

# MetaBlockPlus

*A combination formula using:*

*HCA*

*Alpha Lipoic Acid*

*Capsicum*

## **SUPPLEMENT COMBINATION GOALS**

Hydroxycitric Acid	.....	3000 mg
Alpha Lipoic Acid	.....	1800 mg
Capsicum	.....	1500 mg

## **Key Features**

**Developed by  
researchers in France and Italy,  
this combination of natural substances  
is designed to target and inhibit  
specific metabolic pathways  
used by cancer cells to grow.**

**Although the formula is  
not available commercially,  
by combining these 3 supplements,  
we are able to offer the same nutrients  
used in the research studies.**

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the Food and Drug Administration.  
This product is not intended to diagnose,  
treat, cure, or prevent any disease.



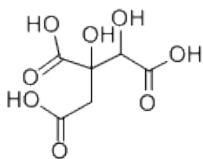
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## Hydroxycitric Acid

Hydroxycitrate is derived from the tropical fruit *Garcinia Cambogia*.

Also known as HCA, it is a natural compound that is a known inhibitor of ATP citrate lyase, an enzyme which is overexpressed in cancer cells.



## Alpha Lipoic Acid

Also called thioctic acid, it is made naturally in the body and may protect against cell damage in a variety of conditions. Known as the “universal oxidant,” it has been used for decades in Europe, especially Germany, to treat nerve conditions, including nerve damage resulting from poorly controlled diabetes.



ALA is a cofactor of the enzyme pyruvate dehydrogenase (PDH), which is down-regulated in cancer cells.

## Capsicum

Derived from the cayenne pepper plant, capsicum has been used for generations for its warming and stimulating nature.

A new component to the original formula, the addition of capsaicin further delays tumor growth in mice in a dose dependant manner.



## Research Summary

The underlying theory for this combination goes back to the seminal work of nobel prize winner (physiology) Otto Warburg, who showed that cancers cells use altered metabolism for growth compared to normal cells. Researchers used knowledge of the metabolic dysregulation of tumor cells to chose substances that would inhibit specific pathways advantageous to cancer cells, and promote normal cell development.

The first study on a combination of hydroxycitrate and alpha lipoic acid as a treatment for tumors was published in 2010. Studies in cell cultures, animal models and early human trials have shown tumor regression and improved survival, equal to that of chemotherapy. Using the formula along with chemotherapy provided an enhanced, synergistic effect in some cases.

## References

Guais, A., G. Baronzio, et al. (2012). "Adding a combination of hydroxycitrate and lipoic acid (METABLOC) to chemotherapy improves effectiveness against tumor development: experimental results and case report." *Invest New Drugs* 30(1): 200-211.

Altered metabolism of cancer first highlighted by Otto Warburg has a long history. Although ignored for a considerable amount of time, it is now receiving substantial attention. We recently published results obtained with a combination of two drugs, lipoic acid and hydroxycitrate, targeting metabolic enzymes particularly affected in cancer: ATP citrate lyase and pyruvate dehydrogenase kinase. This treatment was as efficient as chemotherapy in the three mouse cancer models that were tested. In this work, we asked if our drug combination could be used in conjunction with standard cytotoxic chemotherapy, in particular cisplatin, to improve basic protocol efficacy. A combination of lipoic acid and hydroxycitrate was administered to mice implanted with syngeneic cancer cells, LL/2 lung carcinoma and MBT-2 bladder carcinoma, concomitantly with classical chemotherapy (cisplatin or methotrexate).

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We demonstrate that the triple combination lipoic acid + hydroxycitrate + cisplatin or methotrexate is more efficient than cisplatin or methotrexate used individually or the combination of lipoic acid and hydroxycitrate administered alone. Of particular note are the results obtained in the treatment of an 80 year-old female who presented with ductal adenocarcinoma of the pancreas accompanied by liver metastases. A treatment course using gemcitabine plus alpha-lipoic acid and hydroxycitrate gave highly promising results. The in vivo data, coupled with the case study results, suggest a possible advantage in using a treatment targeted at cancer metabolism in association with classical chemotherapy.

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The metabolism of tumor cells plays an important role in cancer development. Although aerobic glycolysis is inefficient from the standpoint of ATP production, it provides cancer cells with biomolecules implicated in the synthesis of lipids and nucleotides required for cellular proliferation. Thus, targeting aerobic glycolysis has clearly been recognized as a potentially fruitful approach for the treatment of cancer. The inhibition of aerobic glycolysis by a combination of alpha lipoic acid and hydroxycitrate (METABLOC) is efficient to inhibit tumor development in several mouse models. In association with chemotherapy, it seems to improve survival of patients with tumors difficult to treat when compared to a single chemotherapy regimen. We herein report our preliminary cases on both the clinical efficacy and side effects of METABLOC. Eleven patients with advanced metastatic cancer from were treated with per os 0.4 to 1.8 g of lipoic acid and 1.2 to 3 g of hydroxycitrate during 2 to 21 months in addition to their normal chemotherapeutic regimen. Side effects occurred in half of the patients but were mild (grade 1-3) and limited to gastrointestinal disorders that disappeared on using proton pump inhibitors or decreasing the doses. Five patients were characterized by a partial regression, 3 by a stable disease, and 3 by disease progression. In conclusion the results from these preliminary treatments support that METABLOC can be used safely with various common standard

chemotherapeutic regimens. It also suggests that its use may slow down tumor growth, an observation that needs to be confirmed by a randomized controlled trial.

Abolhassani, M., A. Guais, et al. (2012). "Screening of well-established drugs targeting cancer metabolism: reproducibility of the efficacy of a highly effective drug combination in mice." *Invest New Drugs* 30(4): 1331-1342.

Alterations in metabolic pathways are known to characterize cancer. In order to suppress cancer growth, however, multiple proteins involved in these pathways have to be targeted simultaneously. We have developed a screening method to assess the best drug combination for cancer treatment based on targeting several factors implicated in tumor specific metabolism. Following a review of the literature, we identified those enzymes known to be deregulated in cancer and established a list of sixty-two drugs targeting them. These molecules are used routinely in clinical settings for diseases other than cancer. We screened a first library in vitro against four cell lines and then evaluated the most promising binary combinations in vivo against three murine syngeneic cancer models, (LL/2, Lewis lung carcinoma; B16-F10, melanoma; and MBT-2, bladder cancer). The optimum result was obtained using a combination of alpha-lipoic acid and hydroxycitrate (METABLOC(TM)). In this study, a third agent was added by in vivo evaluation of a large number of combinations. The addition of octreotide strongly reduced tumor development (T/C% value of 30.2 to 34.5%;  $P < 0.001$ ) in the same models and prolonged animal survival ( $P < 0.001$ ) as compared to cisplatin. These results were confirmed in a different laboratory setting using a human xenograft model (NCI-H69, small cell lung cancer). None of these three molecules are known to target DNA. The effectiveness of this combination in several animal models, as well as the low toxicity of these inexpensive drugs, emphasizes the necessity of rapidly setting up a clinical trial.

Schwartz, L., A. Guais, et al. (2012). "Tumor regression with a combination of drugs interfering with the tumor

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this work, we demonstrate that the addition of capsaicin further delays tumor growth in mice in a dose dependant manner. This is true for the three animal model tested: lung (LLC) cancer, bladder cancer (MBT-2) and melanoma B16F10. There was no apparent side effect of this ternary combination. The addition of a fourth drug (octreotide) is even more effective resulting in tumor regression in mice bearing LLC cancer. These four compounds are all known to target the cellular metabolism not its DNA. The efficacy, the apparent lack of toxicity, the long clinical track records of these medications in human medicine, all points toward the need for a clinical trial. The dramatic efficacy of treatment suggests that cancer may simply be a disease of dysregulated cellular metabolism.

Schwartz, L., M. Abolhassani, et al. (2010). "A combination of alpha lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models: preliminary results." *Oncol Rep* 23(5): 1407-1416.

The impact of metabolic dysregulation on tumor development has long been established. We have targeted two enzymes that are altered during carcinogenesis: pyruvate dehydrogenase (PDH), which is down-regulated, and ATP citrate lyase, which is overexpressed in cancer cells. Alpha lipoic acid is a cofactor of PDH, while hydroxycitrate is a known inhibitor of ATP citrate lyase. Our hypothesis is that a combination of these drugs may have antitumoral potential. The efficacy of these molecules was screened in vitro by treatment of different human cancer and murine cell lines. Lipoic acid reduced the cell number by 10-50% depending on concentrations (0.1-10 microM) and cell types. Calcium hydroxycitrate reduced the cell number by 5-60% at different concentrations (10-500 microM). When hydroxycitrate and lipoic acid were used together, there was a major cytotoxic effect: complete cell death was seen following 8 microM lipoic acid and 300 microM hydroxycitrate treatment for 72 h. The combination of alpha lipoic acid and hydroxycitrate was administered to healthy mice, at doses currently utilized for other indications than cancer; no demonstrable toxicity was observed. The combination was used to treat mouse syngenic cancer models: MBT-2 bladder transitional cell carcinoma, B16-F10 melanoma and LL/2 Lewis lung carcinoma. The efficacy of this combination appears similar to conventional chemotherapy (cisplatin or 5-fluorouracil) as it resulted in

significant tumor growth retardation and enhanced survival. This preliminary study suggests that this combination of drugs is efficient against cancer cell proliferation both in vitro and in vivo. A clinical trial is warranted.

(2010). “A combination of calcium hydroxycitrate and lipoic acid added to classical chemotherapy improves effectiveness against tumor development.”

Since the seminal work of Otto Warburg (Warburg 1956), it is known that cancer cells are characterized by an increased uptake of glucose and an elevated secretion of lactic acid accompanied by a significant decrease of involvement of the tricarboxylic acid (TCA or Krebs) cycle (frequently called the Warburg effect). Although hypoxia could cause this altered metabolism, many types of cancer cells metabolise glucose directly to lactic acid even under normoxic conditions, hence the term aerobic glycolysis. There is general agreement that this metabolic alteration provides a proliferative advantage to the cancer cell resulting from a redirection of glucose metabolism that allows the cancer cell to maximize the synthesis of key biomolecules, such as nucleic acids and lipids. There is also a prevailing opinion that the redirection of glucose metabolism is under the control of a variety of oncogenic proteins, such as Akt, c-Myc, and Ras.

Among the numerous changes involved in aerobic glycolysis in cancer cells some are particularly important, for instance: increased up-take of glucose in particular by increased levels of glucose transporter-1, utilization of hexokinase-II as the principle isoform, reduction of pyruvate kinase activity, inactivation of pyruvate dehydrogenase, and upregulation of ATP citrate lyase. Our hypothesis was that targeting two or more of these specific alterations could be an efficient strategy to inhibit cancer growth.

We initially decided to target both pyruvate dehydrogenase and ATP citrate lyase, encouraged by the recent results of Bonnet et al. (2007) and Hatzivassiliou et al. (2005). We chose to target restoration of PDH activity through the use of alpha lipoic acid (ALA), a known inhibitor of PDHK1, which is in turn an inhibitor of PDH (Korotchkina et al. 2004), and to inhibit ATP citrate lyase by using a known

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inhibitor, calcium hydroxycitrate (HCA) (Berkhout et al. 1990).

In a first series of experiments, we reported that these two non-toxic and easily available drugs were highly effective in mouse cancer models when used in combination (Schwartz et al. 2010). The efficacy of this combination appeared to be similar to conventional chemotherapy (cisplatin or 5-FU).

### Conclusions

The combination of alpha lipoic acid (pyruvate dehydrogenase activator) and calcium hydroxycitrate (ATP citrate lyase inhibitor) inhibits tumor growth in LLC and MBT-2 mouse cancer models.

The ALA+HCA combination potentiates the effectiveness of standard chemotherapeutic drugs such as cisplatin and methotrexate.

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