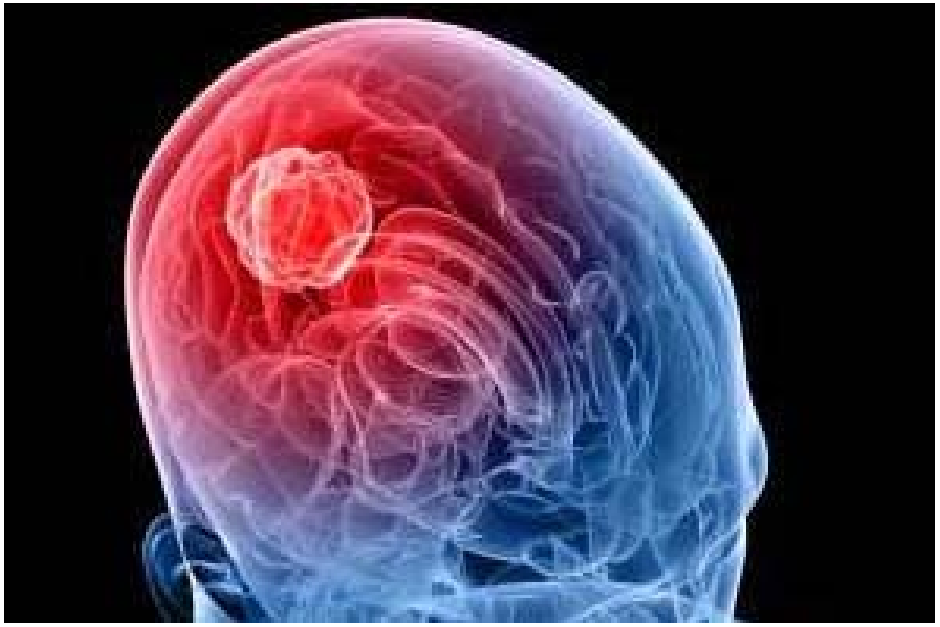
Brain Cancers
A Metabolic Approach



Dr. Paul S. Anderson

Cancer Control Society – 2017

Dr. Paul Anderson - Background

- CEO – Anderson Medical Group
- Full Research Professor – Bastyr University
- Medical advisor – Sanoviv' Hospital
- Research Partner in NIH and other national funding sourced projects with the CUSIOS group and University of Washington, Seattle Cancer Care Alliance and Fred Hutchinson Research Center.
- Original site director of "US Site-1" for the CUSIOS Oncology study.
- Featured Lecturer at many continuing medical education groups and conferences.

Advanced Medical Therapies (Seattle, Washington)

- IV Therapies
- Mild-Moderate Hyperthermia
- Hyperbaric Oxygen
- Other specialty therapies
- Care focus is on cancer and advanced chronic illness.

Sanoviv' Hospital (Rosarito, Mexico)

- Inpatient facility
- IV Therapies
- Metronomic chemotherapy
- Multi-place HBOT
- Hyperthermia
- Cancer vaccine and Rigvir programs
- etc. etc.
- Care for patients with Cancer and Chronic Illnesses.

DISCLAIMER:

This information is ONLY a summary of our experience with patients and in NO WAY constitutes medical advice. It is for educational purposes only. Any medical decisions including diet, lifestyle changes and medications should be discussed with and monitored by a physician.

Brain Cancers – A Metabolic Approach

The “Big Three”

DIET:

SUPPORTIVE SUPPLEMENTS:

MENTAL WORK:

DIET:

If **diet** isn't the **first and last therapy** in cancer **nothing** else will work very well.

Critical Reviews in Oncology/Hematology 112 (2017) 41–58

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Role of ketogenic metabolic therapy in malignant glioma: A systematic review

Sebastian F. Winter[a,b], Franziska Loebel[b,c], Jorg Dietrich[a,d,*]

Conclusions:

While clinical evidence is still limited in this evolving field, increasing numbers of ongoing clinical trials suggest that KMT is emerging as a potential therapeutic option and might be combinable with existing anti-neoplastic treatments for malignant glioma. Emerging clinical data will help answer questions concerning safety and efficacy of KMT, and are aiming to identify the most promising KMT regimen, compatibility with other anti-cancer treatments, ethical aspects, and impact on quality of life of cancer patients.

Schwartz et al. Cancer & Metabolism (2015) 3:3
DOI 10.1186/s40170-015-0129-1

Cancer & Metabolism

CASE REPORT Open Access

Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature

Kenneth Schwartz[1*], Howard T Chang[2,3], Michele Nikolai[6], Joseph Pernicone[5], Sherman Rhee[5], Karl Olson[7], Peter C Kurniali[1], Norman G Hord[8] and Mary Noel[4]

Conclusions

We conclude that:

1. KD is safe and without major side effects;
2. ketosis can be induced using customary foods;
3. treatment with KD may be effective in controlling the progression of some gliomas;
4. further studies are needed to determine factors that influence the effectiveness of KD, whether as a monotherapy, or as adjunctive or supplemental therapy in treating glioma patients.

Synergy!

OPEN ACCESS Freely available online

PLOS ONE

The Ketogenic Diet and Hyperbaric Oxygen Therapy Prolong Survival in Mice with Systemic Metastatic Cancer

Angela M. Poff[1]*, Csilla Ari[1], Thomas N. Seyfried[2], Dominic P. D'Agostino[1]

1 Department of Molecular Pharmacology and Physiology, University of South Florida, Tampa, Florida, United States of America, 2 Department of Biology, Boston College, Chestnut Hill, Massachusetts, United States of America

Abstract

Introduction: Abnormal cancer metabolism creates a glycolytic-dependency which can be exploited by lowering glucose availability to the tumor. The ketogenic diet (KD) is a low carbohydrate, high fat diet which decreases blood glucose and elevates blood ketones and has been shown to slow cancer progression in animals and humans. Abnormal tumor vasculature creates hypoxic pockets which promote cancer progression and further increase the glycolytic-dependency of cancers. Hyperbaric oxygen therapy (HBO_2T) saturates tumors with oxygen, reversing the cancer promoting effects of tumor hypoxia. Since these non-toxic therapies exploit overlapping metabolic deficiencies of cancer, we tested their combined effects on cancer progression in a natural model of metastatic disease.

Methods: We used the firefly luciferase-tagged VM-M3 mouse model of metastatic cancer to compare tumor progression and survival in mice fed standard or KD *ad libitum* with or without HBO_2T (2.5 ATM absolute, 90 min, 3x/week). Tumor growth was monitored by *in vivo* bioluminescent imaging.

Results: KD alone significantly decreased blood glucose, slowed tumor growth, and increased mean survival time by 56.7% in mice with systemic metastatic cancer. While HBO_2T alone did not influence cancer progression, combining the KD with HBO_2T elicited a significant decrease in blood glucose, tumor growth rate, and 77.9% increase in mean survival time compared to controls.

Conclusions: KD and HBO_2T produce significant anti-cancer effects when combined in a natural model of systemic metastatic cancer. Our evidence suggests that these therapies should be further investigated as potential non-toxic treatments or adjuvant therapies to standard care for patients with systemic metastatic disease.

Why?

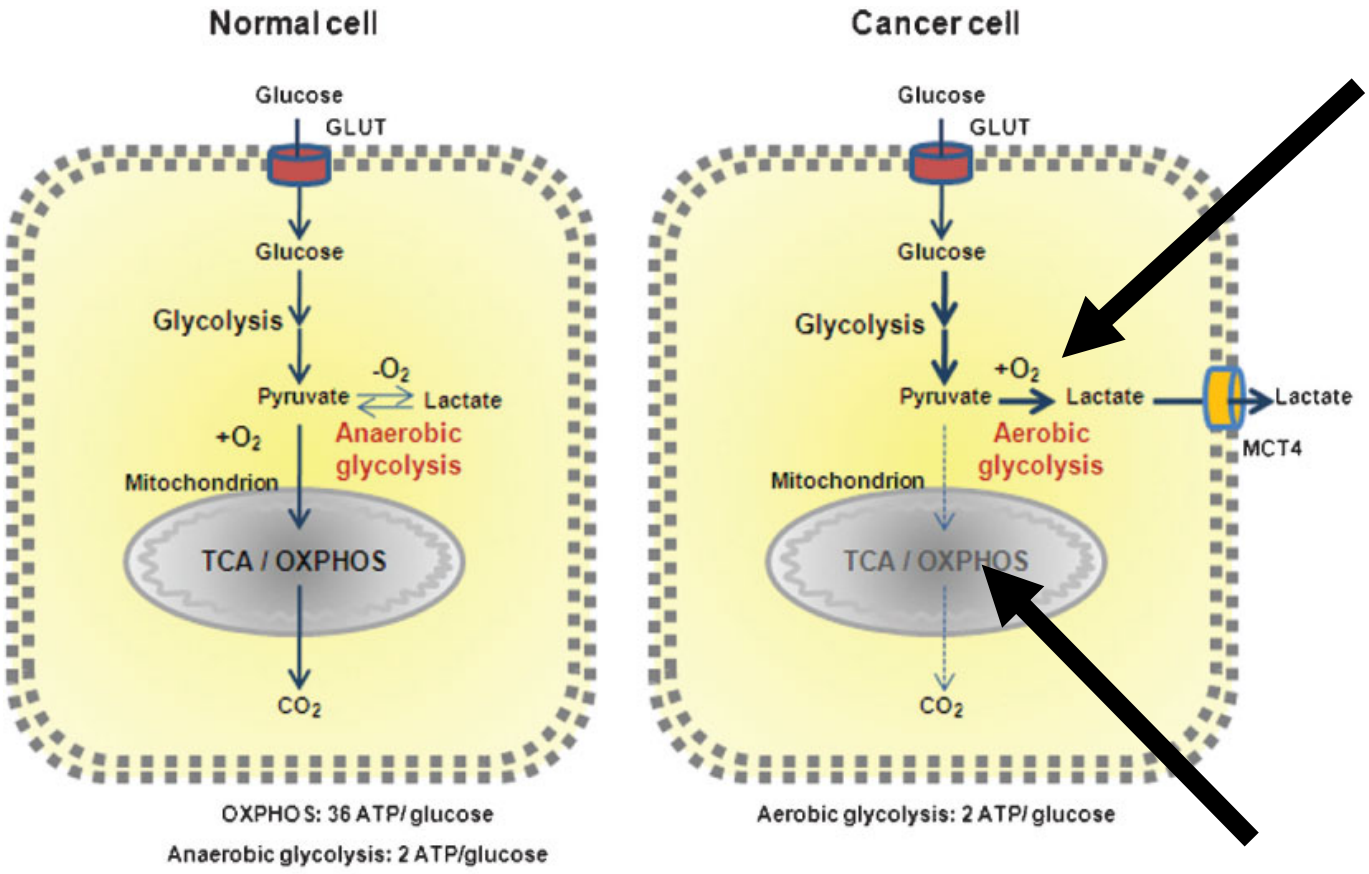
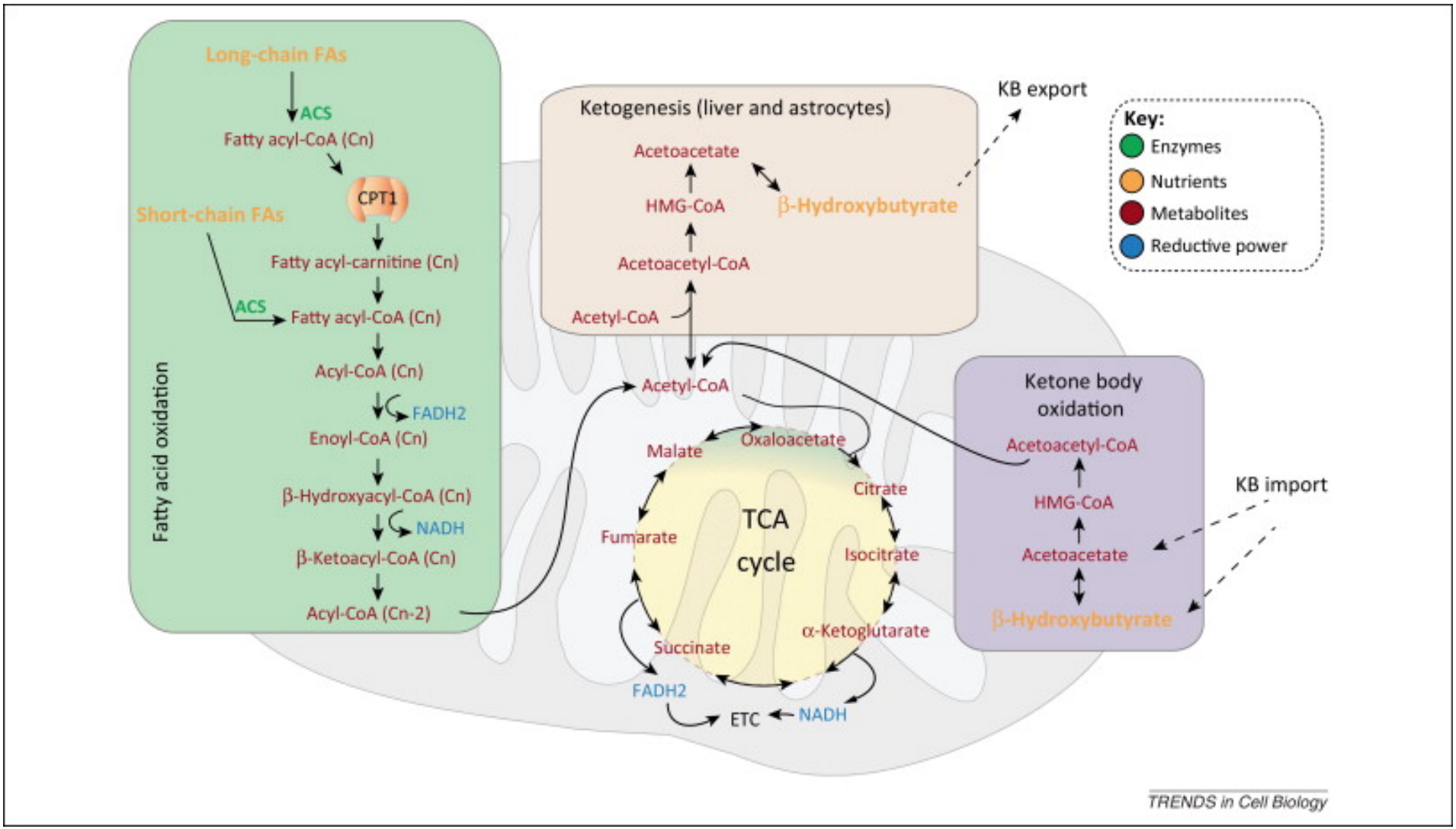
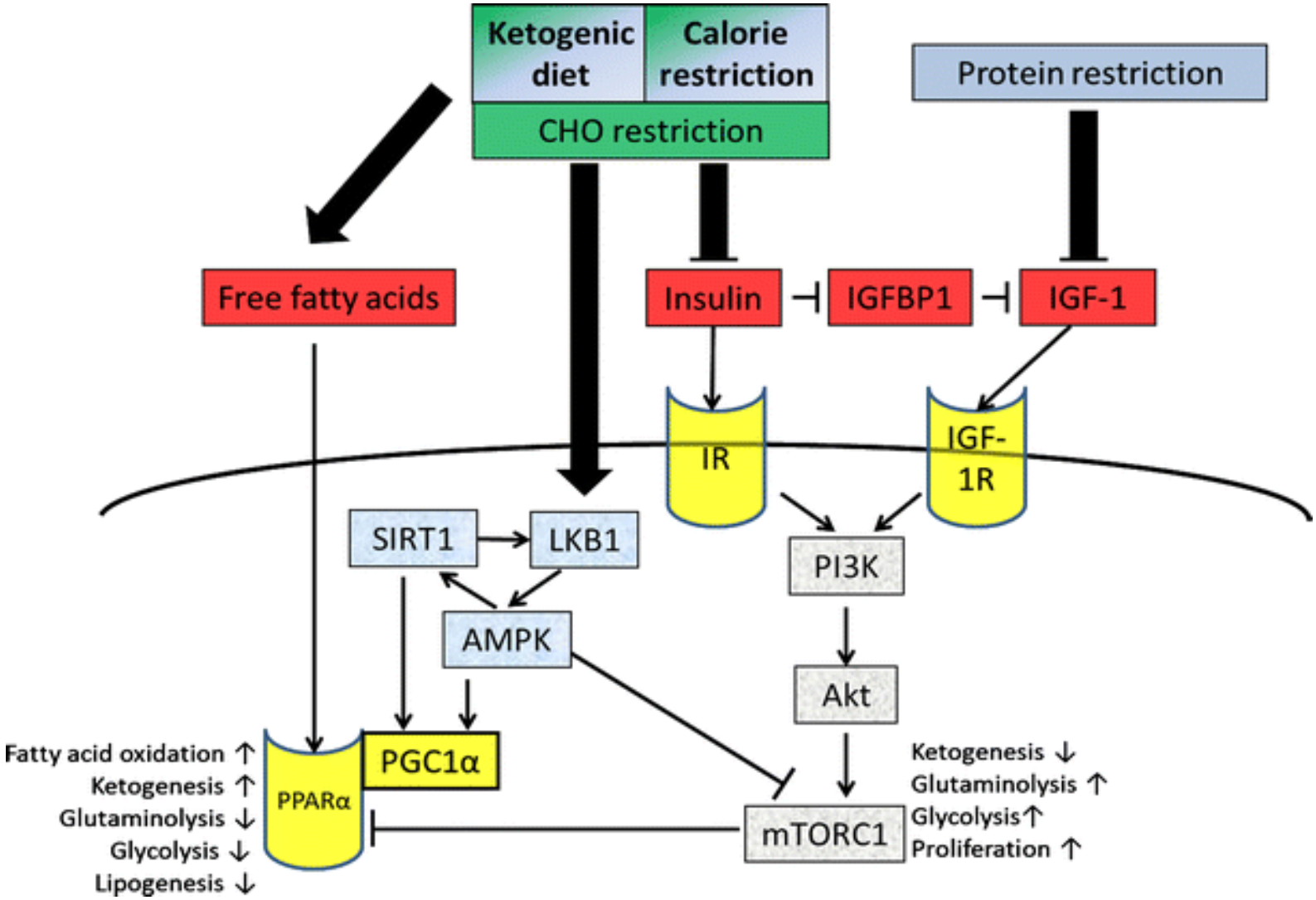


Figure 1 - Metabolic differences between normal and cancer cells. Normal cells primarily metabolize glucose to pyruvate for growth and survival, followed by complete oxidation of pyruvate to CO_2 through the TCA cycle and the OXPHOS process in the mitochondria, generating 36 ATPs per glucose. O_2 is 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.


Long-chain FAs
ACS
Fatty acyl-CoA (Cn)
CPT1
Short-chain FAs
Fatty acyl-carnitine (Cn)
ACS
Fatty acyl-CoA (Cn)
Acyl-CoA (Cn)
FADH2
Enoyl-CoA (Cn)
β-Hydroxyacyl-CoA (Cn)
NADH
β-Ketoacyl-CoA (Cn)
Acyl-CoA (Cn-2)
Fatty acid oxidation
Ketogenesis (liver and astrocytes)
Acetoacetate
HMG-CoA
β-Hydroxybutyrate
Acetoacetyl-CoA
Acetyl-CoA
KB export
Key:
Enzymes
Nutrients
Metabolites
Reductive power
Acetyl-CoA
Malate
Oxaloacetate
Citrate
Fumarate
TCA cycle
Isocitrate
α-Ketoglutarate
Succinate
FADH2
ETC
NADH
Ketone body oxidation
Acetoacetyl-CoA
HMG-CoA
Acetoacetate
β-Hydroxybutyrate
KB import
TRENDS in Cell Biology


Ketogenic diet
Calorie restriction
CHO restriction
Protein restriction
Free fatty acids
Insulin
IGFBP1
IGF-1
IR
IGF-1R
SIRT1
LKB1
PI3K
AMPK
Akt
PGC1α
PPARα
mTORC1
Fatty acid oxidation ↑
Ketogenesis ↑
Glutaminolysis ↓
Glycolysis ↓
Lipogenesis ↓
Ketogenesis ↓
Glutaminolysis ↑
Glycolysis ↑
Proliferation ↑

Redox Biology 2 (2014) 963–970

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Review Article

Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism

Bryan G. Allen *,[1], Sudershan K. Bhatia [1], Carryn M. Anderson, Julie M. Eichenberger-Gilmore, Zita A. Sibenaller, Kranti A. Mapuskar, Joshua D. Schoenfeld, John M. Buatti, Douglas R. Spitz, Melissa A. Fath

The Ketogenic Diet and HBOT for Cancer

Dominic P. D'Agostino, PhD
Assistant Professor
Hyperbaric Biomedical Research Lab
University of South Florida Morsani College of Medicine

The following six slides are from this presentation given at the Hyperbaric Oxygen Therapy Symposium, Albuquerque NM 2014.

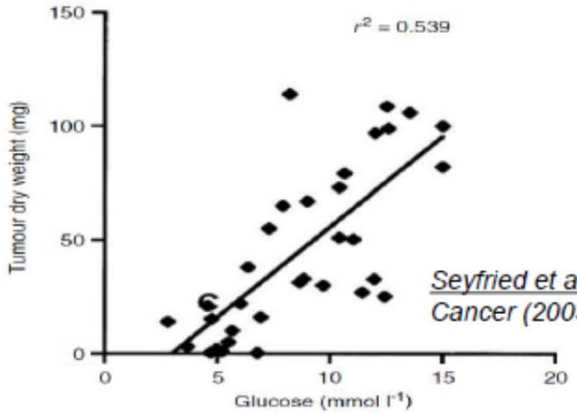
Hyperglycemia and Tumor Hypoxia Drive the Warburg Effect

Gnagnarella, et al; 2008

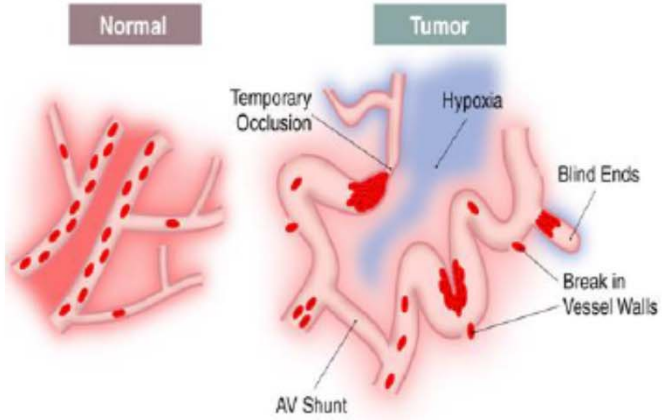
The American Journal of CLINICAL NUTRITION

Glycemic index, glycemic load, and cancer risk: a meta-analysis

- High glycemic diets increase risk of cancer
- Hyperglycemia = poor prognosis
- Blood glucose correlated to tumor growth
- Ketogenic diet: 4:1 fat : protein+carbs
  - Induces ketosis
  - Anti-inflammatory
  - Suppresses insulin and IGF-1



Seyfried et al. British Journal of Cancer (2003) 89, 1375 – 1382

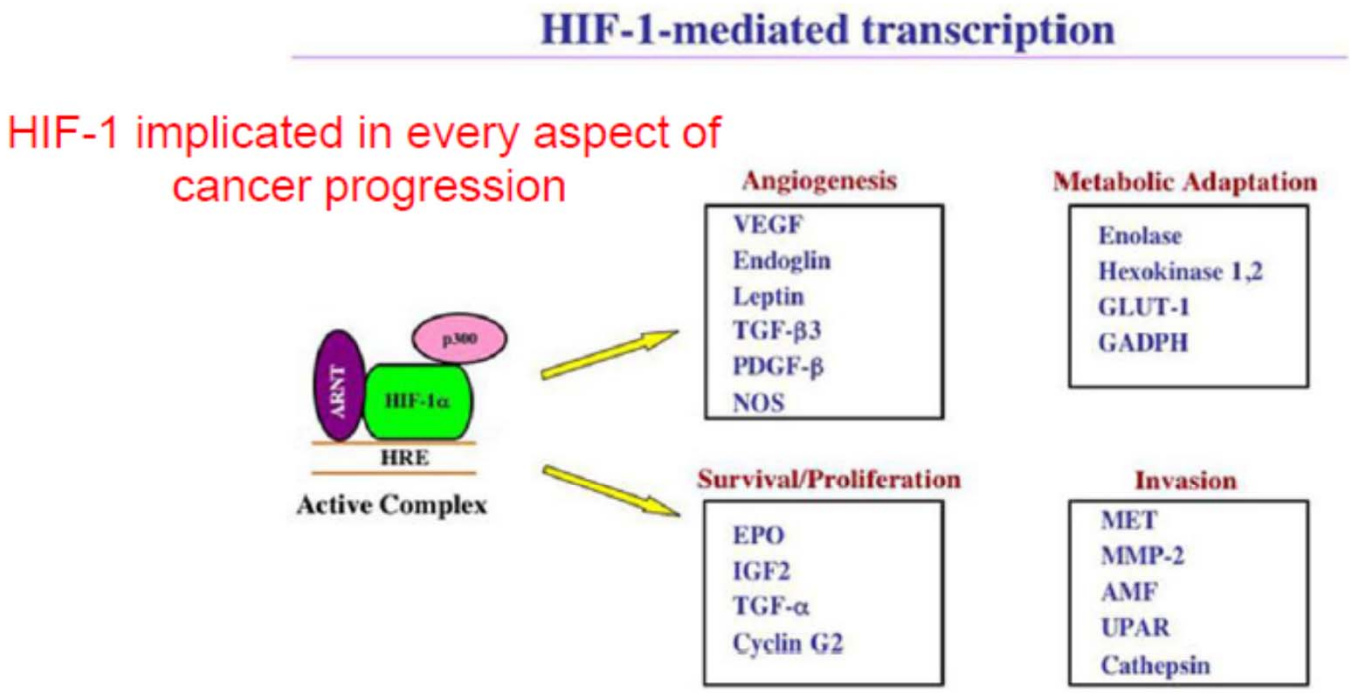


30-60 mmHg 2-30 mmHg

Average PO_2

****Causes chemo/radioresistance**

Tumor hypoxia promotes cancer progression and the Warburg Effect



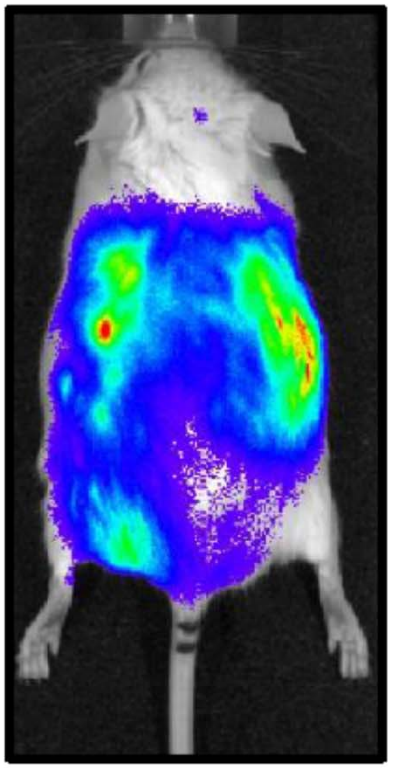
Regulation of cancer cell metabolism by hypoxia-inducible factor 1; Semenza, G.

The VM-M3 Model of Metastatic Cancer

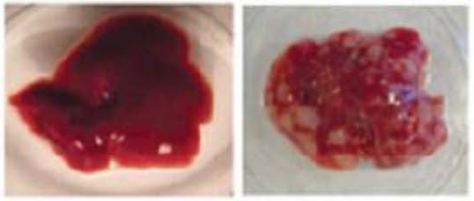
Developed by Dr. Thomas Seyfried, Boston College

IJC, Volume 126

- Cells from spontaneous brain tumor
  - Natural tumorigenesis
- Syngeneic with VM/dK mice
  - Immunocompetent
- S.C. implantation → systemic metastasis
  - Shares many molecular and behavioral characteristics of human metastatic cancers
- Transduced with firefly luciferase gene
  - *In vivo* bioluminescence imaging



Liver Metastasis



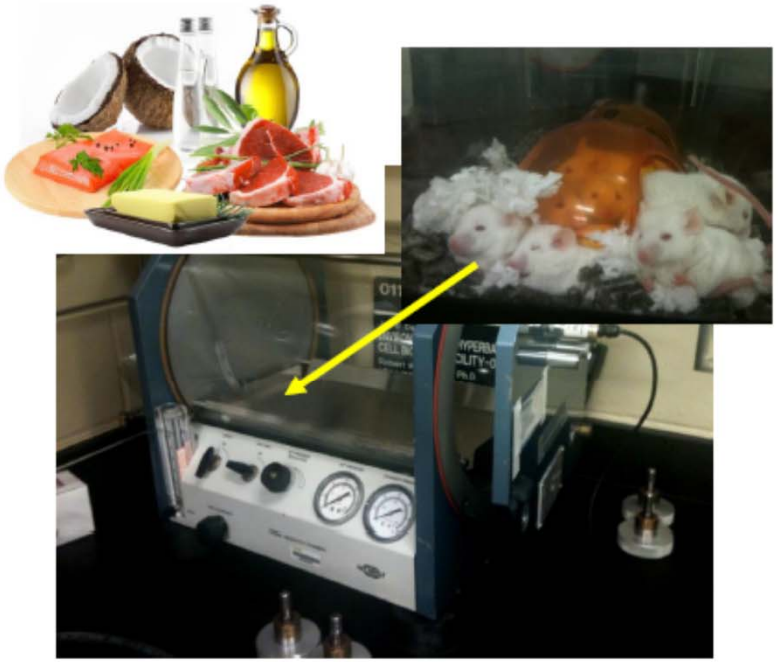
Shelton, et. Al, 2009

Combining the Ketogenic Diet with Hyperbaric Oxygen

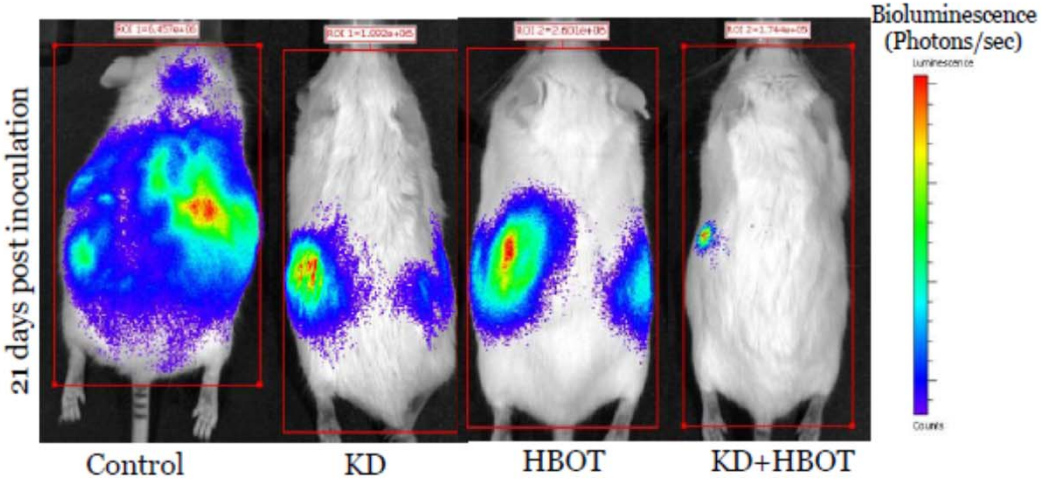
Methods: Treatment Groups

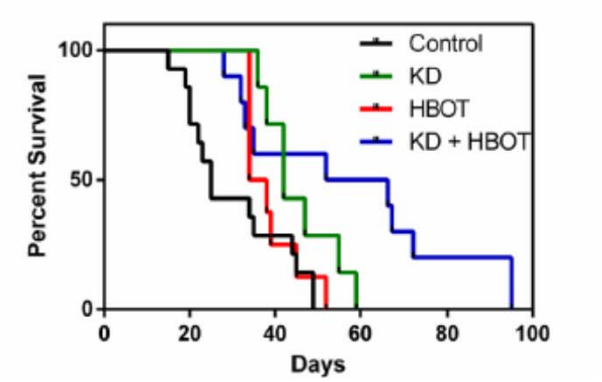
VM-M3 Survival Study:

- Control: Standard Diet *ad libitum*
- KD: Ketovolve *ad libitum*
- HBOT
  - Diet: SD *ad libitum*
  - HBOT: 2.5 ATA, 90 min, 3/week
- KD+HBOT:
  - Diet: Ketovolve (Solace) *ad libitum*
  - HBOT: 2.5 ATA, 90 min, 3/week



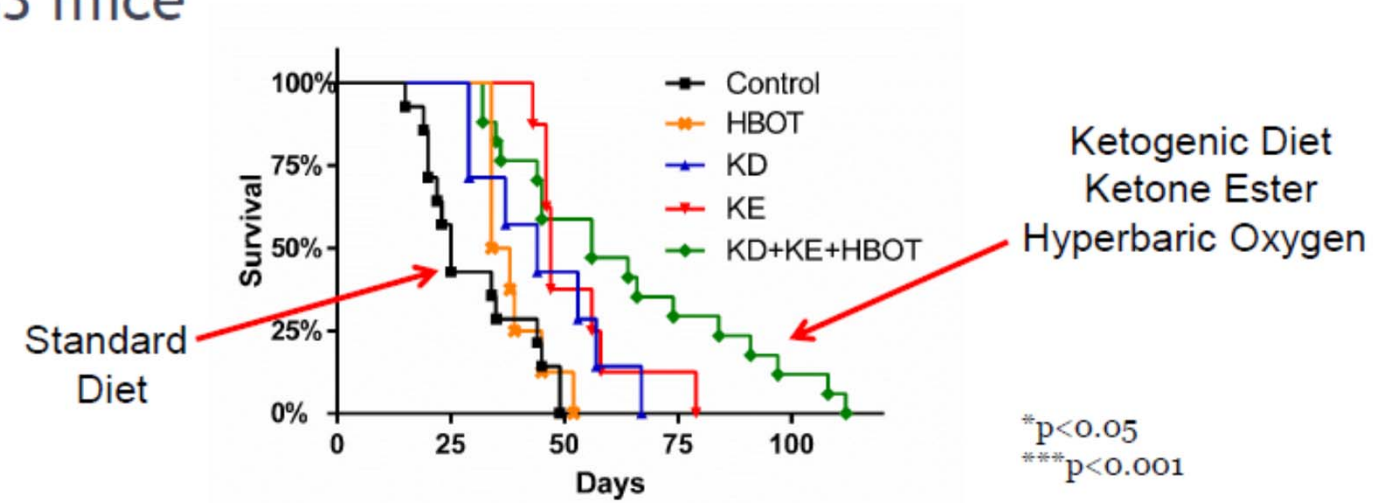
KD+HBOT inhibits tumor growth and increases survival against metastatic cancer





Poff A, et al. *PLoS ONE*, 2013; 8 (6)

Combination therapy doubles survival time in VM-M3 mice



Treatment	Cohort Size (N)	Mean Survival (days)	Increase in Survival Time
Control	11	33.7	-----
HBOT	8	38.8	24.4%
Ketogenic Diet (KD)	7	45.1	44.6%*
Ketone Ester (KE)	8	52.8	69.2%***
KD+HBOT	11	55.5	77.9%***
KD+KE+HBOT	**17**	**63.4**	**103.0%***

International Journal of Cancer: IJC-13-2481, 2013 *PLoS ONE*, 2013; 8 (6): e65522 DOI:

Why Poly-MVA

and

Vitamin A Together?

Poly-MVA 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.

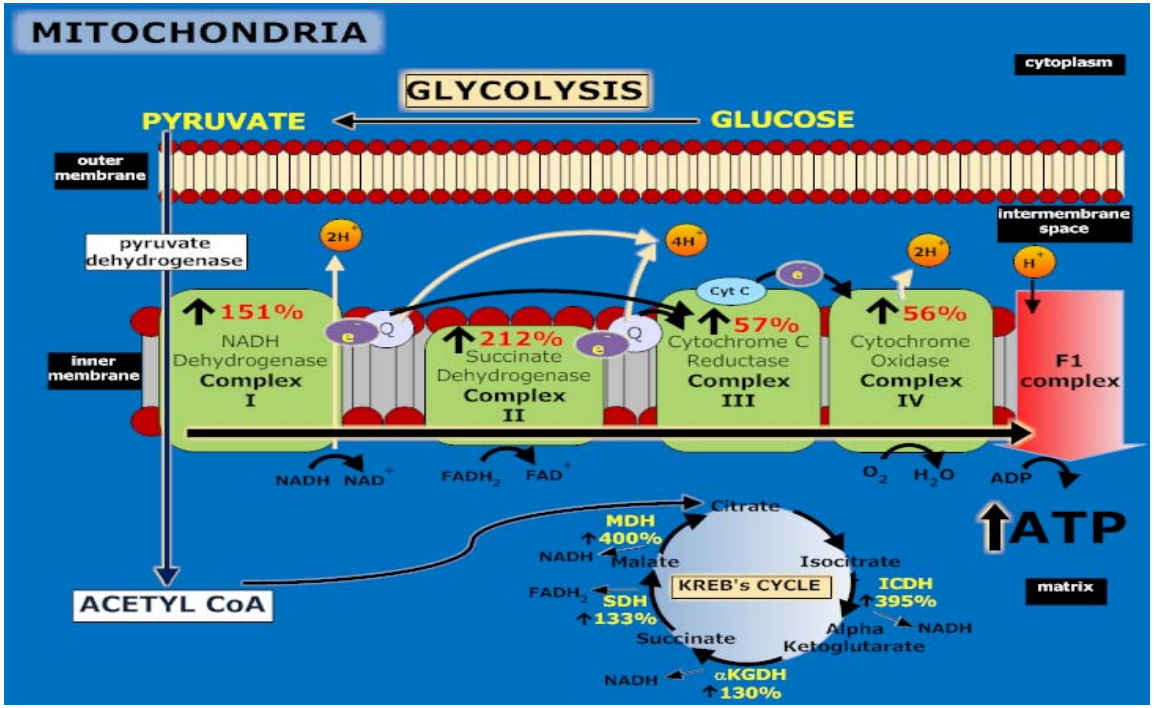
Poly-MVA– Vitamin A

Poly 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



Poly-MVA 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.

Poly-MVA – 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.

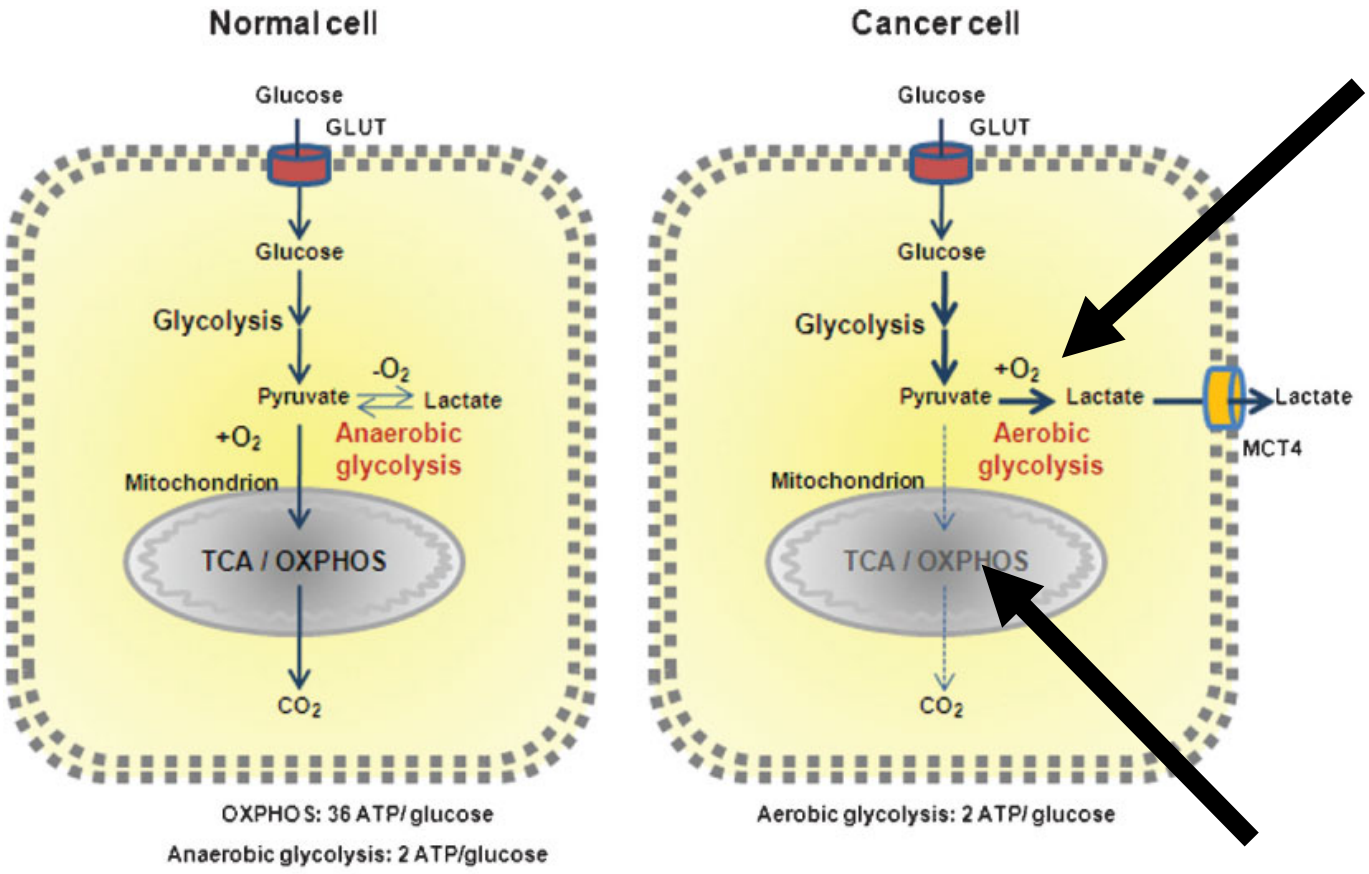


Figure 1 - Metabolic differences between normal and cancer cells. Normal cells primarily metabolize glucose to pyruvate for growth and survival, followed by complete oxidation of pyruvate to CO_2 through the TCA cycle and the OXPHOS process in the mitochondria, generating 36 ATPs per glucose. O_2 is 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.

Why consider Metabolic Synergy Therapies in non-responders?

- **Protocol as developed by Dr. Anderson for the NIH research and AMT Clinic:**
  - Current combination therapy in trial using both oral and IV Poly-MVA and Metabolic Therapy 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 Retinol (lipid soluble Vitamin A) PO QD**

Original case series (2010-14):

n (number of patients) = 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	

Between 2014 and now

we updated the protocols:

DIET:

DIET:

- All organic sources of food and filtered water.
- Ketogenic diet is preferred.
- If possible daily intermittent fasting (16 hours water only / 8 hours eating time period)
- Second choice is a high fiber vegetable based low carbohydrate diet supplemented with MCT Oil (4-8 tablespoons daily.)

SUPPORTIVE SUPPLEMENTS:

Brain Cancers – A Metabolic Approach

SUPPORTIVE SUPPLEMENTS:

- **Support oxidative (normal cell) metabolism / Oppose glycolytic (lactate) metabolism:**
  - **Poly-MVA (8 teaspoons divided through the day 4 to 5 days weekly) http://www.polymva.com/**
  - **benaGene - Oxaloacetate (100-300 mg twice a day) www.TerraBiological.com**
  - **Berberine (250 – 500 mg twice a day with food)**

Brain Cancers – A Metabolic Approach

SUPPORTIVE SUPPLEMENTS:

- **Synergy for metabolic therapy / Direct brain tumor activity:**
  - **Co-Q-10 (100 – 200 mg twice a day)**
  - **Retinyl palmitate (5000 IU daily)**
  - **Vitamin K-2 – Menaquinone (MK-4 50 mg once to twice daily)**
  - **Vitamin D – (5,000 – 10,000 dialy)**
  - **Boswellia (250 – 500 mg three times daily with food)**
  - **Curcumin (1000 mg three times daily with food)**
  - **Ketone supplement (Ketone salt form drink 2.5 to 10 grams daily)**
  - **CBD-THC (dose depends on product and legality)**
  - **Hyperbaric Oxygen Therapy two to three times weekly as a trial if available**

SUPPORTIVE SUPPLEMENTS:

Some Background References:

- K2: Sakagami H, Hashimoto K, Suzuki F, Ishihara M, Kikuchi H, Katayama T, Satoh K. Tumor-specificity and type of cell death induced by vitamin K2 derivatives and prenylalcohols. Anticancer Res. 2008 Jan-Feb;28(1A):151-8. PMID: 18383839
- Boswellia: SCHNEIDER H, WELLER M. Boswellic acid activity against glioblastoma stem-like cells. Oncology Letters. 2016;11(6):4187-4192. doi:10.3892/ol.2016.4516.
- Vitamin D&A: Magrassi L, Butti G, Pezzotta S, Infuso L, Milanesi G. Effects of vitamin D and retinoic acid on human glioblastoma cell lines. Acta Neurochir (Wien). 1995;133(3-4):184-90. PMID: 8748764
- CoQ-10: Hodges, Stephen & Hertz, N & Lockwood, K & Lister, R. (1999). CoQ10: Could it have a role in cancer management?. BioFactors (Oxford, England). 9. 365-70.
- CoQ-10: Jeng I, Klemm N, Proctor B. Insensitivity of ubiquinone biosynthesis in glioblastoma cells to an epileptogenic drug, U18666A. J Neurochem. 1984 Nov;43(5):1409-14. PMID: 6567656

Some Background References:

- Vitamin A:
  - Mawson AR. Retinoids in the treatment of glioma: a new perspective. Cancer Management and Research. 2012;4:233-241. doi:10.2147/CMAR.S32449.
  - Bushue N, Wan Y-JY. Retinoid Pathway and Cancer Therapeutics. Advanced drug delivery reviews. 2010;62(13):1285-1298. doi:10.1016/j.addr.2010.07.003.
  - Campos B, et.al. Retinoid resistance and multifaceted impairment of retinoic acid synthesis in glioblastoma. Glia. 2015 Oct;63(10):1850-9. doi: 10.1002/glia.22849. Epub 2015 May 6. PMID: 25944104
  - Wang CJ, Lin JK. Inhibitory effects of carotenoids and retinoids on the in vitro growth of rat C-6 glioma cells. Proc Natl Sci Counc Repub China B. 1989 Jul;13(3):176-83. PMID: 2480612
- Oxaloacetate: Angela Ruban & Tamara Berkutzki & Itzik Cooper & Boaz Mohar & Vivian I. Teichberg. Blood glutamate scavengers prolong the survival of rats and mice with brain-implanted gliomas. Invest New Drugs (2012) 30:2226–2235 DOI 10.1007/s10637-012-9794-x
- Cannabinoids: Twelves C, Short S and Wright S. A two-part safety and exploratory efficacy randomized double-blind, placebo-controlled study of a 1:1 ratio of the cannabinoids cannabidiol and delta-9-tetrahydrocannabinol (CBD:THC) plus dose-intense temozolomide in patients with recurrent glioblastoma multiforme (GBM). Journal of Clinical Oncology 2017 35:15_suppl, 2046-2046

MENTAL WORK:

Our Brain, Thoughts and Goals:

We are only as healthy as our thoughts.

Cancer is one diagnosis that can critically “sideline” a person’s fight and will to live.

It is crucial to have positive support, work on your mind and keep a forward look to good things in the future.

Thank you!