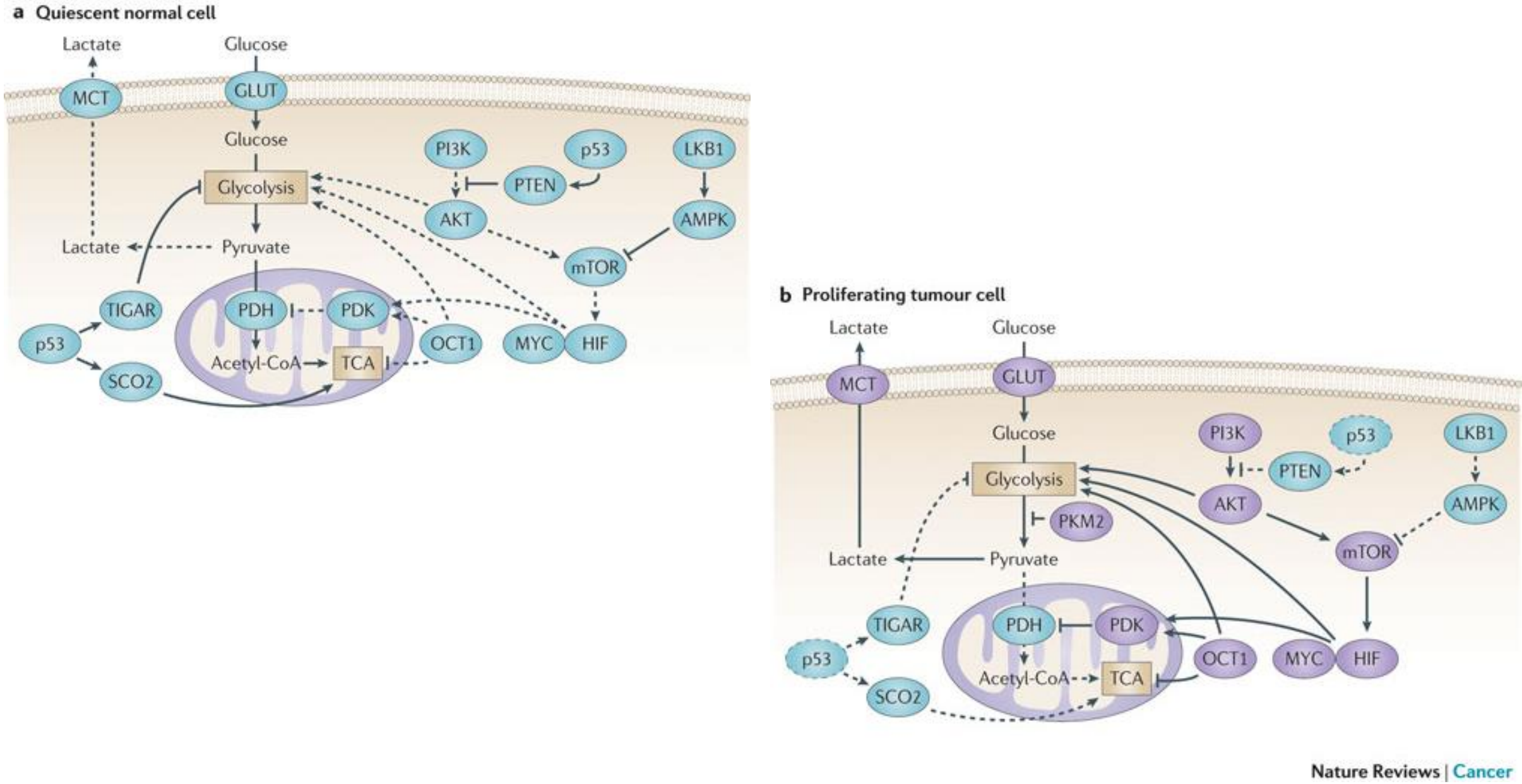
Ketogenic – HBOT – DCA in Oncology

Virginia Osborne ND, Paul Anderson ND and Brenden Cochran ND

Ketogenesis



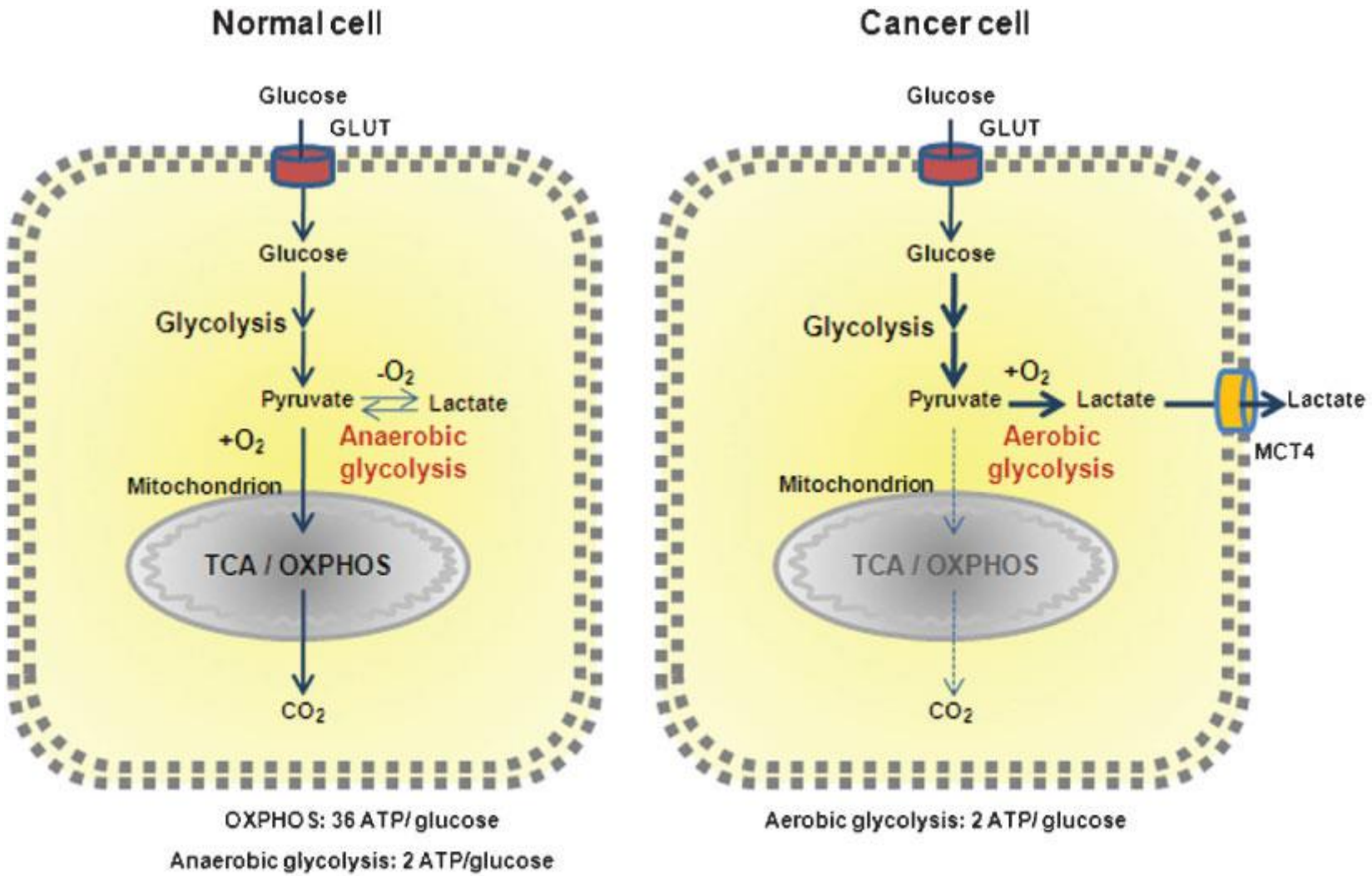
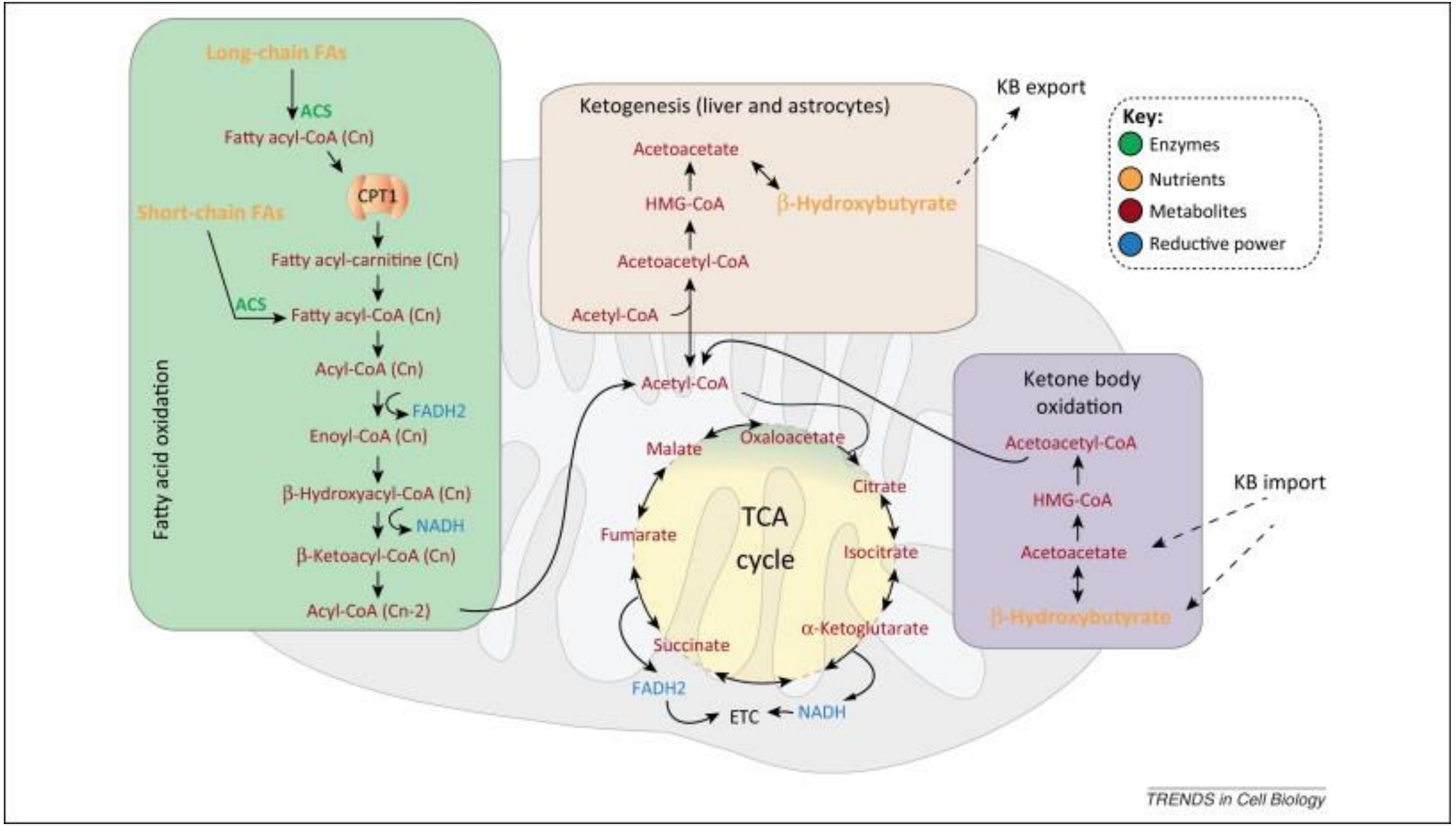
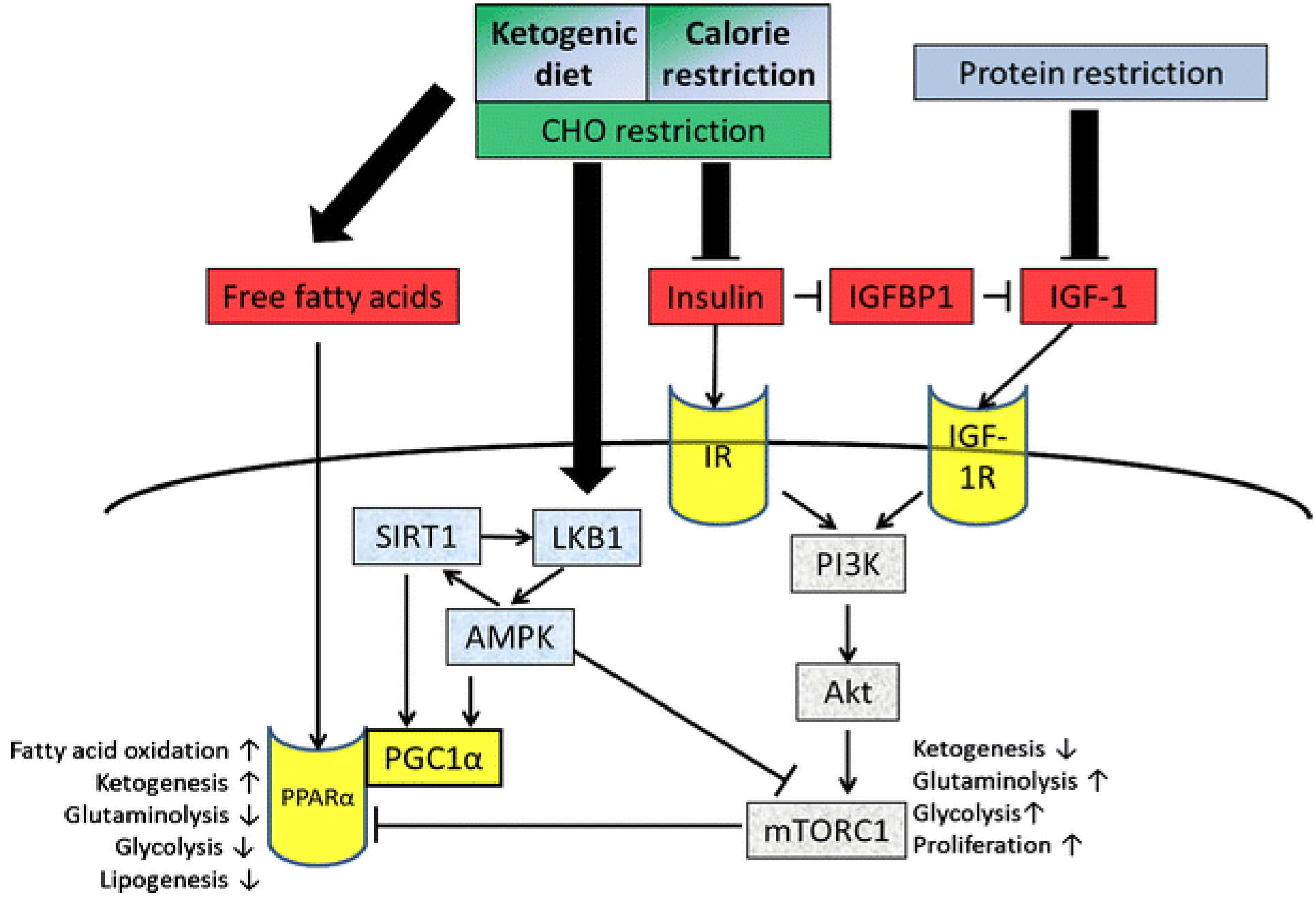


Figure 1 - Metabolic differences between normal and cancer cells. Normal cells primarily metabolize glucose to pyruvate for growth and survival, followed by complete oxidation of pyruvate to CO_2 through the TCA cycle and the OXPHOS process in the mitochondria, generating 36 ATPs per glucose. O_2 is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





frontiers in
PHARMACOLOGY

REVIEW ARTICLE
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The ketogenic diet as a treatment paradigm for diverse neurological disorders

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Stafstrom and Rho:

bolic pathway might be influenced by a variety of dietary interventions. The most notable example of a dietary treatment with proven efficacy against a neurological condition is the high-fat, low-carbohydrate ketogenic diet (KD) used in patients with medically intractable epilepsy. While the mechanisms through which the KD works remain unclear, there is now compelling evidence that its efficacy is likely related to the normalization of aberrant energy metabolism. The concept that many neurological conditions are linked pathophysiologically to energy dysregulation could well provide a common research and experimental therapeutics platform, from which the course of several neurological diseases could be favorably influenced by dietary means. Here we provide an overview of studies using the KD in a wide panoply of neurologic disorders in which neuroprotection is an essential component.

Very-low-carbohydrate diets or ketogenic diets have been in use since the 1920s as a therapy for epilepsy and can, in some cases, completely remove the need for medication. From the 1960s onwards they have become widely known as one of the most common methods for obesity treatment. Recent work over the last decade or so has provided evidence of the therapeutic potential of ketogenic diets in many pathological conditions, such as diabetes, polycystic ovary syndrome, acne, neurological diseases, cancer and the amelioration of respiratory and cardiovascular disease risk factors. The possibility that modifying food intake can be useful for reducing or eliminating pharmaceutical methods of treatment, which are often lifelong with significant side effects, calls for serious investigation. This review revisits the meaning of physiological ketosis in the light of this evidence and considers possible mechanisms for the therapeutic actions of the ketogenic diet on different diseases. The present review also questions whether there are still some preconceived ideas about ketogenic diets, which may be presenting unnecessary barriers to their use as therapeutic tools in the physician's hand.

European Journal of Clinical Nutrition (2013) **67,** 789–796; doi:10.1038/ejcn.2013.116; published online 26 June 2013

Conclusions: Compared with a low-fat diet, a low-carbohydrate diet program had better participant retention and greater weight loss. During active weight loss, serum triglyceride levels decreased more and high-density lipoprotein cholesterol level increased more with the low-carbohydrate diet than with the low-fat diet.

Ann Intern Med. 2004;140:769-777. www.annals.org

Redox Biology 2 (2014) 963–970

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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

Cancer cells, relative to normal cells, demonstrate significant alterations in metabolism that are proposed to result in increased steady-state levels of mitochondrial-derived reactive oxygen species (ROS) such as $O_2^{\bullet -}$ and H_2O_2. It has also been proposed that cancer cells increase glucose and hydroperoxide metabolism to compensate for increased levels of ROS. Given this theoretical construct, it is reasonable to propose that forcing cancer cells to use mitochondrial oxidative metabolism by feeding ketogenic diets that are high in fats and low in glucose and other carbohydrates, would selectively cause metabolic oxidative stress in cancer versus normal cells. Increased metabolic oxidative stress in cancer cells would in turn be predicted to selectively sensitize cancer cells to conventional radiation and chemotherapies. This review summarizes the evidence supporting the hypothesis that ketogenic diets may be safely used as an adjuvant therapy to conventional radiation and chemotherapies and discusses the proposed mechanisms by which ketogenic diets may enhance cancer cell therapeutic responses.

The Ketogenic Diet and HBOT for Cancer

Dominic P. D'Agostino, PhD
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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.

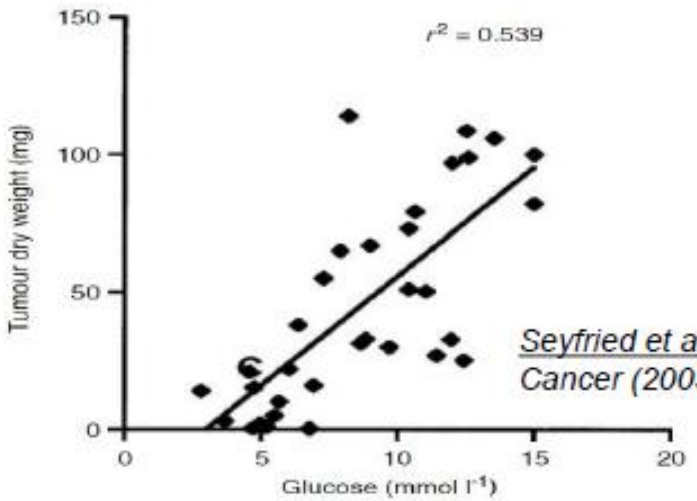
Hyperglycemia and Tumor Hypoxia Drive the Warburg Effect

Gnagnarella, et al; 2008

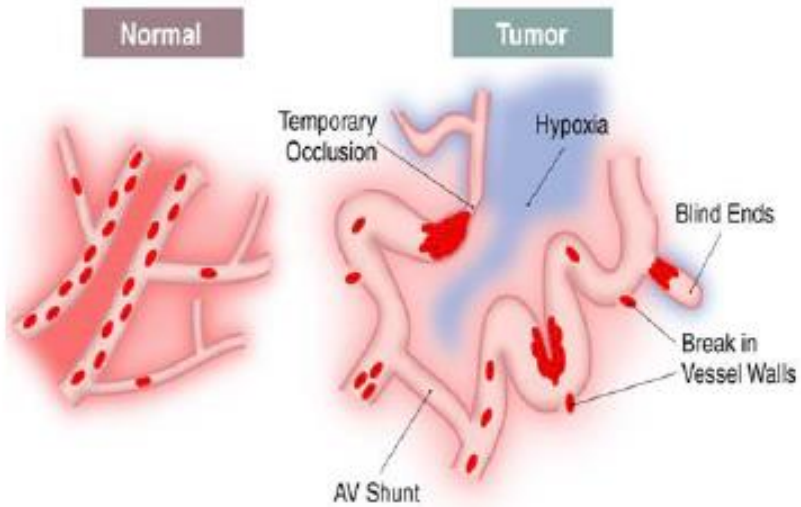
The American Journal of CLINICAL NUTRITION

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

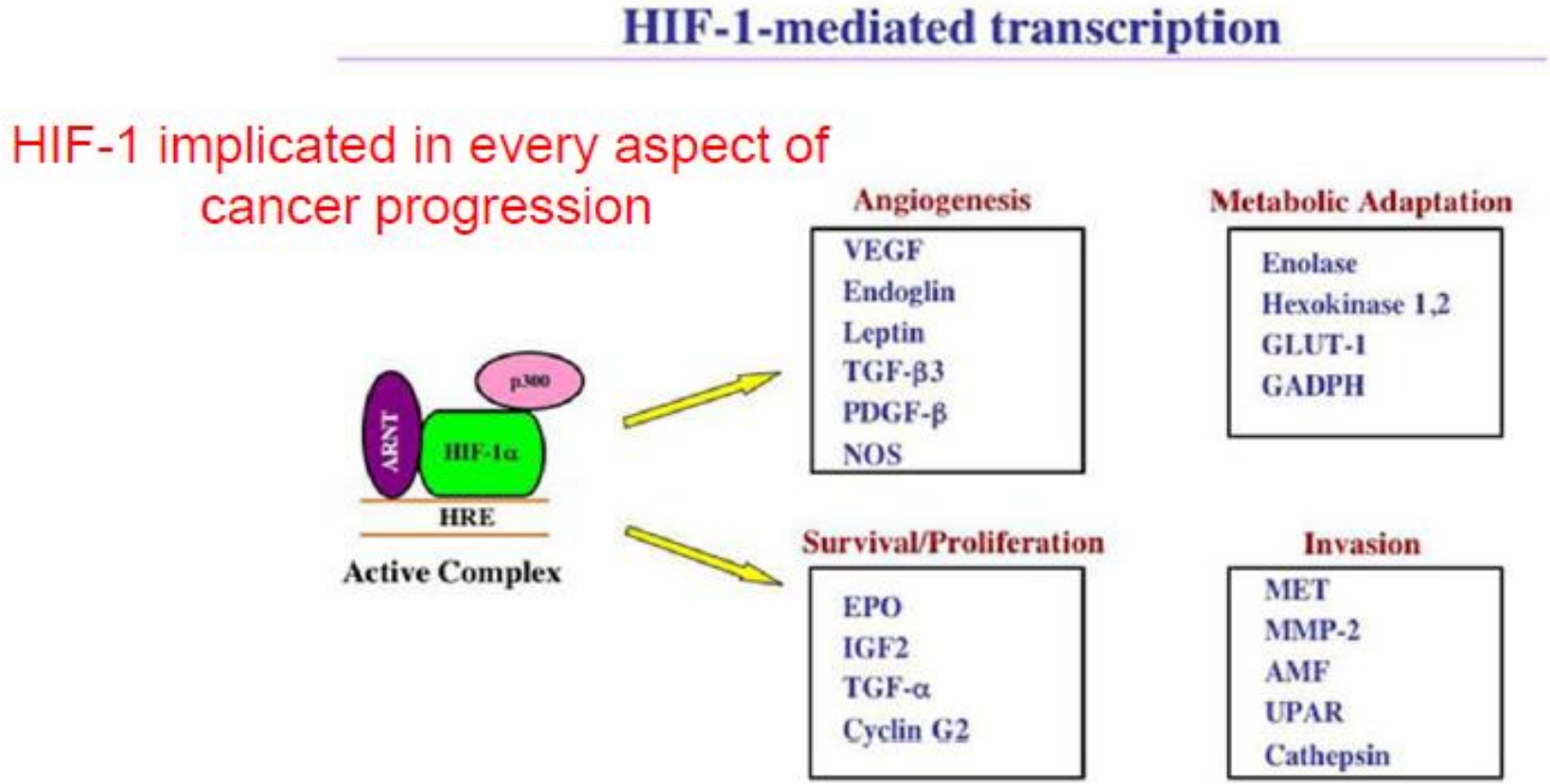


30-60 mmHg 2-30 mmHg

Average PO_2

****Causes chemo/radioresistance**

Tumor hypoxia promotes cancer progression and the Warburg Effect



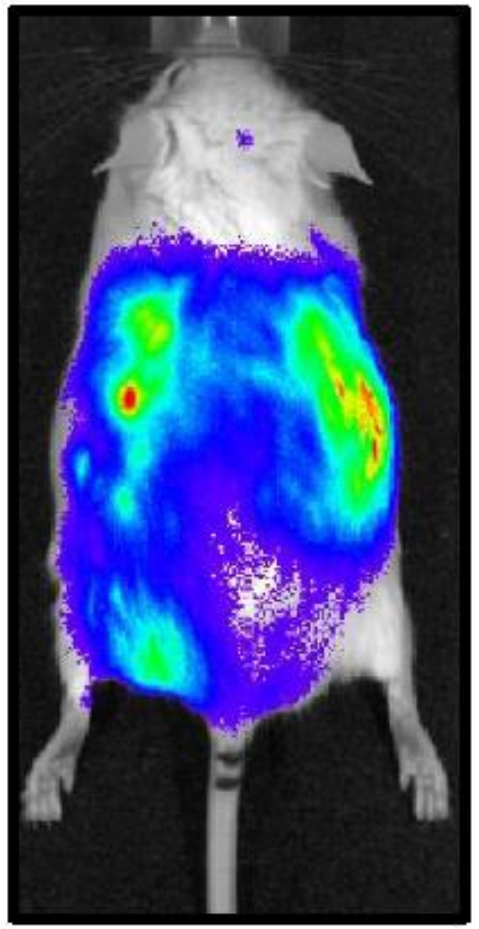
Regulation of cancer cell metabolism by hypoxia-inducible factor 1; Semenza, G.

The VM-M3 Model of Metastatic Cancer

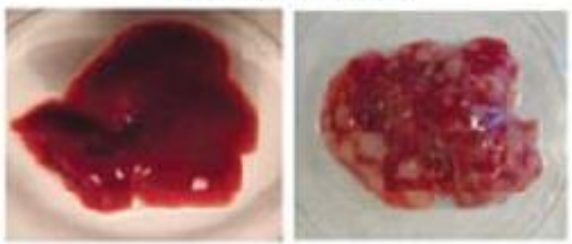
Developed by Dr. Thomas Seyfried, Boston College

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



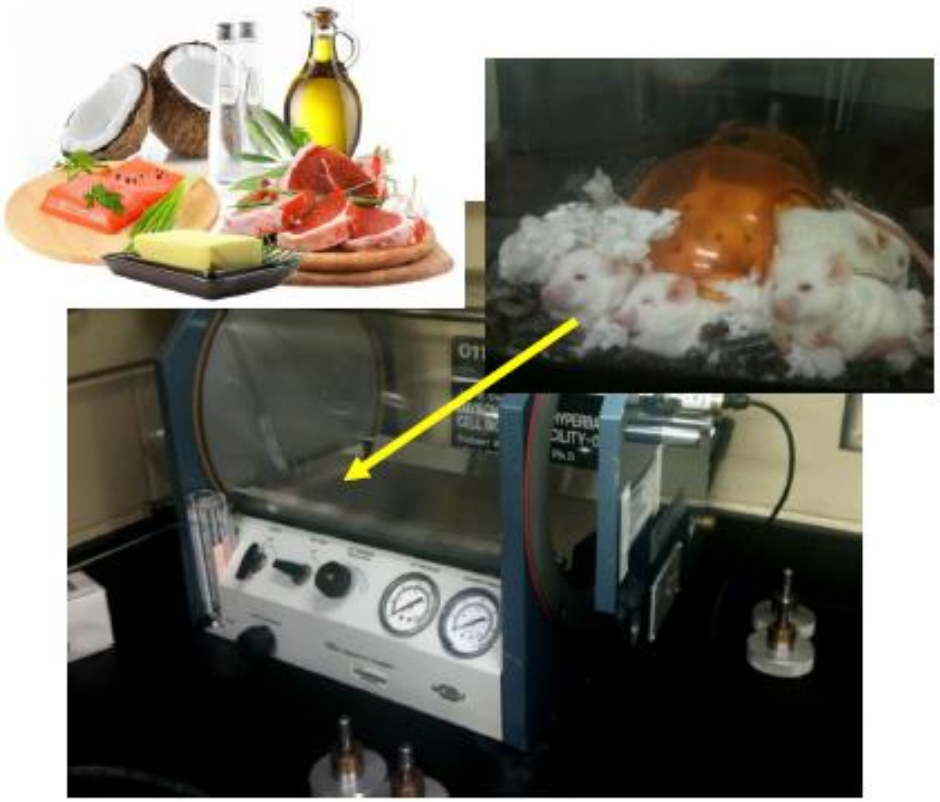
Shelton, et. Al, 2009

Combining the Ketogenic Diet with Hyperbaric Oxygen

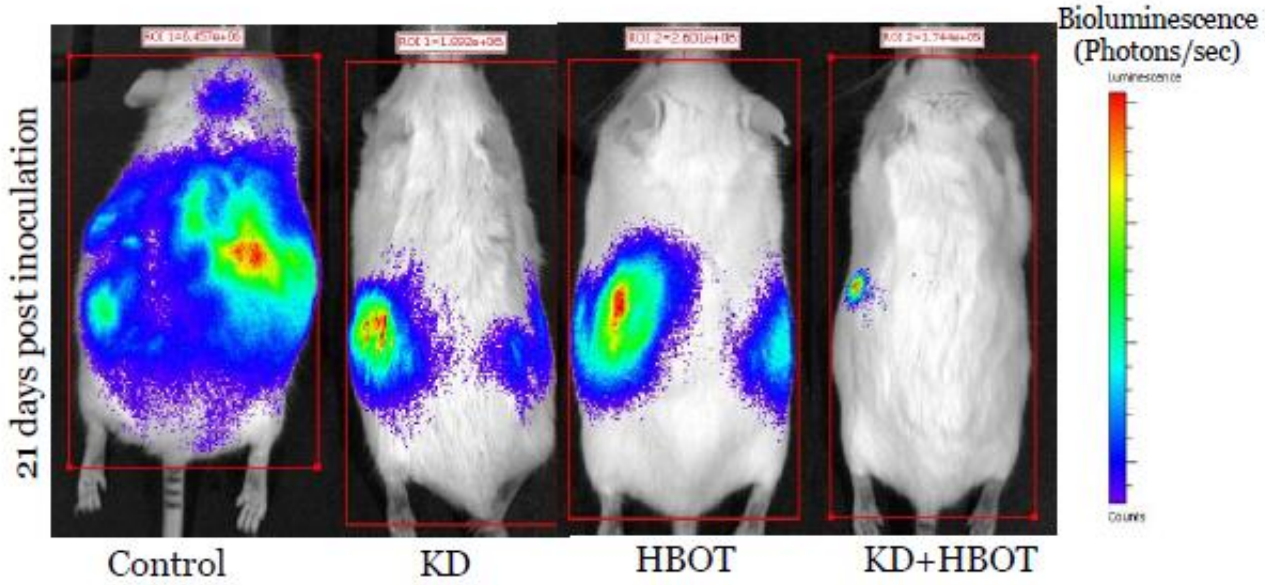
Methods: Treatment Groups

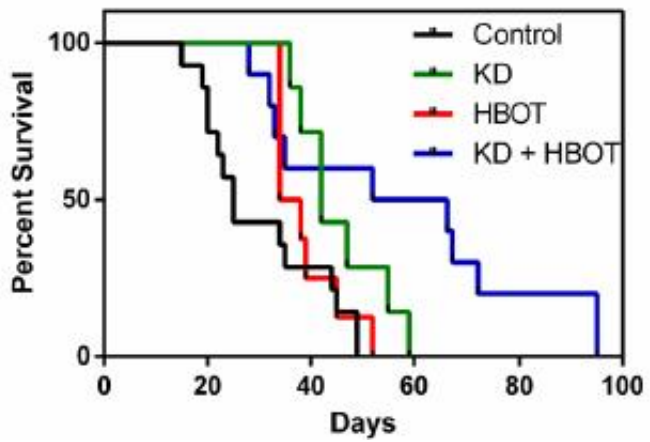
VM-M3 Survival Study:

- 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



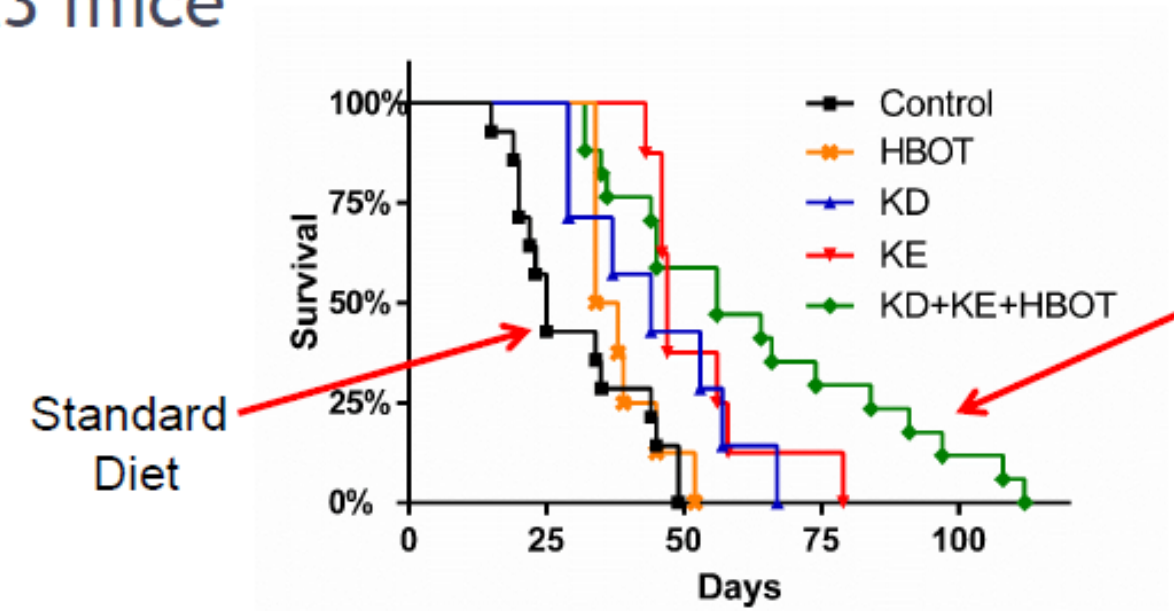
KD+HBOT inhibits tumor growth and increases survival against metastatic cancer





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

Combination therapy doubles survival time in VM-M3 mice



Standard Diet

Ketogenic Diet
Ketone Ester
Hyperbaric Oxygen

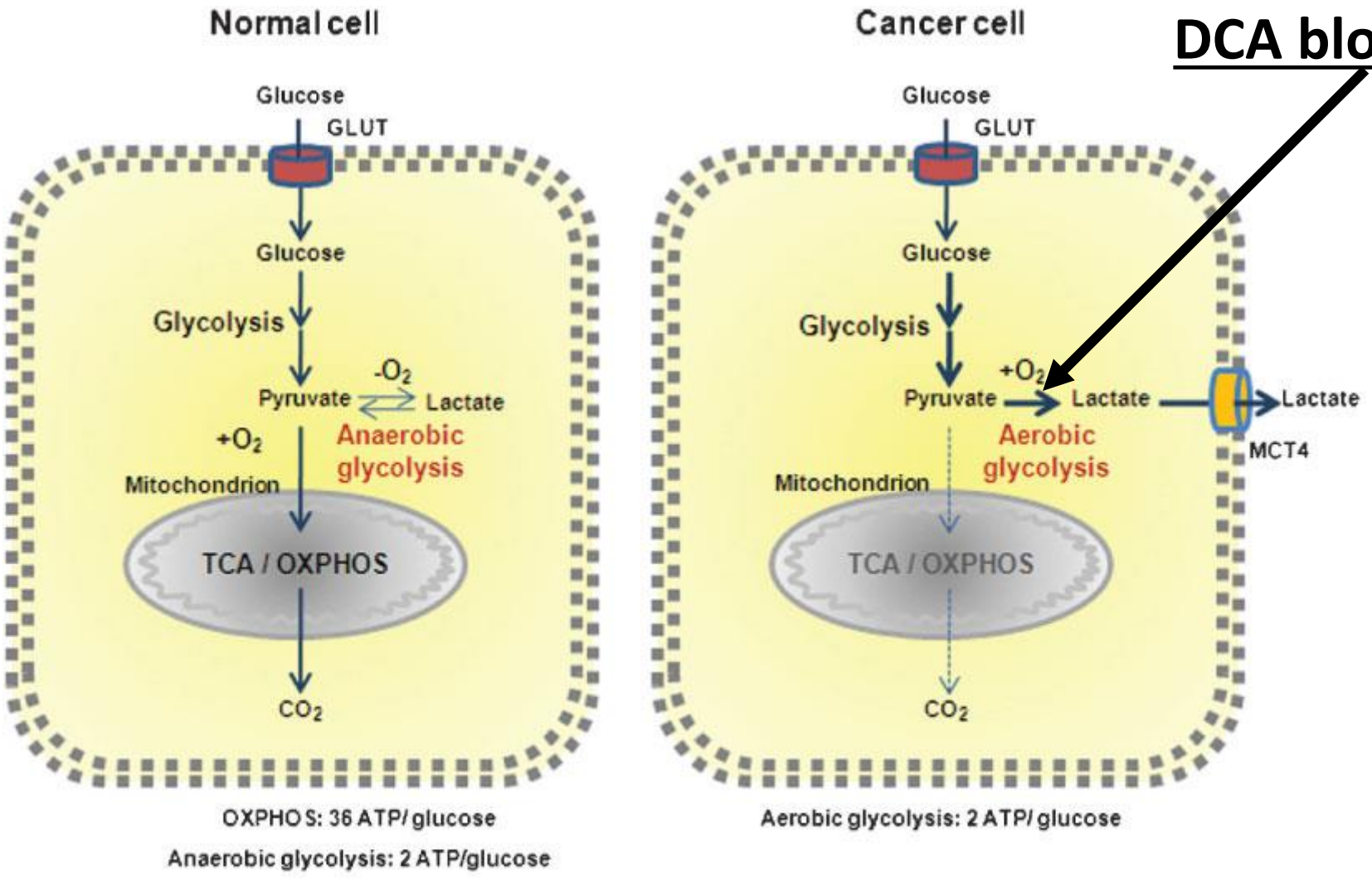
*p<0.05
***p<0.001

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:

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).



DCA blocks this step:

2DG
3BP
Also block

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.

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.

DCA

Protocols Reported:

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

If adding to a high dose IV ascorbate approach a reasonable protocol would be to alternate concomitant use of DCA plus High Dose IV Vitamin C, and DCA plus glutathione support (two separate IV's).

- IV-1 DCA plus Support Nutrients, with IV GSH
- IV-2 DCA plus high dose IVC

DCA – See synergy notes below

Protocols Reported:

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:

- Lipoic Acid Mineral Complex (Poly MVA 20-40 mL)

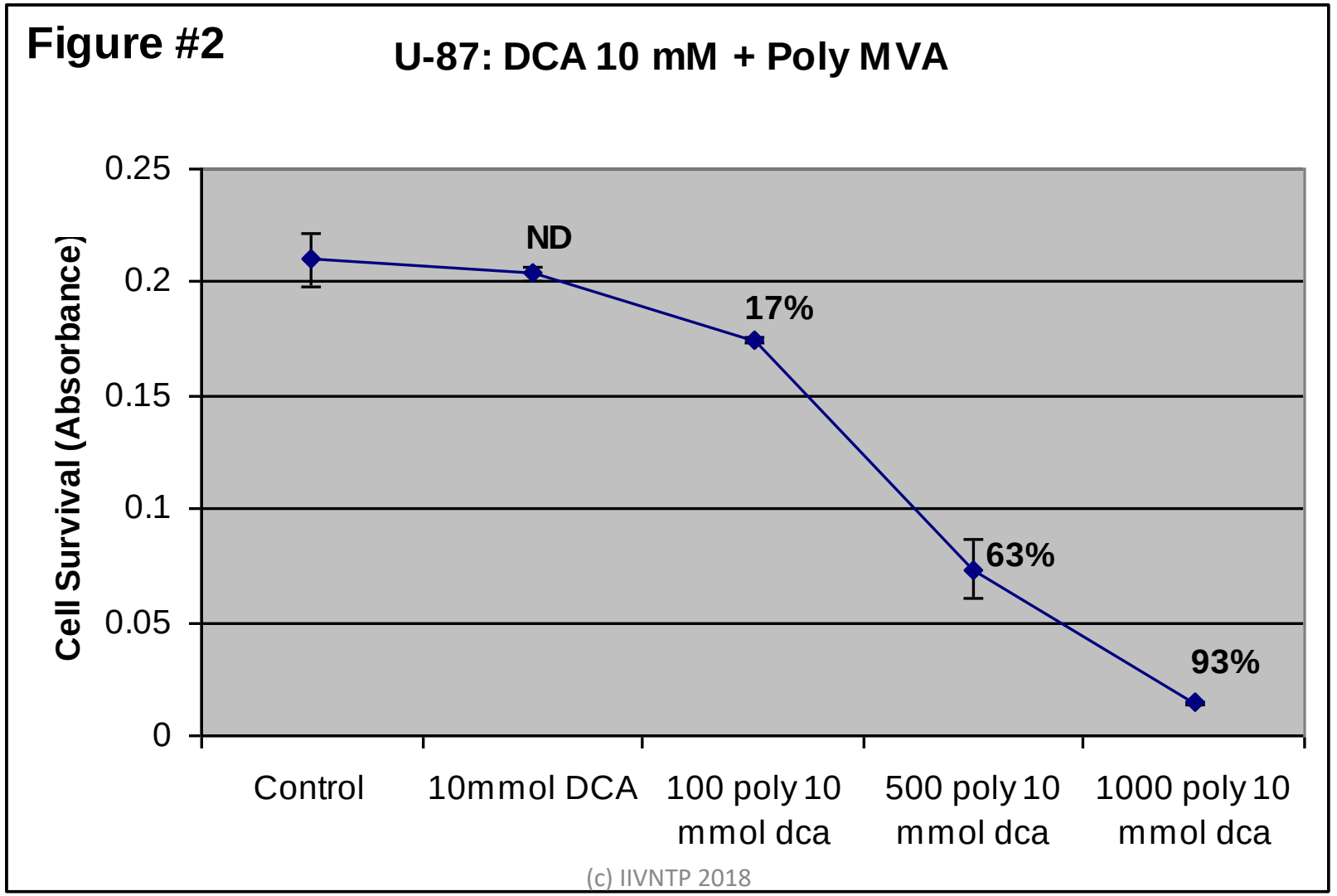
The addition of a Ketogenic Diet is reasonable, as both DCA and the ketogenic diet take advantage of the Warburg effect of neoplastic metabolism. Recommend either a full (20 gram carbohydrate) or modified (50 gram carbohydrate) ketogenic diet plan.

DCA Plus LAMC

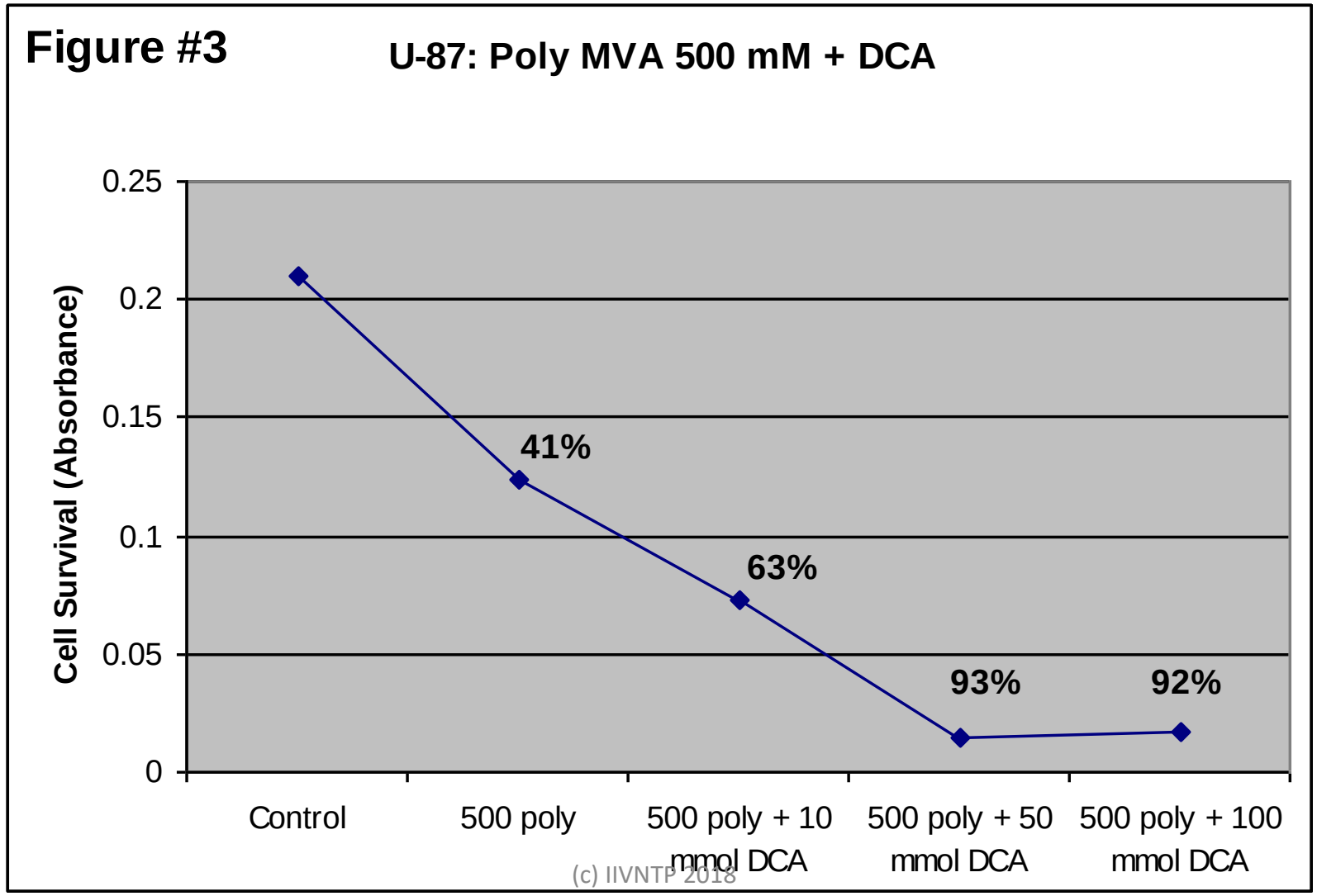
- We completed the assays using DCA and LAMC. These cell death assays utilized the U-87 glioblastoma cell line. This SRB protocol is identical to the one used by the NCI in their chemotherapy screen.
- Protocol:
  - In this experiment we chose 3 dosages of LAMC [As the proprietary formulation Palladium-Lipoic 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

Figure #2

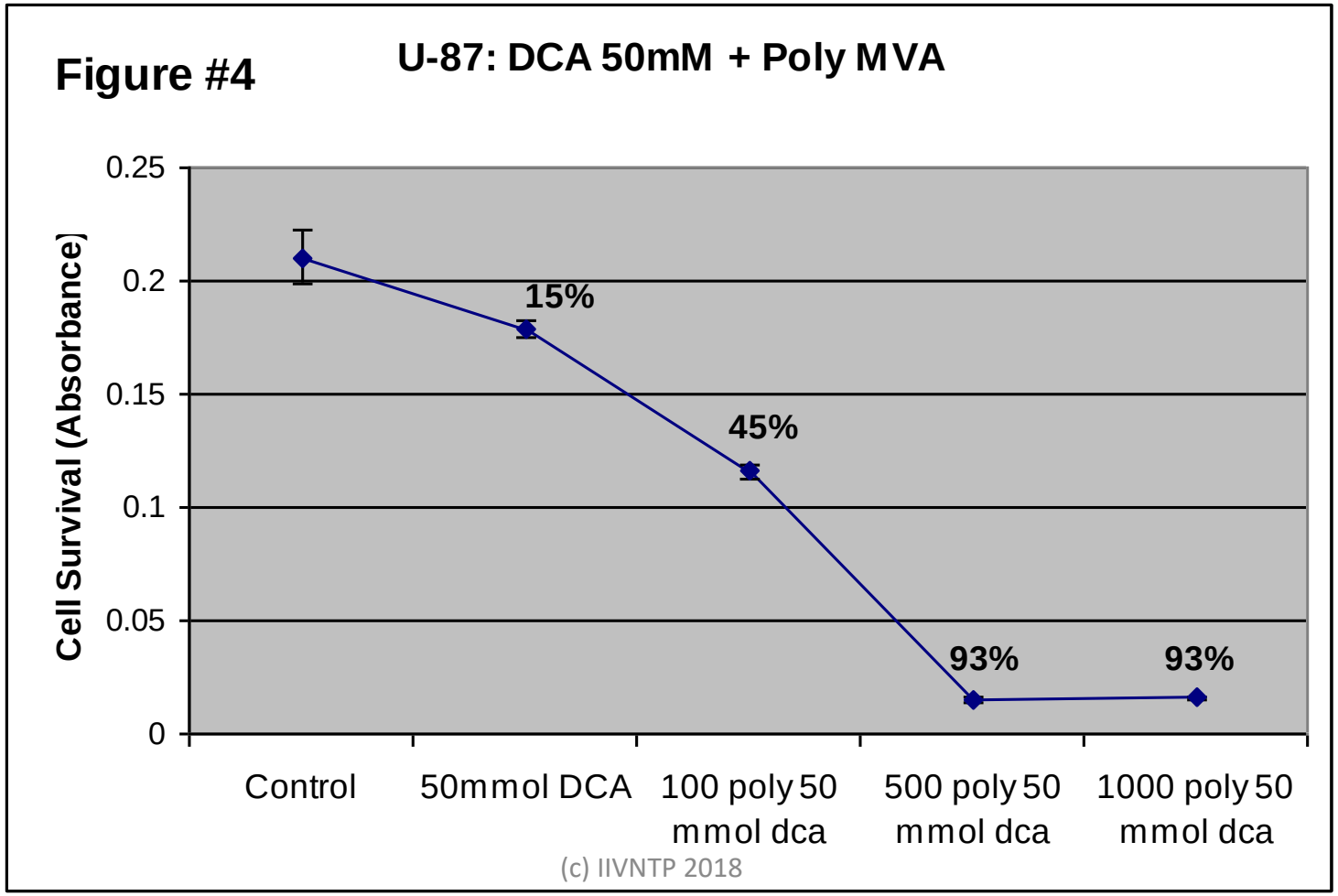


DCA Plus LAMC



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

- 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 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 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

- LAMC (PolyMVA) at 40 mL (Adult dose) - (PO in divided doses or IV in one dose)
  - RAMP Poly Dose up: 5-10 mL first IV, then 15-20 then 25-30 then 40 mL
- DCA dose:
  - 50-80 mg/kg IV
  - 15-20 mg/kg BID-TID

OPEN ACCESS Freely available online

PLOS ONE

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

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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.

Latest “full” Protocol (Sanoviv Hospital and AMT)

1. Keto, Keto Adapted or (at least) Low CHO diet
2. Oral Retinol (see below)
3. Lactate and Mito agents (DCA-Poly, see below)
4. HBOT 3-5X weekly
5. Keto-esters (Ketoforce) daily

DCA References:

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