Jeffrey Dach MD
*Bioidentical Hormones Natural Thyroid*

# Alpha Lipoic Acid Anticancer Agent Burt Berkson MD

Posted on **May 31 2016**

**Alpha Lipoic Acid**

**Anti-Cancer Update**

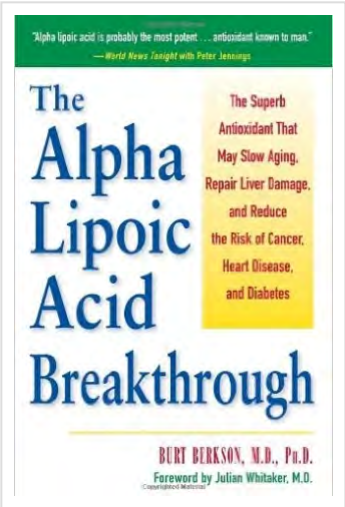
**with Burt Berkson MD**

Medical meetings these days force us to endure hours of boredom, until we finally get to the “really useful and important stuff”. So it was at a recent meeting at the Diplomat Hotel here in Hollywood, Florida. *Upper left image, Poison Mushroom called “The Destroying Angel”, Amanita Verna, courtesy of ActaFungorum.org*

**Presentation by Bert Berkson MD**

The hidden gem that made the trip worthwhile was Burt Berkson’s presentation on Alpha Lipoic Acid during an afternoon breakout session. *Left image Alpha Lipoic Acid Book Cover Courtesy of Burton Berkson MD.*

In the year 1977, I was was just finishing medical school. This same year, Burton Berkson was saving his first patient from an agonizing death from hepatic necrosis after eating the poison mushroom, Amanita Verna, **“The Destroying Angel”**.




Apparently, Dr Berkson had studied mycology at Rutgers, earning his PhD in the field. Later on, during his first year as a medical resident, he was responsible for the care of an unfortunate patient dying of hepatic failure from acute mushroom poisoning. He recalled he had read an article about Alpha Lipoic Acid as an antidote for mushroom poisoning.(6) So, he placed a call to Fred Bartter at the NIH, and asked for a prompt overnight air shipment of Alpha Lipoic Acid. Upon infusing the drug into the dying patient, much to the disbelief of his superiors, the patient miraculously recovered and is still alive today.(1-5)

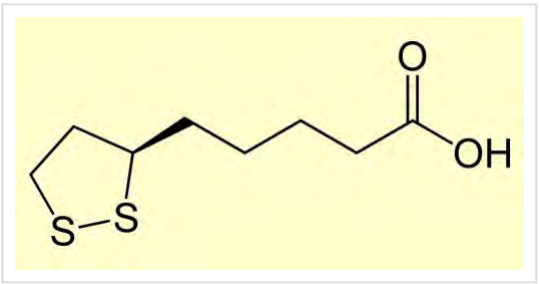
**75 of 79 Patients Survived**

Over time, Drs Burt Berkson and Fred Bartter collaborated in the treatment of 79 similar patients, all dying of hepatic failure. 75 of the 79 patients survived with the intravenous alpha lipoic acid treatment , a remarkable accomplishment.(7)
(Note: alpha lipoic acid is also called Thioctic Acid)

*Above Image: 1978 (center) Burt Berkson MD PhD and left Fred C Bartter MD (Chief NIH), (right) Barry Rumack MD , visiting at the Max Planck Institute in Heidelberg, Germany. Courtesy of Burton Berkson MD slide presentation.(5-6)*

Drs Bartter and Berkson filed for an NDA with the FDA (New Drug Application 9957), and for the next 23 years, Dr Berkson was deemed “FDA principal investigator” for alpha lipoic acid.(7)

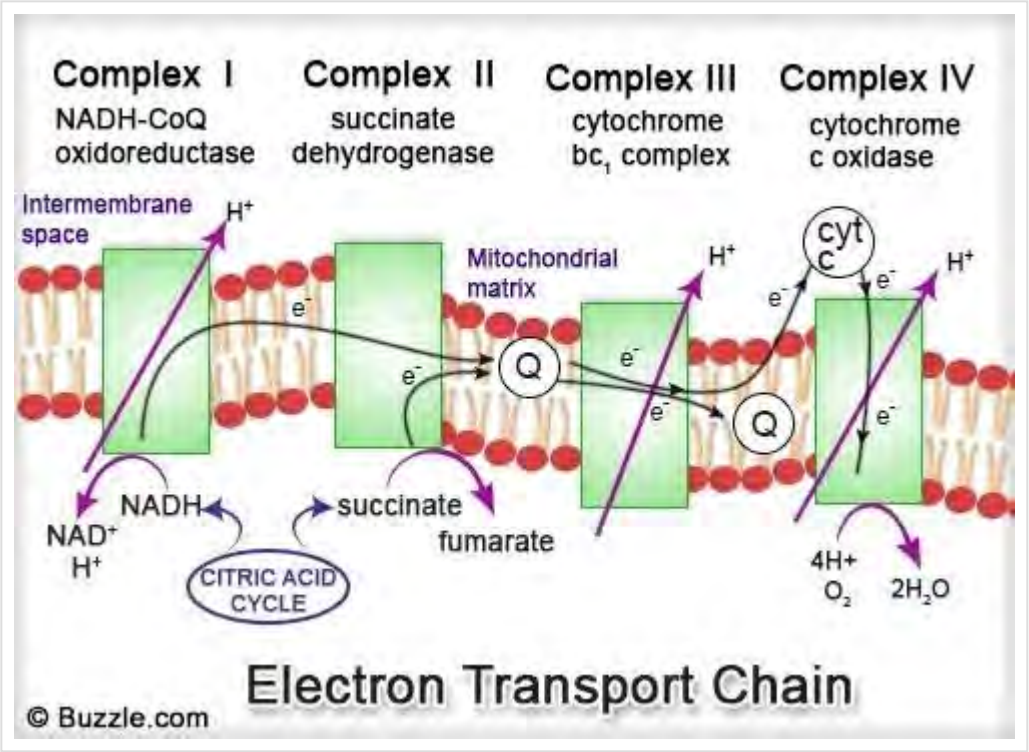
### A New Discovery: ALA Effective for Cancer




Early on, while embarking on his medical career treating out-patients with liver disease at his clinic Las Cruces, New Mexico, Dr Berkson observed an unexpected finding in his patients who coincidentally had cancer. Pancreatic and hepatic cancer patients went into remission after IV alpha lipoic acid treatment. (3) The alpha lipoic acid had a beneficial effect, selectively killing cancer cells while leaving normal cells unharmed. *Left Image Alpha Lipoic Acid Chemical Structure Courtesy of wikimedia commons.*

### Molecular Mechanism of ALA Effect on Cancer Cells

The exact molecular mechanism for this remarkable cell killing effect of ALA on cancer cells was elucidated in a series of studies by Drs. Paul Bingham (15), Bastian Dörsam, Perrine Kafara, Lioubov G Korotchkina, Uwe Wenzel , and Benedikt Feuerecker (9-15)



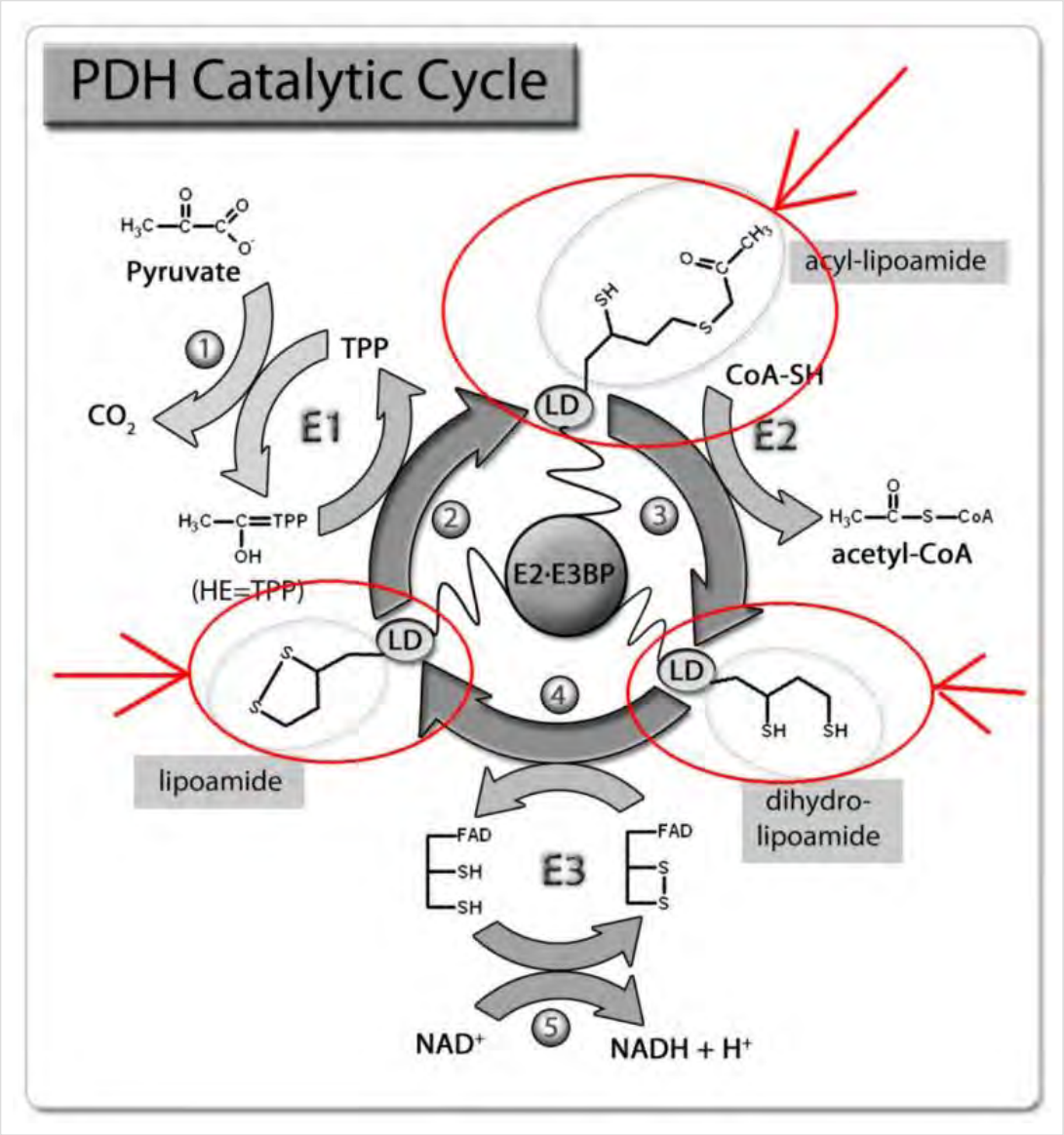

*Above image: Electron Transport Chain courtesy of Buzzle.com*

### Pyruvate Dehydrogenase Complex

Alpha lipoic acid is the key enzyme and regulator of the Pyruvate Dehydrogenase Complex, primary gateway for carbon into the TCA (Tri Carboxylic Acid Cycle) which drives the oxygen dependent mitochondrial electron transport chain.(15).

Diagram below shows key role of Lipoic Acid (LD), (see Red Arrows) in the pyruvate dehyrogenase cycle which converts pyruvate to acetyl Co-A. Notice co-factor TPP, this is Thiamine-pyro-phosphate. Another needed

cofactor is Carnitine which shuttles the Acetyl-CoA into the mitochondria (not shown).(15)




*Above Left Image courtesy of Chapter 3 The Pyruvate Dehydrogenase Complex in Cancer: Implications for the Transformed State and Cancer Chemotherapy By Paul M. Bingham and Zuzana Zachar in Biochemistry, Genetics and Molecular Biology edited by Rosa Angela Canuto, Published: November 14, 2012. (15)*

**PDK Upregulateion Central Element of Cancer Cell Metabolism**

Firstly, the cancer cell's metabolism is upregulated, with increased uptake of both glucose and glutamine. Secondly, the cancer cell metabolism is redirected to provide increased levels of anabolic substrates for nucleotide and amino acid synthesis, needed for rapid cell proliferation. Thirdly, PDK (pyruvate dehydrogense kinase) is frequently upregulated in cancer cells. thus inhibiting PDC (pyruvate dehydrogenase complex) which down regulates carbon flow through the PDH pathway.(15) Indeed this upregulation of PDK, and downregulation of PDC is the central element in cancer cell metabolism.

**Lipoic Acid Increases PDC Activity**

According to Dr. Korotchkina (12):

> *"An inhibitory effect of lipoic acid on PDKs would result in… increased PDC pyruvate dehydrogenase complex (PDC) activity. This finding provides a possible mechanism for a glucose (and lactate) lowering effect of R-lipoic acid in diabetic subjects."*

Dr Wenzel studied the effect of Lipoic Acid on Colon cancer cells, finding:

> *"ALA was able to increase Oxygen generation inside mitochondria. Increased mitochondrial O2 production was preceded by an increased influx of lactate or pyruvate into mitochondria, and resulted in the down-regulation of the anti-apoptotic protein bcl….In contrast to HT-29 (colon cancer) cells, no apoptosis was observed in non-transformed human colonocytes (normal cells) in response to ALA."*

In 2012, Dr Benedikt Feuerecker studied the effect of ALA on neuroblastoma cells and breast cancer cells. He found the following:

> *Lipoic Acid can (1) reduce cancer cell viability/proliferation, (2) reduce uptake of glucose ([18F]-FDG) (3) reduce lactate production and (4) increase apoptosis in all investigated cancer cell lines.*

This is how Dr Berkson explained it in his talk:

Cancer cells use the Warburg Effect, preferentially metabolizing carbon via anaerobic pathways that produce lactic acid. Although this pathway is inefficient, it shunts much needed carbons into building materials for rapid cell replication. *Left image courtesy of Burton Berkson MD.*

Normal cells use the PDC Pyruvate Dehydrogenase enzyme to direct pyruvate (carbon) into the more efficient mitochondrial electron transport chain, producing large amounts of energy per carbon atom. Operating this electron transport chain produces damaging oxidative byproducts called ROS reactive oxygen species. This is no problem for the normal cell which has anti-oxidant protection. The cancer cell, on the other hand, has little protection from this oxidative onslaught, making the cancer cell susceptible to oxidative therapies such as alpha lipoic acid.

**Shunting Carbon Into Mitochondrial Electron Transport**

As mentioned above, the central metabolic feature of the cancer cell is the inhibition of the PDC which blocks entry of carbon into the electron transport chain. If we could find some way to force the Cancer Cell to use the mitochondrial electron transport chain, this would overwhelm the mitochondria which would then "burn up" and trigger apoptosis, i.e. programmed cell death. This is exactly what alpha lipoic acid does at the molecular level.

**PDC Gateway for Carbon Into Metabolic Pathway**

The PDC and PDK enzyme are the primary gateway for carbon metabolism. The alpha lipoic acid inhibits pyruvate dehydrogenase kinase (PDK), which upregulates the pyruvate dehydrogenase complex (PDC). This forces the cancer cell to use the mitochondrial electron transport chain, an intolerable state inducing mitochondrial

apoptosis of the cancer cell. The net result looks something like the transmission electron microscope images from Vigil et al below.(7)



Left Image:

Healthy control mitochondria in a monkey.

Notice intact membranes and cristae ultrastructure Fig 1 Vigil et al.(7)

Next we have an abnormal mitochondria image:



Left Image:

Disrupted Ultrastructure of Mitochondria caused by excess Alpha Lipoic Acid inducing ROS and lipid peroxidation. Fig 2 Vigil.et al (7)

Although these images are from a study using excess amounts of alpha lipoic acid in a monkey model, (Vigil)(7), a similar effect occurs in cancer cells which cannot tolerate the increased electron flux through the mitochondrial respiratory chain, resulting in lipid peroxidation, oxidative damage to the ultrastructure of the membranes and cristae, triggering release of cytochrome C, and caspace induced mitochondrial apoptosis. This alpha lipoic effect effect is synergistic with high dose Intravenous vitamin C which also acts as a pro-oxidant in the mitochondria as demonstrated by Dr Jiliang in his study "Multiple myeloma tumor cells are selectively killed by pharmacologically-dosed ascorbic acid." published in 2017 in EBioMedicine.

**Addition of Hydroxy Citrate improves effect of ALA**

In a series of studies authored by Laurent Schwartz, the addition of hydroxycitrate increases the effect of ALA. Hydroxycitrate is a known inhibitor of ATP citrate lyase ( also called **ATP-citric synthase)**, an enzyme frequently upregulated in cancer cells, a useful anti-cancer target, and the subject of a patent. (46,47).

*Above image: Pyruvate Dehydrogenase Complex with Alpha Lipoic Acid) as "swinging arm" and central spokes of the wheel (blue molecules with E2 in center) Courtesy of Principles of Biochemistry 2006 Pearson.*

**Benfotiamine (Thiamine) and Carnitine**

Both thiamine and carnitine are cofactors for PDC delivery of carbon to the TCA and mitochondrial electron transport chain. Adding these vitamins might enhance the Alpha Lipoic Acid anti-cancer effect, as they increase PDC activity, driving carbon flux into mitochondrial electron transport chain, causing apoptosis of the cancer cell. These effects have been reported. (27)(39-41) However we await combination studies showing the effect of thiamine and carnitine in combination with ALA.

**Ovarian Cancer ALA, Vitamin K2 and CoQ10(44)**

Dr Kafara reported in 2015 alpha lipoic acid effective against ovarian cancer cells (11) Dr Shibayama-Imazu reported in 2006 vitamin K2 produces superoxide and mitochondrial apoptosis in ovarian cancer cells.(29-31) Vitamin K2, like Ubiquinone (CoQ10) is an electron carrier in the mitochondria, thus "rescuing" defective mitochondria in cancer cells, making them run oxidative phosphorylation, which triggers mitochondrial apoptosis. I would theorize that both Ubiquinone (CoQ10) and Vitamin K2 would augment the effect of Alpha Lipoic Acid, working together in synergy to kill the cancer cells.(44) However, we await confirmation with combination studies. (44) Vitamin K3 (menadione) studies show synergy with anti-cancer effects of high dose Intravenous vitamin C.

**ALA Synergy with Melatonin**

Melatonin enhances mitochondrial ATP production and scavenges ROS in normal cells, yet, selectively causes apoptosis in cancer cells by downregulating the Warburg effect. (58-70) Dr Reiter says(59-60):

> *"Melatonin behaves as a 'smart killer', i.e., modulating anti-apoptotic processes in normal cells, and **triggering pro-apoptotic signals** in **cancer cells"** …. "This pro-apoptotic action of melatonin in cancer cells is diametrically opposite to its anti-apoptotic function in normal cells, a differential action that has been difficult to explain.*

Dr Nicola Pacini from Florence wrote a brilliant review of melatonin's anticancer effects in Int J Mol Sciences 2016. (69) Dr Nicola Pacini says:

> *"mitochondria of **neoplastic cells actually have a strong decoupling of the oxidative phosphorylation**." ….." the **production of ROS is extremely harmful for the mitochondrial structures…..**"the paradoxical action of MLT (melatonin), able to induce cellular death in cancer cells and cytoprotection in models of neurodegeneration, is quite appropriate. This molecule (melatonin), in fact, **stimulates the activity of respiratory complexes I, II, and IV, and has a marked effect on complex III**, thus being able to **achieve a strong perturbation of the electron transport chain in neoplastic cells**, also preventing the braking action of BCL-2 and overstimulating an already metastable cellular system, characterized by a **high electron flow through the electron transport chain, high oxygen consumption, UCP-mediated uncoupling and high sensitivity to ROS."***
>
> *" **substances that, also at the end of respiratory complexes, force the cellular respiration, such as dichloroacetate, thiamine or . R-lipoic acid, induce ROS-mediated cell death in neoplastic cells and neuroprotection in many neurodegenerative diseases."(69)***

Since both ALA (Alpha Lipoic Acid) and Melatonin act to force cancer cell mitochondrial respiration with increased electron flux through the mitochondrial electron transport chain, one might speculate on synergistic anti-cancer effects. However, we await further studies for confirmation of the hypothesis.(58-70)

**Artemisinin in Combination with ALA**

My previous article discussed the anti-cancer, anti-malarial, botanical extract, artemisinin, which contains the endoperoxide bridge, two oxygen molecules which react with iron in the lysosome of the cancer cell, thus causing "ferro-apoptosis". These oxidative byproducts are delivered to the mitochondria which in turn induce mitochondrial apoptosis (cell death). Since the effect of ALA is to drive oxidative cancer cell death, I would expect artemisinin and Alpha Lipoic Acid to work well in combination, producing synergistic effects. However, we await the results of these combination studies.

**ALA Synergy with Sulforaphane**

Sulforaphane, a sulfur containing extract from broccoli sprouts, has anti-cancer stem cell activity, and is known to downregulate intracellular glutathione, thus making the cancer cell more susceptible to the damaging effects of ROS (reactive oxygen species) produced by the alpha lipioic acid treatment. One might speculate on synergistic effects of sulforaphane with alpha lipoic acid, however, we await these combination studies for confirmation. See my previous **article** which reviews sulforaphane.

**Adding in Low Dose Naltrexone LDN**

Dr Berkson discussed Dr Zagon's work showing that low dose naltrexone (LDN) serves as an opiate blocker, and also an anticancer agent. (52)(56-57) LDN shows remarkable benefits for Systemic Lupus, Rheumatoid arthritis, Multiple Sclerosis, Hasimotos thyroiditis, and other autoimmune disease. In addition, giving the cancer patient opiate drugs for pain relief may actually be counterproductive, as these drugs stimulate cancer growth and proliferation. See my **previous articles** on LDN.

**ALA and Silver Particles**

One of my colleagues is known for his treatment with intravenous nano-silver particles (**Argentyn 23**) for cancer and infectious disease. Dr Lee reports that silver particles affect glucose metabolism in the cancer cell via production of ROS. (71) Thus one might speculate on a synergistic effect of ALA with silver particles such as **Argentyn 23.**

**ALA for Diabetic Neuropathy and Autonomic Neuropathy**

A large number of studies show that IV or oral alpha lipoic acid is beneficial in diabetic peripheral neuropathy.(42-43), and in autonomic neuropathy(48) ALA also protects the patient from chemotherapy induced neuropathy, such as cis-platinum induced ototoxicty.(45)

**ALA and PQQ**

**PQQ, Pyrroloquinoline-quinine**, is a newly discovered vitamin cofactor which has "**exceptionally high redox recycling ability"** making it useful as an anti-neurodegenerative agent, and anticancer agent. (81) According to Dr Misra in a 2012 report, PQQ stimulates mitochondrial complex 1 activity in vitro."(81)

In 2010, Dr Shankar studied the effect of PQQ on leukemia cells finding, "**PQQ induced apoptosis in human promonocytic leukemia U937 cells, accompanied by depletion of the major cellular antioxidant glutathione and increase in intracellular reactive oxygen species (ROS)."** (82)

In a 2014 report by Dr. Min in Journal of Cancer Recently, he remarks that "PQQ could induce apoptosis in human promonocytic leukemia U937 and lymphoma EL-4 cells. **The underlying mechanism might be relevant to the increase of intracellular reactive oxygen species (ROS) and depletion of glutathione**."(83)

The molecular mechanism of PQQ was further elucidated by Dr Mitsuga in 2016.(84) He reports that PQQ "enhances the conversion of lactate to pyruvate in the presence of NAD+", facilitating pyruvate formation, and enhances energy production via mitochondrial TCA cycle and oxidative phosphorylation.(84) PQQ is also neuroprotective.(65-86)

These finding suggest PQQ would work in synergy with Alpha Lipoic Acid to increase electron flux through the mitochondrial electron transport chain, thus increasing ROS, depleting glutathione and causing mitochondrial apoptosis in the cancer cell. However we await further studies for confirmation of this hypothesis.

**DCA (Dichloro-Acetate) and Alpha Lipoic Acid Combination**

Dr Paul Anderson's book on "Out of the Box Cancer Treatments" discusses the combination of Poly-MVA and DCA Dichloroacette as an important tool in theiranti-cancer armamentarium .(90) Poly-MVA is a proprietary palladium- alpha-lipoic acid complex.

Dr. Dana Flavin reported in 2010 of a remarkable case of remission from NHL (Non-Hodgkins Lymphoma) with DCA.(88) DCA " *inhibits pyruvate dehydrogenase kinase (PDK). PDK blocks pyruvate dehydrogenase (PDH)* "(88) Thus, the metabolic effect of DCA is similar to Alpha lipoic acid. They both block glycolysis and drive electron flux through the mitochondria which is intolerable to cancer cells.(89-90)

**Remission from Mantle cell Lymphoma : Judy Dowell.**

Judy Dowell is administrator of **Facebook Group** : **Mantle Cell Lymphoma Support for Alternative and/or chemo approach.** In it, she describes her story of long term mission from Mantle cell Lymphoma with DCA. (91-94)

**Conclusion:** The experience of Dr Berkson with Alpha Lipoic Acid as an anti-cancer agent is intriguing. ALA combined with other agents such as DCA may provide additional synergy.

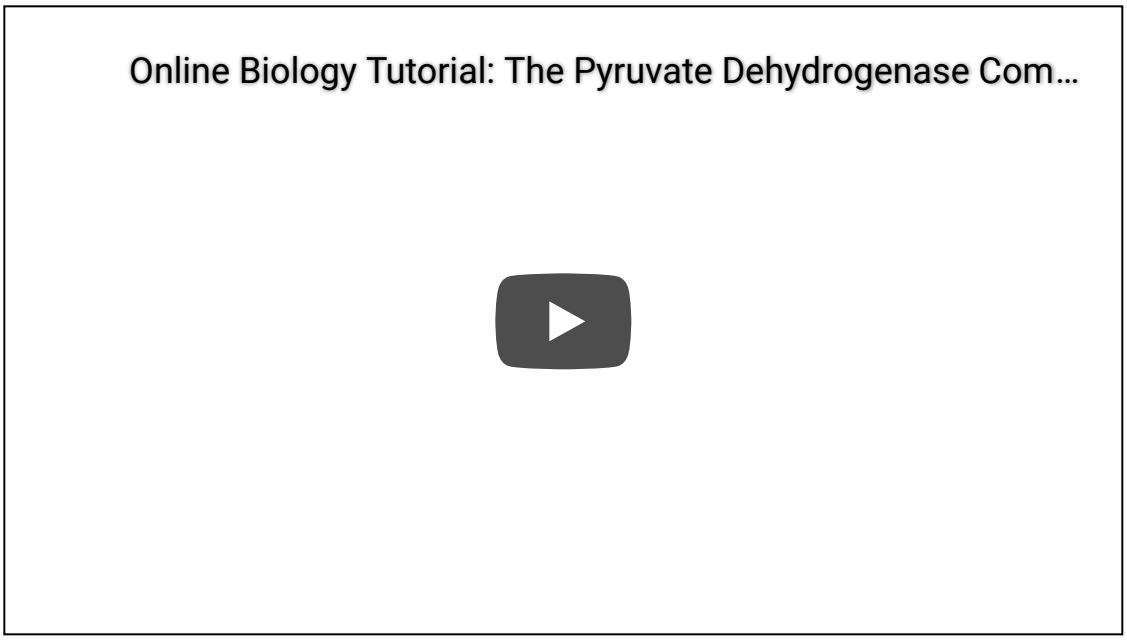
Buy Alpha Lipoic Acid on Amazon

Buy PQQ on Amazon

**Conclusion:**

Alpha Lipoic Acid is a remarkably safe and effective anti-cancer agent which may serve as a cornerstone for any cancer prevention or treatment program.

Understanding Pyruvate Dehydrogenase Complex:



**Understanding the Mitochondrial Electron Transport Chain:**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**Article with Related Interest:**

**Artemisinin Anticancer Weapon Gift from China**

**Cancer as a Parasitic Disease**

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**Low Dose Naltrexone in Cancer Part Two**

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**Links and References**

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Alpha-Lipoic Acid (Thioctic Acid):My Experience With This Outstanding Therapeutic Agent Burton M. Berkson, M.D., Ph.D.

2) http://www.townsendletter.com/Dec2007/alphalipo1207.htm
Alpha Lipoic Acid and Liver Disease by Burton M. Berkson, MD, MS, PhD
Townsend Letter Dec 2007

3) Berkson, Burton M., Daniel M. Rubin, and Arthur J. Berkson.
“Revisiting the ALA/N (α-Lipoic Acid/Low-Dose Naltrexone) protocol for people with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases.” Integrative cancer therapies 8.4 (2009): 416-422.Berkson Burton ALA Alpha Lipoic Acid Low Dose Naltrexone pancreatic cancer Int cancer ther 2009

The major therapeutic agents were intravenous (IV) !-lipoic acid (ALA), 300 to 600 mg, 2 days per week, and low-dose naltrexone (LDN), 4.5 mg by mouth at bedtime. In addition, a triple antioxidant regimen consisting of oral ALA (600 mg per day), selenium (200 mcg twice daily), and silymarin (300 mg 4 times a day) was started.

4) slides of talk 2013
Experience with Alpha-Lipoic Acid plus Low-Dose Naltrexone (ALA/N) for various cancers and autoimmune disease. Invitational Lecture National Cancer Institute 2012 and 2013 LDN Conference Harper College Palatine, Illinois Burt Berkson 2013 Alpha-Lipoic Acid Low Dose Naltrexone ALA for Cancers and Autoimmune

5) Slides of Talk 2016 Burt Berkson Alpha Lipoic Acid 2016 Slides

6) Becker, Charles E., et al. “Diagnosis and treatment of Amanita phalloides-type mushroom poisoning: use of thioctic acid.” Western Journal of Medicine 125.2 (1976): 100. Becker Charles Amanita mushroom poisoning thioctic acid ALA Alpha Lipoic Acid West J Med 1976

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Images of Primate mitochondria after exposure to extremely high doses of intravenous alpha lipoic acid. Note gross swelling and damage to cristae.

2014

7) Vigil, Michael, Burton M. Berkson, and Ana Patricia Garcia. "Adverse effects of high doses of intravenous alpha lipoic acid on liver mitochondria." Global Advances in Health and Medicine 3.1 (2014): 25-27.

8) Bunik, Victoria, et al. "Inhibition of mitochondrial 2-oxoglutarate dehydrogenase impairs viability of cancer cells in a cell-specific metabolism-dependent manner." Oncotarget 7.18 (2016): 26400-26421. Bunik Victoria Inhibition of mitochondrial 2oxoglutarate dehydrogenase impairs viability cancer Oncotarget 2016

Key Article !!!!!!!

9) Bingham, Paul M., Shawn D. Stuart, and Zuzana Zachar. "Lipoic acid and lipoic acid analogs in cancer metabolism and chemotherapy." Expert review of clinical pharmacology 7.6 (2014): 837-846. Bingham Paul Lipoic acid in cancer metabolism and chemotherapy Exp review clin pharm 2014

2016

10) Dörsam, Bastian, and Jörg Fahrer. "The disulfide compound a-lipoic acid and its derivatives: A novel class of anticancer agents targeting mitochondria." Cancer letters 371.1 (2016): 12-19.
•a-lipoic acid (LA) is a mitochondrial co-factor and antioxidant.
•LA induces apoptosis in cancer cells, but hardly affects non-transformed primary cells.
•LA down-regulates oncogenic signaling and displays anti-metastatic activity.
•LA is non-genotoxic and synergizes with established anticancer drugs.
•LA and its synthetic derivatives exert anti-tumor activity in vivo.

The endogenous disulfide a-lipoic acid (LA) is an essential mitochondrial co-factor. In addition, LA and its reduced counterpart dihydro lipoic acid form a potent redox couple with antioxidative functions, for which it is used as dietary supplement and therapeutic. Recently, it has gained attention due to its cytotoxic effects in cancer cells, which is the key aspect of this review. We initially recapitulate the dietary occurrence, gastrointestinal absorption and pharmacokinetics of LA, illustrating its diverse antioxidative mechanisms. We then focus on its mode of action in cancer cells, in which it triggers primarily the mitochondrial pathway of apoptosis, whereas non-transformed primary cells are hardly affected. Furthermore, LA impairs oncogenic signaling and displays anti-metastatic potential. Novel LA derivatives such as CPI-613, which target mitochondrial energy metabolism, are described and recent pre-clinical studies are presented, which demonstrate that LA and its derivatives exert antitumor activity in vivo. Finally, we highlight clinical studies currently performed with the LA analog CPI-613. In summary, LA and its derivatives are promising candidates to complement the arsenal of established anticancer drugs due to their mitochondria-targeted mode of action and non-genotoxic properties.

11) Kafara, Perrine, et al. "Lipoic acid decreases Mcl-1, Bcl-x L and up regulates Bim on ovarian carcinoma cells leading to cell death." Journal of ovarian research 8.1 (2015): 1.

ALA inhibits PDK, Increases PDC, more oxidative metabolism in Cancer cell

12) http://www.ncbi.nlm.nih.gov/pubmed/15512796
Free Radic Res. 2004 Oct;38(10):1083-92. R-lipoic acid inhibits mammalian pyruvate dehydrogenase kinase. **Korotchkina** LG1, Sidhu S, Patel MS. 1Department of Biochemistry, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, 140 Farber Hall, 3435 Main Street, Buffalo, NY 14214, USA. The four pyruvate dehydrogenase kinase (PDK) and two pyruvate dehydrogenase phosphatase (PDP) isoenzymes that are present in mammalian tissues regulate activity of the **pyruvate dehydrogenase complex (PDC)** by phosphorylation/dephosphorylation of its pyruvate dehydrogenase (E1) component. The effect of lipoic

acids on the activity of PDKs and PDPs was investigated in purified proteins system. R-lipoic acid, S-lipoic acid and R-dihydrolipoic acid did not significantly affect activities of PDPs and at the same time **inhibited PDKs to different extents** (PDK1>PDK4 approximately PDK2>PDK3 for R-LA). Since lipoic acids inhibited PDKs activity both when reconstituted in PDC and in the presence of E1 alone, dissociation of PDK from the lipoyl domains of dihydrolipoamide acetyltransferase in the presence of lipoic acids is not a likely explanation for inhibition. The activity of PDK1 towards phosphorylation sites 1, 2 and 3 of E1 was decreased to the same extent in the presence of R-lipoic acid, thus excluding protection of the E1 active site by lipoic acid from phosphorylation. R-lipoic acid inhibited autophosphorylation of PDK2 indicating that it exerted its effect on PDKs directly. Inhibition of PDK1 by R-lipoic acid was not altered by ADP but was decreased in the presence of pyruvate which itself inhibits PDKs. **An inhibitory effect of lipoic acid on PDKs would result in less phosphorylation of E1 and hence increased PDC pyruvate dehydrogenase complex (PDC) activity**. **This finding provides a possible mechanism for a glucose (and lactate) lowering effect of R-lipoic acid in diabetic subjects.**

13) Apoptosis. 2005 Mar;10(2):359-68.
**Alpha-Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant O2-*-generation.** **Wenzel** U1, Nickel A, Daniel H.

The antioxidant alpha-lipoic acid (ALA) has been shown to affect a variety of biological processes associated with oxidative stress including cancer. We determined in HT-29 human colon cancer cells whether ALA is able to affect apoptosis, as an important parameter disregulated in tumour development. Exposure of cells to ALA or its reduced form dihydrolipoic acid (DHLA) for 24 h dose dependently increased caspase-3-like activity and was associated with DNA-fragmentation. DHLA but not ALA was able to scavenge cytosolic O2-* in HT-29 cells whereas **both compounds increased O2-*-generation inside mitochondria. Increased mitochondrial O2-*-production was preceded by an increased influx of lactate or pyruvate into mitochondria and resulted in the down-regulation of the anti-apoptotic protein bcl-X(L).** Mitochondrial O2-*-generation and apoptosis induced by ALA and DHLA could be prevented by the O2-*-scavenger benzoquinone. Moreover, when the lactate/pyruvate transporter was inhibited by 5-nitro-2-(3-phenylpropylamino) benzoate, ALA- and DHLA-induced mitochondrial ROS-production and apoptosis were blocked. In contrast to HT-29 cells, no apoptosis was observed in non-transformed human colonocytes in response to ALA or DHLA addition. In conclusion, our study provides evidence that ALA and DHLA can effectively induce apoptosis in human colon cancer cells by a **prooxidant mechanism** that is initiated by an increased uptake of **oxidizable substrates into mitochondria**.

Apoptosis induction in the human colorectal cancer cell line HT-29 is strictly related to the generation of O−.2 in mitochondria that is followed by a down-regulation of the mitochondrial anti-apoptotic protein bcl-XL and by caspase-3 activation.14

In conclusion, our studies demonstrate that the antioxidants ALA and DHLA do effectively induce apoptosis in HT-29 human colon cancer cells via an **increased ROS production in mitochondria**. Although at least DHLA acts as a potent O−.2 -scavenger in the cytosol, both compounds increase substantially mitochondiral O−2 production that can obviously not be quenched or detoxified. **The underlying mechanism seems to be an enhancement of the uptake of monocarboxylates (pyruvate/lactate) from glycolysis into mitochondria followed by their oxidation in**
**the citric acid cycle** with increased delivery of reduction equivalents to the respiratory chain which in turn drastically increases mitochondrial O−. 2 -production. **This high O−. 2 -burden appears to overcome the intrinsically high antioxidative capacity of antiapoptotic proteins and allows apoptosis in tumor cells to be executed.**

14) Feuerecker, Benedikt, et al. “Lipoic acid inhibits cell proliferation of tumor cells in vitro and in vivo.” Cancer biology & therapy 13.14 (2012): 1425-1435.

Inhibition of aerobic glycolysis by activation of enzymes that cause a shift in metabolism toward complete oxidation of glucose should be effective in eradication of tumor cells. In this regard (R)-(+)-α-lipoic acid and dichloroacetate that both support **pyruvate dehydrogenase** reaction have turned out as promising compounds.

**Additionally LPA can inhibit pyruvate dehydrogenase kinase, thus increasing the activity of the pyruvate dehydrogenase complex.** Cancer cells convert glucose preferentially to lactate even in the presence of oxygen (aerobic glycolysis–Warburg effect). New concepts in cancer treatment aim at inhibition of aerobic glycolysis. **Pyruvate dehydrogenase converts pyruvate to acetylCoA thus preventing lactate formation**. Therefore, the aim of this study was to evaluate compounds that could activate pyruvate dehydrogenase in cancer cells. We investigated the effects of (R)-(+)-α-lipoic acid (LPA) and dichloroacetate (DCA), possible activators of pyruvate dehydrogenase, on suppression of aerobic glycolysis and induction of cell death.
The neuroblastoma cell lines Kelly, SK-N-SH, Neuro-2a and the breast cancer cell line SkBr3 were incubated with different concentrations (0.1–30 mM) of LPA and DCA. The effects of both compounds on cell viability/proliferation (WST-1 assay), [18F]-FDG uptake, lactate production and induction of apoptosis (flow cytometric detection of caspase-3) were evaluated.
These data suggests that LPA can reduce
**(1) cell viability/proliferation,**
**(2) uptake of [18F]-FDG and**
**(3) lactate production** and **increase apoptosis** in all investigated cell lines.
In contrast, DCA was almost ineffective. In the mouse xenograft model with s.c. SkBr3 cells, daily treatment with LPA retarded tumor progression. Therefore, LPA seems to be a promising compound for cancer treatment.
The hypothesis that LPA could possibly change the glucose uptake in Kelly, Neuro-2a, SK-N-SH and SkBr3 cells was investigated by [18F]-FDG uptake experiments. The data support this idea because in our in vitro experiments all cells showed a dose dependent decrease of uptake. The impaired uptake might be in part due to decreased cell proliferation and/or cell death caused by LPA. However, it is also possible that a shift to oxidative turnover caused cells to reduce uptake since less glucose is needed to meet the demands for energy by switching over to oxidative respiration

15) The Pyruvate Dehydrogenase Complex in Cancer: Implications for the Transformed State and Cancer Chemotherapy
By Paul M. Bingham and Zuzana Zachar Biochemistry, Genetics and Molecular Biology » “Dehydrogenases”, book edited by Rosa Angela Canuto, ISBN 978-953-307-019-3, Published: November 14, 2012 under CC BY 3.0 license. © The Author(s). Chapter 3.

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16) How Lipoic Acid Preserves Critical Mitochondrial Function

17) https://www.youtube.com/watch?v=DT2HcUk4_EQ
Dr Laurent Schwartz metabolic treatment – You Tube

**The combination of hydroxycitrate and lipoic acid**

18) Schwartz, Laurent, et al. “Metabolic treatment of cancer: intermediate results of a prospective case series.” Anticancer research 34.2 (2014): 973-980.

The combination of hydroxycitrate and lipoic acid has been demonstrated by several laboratories to be effective in reducing murine cancer growth. Patients and Methods: All patients had failed standard chemotherapy and were offered only palliative care by their referring oncologist. Karnofsky status was between 50 and 80. Life expectancy was estimated to be between 2 and 6 months. Ten consecutive patients with chemoresistant advanced metastatic cancer were offered compassionate metabolic treatment. They were treated with a combination of lipoic acid at 600 mg i.v. (Thioctacid), hydroxycitrate at 500 mg t.i.d. (Solgar) and low-dose naltrexone at 5 mg (Revia) at bedtime. Primary sites were lung carcinoma (n=2), colonic carcinoma (n=2), ovarian carcinoma (n=1), esophageal carcinoma (n=1), uterine sarcoma (n=1), cholangiocarcinoma (n=1), parotid carcinoma (n=1) and unknown primary (n=1). The patients had been heavily pre-treated. One patient had received four lines of chemotherapy, four patients three lines, four patients two lines and one patient had received radiation therapy and chemotherapy. An eleventh patient with advanced prostate cancer resistant to hormonotherapy treated with hydroxycitrate, lipoic acid and anti-androgen is also reported. Results: One patient was unable to receive i.v. lipoic acid and was switched to oral lipoic acid (Tiobec). Toxicity was limited to transient nausea and vomiting. Two patients died of progressive disease within two months. Two other patients had to be switched to conventional chemotherapy combined with metabolic treatment, one of when had a subsequent dramatic tumor response. Disease in the other patients was either stable or very slowly progressive. The patient with hormone-resistant prostate cancer had a dramatic fall in Prostate-Specific Antigen (90%), which is still decreasing. Conclusion: These very primary results suggest the lack of toxicity and the probable efficacy of metabolic treatment in chemoresistant advanced carcinoma. It is also probable that metabolic treatment enhances the efficacy of cytotoxic chemotherapy. These results are in line with published animal data. A randomized clinical trial is warranted.

19) Invest New Drugs. 2013 Apr;31(2):256-64. Tumor regression with a combination of drugs interfering with the tumor metabolism: efficacy of **hydroxycitrate, lipoic acid and capsaicin.**
Schwartz L1, Guais A, Israël M, Junod B, Steyaert JM, Crespi E, Baronzio G, Abolhassani M. 1Ecole Polytechnique, Laboratoire d'Informatique, Palaiseau, France.

Cellular metabolic alterations are now well described as implicated in cancer and some strategies are currently developed to target these different pathways. In previous papers, we demonstrated that a combination of molecules (**namely alpha-lipoic acid and hydroxycitrate, i.e. Metabloc™**) targeting the cancer metabolism markedly decreased tumor cell growth in mice. In 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.

20) Invest New Drugs. 2012 Feb;30(1):200-11.
**Adding a combination of hydroxycitrate and lipoic acid (METABLOC™) to chemotherapy improves effectiveness against tumor development: experimental results and case report.** Guais A1, Baronzio G, Sanders E, Campion F, Mainini C, Fiorentini G, Montagnani F, Behzadi M, Schwartz L, Abolhassani M.
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, concommitantly with classical chemotherapy (cisplatin or methotrexate). 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 a-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.

21) **A combination of alpha lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models:** Preliminary results
Authors: Laurent Schwartz Mohammad Abolhassani Adeline Guais Edward Sanders Jean-Marc Steyaert Frederic Campion Maurice Israël
View Affiliations May 1, 2010

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 μM) and cell types. Calcium hydroxycitrate reduced the cell number by 5-60% at different concentrations (10-500 μM). When hydroxycitrate and lipoic acid were used together, there was a major cytotoxic effect: complete cell death was seen following 8 μM lipoic acid and 300 μM 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.

Lipoic acid and calcium hydroxycitrate, when administrated alone, have at best a cytostatic effect on tumor cells (Fig. 1). The rate of response is slow, clearly different from conventional chemotherapy. **When the drugs are combined, however, there is a major cytotoxic effect similar to results obtained with conventional cytotoxic chemotherapy**. In vitro, cancer cells are killed within hours when exposed to cytotoxic drugs

22) **PHI Test Dr Emil Schandl AMerican Metabolic Lab Hollywood Florida** Published on Jun 25, 2015
The Role of Human Autocrine Motility Factor in Tumor Malignancy.
Recorded at the A4M 23rd Annual World Congress on Anti-Aging Medicine, in Hollywood, FL on May 2015. PHI, the Human Autocrine Motility Factor (AMF) is an extremely important tumor marker .

**ovarian ca markers – CA 125, CEA, CA 19-9**

http://www.ncbi.nlm.nih.gov/pubmed/10873403
23) Gynecol Oncol. 2000 Jul;78(1):16-20.
Serum CA 125, carcinoembryonic antigen, and CA 19-9 as tumor markers in borderline ovarian tumors. Engelen MJ1, de Bruijn HW, Hollema H, ten Hoor KA, Willemse PH, Aalders JG, van der Zee AG.

The goals of this study were to analyze preoperative serum levels of CA 125, carcinoembryonic antigen (CEA), and CA 19-9 in patients with borderline ovarian tumors and to investigate if routine assessment of these markers in follow-up may lead to earlier detection of recurrence.
METHODS:For patient identification a database was used, in which data from all patients treated for gynecologic malignancies in the Department of Gynecologic Oncology, University Hospital Groningen, The Netherlands, are compiled. Between 1982 and 1997, 44 patients with borderline ovarian tumors were identified. Clinical data and serum CA-125 and CEA levels were retrieved from the database. CA 19-9 levels were determined in retrospect in available stored preoperative (24 patients) and follow-up (43 patients) serum samples.
RESULTS:Preoperative CA 125 levels were elevated in 8 of 33 (24%), CEA levels in 3 of 32 (9%), and CA 19-9 levels in 11 of 24 (46%) cases. In patients with mucinous tumors preoperative CA 19-9 was more frequently elevated (8/14, 57%) than CA 125 (3/20, 15%) (P = 0.02) or CEA (2/18, 11%) (P = 0.02). Complete follow-up serum CA 125, CEA, and CA 19-9 levels were available for 43 of 44 patients. Median follow-up was 84 months (range, 22-204). During follow-up two patients (5%) had recurrent disease. In one patient CA 125 became elevated at the time of recurrence; in the other patient (in retrospect) the CA 19-9 level did not return to normal after surgery, but kept rising, preceding clinical symptoms of recurrence for 13 months.
CONCLUSIONS:If one chooses to use serum markers in follow-up of mucinous borderline ovarian tumors CA 19-9 should be included. Measurement of serum tumor markers in the follow-up of patients with borderline ovarian tumors may lead to earlier detection of recurrence in only a very small proportion of patients, while the clinical value of earlier detection of recurrence remains to be established.

24) Am J Obstet Gynecol. 1984 Jul 1;149(5):553-9.
Monitoring human ovarian carcinoma with a combination of CA 125, CA 19-9, and carcinoembryonic antigen. Bast RC Jr, Klug TL, Schaetzl E, Lavin P, Niloff JM, Greber TF, Zurawski VR Jr, Knapp RC.

CA 125 and CA 19-9 are antigenic determinants associated with human epithelial ovarian carcinomas. Murine monoclonal antibodies have been raised against these determinants, and immunoradiometric assays have been developed to monitor antigen levels in the serum of cancer patients. This study was undertaken to determine whether concomitant measurement of CA 125, CA 19-9, and carcinoembryonic antigen would provide a more precise correlation with tumor progression or regression than could be obtained with any single assay. Among 105 patients with surgically demonstrable epithelial ovarian carcinoma, serum CA 125 levels were elevated (greater than 35 U/ml) in 83%, CA 19-9, levels (greater than 37 U/ml) in 17%, and carcinoembryonic antigen levels (greater than or equal to 2.5 ng/ml) in 37%. Within individual samples, no correlation was found among values for the three markers, but patients with elevated CA 19-9 levels also had increased levels of CA 125. At least one of the three markers was elevated in 90% of the subjects. When 41 patients were monitored serially over 2 to 60 months, alterations in CA 125 levels correlated with disease progression or regression in 94% of instances, whereas alterations in CA 19-9 levels correlated in 33% and alterations in carcinoembryonic antigen levels in 25% of instances. Concomitant measurement of CA 125, CA 19-9, and carcinoembryonic antigen did not prove superior to measurement of CA 125 alone in the monitoring of patients with epithelial ovarian carcinoma.

**breast cancer markers CEA, CA 15-3, and MCA**

25) http://www.ncbi.nlm.nih.gov/pubmed/9018092
Cancer Lett. 1996 Dec 20;110(1-2):137-44.

Clinical evaluation of potential usefulness of CEA, CA 15-3, and MCA in follow-up of **breast cancer patients**.
Jezersek B1, Cervek J, Rudolf Z, Novaković S.
The potential usefulness of MCA, CA 15-3 and CEA in monitoring of breast cancer patients was evaluated in 135 female patients with histologically confirmed breast cancer. The patients were classified into two groups as follows: group of patients with no evidence of disease, NED; and group of patients with progressive disease, PD. In total, 2106 measurements of CEA, CA 15-3, and MCA were performed using an enzyme immunoassay. Serum levels of all three markers in the NED group differed significantly from those of patients with PD. The observed differences in the sensitivity and specificity of CEA, CA 15-3, and MCA tests were not significant. The serum concentrations of a particular marker correlated well with the concentrations of the other two markers, except when CEA was correlated with MCA or CA 15-3 in NED group patients. The elevation of tumor markers preceded by some 7 months the clinical evidence of dissemination, and marker levels reflected at a high percentage the response to therapy in PD patients. Therefore, this clinical study confirmed that MCA, CA 15-3 and also CEA are suited to discriminate between disease and disease-free periods, and also validated the usefulness of markers for treatment response monitoring.

26) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4514648/
Shao, Yingbo, et al. “Elevated Levels of Serum Tumor Markers CEA and CA15-3 Are Prognostic Parameters for Different Molecular Subtypes of Breast Cancer.” PloS one 10.7 (2015): e0133830.

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**Carnitine induces Apoptosis in Cancer Cells**

27) http://www.ncbi.nlm.nih.gov/pubmed/15930461
J Nutr. 2005 Jun;135(6):1510-4. **Increased carnitine-dependent fatty acid uptake into mitochondria of human colon cancer cells induces apoptosis.** Wenzel U1, Nickel A, Daniel H.
Carnitine-dependent fatty acid import into mitochondria and beta-oxidation seem to be impaired in tumor cells. In the present study we show that a supply of palmitoylcarnitine together with L-carnitine potently induces apoptosis in HT-29 human colon cancer cells as a consequence of accelerated fatty acid oxidation. Caspase-3-like activities, measured by the cleavage rate of a fluorogenic tetrapeptide substrate and nuclear fragmentation determined after DNA labeling in fixed cells by fluorescence microscopy, served as indicators of apoptosis. Neither L-carnitine nor palmitoylcarnitine alone were able to increase caspase-3-like activities and DNA fragmentation, but when provided together, apoptosis occurred. That exogenous carnitine was indeed able to enhance fatty acid uptake into mitochondria was demonstrated by an increased influx of a fluorescent palmitic acid analog. Enhanced fatty acid availability in mitochondria led to an increased generation of O*2-, as detected by a O*2- -sensitive fluorogenic dye, indicating oxidation of delivered substrates. Benzoquinone, an O*2- scavenger, blocked O*2- generation and prevented apoptosis as initiated by the combination of palmitoylcarnitine and carnitine. The lack of effect of the ceramide synthesis inhibitor fumonisin on palmitoylcarnitine/carnitine-induced apoptosis further supports the notion that apoptotic cell death is specifically due to fatty acid oxidation. In contrast to HT-29 cells, nontransformed human colonocytes did not respond to exogenous palmitoylcarnitine/carnitine and no apoptosis was observed. In conclusion, our studies provide evidence that a limited mitochondrial fatty acid import in human colon cancer cells prevents high rates of mitochondrial O*2- production and protects colon cancer cells from apoptosis that can be overcome by an exogenous carnitine supply.

A diminished mitochondrial oxidation of acetyl-CoA from glucose and fatty acid breakdown is a hallmark of cancer cell metabolism (1). Because a low mitochondrial respiration also reduces the ROS burden, tumor cells appear to be particularly well protected from oxidative stress (2). Redirecting cancer cell metabolism toward a normal phenotype could therefore result in specific apoptosis induction by an increased ROS production. We

demonstrated recently that when lactate/pyruvate uptake into mitochondria is increased and in turn substrate availability for oxidative metabolism is specifically enhanced in HT-29 human colon cancer cells, mitochondrial O2−· generation is drastically accelerated and in turn cells undergo apoptosis (3).

**curcumin Beta Cateninin**

28) FEBS Lett. 2005 May 23;579(13):2965-71. Epub 2005 Apr 21.
The inhibitory mechanism of curcumin and its derivative against beta-catenin/Tcf signaling. Park CH1, Hahm ER, Park S, Kim HK, Yang CH.
We investigated the inhibitory mechanism of curcumin and its derivative (CHC007) against beta-catenin/T-cell factor (Tcf) signaling in various cancer cell lines. Curcumin is known to inhibit beta-catenin/Tcf transcriptional activity in HCT116 cells but not in SW620 cells. To clarify the inhibitory effect of curcumin against beta-catenin/Tcf signaling, we tested several cancer cell lines. In addition, in order to verify the inhibitory mechanism, we performed reporter gene assay, Western blot, immunoprecipitation, and electrophoretic mobility shift assay. Since inhibitors downregulated the transcriptional activity of beta-catenin/Tcf in HEK293 cells transiently transfected with S33Y mutant beta-catenin gene, whose product is not induced to be degraded by adenomatous polyposis coli-Axin-glycogen synthase kinase 3beta complex, we concluded that the inhibitory mechanism was related to beta-catenin itself or downstream components. Western blot analysis suggested that no change in the amount of cytosolic and membranous beta-catenin in a cell occurred; however, nuclear beta-catenin and Tcf-4 proteins were markedly reduced by inhibitors and this lead to the diminished association of beta-catenin with Tcf-4 and to the reduced binding to the consensus DNA. In the present study, we demonstrate that curcumin and its derivative are excellent inhibitors of beta-catenin/Tcf signaling in all tested cancer cell lines and the reduced beta-catenin/Tcf transcriptional activity is due to the decreased nuclear beta-catenin and Tcf-4.

In all cell lines tested, β-catenin's transcriptional activity was suppressed by inhibitors dependent on the concentration. In this regard, we assume that the antitumor activity of curcumin occurs via the inhibition of the β-catenin/Tcf signaling pathway by reducing the nuclear β-catenin and Tcf-4 proteins.

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**Vitamin K mitochondria –ovarian cancer**

29) Apoptosis. 2006 Sep;11(9):1535-43.
Production of superoxide and dissipation of mitochondrial transmembrane potential by vitamin K2 trigger apoptosis in human ovarian cancer TYK-nu cells. Shibayama-Imazu T1, Sonoda I, Sakairi S, Aiuchi T, Ann WW, Nakajo S, Itabe H, Nakaya K.
We reported previously that **vitamin K(2) selectively induces apoptosis in human ovary cancer cells** (TYK-nu cells) and pancreatic cancer cells (MIA PaCa-2 cells) through a mitochondrion-dependent pathway. In the present study, we examined the details of the mechanism of vitamin K(2)-induced apoptosis in TYK-nu cells. We found that superoxide (O(2)(*-)) was produced by TYK-nu cells between 2 and 3 days after the start of treatment with vitamin K(2), whereas it was produced within 30 min after the start of treatment with geranylgeraniol. The vitamin K(2)-induced apoptosis was inhibited by anti-oxidants, such as alpha-tocopherol, Tiron and N-acetyl-L-cysteine (NAC). Furthermore, both the production of superoxide and the induction of apoptosis by vitamin K(2) were inhibited almost completely by cycloheximide, an inhibitor of protein synthesis, suggesting that the synthesis of enzymes for the production of superoxide might be required for these processes. In parallel with the production of superoxide, the mitochondrial transmembrane potential, as measured by staining with Mitotracker Red CMXRos, dissipated during treatment of TYK-nu cells with vitamin K(2) for 3 days. The vitamin K(2)-induced depolarization of mitochondrial membranes was completely inhibited by alpha-tocopherol and, to a lesser extent, by Tiron and NAC.

Since alpha-tocopherol reacts with oxygen radicals, such as superoxide, within the hydrophobic environment of the mitochondrial membrane, we postulate that vitamin K(2)-induced oxidative stress in mitochondria might damage mitochondrial membranes, with subsequent release of cytochrome c, the activation of procaspase 3 and, eventually, apoptosis.

30) Vitam Horm. 2008;78:211-26. **Vitamin K2-mediated apoptosis in cancer cells: role of mitochondrial transmembrane potential.** Shibayama-Imazu T1, Aiuchi T, Nakaya K.
Vitamin K2 induces differentiation and apoptosis in a wide array of human cancer cell lines. Vitamin K2-mediated apoptosis proceeds much more slowly than the apoptosis induced by conventional anticancer agents. Thus, it is possible to analyze the underlying mechanism in detail. In this chapter, we focus on the pro-apoptotic effects of vitamin K2 on mitochondrial physiology with particular emphasis on changes in mitochondrial membrane potential (DeltaPsim). Upon treatment of **ovarian cancer** TYK-nu cells with vitamin K2, **superoxide** is produced after two to three days, followed shortly thereafter by release of **mitochondrial cytochrome c**. This is accompanied by other apoptotic features such as characteristic morphological changes and DNA fragmentation by day four. Data suggest that **superoxide production** might cause damage to mitochondrial membranes, open permeability transition pores, and result in disruption of DeltaPsim with subsequent release of cytochrome c. Both vitamin K2-induced production of superoxide and reduction of DeltaPsim are completely **inhibited by alpha-tocopherol** such that cell viability is retained. Thus, we propose that the loss of DeltaPsim caused by superoxide might be the major cause of apoptosis following exposure to vitamin K2. However, other pathways may be involved since cyclosporin A failed to completely inhibit vitamin K2-induced apoptosis.

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31) Nakaya, K., et al. **Vitamin K2 as a Chemotherapeutic Agent for Treating Ovarian Cancer.** INTECH Open Access Publisher, 2012. Vitamin K2 as a Chemotherapeutic Agent for Treating Ovarian Cancer. INTECH Nakaya 2012

Vitamin K2 has anti-cancer activity, whereas vitamin K1 does not. Vitamin K1 is converted to vitamin K2 in animals and humans (Thijssen & Drittij-Reijnders, 1996); vitamin K2 has isoprenoid side chains of various lengths attached to the 3 position of the vitamin K3 ring structure. The different forms of vitamin K2, menaquinone-n (MK-n), are categorized according to the number of repeating isoprenoid residues in the side chain. The most common form of vitamin K2 in animals is menaquinone-4 (MK-4), which has four isoprenoid residues as its side chain. MK-4 is the most biological active form of the vitamin and is produced by intestinal bacteria. Long chain menaquinones, MK-7 to MK-10, are synthesized by bacteria and are present in fermented products such as cheese. Vitamin K2 MK-4 has a geranylgeranyl side chain and is commonly used for the treatment of a variety of cancer cells.

The slow rate of apoptosis is one of the characteristic features of vitamin K2-induced apoptosis, compared to apoptosis induced by conventional anticancer agents such as camptothecin and etoposide, and by geranaylgeraniol (Masuda et al., 2000; Shibayama-Imazu et al., 2003).

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32) Kiely, Maeve, et al. “Real-time cell analysis of the inhibitory effect of vitamin K 2 on adhesion and proliferation of **breast cancer cells**.” Nutrition Research 35.8 (2015): 736-743.linhibitory effect of vitamin K2 on proliferation of breast cancer Kiely Maeve Nutrition Research 2015

Our hypothesis was that MK-4, the most common form of VK2, is an effective anticancer agent against breast cancer cell types.

**Mitochondrial Fumarate Reductase**

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33) Sakai, Chika, et al. “Mitochondrial fumarate reductase as a target of chemotherapy: from parasites to cancer cells.” Biochimica et Biophysica Acta (BBA)-General Subjects 1820.5 (2012): 643-651. Mitochondrial fumarate reductase target chemotherapy parasites cancer 2012 Sakai Chika
A leading drug in the treatment of Ascaris infection is Ivermectin, a semi-synthetic derivative of the natural product of a streptomyces species; Avermectin B1a.

**Pyrvinium** full free pdf

34) Tomitsuka, Eriko, Kiyoshi Kita, and Hiroyasu Esumi. “An anticancer agent, pyrvinium pamoate **inhibits the NADH–fumarate reductase system**—a unique mitochondrial energy metabolism in tumour microenvironments.” Journal of biochemistry 152.2 (2012): 171-183. Anticancer pyrvinium pamoate inhibits NADH fumarate reductase in tumour 2012 Tomitsuka Eriko J Biochem

PP inhibited the hypoxic ETC, NADH FR system in both parasitic and mammalian mitochondria, showing that the NADH FR system is active in both parasitic and mammalian mitochondria. Key effects of PP such as its anticancer and selective cytotoxic effects, may arise through the **inhibition of the NADH FR system.** Therefore, the NADH FR system is a good target for anticancer therapy.

**ALA in Diabetes**

35) Porasuphatana S, et al. Glycemic and oxidative status of patients with type 2 diabetes mellitus following oral administration of alphalipoic acid: a randomized double-blinded placebocontrolled study. Asia Pac J ClinNutr. 2012;21(1):12-21 Diabetes mellitus following oral alphalipoic acid 2012 Porasuphatana Supatra

36) McNeillyAM, et al. Effect of a-lipoic acid and exercise training on cardiovascular disease risk in obesity with impaired glucose tolerance. Lipids Health Dis. 2011 Nov;10:217.

37) Gomes MB and Negrato CA. Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. DiabetolMetabSyndr. 2014 Jul;6:80.

38) Abdan MAL. Alpha-Lipoic Acid Controls Tumor Growth and Modulates Hepatic Redox State in Ehrlich-Ascites-Carcinoma-Bearing Mice. Sci W J. 2012;2012.
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Thiamine B1

39) Zastre, Jason A., et al. “Linking vitamin B1 with cancer cell metabolism.” Cancer Metab 1.1 (2013): 16. Interestingly, **restoration of PDH activity in cancer cells has been shown to promote apoptosis and is actively being assessed as a potential therapeutic strategy.**

Another regulator of PDH phosphorylation is the thiamine cofactor TPP, which, when bound to PDH, reduces the rate and extent of PDK-mediated phosphorylation
[110]. **Thus increasing concentrations of TPP through thiamine supplementation may be proapoptotic through restoration of PDH activity in cancer cells.**

This may explain why a reduction in tumor growth was observed with high-dose thiamine supplementation [58].

40) Eur J Biochem. 2001 Aug;268(15):4177-82.
The effect of thiamine supplementation on tumour proliferation. A metabolic control analysis study. Comín-Anduix B1, Boren J, Martinez S, Moro C, Centelles JJ, Trebukhina R, Petushok N, Lee WN, Boros LG, Cascante M.

Thiamine deficiency frequently occurs in patients with advanced cancer and therefore thiamine supplementation is used as nutritional support. Thiamine (vitamin B1) is metabolized to thiamine pyrophosphate, the cofactor of transketolase, which is involved in ribose synthesis, necessary for cell replication. Thus, it is important to determine whether the benefits of thiamine supplementation outweigh the risks of tumor proliferation. Using oxythiamine (an irreversible inhibitor of transketolase) and metabolic control analysis (MCA) methods, we measured an in vivo tumour growth control coefficient of 0.9 for the thiamine-transketolase complex in mice with Ehrlich's ascites tumour. Thus, transketolase enzyme and thiamine clearly determine cell proliferation in the Ehrlich's ascites tumour model. This high control coefficient allows us to predict that in advanced tumours, which are commonly thiamine deficient, supplementation of thiamine could significantly increase tumour growth through transketolase activation. The effect of thiamine supplementation on tumour proliferation was demonstrated by in vivo experiments in mice with the ascites tumour. Thiamine supplementation in doses between 12.5 and 250 times the recommended dietary allowance (RDA) for mice were administered starting on day four of tumour inoculation. We observed a high stimulatory effect on tumour growth of 164% compared to controls at a thiamine dose of 25 times the RDA. This growth stimulatory effect was predicted on the basis of correction of the pre-existing level of thiamine deficiency (42%), as assayed by the cofactor/enzyme ratio. Interestingly, at very high overdoses of thiamine, approximately 2500 times the RDA, thiamine supplementation had the opposite effect and caused 10% inhibition of tumour growth. This effect was heightened, resulting in a 36% decrease, when thiamine supplementation was administered from the 7th day prior to tumour inoculation. Our results show that thiamine supplementation sufficient to correct existing thiamine deficiency stimulates tumour proliferation as predicted by MCA. The tumour inhibitory effect at high doses of thiamine is unexplained and merits further study.

41) Hanberry, Bradley S., Ryan Berger, and Jason A. Zastre. "High-dose vitamin B1 reduces proliferation in cancer cell lines analogous to dichloroacetate." Cancer chemotherapy and pharmacology 73.3 (2014): 585-594.

The dichotomous effect of thiamine supplementation on cancer cell growth is characterized by growth stimulation at low doses and growth suppression at high doses. Unfortunately, how **thiamine** reduces cancer cell proliferation is currently unknown. Recent focuses on metabolic targets for cancer therapy have exploited the altered regulation of the thiamine-dependent enzyme pyruvate dehydrogenase (PDH). Cancer cells inactivate PDH through phosphorylation by **overexpression of** p**yruvate dehydrogenase kinases (PDKs)**. Inhibition of PDKs by dichloracetate (DCA) exhibits a growth suppressive effect in many cancers. Recently it has been shown that the thiamine co-enzyme, **thiamine pyrophosphate reduces PDK mediated phosphorylation of PDH**. Therefore, the objective of this study was to determine if high dose thiamine supplementation reduces cell proliferation through a DCA like mechanism.

Thiamine exhibited a lower IC50 value in both cell lines compared to DCA. Both thiamine and DCA reduced the extent of PDH phosphorylation, reduced glucose consumption, lactate production, and mitochondrial membrane potential. High dose thiamine and DCA did not increase ROS but increased caspase-3 activity.
Conclusion: Our findings suggest that **high dose thiamine reduces cancer cell proliferation** by a mechanism similar to that described for dichloroacetate.

**ALA for Diabetic Neuropathy**

42) Ziegler, D., et al. "Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a meta-analysis." Diabetic Medicine 21.2 (2004): 114-121.

To determine the efficacy and safety of 600 mg of alpha-lipoic acid given intravenously over 3 weeks in diabetic patients with symptomatic polyneuropathy.
METHODS: We searched the database of VIATRIS GmbH, Frankfurt, Germany, for clinical trials of alpha-lipoic acid according to the following prerequisites: randomized, double-masked, placebo-controlled, parallel-group trial using alpha-lipoic acid infusions of 600 mg i.v. per day for 3 weeks, except for weekends, in diabetic patients with positive sensory symptoms of polyneuropathy which were scored by the Total Symptom Score (TSS) in the feet on a daily basis. Four trials (ALADIN I, ALADIN III, SYDNEY, NATHAN II) comprised n=1258 patients (alpha-lipoic acid n=716; placebo n=542) met these eligibility criteria and were included in a meta-analysis based on the intention-to-treat principle. Primary analysis involved a comparison of the differences in TSS from baseline to the end of i.v. Treatment between the groups treated with alpha-lipoic acid or placebo. Secondary analyses included daily changes in TSS, responder rates (> or =50% improvement in TSS), individual TSS components, Neuropathy Impairment Score (NIS), NIS of the lower limbs (NIS-LL), individual NIS-LL components, and the rates of adverse events.
RESULTS: After 3 weeks the relative difference in favour of alpha-lipoic acid vs. placebo was 24.1% (13.5, 33.4) (geometric mean with 95% confidence interval) for TSS and 16.0% (5.7, 25.2) for NIS-LL. The responder rates were 52.7% in patients treated with alpha-lipoic acid and 36.9% in those on placebo (P<0.05). On a daily basis there was a continuous increase in the magnitude of TSS improvement in favour of alpha-lipoic acid vs. placebo which was noted first after 8 days of treatment. Among the individual components of the TSS, pain, burning, and numbness decreased in favour of alpha-lipoic acid compared with placebo, while among the NIS-LL components pin-prick and touch-pressure sensation as well as ankle reflexes were improved in favour of alpha-lipoic acid after 3 weeks. The rates of adverse events did not differ between the groups.
CONCLUSIONS:The results of this meta-analysis provide evidence that treatment with alpha-lipoic acid (600 mg/day i.v.) over 3 weeks is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy.

43) Han, T., et al. "A systematic review and meta-analysis of α-lipoic acid in the treatment of diabetic peripheral neuropathy." European journal of endocrinology/European Federation of Endocrine Societies 167.4 (2012): 465.
OBJECTIVE: To evaluate the effects and safety of 300-600 mg α-lipoic acid (ALA) given i.v. for diabetic peripheral neuropathy (DPN).
METHODS:We searched the databases of Medline, Embase, and Cochrane central register of Controlled Trials and Chinese biological medicine for clinical trials of ALA in the treatment of DPN. Data were extracted to examine methodological quality and describe characteristics of studies. The primary outcomes were efficacy, median motor nerve conduction velocity (MNCV), median sensory nerve conduction velocity (SNCV), peroneal MNCV, and peroneal SNCV. Secondary outcomes were adverse events.
RESULTS:Fifteen randomized controlled trials met the inclusion criteria. The treatment group involved the administration of ALA 300-600 mg i.v. per day. And the control group used the same interventions except for ALA. Compared with the control group, nerve conduction velocities increased significantly in the treatment group. The weighted mean differences in nerve conduction velocities were 4.63 (95% confidence interval 3.58-5.67) for median MNCV, 3.17 (1.75-4.59) for median SNCV, 4.25 (2.78-5.72) for peroneal MNCV, and 3.65 (1.50-5.80) for peroneal SNCV in favor of the treatment group. The odds ratio in terms of efficacy was 4.03 (2.73-5.94) for ALA. Furthermore, no serious adverse events were observed during the treatment period.
CONCLUSIONS: The results of this meta-analysis provide evidence that treatment with ALA (300-600 mg/day i.v. for 2-4 weeks) is safe and that the treatment can significantly improve both nerve conduction velocity and positive neuropathic symptoms. However, the evidence may not be strong because most of the studies included in this meta-analysis have poor methodological quality.

**Ubiquinone CoQ10**

44) Biochem Biophys Res Commun. 1995 Jul 6;212(1):172-7.
Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases. Lockwood K1, Moesgaard S, Yamamoto T, Folkers K.

Over 35 years, data and knowledge have internationally evolved from biochemical, biomedical and clinical research on vitamin Q10 (coenzyme Q10; CoQ10) and cancer, which led in 1993 to **overt complete regression of the tumors in two cases of breast cancer.** Continuing this research, three additional breast cancer patients also underwent a conventional protocol of therapy which included a daily oral dosage of 390 mg of vitamin Q10 (Bio-Quinone of Pharma Nord) during the complete trials over 3-5 years. The **numerous metastases in the liver of a 44-year-old patient "disappeared," and no signs of metastases were found elsewhere. A 49-year-old patient, on a dosage of 390 mg of vitamin Q10, revealed no signs of tumor in the pleural cavity after six months, and her condition was excellent. A 75-year-old patient with carcinoma in one breast, after lumpectomy and 390 mg of CoQ10, showed no cancer in the tumor bed or metastases.** Control blood levels of CoQ10 of 0.83-0.97 and of 0.62 micrograms/ml increased to 3.34-3.64 and to 3.77 micrograms/ml, respectively, on therapy with CoQ10 for patients A-MRH and EEL.

45) Kim, Jeongho, et al. "Alpha-lipoic acid protects against cisplatin-induced ototoxicity via the regulation of MAPKs and proinflammatory cytokines." *Biochemical and biophysical research communications* 449.2 (2014): 183-189.

46) Recent Pat Anticancer Drug Discov. 2012 May 1;7(2):154-67.
ATP citrate lyase inhibitors as novel cancer therapeutic agents.
Zu XY1, Zhang QH, Liu JH, Cao RX, Zhong J, Yi GH, Quan ZH, Pizzorno G.
Author information
AbstractATP citrate lyase (ACL or ACLY) is an extra-mitochondrial enzyme widely distributed in various human and animal tissues. ACL links glucose and lipid metabolism by catalyzing the formation of acetyl-CoA and oxaloacetate from citrate produced by glycolysis in the presence of ATP and CoA. ACL is aberrantly expressed in many immortalized cells and tumors, such as breast, liver, colon, lung and prostate cancers, and is correlated reversely with tumor stage and differentiation, serving as a negative prognostic marker. ACL is an upstream enzyme of the long chain fatty acid synthesis, providing acetyl-CoA as an essential component of the fatty acid synthesis. Therefore, ACL is a key enzyme of cellular lipogenesis and potent target for cancer therapy. As a hypolipidemic strategy of metabolic syndrome and cancer treatment, many small chemicals targeting ACL have been designed and developed. This review article provides an update for the research and development of ACL inhibitors with a focus on their patent status, offering a new insight into their potential application.

47) Curr Drug Targets. 2015;16(2):156-63. ATP citrate lyase (ACLY): a promising target for cancer prevention and treatment.

Khwairakpam AD, Shyamananda MS, Sailo BL, Rathnakaram SR, Padmavathi G, Kotoky J, Kunnumakkara AB1.ATP citrate lyase (ACLY), an important enzyme involved in lipid biogenesis linked with glucose metabolism, catalyzes the conversion of citrate to oxaloacetic acid (OAA) and acetyl-CoA. The obtained acetyl-CoA is required for lipid synthesis during membrane biogenesis, as well as for histone acetylation reactions to regulate the expression of certain proteins in aberrantly proliferating cancer cells. Studies have shown a role for ACLY in tumorigenesis whereby increased levels of the enzyme leads to increased metabolic activity via activation of Akt signaling. Increasing lines of evidence suggest that enzymes involved in lipid biogenesis play a significant role in cancer cell proliferation and progression. In many cancer types such as glioblastoma, colorectal cancer, breast

cancer, non-small cell lung cancer, hepatocellular carcinoma etc., the level of ACLY has been found to be quite high as compared to normal cells. Cancer cell growth related to overexpression of ACLY can be inhibited by using chemical inhibitors or by the knockdown of ACLY gene. Inhibition of ACLY leads to changes in cancer cell metabolism that promotes tumor growth and proliferation. This review summarizes the role of ACLY in cancer development and its inhibitors in cancer treatment.

48) Tankova, Tsvetalina, D. Koev, and L. Dakovska. "Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy (controlled, randomized, open-label study)." Romanian journal of internal medicine= Revue roumaine de medecine interne 42.2 (2003): 457-464.

Aim: to evaluate the effect of alpha-lipoic acid in autonomic diabetic neuropathy in a controlled, randomized, open-label study.
MATERIAL AND METHODS: 46 patients with type 1 diabetes and different forms of autonomic neuropathy, of mean age 38.1 +/- 12.5 years and mean duration of diabetes 16.8 +/- 8.9 years were treated with alpha-lipoic acid for 10 days 600mg daily iv, thereafter one film tablet of 600mg daily for 50 days. 29 type 1 diabetic patients with autonomic diabetic neuropathy, of mean age 40.2 +/- 9.3 years and mean duration of diabetes 15.4 +/- 7.9 years served as a control group. We have followed-up patients' complaints, Ewing's tests, laboratory parameters of oxidative stress.
RESULTS: There was a significant improvement after treatment in the score for severity of cardiovascular autonomic neuropathy–from 6.43 +/- 0.9 to 4.24 +/- 1.8 ($p<0.001$), while in the control group it worsened from 6.18 +/- 1.3 to 6.52 +/- 0.9 ($p>0.1$). We found improvement in the Valsalva manoeuvre after treatment – from 1.05 +/- 0.04 to 1.13 +/- 0.08 ($p<0.001$); in the deep-breathing test -from 3.4 +/- 2.8 to 10.4 +/- 5.7 ($p<0.001$); and in the lying-to-standing test–from 0.99 +/- 0.01 to 1.01 +/- 0.02 ($p>0.1$), while in the control group there was no improvement. There was a beneficial effect of treatment on the change of systolic blood pressure at the lying-to-standing test–from 22.7 +/- 11.5 to 9.8 +/- 7.9 ($p<0.001$), while in the control group the change was 20.5 +/- 11.1 mmHg and 19.7 +/- 12.9 mmHg ($p>0.1$), respectively. We found improvement in diabetic enteropathy in six patients; in the complaints of dizziness, instability upon standing in six patients; in neuropathic edema of the lower extremities in four patients and in erectile dysfunction in four patients after treatment, while in the control group no change was reported in the symptoms and signs of autonomic neuropathy by the end of the follow-up period. There were changes in the laboratory parameters of oxidative stress after therapy–total serum antioxidant capacity increased from 20.42 +/- 1.8 to 22.96 +/- 2.3 microgH2O2/ml/min ($p<0.05$), serum SOD activity – from 269.8 +/- 31.1 to 319.8 +/- 29.IU/l ($p=0.02$) and erythrocyte SOD–from 0.89 +/- 0.10 to 1.11 +/- 0.09 U/gHb ($p=0.04$).
CONCLUSION: Our results demonstrate that alpha-lipoic acid (Thiogamma) appears to be an effective drug in the treatment of the different forms of **autonomic diabetic neuropathy.**

49) 2015 Slides Berton Berkson Alpha Lipoic Acid Cancer Toronto 2015 Slides

**Non-Standard Cancer Protocol at IMCNM**
• Intravenous Alpha Lipoic Acid (ALA) (Bartter and Berkson).
•Intravenous Vitamin C.
•Low Dose Naltrexone (LDN) (after Zagon and Bihari.)
•Hydroxycitrate (HCA) (after Schwartz L.).
•Healthy diet and life style.
•Supplements (**artemesinin, curcumin**, etc)
•Prescription drugs (**metformin, xanax, cimetidine**, etc.)

50) full pdf
Berkson, Burton M., Daniel M. Rubin, and Arthur J. Berkson. "Reversal of signs and symptoms of a B-cell

lymphoma in a patient using only low-dose naltrexone." Integrative cancer therapies 6.3 (2007): 293-296.Reversal of B CELL LYMPHOMA with LDN Burton Berkson 2007

51) Berkson, Burton M., Daniel M. Rubin, and Arthur J. Berkson. "The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous α-lipoic acid/low-dose naltrexone protocol." Integrative cancer therapies 5.1 (2006): 83-89.

52) Monday, 31 October 2011 Q&A With Dr Burt Berkson – Low Dose Naltrexone and Alpha Lipoic Acid Anticancer.org.uk

53) Alpha Lipoic Acid: The Workhorse Antioxidant Published September 15, 2015 HealthyBlanceMD

54) deleted

55) Interview with Burt Berkson May 2015 LAs Cruces New Mexico LDNscience.org

56) Cancer Treatment Using Low Dose Naltrexone and Alpha-Lipoic Acid
December 16, 2010Cancer Treatments and Prevention

57) Liu, W., et al. "Naltrexone at low doses upregulates a unique gene expression not seen with normal doses: Implications for its use in cancer therapy." International Journal of Oncology (2016).

**Anti-Cancer Effects of Melatonin**

58) Abstract A91: Over-the-counter melatonin supplementation in human subjects: A potentially novel chronotherapeutic approach targeting the Warburg effect and fatty acid metabolism in breast cancer therapy/prevention
David E. Blask, Robert T. Dauchy, Erin M. Dauchy, Steven M. Hill, Lulu Mao, Melissa M. Wren, Mary M.C. Meyaski-Schluter, and Lin Yuan
Tulane University School of Medicine, New Orleans, LA.
Abstracts: AACR Special Conference: Metabolism and Cancer; June 7-10, 2015; Bellevue, WA
Melatonin, a circadian anti-cancer hormone produced by the pineal gland during darkness at night suppresses the Warburg effect, linoleic acid (LA) uptake/metabolism and tumor cell proliferation in both estrogen receptor (ERα+) and ERα- in tissue-isolated human breast cancer xenografts. The nighttime circadian melatonin signal regulates circadian rhythms in tumor glucose and fatty acid metabolism as well as related signaling pathways that are important in controlling cell proliferative and survival mechanisms. Over-the-counter (OTC) melatonin supplements are used by millions of individuals to treat insomnia and/or jet-lag. The present study addressed the hypothesis that oral ingestion of OTC melatonin supplements by normal adult human female volunteers results in blood levels of melatonin that suppress LA uptake/metabolism, aerobic glycolysis and cell proliferative activity in human breast cancer xenografts, growing in nude female rats, directly perfused in situ with human subject donor whole-blood following melatonin intake. Twelve young, healthy premenopausal women were recruited to ingest an OTC melatonin supplement at a single dose of either 75μg, 150μg, 300μg or 1 mg during midday (low endogenous melatonin levels) resulting in low to high pharmacological blood concentrations of melatonin. A pre-supplement venous blood sample was collected from the antecubital vein of the forearm. Each subject then ingested a randomly selected oral dose of melatonin followed approximately 1 hour later by the withdrawal of a post-supplement venous blood sample. On the following day, the pre- and post-supplement whole-blood samples collected from a given subject were separately placed into a tumor perfusion reservoir. Tissue-isolated ERα- MCF-7 human breast cancer xenografts grown in female nude rats were then directly perfused in situ for 1 hour with

either pre- or post-supplement oxygenated blood (37°C). Irrespective of the dose tested, melatonin induced a 50% decrease in both tumor glucose uptake and lactate release, 22% and 44% deceases in O2 uptake and CO2 production, respectively, 50% decrease in cAMP concentrations, and a 100% decrease in linoleic acid (LA) uptake and 13-hydroxyoctadecadienoic acid (13-HODE) formation. Melatonin also caused a marked decrease in the expression of phospho-AKT, GSK3β and ERK1/2, and an 85% decrease in the incorporation of [3H]thymidine into DNA. Similar results were obtained at the lowest dose of melatonin (e.g., 75μg) in ERα+ human breast cancer xenografts. The melatonin-induced suppression tumor proliferative and metabolic activity in both ERα- and ERα+ breast cancer xenografts was completely prevented by the co-perfusion with the non-selective MT1/MT22 melatonin receptor blocker S20928 consistent with the involvement of a melatonin receptor-mediated mechanism. These results indicate that oral administration of an OTC melatonin supplement at a variety of low to high doses were equally effective in suppressing the Warburg effect and key tumor proliferative and survival signaling pathways, cAMP-dependent LA uptake and metabolism to mitogenically active 13-HODE and ultimately cell proliferation in tissue-isolated human breast xenografts irrespective of ERα status via a melatonin receptor-mediated mechanism. These findings suggest that even low doses of OTC melatonin preparations may play a potentially important role as a new chronotherapeutic agent in human breast cancer treatment and/or prevention by targeting aerobic glycolysis and fatty acid signaling and metabolism. Supported by NIH Grants R21CA129875 (DEB) and R01CA54152 (SMH).

59) Expert Opin Ther Targets. 2013 Dec;17(12):1483-96. Epub 2013 Sep 14. Molecular mechanisms of the pro-apoptotic actions of melatonin in cancer: a review. Bizzarri M1, Proietti S, Cucina A, Reiter RJ.
Compelling evidence has highlighted the complex pleiotropic functions elicited by the melatonin in cancer cells. **Melatonin** behaves as a 'smart killer', i.e., modulating anti-apoptotic processes in normal cells, and triggering pro-apoptotic signals in cancer cells.
AREAS COVERED: Melatonin induces programmed cell death in a wide range of different tumors (breast, gastro-intestinal, hematological, prostate, osteosarcoma, melanoma, kidney, etc…). Mechanisms of action and molecular pathways involved in pro-apoptotic processes under melatonin treatment are discussed.
EXPERT OPINION: Melatonin involvement in apoptotic processes is a new and relevant field of investigation. Even in tumor models unresponsive to melatonin alone, this hormone can significantly amplify the cytostatic and the cytotoxic effects triggered by other compounds or conventional drugs. We are far from having a satisfactory understanding about how and when melatonin exerts its beneficial effects. Melatonin in the nanomolar range activates the intrinsic and/or the extrinsic apoptotic pathway in cancer cells, namely through an increase in the p53/MDM2p ratio and downregulation of Sirt1. This finding is of great relevance since there is intense research ongoing to identify nontoxic feasible inhibitors of MDM2 and Sirt1. Melatonin should be evaluated for the management of those cancers where both of these are overexpressed and functionally strategic.

60) Reiter, Russel J., Dun Xian Tan, and Annia Galano. "Melatonin: exceeding expectations." Physiology 29.5 (2014): 325-333.
This pro-apoptotic action of melatonin in cancer cells is diametrically opposite to its anti-apoptotic function in normal cells, a differential
action that has been difficult to explain (6).

61) Melatonin enhances mitochondrial ATP synthesis, reduces ROS formation and mediates translocation of the nuclear erythroid 2-related factor 2 resulting in activation of phase-2 antioxidant enzymes (γ-GCS, HO-1, NQO1) in UVR-treated normal human epidermal keratinocytes (NHEK).
(PMID:27117941) Kleszczyński K , Zillikens D , Fischer TW
Department of Dermatology, University of Lübeck, Ratzeburger Allee 160, 23538, Lübeck, Germany. Journal of Pineal Research [2016]
Melatonin is an ubiquitous molecule with a variety of functions including potent antioxidative properties. Due to its

lipophilic character, it easily crosses cellular and intracellular membranes and reaches all subcellular organelles. Because of its ability to scavenge free radicals, melatonin protects against oxidative stress, e.g. induced by ultraviolet radiation (UVR). Here, we investigated in a dose- (0, 10, 25, 50 mJ/cm(2) ) and time-dependent (0, 4, 24, 48 hr post-UVR) manner, whether melatonin prevents the UVR-mediated alterations in ATP synthesis and the generation of reactive oxygen species (ROS) in normal human epidermal keratinocytes (NHEK). Additionally, we evaluated the molecular mechanism of action of melatonin with regard to activation of phase-2 antioxidative enzymes via nuclear erythroid 2-related factor (Nrf2). We found that (i) melatonin counteracted UVR-induced alterations in the ATP synthesis and reduced free radical formation; (ii) melatonin induced the translocation of Nrf2 transcription factor from the cytosol into the nucleus resulting in, (iii) enhanced gene expression of phase-2 antioxidative enzymes including γ-glutamylcysteine synthetase (γ-GCS), heme oxygenase-1 (HO-1) and NADPH: quinone dehydrogenase-1 (NQO1) representing an elevated antioxidative response of keratinocytes. These results suggest that melatonin not only directly scavenges ROS, but also significantly induces the activation of phase-2 antioxidative enzymes via the Nrf2 pathway uncovering a new action mechanism that supports the ability of keratinocytes to protect themselves from UVR-mediated oxidative stress.

62) J Pineal Res. 2014 Aug;57(1):43-52. Antitumour activity of melatonin in a mouse model of human prostate cancer: relationship with hypoxia signalling. Paroni R1, Terraneo L, Bonomini F, Finati E, Virgili E, Bianciardi P, Favero G, Fraschini F, Reiter RJ, Rezzani R, Samaja M.
Melatonin is known to exert antitumour activity in several types of human cancers, but the underlying mechanisms as well as the efficacy of different doses of melatonin are not well defined. Here, we test the hypothesis whether melatonin in the **nanomolar range is effective in exerting antitumour activity in vivo** and examine the correlation with the hypoxia signalling mechanism, which may be a major molecular mechanism by which melatonin antagonizes cancer. To test this hypothesis, LNCaP human prostate cancer cells were xenografted into seven-wk-old Foxn1nu/nu male mice that were treated with melatonin (18 i.p. injections of 1 mg/kg in 41 days). Saline-treated mice served as control. We found that the melatonin levels in plasma and xenografted tissue were 4× and 60× higher, respectively, than in control samples. Melatonin tended to restore the redox imbalance by **increasing expression of Nrf2**. As part of the phenotypic response to these perturbations, **xenograft microvessel density was less in melatonin-treated animals, indicative of lower angiogenesis, and the xenograft growth rate was slower** ($P < 0.0001$). These changes were accompanied by a **reduced expression of Ki67**, elevated expression of HIF-1α and increased phosphorylation of Akt in melatonin than saline-treated mice. We conclude that the beneficial effect of melatonin in reducing cancer growth in vivo was evident at **melatonin plasma levels as low as 4 nm** and was **associated with decreased angiogenesis**. Higher HIF-1α expression in xenograft tissue indicates that the antitumour effect cannot be due to a postulated antihypoxic effect, but may stem from lower angiogenesis potential.
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63) Oncol Rep. 2015 Jul;34(1):279-87. Melatonin decreases cell proliferation, impairs myogenic differentiation and triggers apoptotic cell death in rhabdomyosarcoma cell lines. Codenotti S1, Battistelli M2, Burattini S2, Salucci S2, Falcieri E2, Rezzani R3, Faggi F1, Colombi M1, Monti E1, Fanzani A1.
Melatonin is a small indole produced by the pineal gland and other tissues, and has numerous functions that aid in the maintenance of the whole body homeostasis, ranging from the regulation of circadian rhythms and sleep to protection from oxidative stress. Melatonin has also been reported to counteract cell growth and chemoresistance in different types of cancer. In the present study, we investigated the effects of exogenous melatonin administration on different human cell lines and primary mouse tumor cultures of rhabdomyosarcoma (RMS), the most frequent soft tissue sarcoma affecting childhood. The results showed that melatonin significantly affected the behavior of RMS cells, leading to inhibition of cell proliferation and impairment of myogenic differentiation followed by increased apoptotic cell death, as observed by immunoblotting analysis of apoptosis-related markers including Bax, Bcl-2 and caspase-3. Similar findings were observed using a combination of microscopy techniques,

including scanning/transmission electron and confocal microscopy. Furthermore, melatonin in combination with doxorubicin or cisplatin, two compounds commonly used for the treatment of solid tumors, increased the sensitivity of RMS cells to apoptosis. These data indicated that melatonin may be effective in counteracting RMS tumor growth and chemoresistance.

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64) Cardinali, D., et al. "Melatonin-Induced Oncostasis, Mechanisms and Clinical Relevance." J Integr Oncol S 1 (2016): 2.

65) J Pineal Res. 2015 May;58(4):375-87. doi: 10.1111/jpi.12227. Epub 2015 Mar 23. Melatonin as a treatment for gastrointestinal cancer: a review.
Xin Z1, Jiang S, Jiang P, Yan X, Fan C, Di S, Wu G, Yang Y, Reiter RJ, Ji G.
Gastrointestinal cancer is a disease that affects the population worldwide with high morbidity and mortality. Melatonin, an endogenously produced molecule, may provide a defense against a variety of cancer types. In particular, the **ability of melatonin to inhibit gastrointestinal cancer is substantial.** In this review, we first clarify the relationship between the disruption of the melatonin rhythm and gastrointestinal cancer (based on epidemiologic surveys and animal and human studies) and summarize the preventive effect of melatonin on carcinogenesis. Thereafter, the mechanisms through which melatonin exerts its anti-gastrointestinal cancer actions are explained, including **inhibition of proliferation, invasion, metastasis, and angiogenesis, and promotion of apoptosis and cancer immunity**. Moreover, we discuss the drug synergy effects and the role of melatonin receptors involved in the growth-inhibitory effects on gastrointestinal cancer.

66) Sanchez-Sanchez, Ana M., et al. "**Melatonin cytotoxicity is associated to warburg effect inhibition in ewing sarcoma cells**." PloS one 10.8 (2015): e0135420.
Melatonin kills or inhibits the proliferation of different cancer cell types, and this is associated with an increase or a decrease in reactive oxygen species, respectively. Intracellular oxidants originate mainly from oxidative metabolism, and cancer cells frequently show alterations in this metabolic pathway, such as the Warburg effect (aerobic glycolysis). Thus, we hypothesized that melatonin could also regulate differentially oxidative metabolism in cells where it is cytotoxic (Ewing sarcoma cells) and in cells where it inhibits proliferation (chondrosarcoma cells). Ewing sarcoma cells but not chondrosarcoma cells showed a metabolic profile consistent with aerobic glycolysis, i.e. increased glucose uptake, LDH activity, lactate production and HIF-1α activation. **Melatonin reversed Ewing sarcoma metabolic profile and this effect was associated with its cytotoxicity. The differential regulation of metabolism by melatonin could explain why the hormone is harmless for a wide spectrum of normal and only a few tumoral cells, while it kills specific tumor cell types.**

cytotoxicity of melatonin in Ewing sarcoma cells is mediated by an increase in ROS. We show for the first time that melatonin regulates this metabolism, inhibiting the hallmarks of Warburg effect in Ewing sarcoma cells. Such inhibition is associated to the inactivation of HIF-1α, the main regulator of aerobic glycolysis, and to melatonin´s cytotoxicity.

67) full free Ovarian Cancer
Shen, Ching-Ju, et al. "Melatonin suppresses the growth of **ovarian cancer** cell lines (OVCAR-429 and PA-1) and potentiates the effect of G1 arrest by targeting CDKs." International journal of molecular sciences 17.2 (2016): 176.

68) Loureiro, Rute, et al. "Melatonin antiproliferative effects require active mitochondrial function in embryonal carcinoma cells." Oncotarget 6.19 (2015): 17081.

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69) Pacini, Nicola, and Fabio Borziani. “Oncostatic-Cytoprotective Effect of Melatonin and Other Bioactive Molecules: A Common Target in Mitochondrial Respiration.” International journal of molecular sciences 17.3 (2016): 341. Pacini Nicola Fabio Borziani Oncostatic Melatonin Target Mitochondrial Respiration Int J Mol Sciences 2016

mitochondria of neoplastic cells actually have a strong decoupling of the oxidative phosphorylation, that is of oxidation of phosphorylation.

the production of ROS is extremely harmful for the mitochondrial structures,
but also for the whole cell, where it can come out through the voltage-dependent anion channel

the paradoxical action of MLT, able to induce cellular death in cancer cells and cytoprotection in models of neurodegeneration, is quite appropriate. This molecule, in fact, stimulates the activity of respiratory complexes I, II, and IV, and has a marked effect on complex III, thus being able to achieve a strong perturbation of the electron transport chain in neoplastic cells, also preventing the braking action of BCL-2 and overstimulating an already metastable cellular system, characterized by a high electron flow through the electron transport chain, high oxygen consumption, UCP-mediated
uncoupling and high sensitivity to ROS.

mechanisms of the electron transport chain, in view of the recent findings on the metabolome, likely represent the essential core of the effects of these molecules.

On the other hand **substances that, also at the end of respiratory complexes, force the cellular respiration, such as dichloroacetate, thiamine or . -lipoic acid, induce ROS-mediated cell death in neoplastic cells and neuroprotection in many neurodegenerative diseases.**

70) J Pineal Res. 2012 Nov;53(4):366-73. doi: 10.1111/j.1600-079X.2012.01006.x. Epub 2012 May 14. Melatonin inhibits cell proliferation and induces caspase activation and apoptosis in human malignant lymphoid cell lines.
Sánchez-Hidalgo M1, Lee M, de la Lastra CA, Guerrero JM, Packham G.

71) Lee, Mi Jin, et al. “Silver nanoparticles affect glucose metabolism in hepatoma cells through production of reactive oxygen species.” International journal of nanomedicine 11 (2016): 55.

72) Novotny L, Rauko P, Cojocel C. alpha-Lipoic acid: the potential for use in cancer therapy. Neoplasma. 2008;55(2):81-6.Novotny alpha Lipoic acid potential use cancer therapy Neoplasma 2008

73) Dadhania VP, Tripathi DN, Vikram A, Ramarao P, Jena GB. Intervention of alpha-lipoic acid ameliorates methotrexate-induced oxidative stress and genotoxicity: A study in rat intestine. Chem Biol Interact. 2010 Jan 5;183(1):85-97.

74) Selvakumar E, Hsieh TC. Regulation of cell cycle transition and induction of apoptosis in HL-60 leukemia cells by lipoic acid: role in cancer prevention and therapy. J Hematol Oncol. 2008;1:4.

75) Na MH, Seo EY, Kim WK. Effects of alpha-lipoic acid on cell proliferation and apoptosis in MDA-MB-231 human breast cells. Nutr Res Pract. 2009 Winter;3(4):265-71.

76) Shi DY, Liu HL, Stern JS, Yu PZ, Liu SL. Alpha-lipoic acid induces apoptosis in hepatoma cells via the PTEN/Akt pathway. FEBS Lett. 2008 May 28;582(12):1667-71.

77) Choi SY, Yu JH, Kim H. Mechanism of alpha-lipoic acid-induced apoptosis of lung cancer cells. Ann N Y Acad Sci. 2009 Aug;1171:149-55. Choi alpha lipoic acid induced apoptosis lung cancer Ann N Y Acad Sci 2009

78) Dozio E, Ruscica M, Passafaro L, et al. The natural antioxidant alpha-lipoic acid induces p27(Kip1)-dependent cell cycle arrest and apoptosis in MCF-7 human breast cancer cells. Eur J Pharmacol. 2010 Sep 1;641(1):29-34. Dozio alpha-lipoic acid induces apoptosis in MCF7 human breast cancer Eur J Pharmacol 2010

79) Lee HS, Na MH, Kim WK. alpha-Lipoic acid reduces matrix metalloproteinase activity in MDA-MB-231 human breast cancer cells. Nutr Res. 2010 Jun;30(6):403-9

PQQ

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80) Rucker, Robert, Winyoo Chowanadisai, and Masahiko Nakano. Potential physiological importance of pyrroloquinoline quinone " Alternative Medicine Review 14.3 (2009): 268.

81) Misra, H. S., Y. S. Rajpurohit, and N. P. Khairnar. "Pyrroloquinoline-quinone and its versatile roles in biological processes." Journal of biosciences 37.2 (2012): 313.Pyrroloquinoline quinone and its versatile roles in biological processes Misra 2012

Pyrroloquinoline-quinine (PQQ) was initially characterized as a redox cofactor for **membrane-bound dehydrogenases** in the bacterial system. Subsequently, PQQ was shown to be an antioxidant protecting the living cells from oxidative damage in vivo and the biomolecules from artificially produced reaction oxygen species in vitro. The presence of PQQ has been documented from different biological samples. It functions as a nutrient and vitamin for supporting the growth and protection of living cells under stress. Recently, the role of PQQ has also been shown as a bio-control agent for plant fungal pathogens, an inducer for proteins kinases involved in cellular differentiation of mammalian cells and as a redox sensor leading to development of biosensor. Recent reviews published on PQQ and enzymes requiring this cofactor have brought forth the case specific roles of PQQ. This review covers the comprehensive information on various aspects of PQQ known till date. These include the roles of PQQ in the regulation of cellular growth and differentiation in mammalian system, as a nutrient and vitamin in stress tolerance, in crop productivity through increasing the availability of insoluble phosphate and as a bio-control agent, and as a redox agent leading to the biosensor development. Most recent findings correlating the **exceptionally high redox recycling ability of PQQ to its potential as anti-neurodegenerative, anticancer and pharmacological agents,** and as a signalling molecule have been distinctly brought out.

They have shown that **PQQ stimulates mitochondrial complex 1 activity in vitro** and counters the effect of mitochondrial complex 1 inhibitor diphenylene iodonium action in vivo.

**PQQ depletes glutathione !!!**

82) Redox Rep. 2010;15(4):146-54. Role of glutathione in augmenting the anticancer activity of pyrroloquinoline quinone (PQQ).
Shankar BS1, Pandey R, Amin P, Misra HS, Sainis KB.

Pyrroloquinoline quinone (PQQ), a bacterial redox co-factor and antioxidant, is highly reactive with nucleophilic compounds present in biological fluids. **PQQ induced apoptosis in human promonocytic leukemia U937 cells and this was accompanied by depletion of the major cellular antioxidant glutathione and increase in intracellular reactive oxygen species (ROS).** Treatment with glutathione (GSH) or N-acetyl-L-cysteine (NAC) **did not spare PQQ toxicity** but resulted in a 2-5-fold increase in PQQ-induced apoptosis in U937 cells. Cellular GSH levels increased following treatment by NAC alone but were severely depleted by co-treatment with NAC and PQQ. This was accompanied by an **increase in intracellular ROS**. Alternatively, depletion of glutathione also resulted in increased PQQ cytotoxicity. However, the cells underwent necrosis as evidenced by dual labeling with annexin V and propidium iodide. PQQ-induced cytotoxicity is thus critically regulated by the cellular redox status. An increase in GSH can augment apoptosis and its depletion can switch the mode of cell death to necrosis in the presence of PQQ. Our data suggest that **modulation of intracellular GSH can be used as an effective strategy to potentiate cytotoxicity of quinones like PQQ.**

83) Min, Zhihui, et al. "Pyrroloquinoline Quinone Induces Cancer Cell Apoptosis via Mitochondrial-Dependent Pathway and Down-Regulating Cellular Bcl-2 Protein Expression." Journal of Cancer 5.7 (2014): 609-624.
Recently, studies showed that PQQ could induce apoptosis in human promonocytic leukemia U937 and lymphoma EL-4 cells, as well as Jurkat cell programmed death [5]. **The underlying mechanism might be relevant to the increase of intracellular reactive oxygen species (ROS) and depletion of glutathione**[9].

!!!!!!!!!!!!!!!!! 2016 PQQ **enhanced energy production via mitochondrial TCA cycle and oxidative phosphorylation**

84) full free
Sci Rep. 2016; 6: 26723. Identification of lactate dehydrogenase as a mammalian pyrroloquinoline quinone (PQQ)-binding protein
Mitsugu Akagawa,a,1,* Kenji Minematsu,1,* Takahiro Shibata,2,3 Tatsuhiko Kondo,2 Takeshi Ishii,4 and Koji Uchidab,2
Pyrroloquinoline quinone (PQQ), a redox-active o-quinone, is an important nutrient involved in numerous physiological and biochemical processes in mammals. Despite such beneficial functions, the underlying molecular mechanisms remain to be established. In the present study, using PQQ-immobilized Sepharose beads as a probe, we examined the presence of protein(s) that are capable of binding PQQ in mouse NIH/3T3 fibroblasts and identified five cellular proteins, including l-lactate dehydrogenase (LDH) A chain, as potential mammalian PQQ-binding proteins. In vitro studies using a purified rabbit muscle LDH show that PQQ inhibits the formation of lactate from pyruvate in the presence of NADH (forward reaction), whereas it enhances the conversion of lactate to pyruvate in the presence of NAD+ (reverse reaction). The molecular mechanism underlying PQQ-mediated regulation of LDH activity is attributed to the oxidation of NADH to NAD+ by PQQ. **Indeed, the PQQ-bound LDH oxidizes NADH, generating NAD+, and significantly catalyzes the conversion of lactate to pyruvate**. Furthermore, PQQ attenuates cellular lactate release and increases intracellular ATP levels in the NIH/3T3 fibroblasts. Our results suggest that **PQQ, modulating LDH activity to facilitate pyruvate formation through its redox-cycling activity, may be involved in the enhanced energy production via mitochondrial TCA cycle and oxidative phosphorylation**.
PQQ prevents skeletal muscle atrophy

85) Kuo, Yung-Ting, et al. "Pyrroloquinoline Quinone Resists Denervation-Induced Skeletal Muscle Atrophy by Activating PGC-1α and Integrating Mitochondrial Electron Transport Chain Complexes." PloS one 10.12 (2015): e0143600.
**skeletal muscle atrophy** results from the loss of electric stimulation and leads to protein degradation, which is critically regulated by the well-confirmed transcriptional co-activator peroxisome proliferator co-activator 1 alpha

(PGC-1α). No adequate treatments of muscle wasting are available. **Pyrroloquinoline quinone (PQQ), a naturally occurring antioxidant component with multiple functions including mitochondrial modulation, demonstrates the ability to protect against muscle dysfunction.** However, it remains unclear whether PQQ enhances PGC-1α activation and resists skeletal muscle atrophy in mice subjected to a denervation operation. This work investigates the expression of PGC-1α and mitochondrial function in the skeletal muscle of denervated mice administered PQQ. The C57BL6/J mouse was subjected to a hindlimb sciatic axotomy. A PQQ-containing ALZET® osmotic pump (equivalent to 4.5 mg/day/kg b.w.) was implanted subcutaneously into the right lower abdomen of the mouse. In the time course study, the mouse was sacrificed and the gastrocnemius muscle was prepared for further myopathological staining, energy metabolism analysis, western blotting, and real-time quantitative PCR studies. We observed that **PQQ administration abolished the denervation-induced decrease in muscle mass and reduced mitochondrial activities**, as evidenced by the reduced fiber size and the decreased expression of cytochrome c oxidase and NADH-tetrazolium reductase. Bioenergetic analysis demonstrated that PQQ reprogrammed the denervation-induced increase in the mitochondrial oxygen consumption rate (OCR) and led to an increase in the extracellular acidification rate (ECAR), a measurement of the glycolytic metabolism. The protein levels of PGC-1α and the **electron transport chain (ETC) complexes were also increased by treatment with PQQ**. Furthermore, PQQ administration highly enhanced the expression of oxidative fibers and maintained the type II glycolytic fibers. **This pre-clinical in vivo study suggests that PQQ may provide a potent therapeutic benefit for the treatment of denervation-induced atrophy** by activating PGC-1α and maintaining the mitochondrial ETC complex in skeletal muscles.

**neuroprotective with lithium pqq**

86) Zhao, Lei, et al. "Beneficial synergistic effects of microdose lithium with pyrroloquinoline quinone in an Alzheimer's disease mouse model." Neurobiology of aging 35.12 (2014): 2736-2745.
Nunome, Kana, et al. "Pyrroloquinoline quinone prevents oxidative stress-induced neuronal death probably through changes in oxidative status of DJ-1." Biological and Pharmaceutical Bulletin 31.7 (2008): 1321-1326.

**ALA inhibits PDK which upregulates PDC**

87) Zhang, Wen, et al. "Targeting tumor metabolism for cancer treatment: is pyruvate dehydrogenase kinases (PDKs) a viable anticancer target?." International journal of biological sciences 11.12 (2015): 1390.

inhibition of PDKs could upregulate the activity of PDC and rectify the balance between the demand and supply of oxygen, which could lead to cancer cell death. Thus, inhibitors targeting PDKs represent a promising strategy for cancer treatment by acting on glycolytic tumors while showing minimal side effects on the oxidative healthy organs. This review considers the role of **PDKs as regulator of PDC that catalyzes the oxidative decarboxylation of pyruvate in mitochondrion**. It is concluded that PDKs are solid therapeutic targets. **Inhibition of PDKs could be an attractive therapeutic approach for the development of anti-cancer drugs.**

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**DCA dichloroacetate**

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88) Flavin, Dana F. "Non-Hodgkin's lymphoma reversal with dichloroacetate." Journal of oncology 2010 (2010).

In June 2007, a 48-year-old male patient, diagnosed with **Stage 4 Non-Hodgkin's Follicular Lymphoma (NHL),** was treated for 3 months with conventional chemotherapy resulting in a complete remission. Almost one year later tumors returned in the nasopharynx and neck lymph glands. Refusing all suggested chemotherapies, the patient began self-administering **dichloroacetate (DCA) 900 mg daily** with a PET scan showing **complete remission four months later.** Since his last PET scan, May, 2009, he remains tumor-free from continuous DCA usage.

First and foremost DCA inhibits pyruvate dehydrogenase kinase (PDK). PDK blocks pyruvate dehydrogenase (PDH) through its phosphorylation activity.

DCA has been shown to block this phosphorylation by PDK at the mitochondrial membrane level and decrease glycolysis in favor of glucose oxidation. This return to a normal metabolism of glucose allows for major changes including a decrease in Ca++ intracellularly, and stabilization of the mitochondria allowing a reactivation of caspases in cancer cells leading to apoptosis [19]

The effects of DCA, caused by reactivation of mitochondrial respiration, are not without complications although it inexplicably seems to be predominantly limited to cancer cells while most normal cells remain unaffected [24]. A reversible, **minimal nerve damage can be considerably reduced by a daily thiamine intake of several hundred milligrams for humans [23] and animals [15]. The thiamine amount varies from 50 mg/day to 100 mg/day depending on whether it is administered orally or injected intramuscularly [23].**

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89) Lemmo, Walter, and Gerard Tan. "Prolonged Survival After Dichloroacetate Treatment of Non-Small-Cell Lung Carcinoma-Related Leptomeningeal Carcinomatosis." Journal of Medical Cases 7.4 (2016): 136-142. Prolonged Survival Dichloroacetate NonSmall-Cell Lung Carcinoma Lemmo Walter J Medical Cases 2016

90) Villalba, Martin, et al. "Chemical metabolic inhibitors for the treatment of blood-borne cancers." Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 14.2 (2014): 223-232.

One enzyme implicated in tumor metabolic remodeling and whose expression is regulated by oncogenic transcription factors is pyruvate dehydrogenase kinase 1 (PDK1), [3]), which is inhibited by dichloroacetate (DCA). PDK1 inhibition leads to pyruvate dehydrogenase (PDH) activation and forces cells to use mitochondria as the main ATP generator. As a result, glycolysis is vastly diminished.

90) Dr Paul Amderson book chapter on DCA combined with poly-MVA (alpha lipoic acid) Outside-the-Box-Cancer-Therapies-Paul Anderson _Mark-Stengler

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**(91)**

**Mantle Cell Lymphoma Support for Alternative and/or chemo approach. Facebook Group** Judy Dowell is administrator. She went into long term mission from Mantle cell Lymphoma with DCA

https://www.facebook.com/groups/9603394299/permalink/10155654596364300/

https://therenodispatch.blogspot.com/2012/10/what-is-dca-real-story-behind-this.html?showComment=1397939232783#c140943722525964779

Judy Dowell April 19, 2014 at 1:27 PM

In 2006 I was diagnosed with stage 4e mantle cell lymphoma, non-hogekins. It was overwhelming to be told I had a prognosis of six months with or without chemo. It's a long story how I found dca, but I studied medical and science sites about my cancer, down to the molecular level. I was convinced the orphaned drug creisine (dichloroacetate) was my answer. Abbreviated NaDCA, sodium dichloroacetate dissolves in water and is taken orally once a day. For my 150 pound body weight, 1/8 teaspoon in water was all I needed. I took thiamin (vitamin B1, 500 mg. Daily) to help counter effect the slight neuropothy which completely goes away as soon as you discontinue using DCA. It's that simple. DCA has proven through medic or human trials to be harmless to the healthy cells. It's fatal to cancer cells! It reverses the warburg effect so that bad cancer cells realize they are not normal and committee suicide, so the cells die off pretty fast. Dr. Akbar Kahn did human trials at medic or cancer center in Toronto, Canada as well as at the university of Alberta in Edmonton. Go to www.thedcasite for old info from 2007. Check out the medic or cancer center for recent up to the minute info. Dr. Humaira Kahn and Akbar Kahn, as well as others have found that DCA does in fact work. DCA is available today. If your doctor will not appease you by looking into this, find a doctor who will. Chemo makes the doctor $13,000. Per dose, so if your getting rchop or bcnu…chemo, they rake in around $50,000. Per patient! Look around that chemo lab at all the faces, then count how much money that lab is raking in. Compare that to the cost of a sure cure that costs about $100.00 per six months. Get the picture? I spent over $100. In gas to go to the doctor in six months, I cured my cancer with DCA and spent $100. I'm not thrifty, I'm alive which is more than they could offer me!

(92) Judy Dowell-Bundschuh shared a link.
https://www.facebook.com/groups/9603394299/permalink/10155654596364300/

Judy Dowell-Bundschuh I went back on dca since the stem cell transplant only gave me a year remission (2009-2010) and then had four months of b&r (that gets me to 2011) then I went back on dca and i didn't get any worse while taking dca but I had a ct scan twice, about 4 months apart, then the last ct scan results were that i was finally in remission (Dec 2013). I just had a ct scan today and my Dr called to tell me there is no sign of disease. Yay!

(93) DCA LAB

Our Laboratory: All the products we offer are produced by us in our own laboratory. We are based in EU, have strict quality control and provide Sodium Dichloroacetate of the highest quality. We provide free and fast worldwide shipping. For those in need, we included an option to have DCA delivered by your door in one business day.

94) DCA dosage calculator

8/20/19 IM sent to Judy:

95) Khan, Akbar, Douglas Andrews, and Anneke C. Blackburn. "Long-term stabilization of stage 4 colon cancer using sodium dichloroacetate therapy." World journal of clinical cases 4.10 (2016): 336.
Oral dichloroacetate sodium (DCA) has been investigated as a novel metabolic therapy for various cancers since 2007, based on data from Bonnet et al that DCA can trigger apoptosis of human lung, breast and brain cancer cells. Response to therapy in human studies is measured by standard RECIST definitions, which define "response" by the degree of tumour reduction, or tumour disappearance on imaging. However, Blackburn et al have demonstrated that DCA can also act as a cytostatic agent in vitro and in vivo, without causing apoptosis (programmed cell death). A case is presented in which oral DCA therapy resulted in tumour stabilization of stage 4 colon cancer in a 57 years old female for a period of nearly 4 years, with no serious toxicity. Since the natural history of stage 4 colon cancer consists of steady progression leading to disability and death, this case highlights a

novel use of DCA as a cytostatic agent with a potential to maintain long-term stability of advanced-stage cancer. Keywords: Dichloroacetate, Cancer, Colon, Colorectal, Cytostatic, Stabilization, Growth inhibition, Intravenous Core tip: Oral dichloroacetate sodium (DCA) has been investigated as a novel metabolic therapy for various cancers. Response to therapy in human studies is measured by standard RECIST definitions, which define "response" by the degree of tumour reduction, or tumour disappearance on imaging. However, DCA can also act as a cytostatic agent, without causing apoptosis (programmed cell death). A case is presented in which oral DCA therapy resulted in tumour stabilization of stage 4 colon cancer in a 57 years old female for a period of nearly 4 years, with no serious toxicity.

The oral DCA regimen that was developed included three natural medications acetyl L-carnitine[29-31], R-alpha lipoic acid[32-34] and benfotiamine[35-37], for the primary purpose of neuropathy prevention.

Observational data collected from more than 300 cancer patients with advanced disease revealed measurable benefits from DCA therapy in 60%-70% of cases. The neuropathy risk with inclusion of natural neuroprotective agents was roughly 20% with 20-25 mg/kg per day dosing on a 2 wk on/1 wk off cycle. Reversible liver enzyme elevation was noted in approximately 2% in this patient group (clinic observational data published online at

Chu et al[11] reported on 24 patients treated for a median time of 2 mo at either 6.25 or 12.5 mg/kg BID, on continuous oral DCA without neuroprotective supplements. They concluded that the recommended phase 2 dose was 6.25 mg/kg BID (12.5 mg/kg per day), with careful monitoring of neuropathy being needed. Dunbar et al[9] recommended 5 mg/kg BID as a starting dose for most patients, with their trial administering 4, 8 or 12.5 mg/kg BID continuously (median time on DCA 34 d), also without neuroprotective supplements. The patient in this report took 500 mg BID, equivalent to 8.2 mg/kg BID, 2 wk on/1 wk off, but could not tolerate this dose three times a day (total of 25 mg/kg per day)

96) Khan, Akbar, et al. "Long-term stabilization of metastatic melanoma with sodium dichloroacetate." World journal of clinical oncology 8.4 (2017): 371.
Correspondence to: Akbar Khan, MD, Medical Director, Medicor Cancer Centres Inc, 4576 Yonge St., Suite 301, Toronto, ON M2N 6N4, Canada. moc.recnacrocidem@nahka

Sodium dichloroacetate (DCA) has been studied as a metabolic cancer therapy since 2007, based on a publication from Bonnet et al demonstrating that DCA can induce apoptosis (programmed cell death) in human breast, lung and brain cancer cells. Classically, the response of cancer to a medical therapy in human research is measured by Response Evaluation Criterial for Solid Tumours definitions, which define "response" by the degree of tumour reduction, or tumour disappearance on imaging, however disease stabilization is also a beneficial clinical outcome. It has been shown that DCA can function as a cytostatic agent in vitro and in vivo, without causing apoptosis. A case of a 32-year-old male is presented in which DCA therapy, with no concurrent conventional therapy, resulted in regression and stabilization of recurrent metastatic melanoma for over 4 years' duration, with trivial side effects. This case demonstrates that DCA can be used to reduce disease volume and maintain long-term stability in patients with advanced melanoma.

97) Ruggieri, Vitalba, et al. "Dichloroacetate, a selective mitochondria-targeting drug for oral squamous cell carcinoma: a metabolic perspective of treatment." Oncotarget 6.2 (2015): 1217.
Reprogramming of metabolism is a well-established property of cancer cells that is receiving growing attention as potential therapeutic target. Oral squamous cell carcinomas (OSCC) are aggressive and drugs-resistant human tumours displaying wide metabolic heterogeneity depending on their malignant genotype and stage of development. Dichloroacetate (DCA) is a specific inhibitor of the PDH-regulator PDK proved to foster mitochondrial oxidation of pyruvate. In this study we tested comparatively the effects of DCA on three different

OSCC-derived cell lines, HSC-2, HSC-3, PE15. Characterization of the three cell lines unveiled for HSC-2 and HSC-3 a glycolysis-reliant metabolism whereas PE15 accomplished an efficient mitochondrial oxidative phosphorylation. DCA treatment of the three OSCC cell lines, at pharmacological concentrations, resulted in stimulation of the respiratory activity and caused a remarkably distinctive pro-apoptotic/cytostatic effect on HSC-2 and HSC-3. This was accompanied with a large remodeling of the mitochondrial network, never documented before, leading to organelle fragmentation and with enhanced production of reactive oxygen species. The data here presented indicate that the therapeutic efficacy of DCA may depend on the specific metabolic profile adopted by the cancer cells with those exhibiting a deficient mitochondrial oxidative phosphorylation resulting more sensitive to the drug treatment.

98) Kan, Ping-Chuan, et al. “Coupling dichloroacetate treatment with curcumin significantly enhances anticancer potential.” Anticancer research 38.11 (2018): 6253-6261.

99) Brandsma, Dieta, et al. “Severe encephalopathy and polyneuropathy induced by dichloroacetate.” Journal of neurology 257.12 (2010): 2099-2100.

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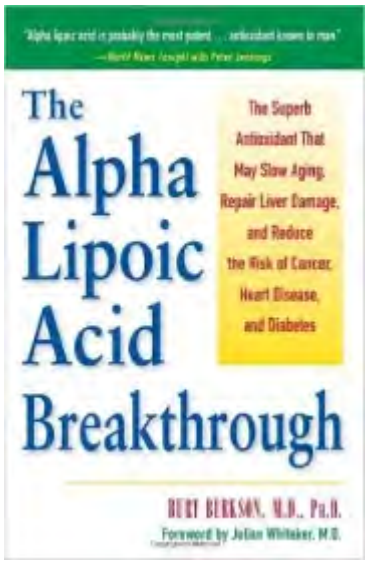


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