into tumor-feeding arteries, TACE not only accurately delivers anticancer drugs into the tumor but also starves cancer cells by blocking major vessels. However, according to a systematic review of 14 randomized clinical trials,[2] the objective response rate (ORR) of this procedure is only 35% (range = 16% to 61%). For the ORR for large HCC (>10 cm) lesions, it is much lower. Thus, physicians have invested substantial efforts in improving this operation, such as drug-eluting bead TACE[3] or combination with radiofrequency ablation (RFA)[4] and systematic targeted therapy.[5] However, the therapeutic efficacy was only increased to a certain extent, and thus, further studies are needed.

The acidic microenvironment fosters cancer progression, and after conventional TACE, the pH value of this tumor microenvironment is further decreased.[6] This change explains the low control and high recurrence rate of tumors treated with conventional TACE. Therefore, the addition of some alkaline substances to neutralize acidity may be a viable approach to solve this problem. Chao et al[6] added 5% sodium bicarbonate to the cytotoxic drugs (doxorubicin or oxaliplatin) and then performed chemoembolization, which is described as targeting intratumor lactic acidosis–TACE (TILA-TACE). Amazingly, 100% of patients treated with this modified TACE procedure achieved complete or partial remission.

TILA-TACE is undoubtedly a successful working example of translational medicine. More important, we should pay attention to sodium bicarbonate, a low-cost and ordinary alkalescent antacid, as a novel cancer treatment strategy. In this mini review, we will summarize the effects of acidic microenvironment on tumor development, followed by a review of the findings from preclinical studies investigating the therapeutic effects of sodium bicarbonate alone or in combination with other anticancer therapies on cancer. Finally, we discuss its feasible applications in treating various malignancies.

[1]The Second Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, China

Corresponding Author:
Xian Zhong, Department of Medical Oncology, the Second Affiliated Hospital, Zhejiang University School of Medicine, No. 88 Jiefang Road, Hangzhou, Zhejiang 310009, China.
Email: zhongxian@zju.edu.cn

Table 1. In Vivo Experiments of Sodium Bicarbonate Monotherapy in Anticancer Treatment.

Tumor Type	Model	Administration of $NaHCO_3$	Reference
Inhibition of metastases			
Breast cancer	MDA-MB-231 xenograft intrasplenic injection	200 mM $NaHCO_3$ po ad libitum	20
Prostate cancer	PC3M xenograft tail vein injection	200 mM $NaHCO_3$ po ad libitum	20
Melanoma	B16 allograft tail vein injection	200 mM $NaHCO_3$ po ad libitum	20
Inducing tumor growth delay			
Prostate cancer	TRAMP	200 mM $NaHCO_3$ po ad libitum	24
Breast cancer	MDA-MB-231 cells mice dorsal window chamber	200 mM $NaHCO_3$ po ad libitum	15
Colorectal cancer	HCT116 cells mice dorsal window chamber	200 mM $NaHCO_3$ po ad libitum	15
Breast cancer	MDA-MB-231 xenograft	A single dose of 21 mg or 84 mg NaHCO3 po 1 mL 1M $NaHCO_3$ ip injection	27
Enhancement immune system			
Melanoma	Yumm 1.1 allograft (CD8+ T-cell)	200 mM $NaHCO_3$ po ad libitum	25
B-cell lymphoma	λ-myc mice (NK cells)	200 mM $NaHCO_3$ po ad libitum	26

Abbreviations: SCID, severe combined immunodeficiency; TRAMP, transgenic adenocarcinoma of mouse prostate; ip, intraperitoneal; po, per os (orally); NK, natural killer.

Acidic Microenvironment Promotes Tumor Development

An acidic extracellular pH (pHe) ranging from 6.5 to 6.9 exists in various malignant tumors,[7] whereas the pHe of normal tissue is within the physiological range (pHe = 7.2-7.4). The origin of tumor acidosis starts from the unique metabolic patterns of tumor cells, which is closely associated with the distance from the blood vessels.[8] Capillaries have a quite limited range of oxygen supply, so the cells in the area far away from the vessels suffer severe hypoxia.[9] According to the oxygen supply, the tumor mass can be roughly divided into the following 3 parts. In the region of deep hypoxia, the cancer cells can only utilize glycolysis to produce energy and the main metabolites are lactate and H^+ ions.[10] In the moderate hypoxic region, there are a variety of substrates, including glutamine, fatty acid, as well as lactate from cells with enhanced glycolysis. Through oxidative phosphorylation, the cancer cells make the most of the oxygen in this environment to generate energy.[11,12] As a result, CO_2 diffuses out of the cells.[13] In the normoxic area near the blood vessels, even with adequate oxygen, the tumor cells still tend to generate ATP (adenosine triphosphate) through enhanced glycolysis, known as the Warburg effect.[14]

In summary, the primary metabolites in the tumor microenvironment include H^+ ions, lactate, and CO_2. Due to lactic acid, free H^+ ions and CO_2 hydration, it is common to see that the pHe of solid tumors is acidic. Numerous scholars have proposed that the acidic microenvironment is a weapon for the tumor to protect itself and attack normal tissues and immune cells. Its pro-tumorigenic effects involve local invasion,[15-17] angiogenesis,[18] and distant metastasis.[19-21] Moreover, the initiation and development of a tumor, to a large extent, are attributed to the suppression of the immune system.[22] Huber et al[23] have fully detailed the effects of low pH on tumor immunity and the relative pathways of acidity-driven immunosuppression.

Sodium Bicarbonate "Kills" Cancer Cells

The acidic tumor microenvironment is so closely related to cancer development that strategies targeting this tumor hallmark may be a practical treatment. The utilization of sodium bicarbonate to neutralize the acidity and increase the tumor pHe might control cancer cells progression. Gatenby, Gillies, and colleagues have conducted several in vivo experiments to explore the anticancer effects of sodium bicarbonate (summarized in Table 1).[15,20,24-27]

Sodium bicarbonate reduces the formation of spontaneous metastases and the rate of lymph node involvement in mouse models of metastatic breast cancer. However, the data did not reveal an effect on the number of circulating tumor cells.[20] Based on experiments employing the transgenic adenocarcinoma of mouse prostate (TRAMP) model, the administration of 200 mM bicarbonate to 4-week-old TRAMP mice (weaning at 3 weeks) effectively perturbs the in situ evolution of cancer to a microinvasive disease.[24] In the C57BL/6 mice bearing syngeneic Yumm 1.1 melanoma, sodium bicarbonate significantly controls tumor growth and improves $CD8^+$ T-cell infiltration.[25] Natural killer (NK) cell activity is also increased in a B-cell lymphoma mouse model following the systemic administration of a buffer therapy.[26]

Regarding the clinical evidence presented in the published literatures, apart from TILA-TACE, a study by Silva and colleagues, members of Gatenby and Gilles groups,[28] included the following statement:

> we include the experience of a 79-year-old man with widely metastatic renal cancer at the Moffitt Cancer Center. After failing first-line treatment, he discontinued conventional therapy and began a self-administered course of vitamins, supplements, and 60 g of bicarbonate mixed in water daily. As of this submission, he has remained well with stable tumor for 10 months.

Table 2. In Vivo Experiments of Combination Sodium Bicarbonate With Other Anticancer Therapies.

Anticancer Therapy	Tumor Type	Animal Models	Administration of $NaHCO_3$	Outcomes (Anticancer Therapy+ $NaHCO_3$ Versus Anticancer Therapy)	Reference
Chemotherapy					
Doxorubicin (2.0 mg/kg ip)	Breast cancer	MCF-7 xenograft	200 mM $NaHCO_3$ po ad libitum	pHe of MCF-7 xenografts raised the therapeutic effectiveness improved	29
Mitoxantrone (12 mg/kg iv)	Breast cancer	C3H allograft	0.7 mL 1M $NaHCO_3$ by gavage	3.3-fold increase of therapeutic index 0.7 mL 1M $NaHCO_3$ ip injection	30
Molecular targeting therapy					
VEGFR2 inhibitor: sunitinib (40 mg/kg po)	Colorectal cancer	HT29 xenograft	200 mM $NaHCO_3$ po ad libitum	Tumor growth delayed; the number of blood vessels decreased; tumor necrosis increased; VEGFR2 expression in the vessels increased tumor growth delayed MC-38 allograft	34
mTORC1 inhibitor: rapamycin (3 mg/kg ip)	Colorectal cancer	HT29 xenograft	200 mM $NaHCO_3$ po ad libitum	Tumor growth delayed; tumor necrosis increased; necrotic tumor surface increased MC-38 allograft	33
Immunotherapy					
Anti-PD1 therapy	Melanoma	B16 allograft	200mM $NaHCO_3$ po ad libitum	Modest effect on tumor growth ($P < .05$)	25
	Pancreatic cancer	Panc02 allograft		Tumor growth delayed ($P < .005$)	
Anti-CTLA4 therapy	Melanoma	B16 allograft		No effect on tumor growth ($P = .54$)	
Anti PD1/CTLA4	Melanoma	B16 allograft		No effect on tumor growth	
Adoptive T-cell therapy	Melanoma	B16 allograft		No effect on tumor growth Long-term (120 day) survival rate (40% vs 10%) T-cell persistence increased	

Abbreviations: ip, intraperitoneal; po, per os (orally); iv, intravenous; VEGFR2, vascular endothelial growth factor rectptor-2; mTORC1, mechanistic target of rapamycin complex-1; CTLA-4, cytolytic T lymphocyte-associated antigen-4; PD-1, programmed death-1.

We must emphasize that baking soda alone without any other anticancer therapies is only effective for some cancer cell lines with less aggressiveness, such as breast cancer MDA-MB-231 cell line and prostate cancer PC3M cell line,[15,20,24] while mice bearing tumors with more aggressive phenotypes, like B16 melanoma and Panc02 pancreatic cancer, died of a substantial tumor burden after a short time.[20] Moreover, the above are the results from preclinical studies, and there are insufficient clinical evidences to support that routine anticancer therapy could be replaced with drinking water containing baking soda.

Methods for Using Sodium Bicarbonate as a Cancer Treatment

Here, a question arises of how to use sodium bicarbonate as a cancer treatment in the clinic. The acidic microenvironment can not only promote carcinogenesis and development but also have a negative impact on various antitumor agents, such as weak-base chemotherapeutic drugs,[29-32] some drugs targeting specific molecules,[33,34] and immunotherapeutic drugs.[35,36] Therefore, sodium bicarbonate could be used as an adjuvant therapy to enhance the efficacy of conventional treatments. Several in vivo experiments have assessed whether sodium bicarbonate cooperates with traditional anticancer therapies (summarized in Table 2)[25,29,30,33,34]

SCID (severe combined immunodeficient) mice with MCF-7 human breast cancer xenografts were administered bicarbonate-supplemented water to drink at the same time they received doxorubicin. Surprisingly, extracellular alkalization induced a 2- to 3-fold increase in the efficacy of doxorubicin.[29] However, while sodium bicarbonate increases the uptake of weak-base drugs through elevating the pHe, it greatly reduces the efficacy of some weak acidic chemotherapeutics, such as chlorambucil.[37,38] Thus, it is not wise to combine baking soda with acidic agents.

In the aforementioned animal experiments, researchers delivered sodium bicarbonate through the drinking water at a concentration of 200 mM $NaHCO_3$ as a substitute for ordinary drinking water. Some researchers are concerned

that the chronic administration of sodium bicarbonate may cause hypernatremia and other metabolic disorders. The authors tested the effectiveness and practicability of acute alkalization, via an intraperitoneal injection and gavage. The anticancer effect of sodium bicarbonate was not influenced by the mode of drug delivery.[27,30]

What is the proper use of baking soda as an auxiliary medication in the clinic? Taking oral administration as an example, the first consideration is an appropriate dose of sodium bicarbonate. In animal experiments, a mouse with average weight of 23 g drinks 4.2 mL 200 mM (16.8 g/L) sodium bicarbonate, which is equal to an intake of 3 g/kg.[39] For a 70 kg human, the consumption of 210 g of sodium bicarbonate per day is undoubtedly impractical for popularization. In consideration of tolerance, a modified dose of sodium bicarbonate is necessary. A phase 1 clinical trial (NCT02531919) launched by Robey started in August 2015, and was completed in April 2016. This study intended to explore the practicability and tolerance of 0.5 g/kg/day sodium bicarbonate administered for a short-term (10 days) or a long-term (90 days) period. The results have not yet been published. The optimal dose of sodium bicarbonate for humans is still in dispute. Moreover, during the administration of the medication, both urine and blood pH must be monitored to prevent health hazards, such as renal complications and indigestion.

In addition to systemic administration, a local application of sodium bicarbonate is also, a great choice. Intratumor injections, such as TILA-TACE, are quite more difficult to perform compared with oral delivery. But from another perspective, these routes accurately target the tumor microenvironment and are less likely to change the systemic pH. Furthermore, sodium bicarbonate may increase doxorubicin uptake, which may be the crux of the whole procedure. Analogously, we wonder whether sodium bicarbonate could be combined with hyperthermal intraperitoneal chemotherapy to treat peritoneal metastases, particularly using alkalescent chemotherapeutic agents.

Discussion

Buffer therapy, or targeting the tumor acidity through alkalization, has been a widespread anticancer therapy.[40] In addition to baking soda, researchers have found several other buffering agents to manipulate the tumor pHe, including Tris-base,[41] 2-imidazole-1-yl-3-ethoxycarbonylpropionic acid,[42] and free base lysine.[43] Similar to sodium bicarbonate, these agents have been confirmed to inhibit tumor progression in the preclinical studies.[41-43] Apart from neutralization of acidity, suppression of H^+ ion discharge can also elevate the tumor pHe. Thus, the inhibitor of the proton pump, such as omeprazole or esomeprazole, which potently hamper the export of H^+ from the tumor cells to the extracellular space, could be used for anticancer treatment.[44] According to the results of a phase III clinical trial, an intermittent high dose of esomeprazole enhances the effects of docetaxel-cisplatin on metastatic breast cancer in patients, without additional toxicity.[45] A retrospective study suggested that omeprazole exerts a synergetic effect with chemoradiotherapy and significantly decreases the recurrence of rectal cancer.[46]

No matter what kind of agents, monitoring the tumor pHe value is the key to the translation of buffering therapy from bench to bedside. There are various imaging technologies available for mapping tumor pH in vivo.[47-49] Among them, magnetic resonance imaging-chemical exchange saturation transfer with iopamidol has been proved as a noninvasive imaging protocol for assessing tumor acidosis with good sensitivity.[50]

As mentioned above, H+ ions, CO_2 as well as lactate are produced during tumor metabolism. Some scientists have supposed that lactate also contributes to tumor progression. First, lactate enables to facilitate the survival of cancer cells under hypoxic conditions via inducing metabolic symbiosis.[51] Second, it has also been documented to stimulate angiogenesis by activating some signaling pathways, such as the VEGF/VEGFR2 (vascular endothelial growth factor/VEGF receptor 2)[18] and NF-κB/interleukin-8 pathways,[52] providing the fertile soil for tumor growth and metastases.[18,53-55] Last but not least, lactate exerts inhibitory effects on the immune system to achieve "immune escape," including T lymphocytes,[56,57] monocytes,[53] macrophages,[58] dendritic cells,[59,60] and NK cells.[61,62] Based on the pro-tumor influences of lactate, glycolysis inhibitors, such as dichloroacetate[63-65] as well as lactate transport inhibitors, like monocarboxylate transporter 1 (MCT1) and MCT4,[55,66,67] may have a more substantial effect on cancer cells than sodium bicarbonate. Actually, the clinical studies of these 2 kinds of agents are not going well. Inhibiting glycolysis or lactate transport could lead to severe adverse events, because these processes are also crucial for some immune cells and other normal cells.[58,68,69]

The preclinical studies exploring the anti-cancer effects of sodium bicarbonate have begun as early as the 1990s, but the translation from bench to bedside is quite tardy. That is why the results of TILA-TACE,[6] a small-scale pilot study, caused a great sensation in China, and suggested a wide application foreground of sodium bicarbonate in cancer treatment. We propose that the research design of this clinical trial is worth some deep thinking. First, the trial used a unique mode to deliver sodium bicarbonate. Next, it took advantage of the coordinated effects of sodium bicarbonate and doxorubicin. Above all, this study gained a positive result largely due to its distinctive methods of evaluation, visible tumor residues (VTRs). VTRs are rarely used in traditional clinical research, the common endpoints of which are recurrence rate and overall survival. The investigators proposed that lower VTRs and better local control are independent prognostic factors for patient survival. Thus, even without overall survival results from the randomized clinical trial, they concluded that bicarbonate remarkably enhanced the anticancer activity of TACE.

Conclusions

The distinctive metabolic mode of solid tumors leads to acidity in the tumor microenvironment, which results in the activation of multiple factors contributing to tumor development. The most direct method to conquer the acidity is neutralization. Several in vivo experiments have revealed potential anticancer effects of sodium bicarbonate alone or in combination with other therapies. The use of TILA-TACE has confirmed that local application potentially represents an ideal administration method, and the combination of sodium bicarbonate with other anticancer therapies might be more effective. However, a large-scale clinical trial is necessary to test and verify this hypothesis and we hope it will be confirmed.

Author Contributions

MYY collected data and was a major contributor in writing the original draft. XZ contributed to the conception of this review and revised the manuscript. YY gave final approval of the version and acquired funding. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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ORCID iDs

Xian Zhong https://orcid.org/0000-0001-5915-5531
Ying Yuan https://orcid.org/0000-0002-3922-9553

References

1. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology*. 2006;131:461-469.
2. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003;37:429-442.
3. Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin Drug Eluting Beads (DEB) for unresectable Hepatocelluar Carcinoma (HCC). *J Surg Oncol*. 2010;101:476-480.
4. Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur Radiol*. 2006;16:661-669.
5. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): phase II, randomized, double-blind SPACE trial. *J Clin Oncol*. 2012;30(4 suppl):LBA154.
6. Chao M, Wu H, Jin K, et al. A nonrandomized cohort and a randomized study of local control of large hepatocarcinoma by targeting intratumoral lactic acidosis. *eLife*. 2016;5:e15691.
7. Stubbs M, McSheehy PM, Griffiths JR, Bashford CL. Causes and consequences of tumour acidity and implications for treatment. *Mol Med Today*. 2000;6:15-19.
8. Corbet C, Feron O. Tumour acidosis: from the passenger to the driver's seat. *Nat Rev Cancer*. 2017;17:577-593.
9. Secomb TW, Dewhirst MW, Pries AR. Structural adaptation of normal and tumour vascular networks. *Basic Clin Pharmacol Toxicol*. 2012;110:63-69.
10. Zu XL, Guppy M. Cancer metabolism: facts, fantasy, and fiction. *Biochem Biophys Res Commun*. 2004;313:459-465.
11. Khacho M, Tarabay M, Patten D, et al. Acidosis overrides oxygen deprivation to maintain mitochondrial function and cell survival. *Nat Commun*. 2014;5:3550.
12. Mookerjee SA, Goncalves RLS, Gerencser AA, Nicholls DG, Brand MD. The contributions of respiration and glycolysis to extracellular acid production. *Biochim Biophys Acta*. 2015;1847:171-181.
13. Hulikova A, Swietach P. Rapid CO2 permeation across biological membranes: implications for CO2 venting from tissue. *FASEB J*. 2014;28:2762-2774.
14. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*. 2009;324:1029-1033.
15. Estrella V, Chen T, Lloyd M, et al. Acidity generated by the tumor microenvironment drives local invasion. *Cancer Res*. 2013;73:1524-1535.
16. Martínez-Zaguilán R, Seftor EA, Seftor RE, Chu YW, Gillies RJ, Hendrix MJ. Acidic pH enhances the invasive behavior of human melanoma cells. *Clin Exp Metastasis*. 1996;14:176-186.
17. Kato Y, Ozawa S, Tsukuda M, et al. Acidic extracellular pH increases calcium influx-triggered phospholipase D activity along with acidic sphingomyelinase activation to induce matrix metalloproteinase-9 expression in mouse metastatic melanoma. *FEBS J*. 2007;274:3171-3183.
18. Shi Q, Le X, Wang B, et al. Regulation of vascular endothelial growth factor expression by acidosis in human cancer cells. *Oncogene*. 2001;20:3751-3756.
19. Rofstad EK, Mathiesen B, Kindem K, Galappathi K. Acidic extracellular pH promotes experimental metastasis of human melanoma cells in athymic nude mice. *Cancer Res*. 2006;66:6699-6707.
20. Robey IF, Baggett BK, Kirkpatrick ND, et al. Bicarbonate increases tumor pH and inhibits spontaneous metastases. *Cancer Res*. 2009;69:2260-2268.
21. Chen Y, Kung HN, Chen CH, Huang SH, Chen KH, Wang SM. Acidic extracellular pH induces p120-catenin-mediated disruption of adherens junctions via the Src kinase-PKCδ pathway. *FEBS Lett*. 2011;585:705-710.

22. Reiche EMV, Nunes SOV, Morimoto HK. Stress, depression, the immune system, and cancer. *Lancet Oncol*. 2004;5:617-625.
23. Huber V, Camisaschi C, Berzi A, et al. Cancer acidity: an ultimate frontier of tumor immune escape and a novel target of immunomodulation. *Semin Cancer Biol*. 2017;43:74-89.
24. Ibrahim-Hashim A, Cornnell HH, Abrahams D, et al. Systemic buffers inhibit carcinogenesis in TRAMP mice. *J Urol*. 2012;188:624-631.
25. Pilon-Thomas S, Kodumudi KN, El-Kenawi AE, et al. Neutralization of tumor acidity improves antitumor responses to immunotherapy. *Cancer Res*. 2016;76:1381-1390.
26. Pötzl J, Roser D, Bankel L, et al. Reversal of tumor acidosis by systemic buffering reactivates NK cells to express IFN-γ and induces NK cell-dependent lymphoma control without other immunotherapies. *Int J Cancer*. 2017;140:2125-2133.
27. Robey IF, Nesbit LA. Investigating mechanisms of alkalinization for reducing primary breast tumor invasion. *Biomed Res Int*. 2013;2013:485196.
28. Silva AS, Yunes JA, Gillies RJ, et al. The potential role of systemic buffers in reducing intratumoral extracellular pH and acid-mediated invasion. *Cancer Res*. 2009;69:2677-2684.
29. Raghunand N, He X, van Sluis R, et al. Enhancement of chemotherapy by manipulation of tumour pH. *Br J Cancer*. 1999;80:1005-1011.
30. Raghunand N, Mahoney B, van Sluis R, Baggett B, Gillies RJ. Acute metabolic alkalosis enhances response of C3H mouse mammary tumors to the weak base mitoxantrone. *Neoplasia*. 2001;3:227-235.
31. Wen Q, Meng X, Xie P, Wang S, Sun X, Yu J. Evaluation of factors associated with platinum-sensitivity status and survival in limited-stage small cell lung cancer patients treated with chemoradiotherapy. *Oncotarget*. 2017;8:81405-81418.
32. Sauvant C, Nowak M, Wirth C, et al. Acidosis induces multidrug resistance in rat prostate cancer cells (AT1) in vitro and in vivo by increasing the activity of the p-glycoprotein via activation of p38. *Int J Cancer*. 2008;123:2532-2542.
33. Faes S, Duval AP, Planche A, et al. Acidic tumor microenvironment abrogates the efficacy of mTORC1 inhibitors. *Mol Cancer*. 2016;15:78.
34. Faes S, Uldry E, Planche A, et al. Acidic pH reduces VEGF-mediated endothelial cell responses by downregulation of VEGFR-2; relevance for anti-angiogenic therapies. *Oncotarget*. 2016;7:86026-86038.
35. Martens A, Wistuba-Hamprecht K, Foppen MG, et al. Baseline peripheral blood biomarkers associated with clinical outcome of advanced melanoma patients treated with ipilimumab. *Clin Cancer Res*. 2016;22:2908-2918.
36. Weide B, Martens A, Hassel JC, et al. Baseline biomarkers for outcome of melanoma patients treated with pembrolizumab. *Clin Cancer Res*. 2016;22:5487-5496.
37. Gerweck LE, Vijayappa S, Kozin S. Tumor pH controls the in vivo efficacy of weak acid and base chemotherapeutics. *Mol Cancer Ther*. 2006;5:1275-1279.
38. Wojtkowiak JW, Verduzco D, Schramm KJ, Gillies RJ. Drug resistance and cellular adaptation to tumor acidic pH microenvironment. *Mol Pharm*. 2011;8:2032-2038.
39. Martin NK, Robey IF, Gaffney EA, Gillies RJ, Gatenby RA, Maini PK. Predicting the safety and efficacy of buffer therapy to raise tumour pHe: an integrative modelling study. *Br J Cancer*. 2012;106:1280-1287.
40. Mccarty MF, Whitaker J. Manipulating tumor acidification as a cancer treatment strategy. *Med Hypotheses*. 2010;15:264-272.
41. Ibrahim-Hashim A, Abrahams D, Enriquez-Navas PM, Luddy K, Gatenby RA, Gillies RJ. Tris-base buffer: a promising new inhibitor for cancer progression and metastasis. *Cancer Med*. 2017;6:1720-1729.
42. Hashim AI, Cornnell HH, de Lourdes Coelho Ribeiro M, et al. Reduction of metastasis using a non-volatile buffer. *Clin Exp Metastasis*. 2011;28:841-849.
43. Ibrahim-Hashim A, Wojtkowiak JW, de Lourdes Coelho Ribeiro M, et al. Free base lysine increases survival and reduces metastasis in prostate cancer model. *J Cancer Sci Ther*. 2011;suppl 1(4)):JCST-S1-004.
44. Vishvakarma NK, Singh SM. Immunopotentiating effect of proton pump inhibitor pantoprazole in a lymphoma-bearing murine host: Implication in antitumor activation of tumor-associated macrophages. *Immunol Lett*. 2010;134:83-92.
45. Wang BY, Zhang J, Wang JL, et al. Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. *J Exp Clin Cancer Res*. 2015;34:85.
46. Zhang JL, Liu M, Yang Q, et al. Effects of omeprazole in improving concurrent chemoradiotherapy efficacy in rectal cancer. *World J Gastroenterol*. 2017;23:2575-2584.
47. Anemone A, Consolino L, Arena F, Capozza M, Longo DL. Imaging tumor acidosis: a survey of the available techniques for mapping in vivo tumor pH. *Cancer Metastasis Rev*. 2019;38:25-49.
48. Hashim AI, Zhang X, Wojtkowiak JW, Martinez GV, Gillies RJ. Imaging pH and metastasis. *NMR Biomed*. 2011;24:582-591.
49. Chen LQ, Pagel MD. Evaluating pH in the extracellular tumor microenvironment using CEST MRI and other imaging methods. *Adv Radiol*. 2015;2015:206405.
50. van Zijl PCM, Yadav NN. Chemical exchange saturation transfer (CEST): what is in a name and what isn't? *Magn Reson Med*. 2011;65:927-948.
51. Sonveaux P, Végran F, Schroeder T, et al. Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *J Clin Invest*. 2008;118:3930-3942.
52. Végran F, Boidot R, Michiels C, Sonveaux P, Feron O. Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-κB/IL-8 pathway that drives tumor angiogenesis. *Cancer Res*. 2011;71:2550-2560.
53. Goetze K, Walenta S, Ksiazkiewicz M, Kunz-Schughart LA, Mueller-Klieser W. Lactate enhances motility of tumor cells and inhibits monocyte migration and cytokine release. *Int J Oncol*. 2011;39:453-463.
54. Hunt TK, Aslam RS, Beckert S, et al. Aerobically derived lactate stimulates revascularization and tissue repair via redox mechanisms. *Antioxid Redox Signal*. 2007;9:1115-1124.
55. Sonveaux P, Copetti T, De Saedeleer CJ, et al. Targeting the lactate transporter MCT1 in endothelial cells inhibits lactate-induced HIF-1 activation and tumor angiogenesis. *PLoS One*. 2012;7:e33418.
56. Fischer K, Hoffmann P, Voelkl S, et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood*. 2015;109:3812-3820.

57. Mendler AN, Hu B, Prinz PU, Kreutz M, Gottfried E, Noessner E. Tumor lactic acidosis suppresses CTL function by inhibition of p38 and JNK/c-Jun activation. *Int J Cancer*. 2012;131:633-640.
58. Errea A, Cayet D, Marchetti P, et al. Lactate inhibits the pro-inflammatory response and metabolic reprogramming in murine macrophages in a GPR81-independent manner. *PLoS One*. 2016;11:e0163694.
59. Gottfried E, Kunz-Schughart LA, Ebner S, et al. Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. *Blood*. 2006;107:2013-2021.
60. Nasi A, Fekete T, Krishnamurthy A, et al. Dendritic cell reprogramming by endogenously produced lactic acid. *J Immunol*. 2013;191:3090-3099.
61. Husain Z, Huang Y, Seth P, Sukhatme VP. Tumor-Derived lactate modifies antitumor immune response: effect on myeloid-derived suppressor cells and NK Cells. *J Immunol*. 2013;191:1486-1495.
62. Brand A, Singer K, Koehl GE, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab*. 2016;24:657-671.
63. Robey IF, Martin NK. Bicarbonate and dichloroacetate: evaluating pH altering therapies in a mouse model for metastatic breast cancer. *BMC Cancer*. 2011;11:235. doi: 10.1186/1471-2407-11-235
64. Park JM, Recht LD, Josan S, et al. Metabolic response of glioma to dichloroacetate measured in vivo by hyperpolarized ^{13}C magnetic resonance spectroscopic imaging. *Neuro Oncol*. 2013;15:433-441.
65. Anemone A, Consolino L, Conti L, et al. In vivo evaluation of tumour acidosis for assessing the early metabolic response and onset of resistance to dichloroacetate by using magnetic resonance pH imaging. *Int J Oncol*. 2017;51:498-506.
66. Pértega-Gomes N, Vizcaíno JR, Miranda-Gonçalves V, et al. Monocarboxylate transporter 4 (MCT4) and CD147 overexpression is associated with poor prognosis in prostate cancer. *BMC Cancer*. 2011;11:312.
67. Gallagher SM, Castorino JJ, Wang D, Philp NJ. Monocarboxylate transporter 4 regulates maturation and trafficking of CD147 to the plasma membrane in the metastatic breast cancer cell line MDA-MB-231. *Cancer Res*. 2007;67:4182-4189.
68. Keating SE, Zaiatz-Bittencourt V, Loftus RM, et al. Metabolic reprogramming supports IFN-γ production by CD56bright NK cells. *J Immunol*. 2016;196:2552-2560.
69. Donnelly RP, Loftus RM, Keating SE, et al. mTORC1-dependent metabolic reprogramming is a prerequisite for NK cell effector function. *J Immunol*. 2014;193:4477-4484.