Cancer: A Metabolic Disease with Metabolic Solutions

Thomas N. Seyfried
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Provocative Question

Is cancer a nuclear genetic disease or a mitochondrial metabolic disease?

Current Dogma:
Cancer is a Genetic Disease

Hallmarks of Cancer: The Next Generation

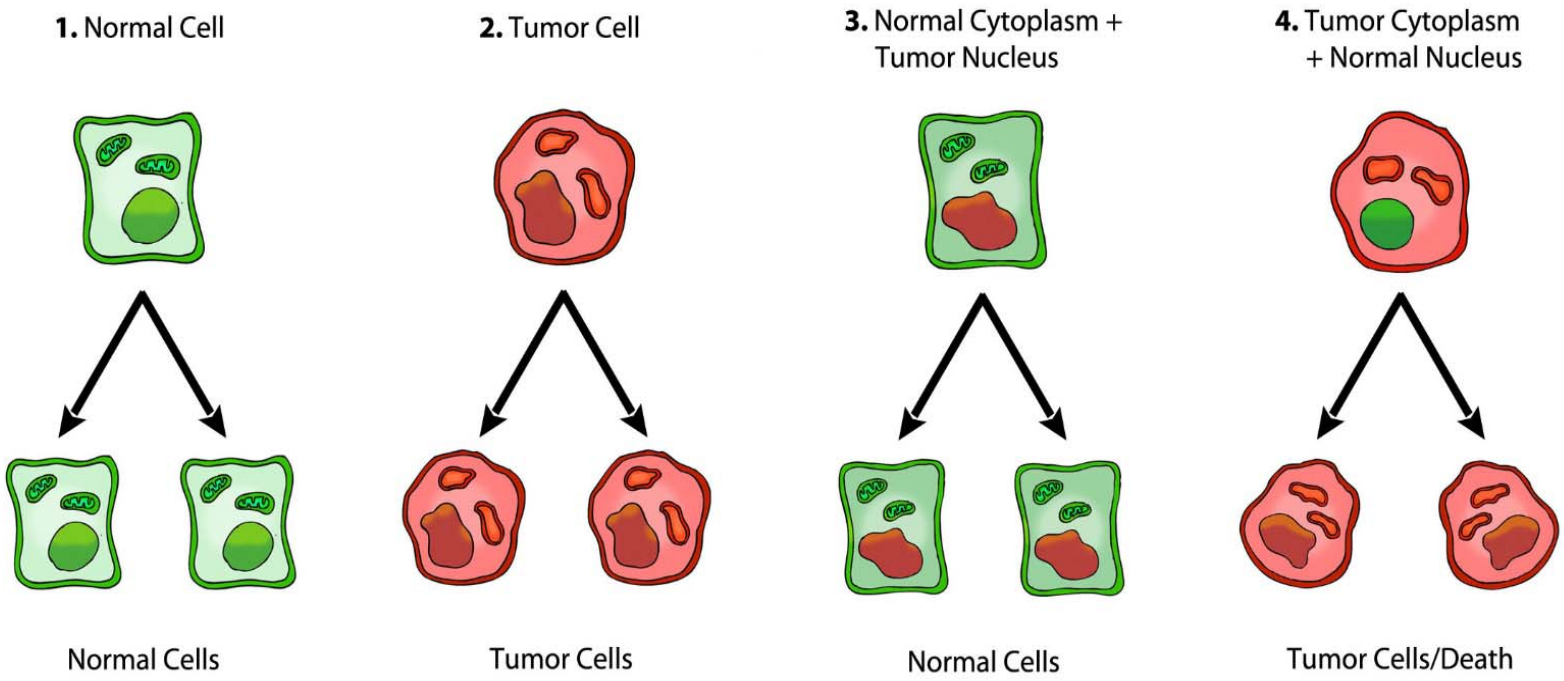
Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

Cell 144, March 4, 2011

Cancer cells carry the oncogenic and tumor suppressor mutations that define cancer as a “Genetic Disease”.

Evidence that challenges the somatic mutation theory of cancer

Role of the mitochondria in the origin of tumors



Seyfried, *Cancer as a Metabolic Disease*, 2012 John Wiley Press; Seyfried et al., 2014, *Carcinogenesis*

If somatic mutations are not the origin of cancer, then how do cancer cells arise?

On the Origin of Cancer Cells

Otto Warburg (Science, 24 February,1956)

Warburg Theory of Cancer

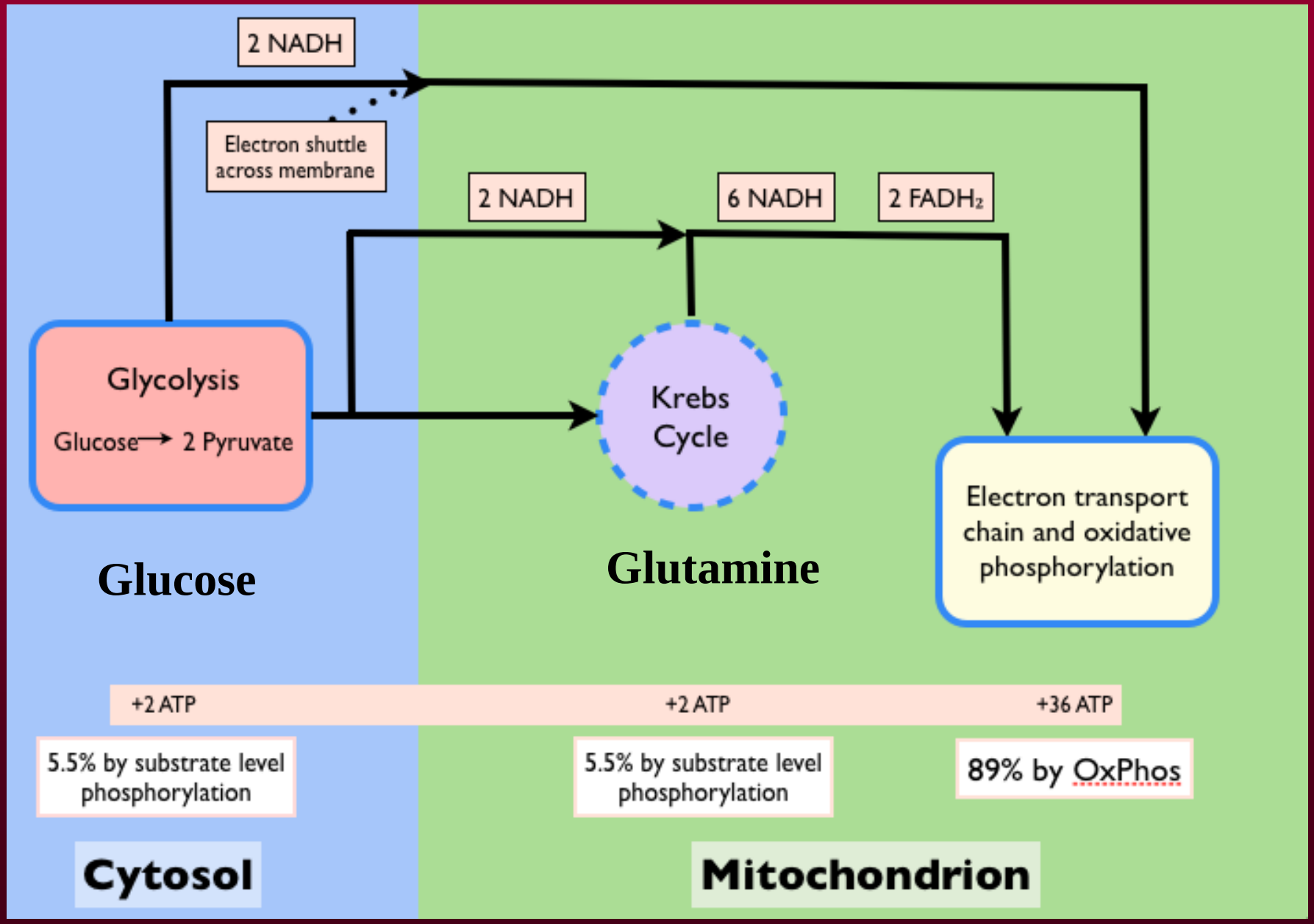
1. **Cancer arises from damage to cellular respiration.**

2. **Energy through fermentation gradually compensates for insufficient respiration.**

3. **Cancer cells continue to ferment lactate in the presence of oxygen (Warburg effect).**

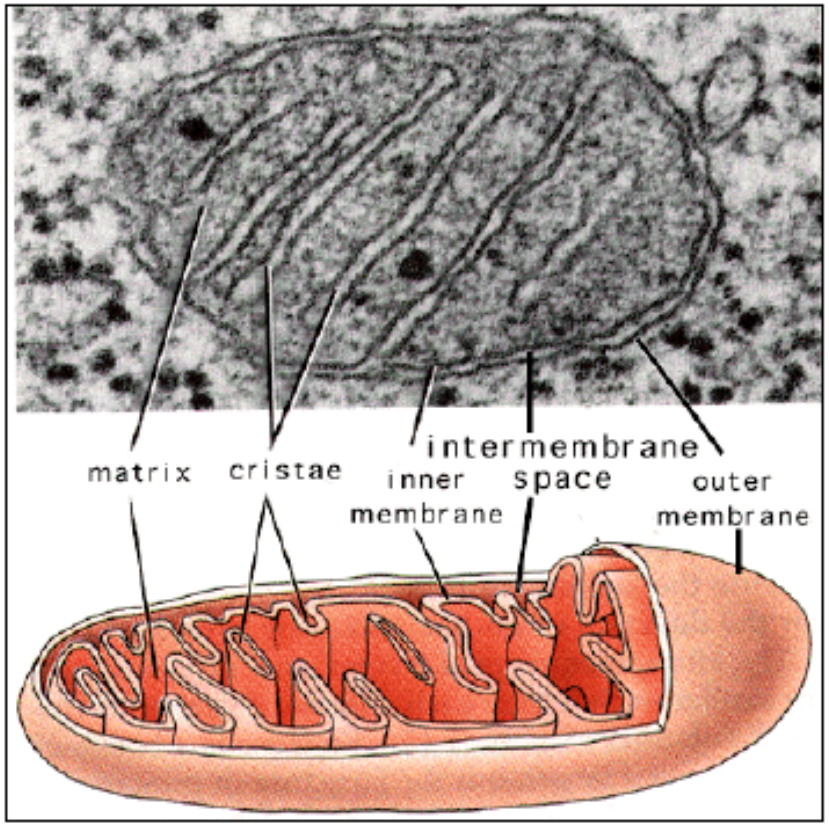
4. **Enhanced fermentation is the signature metabolic malady of all cancer cells.**

Cellular Energy Metabolism

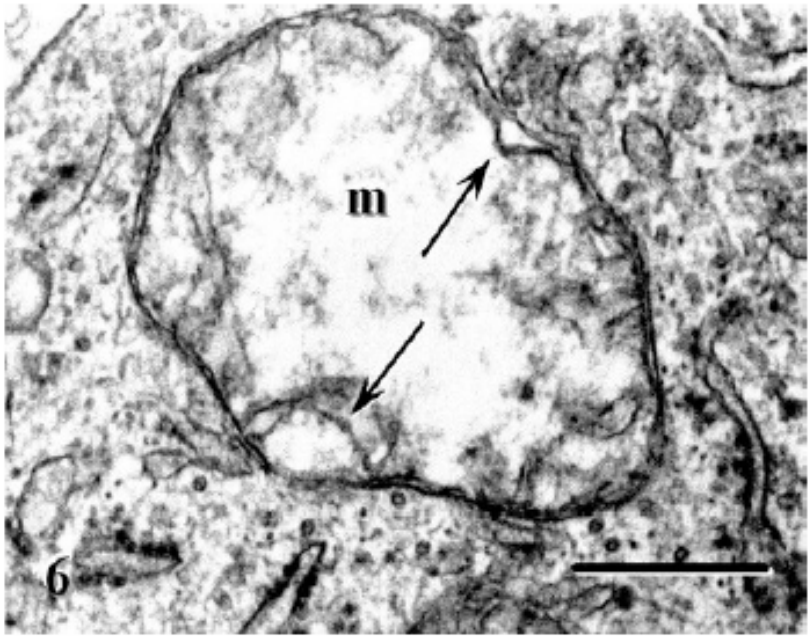


Mitochondrial Morphology

Normal Mitochondria



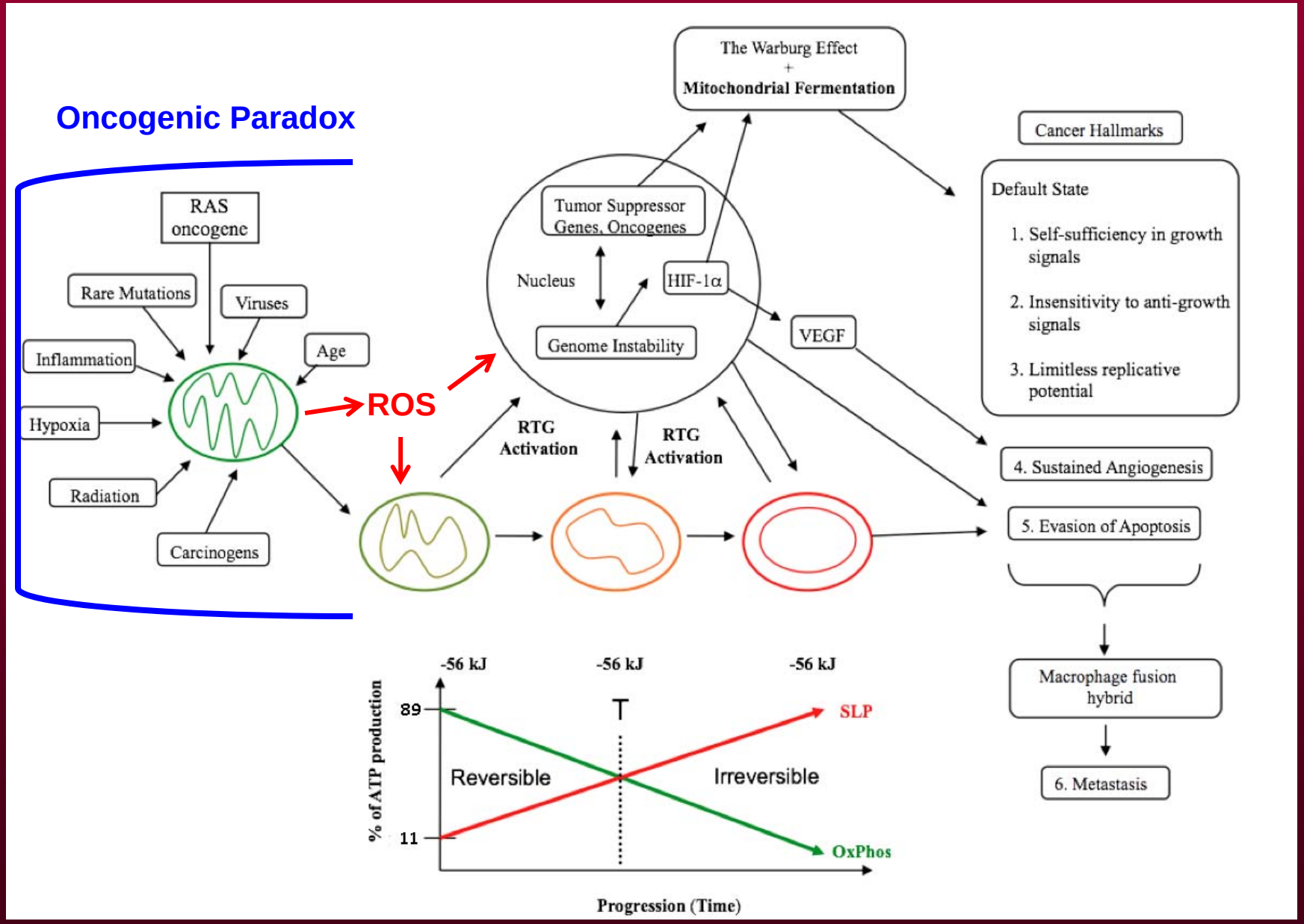
GBM Mitochondria



cristolysis

Arismendi-Morillo *Int J Biochem Cell Biol* **41,** 2062-68, 2009

Cancer as a Mitochondrial Metabolic Disease



Seyfried, *Cancer as a Metabolic Disease*, 2012 John Wiley Press; Seyfried et al., 2014, *Carcinogenesis*

If most cancers express the Warburg effect as the result of impaired respiration, then what therapies might be effective for managing tumors?

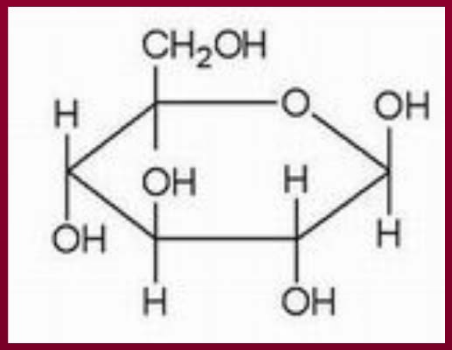
One strategy is to reduce levels of fermentable fuels while elevating levels non-fermentable fuels

Calorie Restriction (CR): A Metabolic Cancer Intervention

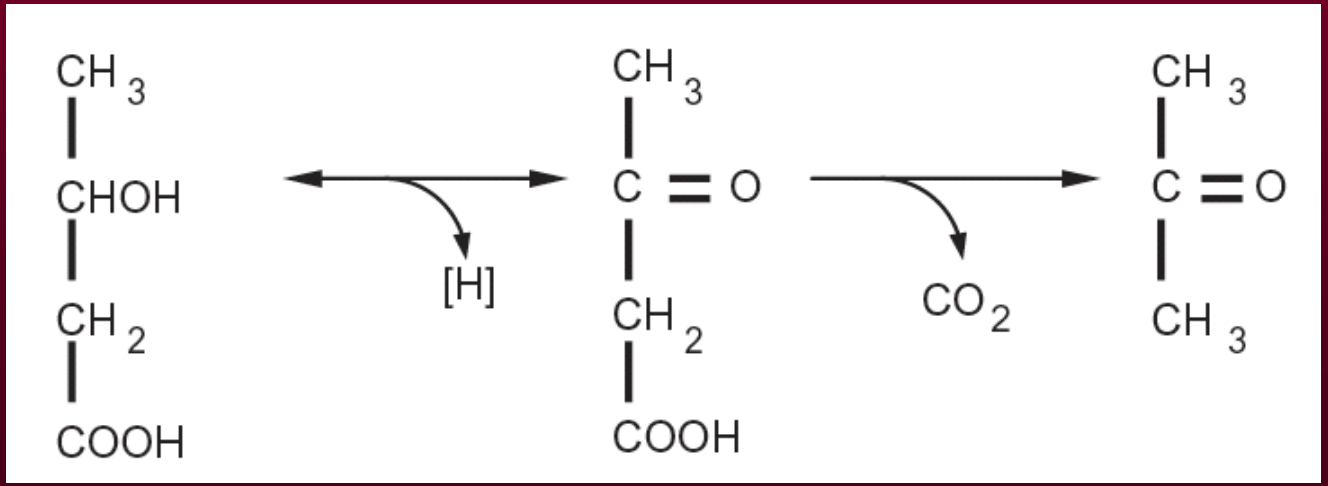
- Involves a total dietary restriction
- Differs from starvation
- Maintains minerals and nutrients
- Enhances mitochondrial biogenesis & OxPhos
- CR in mice mimics water-only therapeutic fasting in humans

Biomarkers for Calorie Restriction

1. Reduced Blood Glucose



2. Elevated Blood Ketone Bodies



β-Hydroxybutyrate (β-OHB)

Acetoacetate

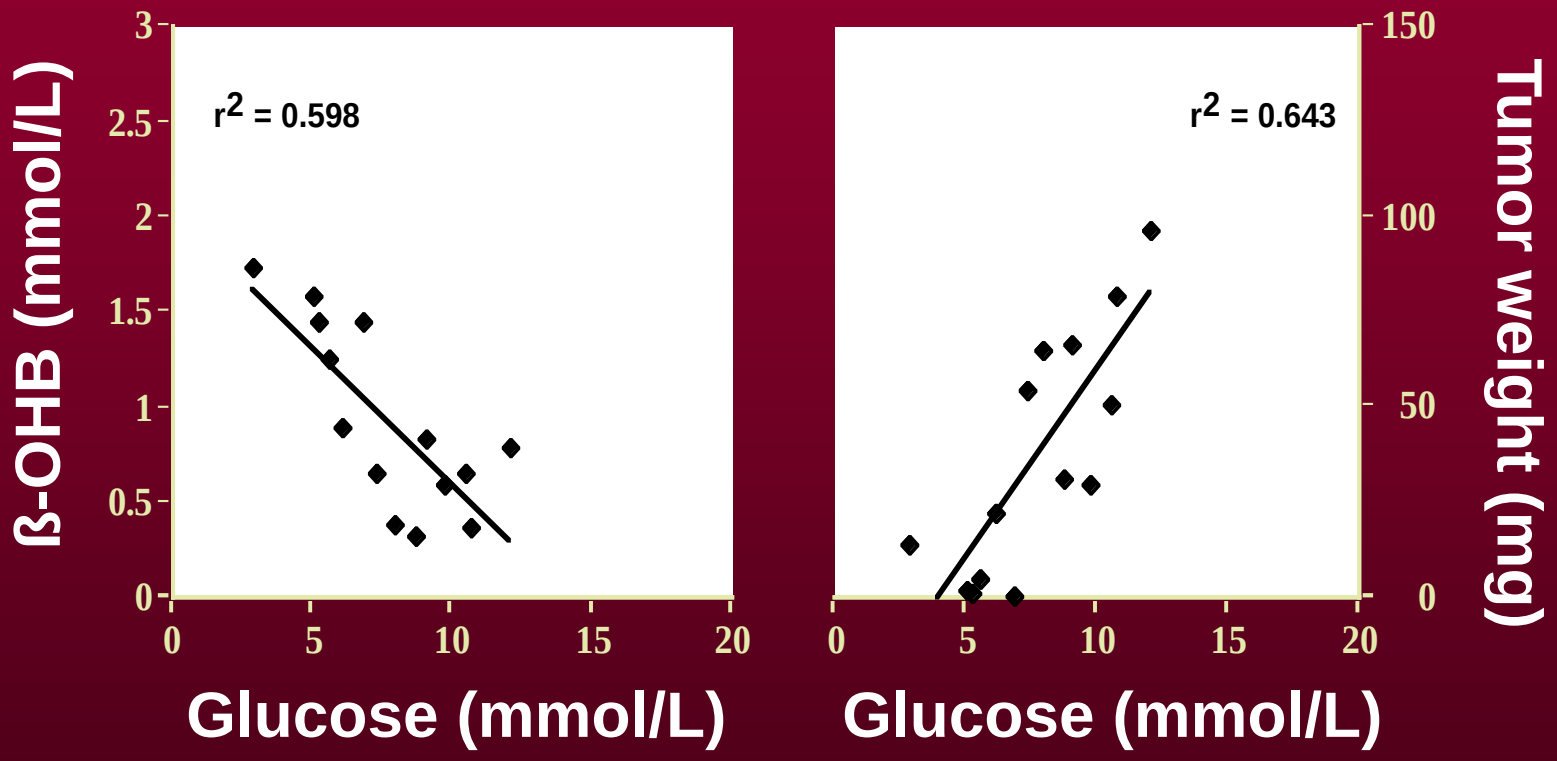
Acetone

Calorie restriction reduces intracerebral growth of the CT-2A astrocytoma

AL **CR**

40% CR initiated 3 days post-inoculation

Plasma glucose predicts ketone body levels and CT-2A tumor growth



Seyfried et al, *Brit. J. Cancer*, 2003

Anti-Tumor Effects of Calorie Restriction

1. **Anti-angiogenic**

   Mukherjee et al., Clin. Cancer Res., 2004

2. **Anti-inflammatory**

   Mulrooney et al., PLOS One, 2011

3. **Pro-apoptotic**

   Mukherjee et al., Brit. J. Cancer 2002

Research Question

Can a restricted ketogenic diet manage brain cancer in mice?

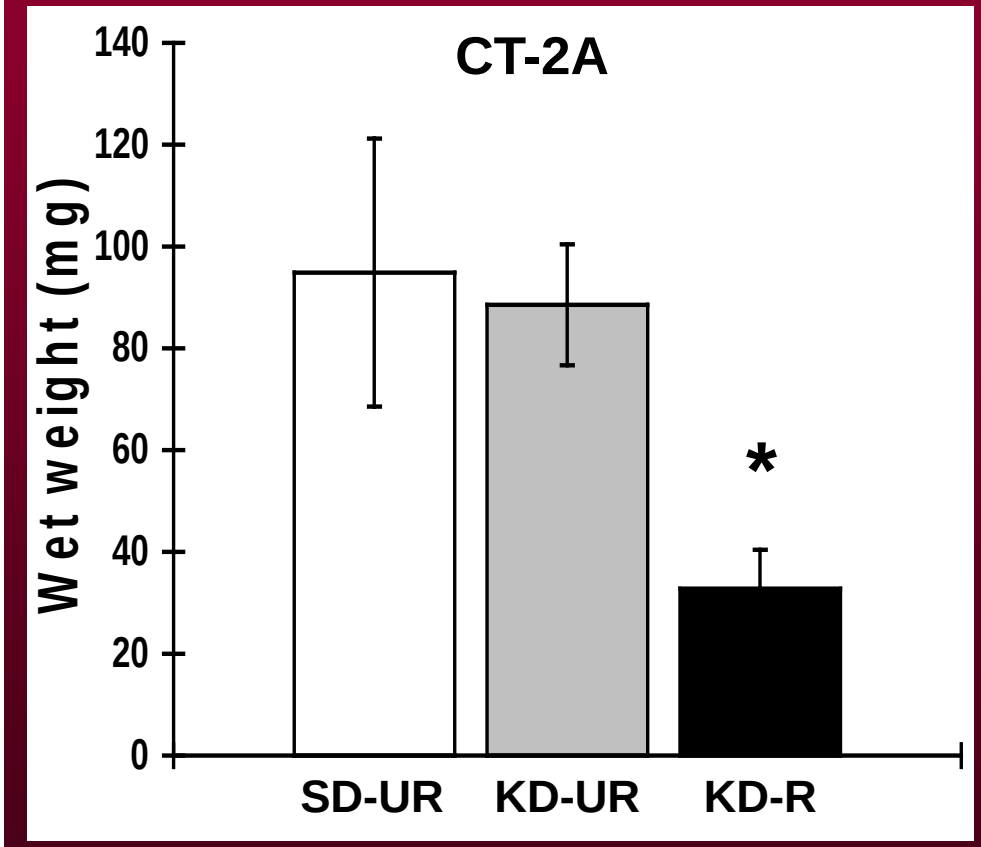
Composition (%) of the standard diet (SD) and the ketogenic diet (KD)

Components	Standard Diet (SD)	Ketogenic Diet (KD)
Carbohydrate	62	3
Fat	6	72
Protein	27	15
Energy (Kcal/gr)	4.4	7.2
F/ (P + C)	0.07	4

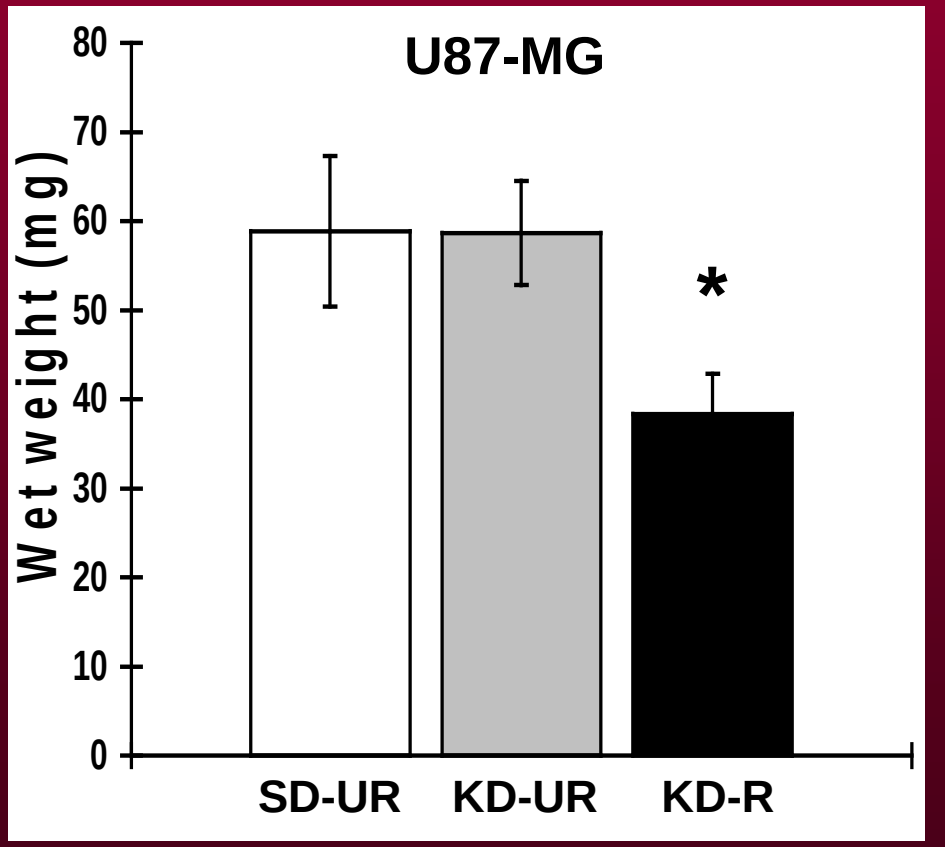
* The ketogenic diet should always be consumed in restricted amounts!

The KD-R Reduces Intracerebral Growth of Mouse and Human Brain Tumors

Mouse Brain Tumor Growth



Human Brain Tumor Growth



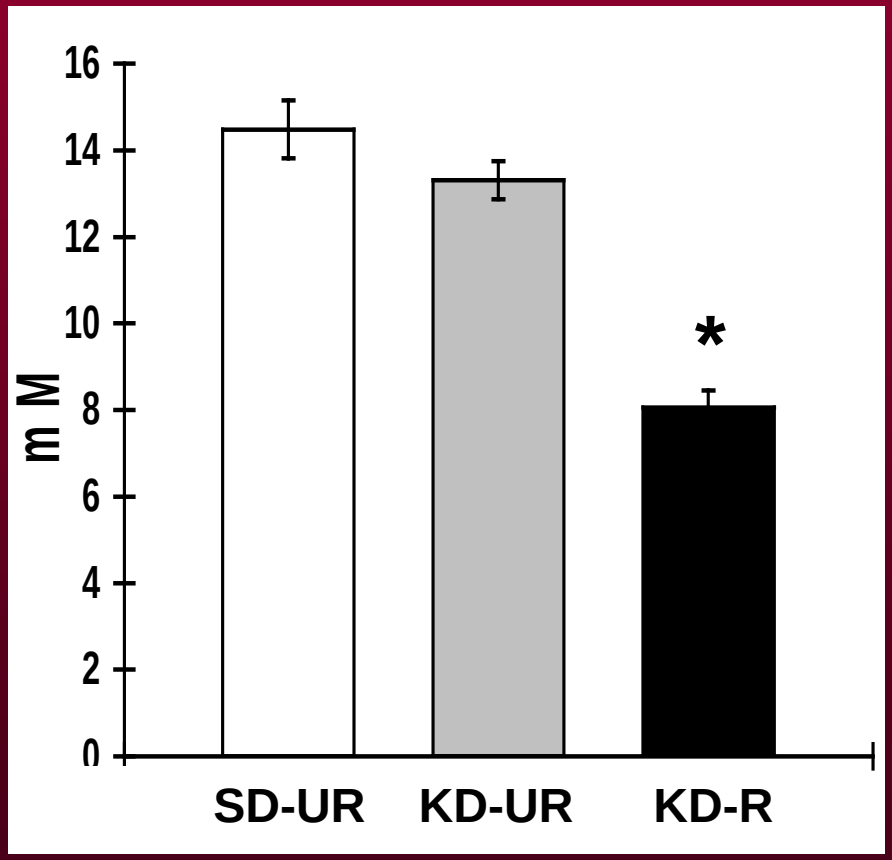
n = 11-14 mice/group

Zhou et al., *Nut & Met*, 2007

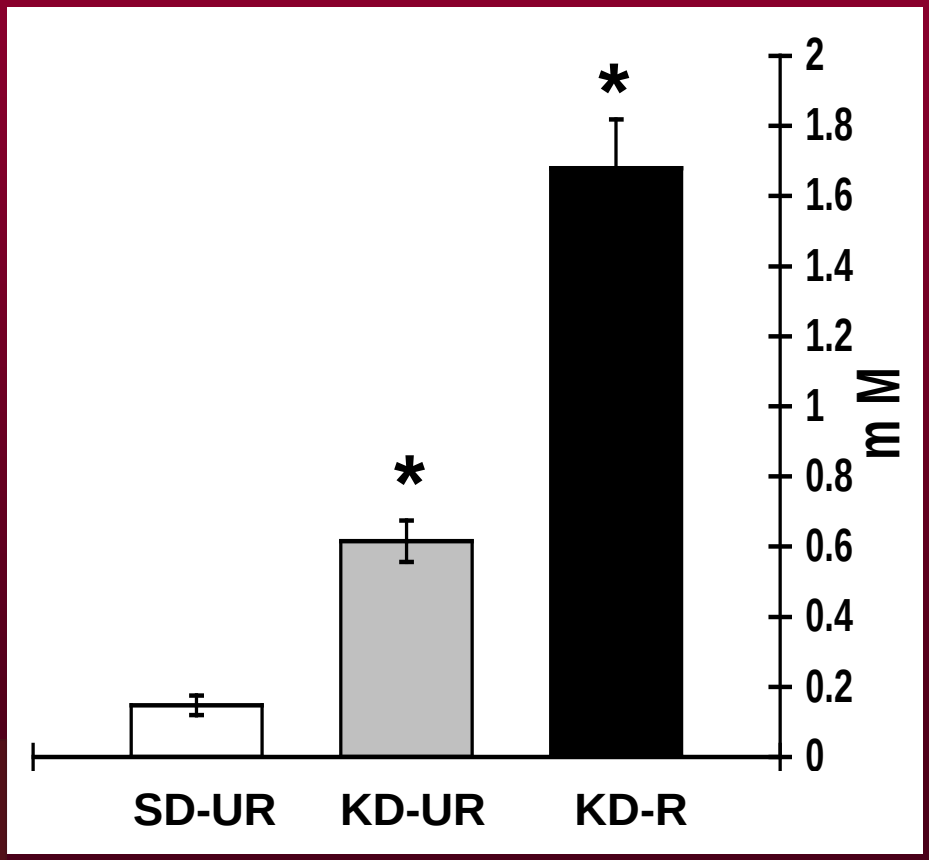
* P < 0.01

Influence of the KD-R on Plasma Glucose and β-OHB Levels in CT-2A Tumor-Bearing Mice

Blood Glucose



Blood β-OHB

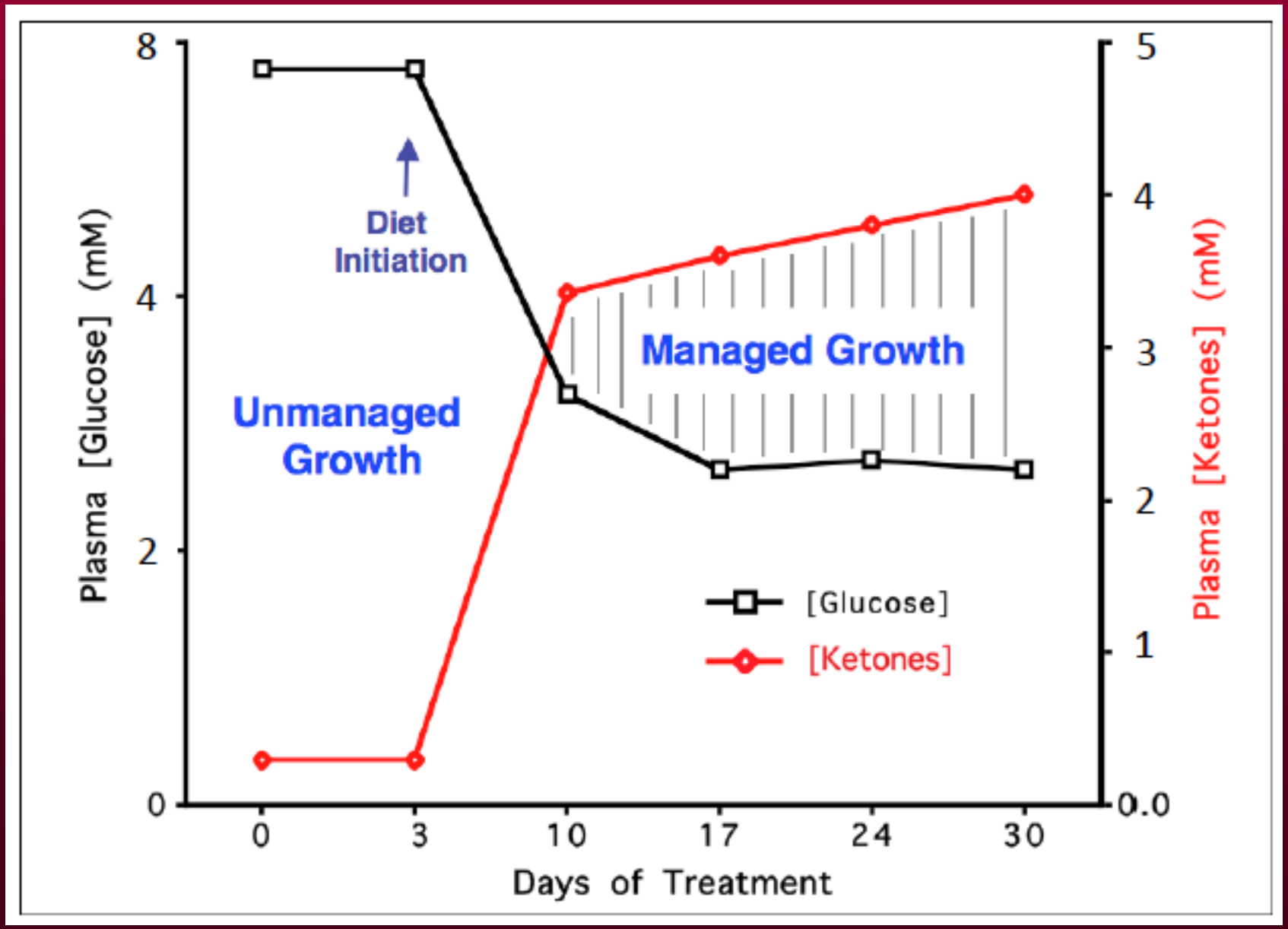


n = 11-14 mice/group

Zhou et al., *Nut & Met*, 2007

* P < 0.01

Metabolic management of cancer following changes in plasma glucose & ketones



Clinical Question

Can the KD-R be effective for the metabolic management of malignant brain cancer in patients?

Effects of a Ketogenic Diet on Tumor Metabolism and Nutritional Status in Pediatric Oncology Patients: Two Case Reports

Linda C. Nebeling, PhD, MPH, RD, Floro Miraldi, MD, PhD, Susan B. Shurin, MD, and Edith Lerner, PhD, LD, FACN

Journal of the American College of Nutrition, Vol. 14, No. 2, 202–208 (1995)

The results showed that a ketogenic diet, which reduced blood glucose and elevated blood ketones, could provide long-term management in two children with recurrent inoperable brain tumors

Zuccoli *et al. Nutrition & Metabolism* 2010, **7**:33
http://www.nutritionandmetabolism.com/content/7/1/33

Nutrition&Metabolism

BRIEF COMMUNICATION Open Access

Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case Report

Giulio Zuccoli*[1,5], Norina Marcello[2], Anna Pisanello[2], Franco Servadei[3], Salvatore Vaccaro[4], Purna Mukherjee[6] and Thomas N Seyfried*[6]

Patient: Female 65 yrs old, 64 kg (141 lbs)

12/5/08: Progressive memory loss, chronic headaches, nausea

GBM is Responsive to Metabolic Therapy

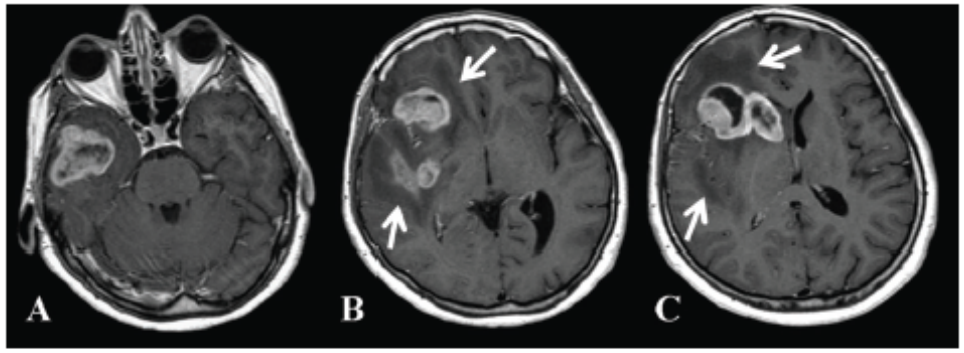


Figure 1 MRI contrast enhanced images of a large multi-centric mass involving the right hemisphere pole. (A) Temporal pole, (B) frontal operculum, insular lobe, posterior putamen, (C) frontal operculum, head of caudate nucleus. Note the presence of peripheral edema (arrows).

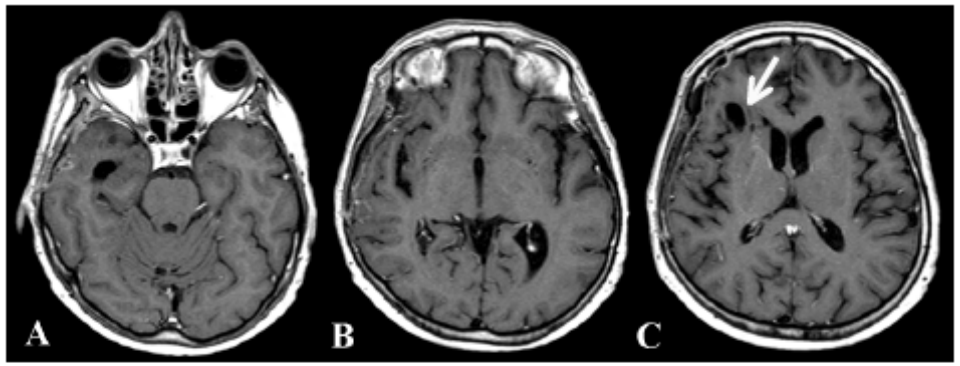


Figure 4 Brain MRI taken a few days after ending the standard radiotherapy plus concomitant temozolomide therapy together with KD-CR protocol. No clear evidence of tumor tissue or associated edema was seen. Arrow indicates porencephaly.

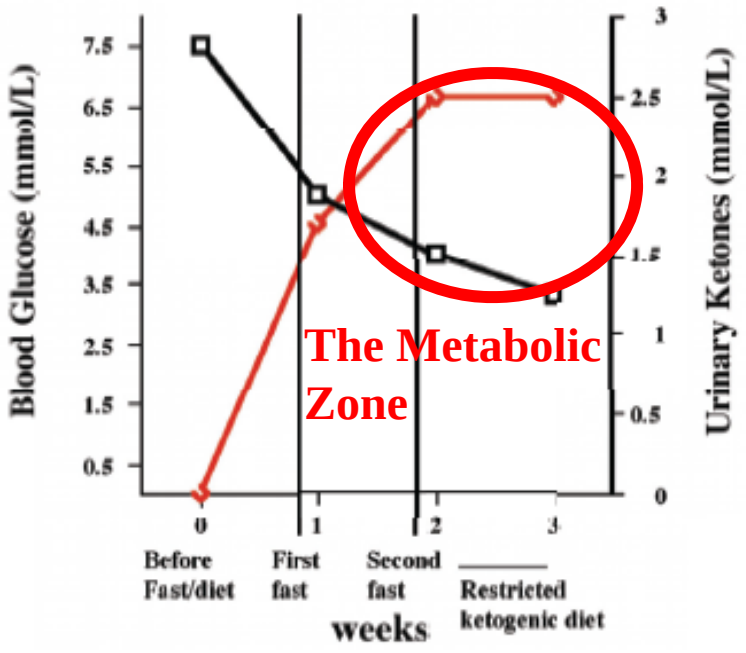
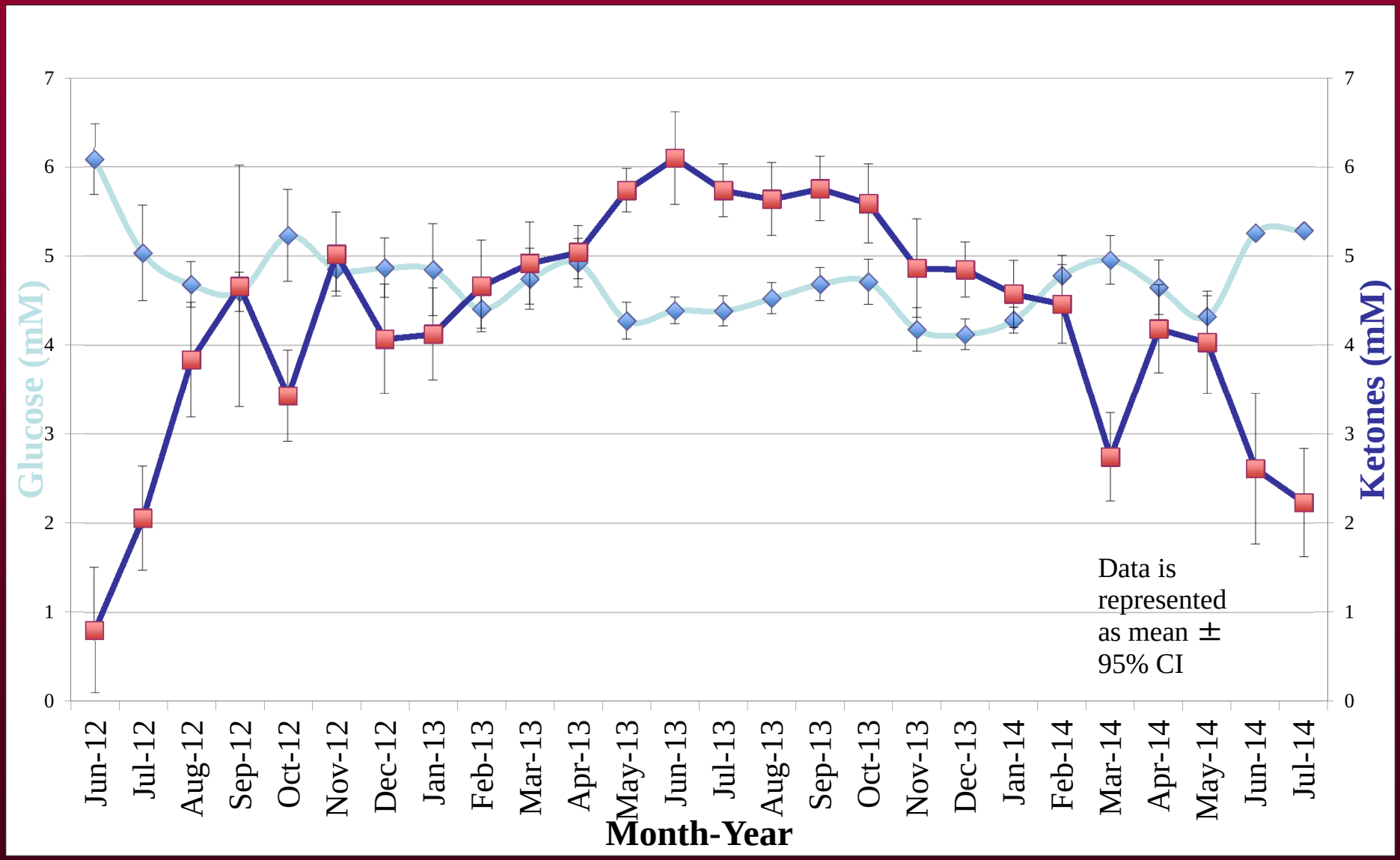


Figure 3 Levels of circulating glucose (black line) and urinary ketones (red line) in the patient during the period from January 8 to February 7, 2009. The values are within normal physiological ranges for people who maintain low calorie dieting [46].

Influence of a natural ketogenic diet on blood glucose and ketone levels in an adult patient with a diffuse, infiltrative brainstem glioma



Meidenbauer *et al. Nutrition & Metabolism* (2015) 12:12
DOI 10.1186/s12986-015-0009-2

Nutrition&Metabolism

METHODOLOGY Open Access

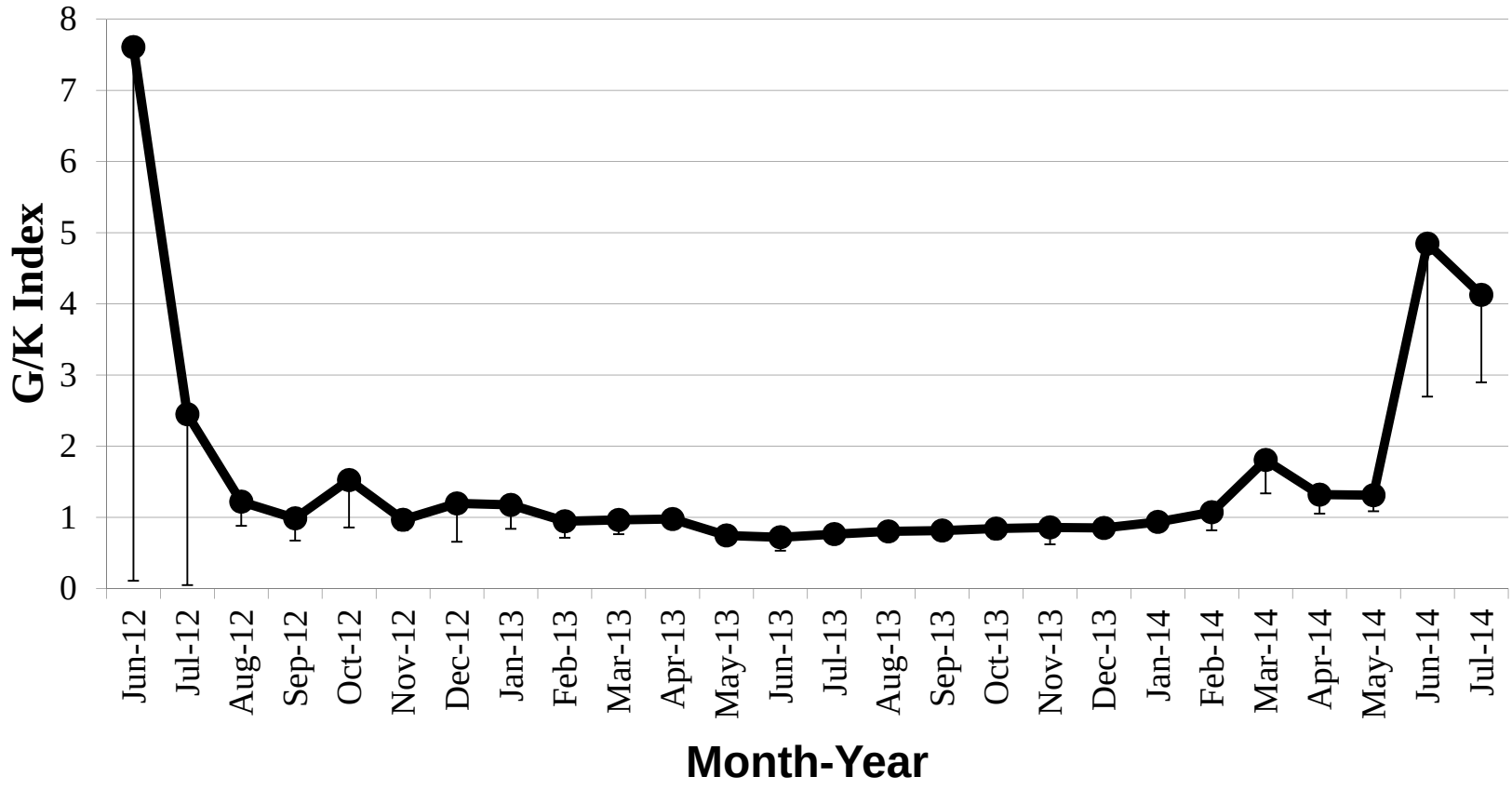
The glucose ketone index calculator: a simple tool to monitor therapeutic efficacy for metabolic management of brain cancer

Joshua J Meidenbauer, Purna Mukherjee and Thomas N Seyfried*

Glucose (mmol)/Ketone (mmol) = GKI

Therapeutic efficacy is considered best with index values approaching 1.0 or below

Influence of a natural ketogenic diet alone on the G/K Index in an adult patient with a diffuse, infiltrative brainstem glioma



n = 5-24 for Jun-12 – Sep-12
n = 28-32 for Oct-12 – Feb-14

Data is represented as mean ± 95% CI

The Press-Pulse Paradigm: A Novel Therapeutic Strategy for the Metabolic Management of Cancer

1. Cyclic Energy Stress Targets Mutated Tumor Cells:

   a. Calorie restricted ketogenic diet.

   b. Calorie restricted raw vegan diet.

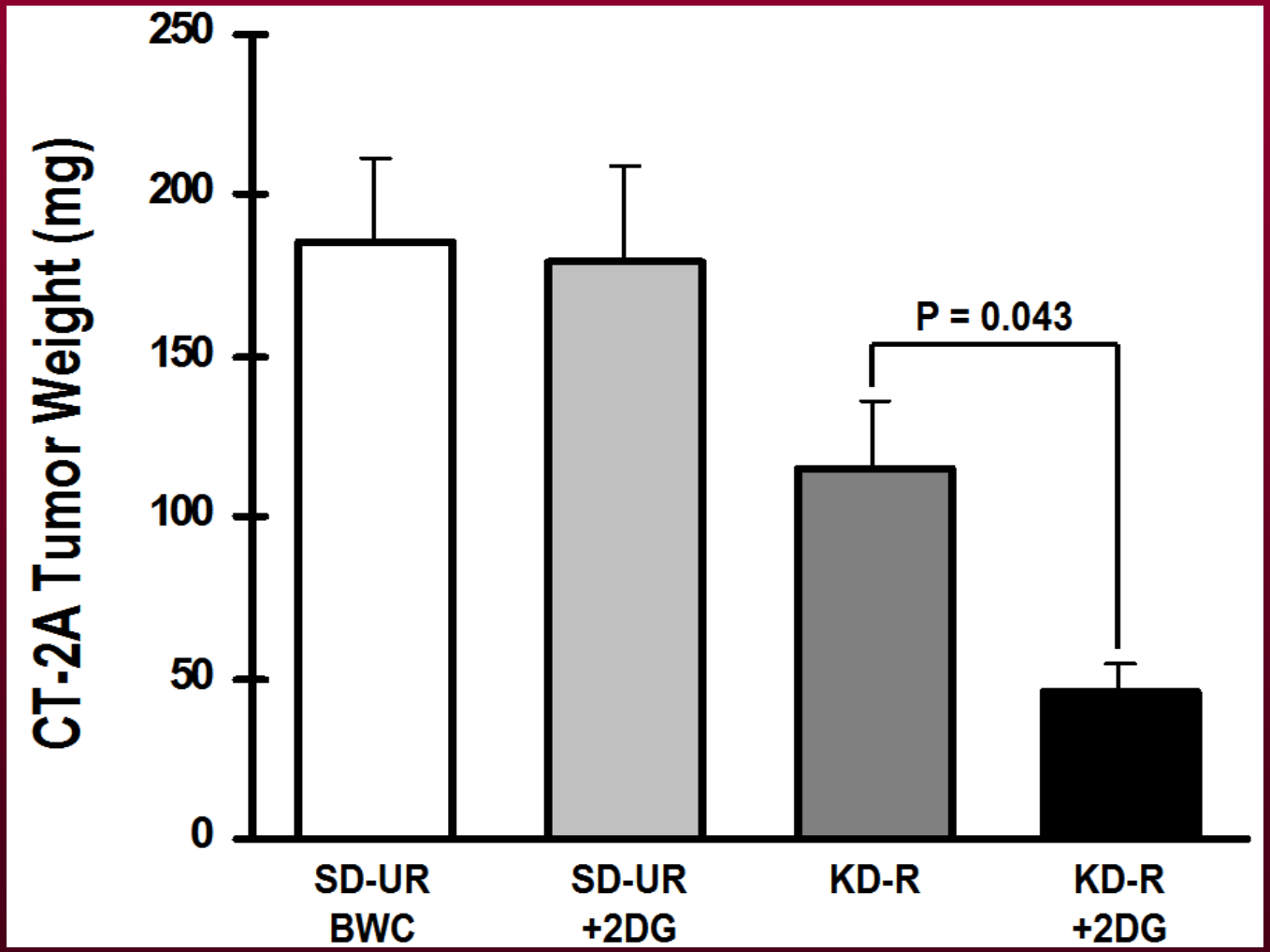
   } Press

   c. Hyperbaric oxygen therapy.

   d. Non-toxic drugs.

   } Pulse

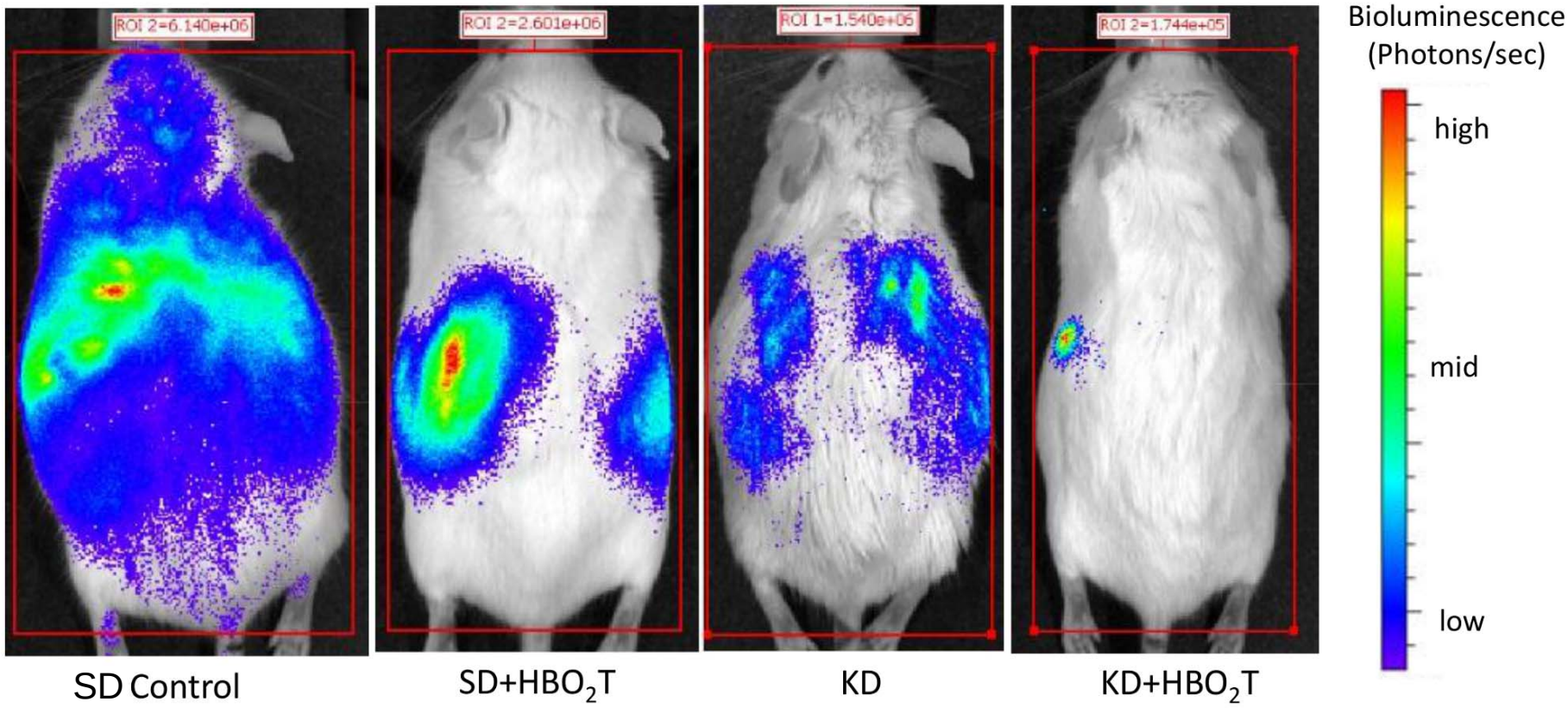
Press-Pulse therapy using the KD-R with the glycolysis inhibitor 2-DG for managing CT-2A astrocytoma



Dose: 25 mg/kg BW n = 3-6/group

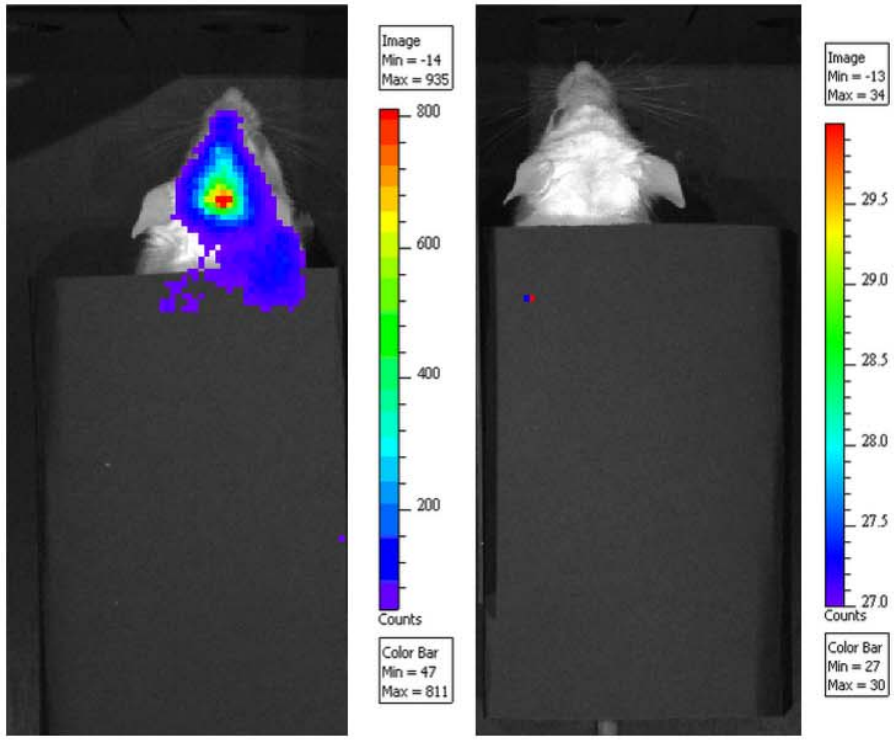
Marsh et al., Nutrition & Met

Press-Pulse therapy using the KD with hyperbaric oxygen for managing systemic metastatic cancer in VM mice

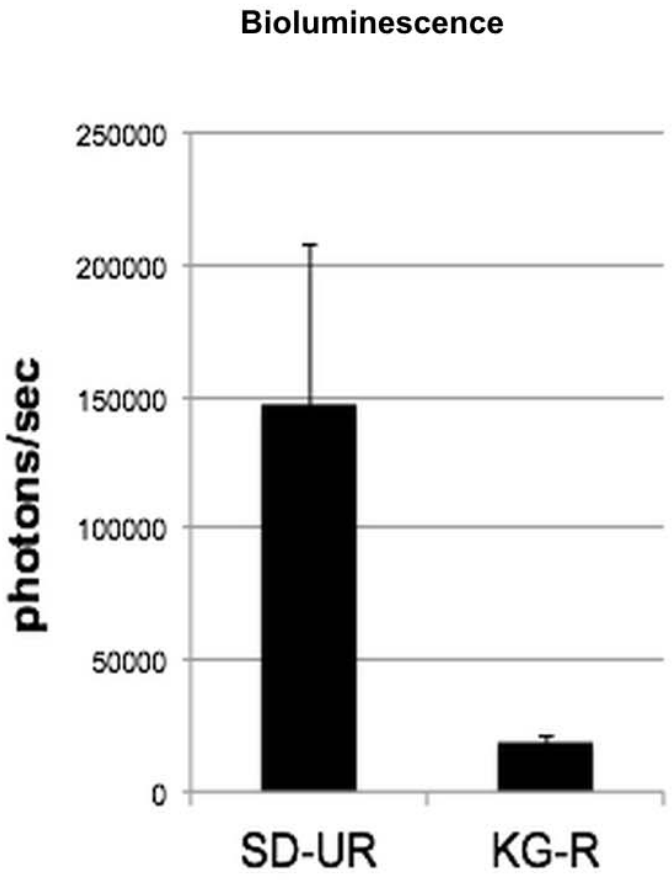


Poff, A., C. Ari, T. N. Seyfried, and D. P. D'Agostino (PLoS One, 2013)

Influence of a restricted ketogenic diet on brain metastases of the VM-M3 tumor cells:



SD-UR KG-R



N = 6/group

Akgoc et al (unpublished)

Influence of raw KD-R on mast cell tumor in a dog

July 2013

September 2013

April 2014

January 2015

introduction

Thematic Review Series: Calorie Restriction and Ketogenic Diets

Ketone Strong: Emerging evidence for a therapeutic role of ketone bodies in neurological and neurodegenerative diseases

Thomas N. Seyfried, ***Editorial Board***[1]

Biology Department, Boston College, Chestnut Hill, MA 02467

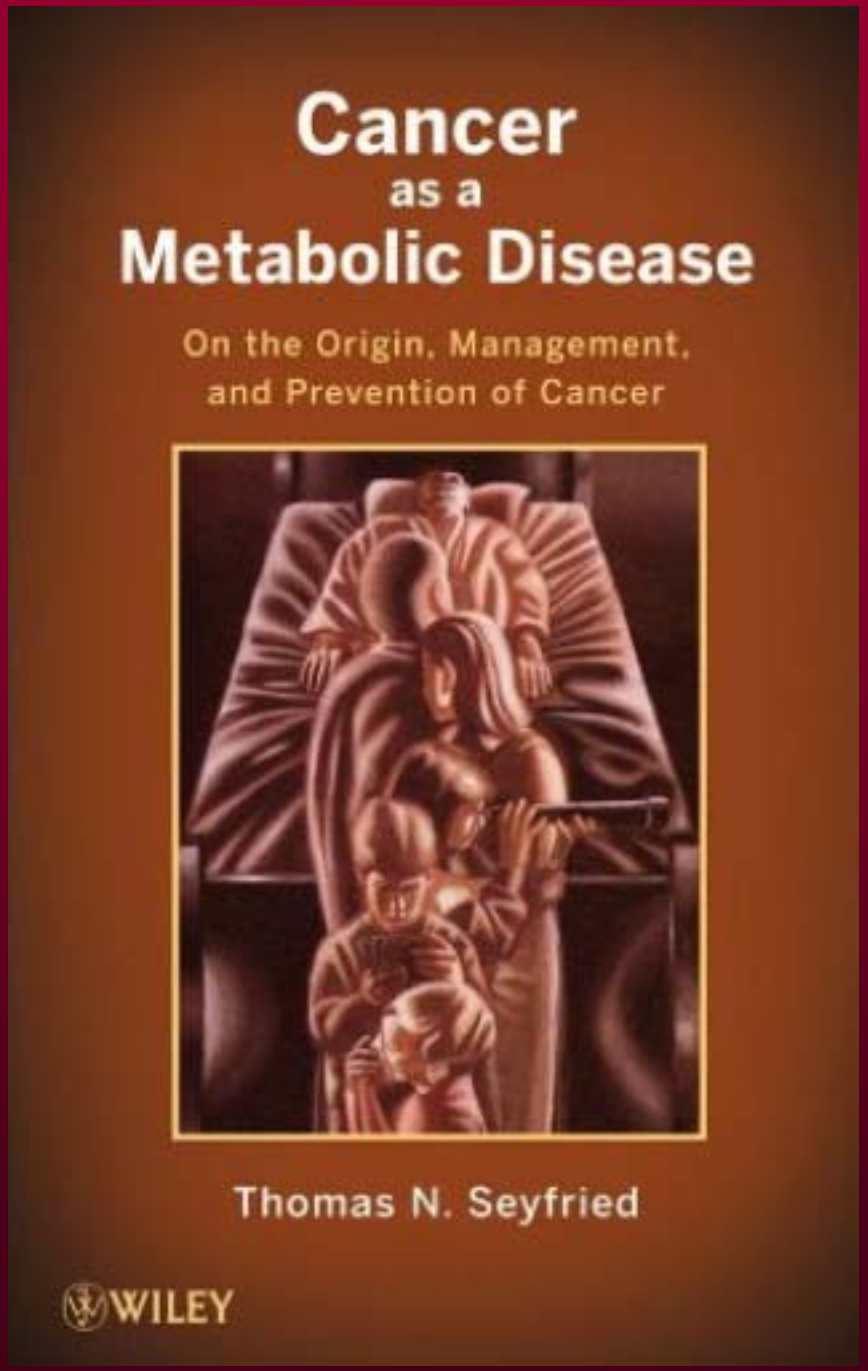
***Journal of Lipid Research*, Sep;55(9):1815-7, 2014**

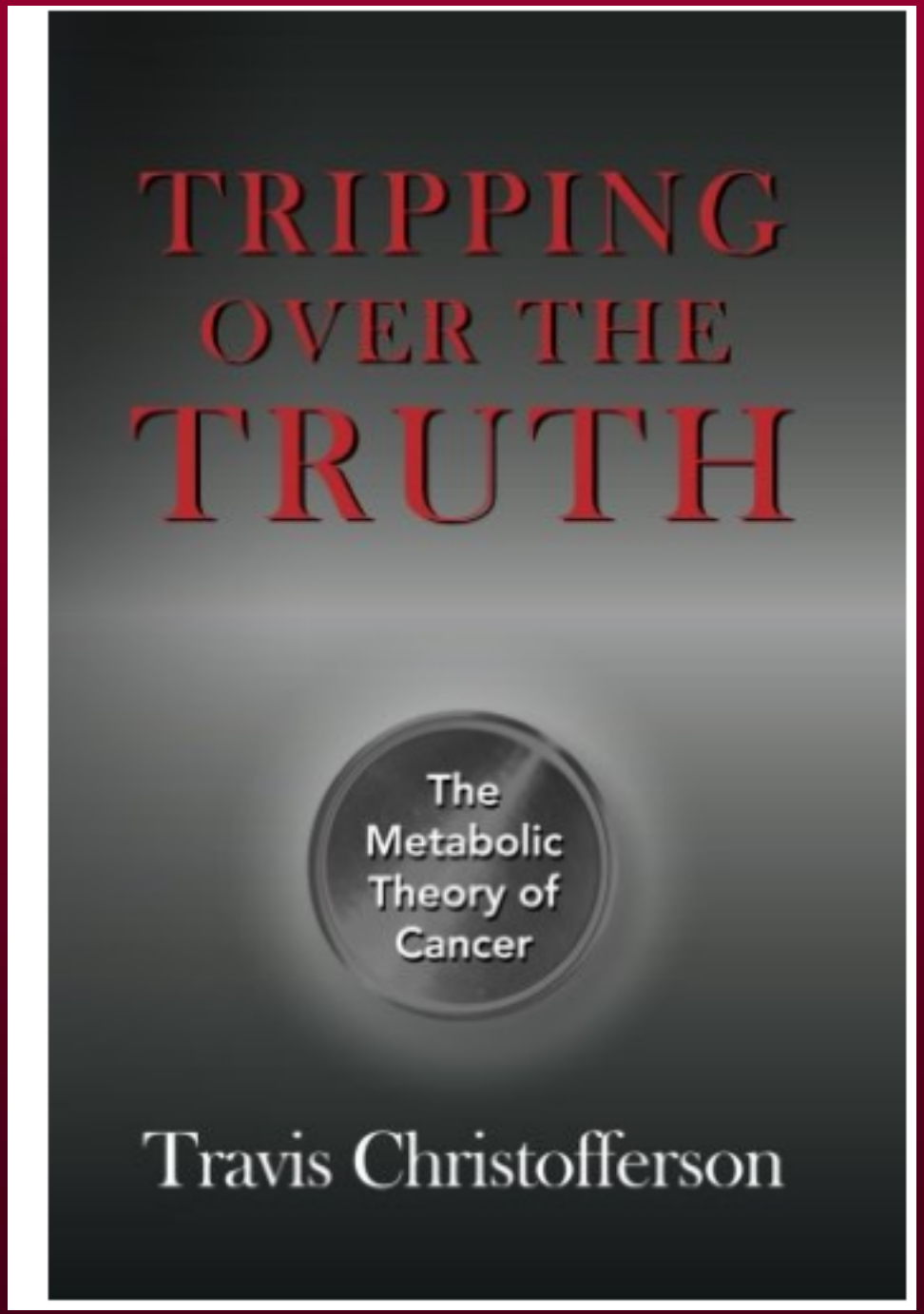
Conclusions

1.Cancer is a type of mitochondrial metabolic disease.

2. The GKI can be used to monitor success of metabolic therapy for cancer management.

3. The “Press-Pulse” paradigm can serve as a non-toxic therapeutic approach to cancer management.


Cancer
as a
Metabolic Disease
On the Origin, Management,
and Prevention of Cancer
Thomas N. Seyfried
WILEY


TRIPPING
OVER THE
TRUTH
The
Metabolic
Theory of
Cancer
Travis Christofferson

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