Metabolic Oncology

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HBOT, Cancer and Metabolic Therapy: Evolution

2009 – 2015 NIH Research

- Five year NIH funded patient outcome study.
- Survival in Stage-4 cancer
  - “Does integrative Oncology improve survival over SEER matched controls who used SOC?”
- I was Chief of IV Services / interventions

Standish L, Anderson P, et.al. Can Integrative Oncology Extend Life in Advanced Disease? 10th International Conference of the Society for Integrative Oncology (SIO): Abstract 79. Presented October 21, 2013.

VANCOUVER, British Columbia — Integrative oncology might be helping to extend the lives of patients with advanced cancer, new research indicates.

Medscape Medical News > Conference News; Roxanne Nelson; October 25, 2013 http://www.medscape.com/viewarticle/813217

2009 – 2015 NIH Research

- Multiple discoveries were made.
- Many are those I will here and in other venues / publications
  - Radiation recovery / protection
  - Artesunate in cancer
  - High dose IV Curcumin
  - Etc…

2009 – 2015 NIH Research

- But: I wanted to resurrect the use of Dichloroacetate (DCA) as an adjunct to metabolic therapies in advanced cancer.

2009 – 2015 NIH Research

Why did DCA need "resurrecting"?

DCA

DCA is a relatively small molecule, which has been used as treatment for lactic acidosis. It inhibits lactate formation and releases pyruvate dehydrogenase kinase from negative regulation, thus promoting pyruvate entry into the TCA cycle (3). This increases oxygen consumption and reactive oxygen species (ROS) formation while glycolysis and lactate formation are repressed (3). Non-cancerous human cells prefer this aerobic pathway for energy formation via the electron transport chain (ETC) use. Cancerous cells experience the Warburg Effect where most glucose is converted to lactate regardless of oxygen availability (9). Forcing a cancerous cell into TCA / ETC use thereby increases ROS formation and oxygen consumption (6).

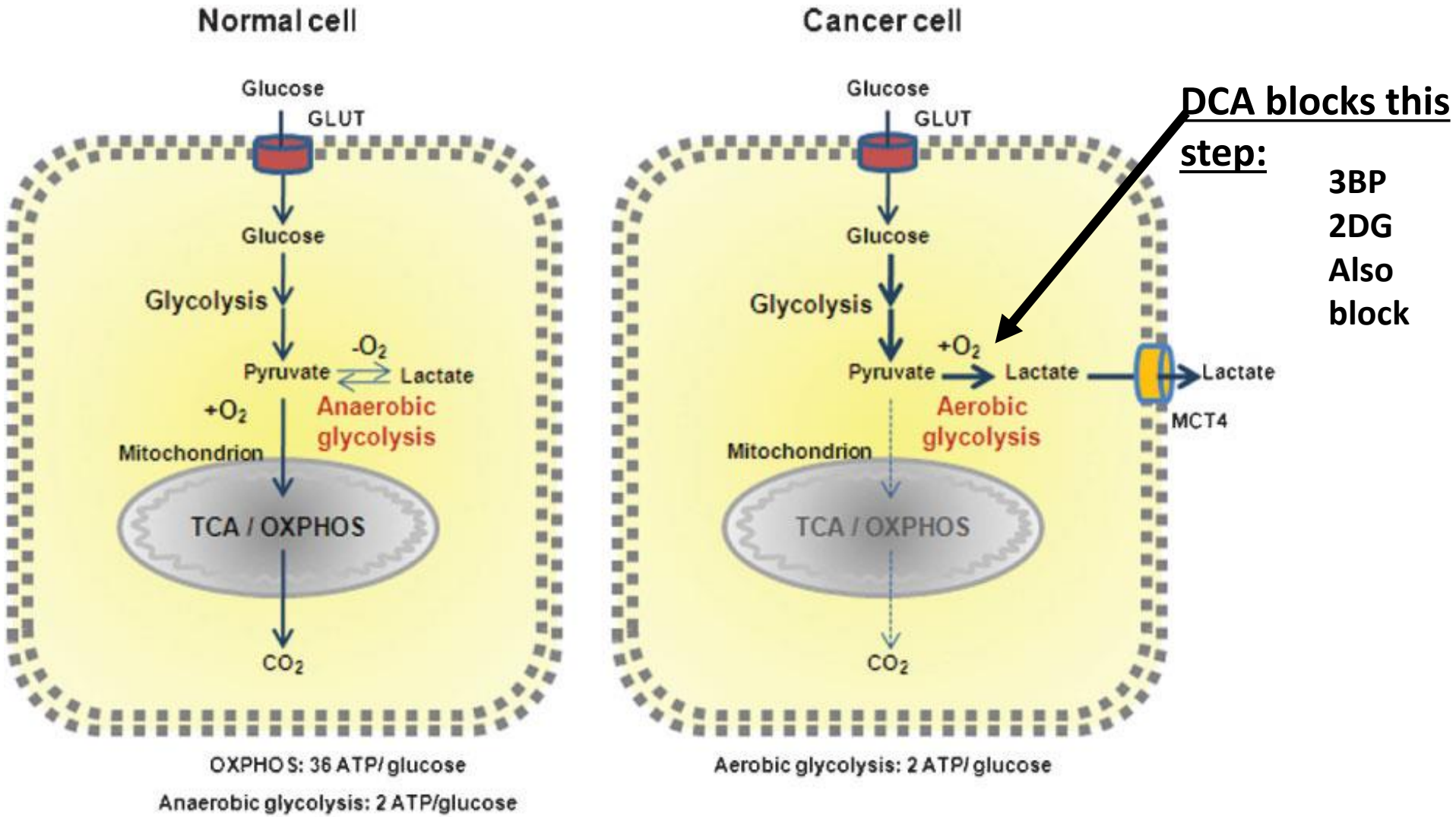


Figure 1 - Metabolic differences between normal and cancer cells. Normal cells primarily metabolize glucose to pyruvate for growth and survival, followed by complete oxidation of pyruvate to CO_2 through the TCA cycle and the OXPHOS process in the mitochondria, generating 36 ATPs per glucose. O_2 is essential once it is required as the final acceptor of electrons. When O_2 is limited, pyruvate is metabolized to lactate. Cancer cells convert most glucose to lactate regardless of the availability of O_2 (the Warburg effect), diverting glucose metabolites from energy production to anabolic process to accelerate cell proliferation, at the expense of generating only two ATPs per glucose.

Seems like magic…

What's the problem?

DCA Side effects and Toxicity:

The **most common toxicity is a dose dependent reversible peripheral neuropathy**. Other reactions appear to be mediated by a slowing of glutathione activity via the GSTz pathway: "From the Abstract: Dichloroacetate (DCA) inhibits its own metabolism and is converted to glyoxylate by glutathione S-transferase zeta (GSTz). … Moreover, DCA-induced inhibition of tyrosine catabolism may account for the toxicity of this xenobiotic in humans and other species." (11)

As clinically most toxicity effects appear to be mitigated either by slowing infusion, adding glutathione and nutrient support or both the use of such additional measures is indicated.

Original DCA Protocols Reported: DO NOT USE THESE

IV Administration of the DCA if possible in the early weeks of treatment, and in anyone with oral intolerance of the drug, ideally two non-consecutive days per week.

- 50-80 mg/kg IV DCA (10) plus support nutrients

  IV DCA plus Support Nutrients, with IV GSH

- The use of DCA orally for long term therapy (if tolerated).

  15-20 mg/kg Oral dose (10) cycle14 days on and 7 days off.

Appropriate neurological support:

B-1 100 mg BID-TID (or Benfotiamine 80 mg BID), glutathione precursors (ALA 300 mg BID) or IV administration of glutathione, Acetyl-l-Carnitine 500 mg BID-TID. (10)

The addition of a Ketogenic Diet is reasonable, as both DCA and the ketogenic diet take advantage of the Warburg effect of neoplastic metabolism. Recommend either a full (20 gram carbohydrate) or modified (50 gram carbohydrate) ketogenic diet plan.

Two ideas to update the protocol:

1. Can we create cell protection and side effect mitigation more simply?
2. Could we locate another agent that would synergize the DCA?

Myself and another clinician had an idea: Would DCA Plus Lipoic Acid Mineral Complex (LAMC) provide synergy and cell protection?

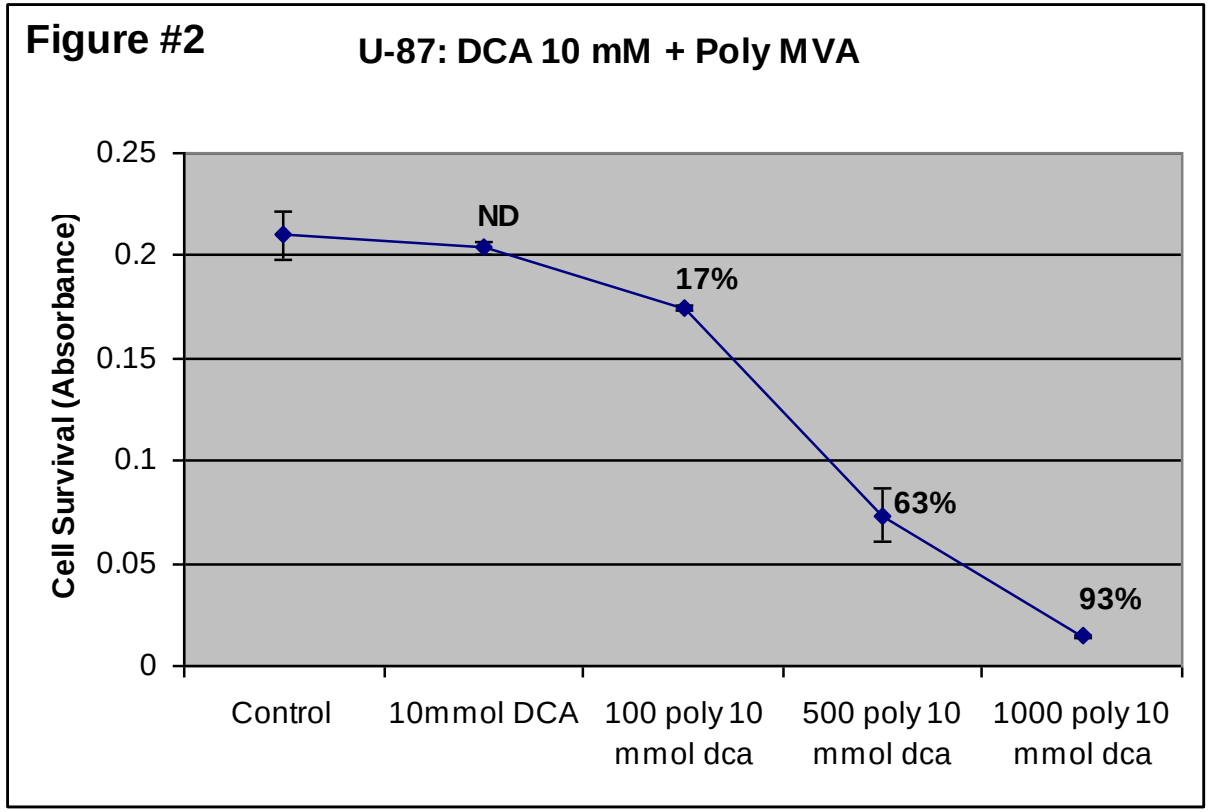
Cell death assay (U-87 glioblastoma cell line) provided by:

- Frank Antonawich, Ph.D.
  Senior Scientist and Clinical Research Administrator Garnett McKeen Laboratory, Inc.

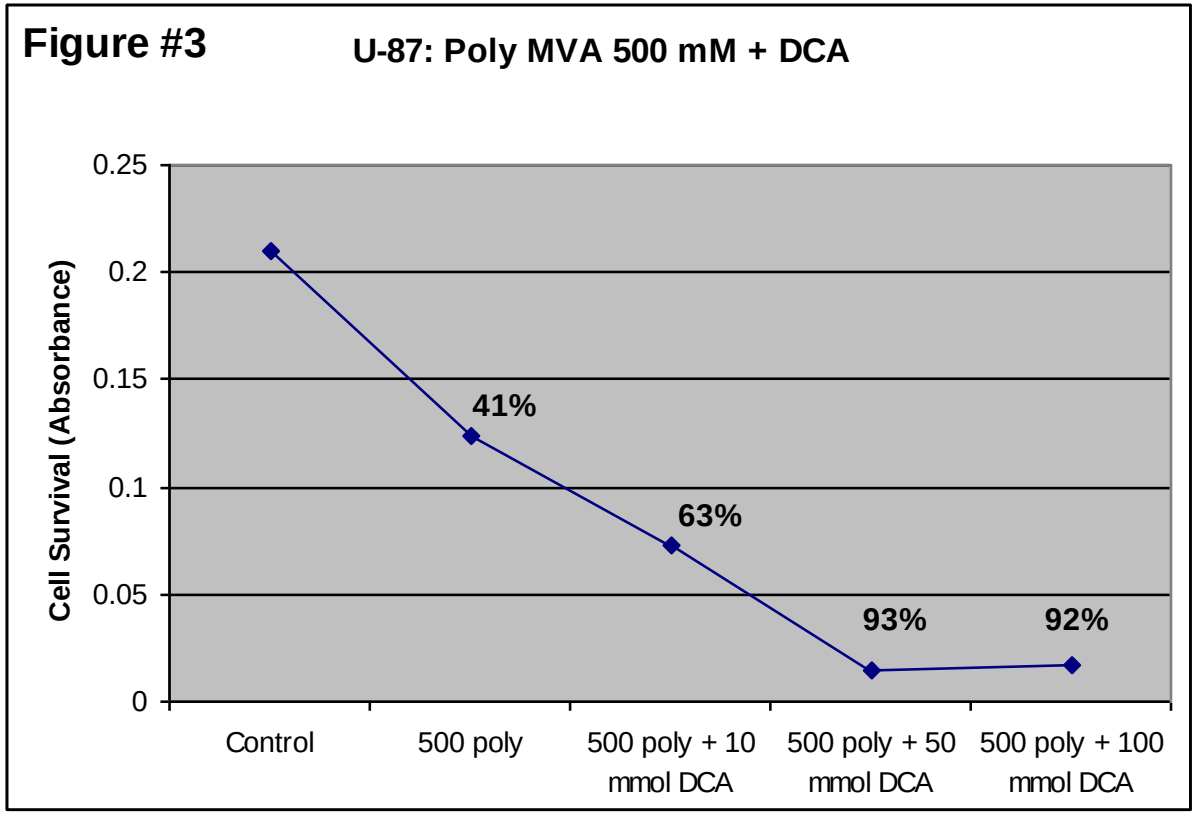
DCA Plus LAMC

- We completed the assays using DCA and LAMC. These cell death assays utilized the U-87 glioblastoma cell line. This SRB protocol is identical to the one used by the NCI in their chemotherapy screen.
- Protocol:
  - In this experiment we chose 3 dosages of LAMC [As the proprietary formulation Palladium-Lipoic Acid Complex] (1,000; 500 and 100 mM) and 3 dosages of DCA (100, 50 and 10 mM). The glioblastoma cells are allowed to adhere to the culture plates for 24 hours. This was followed by a 48 hour exposure to LAMC alone, DCA alone and LAMC + DCA. The cells were then stained for viable cells and absorbance read for quantification.

DCA Plus LAMC

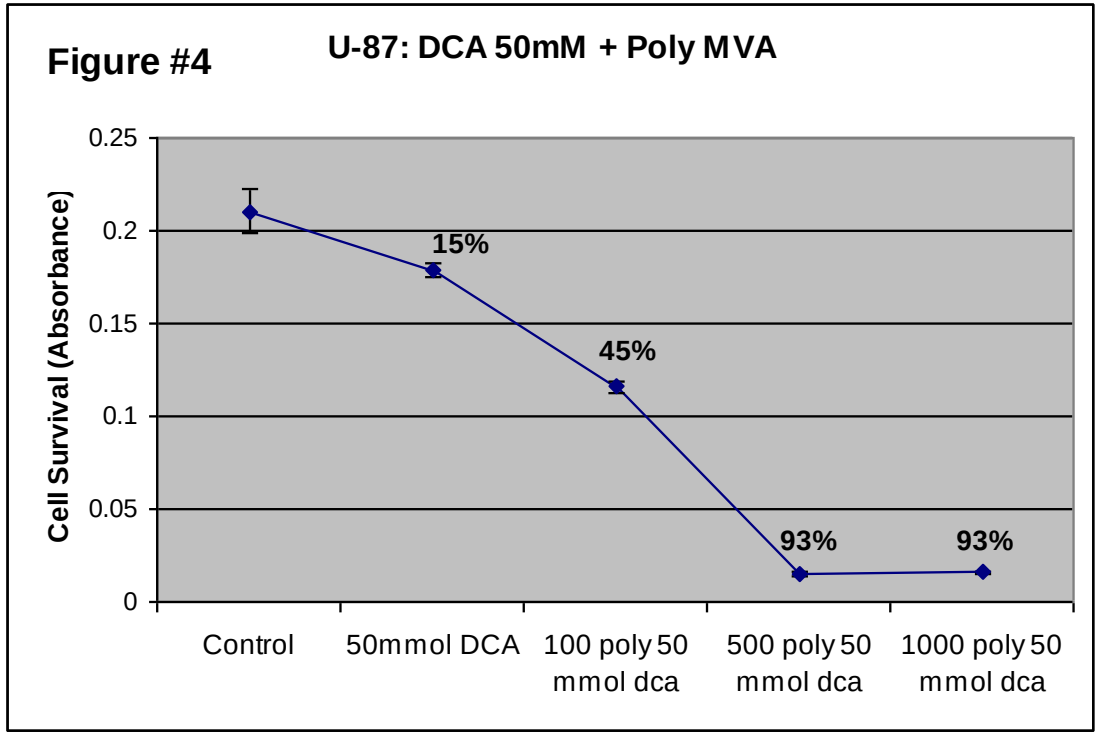


DCA Plus LAMC



In addition, the 50 mM DCA alone, which resulted in an only 15% reduction in cell survival, jumped to a statistically significant 45% reduction when only 100mM of LAMC was added. Interestingly, 5x less DCA (50mM below versus 10mM above) was needed to get about a 15% reduction decrease in cell survival when only 100 mM of LAMC was added to the 10mM DCA.

Figure #4



DCA Plus LAMC Synergy

In summary, the ability of LAMC and DCA to manipulate the metabolic cascade **resulted is a synergistic effectiveness**. This allowed **less DCA to be utilized and still demonstrate maximum effectiveness**. These in vitro data support the concept that LAMC and DCA could be used to together effectively, since they **both potentiate the effectiveness of the other**. [from the cell line study]

Why LAMC and Vitamin A Together?

LAMC Mechanism of Action

- A redox molecule that facilitates energy charge transfer at the cellular level with regards to the cellular transport chain, it can therefore protect and provide energy. Mimics the electron transport chain.
- Differs from free radical scavengers (e.g. alpha-lipoic acid) since there is **no free lipoic acid or palladium**. They are irreversibly bound together resulting in a molecule that is both fat and water soluble.
- LAMC [as 'Palladium-Lipoic Acid Complex'] is a **polymer (liquid crystal) rather than a single molecule. Therefore, the polymer provides a unified redox (accept charge and donate charge) reaction.**
- In summary it is an extremely effective energy transferring molecule.

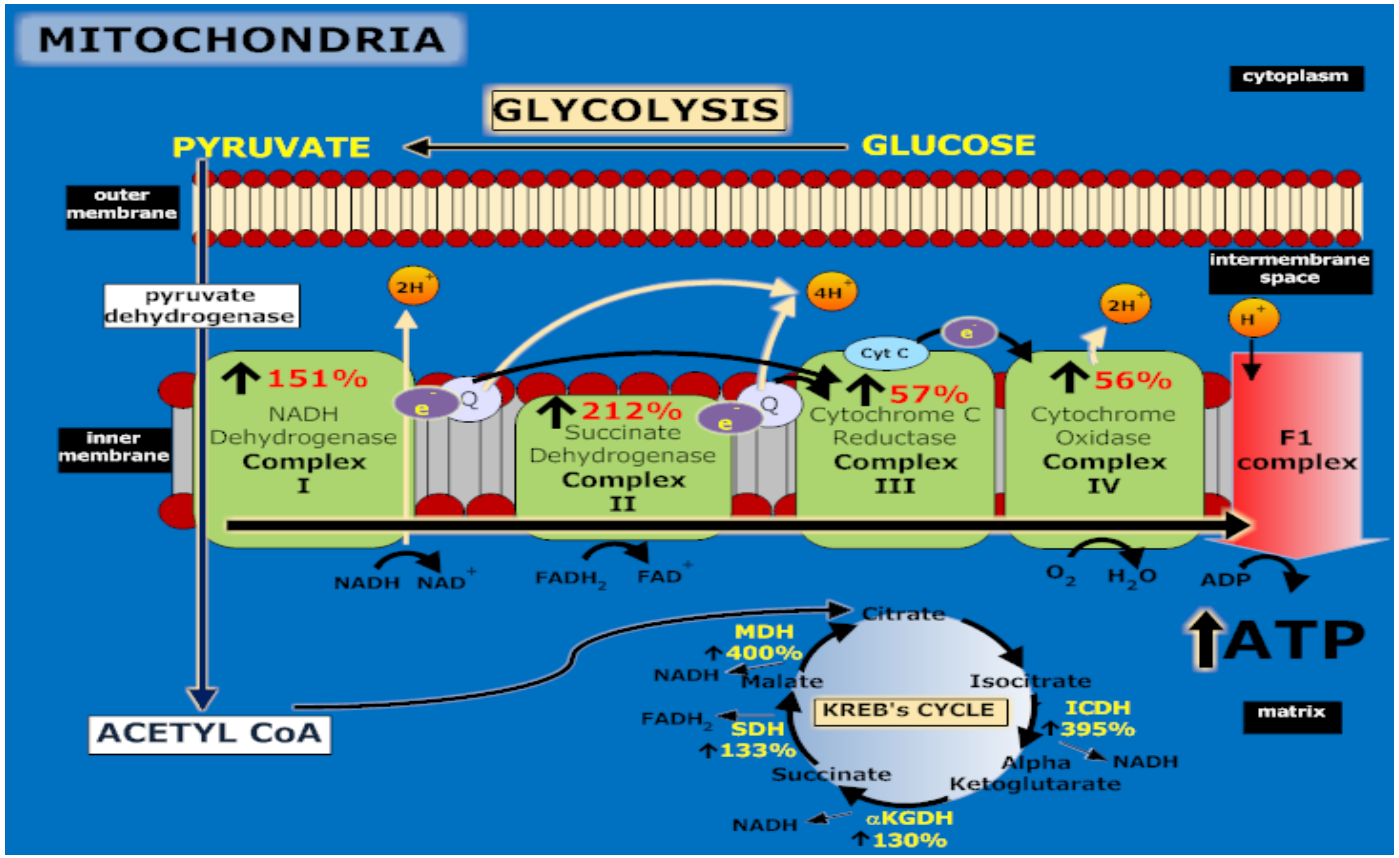
LAMC – Vitamin A

LAMC can:

- Increase aerobic metabolism and ATP levels
- Demonstrate anti-oxidant activity
- Provide DNA and chromosome protection
- Enhance DNA repair
- Attenuate radiation-induced weight loss, protect blood cells and increase spleen colony formation
- Repair radiation-induced mitochondrial damage
- Enhance radio and chemotherapy

Vitamin A can:

- Enhance the visual system
- Benefit skin: aging, acne, dryness
- Strengthen the immune system
- Improve health of bones and teeth
- Facilitate erythrocyte specialization and hemoglobin content



LAMC increases aerobic metabolism, demonstrated by statistically significant increases in three areas:

Kreb's Cycle Enzymes, Electron Transport Chain Complexes and ATP synthesis

Sudheesh, et al., 2009; Ajith et al., 2014

Vitamin A aerobic metabolism benefits:

- Facilitates iron mobilization to form hemoglobin in red blood cells.

- Semba RD, Bloem MW. The anemia of vitamin A deficiency: epidemiology and pathogenesis. Eur J Clin Nutr. 2002;56(4):271-281.
- Allen LH. Iron supplements: scientific issues concerning efficacy and implications for research and programs. J Nutr. 2002;132(4 Suppl):813S-819S.

- Reduces anemia

- Suharno, D., West, C. E., Muhilal, Karyadi, D. & Hautvast, J. G. (1993) Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. Lancet 342: 1325–1328. 37.
- Mejia, L. A. & Chew, F. (1988) Hematological effect of supplementing anemic children. Am. J. Clin. Nutr. 48: 595–600.

- When cells are deprived of Vitamin A the synthesis of ATP decreases as did respiration, but such declines were restored when vitamin A levels were restored.

- Acin-Perez, R., et al., (2010) Control of oxidative phosphorylation by vitamin A illuminates a fundamental role in mitochondrial energy homeostasis. FASEB Journal 24: 627-636.

LAMC – Vitamin A Synergy

Therefore, vitamin A appears to work synergistically with the LAMC due to its ability to potentiate oxygen delivery to the aerobic cascade.

Group	Hemoglobin g/dl	Total RBC Count Million/cu mm	Platelet count Lakh/cu mm
Normal	14.50 ± 0.56	5.95 ± 0.35	5.33 ± 0.75
LAMC-PLUS + 5 Gy	16.00 ± 0.84^{**,b}	6.30 ± 0.28^{a}	3.95 ± 0.07^{***,b}
Radiation 5 Gy	13.73 ± 0.40	5.60 ± 0.14	2.15 ± 0.07***

Table 1. Effect of LAMC-PLUS on hematological parameters in radiation (5Gy) exposed animals.

P< 0.05, ** P <0.01 and ***P<0.001 (Bonferroni multiple comparison test) significantly different from the normal group. Others are non-significant (p>0.05); a p<0.05, b p<0.01 (Dunnett multiple comparison test) significantly different from the control (radiation) group.

2009 – 2015 NIH Research

What we developed

To make it safe at high enough doses to work:

How did we do it?

Dietary and Retinoid PO intervention

And

DCA / LAMC protocol

Who could we try this completely novel

(and untested)

metabolic cancer therapy on?

Novel Combination Therapy in Non-responders DCA and LAMC

Theoretical overview for the potential synergy of Lipoic Acid Mineral Complex (LAMC) and Dichloroacetate (DCA) - The cell line study recounted above as well as the potential for the two agents to have not only physiologic mutual benefit but a theoretical collaborative anti-tumor benefit.

The proposed anti-tumor benefit is that the two agents may work in similar manners to effect tumor cell damage.

The potential physiological benefit is that typical DCA use requires cell protective support during treatment. LAMC has been shown to be neuro-protective and helpful in supporting the mitochondrial complex. (2,3,4,5)

Why consider LAMC + DCA in non-responders?

- DCA is effective but has neurological side effects
- LAMC (Poly-MVA) has some collateral potential anti-cancer effect AND the ability to be cell protective.
- The cell line study gave us some data to believe this may work.

Why consider LAMC + DCA in non-responders?

- **Protocol as developed at Anderson Medical Specialty Associates:**
  - Current combination therapy in trial using both oral and IV DCA-LAMC regimens
  - Patient Selection:
    - Patients chosen due to lack of response or failure of other therapies
      - Includes failure of standard treatment plus at least one alternative therapy
- **Dietary Intervention:**
  - Patients are on a modified ketogenic or low carbohydrate diet
  - Patients are taking **Vitamin A orally at 25,000 – 50,000 IU Retinol (lipid soluble Vitamin A) PO QD**

DCA Plus LAMC

- Current combination therapy in trial using both oral and IV DCA-LAMC regimens.
  - Patients are on a modified ketogenic diet
  - Patients chosen due to lack of response or failure of other therapies

NOTE: All doses start with a test dose of 10-25% listed dose!

- LAMC 40 mL - (PO in divided doses or IV in one dose)
- DCA dose:
  - IV: 50-80 mg/kg IV (2-3 days per week)
  - PO: 15-20 mg/kg in divided doses BID-TID (3-4 days per week)

Original case series (2010-14):

n = 9	Dz. Progression	Stable Disease	Improved QOL	Dz. Regression
66 YO Male NHL				XXX
5 YO Female Mixed Acute Leukemia (MLL+)				XXX
71 YO Female Multiple Myeloma				XXX
68 YO Female Multiple Myeloma				XXX
72 YO Female CLL			XXX	
65 YO Male Metastatic Melanoma	XXX			
3 GBM Post Surgery			XXX	

DCA References Cited:

1. Michelakis E D, et. al. Metabolic Modulation of Glioblastoma with Dichloroacetate. Sci Transl Med 12 May 2010: Vol. 2, Issue 31

2. Ammini V A, Stacpool P W. Biotransformation, Toxicology and Pharmicogenomics of Dichloroacetate. The Handbook of Env Chem Vol 3, Part P, 215-234. 2003

3. Stockwin L H, et. al. Sodium dichloroacetate selectively targets cells with defects in the mitochondrial ETC. Int J Cancer Online 7 June 2010. DOI 10.1002/ijc.25499

4. Hassoun E A, Cearfoss J. Dichloroacetate- and trichloroacetate-induced modulation of superoxide dismutase, catalase, and glutathione peroxidase activities and glutathione level in the livers of mice after subacute and subchronic exposures. Toxicological & Environmental Chemistry, 93(2), 332-344. (2011). doi:10.1080/02772248.2010.509602

5. Lemmo W. "DCA for CNS Malignancies?" Scientific Presentation. NOAC Meeting. Seattle, Washington. 2010.

6. Lopez-Lazaro M. A new view of carcinogenesis and an alternative approach to cancer therapy. Mol Med 16(3-4) 144-153, March-April 2010.

7. Yang B, Reynolds C P. Tirapazamine cytotoxicity for neuroblastoma is p53 dependent. Clin Cancer Res 2005;11(7) April 1, 2005

8. Armstrong J S. et. al. Role of glutathione depletion and reactive oxygen species generation in apoptotic signaling in human B lymphoma cell line. Cell death and Differentiation (2002) 9, 252-263. DOI: 10.1038/sj/cdd/4400959.

9. Vander Heiden M G. et. al. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science 324, 1029 (2009); DOI: 10,1126/science.1160809

10. Kahn A. "DCA- Guidelines for clinical use" Scientific Presentation. Oncology Association of Naturopathic Physicians Second Annual Meeting. Phoenix, Arizona. February, 2013.

11. Cornett R, James MO, Henderson GN, Cheung J, Shroads AL, Stacpoole PW. Inhibition of glutathione S-transferase zeta and tyrosine metabolism by dichloroacetate: a potential unifying mechanism for its altered biotransformation and toxicity. Biochem Biophys Res Commun. 1999 Sep 7;262(3):752-6. PMID: 10471397

Current Human Data:

- The following papers are human case reports and trials published between 2010 and 2016 – listed in descending order.
- These data show:
  - Efficacy in quality of life, extension of life and tumor response parameters
  - Very low side effect profile
  - Very high safety index

Human Data (2010-2016) – DCA:

- Lemmo W and Tan G. Prolonged Survival After Dichloroacetate Treatment of Non-Small-Cell Lung Carcinoma-Related Leptomeningeal Carcinomatosis. J Med Cases. 2016;7(4):136-142
- Chu QS, Sangha R, Spratlin J, Vos LJ, Mackey JR, McEwan AJ, Venner P, et al. A phase I open-labeled, singlearm, dose-escalation, study of dichloroacetate (DCA) in patients with advanced solid tumors. Invest New Drugs. 2015;33(3):603-610.
- Dunbar EM, Coats BS, Shroads AL, Langaee T, Lew A, Forder JR, Shuster JJ, et al. Phase 1 trial of dichloroacetate (DCA) in adults with recurrent malignant brain tumors. Invest New Drugs. 2014;32(3):452-464.
- Khan A, Marier D, Marsden E, Andrews D, Eliaz I. A novel form of dichloroacetate therapy for patients with advanced cancer: a report of 3 cases. Altern Ther Health Med. 2014;20(Suppl 2):21-28.
- Strum SB, Adalsteinsson O, Black RR, Segal D, Peress NL, Waldenfels J. Case report: Sodium dichloroacetate (DCA) inhibition of the "Warburg Effect" in a human cancer patient: complete response in non-Hodgkin's lymphoma after disease progression with rituximab-CHOP. J Bioenerg Biomembr. 2013;45(3):307-315.
- Strum S, Adalsteinsson O, Black R, Segal D, Peress N, Waldenfels J. Erratum to: Case Report: Sodium dichloroacetate (DCA) inhibition of the 'Warburg Effect' in a human cancer patient: complete response in non-Hodgkin's lymphoma after disease progression with rituximab- CHOP. J Bioenerg Biomembr. 2013;45(3):317.
- Khan A. Case Report of Long Term Complete Remission of Metastatic Renal Squamous Cell Carcinoma after Palliative Radiotherapy and Adjuvant Dichloroacetate. Advances in Cancer: Research & Treatment http://www.ibimapublishing.com/journals/ACRT/acrt.html. Vol. 2012 (2012), Article ID 441895, 7 pages DOI: 10.5171/2012.441895
- Khan A. Use of oral dichloroacetate for palliation of leg pain arising from metastatic poorly differentiated carcinoma: a case report. J Palliat Med. 2011;14(8):973-977.
- Flavin DF. Non-Hodgkin's Lymphoma Reversal with Dichloroacetate. J Oncol. 2010;2010
- Flavin D. Medullary thyroid carcinoma relapse reversed with dichloroacetate: A case report. Oncol Lett. 2010;1(5):889-891.

Select Non Human Current Research:

- Ohashi T, Akazawa T, Aoki M, Kuze B, Mizuta K, Ito Y, Inoue N. Dichloroacetate improves immune dysfunction caused by tumor-secreted lactic acid and increases antitumor immunoreactivity. Int J Cancer. 2013;133(5):1107-1118.
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- Heshe D, Hoogestraat S, Brauckmann C, Karst U, Boos J, Lanvers-Kaminsky C. Dichloroacetate metabolically targeted therapy defeats cytotoxicity of standard anticancer drugs. Cancer Chemother Pharmacol. 2011;67(3):647- 655.
- Lin G, Hill DK, Andrejeva G, Boult JK, Troy H, Fong AC, Orton MR, et al. Dichloroacetate induces autophagy in colorectal cancer cells and tumours. Br J Cancer. 2014;111(2):375-385.
- Shahrzad S, Lacombe K, Adamcic U, Minhas K, Coomber BL. Sodium dichloroacetate (DCA) reduces apoptosis in colorectal tumor hypoxia. Cancer Lett. 2010;297(1):75- 83.