Written 12/7/2015

THE DISCOVERY AND/OR INNOVATION OF EEA (ENHANCED ENERGY APPLICATIONS) BEGINNING IN JANUARY, 2013

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This discovery speaks to the introduction of two concepts that are synergistic to the treatment process of High Intensity Focused Ultrasound (HIFU). To be more specific, there is no prior art that speaks to the application of additional energy to a hypermetabolic cellular state nor to the concept of supersaturation of the cellular structures treated using the HIFU technology. While HIFU has been available worldwide for more than 33 years, neither the patent art nor a clear understanding of its application and clinical benefit has been explained adequately until now.

Original patent art was presented more than three decades ago in the European marketplace with the intention to compete with treatment procedures such as radical prostatectomy and radiation therapy, including, but not limited to, brachy therapy, intensity modulated radiation therapy (IMRT), and proton beam. Clinically speaking, Capsure data (c.2008), representing community-based data regarding the efficacy of radical prostatectomy and radiation (both delivered with any technology or format) are only average therapies at best in treating the number one scourge that men face health wise, namely, prostate cancer affecting hundred of thousands of men worldwide per year, including more than 230,000 men in the United States of America per year alone. While these two therapies have been industry standards for decades, they have failed (for the most part) to alter treatment outcomes predictably while attempting to cure disease. In many cases, it could be argued that the treatment itself was worse than the disease contracted. HIFU as a treatment entity was anticipated to be safer and more effective than the aforementioned therapies. Unfortunately, the patents issued for HIFU never delivered in becoming a disease altering concept in particular for aggressive prostate cancer. Arguably about 50% of all cases diagnosed regardless of the diagnostic technique utilized, namely a biopsy or MRI imaging. To be sure, there was no change or alteration in clinical outcome data until 2013.

What took place in 2013 was nothing short of incredible as the terms hypermetabolic and supersaturation became relevant to HIFU. The resultant clinical data stands as witness to a quantum curative advantage that this utility patent application intends to yield. Hypermetabolic activity is associated with the application of the thermal energy from any source but expressly acoustic energy associated with any HIFU technology delivered to any organ, including, but not limited to, the prostate and breast. Clinically, the resultant of the addition of thermal energy is seen on ultrasound as a destruction of cells called cavitation or a “popcorn effect”. While cavitation has been described in prior art, it could never have been obvious to anyone that the acoustic energy applied initially was substandard in killing prostate cancer cells predictably.

After all, the results expressed from research substantiated why a patent(s) were granted and issued. Unfortunately, the clinical benefit expected was only seen in the most innocuous of cancer cells consistent with a Gleason score of six or less as well as non-cancerous cells. With this noted, the outcome data from a HIFU prostate procedure showed a 24% failure to cure in men diagnosed by biopsy with a Gleason score of six associated with a four-year Canadian study published in 2012 in the British Journal of Urology, International Edition using the Ablatherm technology. The lead author in the Canadian study was Pinthus, et al.

In a five-year Japanese study (Uchida et al.) showed a 16% failure to cure rate associated with an 84% biochemical cancer free survival rare while treating Gleason six cancers (the most common prostate cancer albeit the least aggressive) using the Sonoblate technology. To state further, this data represents the best clinical data worldwide versus the least aggressive prostate cancer cell type known scientifically to mankind.

After an adequate review of relevant articles discussing principles of physics associated with the application of acoustic energy (HIFU) as well as the shortcomings associated with inferior and substandard clinical data, a unique research experiment took place beginning in January, 2013. I performed the first human experiment ever in the history of medical annals whereby a second passage of hypermetabolic energy (35 to 42 watts), followed immediately a successful initial delivery of energy correlating to the industry's standard "single pass" of energy at 35 to 42 watts. To this point, the HIFU industry had been unable or unwilling to alter a treatment protocol that delivered mediocre clinical results. Collectively the research personnel had to respect the prior art as gospel while accepting the clinical results notwithstanding knowledge of relatively poor clinical results. Clearly, adding additional energy was not obvious to anyone, regardless of intellect or proprietary interest.

My working hypothesis was that the immediate passage of additional acoustic energy (assuming it was safely administered) may transform a very pedestrian treatment process into an exceptional treatment process with a focus on safety and tissue tolerance, while annihilating even the most aggressive cancers. It was also not obvious as to what wattage of power should be used for the second passage. A baseline decision was made to replicate the first passage of energy with the second passage at 35-42 watts of power. In more than 160 consecutive patients with what is now known as a "double pass" of energy, my team and I are assured that no live residual tissue remains within the prostate capsule. Therefore, total destruction of all prostate cellular material was witnessed and validated by functional sequences associated with the follow-up 3T multiparametric MRI scan at 6-12-month intervals from treatment. The HIFU procedure is performed cautiously and expertly by a well-trained urologist.

To state further, no additional HIFU treatments are needed to be performed following a singular "one time" event or experience assuming all facets of the treatment protocol have been carefully adhered to.

Moreover, the addition of a second hypermetabolic event has a synergistic benefit to the first passage of energy allowing for the targeted tissue in question to have received a double dose of energy consistent with the creation of a supersaturated environment or gland. The supersaturated

tissue environment created by a “double pass” of energy has virtually zero chance of recurrence when every qualified gland is treated capsule to capsules (side to side), as well an anterior to posterior. The highest scrutiny relies on a PSA nadir (an analytical metric) to remain low at a number less than 0.1 ng/ml. According to European data, any PSA number less that 0.30 ng/ml is consistent with a cure.

Simplistically speaking, a hypermetabolic supersaturated environment is similar to adding sugar to a teacup of cool water. Assuming you add sufficient sugar, you will begin to seel granules remaining at the bottom of the teacup. In this example, sugar molecules are going in and out of solution (even though our eye cannot discern this activity). This solution can only become supersaturated when adequate heat is added. When the tea water cools sugar granules will come out of the solution. This same process takes place in the prostate as cavitation of all cells will take place when enough heat is placed (equivalent to the “double pass” of energy). Supersaturation equates to all cells melting including every level of cellular activity, including but not limited to the germinal epithelium where cell growth emanates. The kinetics (cellular mass movement as example or hypermetabolic activity associated with cavitation) expressed herein are associated with spectacular results seen expressing in the most aggressive prostate cancers. See the chart previously sent on 38 patients.

A single pass of energy may be all that is necessary with a low-level cancer such as a common Gleason 6 cancer. To be certain, the failure rates with any Gleason grade greater than four translates into a cancer that has high probability of failure without the new and improved treatment protocol.

In accordance with the Canadian study, 402 patients were evaluated. The authors Pinthus and Orovan principally treated Gleason scores of 6 (3+3), 7 (3+4), and 7 (4+3). A 4+3 =7 is more aggressive than a 3+4 =7. A Gleason score of 6 is associated with a cancer that may or may not be treated; however, a rising PSA number should prompt a better understanding for the integrity of the entire gland using a sophisticated 3Tesla Multiparametric Magnetic Resonance Imaging scan (another example) of a diagnostic metric. A scan will show the totality of the entire gland. Even areas of the prostate where a biopsy does not commonly sample. Unfortunately, the Canadians did not correlate any biopsies with imaging. Using a single pass of energy, our Canadian colleagues noted an overall PSA nadir of 0.38 ng/ml, higher than the European standard for cure measured by a nadir less than 0.30 ng/ml. As noted previously, the Canadian study experienced a 24% failure when they treated Gleason 6 prostate cancers and a 30.5% failure rate with Gleason 7 cancers. In their study, no extremely aggressive Gleason scores were treated. Similarly, no aggressive prostate cancers were treated in England, Germany, France or Japan. The European countries and Japan excluded Gleason 7 (4+3) cancers as well as Gleason score is of 8, 9 and 10 from their treatment group, noting these cancers to be too aggressive for a HIFU procedure.

Two other comparative research studies are not worthy for review but not yet published. The two studies compare 43 patients and 38 patients. In the 43 patient subset, Dr. Scionti, associated with Vituro Health, treated all individuals with a single pass of energy. He presented this group of patients at a prostate conference, but failed to list results of imaging studies, PSA numbers or

Gleason scores. His PSA nadir was noted to be 0.69 ng/ml, slightly less than twice as high as the Canadian data while using the Sonoblate 500 technology. As a reminder, the relevant nadir for cure according to European data must be less than .030 ng/ml.

A 38 patient study was conducted by Dr. Wheeler, associated with HIFU Centers of America. Dr. Wheeler's intent was to take the most difficult and aggressive cancers from all he had treated using the Ablatherm technology, also used in the Canadian study. Dr. Wheeler evaluated all patients while using various diagnostic metrics including PSA values (pre and post treatment), biopsy results and a 3T MP MRI scan. Dr. Wheeler's data, while included herein, shows a PSA nadir post HIFU treatment of 0.09 ng/ml. By comparison, Dr. Wheeler's data set was minimally 7.5 times lower than Dr. Scionti's data and greater than 4 times lower than his Canadian colleagues. Dr. Wheeler used his patent-pending discovery uniquely with a "double pass" of energy. Clearly with all data presented, it speaks for itself while using a common technology with a common analytical metric known as the PSA nadir.

Conclusion: For more than 30 years a basic theorem has been in place showing the benefit of acoustic energy to cause cavitation at a cellular level. In regard to the European patent applications, there is very little in discussing the metrics of the energy utilized as it did not involve live human subjects. Understanding the clinical value associated with the most prolific cancer that men contract is when Dr. Wheeler's discovery is all about. It took unprecedented courage, carefully measured risk, and a comprehensive understanding for physics to demonstrate Dr. Wheeler's innovation in a clinical model. The synergistic action of EEA with cells in a hypermetabolic state where supersaturation of tissue was the endpoint was the genius of his innovation and could not have been obvious to anyone under any circumstance. Therefore, the use of acoustic energy in treating the most aggressive cancer through EEA allows for the annihilation of tissue at the cellular level uniquely as proven by nadirnomics and scanning through 3.0T MP MRI imaging.

For all these reasons the value of Dr. Wheeler's research must receive protection through a use patent to the good of all men with aggressive prostate cancer. To do anything less would endanger and subsequently lessen the rights in the lives of those with disease who deserve better. Dr. Wheeler's discovery is believed to be the first time in medical history that the synergistic effect of retreating immediately a hypermetabolic cellular environment to the point of supersaturation utilizing HIFU (acoustic energy) whereby the cessation of cellular function (cell death) is proven by imaging with a 3T MP MRI scan. The process of supersaturation enables an objective scientific methodology to validate total and complete cavitation ensuring 100% destruction regardless of Gleason grade or score, offering future generations more than just hope in their quest to beat prostate cancer once and for all.