Palladium-lipoic acid coordination complex (PLA) was synthesized as a candidate chemotherapy agent. Patents were applied for as a novel composition of matter with therapeutic applications in 1993, and these issued in 1995, 1997, and 1998 (1-3). The original model for the mechanism was based on voltammetric measurements of PLA interacting with DNA. In these electrochemical scans it was shown that the standard potential of PLA was gradually shifted 170 millivolts in the oxidized electro-positive direction by addition of an aliquot of DNA:

PLA was therefore viewed as a charge transfer catalyst and as a synthetic DNA Reductase. Microscopic effects of PLA on tumor cells and on yeast showed that cell nuclei were condensed by PLA in a heterochromatic pattern, and it was assumed that the additional charge on DNA had modulated and compressed the chromatin. Chromatin compression was considered an aspect of gene silencing.

From the beginning we were interested in the intrinsic properties of lipoic acid and also of palladium. They appear to be complicated enough to deserve individual evaluation. Lipoic acid is part of mitochondrial Complex I, pyruvic dehydrogenase, and therefore has direct interaction with the charge relay system of the mitochondria as a source of charge.

But the unique properties contributed by palladium were puzzling. No other metal was suitable in this system. Moreover palladium has an elaborate history of catalytic behavior and use, especially with respect to hydrogen. We became interested in the dynamics of the d-orbital contribution of palladium. Within this large literature several phenomena began to emerge.
The d-orbital configuration of palladium allows an exaggerated extension of the electron radii. This electron range is far enough from the atomic nucleus to minimize its Coulombic attractive force, and give the d-orbital electrons the properties of unpaired electrons. It is a stable state and it imitates the free radical state.

This minimally attracted rotating electron state, manifests an orbital precession with a regular intermittent advance of the electron orbit trajectory. This state is the Larmor precession. Precession may be visualized as a wobbling top or a hula-hoop. When stimulated by a reaction, the rate of precession can increase, and the dynamic effect is described as a Rabi frequency.

According to Maxwell-Faraday-Heaviside laws, a moving charge produces a magnetic field in its path:

\[ \text{Curl } B = 4 \pi C \]

Here Curl is the net circulating magnetic energy, and C is the charge density or rate of charge moving through a cross-section of space or material.

We emphasize this mathematical representation of the behavior of palladium d-orbital electrons. The motion produces an intermittent or pulsed magnetic field. This is paramagnetism. In suitable palladium complexes it introduces a long range molecular signal (magnetic) into chemical systems.

So how do we measure paramagnetism in palladium-lipoic acid? The traditional standard has been to look for electron spin resonance (ESR) in the reaction using an electron spin resonance spectrometer. We pursued and reported this avenue using a continuous wave instrument. We first interacted PLA with DNA and vitamin B12 (4). Second we focused on the interaction of PLA with the guanine base of DNA and B12 (5).

There was a hyperfine transition of 6.5 Gauss produced in both of these interactions. This is the regularly repeated splitting distance between the spectral peaks. This hyperfine value was identified as equivalent to an irradiated excited state of guanine (6).
So the electron spin resonance influence of PLA on DNA, acts on the guanine bases of DNA, and is facilitated by vitamin B12. Therefore the charge transfer to DNA appears catalyzed by a spin resonance, and is a spin enabled current. As a confirmatory method we performed single frequency electrochemical impedance spectroscopy (Mott-Schottky), plotting the inductance parameter vs. the voltage. PLA transfers its magnetic oscillation to DNA in this method. Vitamin B12 is not needed in this experiment, since the instrumentation method has a baseline perturbation energy.

Over the years we have also looked at electrochemical interactions of PLA and also at DNA electronic character using electrochemical impedance spectroscopy of DNA mixed with hyaluronic acid as a dielectric (7). The sample showed its variable capacitance as two semi-circles in the Nyquist plot:

This variable capacitance, dependent on the voltage and frequency, is presumed to underlie the DNA spin resonance response to PLA.

Our present model is that PLA acts by introducing a spin current to DNA, which modulates and compresses the chromatin configuration. To the extent that PLA mimics a physiologic pathway, PLA can be considered to be a producer of mitochondrial Complex I spin current. The chromatin changes suggest the possibility of base stacking and DNA supercoiling, although this area is a subject of debate in the DNA-charge transport literature.

The complexity of internal cellular behavior is emphasized by a report on Topoisomerases (8). These enzymes which help establish chromatin structure, can be elevated by a variety of chemotherapy drugs. The elevations are associated with the appearance of heterochromatin and link it to apoptosis as “apoptosis-associated heterochromatic foci (AAHF)”. Apoptosis is a mitochondrial phenomenon in which hydrolytic enzymes are released in reactions of programmed cell death.

The linkage of apoptosis to heterochromatin correlates mitochondrial activity with the gene state. We believe this ordinarily occurs by mitochondrial production of free radicals and diffusion of the free radicals into the nucleus. As a general process this allows a variety of mitochondrial spin currents to impact the nucleus.
This is a direct metabolic connection to gene regulation, and is the most likely avenue by which PLA has cytotoxic effects, producing both heterochromatin and apoptosis. More generally, it implies that genetics and energetics are intertwined - a new subject. I have called it Electrogenetics in the belief that interactions of DNA and RNA and enzymes, can be approached by electro-analytic methods.

References