

The Open Philanthropy Project retained Prof. Chris Somerville, who serves as a generalist scientific advisor, to evaluate a discussion of [3-bromopyruvate as a potential cancer treatment](#). His thoughts follow.

3-Bromopyruvate: An Emerging Therapeutic for Various Types of Cancer

“In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells instead rely on aerobic glycolysis, a phenomenon termed the Warburg effect.” (Vander Heiden et al., 2009). In a 2009 review of the phenomenon in *Science*, Vander Heiden et al. postulated that the phenomenon is related to the fact that cancer cells are proliferative and, therefore, need a significant supply of carbon and nitrogen for synthesis of cellular constituents, in addition to energy. The mechanistic basis of the effect was not apparent at that time but they noted that (oncogenic) activation of growth factor receptors is known to induce signaling pathways that can upregulate glycolysis.

The dependence of many types of cancer cells on enhanced glycolysis has attracted interest as a potential target for therapy. In principle, if drugs can be identified that specifically reduce flux through glycolysis, cancer cells should be differentially sensitive. However, all animal cells rely on glycolysis so it is probably not feasible to completely block glycolysis in all cells. Thus, some finesse would seem to be required to exploit the disproportionate (but not exclusive) dependence of some cancer cells on glycolysis. 3-bromopyruvate (3BP) has long been known to inhibit glycolysis and in 2000 a researcher named Ko started publishing a series of articles showing evidence that 3BP could be used to differentially kill cancer cells (Ko et al, 2012).

“The first striking report on the anticancer effects of 3BP in animals came from Geschwind¹ et al. who demonstrated that the direct intra-arterial delivery of 3BP to a liver-implanted rabbit tumor was effective in inducing death in most of the cancer cells of the primary tumor. Moreover, systemic delivery of 3BP suppressed “metastatic” tumors arising in the lungs without apparent harm to other organs. These findings achieved on the rabbit Vx-2 tumor have later been confirmed by other research groups in different in vivo models such as the rat AS-30D tumor and the mouse hepatocellular carcinoma (HCC), highlighting the ability of 3BP to eradicate advanced cancers without apparent toxicity or recurrence.” (Cardaci et al., 2012). Since that time, 3BP has been reported to be active against liver cancer (hepatocellular carcinomas), brain tumors (glioblastoma), pancreatic ductal adenocarcinomas², some breast cancers, multiple myeloma cells, mesothelioma and possibly others.

The early literature on the mechanism of action suggested that 3BP was relatively specific and acted by inhibiting several enzymes in glycolysis. However, more recent reports state that the biochemical mechanisms underlying action of the drug are not yet clear (Davidescu et al 2014). Birsoy et al (2012) state that “the toxic effect of 3BP is not a result of its anti-glycolytic effect but rather its highly alkylating nature. The stringent correlation between 3BP sensitivity and expression of its transporter but not that of any previously identified metabolic targets or transporters suggests that 3BP is likely nonspecifically toxic once it enters the cell. Consistent with this idea, 3BP has non-glycolytic targets, such as V-ATPases,

¹ Geshwind is a professor at Johns Hopkins who reportedly obtained permission for the first clinical trial in 2009. However that trial did not appear in the NIH database on 12/1/2015 so appears to be complete or abandoned.

² 4th most common cause of cancer death

sarcoplasmic reticulum Ca²⁺-ATPases (SERCAs), carbonic anhydrases and histone deacetylases (HDACs). Whatever the exact mechanism, 3BP induces autophagy, resulting in shrinkage of tumors. “

A clue to the specificity of the drug toward cancer cells comes from a compelling study by Birsoy et al (2012), who showed that the transporter MCT1 is required for uptake of 3BP into tumor cells. MCT1 is highly upregulated in a subset of cancers and may be subject to regulation by some of the same factors that cause upregulation of glycolysis. Thus for example, breast cancer lines with high amounts of MCT1 protein were sensitive to 3BP, whereas those with low or no MCT1 expression were resistant to even high concentrations of 3BP (Birsoy et al., 2012). An implication from this and related work is that tests for MCT1 expression will serve as a biomarker for identifying tumors likely to respond to 3BP treatment (Birsoy et al., 2012). More generally, it may be possible to develop toxic molecules that, in a fashion analogous to 3BP, exploit these transporters to selectively enter and target cancer cells. (Birsoy et al., 2012)

Although 3BP clearly has the ability to differentially kill some types of cancer cells in vitro, progress to the clinic has been slow because new facts are emerging about the mechanism of action and there is concern about toxicity on non target cells in intact humans. For instance Cardaci et al. (2012) write: “Although no clinical trials are so far documentable, 3BP-based pre-clinical studies against a wide variety of tumors are currently being conducted in many laboratories, indicating the putative feasibility of this alkylating compound in the eradication of many forms of cancer that are frequently refractory to standard therapeutics. However, **the lack of clinical studies undertaken with this compound may derive from its capability to affect also the homeostasis of differentiated non-tumors cells.** Indeed, results from our laboratory indicate that primary cortical neurons treated with 3BP are even more susceptible to death with respect to neuroblastoma cells. Therefore, in line with the current chemotherapeutic strategies affecting the specific metabolic activity of tumors, many studies are aimed at identifying combined treatments able to enhance the killing properties of anticancer agents and at the same time at reducing the development of long-term resistance mechanisms and noxious side effects on normal cells.” (Cardaci et al., 2012). Similar comments are made by Chapiro (2014): “However, due to its alkylating properties, 3BP is associated with significant toxicity when delivered systemically in therapeutic doses, which has impeded the clinical development and use of this drug in patients with cancer.”

However, many groups remain interested and optimistic that the negative effects of 3BP may be alleviated by adjuvants or by special methods of introducing the drug into patients. For instance, Cardaci et al (2012) write “... the results obtained from combined therapies open new perspectives on the therapeutic use of 3BP against cancer, allowing detrimental effects of this compound on untransformed cells to be prevented. Therefore, the development of methodologies aimed at increasing its intra-tumor delivery as well as the identification of metabolic conditions able to increase the selectivity of 3BP targets in neoplastic tissues, could drive the process of clinical translation of 3BP for targeting malignancies.”

There have been two uses of 3BP in humans who had exhausted other options. In one case, a 16 year old boy with liver cancer, 3BP extended the patient’s life for about ten months (Ko, 2012). In the other case, a 28-year-old man presented with stage IV metastatic melanoma affecting the back, left pleura, and lung. The clinicians summarized as follows (El Sayed et al., 2014): “the patient received 3BP intravenous infusions (1-2.2 mg/kg), but the anticancer effect was minimal as indicated by a high serum LDH level. This may have been due to high tumor GSH content. On combining oral paracetamol, which depletes tumor GSH, with 3BP treatment, serum LDH level dropped maximally. Although a slow

intravenous infusion of 3BP appeared to have minimal cytotoxicity, its anticancer efficacy via this delivery method was low.” The patient died approximately 25 days after treatment with 3BP.

Conclusions

1. There is widespread interest in using 3BP as a therapeutic agent and many groups around the world are working on various aspects. The publication *J Bioenerg Biomembr* devoted an entire issue to studies of 3BP in 2012. A search on the word “bromopyruvate” in Google scholar resulted in 1370 articles since 2011. By comparison a similar search for carfilzomib, which has recently been approved for therapy, resulted in 4360 articles. The blockbuster bortezomib, which has been used on 400,000 patients, resulted in 38,500 hits.
2. The promise of the drug has attracted some leading people to investigations of the drug (eg. Bert Vogelstein and David Sabatini). Vogelstein won the Nobel prize in 2012 for his insights into cancer.
3. Investigators are able to obtain grant support for research on the drug (see “sources of Support” below). That does not mean that they could not use more support but it means that the drug is in the mainstream research system (as also indicated by the people who are working on it).
4. The drug appears to be a nonspecific toxic agent. Its effects on cancer cells arise from the fact that a specific transporter is upregulated in some types of cancers (along with glycolysis). Since that transporter does not exist to support the growth of cancer cells, it will be important to find out which NORMAL cell types also express the transporter since those cell types will take up the drug and be killed. The comments by Cardaci about cortical neuron susceptibility are a bad sign.
5. I think the field is unfolding as it should. The main experiment I would like to see right now is an analysis of where and when MCT1 is expressed in humans. If it is always expressed at low levels in all cell types (except certain cancers), I think that would be a positive indication for a clinical trial. If not, I don't think it has a promising future because there would be a lot of collateral damage from a therapeutic use involving introduction into the blood.

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Sources of Support (Examples from several of the papers cited here)

It is apparent that funds from conventional sources are available to study the effects of 3BP in preclinical situation.

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Other resources

A large amount of information about bromopyruvate therapy is available on a website called “The Cancer Cure” that is produced by Dr. Athanassiou <http://www.cancercuremedicine.com/what-we-do.html>. The site advocates for direct lobbying of government agencies to conduct clinical trials.