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EDITORIAL

3-bromopyruvate (3BP) a fast acting, promising, powerful, specific, and effective "small molecule" anti-cancer agent taken from labside to bedside: introduction to a special issue

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Abstract Although the "Warburg effect", i.e., *elevated glucose metabolism to lactic acid (glycolysis) even in the presence of oxygen,* has been recognized as the most common biochemical phenotype of cancer for over 80 years, its biochemical and genetic basis remained unknown for over 50 years. Work focused on elucidating the underlying mechanism(s) of the "Warburg effect" commenced in the author's laboratory in 1969. By 1985 among the novel findings made two related most directly to the basis of the "Warburg effect", the first that the mitochondrial content of tumors exhibiting this phenotype is markedly decreased relative to the tissue of origin, and the second that such mitochondria have markedly elevated amounts of the enzyme hexokinase-2 (HK2) bound to their outer membrane. HK2 is the first of a number of enzymes in cancer cells involved in metabolizing the sugar glucose to lactic acid. At its mitochondrial location HK2 binds at/near the protein VDAC (voltage dependent anion channel), escapes inhibition by its product glucose-6-phosphate, and gains access to mitochondrial produced ATP. As shown by others, it also helps immortalize cancer cells, i.e., prevents cell death. Based on these studies, the author's laboratory commenced experiments to elucidate the gene basis for the overexpression of HK2 in cancer. These studies led to both the discovery of a unique HK2 promoter region markedly activated by both hypoxic conditions and moderately activated by several metabolites (e.g., glucose), Also discovered was the promoter's regulation by epigenetic events (i.e., methylation, demethylation). *Finally, the author's laboratory turned to the most important objective. Could they selectively and completely destroy cancerous tumors in animals?* This led to the discovery in an experiment conceived, designed, and conducted by Young Ko that the small molecule 3-bromopyruvate (3BP), the subject of this mini-review series, is an incredibly powerful and swift acting anticancer agent. Significantly, in subsequent experiments with rodents (19 animals with advanced cancer) Ko led a project in which 3BP was shown in a short treatment period to eradicate all (100%). Ko's and co-author's findings once published attracted global attention leading world-wide to many other studies and publications related to 3BP and its potent anti-cancer effect. This Issue of the *Journal of Bioenergetics and Biomembranes* (JOBB 44-1) captures only a sampling of research conducted to date on 3BP as an anticancer agent, and includes also a Case Report on the first human patient known to the author to be treated with specially formulated 3BP. Suffice it to say in this bottom line, "3BP, a small molecule, results in a remarkable therapeutic effect when it comes to treating cancers exhibiting a "Warburg effect". This includes most cancer types.

Much of the work described herein that related to work of PLP and co-workers was supported by NIH grants CA l0951 and CA 80018. Work spearheaded by Young Ko showing the capacity of the anticancer agent 3BP to eradicate cancerous tumors in animals can be viewed in a seminar presented by PLP at the NIH. (Permanent link: http://videocast.nih.gov/launch.asp?14962)

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Introduction

"Cancer" is perhaps the most feared word of humans on this planet as most know this insidious disease is rarely curable even though the search for a cure has likely been going on since humans inhabited the earth. They know also that the chance of them acquiring this disease (1 of 2 men; 1 of 3 women) is quite high (Hayat et al. 2007) and that cancer does not discriminate. The rich, the poor, the middle class, and the good, the bad, and beautiful throughout the world are all susceptible to acquiring cancer in their lifetime. Moreover, most know that once acquired the prognosis is rarely favorable and treatments that rarely work are expensive. Unless our scientists do better, including the author and his coworkers, one in two men and one of three women in this 21st century will continue to die of cancer. What this tells us is that cancer is very difficult to cure especially after it has metastasized from its primary site of origin to multiple sites throughout the body. The author and his colleagues have really tried very hard to do better and this leads to the subject of this minireview, i.e., the small molecule 3BP. It does give hope that in some cases (with hope for many cases in the future), that we may be able to defeat the demon within.

The author of this Introduction and organizer of this minireview series focused on 3BP, commenced work on the bioenergetics of cancer as a junior faculty member at Johns Hopkins University, School of Medicine, Baltimore, MD in the year 1969. He had just completed work as a Post Doctoral Fellow with the late Albert L. Lehninger, a world renowned biochemist. The author's initial research related to the respiratory capacity of tumor cells, a subject long studied much earlier by the German biochemist, Otto Warburg (1930, 1956). Significantly, Warburg's studies showed that cancers' most common biochemical property (phenotype), i.e., the "Warburg effect", is their high rates of "glycolysis" (high conversion of the sugar glucose to lactic acid) even when oxygen is present. In contrast, most normal cells metabolize glucose completely to carbon dioxide and water, the final steps involving oxygen requiring mitochondria. In most tissues very little lactic acid is formed except in muscle following exercise, particularly prolonged exercise.

Warburg attributed tumors' high glycolytic property to "something different/defective" in the cellular bodies responsible for respiration (oxygen consumption) coupled to "energy" production. Based in large part on the early work of Kennedy and Lehninger (1949), these cellular bodies are now known to exist as numerous cellular organelles (frequently 1–2 thousand/cell) coined "Mitochondria" or "power houses" that make abundant amounts of the "high energy" compound ATP that provides the energy to make all things large and small within our tissues/cells. Although Stockholm awarded Warburg 2 Nobel prizes, he unfortunately was unable to complete two major jobs, i.e., first discovering what causes at a molecular level the aberrant metabolism (high rates of glucose conversion to lactic acid), and second discovering something that will kill it without harming normal cells. Warburg died in 1970, 1 year after the author commenced working on the subject.

Stepping in as a new faculty member at Johns Hopkins University, School of Medicine (JHUSOM) in 1968 the author was very fortunate to be given the opportunity by his Chairman Albert L. Lehninger to conduct biomedical research on whatever he wished. For that he will be forever grateful. The author chose to follow in the footsteps of Warburg. This decision would lead with many excellent students over the next four decades to a number of separate and sequential discoveries about cancers that exhibit the "Warburg effect", i.e., a high rates of conversion of the sugar glucose to the ultimate product lactic acid in the presence of oxygen (Warburg 1930, 1956). Contributors to this research in the author's laboratory, in the order of first to most recent, were James Schreiber, William Catterall, William Coty, Terry Eska, Ernesto Bustamante, Richard Nakashima, Janna Wehrle, David Parry, Marco Paggi, Krishan Arora, Young Ko, Min Gyu Lee, Asish Goel, Annette Rempel, Curt Heese, and Saroj Mathupala representing respectively the following countries of origin: U.S., U.S., U.S., U.S., Peru, U.S., U.S., Canada, Italy, India, Korea/U.S., Korea, India, Germany, U.S., Sri Lanka.

Collectively the discoveries made working with these excellent past students have given the author and hopefully those interested in the rest of the world, a better understanding of the "Warburg effect" and therefore cancer at the organelle, biochemical, bioenergetic, molecular, gene and epigenetic levels. They also helped lead to a very serious focus on discovering a potent anticancer agent. Fortunately these efforts eventually resulted in the "hands on" discovery by Young Ko (Ko et al. 2001) of 3BP whose patented formulation has really worked exceptionally well in animal studies and shown promise in humans, e.g., as described in the Case Report (Ko et al. 2012) presented in this same Volume of the *J. Bioenergetics and Biomembranes*.

Part 1: Cancer related work in the author's laboratory prior to the discovery of 3-bromopyruvate as an anticancer agent

Below is listed a "sampling" of published mitochondrial/glycolytic/Bioenergetic Cancer Related "Discoveries/Finding" made in the author's laboratory prior to the discovery of 3BP as an anticancer agent. Those Discoveries/Findings

included are listed roughly in the order (time sequence) in which they occurred. Studies of Cancers/Cancer cells included were those that exhibit a "Warburg effect", i.e., a high conversion of the sugar glucose to lactic acid even in the presence of oxygen.

Discovery 1 (Schreiber et al. 1970): The finding was made that a rapidly growing liver cancer (hepatoma) that exhibits a "*Warburg effect"* (high glycolysis) contains a much lower content of mitochondria than normal cells. This finding, found also for other tumors exhibiting a Warburg effect, suggests that tumors alter their energy metabolism so they can thrive off either glycolysis or mitochondria (or both) for their energy source (ATP). In this way the tumors' cancer cells can escape death from an agent that targets only the mitochondria or an agent that targets only glycolysis. *It is very important to note that to kill cancer cells based on their energy metabolism one must destroy both energy production factories, mitochondria and glycolysis while leaving normal cells alone.* To a large extent the strategy to win the war on cancer differs little from the strategy used by nations at war. If nation 1 can destroy nation 2's power plants and weapon making factories before nation 2 destroys their own, then nation 1 is likely to win the war. However, nation 1 must be sure they complete the job, i.e., destroy all of nation 2's power plants.

Discovery 2 (Pedersen et al. 1971) including students Catterall and Eska was the finding that mitochondria from a malignant hepatoma failed to exhibit a significant 2,4-dinitrophenol-activated ATPase activity. This finding suggests that at least some and perhaps many cancers block the mitochondrial ATP synthase's reverse reaction by a mechanism that remains unknown but one that assures that when ATP is made it can be used to drive biosynthetic reactions that support tumor growth and not wasted via ATP hydrolysis.

Discovery 3 (Bustamante and Pedersen 1977, Bustamante et al. 1981) was the finding that mitochondrially bound hexokinase, later identified as HK2 (Nakashima et al. 1986) is the Pivotal Player in the "Warburg effect". HK2 as other hexokinases makes glucose-6-P, a major biosynthetic precursor essential for synthesizing cell building blocks. By producing at high rates glucose-6-phosphate (G-6-P), HK2 at its mitochondrial location facilitates cancer cell's growth and division. That HK2 is essential for the "Warburg effect" was shown *via the following experiments:*

1. Addition of tumor mitochondria containing bound HK2 to tumor cytosol lacking mitochondria increases the glycolytic rate to levels of those found for the tumor cytoplasm.
2. Addition of tumor mitochondria containing bound HK2 to liver cytosol (lacking mitochondria) enhanced its glycolytic rate to levels approaching those of the tumor cytoplasm.

These earlier discoveries in the author's laboratory leave little doubt that HK2 is a pivotal player, most likely "the" pivotal player, in the "Warburg effect" common to most cancers that occur in humans, and likely in many animals as well. In addition, mitochondrial bound HK2 by producing large amounts of glucose-6-phosphate facilitates biosynthesis of cell building blocks essential to make more cancer cells following cell division.

Discoveries 4–6 (Rempel et al. 1996; Mathupala et al. 2001; Lee and Pedersen 2003; Goel et al. 2003) were made in the author's laboratory showing that the HK2 gene responsible for the overproduction of HK2 involved in the Warburg effect is a) amplified, b) activated by a number of relevant metabolic factors at its proximal promoter, and c) subject to epigenetic regulation). Collectively, these studies show that although the gene encoding HK2 remains quite silent in most normal cells, it comes very much to life when normal cells are converted to rapidly growing cancer cells.

In addition to the above 6 discoveries made in the author's laboratory as it relates to the importance of HK2 in many cancers, a 7th discovery made by others that HK2 when bound to mitochondria at/near VDAC also suppresses cell death (Pastorino et al. 2002 and Robey and Hay 2005) should be noted. This discovery further emphasizes the insidious role of HK2, not only in contributing to the growth of cancers, but to their immortality as well.

Based on the above 7 discoveries the exceptionally sinister behavior and objectives of cancer cells began to make sense to the author and his colleagues from both a gene based and "bioenergetic" perspective. Thus, during cancer cell development in response to certain local "pressures/signals" HK2 is overexpressed and placed on the

mitochondria (bound at or near VDAC). Here, product inhibition of HK2 by glucose-6-phosphate is prevented, the cancer cells are immortalized, and the bound enzyme obtains preferred access to ATP produced by the mitochondria. This allows these cancer cells to make at their leisure large quantities of glucose-6-P that is used not only for the purposes of "feeding" the glycolytic pathway to provide the energy source ATP (in the absence or presence of oxygen), but to provide also carbon precursors for biosynthesis of building blocks for new cancer cells. In addition, the end product lactic acid that is transported out of the cancer cells, likely *via* its acidity preconditions neighboring normal tissues for invasion. Such has been suggested by others (Gatenby and Gawlinski 2003).

Despite the novel and valuable discoveries reviewed above related to basic research on cancer and the role of HK2 (directly or indirectly) in cancers' genesis, progression, immortality and invasion, it would not be until near the turn of this new century (year 1999) that the author decided his laboratory had learned enough. Now it was time to "stand up to cancer" by discovering how to eradicate aggressive cancers in animals. Then, if successful, move the knowledge gained to human cancer patients. However, this would not be a simple task as an agent had to be identified or synthesized that not only targeted and destroyed cancer cells' two major energy production factories (glycolysis and mitochondria) but one that also left the energy production factories of normal cells alone. That is, the agent must be powerful enough to quickly destroy cancer cells while being non-toxic to normal cells.

As indicated in the abstract, that task was accomplished single handedly by Young Ko with whom the co-authors were collaborating and published at the turn of this new century (Ko et al. 2001). Whether by good fortune, serendipity, brilliance or all three, in Ko's first experiment to find a novel anticancer agent she chose to use the small molecule 3BP among the potential anticancer compounds selected. Significantly, she had worked with this compound at Washington State University prior to coming to Johns Hopkins as a Postdoctoral Fellow and was the only person working on the project with "hands on" knowledgeable about 3BP's unique properties. Of the agents Ko chose to test in her first experiment, 3BP was by far the most potent in killing cancer cells that exhibit a "Warburg effect" (Ko et al. 2001). Later she would lead a team effort that resulted in the complete eradication of cancers growing in 19 animals. Tumors in all 19 animals were eradicated by 3BP treatment and lived out their lives without return of cancer (Ko et al. 2004). Significantly, Ko's work on 3BP led to all that follows below as it relates to 3BP as an effective anti-cancer agent.

Part 2: A brief summary of 3BP related articles comprising this J. Bioenergetics and Biomembranes issue focused on 3BP as a potent anticancer agent

Prior to examining these articles the reader should be aware that 3-bromopyruvate is abbreviated in several different ways. The author of this introductory minireview now uses "3BP". The author of the second mini-review uses the abbreviation 3-BP (Shosan 2012). Finally, the authors of the third mini-review use the abbreviation 3-BrPA (Cardaci et al. 2012). Authors of original research articles included in this issue mostly use one or the other of these three abbreviations, or an abbreviation very similar to one of these.

Following this very brief "overview minireview" this series moves on to a second minireview (Shosan 2012) from the Karolinska Institute in Stockholm. Shosan's article entitled "*3-Bromopyruvate: Targets and Outcomes*" should provide the reader a good starting point to learn about 3BP as an anticancer agent. Shosan's article emphasizes that both mitochondrial and glycolytic targets are involved in the action of 3BP, and emphasizes also that more research is warranted to better understand the pharmacokinetics of 3BP and its potential toxic effects on normal cells. Significantly, it has been the finding of Young Ko while working in the author's laboratory using 3BP in animals that at the doses and formulation used by her and coworkers to eradicate tumors there are no obvious toxic effects (Ko et al. 2004). The same applies also to the first human Case Report using 3BP (Ko et al. 2012) presented in this same JOBB issue (Vol. 44-1). The author of this introductory minireview can confirm the studies in animals as he assisted Ko and personally examined each tumor bearing animal on a daily (morning, evening schedule) until its tumor was shown to decrease in size and completely disappear. To say the least, it was an incredible experience, and also a wonderful experience to see each animal cured of cancer and then live out thereafter a normal life without cancer's return.

In the subsequent minireview (Cardaci et al. 2012) entitled *"Targeting Aerobic Glycolysis: 3-Bromopyruvate a Promising Anticancer Drug"* these authors describe the principal mechanisms of action and what they consider to be the main targets of 3BP. As they emphasize, 3BP as an alkylating agent has impressive antitumor effects in several animal models, findings with which most authors of this review series would likely agree. In addition, they discuss chemo-potentiating strategies that may make unparalleled the putative therapeutic efficacy of 3BP's use in clinical settings.

In addition to these two insightful introductory minireviews, this JOBB Volume contains a number of original research articles that provide new information about 3BP as a potent anticancer agent. These are summarized briefly below.

1. Novel research conducted by Nakano et al. (2012) presented in an article entitled *"The Up-regulation of Hexokinase II in Myeloma Cells: Targeting Myeloma Cells with 3-Bromopyruvate"* reported that HK2 is constitutively overexpressed and that 3BP an inhibitor of this enzyme induces cell death. Here, as noted previously in earlier work of others (Pastorino et al. 2002; Robey 2005), it was shown that HK2 is normally bound to the outer mitochondrial membrane in cancer cells where it suppresses cell death. Therefore, it would appear that 3BP brings about some alteration in HK2 (or a nearby protein) that weakens HK2's binding to the outer mitochondrial membrane sufficiently to promote cell death.
2. Novel research of Rodrigues-Ferreira et al. (2012) presented in an article entitled *"Effect of the Antitumoral Alkylating Agent 3-bromopyruvate on Mitochondrial Respiration: Role of Mitochondrially Bound Hexokinase"* describes several observations made with 3BP in the hepatoma cell line HepG2. Thus, this agent was found to inhibit the membrane potential, oxygen consumption, and dehydrogenase activities. Mitochondrially bound HK2 was also inhibited. These studies make clear the inhibitory power of 3BP once it enters cancer cells. Fortunately, we know from other studies that normal cells generally go unaltered by 3BP accounting for its power as a rather specific anticancer agent.
3. Novel research described in the article of Davidescu et al. (2012) *"Bromopyruvate Mediates Autophagy and Cardiolipin Degradation to Monolyso-Cardiolipin in GL15 glioblastoma cells"* extends the potent anticancer power of 3BP to brain cancer. Significantly, the authors show that 3BP induces GL15 glioblastoma cells to undergo viability loss upon treatment with 3BP. The authors further provide evidence that 3BP triggers activation of an autophagic pathway. Significantly, support for a role for 3BP as a potent anti-brain cancer agent comes also from the work reported in the article of El Sayed et al. (2012) entitled *"3-Bromopyruvate Antagonizes Effects of Lactate and Pyruvate, synergizes with Citrate and Exerts Novel Anti-glioma Effects.* Specifically, these authors clearly demonstrated that 3BP induced a caspase-dependent cell death in human glioblastoma multiform cells.
4. Novel research described by Icard and coworkers in an article entitled *"Experimental Results using 3-Bromopyruvate in Mesothelioma:* in vitro *and* in vivo *Effects"* (2012) have examined the effects of 3BP on a rare form of cancer, i.e., mesothelioma, believed to be caused by exposure to asbestos. Here, these investigators report that 3BP induced cell death in two mesothelioma cell lines. This occurred even in cells that are normally refractory to cisplatin, a commonly used anticancer agent used to treat human cancers. Moreover, these workers showed that the survival of nude mice bearing human mesothelioma was significantly prolonged.

5.,6.,7. In other articles included in the special issue of the *Journal of Bioenergetics and Biomembranes*, the contributing authors describe several other cancer types that are also readily inhibited by 3BP. The article of Verhoeven and van Griensven (2012) focused on human leukemia and breast cancer cells, the article of Yu et al. (2012) on hepatocellular carcinoma cells (liver cancer), and the article of Tang et al. (2012) on Colorectal carcinoma.

8. Novel research on several Breast Cancer Cell Lines by Queiros et al. (2012) not only emphasize the power of 3BP in inhibiting breast cancer cells but show that the anticancer effect of 3BP can be enhanced in the cells by using butyrate. Consistent with this finding was the additional finding that butyrate treatment induced localization of monocarboxylate transporter 1 (MCT1) in the plasma membrane as well as its chaperone CD 147. MCT1 is the transporter believed to be active in transporting 3BP into most types of cancer cells.
9. Finally, in the report of Lis and coworkers (2012), the authors show that yeast may be used as a model system for studying the effectiveness of potential anti-cancer agents. Significantly, it is shown that 3BP enters the *Saccharomyces cerevisiae* cells through the transporter Jen1P, a lactate/pyruvate H^+ symporter, and once inside inhibits yeast cell growth. In fact, in this system 3BP is a more effective inhibitor than the well known anticancer agent Gleevec. Interestingly, the sensitivity of yeast to 3BP is enhanced by buthionine sulfoximine that decreases glutathione. Thus, even though 3BP appears to be one of the most powerful and specific anticancer agents discovered to date, these studies in yeast would suggest that 3BP's anticancer activity may be further enhanced by those agents that enter cancer cells and react with glutathione.
10. Case Report: From Lab Side to Bedside: Although last but certainly not least in this special issue of the *Journal of Bioenergetics and Biomembranes* is a Case Report on the first human cancer patient known to the author to be treated with 3BP (Ko et al. 2012). This patient whose life and quality thereof were improved and extended by 3BP suffered from a form of liver cancer known as fibrolamellar hepatocellular carcinoma.

Concluding remarks

Dr. Young Hee Ko working at the bench side in the author's laboratory 1.Discovered in her first experiment to identify an anticancer agent that 3BP is a potent one (Ko et al. 2001), 2. Showed with collaborators that 3BP acts quickly to eradicate cancerous tumors in animals (Ko et al. 2004), i.e., those tumors that exhibit a "Warburg effect", and 3. Moved her discovery in a team effort from the bench side to the bedside (Ko et al. 2012). What will the future hold for this small and powerful anticancer agent? Hopefully, that will be reported in another Chapter that is very long and brings a smile to the face of all that read it. For other recent related reviews see Mathupala et al. 2009, 2010.

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