**A NUTRITION BASED STRATEGY FOR CONTROLLING CANCER CELL ENERGETICS:**

 **MITOCHONDRIA RESCUE HEALS CANCER**

When a cancerous tumour grows to be a mass of hyper-metabolic cells about 1 to 2 millimeters in diameter, it must get extra blood and lymph vessels or it can’t maintain its abnormal rate of growth. Oxygen and nutrients can passively diffuse only across one millimeter of human tissue before normally growing cells consume it all. As malignant cells run low on oxygen, they release distress signals that recruit peripheral stem cells and immune cells to make chemicals, such as vascular endothelial growth factor VEGF, that sprout new blood and lymph vessels, and ATP energy molecules. This all happens long before a tumour is visible to any current diagnostic test.

Cancer cells do not stop growing when they bump into each other, but continue to grow, and crowd each other. This creates hard lumps of cells all compressed together. Also, chaotic blood vessels in the tumour are typically so leaky they raise the fluid pressure so high it squashes the blood flow, and the tumour develops areas of low oxygen = hypoxia. This often occurs at about 1 centimetre diameter, which is often before diagnosis. Hypoxic cells strongly resist being killed by radiation, and the poor blood supply also precludes adequate chemo drug delivery. There may even be areas that have no oxygen at all = anoxia, and those parts of the tumour will die. Areas with severe anoxia die by necrosis, which creates an inflammatory mess.

The cancer cells survive in a low oxygen condition by switching to fermentation of sugars for energy, which is theoretically about 18 times less efficient than aerobic glycolysis. The lactic acid by-product of fermentation is a potent stimulant of cancer growth and spread. The induction of lactate dehydrogenase 5 drives anaerobic transformation, and LDH-5 strongly stimulates angiogenesis, through hypoxia-inducible factor one alpha HIF-1α. Even more important it’s the signals from the combustion chambers buring the fuel, called mitochondria, to the epigenetic switches on the DNA in the nuclear chromosomes that triggers the mutations that foster cancer.

When the nuclear chromosomes in a cell become mutated, or epigenetics are altered, cancer can arise. There is a built in defense mechanism called apoptosis – the off-switch for mutated, bad, old and damaged cells. This apoptosis program is innate in every human cell, and will turn off and recycle cells found to have passed about 50 doublings or having more than 50,000 to 60,000 errors or mutations in its DNA. The p53 gene runs this check on the DNA at the cell-cycle checkpoint just before copying the cell. It is like the Scandisc utility checking your computer hard-drive for errors. Mitochondria are a key player in the apoptosis process – the off-switch for mutated cells. There are about 1,000 mitochondria in every cell, the little combustion chambers in the cell where sugars are burned or oxidized to make energy. We inherit them from our mother’s egg. They have their own bacteria-like circular DNA and a primitive DNA repair system. They function quite independently from the rest of the cell, including the DNA of the nuclear chromosomes which came from both parents.

Mitochondria low in oxygen build up free radicals of oxygen, particularly hydrogen peroxide. Mitochondria build-up ROS doing their work, but will have excessive ROS due to hypoxia, alterations in cell membrane composition - such as DHA deficiency, and from internal genetic and epigenetic phenomena – such as acetylated/methylated mDNA. They shut down, resistance to apoptosis increases, and the cell is immortalized. It is then a zombie cell that cannot die, no matter how sick and stressed.

Inducing apoptosis is the goal of radiation and chemotherapy, and is obviously a workable strategy to treat and cure cancer. We have known for years how to wake up the mitochondria in patients with chronic fatigue syndrome and fibromyalgia. We have not been keen to try this with cancers because we did not want to give the cancer more energy to grow on! Merely removing lactic acid to “alkalize” the tumour makes no sense, and will not in itself retard tumour growth. Restoring mitochondrial function as a whole, ie. restoring oxidative phosphorylation, has been suggested as a means to restore caspase activity and thereby apoptosis, in most cancers.

Steven Levine and group have proposed “membrane-calming” as a “neuro-bioenergetic” re-balancing for aging and cancer. Membrane hyper-excitability, particularly via inducible over-expression of voltage-gated ion channels, is linked to mitochondrial dysfunction. Hexokinase HK localizes to the outer mitochondrial membrane, suppressing the caspase cascade responsible for apoptosis.

Lactate dehydrogenase LDH is a glycolytic control enzyme. In cancer cells LDH becomes independent of oxygen status, and under both aerobic and anaerobic conditions will convert pyruvate to lactate. Its kinase enzyme is one of the few kinases not turned on in cancer, and in fact it is turned off to allow the mixed metabolic economy of the cancer cell – part aerobic, part anaerobic. Pyruvate dehydrogenase PDH moves pyruvate made by glycolysis into the mitochondria. Its kinase is the other paradoxically suppressed kinase. The biochemical bottleneck this creates reduces energy production, but increases production of materials needed to build new cells – fats, proteins, carbon slkeletons, precursors of nucleic acids, etc. This dual economy of aerobic and anerobic metabolism is essential to tumour growth.

A rat study using the drug dichloroacetate DCA demonstrated that blocking the enzyme pyruvate dehydrogenase kinase - which makes lactate from pyruvate - wakes up the mitochondria in implanted human breast cancer cells, and the cancer cells immediately switch off. The bad news is that DCA can be as toxic as any chemo drug, if not used properly. After a brief flurry of self-prescribing DCA from American internet sites, the only reliable Canadian source is now an MD in Toronto or some progressive pharmacies. With medications to control side-effects, it can be a reasonably safe therapy, and real tumour shrinkage is possible. However, there are a number of absolutely non-toxic natural alternative medicines which also inhibit this enzyme and are proven to wake up the mitochondria in cancer cells in humans. These alternative agents are approved by Health Canada for over-the-counter sale – for other purposes. Each has evidence of activity in human cancers.

 **Natural inhibitors of pyruvate dehydrogenase kinase:**

**\*R-alpha lipoic acid** (natural form) 150 to 300 mg 2 to 3 times daily. DCA inhibits PDK1. Lipoic acid inhibits PDK1 the strongest, inhibits PDK2 and 3 almost equally as strong, and has some inhibition of PDK4. ALA can trigger hypoglycemia – low blood sugar – in sensitive patients. It may also inhibit thyroid function – T4→T3.

**\*Vitamin B-1** or **thiamine**, or the fat-soluble benfotiamine 80 to 160 mg twice daily. Inject 100 mg intramuscular daily. Thiamine at moderate doses intensifiies tumour growth through transketolase activation, so do not use thiamine outside the context of this protocol.

 Other natural agents which evidence suggests will activate the mitochondria to turn off cancer cells, restore oxidative catabolic metabolism, adjust epigenetic switches to restore differentiation and normal growth patterns:

* **\*Niacinamide –** increases mitochondrial metabolism at 500 mg bid
* **\*Acetyl-L-carnitine -**a potent mitochondria booster, but needs ALA to regulate the ROS created. Give acetyl-L-carnitine 500 to 1,000 mg 3 times daily. L-carnitine can inhibit thyroid function. Contra-indicated if on Keppra anti-seizure medication.
* **\*Coenzyme Q-10** - 300 mg ubiquinone or 100 mg ubiquinol daily – absorbs best taken with fats or oils.
* quercitin - 2 of 500 mg capsules 2 to 3 times daily
* grapeseed extract (oligomeric proanthocyanidins) 400–500 mg daily
* omega 3 marine source oils assist in membrane repolarization and stabilization.
* gamma tocopherol (mixed tocopherols or vitamin E) – 400 to 800 IU daily traps peroxynitrite radicals.
* reishi (*Ganoderma lucidum)* mushroom extract - 500 to 1,000 mg 3 times daily
* L-glutamine – primary requisite substrate for maintenance of mitochondrial membrane potential and integrity and for support of the NADPH production needed for redox control and macromolecular synthesis.
* ellagic acid – can be as 8 ounces of unsweetened pomegranate, grape or berry juices
* betulinic acid from birch leaves 20 to 40 mg/kg/day.
* riboflavin (B2) - 50 to 100 mg 2 to 3 times daily
* *Polygonatum spp*. lectins eg Solomon’s Seal root eg ½ tsp (30 drops) tincture 2 to 3 times daily.

 **Rx: NFH brand Mito-SAP 3 capsules twice daily at meals (or 2 tid).**

There are many other agents which basic science research shows can support mitochondrial recovery, including curcumin, melatonin, selenium, SOD, glutathione, resveratrol, coriolus, berberine and iodine. Aerobic exercise can help, and foods such as olive oil, lemongrass, berries, grapes, pomegranate, apples, chili peppers, onions, garlic, the entire cabbage family |(Brasssicas) and whole grains.

Responses to this metabolic approach to cancer have been quite gratifying in some very advanced cases of breast and colon cancer which were escaping control. Even more exciting are the responses seen in cancers I have never had consistent results with in the past, including lung cancers and sarcomas.

These supplements have little interaction with many common oncology drugs, including Coumadin and Dexamethasone. I would not mix this program with cytotoxic chemotherapy or radiation therapy, preferring other supports during these modalities, and for about 3 weeks after the last dose of chemo or radiation. I have conflicting information on curcumin in this context, as it blocks two-pore potassium channels K2P. Therefore I do not currently combine it with ALA when the focus is mitochondrial resuscitation.

 **IV-D-ALA protocol**

* twice weekly for a run of 10 treatments is typical.
* excellent right after the ALA infusions “piggy-back” DCA - eg flush the line with saline and run 250 mg.
* D-ALA from York Downs Pharmacy in Toronto , not the racemic DL-ALA , only the pure D-form!
* 150 mg IV drips –10 mL of 15 mg/mL D-ALA in 250 mL saline.
* nothing else in the bag.
* protect from light, wrap the bag with foil, dim the lights, draw blinds, flush line with saline, get the line into the patient, then add ALA to the bag.
* run at or under 1 drop/sec, takes about 1.5 hours.;
* continue oral dosing; R-ALA 300 mg twice daily at meals

Sanoviv™ and AMT have put together a “mitochondrial rescue” protocol of IV-LAMC (*PolyMVA™*), IV-

DCA (dichlortoacetate), ketogenic or very low carbohydrate diet, MCT (coconut oil, *Brain Octane™* medium chain triglycerides),vitamin A, *Bioforce™* ketone esters,and hyperbaric oxygen.

 **DICHLOROACETATE - DCA**

Dichloroacetate or DCA is a great concept but can be toxic unless used with care. Nerve and liver injury can be very significant. Discontinue if you see dark urine, have liver pain, nausea, vomiting, malaise or jaundice. DCA activates pyruvate dehydrogenase kinase, triggering an influx of acetyl-CoA into mitochondria. This drives more NADH into complex I. Superoxides that form are converted into hydrogen peroxide by manganese- super oxide dismutase. The H2O2 inhibits proton (H+) efflux, reducing mitochondrial membrane potential Δψm. This opens the mitochondrial transition pore (MTP), inhibiting calcium ion entry via voltage-dependent channels. Reduced intra-mitochondrial calcium (Ca++) suppresses a tonic activation of nuclear factor of activated T lymphocytes (NFAT). NFAT1 is a nuclear transcription activator similar in action to activator protein 1 (AP-1) and nuclear factor kappa B (NFκB). This reduces Kv1.5 expression, increasing potassium ion K+ efflux, reducing inhibition of caspases, and finally triggering cancer cell apoptosis (Bonnet 2007).

This is how it is being used:

* Michelakis dosing: 12.5mg/kg bid x 1 month (i.e. 1,500 mg daily for a 60 kg person) and increase to 25mg/kg bid (3000mg qd) , but reduce this by 50% upon development of toxicity. They have reported that doses to 6.25mg/kg bid (750mg qd) have not provoked any peripheral neuropathies – but it is questionable whether this dose is enough for most cancers. They suggest this range for cancers of the brain or nervous system.
* Rx: 12.5 to 50 mg/kg/day. Begin most people on 500 mg capsule or as powder dissolved in juice twice daily for 1-3 weeks.
* **most people do well at 1,000 -1,500 mg daily, that is 500 mg two or three times daily**.
* we may increase the dose to 1,500 mg twice daily, until adverse symptoms arise. Within a few weeks use it can take the myelin off peripheral nerves just like in multiple sclerosis, causing pain, numbness, hand tremor and staggering. It can cause central nervous system damage including confusion, sedation, depression, anxiety, hallucinations and memory impairment. It can be toxic to the liver and it is known that it can cause cancer! It can trigger oxalate-based kidney stones and increase uric acid levels, risking gout.
* use for 1 to 3 weeks, then take 1 week off. Some colleagues dose it 4 days on and 4 days off. Just don’t bull ahead if nerve injury is reducing the quality of life significantly – give a rest to heal up, then try again.
* repeat as needed DCA has a half-life in the cerebro-spinal fluid of 5 days.

*It is mandatoryto give protective supports such as R+ alpha lipoic acid, benfotiamine and acetyl-L-carnitine in full medical doses!* Acetyl-L-carnitine, IV-calcium and magnesium, methyl B-12 and B1 shots and R- alpha lipoic acid are used to repair nerve injury that occurs despite these prophylactic medications.

* **R-alpha lipoic acid** prevents nerve injury and also boosts the effectiveness of the DCA against cancer cells. I prescribe 300 mg R-ALA twice dialy at meals - beware of its hypoglycemic effects at the higher doses – chills, shakiness, irritability, headache, etc. IV-D-ALA at 150 mg twice weekly is very valuable, and really great as a piggy-back after IV-DCA. Nebulize 50 – 100 mg D-ALA up to twice dialy.
* **Thiamine** or B1 prevents peripheral neuropathy and also boosts effectiveness. Dr. Khan uses fat-soluble thiamine called benfotiamine, at 80 mg twice daily. The full dose is 2 of 80 mg capsules twice daily. Plain thiamine at 100 mg bid will also work.
* **Acetyl-L-carnitine** protects the nervous system, and maintains energy. The basic dose Dr. Khan suggests is 500 mg three times daily, and the full dose is 2 0f 500 mg capsules three times daily. Dr. Joe Pizzorno, ND has shown that when ALA and ALC are used together there is a remarkable synergy, and far lower doses are needed. CI: *Folks who suffer from epileptic seizures cannot take acetyl-L-carrnitine.*
* **B-12 as methylcobalamin** protects the nerves. We give an injection of 2,000 mcg in the rump, once weekly, or as needed. Daily sublingual methyl-B-12 from BioClinic Naturals is also recommended.
* **Pantoprazole** ( Pantoloc) PPI at 40 mg prevents heartburn, nausea and indigestion.

Lab tests which may be checked weekly for 4 weeks, then monthly: CBC, sodium, potassium, chloride, calcium, urea, creatinine, albumin, total bilirubin, conjugated bilirubin, AST, ALT, ALKP, GGT, LDH and glucose.

My colleague Dr. Walter Lemmo, ND, FABNO, DCA is far safer given intravenously than orally, due to rapid drug clearance. There is evidence it is quite tolerable up to 100 mg per kg of body weight. Dr. Akbar Khan, MD [www.medicorcancer.com](http://www.medicorcancer.com) discovered suggests starting at 60 mg/kg BW, in 50 mL normal saline, infused over at least 15 minutes. After two infusions, if well tolerated, the dose may be increased step-wise to 70, 80 and even 90 mg/kg BW. The infusions are done twice a week for two weeks, then we give the patient a week break. 3 such cycles over 9 weeks is a common course of therapy. It may be repeated later, as needed.

The Lemmo IV protocol for DCA:

* DCA – 1,000→2,000→3,000 mg ( 4mL, 8mL, 12 mL of 250 mg/mL DCA)
* vitamin C – 2,500mg
* B-complex – 1 cc, B12 – 1 mg, B6 – 100 mg, B5 – 250 mg, B1 – 100 mg
* saline 100 ml infused over 30-60 min.
* evaluate progress after 10 infusions.

My own experience is that the IV administration is far less problematic than oral dosing, but I may still continue oral dosing with aggressive neuroprotection. Just don’t give oral DCA on the days of IV drips of DCA.

**Precede IV-DCA with IV-D-ALA** 150 mg. Avoid DL-ALA, it is much harsher than D-ALA.

IV-D-ALA blunts adverse reactions to the DCA in most cases, and there is a wonderful synergy that dramatically increases responses, including potential tumour shrinkage. Give vit. A p.o. **Monitor for liver or nerve injury.**

It is thought that caffeine can improve responses to DCA, in doses of about 480 mg daily or about 12 cups daily of black tea. Metformin is considered to be highly synergistic. Other suggested synergists are grapeseed extract, curcumin, quercitin, resveratrol, selenium. A colleague suggests DCA and ALA could be supported by pre- and post-treatment with garlic (oral or IV) and/or nitrilosides, aka Laetrile (oral or IV). An interesting new concept is using it only on alternating weeks with artemesinin, as DCA is said to help the cancer cells recharge with iron.

I see DCA as being particularly useful in aerobic cancers – brain and lungs for example, but less so for more anaerobic cancers such as prostate and colorectal. **…………………………………………………………………………………………………………………………..**

**Nebulizing ALA or DCA**: Purchase injectable grade 50 mg/mL D-ALA, 250 mg/mL DCA.. Always keep them out of the light as much as possible. Rent or purchase a nebulizer from a pharmacy. Use a 3 cc syringe to pull out the medicine from the rubber-top multi-dose vial – page 209 of my book describes how we get medicine from the vials – it’s talking about mistletoe, but the principle is the same. Always wipe the top of the vial with alcohol before putting away in the fridge, and keep it shielded from light just as much as you can. Put 1 mL medicine in the medicine cup of the nebulizer, which is protected from light by wrapping it with tinfoil. Over time you can try increasing the dose eg 2 mL of the D-ALA plus 3 to 4 mL sterile saline to make 5 mL total. Normal saline is 0.9% salt, sterile solutions are commonly used for contact lenses.

Turn on the pump and through a face mask or breathing tube breath in the medicine as a mist. Breathe normally. After about 10 minutes the medicine well will go dry and you’ll hear it sputtering. Turn off the nebulizer pump, and rinse everything off for next time. With a doctor’s prescription and supervision you can do this twice a day at home, it is about as effective as an intravenous drip, and a lot cheaper.

In some cases we add DCA (dichloroacetate) 250 mg/mL with the D-ALA. We start with 1 mL of each medicine, plus 3 mL of sterile saline. Later we can go up to 2 mL or 100 mg of the D-ALA per dose. Do not let stand long, as a precipitate can form.

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My final word is: always be grateful that you have food, thank those who grow and deliver it, and bless those who make and serve it. Do not consume worry and stress about food choices, which can poison your meal. You may wish to bless the food to your needs, and visualize your body taking from it that which is good, and leaving the rest. Do your best to be moderate and still take pleasure in food and the sharing of it.