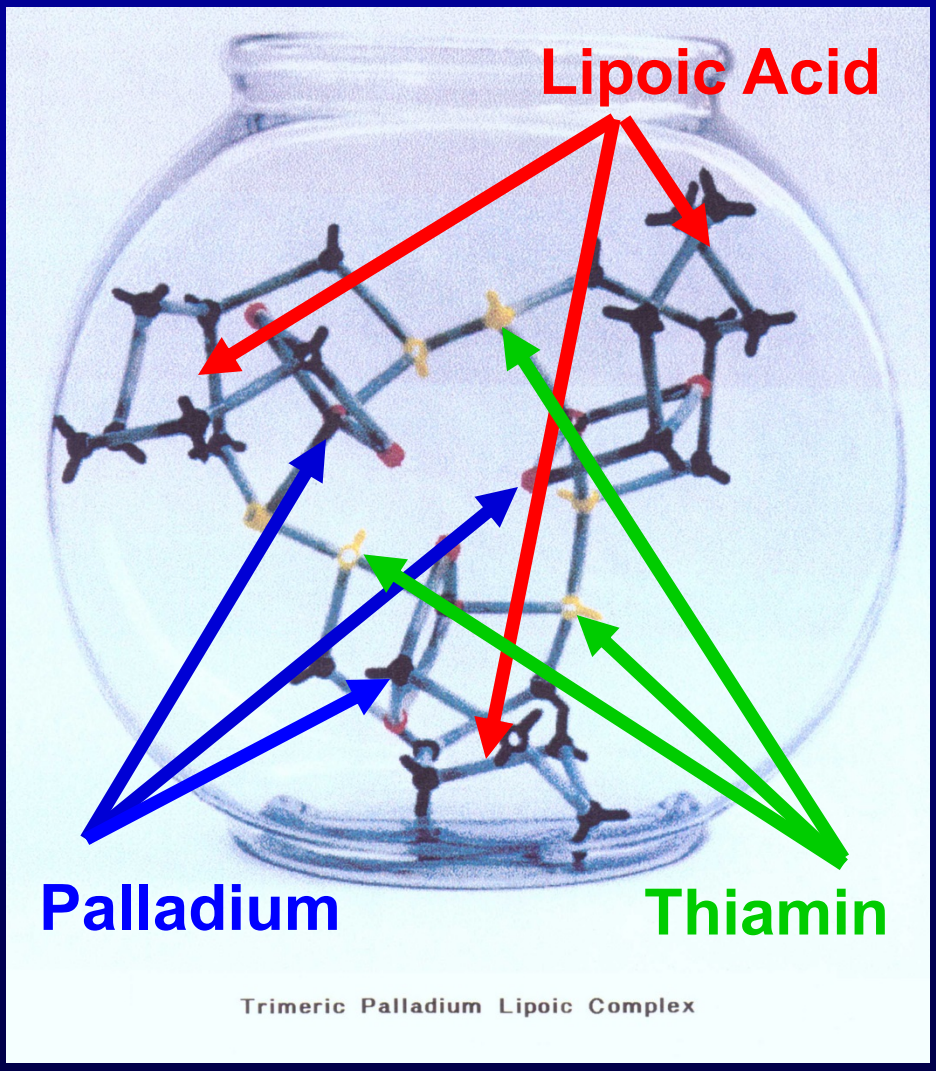
The Metabolic Role of Lipoic Acid Mineral Complex

Mitochondrial Health and Metabolic Regulation of Cellular Function in Degenerative Diseases

Dr. Frank Antonawich

An Introduction to
Lipoic Acid Mineral Complex

Lipoic Acid Mineral Complex (LAMC) belongs to a family of molecules developed by Dr. Merrill Garnett. It exists as alpha lipoic acid covalently bound to the mineral palladium, which is then associated with thiamine.



Lipoic Acid Mineral Complex (LAMC)

- **Differs from the potent free radical scavenger α lipoic acid since there is no free lipoic acid in the product - it is bound to palladium.**
- **This combination enhances its solubility in water and fat.**
- **Enhanced effectiveness – A polymer, rather than a single molecule, it provides a more efficient redox (accepting of a charge and donating the charge) reaction.**
- **This is NOVEL to free radical biology because palladium, which is a transition mineral, serves as a highly efficient aerobic catalyst.** (Stahl et al., 2005).
- **Therefore, LAMC is not only a potent free radical scavenger, but it also provides CELLULAR ENERGY by facilitating aerobic metabolism.**
  - Sudheesh, et al., *Food Chem Toxicol*. 2009 Aug; 47(8): 2124 -8.
  - Menon, et al., *Int. J. Low Radiation*. 2009 Vol. 6 (3): 248-262.
  - Sudheesh, et al., *Food Chem Toxicol*. 2010 Jul;48(7):1858-62.
  - Ramachandran et al., *Cancer Biother Radiopharm*. 2010 Aug; 25(4): 395-9.
  - Krishnan and Garnett, M. "Passivation of Metals and Semiconductors, and Properties of Thin Oxide Layers", 2006, P.Marcus and V. Maurice (Editors), Elsevier, Amsterdam, p 389-394.
  - Janardhanan et al., 2008

ORAC Comparisons

ORAC

(Oxygen Radical Absorbance Capacity)

(expressed as Trolox equivalent per gram)

Vitamin A = 1.60 (2,800)

Vitamin C = 1.12 (1,890)

Vitamin E = 1.00 (1,700)

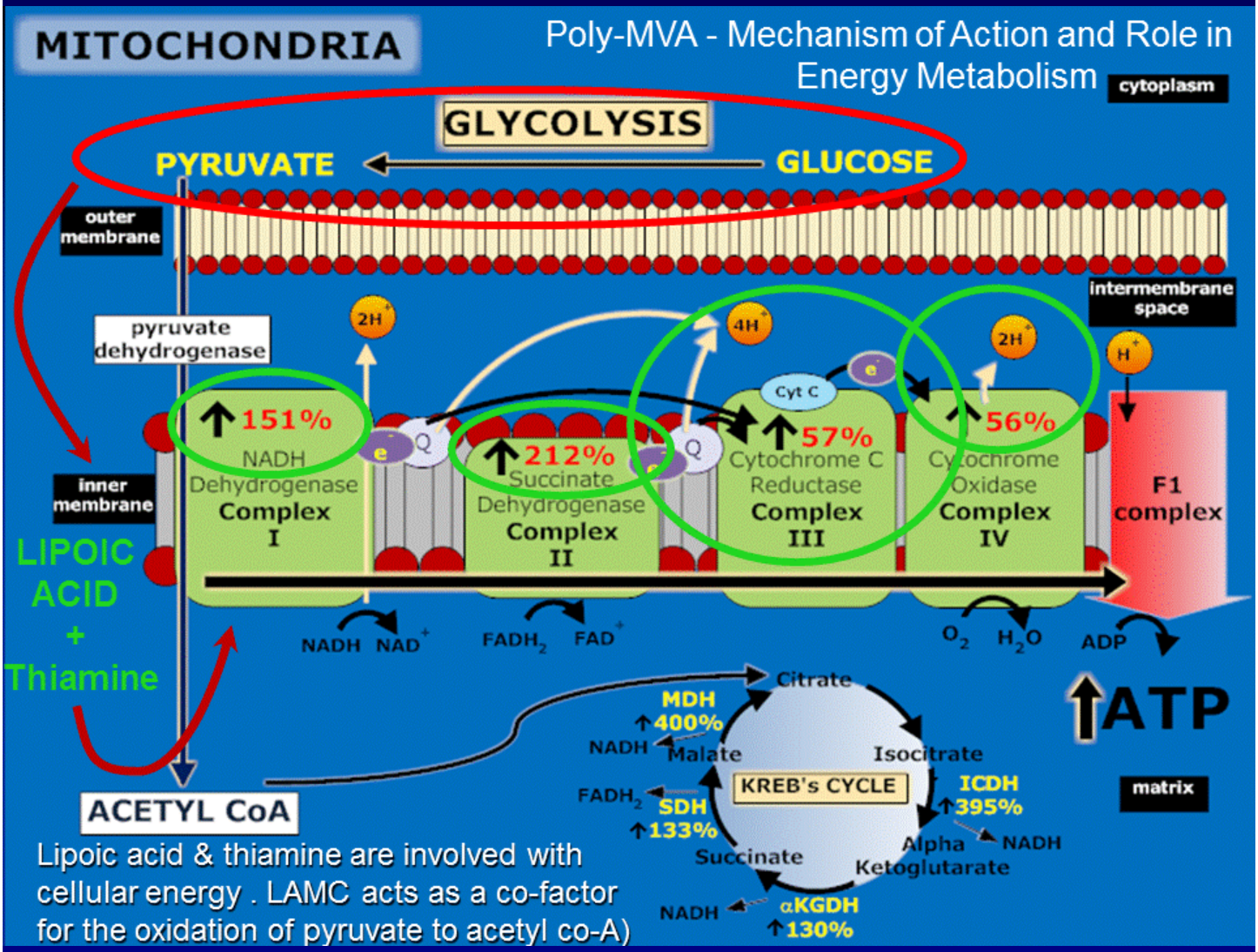
Melatonin = 2.04 (3,468)

Lipoic Acid = 1.40 (2,400)

LAMC = 5.65 (9,605)

Brunswick Labs, Wareham, MA

Benefit of LAMC at the Mitochondria



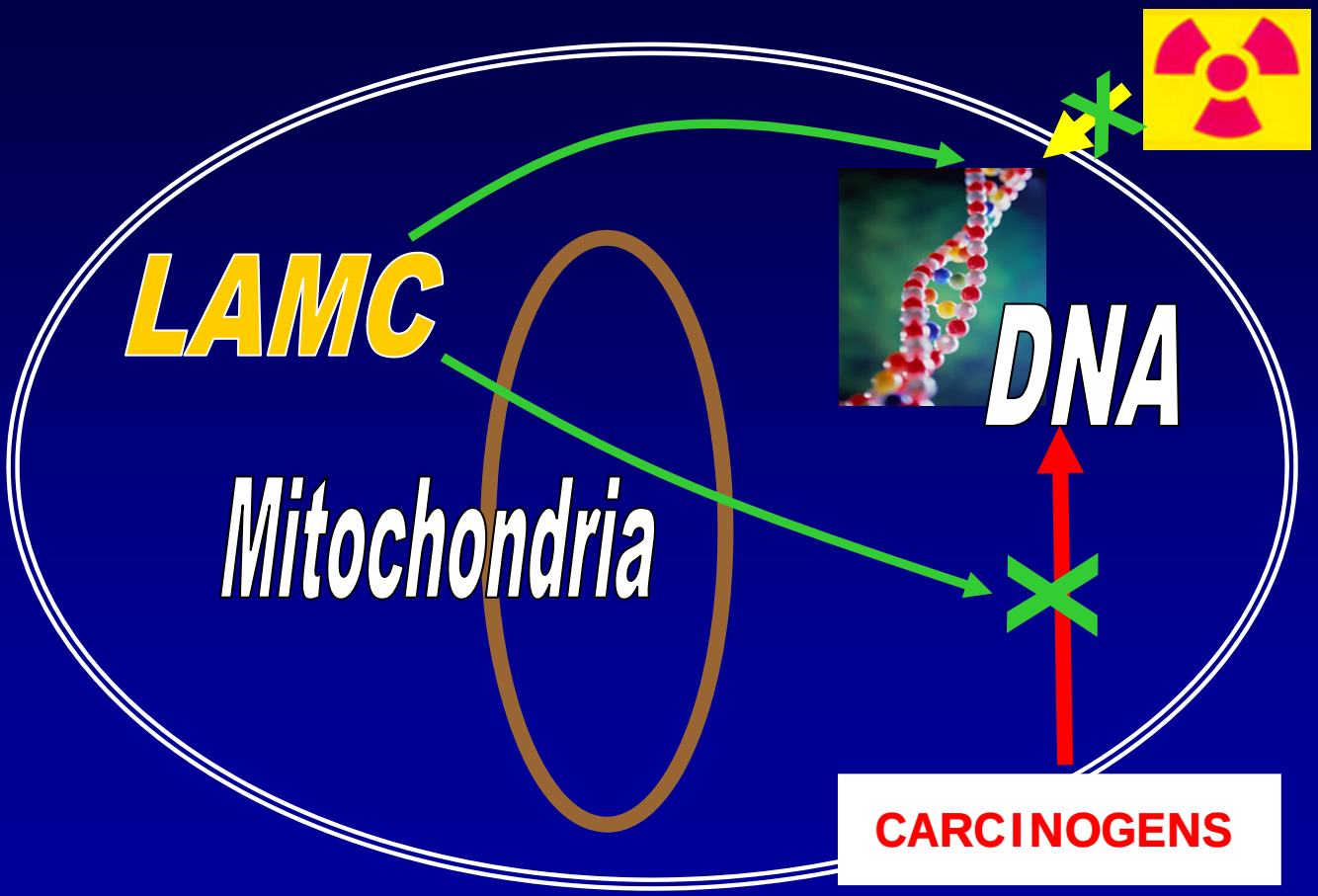
- This figure summarizes the influence of LAMC on the activities of the Krebs cycle enzymes and mitochondrial respiratory enzymes. The percentage increases in enzymatic activities is indicated by an upward arrow.

  – **Sudheesh, et al.,** *Food Chem Toxicol*. 2009 Aug; 47(8): 2124 -8.

Relationship of LAMC and Other Free Radical Scavengers

- Other monomolecular structures (i.e., vitamins C & E, ubiquinone {Co-Q10}, melatonin, glutathione), while beneficial, do not demonstrate or have the same redox potential.
  (see previous ORAC values).

- LAMC and Co-Q10 demonstrate synergism, structurally stabilizing the electron transport chain as well as facilitating electron transfer. In addition, PUFA (e.g. DHA) potentiate LAMC's benefit by providing an additional electron source.



Transfer of Cellular Energy

The original LAMC family member, DNA Reductase, was named for its ability to shunt electron energy from itself to DNA. By donating electrons, DNA can be reduced, and thus oxidation as a result of things like radiation and carcinogens, can be combated.

LAMC and Radiation Protection

- **Peer-reviewed radiation research studies have demonstrated the ability of LAMC to provide:**
  1. **DNA protection and repair**
  2. **Chromosomal protection**
  3. **Blood cell protection**
  4. **Anti-oxidant activity**
  5. **Increased spleen colony formation**
  6. **Attenuation of radiation-induced weight loss**
  7. **Repair cardiac mitochondrial damage in a model of radiation-induced heart disease**

Sridharan, V., Seawright, J., Antonawich, F.J., Garnett, M., Cao, M., Singh, P., Boerma, M. (2017) Late Administration of a Palladium Lipoic Acid Complex (Poly-MVA) Modifies Cardiac Mitochondria but not Functional or Structural Manifestations of Radiation-Induced Heart Disease in a Rat Model. *Journal of Radiation Research* 187(3): 361-366.

LAMC and Radiation Protection

- Applications for radiation protection:
  - Radiation accidents/exposure
  - Diagnostic exposure for staff
  - Protection of patient's normal tissue during radiotherapy
  - Attenuating radiation exposure in outer space

Enhanced Radiotherapy

- **LAMC is a redox molecule that not only has the potential to quench radicals to protect tissues, but at higher dosages it can donate electrons to potentiate radiation therapy.**

- **The combination of LAMC supplement and radiation was better than either of them alone (63% and 64%, respectively) in reducing solid tumor size in rodents (80% inhibition).**

Veena RK, Ajith TA, Janardhanan KK, Antonawich F. (2016) Antitumor Effects of Palladium-α-Lipoic Acid Complex Formulation as an Adjunct in Radiotherapy. *Journal of Environmental Pathology, Toxicology and Oncology*, 35(4):99-107.

SAFETY / TESTING

Ames Tests were conducted by an independent lab (PHARMAKON USA) and all mutation tester strains were NEGATIVE.

Acute toxicity studies (14 days) were conducted. Mice were first administered dosages as high as 5,000 mg/kg to determine tolerance (typical human cancer supplemental amount is only 20 mg/kg). 5,000 mg/kg was administered to 10 mice of both sexes for 14 days. Upon necropsy, all organs were CLEAN and there were no clinical signs following oral administration. (PHARMAKON USA)

CALVERT LABORATORIES, INC. performed chronic toxicity studies (90 days) orally in rats (15 per group in both sexes) at two dosages (18 mg/kg and 36 mg/kg). Chronic studies revealed no animal deaths or clinical symptoms.

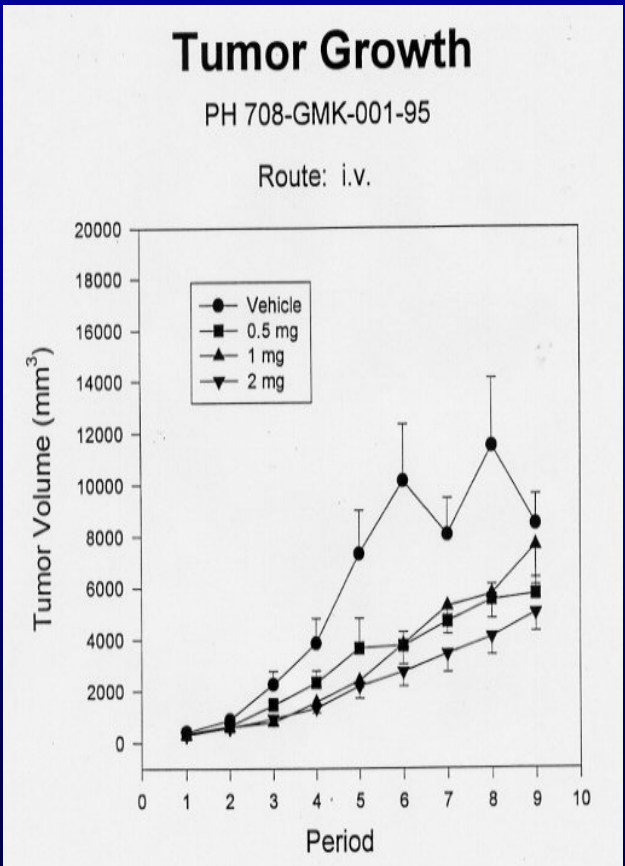
HUMAN LAMC SAFETY

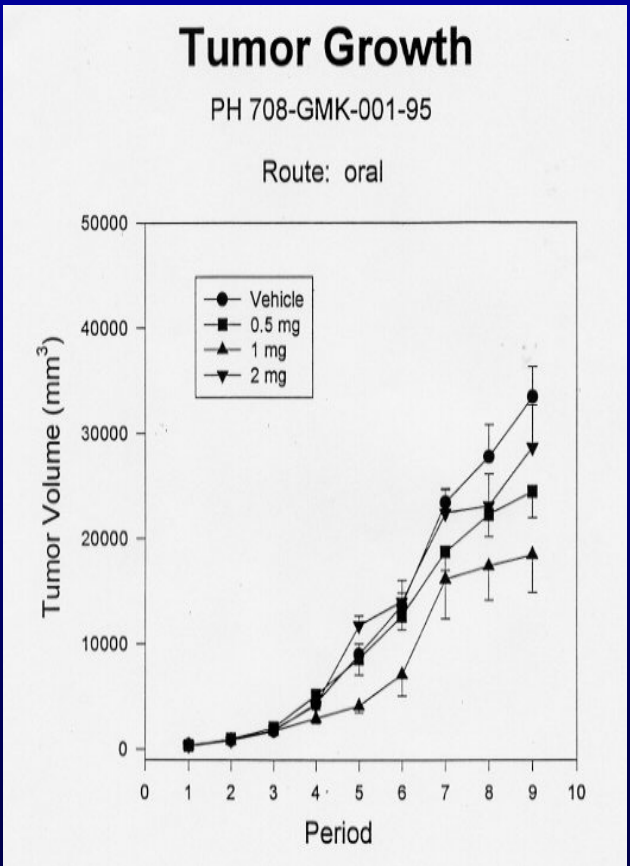
- DESSTINI = Dose Escalation Safety Study In Normal Individuals taking LAMC
  - A major research university completed a dose-escalation safety study (either 2, 4 or 8 tsp./day) and kinetics profile of a LAMC formulation. This was an IRB-approved study which was monitored by a DSMB (Data Safety and Monitoring Board), as well as being granted an IND (Investigational New Drug) from the FDA.
  - There were no SAEs (Serious Adverse Effects) Overall, the tolerability of all three tiers was 93.3% and the DSMB deemed the compound to be safe. In addition, they provided the Investigators consent to continue with a subsequent glioblastoma trial.

EFFECTIVENESS

LAMC effectiveness was first independently demonstrated on the growth of a glioblastoma tumor cell line in nude mice. Tumors were allowed to establish and mice were divided into 8 groups of 10 mice, treated daily for 4 weeks with either vehicle or 0.5, 1, or 2 mg/ mouse. After measuring the tumor size twice a week, both routes of administration reduced its size.

(CALVERT LABORATORIES, INC.)





- **HUMAN:** Thus far, the LAMC complexes have demonstrated anecdotal clinical effectiveness in over 20 different types of cancer.

- **IN VITRO:** KGK Synergize Inc., an independent laboratory in Canada, examined the effectiveness of LAMC on 9 different cell lines to confirm prior research findings. These lines included: melanoma (SKMel-5), liver (Hep G2), lung (Malme-3M), mammary gland (MDA-MB 435), prostate (LNCaP), Colon (HT-29), astrocytoma (U87), glioblastoma (H-80), and osteosarcoma (CCL-183).

- **LAMC** was effective to varying degrees on the entire group of cell lines tested. The varying effectiveness appeared to be a consequence of the particular cell lines used and their associated degree of anaplasia.

Veterinary Safety & Effectiveness

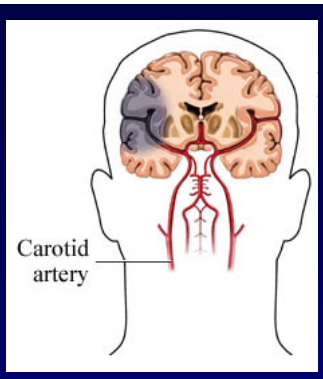
- The largest integrative cancer investigation of LAMC was an open-label veterinary oncology program, with over 900 dogs enrolled since its inception in January 2004.

- The LAMC seemed most effective in the cases of solid tumors (i.e. soft tissue sarcoma, hemangiosarcoma, mast cell, transition cell carcinoma, lung, anal sac carcinoma, renal carcinoma, squamous cell carcinoma, fibrosarcoma, melanoma, menigioma, neuroblastoma, mammary adenocarcinoma)
  - Patients received the LAMC supplement POLY-MVA as part of their chemotherapy, radiation and/or surgical protocol at a dosage of 1mL/5 lbs. P.O. twice daily (equivalent human dose of approximately 8 tsp.).

- In the canine osteosarcoma study, LAMC enhanced median survival, as well as improved objective parameters (i.e. weight, anemia, liver and kidney function).

- The quality of life survey for these animals resulted in an 86% improvement.

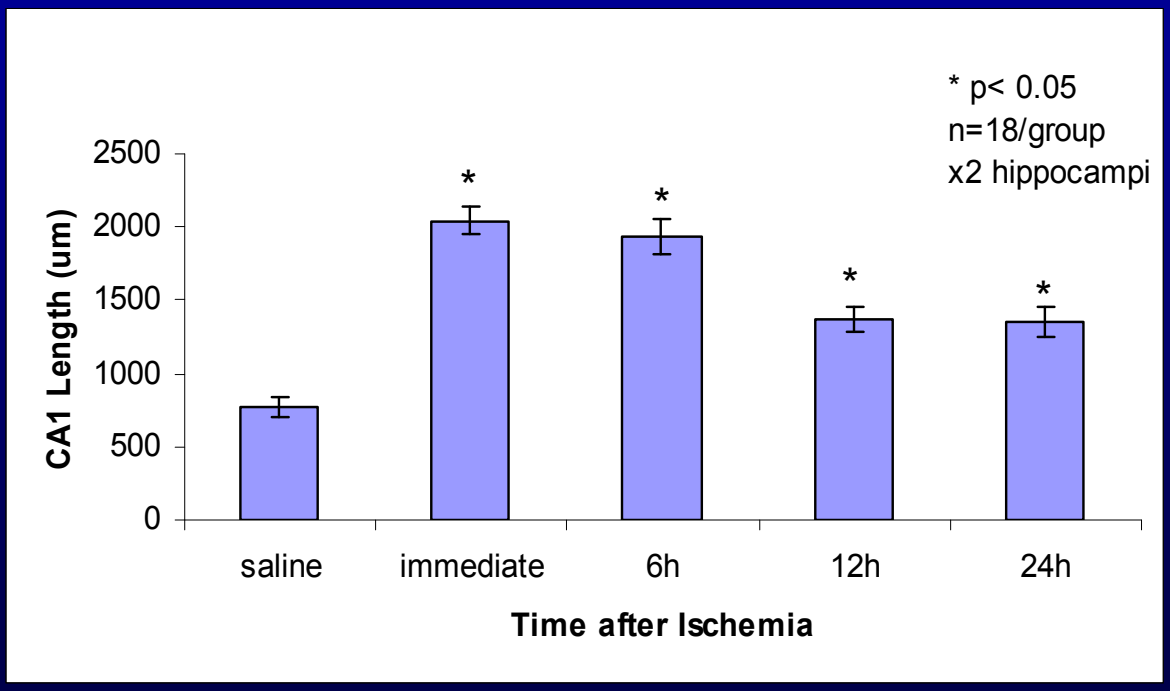
Ischemic Protection



- The ability of LAMC formulation to both quench radical species and shunt electrons down the electron transport chain also makes it **effective in limiting ischemic damage.**

(Antonawich, et al., *Experimental Neurology*, 2004) (Antonawich and Welicky, 2007)

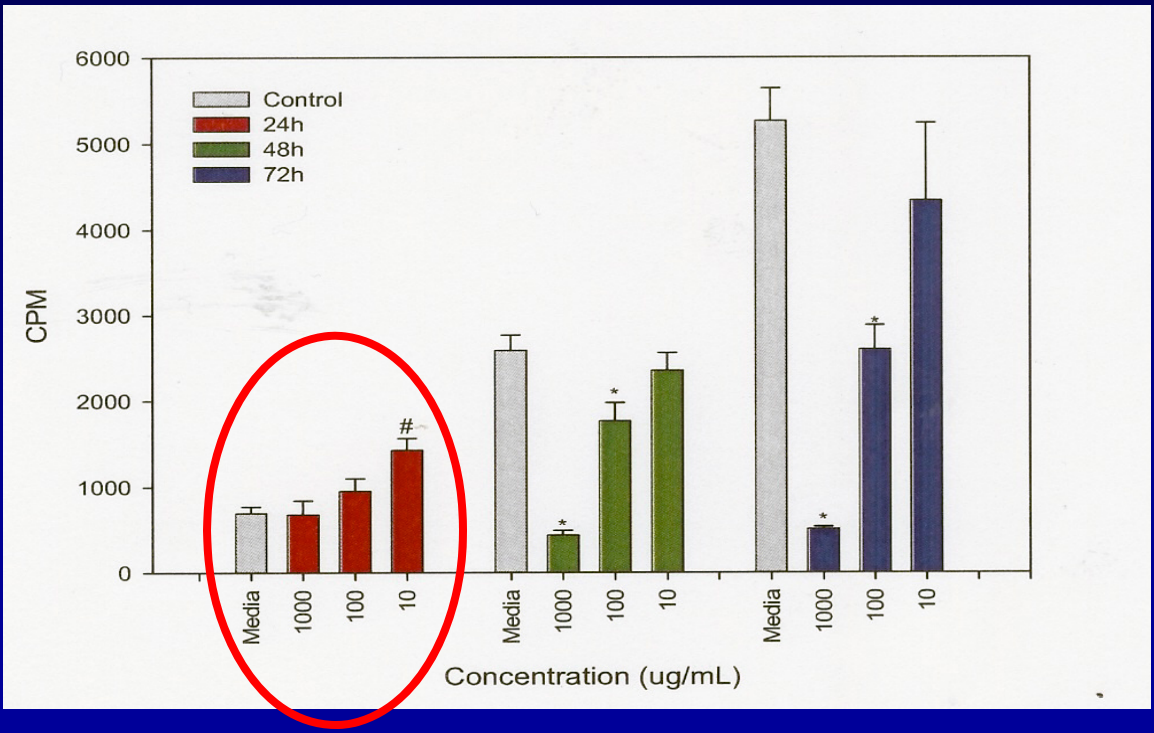
- We have demonstrated that LAMC **protects the CA1 region of the hippocampus** from transient global ischemia, even after delayed administration and **maintains behavioral function as well.**



Mechanism of Action

How can LAMC induce cancer cell death, yet rescue and *provide energy* to an ischemic or normal cell?

Mechanism of Action

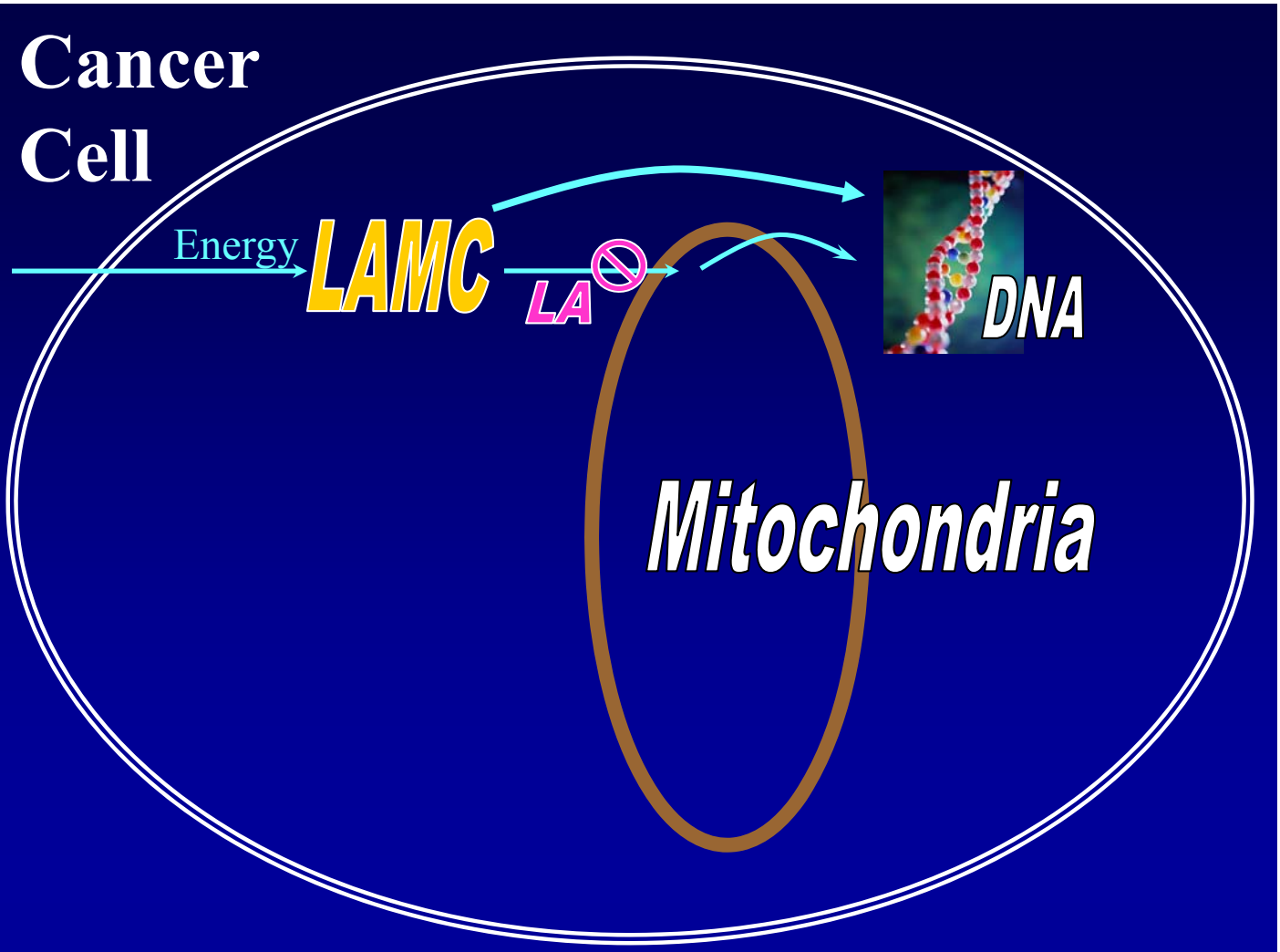


- Peer-reviewed experiments demonstrate an enhanced mitochondrial "load" resulting in **increased metabolic effectiveness.**

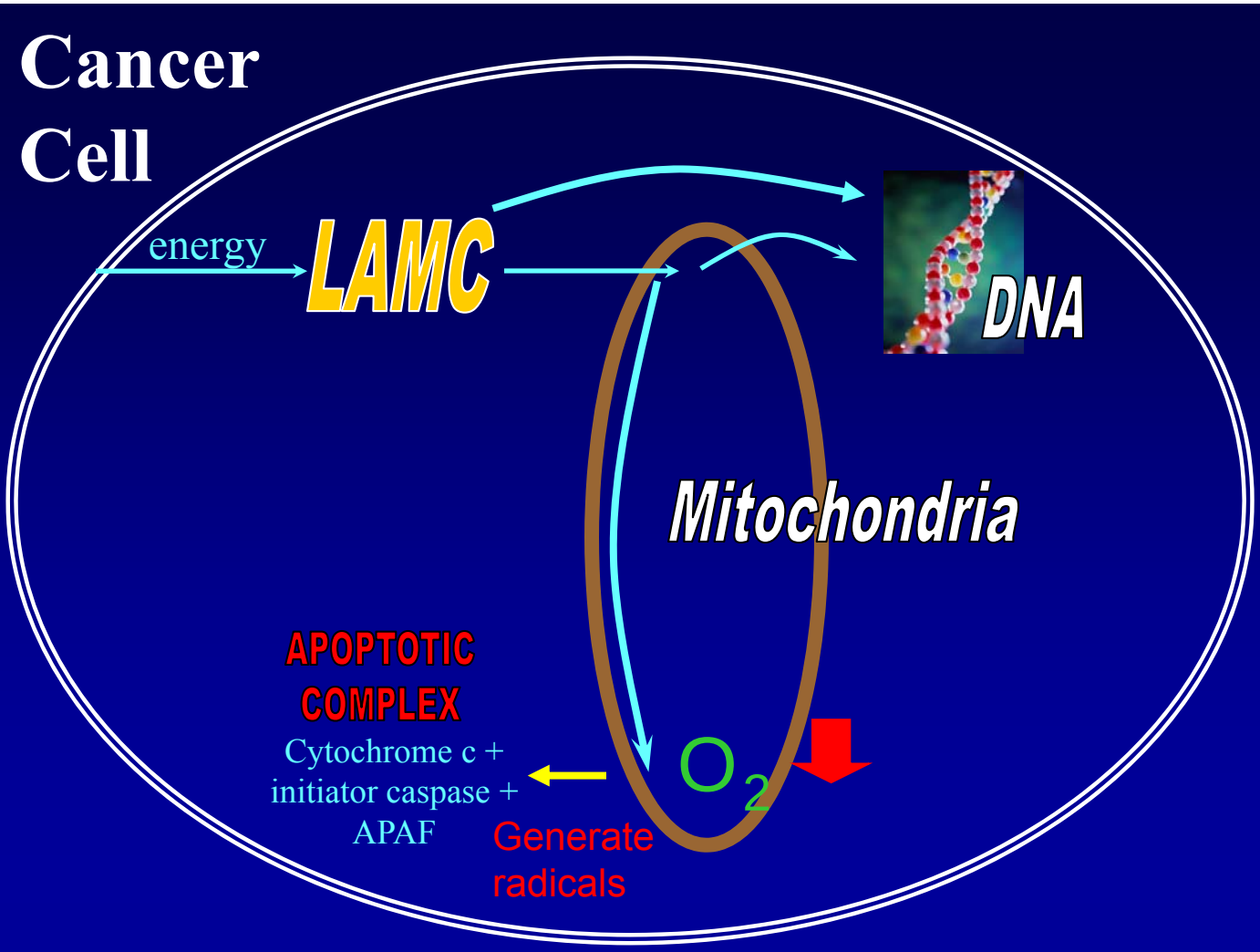
- However, it appears that once an energy "**threshold**" is reached the neoplastic cells die. (Low dosages - need an extended timeframe of exposure to initiate cell death usually via apoptosis. Higher dosages - an early energy boost is followed by necrosis or apoptosis.)

Mechanism of Action

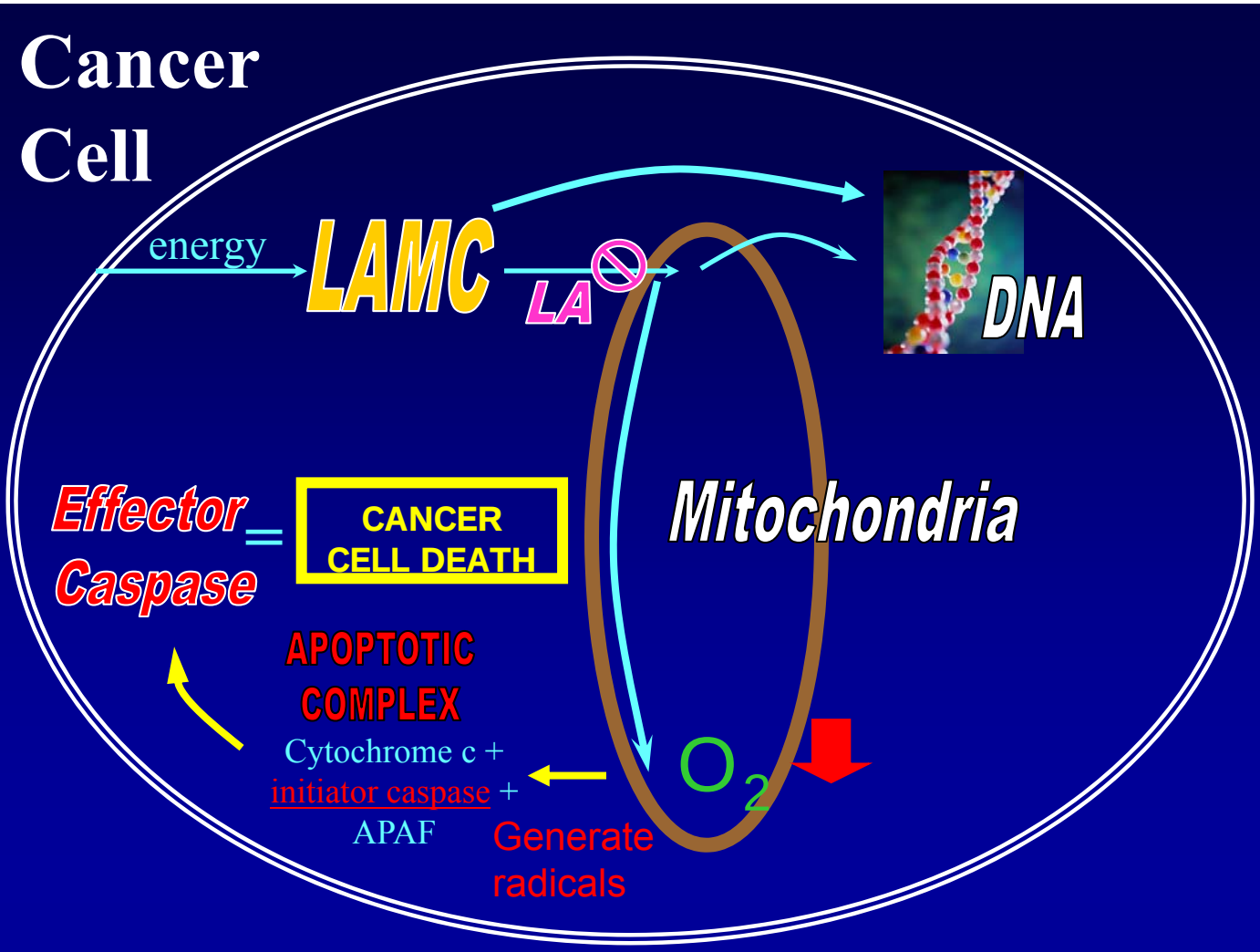
While LAMC has the ability to shuttle energy to each cell, the selective vulnerability of the cancer cell is due to its disrupted metabolic state.
The next few diagrams will outline this mechanism.



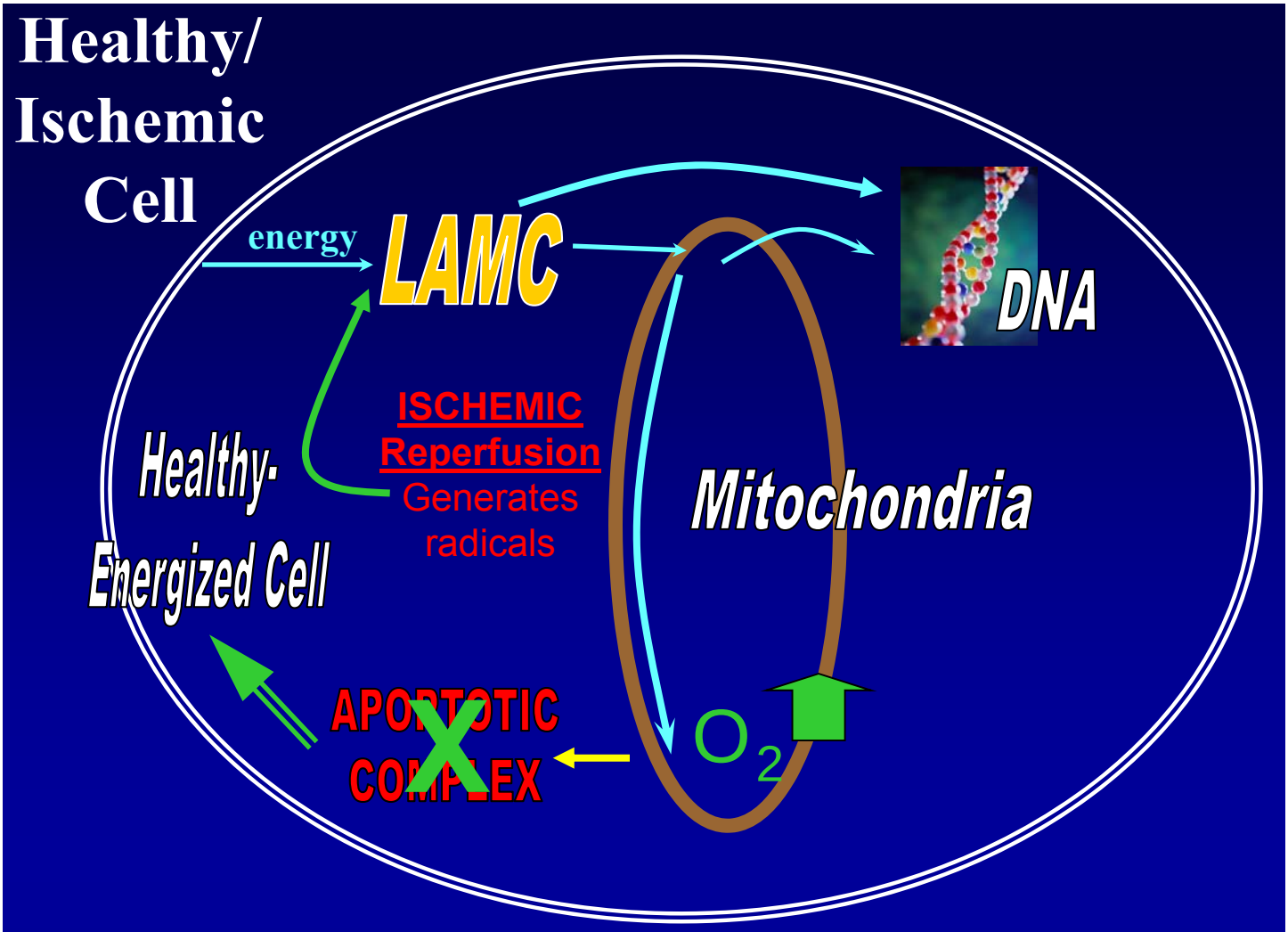
When LAMC is administered to a cell, electrochemistry data demonstrates the **transfer of electrons** from the plasma membrane to DNA (since the plasma membrane is a "fluid" and "flexable" structure, its integrity is not compromised). However, this transfer is also directed **to or via the mitochondria.**



Excess energy that travels down the electron transport chain cannot be accepted since **malignant cells function in an oxygen poor environment (hypoxia).** This results in the generation of local radicals at the mitochondrial membrane, facilitating cytochrome c release and subsequent activation of an apoptotic complex.

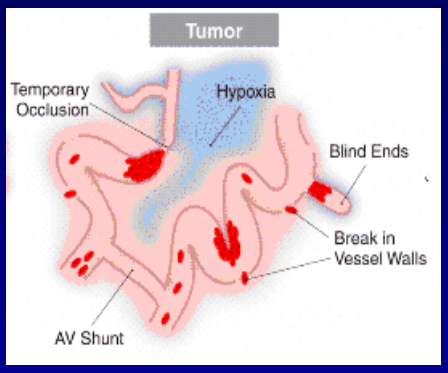


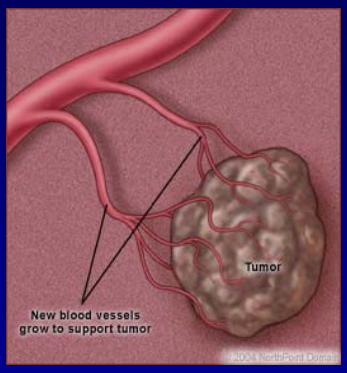
- An activated initiator caspase will turn on others in the caspase family of enzymes. The effector caspases result in cell apoptosis and eventually cancer cell death.

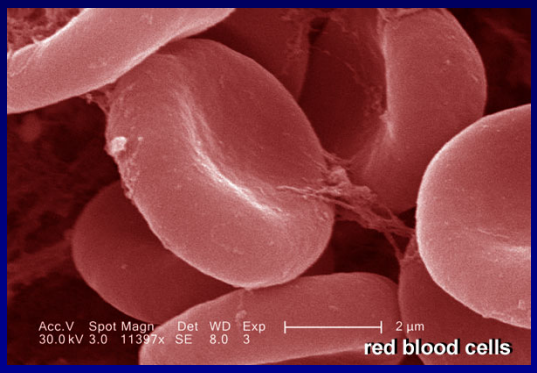


In a healthy or ischemic cell (which was healthy seconds earlier), oxygen is available to absorb the excess energy. This will prevent the formation of the apoptotic complex. Furthermore, the mitochondrial permeability transition will be maintained in the ischemic cell. Since LAMC is a potent free radical scavenger, any generation of radicals via reperfusion can be quenched.

Metabolic Dysfunction in Cancer Cells?







- Low oxygen in cancer cells, due to problems with tissue perfusion and oxygen diffusion, triggers a cascade of events initiated by:

HIF = <u>Hypoxia Inducing Factor</u>

- In a normal oxygen state HIF is catalytically destroyed.
- HOWEVER, in a cancer cell HIF allows them to physiologically adapt to their environment, regardless of subsequent oxygen availability.

Metabolic Dysfunction in Cancer Cells?

- This physiological adaptation occurs when HIF modulates pyruvate kinase, restricting malignant cells to rely primarily on anaerobic metabolism (glycolysis) for energy, which is extremely inefficient.
- This is now being referred to as "metabolic anaplasia", since the cells are regressing in their metabolic specialization.

❖ **LAMC's BENEFIT:**

By directing electrons to the aerobic metabolic cascade, LAMC exploits this dysfunction. Additional studies have demonstrated that LAMC attenuates the increases in HIF.

POSSIBLE LAMC APPLICATIONS

-CANCER SUPPORT

-STROKE and HYPERTENSION

-TRANSIENT ISCHEMIC ATTACK -TIA

-CARDIAC ISCHEMIA

-DEGENERATIVE CONDITIONS

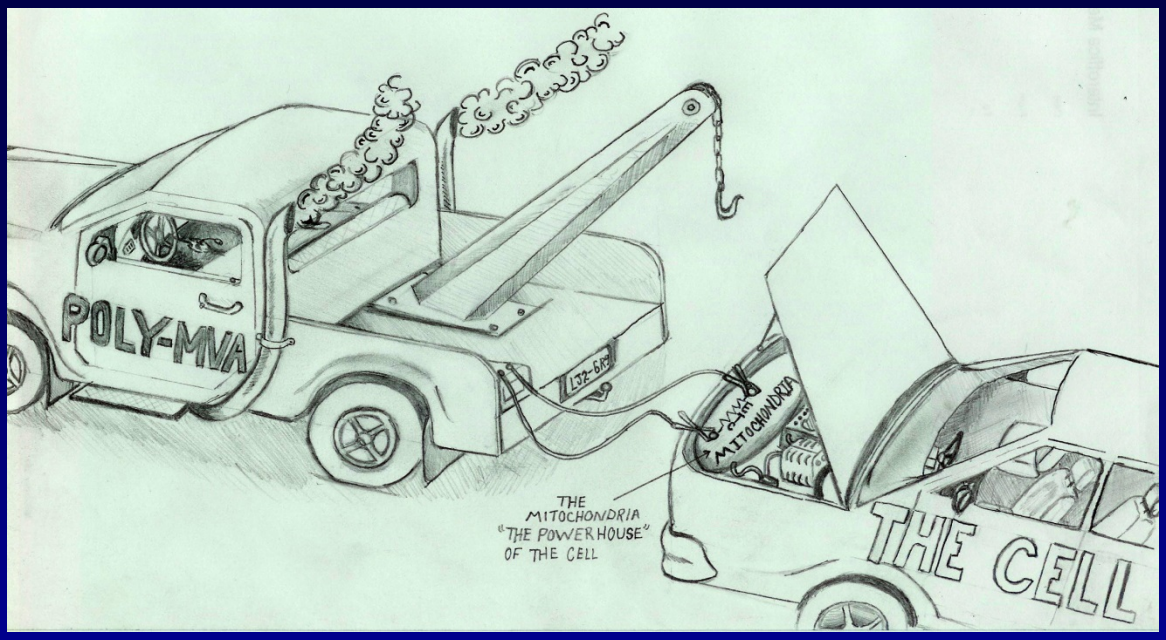
-SUPERIOR ANTIOXIDANT

-CELLULAR PROTECTION

-MITOCHONDRIAL
Damage and Support

-ENERGY AND VITALITY

-ANTI-AGING



By providing this alternative energy source one can:

- **Stabilize the mitochondria in an ischemic cell, as well as quench reperfusion radicals.**
- **Overload a cancer cell on excess energy (electrons) and facilitate cell death.**
- **Support and improve normal cell function increasing the mitochondria**

Methods and Materials

The LAMC used was POLY-MVA,
Supplied by AMARC ENTERPRISES.

Dr. Frank Antonawich is a Professor and the Chairperson of Biology at St. Joseph's College, New York. He is also a Senior Scientist and the Clinical Research Administrator at Garnett McKeen Laboratory, Inc.

FOUNDATION FOR

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