



GARNETT McKEEN LABORATORY, INC.

# **POLY- MVA**

INFORMATION PACKET

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# POLY-MVA

## “A Selective Metabolic Modulator”

(Adapted from: Palladium Lipoic Complex: “Energy to Get the Job Done”  
*Anti-Aging Medicine Therapeutics*, Vol. 8 (2006)

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### WHAT IS POLY-MVA?

Palladium Lipoic Acid Complex (PdLA) is the most active ingredient in a dietary supplement called POLY-MVA. In the palladium lipoic acid complex, the element palladium is covalently bound to the anti-oxidant alpha-lipoic acid. In addition to PdLA, the proprietary blend of POLY-MVA is formulated with minerals, vitamins and amino acids such as molybdenum, rhodium, ruthenium, thiamine, riboflavin, cyanocobalamin, acetyl cysteine, and formyl methionine (Garnett 1995, 1997, 1998).

Dr. Merrill Garnett invented POLY-MVA. While Dr. Garnett was formally trained as a dentist, he has done substantial graduate work and research in biochemistry and electrochemistry over a period of 40 years. His inquiry and screening of thousands of organo-metallic compounds led to the discovery of the non-toxic POLY-MVA supplement. Basic science and anecdotal clinical data suggest POLY-MVA to have chemotherapeutic properties. The principles that led to this finding in the early 90s still drive Dr. Garnett's principal research interests today; **that ultra-low frequency electrical currents are at the heart of all physiological processes and determine such events as the polarization, charge and folding of enzymes, nucleic acids and membrane phospholipids.** He believes that the regulation of charge transfer may form the basis of several new methods of drug discovery and medical treatment.

**In this overview, we would like to address some of the frequently asked questions and misconceptions regarding POLY-MVA that we encounter during our scientific presentations.**

- A number of people are under the impression that the supplement, POLY-MVA, is merely a cocktail of palladium, alpha-lipoic acid, thiamine, riboflavin, cyanocobalamin, formyl-methionine and acetyl-cysteine. This is not true. There is no free alpha-lipoic acid or free palladium in POLY-MVA. They are bound together (Garnett 1995, Krishnan and Garnett 2006). Therefore, comparisons to free palladium or alpha-lipoic acid are irrelevant. This compound was synthesized by Dr. Garnett to create a metallic bioorganic molecule that demonstrates enhanced fat and water-solubility. Furthermore, it is prepared in a unique fashion so it **does not** produce toxic products upon consumption. This is unlike many other chemotherapeutics, which breakdown, accumulate in tissue and eventually become toxic.

- **Is POLY-MVA safe?**
  - The formulation has undergone extensive toxicology study (Calvert Laboratories, Inc; Pharmakon USA, Inc.). The toxicology was conducted both intravenously and orally with PdLA. Mice were administered doses of 5,000 mg/kg (a typical human dose is 20 mg/kg). No deaths or signs of organ damage occurred in the test animals. It was concluded that the LD50 of PdLA exceeds 5,000 mg/kg. The same independent lab conducted the Ames test and no mutagenic effects were observed.
  - While platinum and palladium share many chemical properties, it appears that platinum coordination complexes are carcinogenic and genotoxic. There is no evidence of any mutagenic property for palladium (Bunger et al. 1996). In a study examining human lymphocytes, platinum demonstrated significant genotoxicity, likely mediated by oxidative damage, compared to palladium (Migliore et al. 2002). Furthermore, palladium demonstrated no genotoxicity in mammalian or bacterial cells when tested using the cytokinesis-block micronucleus test (MNT) or SOS chromotest, respectively (Gebel et al. 1997).
  - Human Safety: Recently, a university phase I (SAFETY) study of PdLA was completed. 13 research subjects received study compound (POLY-MVA 10 mL/day) for varying time periods. There were no reported SAEs (Severe Adverse Events) attributed to the product. Nine subjects experienced an AE (Adverse Event) during the study which was considered potentially related to the study compound, while five subjects had AEs which were either possibly or probably related to the study compound. The events which were possibly or probably related to the study compound included: fatigue after cessation of compound, diarrhea, worsening leg cramps, headache, increased urination, light-headedness, difficulty sleeping, increased excitement.
  
- **Palladium is a precious metal and quite expensive. Why was it used?**
  - Dr. Garnett discovered during his electrochemistry studies that DNA (and other biological cellular entities) has select electronic properties. After testing thousands of compounds, Dr. Garnett found that only PdLA complex and DNA shared compatible electronic properties. This characteristic facilitates electron transfer between them (Garnett 1995). This is analogous to the propulsive energy provided to a surfer by a wave. If the surfer is in “sync” with the wave they can ride it all the way in to the beach. However, if he or she isn’t, they will crown right over the top of the wave.
  
- **Why are the other components added to the dietary supplement?**
  - Most people feel the other components are added without regard to the PdLA complex. This is not true. In very early studies with the most active ingredient, palladium lipoic acid complex, elevated temperatures were observed in test subjects. The proprietary blend in the supplement is not inert, but plays a role in buffering the temperature alterations.

- **Is POLY-MVA just a super free radical scavenger?**

- This was our initial thought after our first transient global ischemia experiments with the PdLA complex in POLY-MVA (Antonawich et al. 2004). However, the electrochemistry data of Dr. Garnett and his colleagues demonstrate unique electronic properties for the palladium-lipoic acid complex (Garnett and Garnett 1996, Krishnan and Garnett 2006). After our initial ischemia research findings, we sent some POLY-MVA to Brunswick Labs, Inc. (Wareham, MA) for an ORAC analysis. An ORAC assay measures the oxygen radical absorbance capacity of a compound as compared to Trolox (vitamin E). The table below demonstrates the potent anti-oxidant capacity of POLY-MVA (expressed as Trolox equivalent per gram): The data in parenthesis are the real experimental values and the other data are normalized values with respect to the vitamin E standard.

Vitamin A = 1.6 (2,800)
Vitamin C = 1.12 (1,890)
Vitamin E = 1.0 (1,700)
Melatonin = 2.04 (3,468)
$\alpha$ -lipoic acid = 1.4 (2,400)
POLY-MVA = 5.65 (9,605)

- **Why is this supplement often credited or associated with providing energy?**

- While POLY-MVA does indeed have the ability to be a highly effective free radical scavenger, its ability to donate electrons to the mitochondria of the cell is critical in explaining its dramatic benefits (Antonawich et al. 2004, 2006). Anecdotal clinical evidence of the reports of additional energy, led to our early hypotheses regarding its possible benefits in stroke and ischemia. Following an interruption of blood flow to any tissue, in our particular case the brain, there is deprivation of oxygen and glucose. Providing an alternative energy source can maintain the integrity of the electron transport chain within the mitochondria (Antonawich et al. 2006). The PdLA complex was demonstrated, by Dr. Garnett, to shuttle electrons to oxidized DNA. However, this process does not appear to proceed directly to DNA. By conducting a competition assay with alpha-lipoic acid, which works at complex I of the mitochondria as a cofactor while pyruvate is converted to acetyl CoA, one can attenuate the beneficial effects of POLY-MVA (Antonawich et al. 2004; Garnett McKeen Laboratory, Inc. 2007). This is critical since mitochondrial health is a major concern during myocardial and cerebral ischemia. By providing this alternative energy source, the electron transport chain components do not readily dissociate (coenzyme Q-10 = ubiquinone; cytochrome C). In a normal cell this would obviously provide a boost, and would serve as a supplement to an ischemic cell.
- Since lipoic acid and thiamine are cofactors early in the aerobic cascade, they appear to direct the PdLA complex's energy benefits to the mitochondria. A recently conducted study by Janardhanan et al. (2008)

examined the age-related decline of mitochondrial enzyme activity and respiratory chain complexes in rat hearts. Aged animals orally administered 0.05mL/kg PdLA (equivalent human dose of approximately ½ tsp.) had significantly enhanced Krebs Cycle activity (i.e. enhanced isocitrate dehydrogenase,  $\alpha$ -ketoglutarate dehydrogenase, succinate dehydrogenase and malate dehydrogenase activity). This PdLA-induced activity improvement was also significant at Complexes I & II of the electron transport chain. Thus, it appears that PdLA has the ability to shuttle energy to the aerobic respiration cascade to augment the generation of high energy intermediate molecules within the Krebs's cycle, as well as, directly boost the oxidative phosphorylation pathway responsible for the generation of ATP.

- Furthermore, these basic science findings also translate to clinical cellular energy markers. In a recent pilot observation, 5 fatigued aged canines, in remission from cancer, were orally administered 0.022mL/kg (2 drops per 10 lb.) PdLA for two weeks. The PdLA supplement demonstrated elevated mitochondrial metabolite levels (Genova Laboratory, Inc.), with 41 out of 45 of the parameters demonstrating a cellular energy improvement. This pilot has been developed into a multi-center randomized double blind placebo controlled crossover study.
- **Can the POLY-MVA supplement be taken with other vitamins and free radical scavengers?**
  - Since POLY-MVA is a highly efficient redox molecule, normal daily recommended values of vitamins have not been of consequence in our laboratory studies. However, excessive doses of anti-oxidants may attenuate its benefits. As mentioned above, administration of alpha-lipoic acid in our competition assay hindered the redox benefits of POLY-MVA (Antonawich, et al., 2004; Garnett McKeen Laboratory, Inc. 2007). However, alpha-lipoic acid alone offers only a fraction of the ischemic protection offered by POLY-MVA. In recent energy studies, 13x more alpha-lipoic acid was necessary to obtain the same cellular energy benefits attributed to PdLA complex (Janardhanan et al., 2008).
- **Basic Scientific Evidence**
  - This formulation was studied independently at Calvert Laboratories, Inc. to determine its' effectiveness in halting the growth of glioblastoma cells *in vivo*. Four groups were given daily intravenous (IV) doses of this formulation or placebo; four groups were given intraperitoneal doses of 0.5, 1.0 or 2.0 mg per mouse for a total of four weeks. Tumor volume was measured throughout the study. Compared to the controls that received no formulation, mice receiving the test material orally or intravenously at 0.5, 1.0 or 2.0 mg had a significantly reduced growth of the glioblastoma (50% or greater reduction in tumor size).
  - Dr. Frank Antonawich's university studies examined the non-toxic chemotherapeutic effects of POLY-MVA on brain and breast tumor cell lines. We were investigating the relationship between the degree of anaplasia of malignant cells and effectiveness of the PdLA complex.

Metabolic dysfunction, related to hypoxia and subsequent adaptive gene responses, renders some cells resistant to traditional chemotherapeutics but sensitive to the metabolic modulation of PdLA.

- Our ischemia studies in animals demonstrated that acute, post-ischemic and prophylactic administration of POLY-MVA limits ischemic damage. This appears to be a result of its ability to stabilize the mitochondria by providing energy to the electron transport chain, as well as, quenching free radicals generated as a result of reperfusion (Antonawich et al. 2004). See data below:

### Basic Science Ischemia Studies:

#### 1. ACUTE treatment with POLY-MVA, after TIA, offers behavioral and morphological protection of CA1 hippocampal pyramidal cells.

Antonawich et al., (2004) *Experimental Neurology*

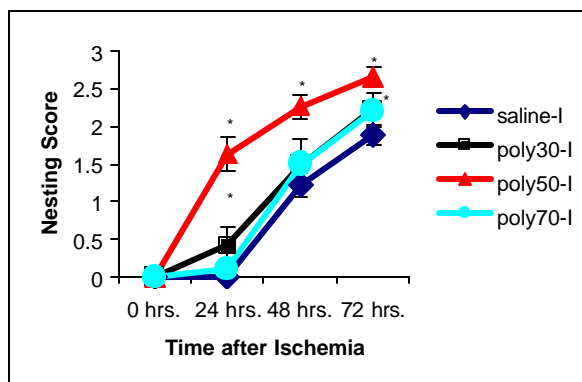


Figure #1 – Behavioral Alterations

Nesting behavior is an inherent behavior in Mongolian gerbils. Following transient global ischemic damage this behavior is impaired. Treatment with POLY-MVA significantly improves nesting following treatment with 50 mg/kg every 24 h ( $P < 0.05$ ) and 30 mg/kg /24h at 24 and 72 hours after ischemia. There were no significant differences after the 70 mg/kg/24h treatment ( $n = 6$  per group, each experiment was conducted in triplicate).

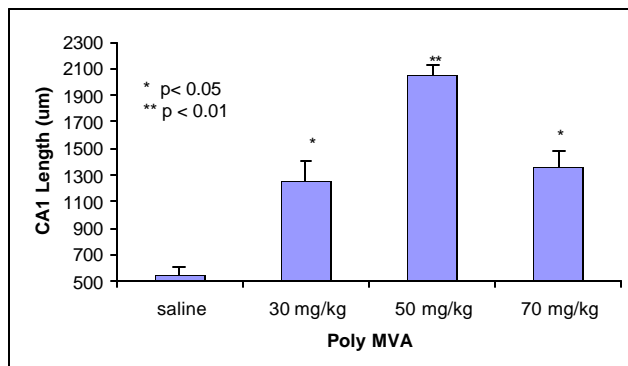


Figure #2 – Morphological Effects

Transient global ischemia results in specific damage to CA1 pyramidal neurons in all species from a mouse to a human. Following bilateral carotid artery occlusion in the Mongolian gerbil, POLY-MVA treatment significantly protected CA1 hippocampal pyramidal cells from transient global ischemia at 30 ( $p < 0.05$ ), 50 ( $p < 0.01$ ), and 70 ( $p < 0.05$ ) mg/kg per 24 h. ( $N = 6$  per group, each experiment was conducted in triplicate).

## 2. DELAYED Administration

Antonawich et al., (2004) *Society for Neuroscience*

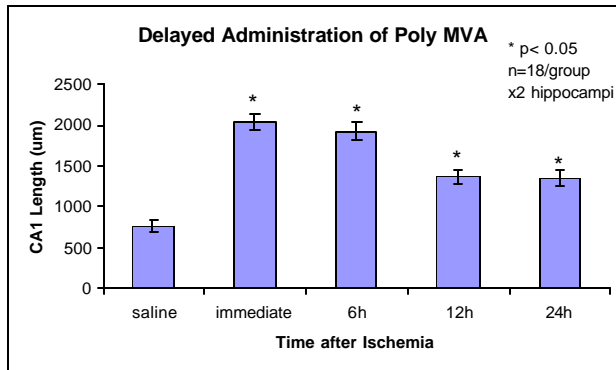


Figure #3. Each animal was given POLY-MVA once daily (times are from the onset of the ischemic insult). One injection at 48 hours was not enough time to elicit an effect. The exciting thing to us is that 6 hours was just as good as giving it immediately at the time of injury! It is still significantly beneficial at preventing cell death 24 hours after ischemia. These data are applicable to various models of cerebral ischemia: TIA (transient ischemic attack, cardiac arrest with resuscitation, drowning with revival, anesthetic accidents and those suffering from chronic hypertension (even when medicated).

## 3. PREVENTATIVE/PROPHYLACTIC Administration

Antonawich et al., (2004) *Society for Neuroscience*

Antonawich et al., (2005b) *A4M Conference*

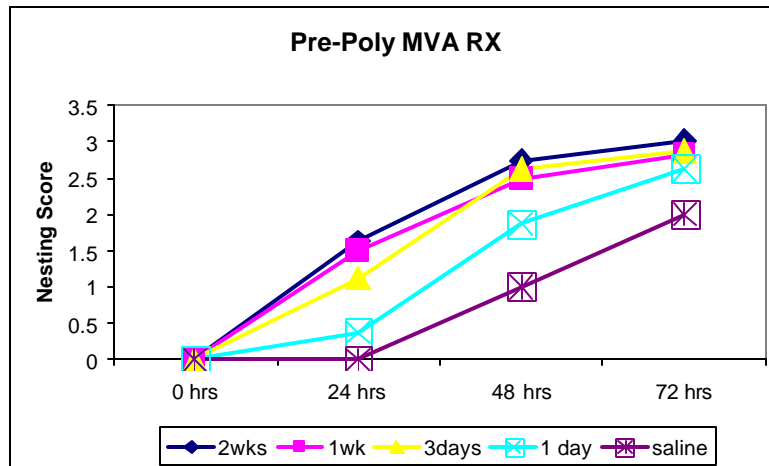
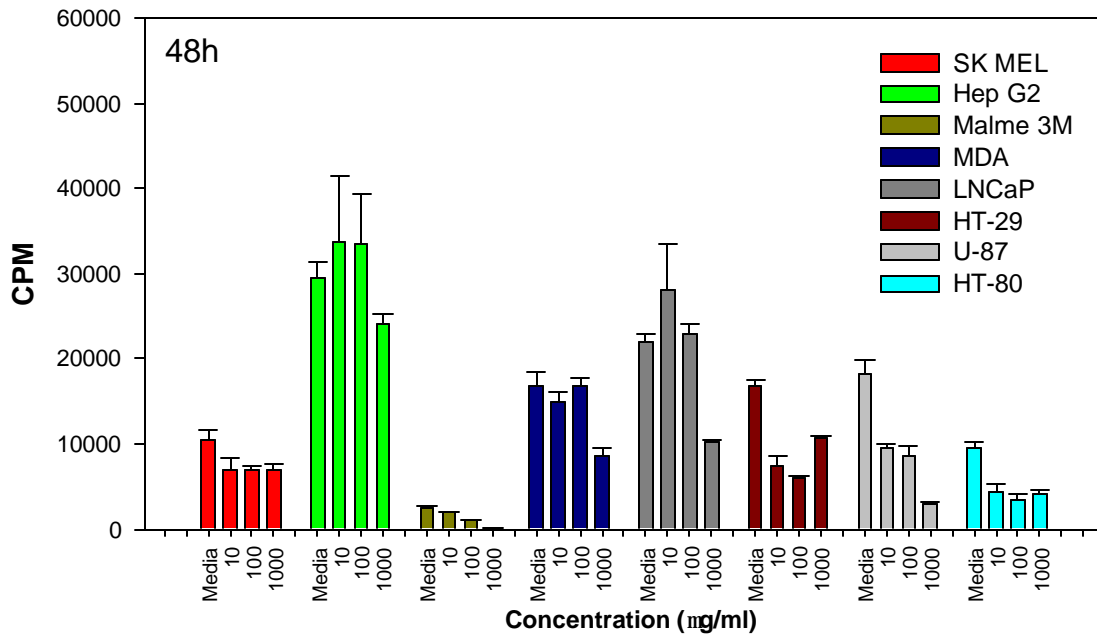


Figure #4. Preventative treatment with 10 mg/kg (based on allometric scaling from rodent to human, 2 tsp – human dosage) offered significant behavioral and morphological improvement from transient global ischemia ( $p < 0.05$ ). While behavioral improvement is apparent with 3 days of pre-treatment, approximately one week of pre-treatment is necessary for morphological rescue.



- In 2007, KGK Synergize Inc., an independent laboratory in Canada, examined the effects of POLY-MVA on 8 different cell lines to confirm our research findings. These lines included:
  - 1) Skin melanoma, human (SKMel-5)
  - 2) Liver, hepatocellular carcinoma, human (Hep G2)
  - 3) Lung, malignant melanoma, human (Malme-3M)
  - 4) Mammary gland, ductal carcinoma, human (MDA-MB 435)
  - 5) Prostate, left supraclavicular lymph node carcinoma, human (LNCaP)
  - 6) Colon, colorectal adenocarcinoma, human (HT-29)
  - 7) Human brain, glioblastoma; astrocytoma (U87)
  - 8) Glioblastoma (HT-80)

POLY-MVA was administered at 3 different dosages and the number of cells was examined after 24, 48 and 72 hours following initial application. POLY-MVA was **effective**, to varying degrees, on the entire group of cell lines tested (melanoma, liver, lung, breast, prostate, colon, astrocytoma and glioblastoma). **The varying effectiveness appears to be a consequence of the particular cell lines used and their associated degree of anaplasia.** The graph below demonstrates the benefit of POLY-MVA after 48 hours of initial exposure: The Y-axis represents the number of cells per mL.

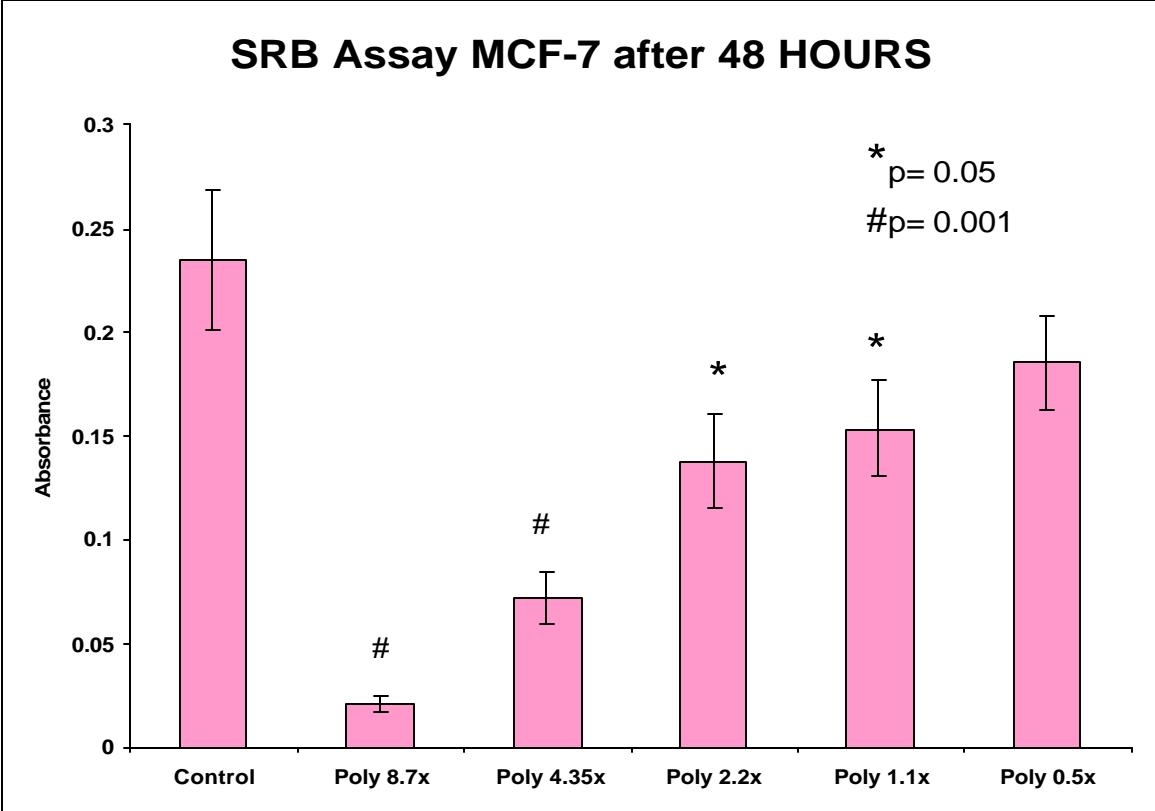


The table below illustrates the statistically significant level of cell death (p must be equal to or less than 0.05) induced by POLY-MVA after 48 hours of initial exposure:

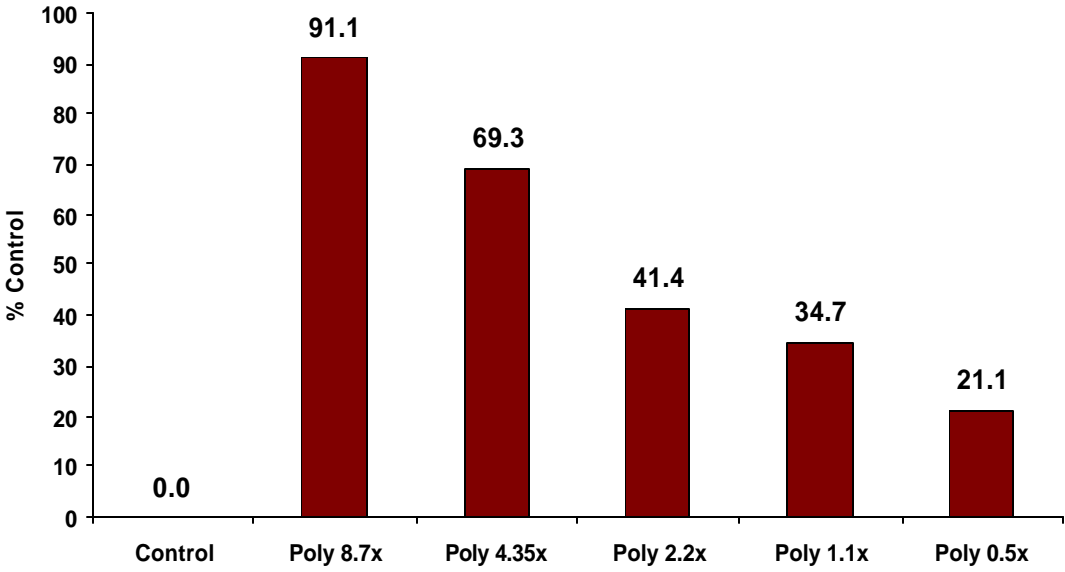
Cancer Cell Type	Cell Line	Statistical Significance	Dosages (ug/ml)
Melanoma	SKMeI-5	p<0.01	100, 1000
Liver	Hep G2	p<0.01	1000
Lung	Malme-3M	p<0.0004	100, 1000
Breast	MDA-MB 435	p<0.001	1000
Prostate	LNCaP	p<0.0005	1000
Colon	HT-29	p<0.03	10, 100, 1000
Astrocytoma	U-87	p<0.05; p<0.01	10, 100; 1000
Glioblastoma	HT-80	p<0.0001	10, 100, 1000

- o Garnett McKeen *In vitro* Cancer Assays: In addition to our formalized efficacy data, Garnett McKeen Laboratory Inc. (GML) has chosen to mimic the National Cancer Institute's (NCI) cell screening protocol. The following cell lines were selected from the NCI repository: MCF-7 (breast adenocarcinoma), A549 (lung non-small cell adenocarcinoma), and DU-145 (prostate carcinoma). The data below represents the completion of the Breast Cancer (MCF-7), Ovarian Cancer (OVCAR-5) and Lung Carcinoma (A549) assay. We have also completed assays using stage IV glioblastoma multiforms (H-80) and astrocytoma (H-4) brain tumor lines. All of the studies demonstrate significant cell death.

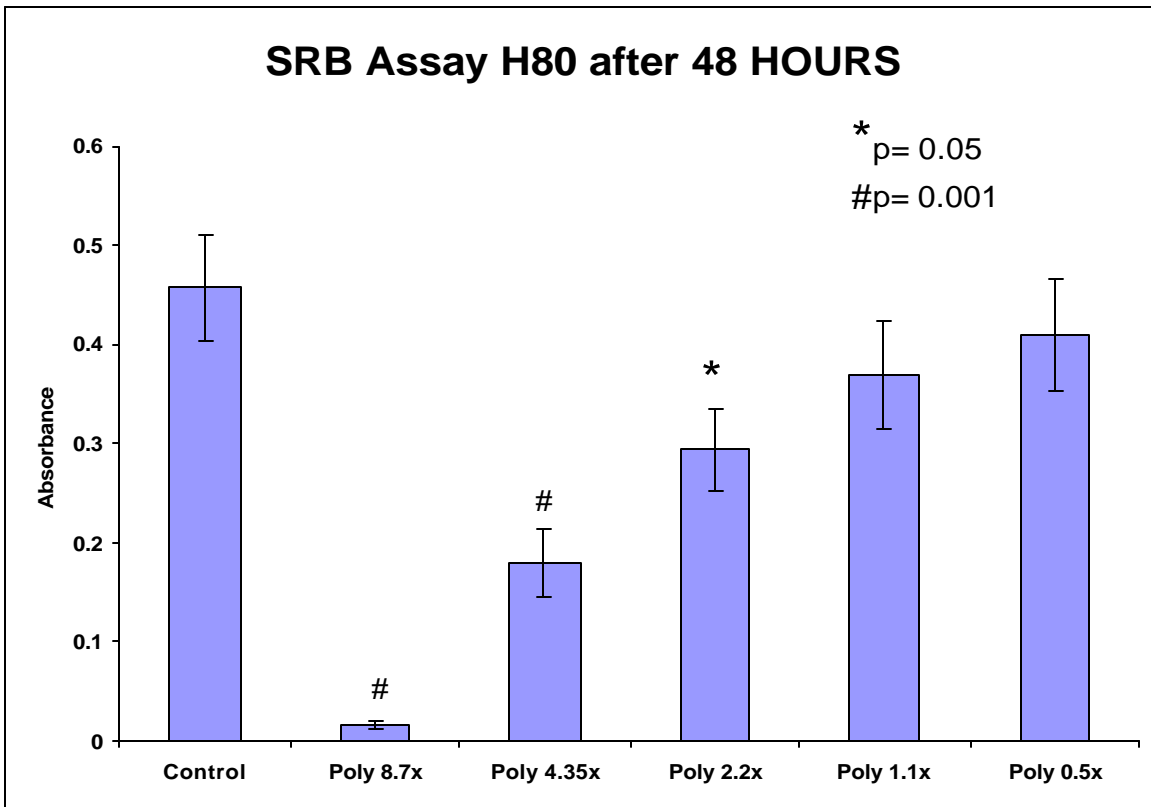
# NCI Assay: Breast Cancer (Adenocarcinoma) – GML



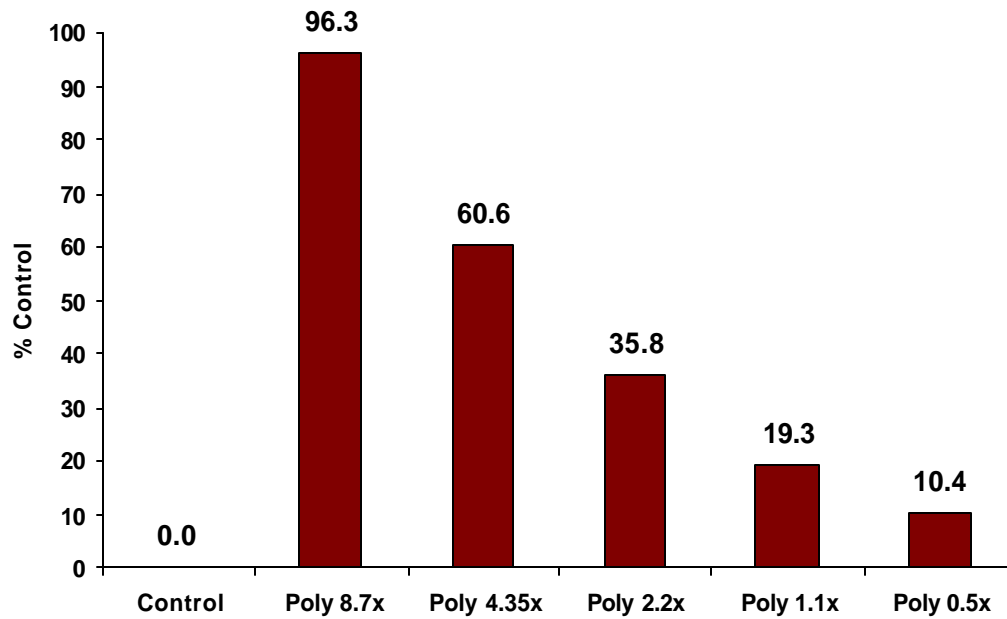
### Percentage of Breast Cancer Cell Death



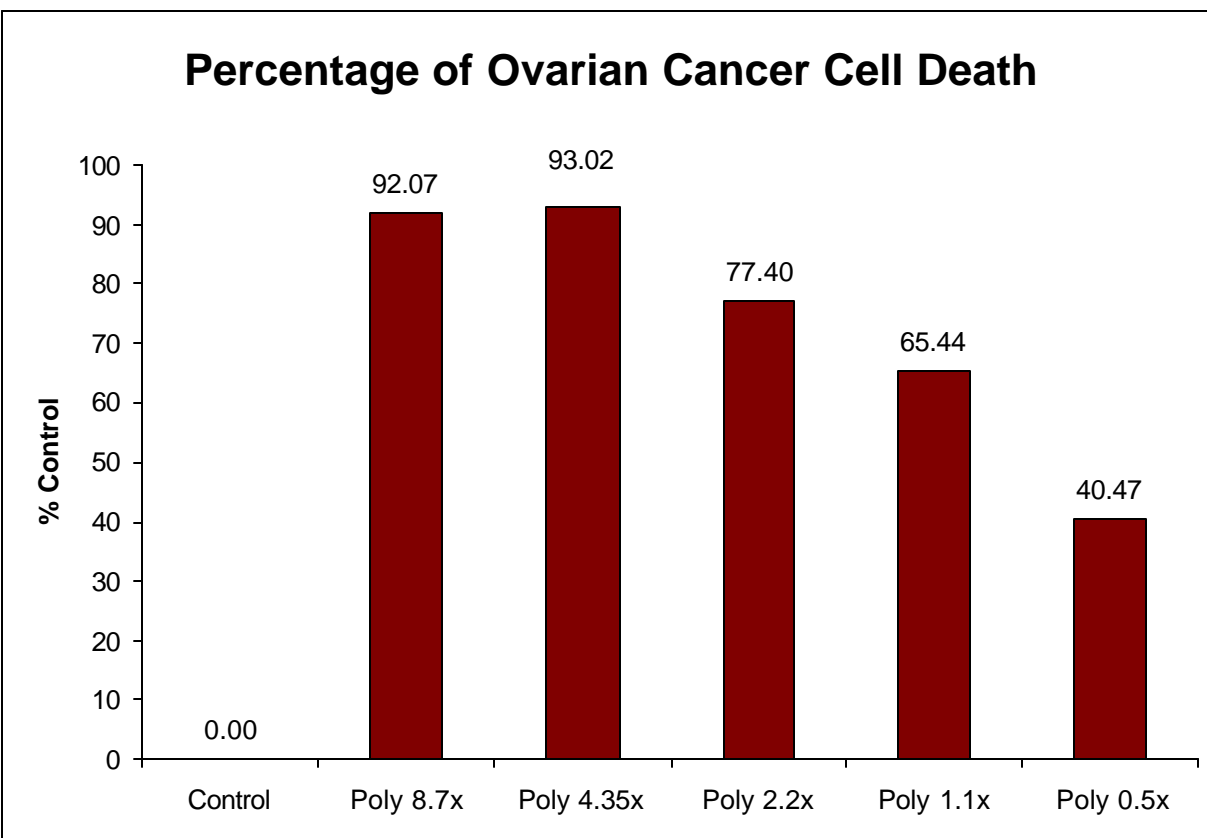
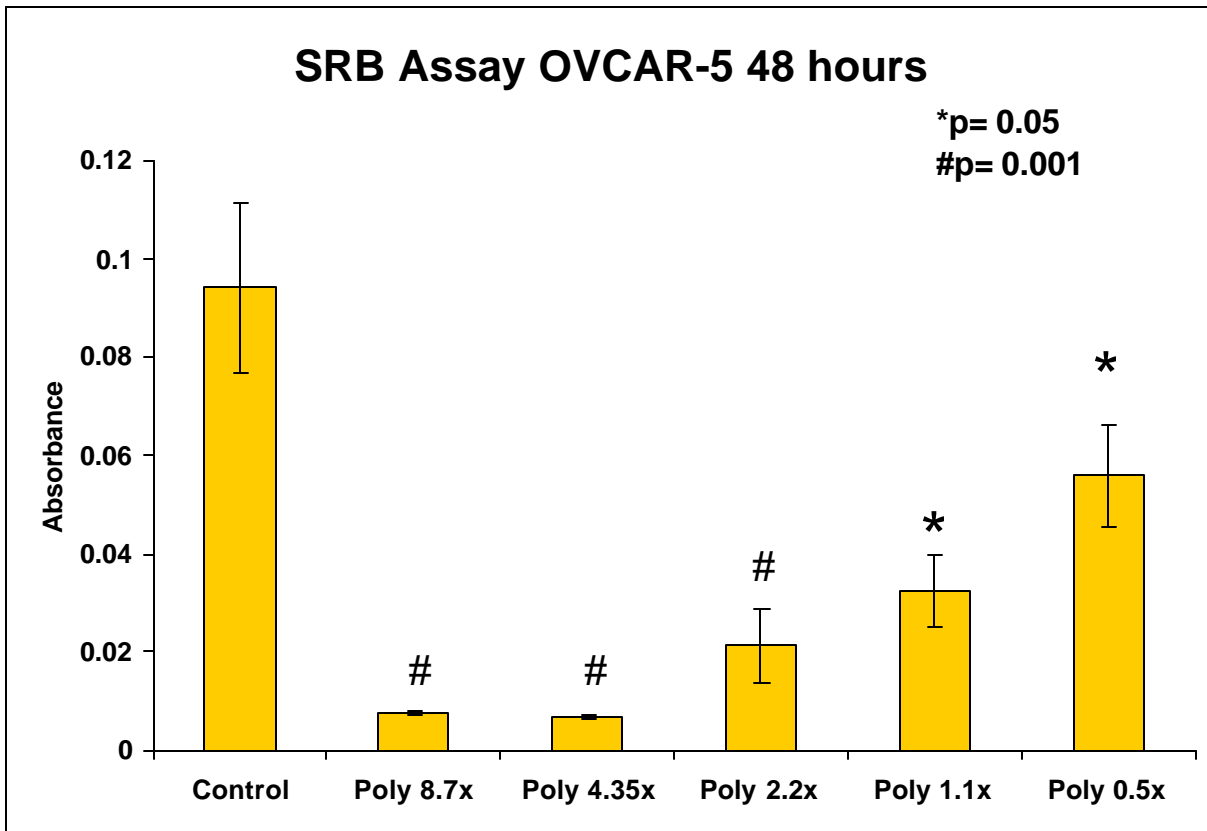
# NCI Assay: Brain Tumor (Glioblastoma) – GML



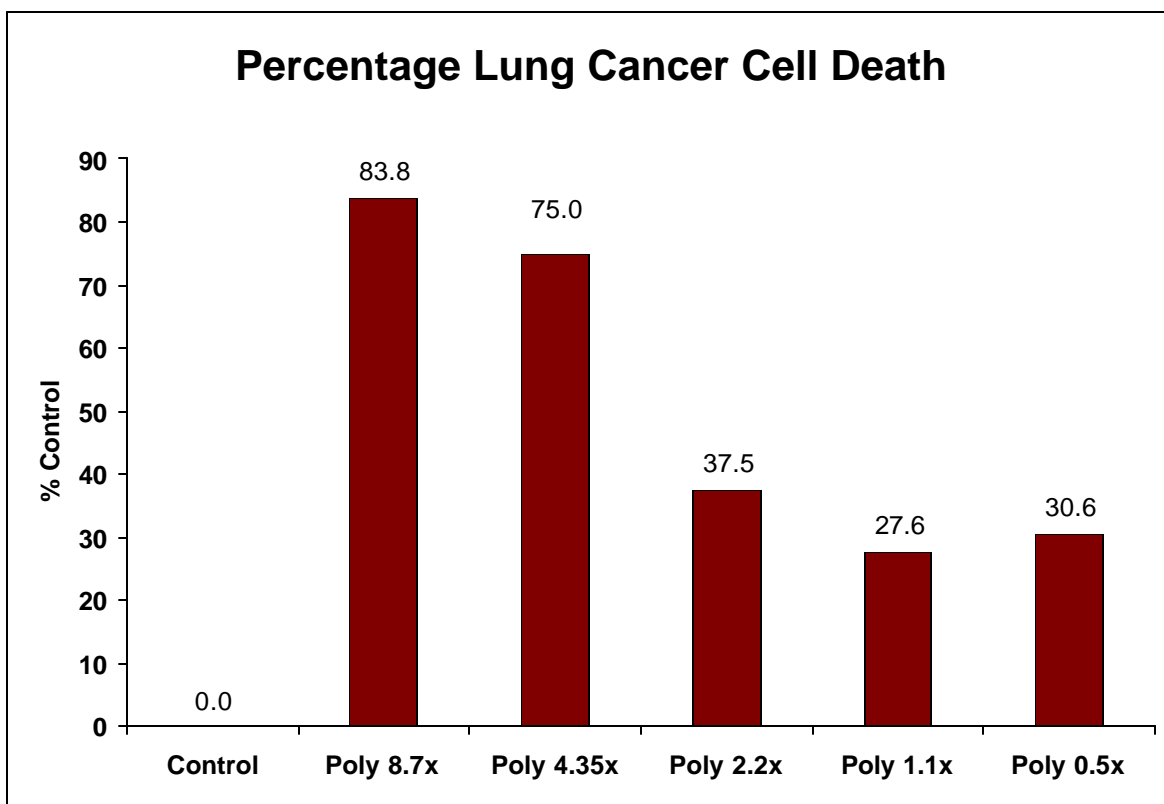
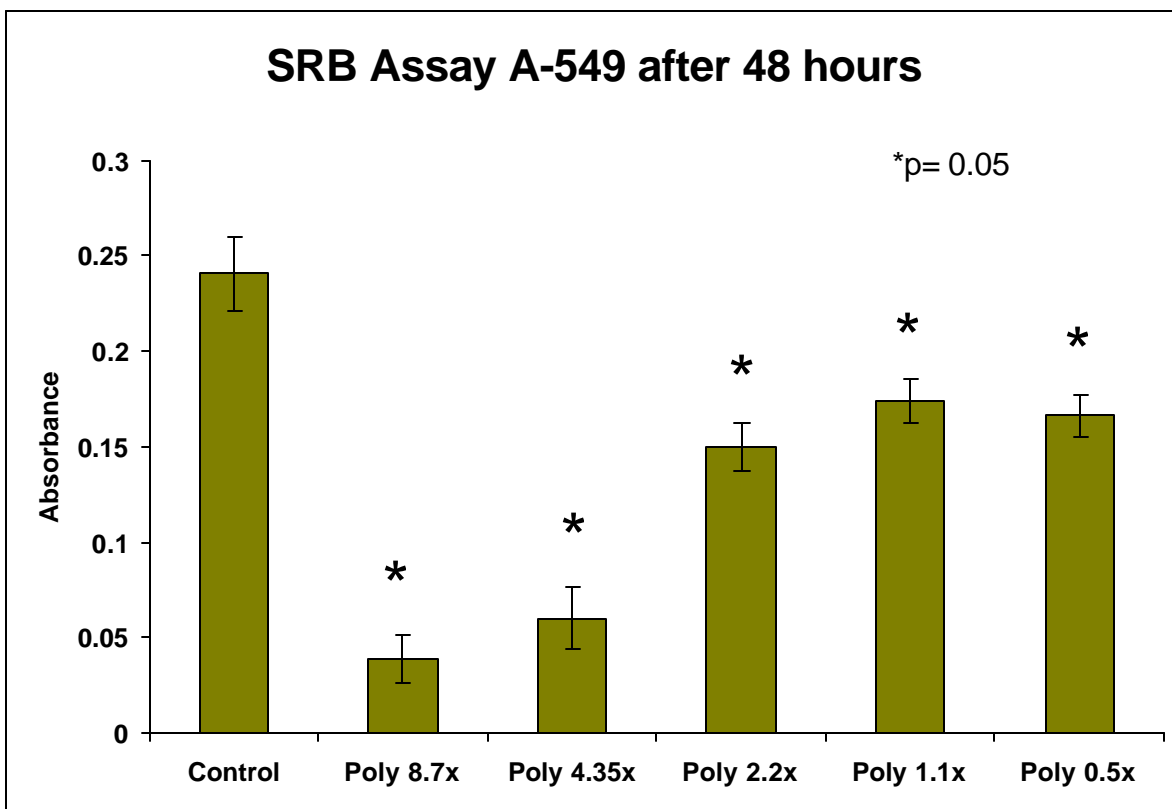
### Percentage of Brain Cancer Cell Death



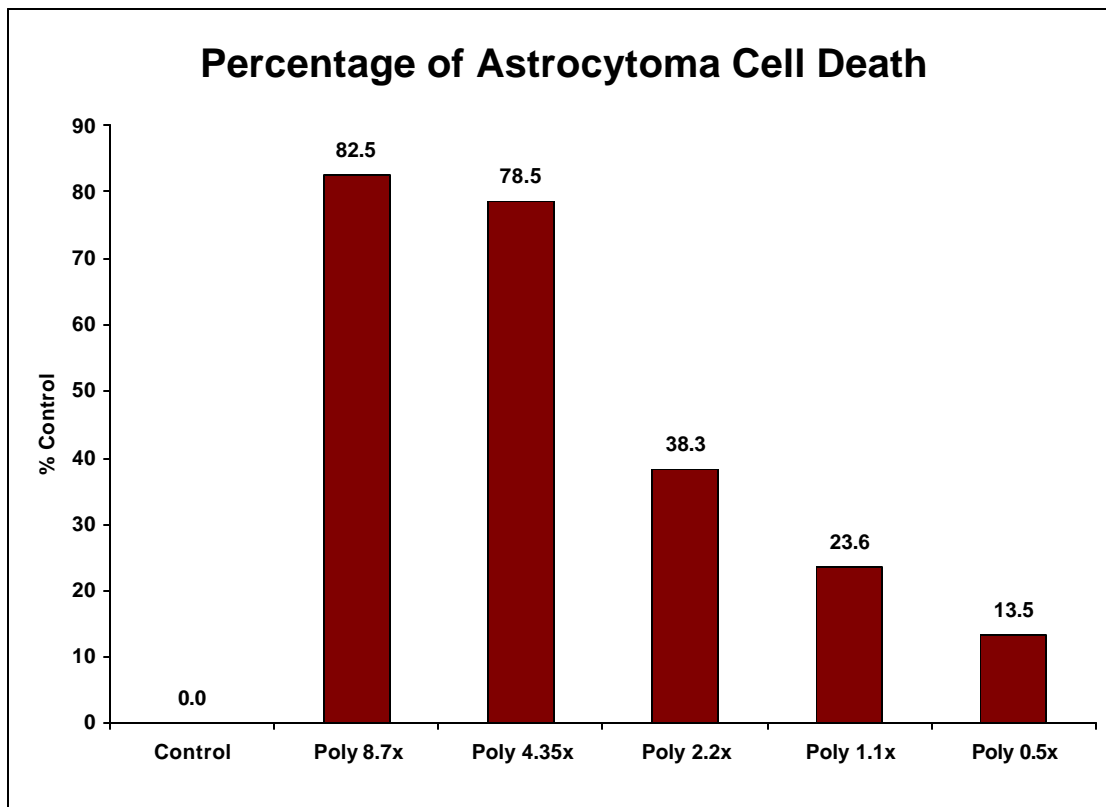
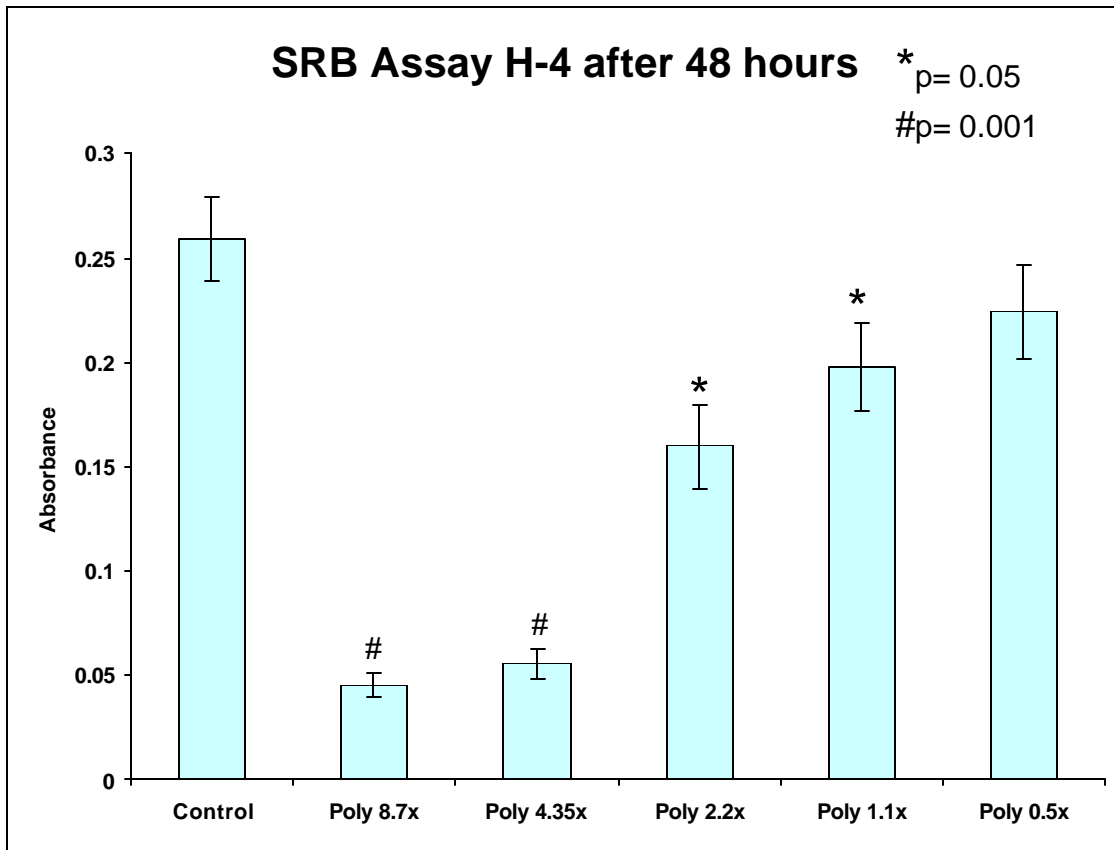
# NCI Assay: Ovarian Tumor – GML



# NCI Assay: Lung (Non-Small Cell Carcinoma) – GML



# NCI Assay: Brain (Astrocytoma) – GML



- **Clinical Human and Veterinary Studies**

- Veterinary - Currently, the largest integrative cancer investigation of PdLA is an open-label, veterinary oncology program with over 900 dogs enrolled, since its inception in January 2004. Patients receive the PdLA 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.). The PdLA seems 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, meningioma, neuroblastoma, mammary adenocarcinoma). Some of the most effective findings are apparent in the osteosarcoma patients. The etiology of osteosarcoma in large dogs is considered identical to the disease progression in humans.
- Veterinary - More importantly, following PdLA complementary support chemotherapeutic animals demonstrate improvements in additional objective parameters (i.e. weight, anemia, liver and kidney function). In addition to these enhanced clinical parameters, a subjective owner quality of life survey resulted in an 86% improvement following the addition of PdLA adjunctive support.
- Human – An observational study of stage IV cancer patients began in January 2004. Over 212 stage IV patients are in this cohort, with prostate, breast and lung cancer being the best responders. The typical oral dosage used is 40 mL or 8 teaspoons per day.
- Human - A regional cancer institute is in the process of developing an ovarian cancer study. An IND (investigational new drug) application was approved by the FDA (6/07).
- Human - A major research university has received IRB approval, as well as, granted an IND from the FDA to carry out a Poly MVA study. They are currently conducting a dose-escalation safety study and kinetics profile of the Palladium Lipoic Acid formulation in preparation for a formal astrocytoma program.

## **Mechanisms of Action**

Is POLY-MVA's proposed mechanism of action directly related to its structural formulation? POLY-MVA's unique electronic and redox properties appear to be the key to its physiological effectiveness.

When glucose enters a cell, it is broken down under anaerobic conditions (absence of oxygen) into pyruvate. Pyruvate subsequently enters the mitochondria, via complex I, and is quickly oxidized, in the presence of alpha-lipoic acid, to acetyl-CoA. In aerobic respiration, acetyl-CoA is then channeled into the Krebs/Citric Acid Cycle to create the reduced forms of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH<sub>2</sub>). NADH and FADH<sub>2</sub> donate their electrons to the electron transport chain to make the high energy molecule ATP. Recent studies in India



(Janardhanan et al., 2008) have demonstrated Palladium Lipoic Acid Complex's ability to facilitate aerobic metabolism, which is responsible for ATP production in healthy cells. The energy needs of the body are supplied by splitting ATP into adenosine diphosphate (ADP) and a free phosphate (Griffin et al. 2006).

Studies have demonstrated that POLY-MVA provides electrons to DNA, via the mitochondria. Electrons are lost in normal cells as a result of oxidative damage from radiation and chemotherapy (Garnett and Garnett 1996). POLY-MVA electron transfer provides an additional energy source to normal cells. However, cancer cells are metabolically challenged, and function in an hypoxic environment. Since there is less oxygen and more free electrons in the cancer cell, generation of free radicals occurs at the tumor mitochondrial membrane (Antonawich et al. 2004). This activates apoptosis by facilitating the release of cytochrome C from the inner mitochondrial membrane, allowing the formation of an apoptotic complex in the cytoplasm. This complex, results in the subsequent activation of the caspase cascade of enzymes that destroy the malignant cells. At significantly higher concentrations of POLY-MVA necrosis becomes apparent in the malignant cell. Given that healthy cells are richly oxygenated, POLY-MVA is nontoxic to them and they actually benefit from the energy boost (Antonawich et. al 2006).

Additional findings have examined the role of PdLA complex and a malignant cell's ability to physiologically adapt to a hypoxic environment. These physiological changes appear to be mediated by a molecule called HIF-1 (hypoxia inducible factor-1), which increases in hypoxic conditions to promote an increase in (Brown et al. 2006; Paul et al. 2004): Vascular Endothelial Growth Factor (VEGF) - a promoter of angiogenesis; Glucose Transport 1 (GLUT1) and glycolytic enzymes – critical components in anaerobic respiration; and Erythropoietin (EPO) – responsible for the differentiation of red blood cells) (Bacon et al 2004; Weinmann et al. 2004). POLY-MVA appears to decrease the production of HIF-1 thus restricting the ability of the cells to adapt to its environment and subsequently making it more vulnerable to the apoptotic cell death discussed above.

In **summary**, the POLY-MVA appears to be a selective metabolic modulator. Since it is a potent redox molecule, it has the ability to provide an alternative energy source to cells. While this is certainly of benefit to both normal and ischemic cells, it is detrimental to malignant cells. Furthermore, its capacity as an anti-oxidant makes it suitable to quench the free radicals associated with aging or as a result of reperfusion injury (cardiac or cerebral).

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