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This issue features an update regarding the subject of salvestrols, which are compounds found in fruit and vegetables that can kill cancer cells by serving as substrate for an enzyme that is highly expressed in cancer cells and present in the cytoplasm at very low levels if at all in normal cells. The enzyme facilitates the conversion of this substrate into a new compound that is cytotoxic and kills the cell. Normal cells are not affected. There has now been over a decade of research directed at identifying the most potent of these compounds and perfecting their extraction and formulation into an oral supplement. Mainstream medicine ignores this achievement. In this issue we report on research that utilizes the presence and action of this unique enzyme for the purposes of identifying circulating cancer cells and monitoring the effectiveness of salvestrols by examining the extent to which they are metabolized. Case studies done to date are also summarized.

Wishing you and your family a safe, healthy and happy summer,

William R. Ware, PhD, Editor

SALVESTROL UPDATE

In previous newsletters the subject of salvestrols was introduced and discussed. Salvestrols are a mixed fruit extract which has remarkable experimentally demonstrated anti-cancer properties, both in the context of prevention and treatment. The original development involved the convergence of two research paths. A number of researchers had observed that a certain enzyme, belonging to the P 450 class, was what is called overexpressed in cancer cells derived from tissue but not normal cells. This observation was verified for a wide variety of cancer tissue in the late 1990s and early 2000s. Professor Gerry Potter and his colleague Professor Dan Burke investigated and reported that this enzyme, called CYP1B1 was able to metabolize plant-derived polyphenolic and similar compounds to produce metabolites that were cytotoxic, resulting in the death of the cancer cells in which the enzyme was expressed at the protein level (rather than as a nuclear mRNA). This suggested that the existence of this enzyme was part of a mechanism that had evolved to use plant polyphenols and other compounds from the diet to kill off adventitious cancer cells which are always being generated at low levels in humans and obviously destroyed or we would not exist as a species.

One might wonder what triggers the overexpression of CYP1B1? The precursor, mRNA is present in normal and cancer cells and something, apparently general to cancer cells independent of site or type, triggers the translation and migration outside the nucleus to ultimately result in the synthesis of the enzyme CYP1B1, termed expression, at the protein level in the cytoplasm. The answer to this interesting and significant question does not appear to exist. If it did, it might provide additional useful information regarding carcinogenesis. However, most researchers are concentrating their attention with regard to CYP1B1 on inhibition since it is viewed as part of a carcinogenesis mechanism involving aromatic hydrocarbons or estrogen. If the patient has cancer, this appears to be a rather insignificant issue compared to the potential for using the enzyme to create a cytotoxin, i.e. the magic bullet.
Cell culture techniques allowed these researchers to examine a huge variety of fruit and vegetable extracts and extraction methods in search of the most potent cytotoxic metabolites of CYP1B1. It was also postulated that these chemicals were historically also present in fruit and vegetables to guard against natural enemies. They were after all concentrated generally in the skin area, were frequently bitter to the taste and, most interesting of all, in comparison with organically grown produce were at remarkably low levels in modern produce grown with insecticides and from highly inbred varieties. Thus to achieve the goal of a highly active concentrate, it was necessary to be careful regarding varieties and to insist on organically grown items.

This work was published but ignored. Your editor wrote and had published a review in Integrative Cancer Therapies in 2009 in an attempt to give this ground-breaking research wider exposure since he agreed with Potter and Burke that this was one of the most important discoveries in cancer research in decades. At the same time your editor published a paper calling attention to the potential offered by this cancer-specific enzyme for photodynamic therapy, diagnosis and establishing surgical margins.

Very recently a book about salvestrols written by Brian Schaefer has become available. Dr. Schaefer has been involved with this project and is also associated with a research project seeking a blood-based cancer diagnosis protocol that makes use of the presence of CYP1B1 in the circulation. In addition, the salvestrols researchers have been looking for the presence of CYP1B1 metabolites in the circulation. Detecting circulating cancer cells is an area which today is attracting much interest. Some of the highlights he reviews in his book will be discussed.

The original observation that CYP1B1 was not expressed in normal cells was found to not be universally true when highly sensitive detection methods were used, although the levels in the few tissue types studied were still vastly lower than found in tumor tissue. In fact, Schaefer’s book lists 26 cancer types where the overexpression has been observed, and for some, there are multiple studies cited. However, the researchers also found considerable problems associated with tissue sampling, extraction and quantification and turned to examining circulating cells in blood. They eventually developed a highly sensitive assay specific for human CYP1B1. In what they call the proteomic approach, they were able to establish a baseline CYP1B1 level in individuals believed to be free of cancer. What Schaefer terms minute but not zero suggests it is normal to have a small number of circulating cancer cells presumably produced by various agents, toxins, radiation, cellular environment, etc. Normal individuals simply deal with these and it is entirely possible that diet derived salvestrols are involved in killing off these cells, a notion in keeping with the evolutionary explanation of their existence. Schaefer estimates that the present level of sensitivity allows cancer detection about 6 years prior to clinical manifestation.

Readers will note that given the very low but finite baseline serum CYP1B1 levels in healthy individuals, this approach is equivalent to screening with a threshold, a subject that has come up a number of times and discussed at various levels of sophistication. The poster child is PSA. As with all screening using a threshold, there are issues of sensitivity and specificity. Until the results of clinical trials currently underway by this group are published, all we have is some data provided by Schaefer’s book from lung cancer patients where CYP1B1 was measured at between 100 and 6000 times normal background and the level was a good match with the degree of disease progression. This suggests a highly successful, perhaps even sensational screening tool.

Schaefer describes a second blood test examined by the research group with which he is associated. It is called the metabolic approach. If one has a sensitive analytical method for testing in blood and urine for both the salvestrol (substrate) and the metabolite produced by CYP1B1, then this offers the opportunity to detect the enzyme and to measure the extent of the cancer by the change in substrate concentration and the amount of metabolite. They first selected a salvestrol that produced large amounts of metabolite not present from dietary sources. They then determined when the peak concentration of the metabolite occurred after ingestion of the salvestrol. This was followed by examining a group of healthy individuals where it was found that salvestrol was recovered unmetabolized in the blood and urine. When cancer patients were given the salvestrol, the presence of the metabolite was found. The analytical method was high performance liquid chromatography, a standard technique. In the cancer patient the amount of substrate metabolized increased with the severity of the disease as estimated from the clinical presentation,
and for severe disease they were unable to detect any substrate, only the metabolite. The tumor was large enough to metabolize all the substrate at the dose given. These observations were made on individuals with breast, stomach, kidney, and prostate cancer and an array of stages but skewed towards more advanced cases. He concludes that this can be taken as evidence of the metabolic manifestation of a universal cancer marker. Another view is that this result is further proof in principle of the role of CYP1B1 in cancer prevention and as a unique target for therapy.

The metabolic approach obviously offers the opportunity to measure the effectiveness of any given salvestrol mixture, to examine individual dose dependencies, and then form a non-invasive judgment regarding when a “cure” or significant regression has been achieved. When one considers that the therapy is non-toxic, that the “chemotherapeutic agent” works only on cancer cells and there is no systemic toxicity, that it is made up of natural products extracted from fruit and taken in dry form in a capsule, it hard not to be very enthusiastic about the salvestrol approach to cancer therapy and the CYP1B1 approach to identifying the presence of cancer with a blood test.

The screening tests under development do not yield site-specific information. The proteomic approach is exquisitely sensitive and close to the state of the art sensitivity for detection of a chemical in the circulation. Thus if screening is done and a positive result is obtained, where is the cancer? A serious problem since it may be small enough as to escape all modern attempts to locate it, e.g. a site specific serum marker or full body CT scan. Thus modern medicine is left helpless since there is no non-specific anticancer treatment in so-called evidence based and officially sanctioned cancer therapy. The integrative therapist might be inclined to try the most modern salvestrol product since it is non-specific, and see if the metabolic or proteomic markers decline, something unthinkable if the problem is being addressed by a modern oncologist.

Mainstream medicine thinks only in terms of their holy grail, the randomized controlled trial, as evidence for even considering a new therapy. Consider the obstacles facing salvestrols. Salvestrols based on natural products cannot be patented. Only Big Pharma or governments not strapped for cash can finance the series of trials necessary for regulatory approval. Cynics claim Big Pharma is not really interested in a cancer cure. It would be hard to find a physician who would take the professional risk of recommending to a cancer patient that they try the salvestrol approach rather than the conventional approach, which would make recruiting almost impossible. Combining salvestrols with conventional treatment is interesting but probably would be hard to implement in more than a very small trial. A trial that might satisfy integrative physicians or those practicing integrative-complementary medicine can be visualized. It would involve patients who have rejected conventional treatment or have advanced cancer where the absence of merit associated with conventional treatment is so clear that they simply reject it as having a benefit/risk ratio of near zero and a huge adverse impact on the quality of their remaining life. These individuals could easily be recruited for an uncontrolled study or an old-fashioned study where the control is based on the average life expectancy of matched untreated patients. Mainstream medicine would look down on such a study and its results because it is not a randomized, controlled trial following the required phase I and II trials. Held in even higher contempt is the case study, although major journals continue to occasionally publish one.

Instead of clinical published clinical trials, so far all we have are handful of case studies involving treatment. In his book, Schaefer mentions 11 published case studies which all had complete recovery from cancer. Sites and stage included:

- Squamous-cell carcinoma of the lung, stage 2-3
- Melanoma, stage 4
- Prostate, 3 cases, one Gleason 3+3
- Breast, stage 3, 2 cases, one aggressive
- Bladder
- Liver stage 2
- Colon
- Hodgkin’s lymphoma, stage 3B

However, aside from some blood-related cancers, the total disappearance of a cancer through conventional chemotherapy is very rare. Oncologists rejoice when they achieve life extension for advanced cancer measured in months.

While total disappearance of any manifestation of cancer has been achieved in these studies, Schaefer in his book points out that there is a large variation in how rapidly the patients respond. Also, not everyone
responds and the reasons are unknown, but it is clear that there is a dose dependence that is individual. Interfering drugs or dietary factors have hardly been studied at all. Even dose studies are difficult under the above described circumstances. Your editor has been told that more case studies are about to be submitted for publication and he will report when they appear. But given the fact that salvestrols are merely selected and concentrated fruit extracts found to work well in cell culture studies where they kill cancer cells but not normal cells, it would seem that the risk of trying this approach is not great. After all, many healthy individuals take mixed fruit polyphenols or individual fruit extracts as preventive supplements. Ignoring the absence of randomized controlled trials may be justified.

Taking low doses of salvestrols for cancer prevention is also not unknown and may be significantly superior to fruit extracts available at the health food store or online because they have laboratory proven cancer cell cytotoxicity. While therapeutic doses are rather expensive and obviously not covered by insurance or government plans, a small dose with preventive potential is not.

As mentioned above, the underlying theory of salvestrols is that CYP1B1 represent a rescue enzyme that humans evolved eons ago in order to deal with cancer cells and destroy them with substances present in the normal diet. Salvestrols can be found in a variety of fruits and vegetables and this partly explains why the dietary intake of these foods can impact cancer. However, as Schaefer points out in his book, the salvestrol content estimated in the Victorian diet is considerably higher than the modern diet, thus diminishing the impact of diet on cancer prevention today. Thus someone with a standard American diet is poorly protected if at all, and the prudent diet rich in fruits and vegetables is only optimally protective in the context of dietary intervention if made up of organically grown fruits and vegetables. Thus if one takes a salvestrol capsule daily with a prudent diet, this provides additional protection and addresses the problem of the scarcity of real organic foods and a selection that is not optimum, but no one knows if this dose is adequate. We may never know. The point is that the selection of the most powerful salvestrols known for the commercial product provides a significant advantage even over what one might judge as an ideal diet. Especially noteworthy is the fact that the potent salvestrols are commonly concentrated in peel or skin of the fruit which may be discarded, and also the fact that the concentration increases upon natural ripening which is absent in produce not locally ripened prior to marketing. These arguments should be compared to the position of mainstream medicine and nutrition that we get all we need from a good diet and do not need supplements. A lot has changed since we ceased to be hunter-gatherers, but our genome was fixed as regards to most of our human biochemistry, microbiology and physiology. Significant aspect of agriculture, diet and lifestyle now do not match that genome. Some call it civilization. Some view it as a disaster.

Salvestrols can be ordered online at www.salvestrol.ca. Dr. Schaefer’s book can be ordered via this link: http://www.salvestrolbook.com. Your editor has no financial interest in salvestrols, does take a daily low dose for prevention, and emphasizes that the above information does not constitute a recommendation, but merely provides information.

Reference List