

Examining the Scientific Basis for a Novel Combination of Growth Factors and Neurotrophic Factors to Decrease Autonomic Over-expression and Rebalance Dysfunctional Cell-signaling Pathways to Attenuate Symptoms Associated with Post-traumatic Stress Disorder (PTSD) – a 4-month Pre-clinical Study

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Abstract

Derived from the scientific research and analysis of disrupted cell signaling factors and their affected pathways, a **novel and clinically-proven paradigm** was presented in this pre-clinical study to demonstrate how a complex of *isoenergetic cell-signaling*[™] factors was able to safely and effectively address the disrupted signaling pathways which give rise to the symptoms of PTSD. This study is the first of its kind to use this type of medicine. The formula created and used for this purpose is composed of select cell signaling factors prepared to non-molecular vibrational levels.

This study quantified its clinical benefits with a small, diverse group of veterans with PTSD. To understand what gives rise to the symptoms associated with PTSD and to be able to effectively resolve this affliction of multiple cell signaling dysfunctions, it was first necessary to understand the neurobiological mechanisms – the cell signaling factors and their pathways associated with the psychological and behavioral components manifesting as PTSD. These pathways include the molecular mechanisms and their corresponding neural circuits which underlie Pavlovian fear conditioning and memory.

A group of select cell-signaling factors was used to create a formula specifically for PTSD (**Post Traumatic Vets Defense**[™]) and, over a 4-month period, 11 veterans with PTSD took the formula three times daily. A monthly Self-assessment of Symptoms Questionnaire (SASQ) containing 91 quality-of-life questions was completed by each participant and their partners (only 3 partners agreed to participate at the time). After Paired t-Test biostatistical analysis using IBM SPSS (R) V 27 software was completed, 55 questions demonstrated statistically significant improvement ($p < 0.05$). Another 10 questions demonstrated *trending* statistical significance ($p < 0.095$). Partner analysis of SASQ forms demonstrated a dramatic concurrence that the formula had worked with partner p values of <0.001 , <0.001 and <0.003 . These positive pre-clinical study results scientifically validated many anecdotal reports received over the previous 8 years. In the words of one participant: *“the benefits I have received have been nothing short of ‘miraculous’.”* **Co-investigator Comments/Clinical Experiences** with *isoenergetic cell-signaling*[™] Cell Function Activator[™] medicines follow this paper's References section, as do brief *biographical sketches* of the authors.

Purpose of this Paper

In a November 2013 article reported by CNN:

“...Every day, 22 veterans take their own lives. That's a suicide every 65 minutes. As shocking as [this] number is, it may actually be higher. [This] figure, released by the Department of Veterans Affairs in February, is based on the agency's own data and numbers reported by 21 states from 1999 through 2011. Those states represent about 40% of the U.S. population. The other states, including the two largest (California and Texas) and the fifth-largest (Illinois), did not make data available....”

An unedited email from an Iraq/Afghan veteran who now lives in California, received after he used the Leptica Research PTSD formula for about 2 weeks, demonstrates some of the **results** we hoped to replicate with this pre-clinical study:

*“Prior to taking the product, I didn’t want to get out of bed in the mornings. I hated facing the days. Now, I **wake up fairly happy** and am **sleeping better**. I am not having such harsh **revelations of past combat experience**, either. I have had a few but [they are not] **not nearly as frequent** as before. Also, I am **not fighting in my sleep** – my wife thanks you for that! She was getting tired of being, as she calls it, ‘fish hooked’ in her sleep.”*

Introduction

PTSD has been around for as long as individuals have experienced trauma that leaves them in a chronic state of altered responses to themselves and their social perceptions. Virtually all aspects of one’s mental and physical well-being are affected. It can happen to anyone at any age who experiences firsthand – or as an observer – natural disasters, war, actual or potential violent or intense physical attacks (e.g. sexual abuse), life-threatening medical conditions, repetitive potential harm, serious accidents and/or other traumatic events. It is far more prevalent than most people realize. According to the National Institute of Mental Health, approximately 3.5% of American adults struggle with PTSD during any given year. It is estimated that 17% of veterans returning from the wars in Iraq and Afghanistan experience PTSD (Cassels, 2010). Per Fulton (2019), approximately 23% of military soldiers deployed to Iraq and Afghanistan for Operation Iraqi Freedom, Operation New Dawn and Operation Enduring Freedom experienced deployment-related physical or emotional trauma upon their return and were subsequently diagnosed with PTSD. (It should be noted, however, that receiving a PTSD diagnosis is *not* an easy process through the VA, so this figure may be low. Underreporting is also not confined to servicepersons. In a personal conversation, the primary author was told by a state trooper that he would be surprised if 50% of state troopers did not already have or were developing PTSD.)

Currently, there are no clinically-proven, long-term or effective pharmaceutical or psychotherapy PTSD protocols available at the VA. **The estimated suicide rate of 22 veteran suicides per day demands that all possibly viable, safe and effective means to address PTSD be considered, especially scientifically-based research**, to address this costly and deadly personal and societal affliction. From the time in 1999 when we developed isopathic recombinant DNA growth hormone and veterans came to us for help, we have known that growth hormone signaling helps inhibit somatostatin hormone, which becomes dominant when the sympathetic nervous system or SNS (flight, fight, freeze - survival mode) is engaged and remains hyper-expressed when one is experiencing PTSD. In recent years, with the advent of additional research on neurotrophic factors and hormones, additional cell signaling factors have been described, including the complex relationship of their intersecting pathways, which could also have an impact on PTSD. Add to this a greater understanding of genetics and the discovery of cell signaling factor isotopes, many pieces of this puzzle can now put together. It is from this research (cited in the References section at the end of this paper) that the *Post Traumatic Vets Defense™* formula was developed.

Risk Factors for PTSD

Genetic risk factors are now recognized that make some individuals more susceptible to PTSD. Additionally, **epigenetic** (environmentally-influenced) factors – e.g. chemical exposure and chronic stress – can lower a person’s threshold and make them more susceptible to PTSD. In a study of police officers’ routine work-environment, *stress* was the factor most strongly associated with sub-syndromal PTSD (Maguen, 2009) and was found to have a greater association with PTSD symptoms than cumulative critical-incident exposure (Lieberman, 2002). In the literature, PTSD stressors are sourced to occupational, social, environmental and financial origins, and *all* are capable of exerting a *cumulative* effect to lower the threshold for PTSD susceptibility and manifestation. It is also recognized that age, gender, ethnicity, current as well as cumulative life events, on-going self-perceptions (e.g. feeling ostracized) and lack of familial and social support systems also play a role in susceptibility to and prevention of the resolution of PTSD.

The following are categories of **daily stressors** which could potentially contribute and have a threshold-lowering, cumulative effect on making one more susceptible to developing chronic PTSD. The frequency of

these stressors, as well as the lack of social support, contribute to the degree of impact of PTSD, and the *degree* of negative affect was also found to contribute to PTSD severity as well (Maia, 2011).

Occupational Stressors

- Supervisor difficulties: criticism, lack of feedback, passive-aggressive behavior
- Coworker challenges: lack of confidentiality, criticism, harassment
- Workload
- Job dissatisfaction
- Lack of work-role clarity and support
- Morale
- Employment security
- Lack of employment availability

Social Stressors

- Discrimination
- Family conflicts, abuse
- Lack of social support
- Sexual harassment and abuse
- Financial hardship
- Lack or inability to have hobbies

Environmental Stressors

- Malevolent environment
- Inadequate sleep – which is a major factor in promoting emotional exhaustion
- Physically-harmful or life-threatening setting

In our experience, impaired sleep quality (reduced, disrupted, non-restful) also contributes significantly to lowering the threshold for and continuance of chronic PTSD due to its impairment of growth hormone production and release. It is important to understand that *chronic* environmental stressors can raise the threshold for susceptibility to PTSD. Marmar, et.al. (2006) found five variables that were significant in predicting PTSD:

- Greater peritraumatic distress – severity of feelings and physical sensations present during and immediately after the traumatic event(s)
- Greater peritraumatic dissociation – changes in the sense of self, time and place during exposure
- Greater problem-solving coping ability – dealing with issues following the aftermath of trauma
- Greater routine work-environment stress
- Lower levels of social support

Some skeptics posit that the only reason the incidence of PTSD seems greater among service members today than during the times of WWII, the Korean War and the Vietnam War is because of better diagnosis. However, given that social stresses are more complex and pollutant levels are more ubiquitous today than in decades past, it is very unlikely that a better diagnosis is actually what contributes to a greater incidence of PTSD. This idea is not unlike the explanation of increased incidence of TBI (traumatic brain injury) in athletes. It was once thought that numerous concussive hits were necessary to develop TBI. However, research has shown that cumulative sub-concussive hits – even as few as three hard, non-concussive hits – are capable of inducing TBI and, if unresolved, leads to CTE (chronic traumatic encephalopathy) over time. [**Note:** our formulas for TBI and CTE are currently in their proof-of-hypothesis analyses and case studies phase of research.]

Diagnosing PTSD

Individuals suffering from traumatic stress symptoms for *three months or more* are generally considered to have PTSD. According to the Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM IV-TR), PTSD has been classified as an anxiety disorder (Coentre, 2011). However, symptoms expressed with this disorder may include dissociations, depression, obsessions and social phobias (Deering, 1996). Our research included having to consider the mechanisms underlying *all* of these symptoms. Anxiety is just one of the PTSD pathways and, in our opinion, should not simply be classified as an “anxiety disorder”.

PTSD diagnosis covers 3 sets of response-related symptoms:

- Re-experiencing the traumatic event through intrusive memories, flashbacks and nightmares – images, sounds, smells and feelings can trigger traumatic flashbacks
- Avoidance of and/or affective numbing to these experiences
- Hyperarousal or hypervigilance

Intense fear, terror and an overwhelming sense of helplessness often accompany these symptoms and, as a result, interfere with one’s ability to have a stable, life and maintain normal relationships (Bowirrat, 2010). Any or all of these symptom sets can have an adverse effect on one’s self-esteem and self-worth, as well as one’s intimate and social relationships, resulting in an overall decrease in one’s quality of life and can even lead to suicidal ideation. Therefore, **it is imperative to know what alterations take place in the expression of the relevant cell-signaling factors in PTSD, as well as the pathways they affect, and then seek to correct these cell-signaling imbalances.**

PTSD and Co-morbid Issues - Auxiliary Psychological Issues

Insofar as the neurotrophic factors that affect diverse neuronal pathways in the brain relate to specific disorders, individuals with symptoms associated with the following conditions should watch for potential profile improvements:

- Agoraphobia – oxytocin signaling increases willingness to socialize
- Anxiety Disorder – leptin is anxiolytic
- Bipolar Disorder – BDNF (brain-derived neurotrophic factor) is involved when found co-morbid with PTSD (Rakofsky, 2012)
Note: antidepressant prescription medications often used for PTSD present a risk for manic induction, if bipolar disorder is present (Leverich, 2006)
- Cravings, especially for simple carbs and sugars – leptin controls cravings by directly affecting the dopaminergic system in the hippocampus and the sweet taste bud cells on the tongue
- Depression – IGF-1 (Insulin-like Growth Factor 1), leptin and BDNF are all recognized as anti-depressive
- Drug Dependence (alcohol, cocaine, meth, tobacco) – GDNF (glial cell-derived neurotrophic factor), IGF-1 and sirtuin (proteins that regulate cellular homeostasis) expression all influence drug dependence
- EHS (Electromagnetic – EMF – hypersensitivity) – IGF-1 and sirtuin expression enhance compromised mitochondrial function, and leptin inhibits influx through voltage-gated calcium channels (VGCCs)
- MCI (mild cognitive impairment) – IGF-1, FGF-2 (fibroblast growth factor 2), BDNF and GDNF help promote axonal extension, dendritic branching and improved energy to neurons

- Obsessive Compulsive Disorder – an outcome of hypervigilance, this disorder involves the ability to sustain attention to a task for a long period of time and is reduced by leptin signaling
- Panic Disorder – a form of extreme anxiety, reduced by leptin signaling
- TBI (traumatic brain injury) – mild TBI may exacerbate the effects of limbic/paralimbic system microstructure on PTSD symptoms (Sydnor, 2020)

[**Note:** Leptica Research has two separate isopathic formulas to address TBI and CTE.]

Failure to Correct PTSD can lead to Future Physical and Cognitive Problems

Failure to comprehensively address dysfunctional signaling pathways in PTSD can lead to additional negative physiological afflictions, including cardiovascular, metabolic and autoimmune conditions (Heppner, 2009). Over time, PTSD can lead to having an increased incidence of infections due to a weakened immune system, including hepatitis and tuberculosis; the advent of musculo-skeletal diseases and fibromyalgia; and circulatory disorders such as cerebrovascular disease, coronary artery disease and hypertension (Hakamata, 2007; Nakas-Iindi, 1998). A study presented by Kristine Yaffe, MD at the International Conference on Alzheimer's Disease in July 2009 reported that, during a 7-year follow-up, veterans with PTSD had an almost 2-fold increased risk of developing dementia. Also, veterans with a greater severity of PTSD are more likely to meet the diagnostic criteria for metabolic syndrome: dyslipidemia (high triglycerides), hyperglycemia (insulin resistance), obesity and hypertension (Heppner, 2009), which is a predictor for developing Type II Diabetes Mellitus.

An analysis of the disrupted pathways tends to validate the above findings. Current allostatic cell-signaling imbalances, if chronic, are not without consequences. Over time, they can lead to chronic degenerative conditions, addictions and even life-threatening challenges – and even more so due to ongoing impact of the CoVid-19 pandemic.

Current Issues

Higher blood pressure
Elevated blood sugar

Decreased endogenous opiates

Concussive episodes or TBI
Stress - higher cortisol levels

Higher epinephrine (adrenaline) levels
Increased lymphocyte glucocorticoid receptors
Phobic anxieties

Depression

Future, Related Issues

Stroke, heart attack
Type II Diabetes
Peripheral neuropathy
Substance Abuse / Addiction
Alcohol
Opioids
Smoking
Pain killers
Marijuana

CTE (chronic traumatic encephalopathy)
Chronic inflammation / pain
Weakened immune system
Dysfunctional HPA axis
Weakened immune system
Cardiovascular issues
Stroke
Heart Attack
Arrhythmias
Dementia/Alzheimer's
Suicide

CoVid-19 Pandemic and PTSD

With the current CoVid-19 pandemic, individuals with PTSD might be at serious risk for greater severity and complications from this novel coronavirus due to a compromised immune system, increased systemic inflammation and circulatory disorders. Please see the coronavirus “white paper” on this subject at www.LepticaMedical.com for additional insights and safe, efficacious and cost-effective options.

External, Environmental and Lifestyle Components Can Prolong or Exacerbate PTSD Recovery

Smoking (Beckham, 1998)

Alcohol (Kessler, 1995)

Poor Diet – leads to increased systemic inflammation

Inactivity, decreased exercise – result in decreased GH (Growth Hormone) and BDNF expression

Unhappy relationship issues – contributes to decreased oxytocin expression

Brain Atrophy with PTSD

A meta-analysis by Karl (2006) found structural abnormalities in the brain (smaller tissue volumes) to be associated with PTSD: smaller hippocampal and left amygdala volumes in adults and smaller corpus callosum and frontal lobe volumes in pediatric samples. From this data, Karl concluded that PTSD is associated with abnormalities in *multiple* frontal-limbic system structures of the brain. It is beyond the scope of this paper to analyze the causality of smaller brain tissue volumes and signaling imbalances underlying these atrophies. However, certain cell signaling factors researched for inclusion in the PTSD formula (e.g. FGF-2, IGF-1 and BDNF) are known for stimulating neuronal development and would thus have implications in addressing decreased brain tissue volume reversal. Because the brain is capable of compensating for altered communication pathways (neuroplasticity), it is interesting to speculate as to what thresholds of regeneration need to be attained to achieve a reduction or complete elimination of PTSD symptoms. It also remains to be seen if *isoenergetic cell signaling*[™] is capable of initiating a recovery of brain tissue volume and function over time – something we hope to discover during our continued longitudinal phase of this pre-clinical study.

Psychological Treatment-based Therapies

A number of psychiatrists and psychologists have developed verbally-based treatment protocols to address PTSD. The efficacy of such protocols should be assessed by how well cell signaling correction takes place as evidenced by hormonal rebalancing over the long term, especially the Growth Hormone / Somatostatin / Insulin-like Growth Factor -1 (GH-STT-IGF1) axis. Psychological treatments include:

- Trauma-focused cognitive behavioral therapy/exposure therapy (TFCBT)
- Stress management therapy (SMT)
- Supportive therapy
- Non-directive counseling
- Psychodynamic therapy
- Hypnotherapy
- Group cognitive behavioral therapy (Group CBT)
- Eye Movement Desensitization and Reprocessing therapy (EMDR)

According to the Anxiety and Depression Association of America (www.AADA.org) website: “It is important for anyone with PTSD to be treated by a mental health care professional who is experienced with PTSD. Some people will need to try different treatments to find what works for their symptoms.” The AADA categorizes their non-cell-signaling PTSD therapies as follows:

- **Exposure therapy** – this therapy helps people face and control their fear by exposing them to the trauma they experienced in a safe way. It uses mental imagery, writing or visits to the place where the event(s) happened. The therapist uses these tools to help people with PTSD cope with their feelings. [Authors' note: we strongly object to this therapy, based on negative descriptions of it from veterans who have tried it.]
- **Cognitive restructuring** – this therapy helps people make sense of the bad memories. Sometimes people remember the event differently than how it happened. They may feel guilt or shame about what is not their fault. The therapist helps people with PTSD look at what happened in a *realistic* way.
- **Stress inoculation training** – this therapy tries to reduce PTSD symptoms by teaching a person how to reduce anxiety. Like cognitive restructuring, this treatment helps people look at their memories in a healthier way.
- **Virtual reality treatment** – this therapy consists of custom virtual environments that have been carefully designed to support exposure therapy of anxiety disorders. The treatment involves exposing the person with PTSD to a virtual environment that contains the feared situation, instead of taking the patient into the actual environment or having the patient imagine the traumatic situation. The therapist controls the virtual environment through a computer keyboard, ensuring full control of the exposure and the ability to manipulate situations to best suit the person within the confines of a therapist's office.

NOTE: Care must be taken in analyzing the evidence and effectiveness of psychological treatments. The considerable unexplained heterogeneity observed in these comparisons, and the potential impact of publication bias on these data, suggest the need for caution in interpreting the results of our review (Bisson, 2007).

Just as physical exercise increases the release of GH and BDNF and social interactions increase oxytocin (OXT), we need to look at the effect of PTSD therapies on achieving cell signaling factor rebalancing. By lessening symptoms, reducing over-expression of the mesolimbic system, as well as stimulating desirable cell signaling, therapies could potentially be made more effective. If pharmaceutical drugs are not proven to eliminate PTSD-causing symptoms, just merely address symptoms resulting from PTSD, then it is problematic – and perhaps even ethically questionable – to include them in any PTSD therapy, given the potential for adverse side effects (e.g. bipolar disorder, emotional numbing, increased depression and even suicidal ideation). **A new paradigm needs to be explored which obviates the danger of creating additional quality-of-life compromises and life-threatening symptoms.** Based on observations and feedback from veterans, it is the authors' conclusion that psychological therapies *alone* are woefully inadequate. If they are combined with pharmaceutical drugs, they seem to have little to no benefit (especially long-term) in *resolving* PTSD and have sometimes caused more harm than good.

Pharmaceutical Drug Treatment-based Therapies

Applications of pharmaceutical drugs have not been proven to rebalance cell signaling through hormonal or analogue applications without unwanted adverse side effects. Anxiolytic and anti-depressant drugs, especially SSRI's, should be carefully reconsidered for use due to side effects and the lack of evidence-based data to show efficacy for PTSD. This includes the potential danger for including someone who might be monopolar bipolar, and even suicidal. As of 2010, six SSRI drugs are currently available on the world market: sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram and escitalopram. Only the first two have FDA approval for PTSD treatment, though the others are also commonly used "off-label" for this purpose. The only double-blind trial comparing acute treatment of 10 weeks for PTSD patients with control subjects who did not get the Rx failed to detect significant differences in overall efficacy, though some symptom improvement was shown by all groups (Tucker, 2003). The trial was not longitudinal, so long-term changes are unknown and improved quality of life was not assessed.

Physical Exercise Treatment-based Therapies

Physical exercise stimulates the release of GH from the anterior pituitary (and consequent IGF-1 release from the liver). Aerobic exercise may be a particularly effective means to enhance BDNF levels, as it induces a cascade of events that leads to increased BDNF gene expression in multiple regions of the CNS, including the hippocampus, cerebellum, cerebral cortex, and spinal cord (Mang, 2013). BDNF has been well-documented to reduce anxiety and stress immediately and over time, as well as improve social interactions and sleep. Veterans with PTSD who have undertaken rigorous exercise regimens report the lessening of their PTSD symptoms (Opheim, unpublished).

An Old Paradigm Repackaged in New Theories = An Inadequate Treatment Response **What is Currently Practiced is Woefully Inadequate as Evidenced by Suicide Rates** **New, Integrative, Holistic Approaches Must be Implemented**

Challenges to Traditional, Drug-based Neurotrophic Factor-derived Applications

1. Delivery System

Extensive efforts have been made to develop trophic factor-based therapies to enhance motor neuron survival. However, achievement of adequate therapeutic delivery to all regions of the corticospinal tract has remained a significant challenge (Dodge, 2010). Intracerebral-ventricular injections are also prohibitive in humans due to safety and infection risk.

2. Duration

The time for restorative function is prolonged. The axons must first grow out of the ventral root sufficiently far enough to reach denervated muscles. It may take a year or more for axons to regrow from the spinal cord to distal skeletal muscles in humans (Grumbles, 2009).

3. Blood Brain Barrier

The blood brain barrier remains an impediment for neurotrophic factors (such as BDNF, GDNF and leptin). These 3 neurotrophic factors have altered expression under PTSD conditions.

4. Molecular Half-Life

With an injectable (molecular) application, some neurotrophic factors have a short half-life, e.g. 2.9 minutes for Cytokine Ciliary Neurotrophic Factor (CNTF) after intravenous injection (Henriques, 2010).

5. Effective vs Safe Dose

The effective dose in an animal may greatly exceed the highest safe dose in a human. For example, CNTF used in animals is about 1mg/kg, whereas the highest safe dose in humans is 200 times lower at 5 mcg/kg (Henriques, 2010).

6. Multiple Pathways are Affected and Require Multiple Neurotrophic Factors

While case studies using GH have proven effective, the influence on the amygdala and memory extinction is not as well-addressed. Thus, a multiple growth factor approach should prove to be the most effective in returning the various axes to balanced functioning.

7. Time is of the Essence

Development of PTSD drugs and subsequent Phase I, II and III trials would take years. In the meantime, millions of individuals, including veterans returning from Afghanistan and Iraq and first responders, are desperately in need of treatment protocols *now* which can deal effectively with their PTSD.

8. Receptor Targeting

Cell signaling factors can have multiple receptors. For example, in the case of Neuropeptide Y (NPY), there are 4: Y1, Y2, Y4, Y5. While NPY can reverse depression-like behaviors in

laboratory studies, only Y1 (and not Y2, Y4, or Y5) has been found to produce anti-depressant-like responses from NPY (Caberlotto, 1998).

Putting the Puzzle Pieces Together **A New Paradigm to Address PTSD Effectively** **Using an Integrative Approach and Isoenergetic Cell Signaling™**

Neurotropic Growth Factors Govern Psycho-Social Behavior

As previously mentioned, there is a recognized *genetic component* to PTSD. Certain genetic alleles are found to predispose a person to respond differently to assaults. Thus, if taking a pharmaceutical approach to treating PTSD, preliminary genetic testing may be involved. When genetic testing reveals deficiencies, vulnerable individuals could be recommended for treatment immediately (Bowirrat, 2010). Early detection is especially important, because early treatment might then have a possibility to improve outcome.

However, it is necessary to point out here that *symptom* treatment is what is primarily targeted. If pharmaceutical drugs are then utilized to address specific symptoms, the almost invariable development of *additional* symptoms (adverse side effects) could potentially create a situation of transference, whereby the problem (PTSD) is not solved or averted, just diverted. This scenario can be especially true when attempting to treat PTSD with psychotropic drugs. Results of the research by Bowirrat suggest the following genes should be tested in persons with PTSD symptoms: serotonergic, dopaminergic (DRD2, DAT, DBH), glucocorticoid, GABAergic (GABRB), apolipoprotein systems (APOE2), brain-derived neurotrophic factors (Monoamine B, CNR1, Myo, CRF-1 and CRF-2 receptors) and neuropeptide Y (NPY). Note that these genes govern the expression of hormones and growth factors which, in turn, govern the diverse cell-signaling pathways. It is the disruption of the expression of these pathways and their functioning which indicates a need to focus on them in order to rebalance the affected diverse cell-signaling systems. This is because it is the disruption of the expression, signaling and pathway functioning which indicates a need to focus on *cell-signaling rebalance* to correct the affected diverse cell-signaling systems.

As previously stated, genetic analysis would most likely be considered, if PTSD was being addressed utilizing the current pharmaceutically-based treatment and therapy approach. A more integrative or holistic approach would analyze the manifestations of symptoms and look at the alterations in the cell-signaling factors. For example, BDNF is under-expressed in individuals with depression and PTSD. GH is under-expressed and STT is over-expressed in PTSD, yet GH expression is directly affected by ghrelin and NPY levels. The main result of GH secretion is to stimulate the secretion of IGF-1 in the liver, and IGF-1 directly affects the depression pathways. IGF-1 and FGF-2 synergistically enhance neuronal development and are compromised by TBI which, not-surprisingly, affects the degree of recovery from TBI. If unresolved, TBI can result in the development of CTE as one ages and compensatory factors in the brain decrease.

Understanding Inter-related Brain Regions and Their Integrated Multiple Signaling Pathways is Crucial

A review of the research titles in the Reference section at the end of this paper clearly establishes the complexity of addressing PTSD in general. Individually, it can be seen that low basal NPY levels, reduction in anterior pituitary GH secretion – and thus reduced hepatic IGF-1 secretion – inadequate sleep, a sustained overactive mesolimbic system, diminished neuroprotective and neuroregenerative actions, etc. all contribute to the development of PTSD as well as its continuation. The research shows that it is not just alterations in the cell signaling factors which affect the cell signaling pathways. There are also alterations in the brain structure itself, especially with chronic PTSD (Yamasue, 2003), such as atrophy in a certain brain region called the prefrontal cortex (PFC) which affects executive function. Thus we see that we have the initial task of correcting the under- and over-expression of contributing cell-signaling factors. Given brain plasticity (neuroplasticity), there is also the

need to stimulate balanced, corrective cell signaling over a period time, in order to recover from physiological changes resulting from under- and over-utilized regions of the brain. How long this might take would depend on the severity of PTSD symptoms, gender, age, genetics, living environment and lifestyle.

As we look at the variety of cell-signaling factors (e.g. ACTH, BDNF, GH, IGF-1, IL-1 β , IL-4, Leptin, NPY, OXT, STT, TNF- α , VEGF) and their diverse positive and negative roles in PTSD, we can see that just targeting *single* cell-signaling pathways by *single* molecules will not be effective. Interactions are simply too complex. The failure of the single-molecule approach is demonstrated by the inability of anti-depressant therapies to achieve satisfactory corrective results. Issues such as anxiety and depression are often found to be comorbid with PTSD, yet their signaling pathways are not the same. From looking at the dosage challenges of different cell-signaling components in research projects with laboratory rodents, we can see that – if these results were to be extrapolated to humans – the safe and effective dosing of not just one but multiple cell-signaling factors would be virtually impossible to arrange. Doing so would produce unacceptable toxicities in humans, due to adverse side effects. Viewed from a lay perspective, it is not unlike a bowl of noodles: think of noodles as cell signaling pathways or *axes*, all intertwined and touching each other at different places along the length of each noodle. How do we most effectively influence them all to individually, yet collectively, be correctly spiced (stimulated) and eaten (activated) for a balanced healthy response? If the dish (body) is corrected spiced (stimulated), this could be achieved.

Based on singularly-focused research and its findings, current drug therapies and conventional thinking focus on the circulatory system for delivery, which is usually administered by pill, tablet, dermal patch, nasal spray, or injection. To date, there are no effective treatment options that are drug-based, and the pharmacological ones which do exist are fraught with potential adverse side effects. A common complaint we have heard from veterans not wanting to take drug medications is that it makes them feel *unemotional* – “like a zombie” – without feelings and having no zest for life. From a veteran’s perspective, the effect is in such marked contrast to the “adrenaline high” and sense of belonging to a team (“tribe”) while being deployed that – for many – this option is simply untenable and depressing, sometimes to the point of contemplating suicide. One result from taking drugs is that some symptoms are lessened or covered up and other problematic ones are sometimes created. Further on in this white paper, we will see the challenges this pharmaceutical approach presents on numerous levels, as we try to understand causative versus resultative over- and under-expression of cell signaling factors.

We will now present a paradigm in cell-signaling and medicine delivery that was first developed in 1995: how to use specific cell-signaling factors to stimulate the body to “self-correct” by activating the appropriate cell receptor sites to address PTSD. Without adverse side effects, this approach enables the cell signaling to go from an allostatic, imbalanced state to one of balanced, healthy homeostasis.

Hippocrates (Greek physician circa 460-375 BC) advocated a homeostasis theory to explain illness. He taught his students that a disruption in homeostasis or balance would lead to the manifestation of illness symptoms. PTSD fits this paradigm, as it is *a chronic state of dysfunctional cell signaling* which reflects an imbalance in hormonal/cell signaling factor axes. Stimulating and rebalancing these axes is thus crucial to enable the body to return to healthy psycho-immuno-neuro-endocrine functioning (homeostasis). An example of this crucial need for balance can be seen in the interaction between GH, NPY and STT. GH acts on the NPY neurons in the arcuate nucleus (ARC) and somatostatin (STT) neurons in the periventricular nucleus (PeV) through the growth hormone (GH) receptors. The activation of these neurons enhances SST release, which subsequently inhibits GH secretion (Minami, 1998). In PTSD, STT is dominant and GH is suppressed, and it is this type of signaling imbalance which does *not* self-correct that gives rise to symptoms associated with PTSD.

Certain Brain Regions Experience Trauma-related Hormonal-signaling Hyperactivity

The mesolimbic system is a recognized center for PTSD action. The hippocampus and amygdala are key structures and have reciprocal interactions with the basal forebrain (BF) with both cholinergic and GABAergic afferent pathways (McDonald, 2012). Cognitive processing (including fear, reward, surprise and anxiety) activate

differing pathways and thus involve different areas of the brain. During trauma-related cognition processes, the following regions show greater activity: hippocampus and para-hippocampal gyrus, dorsal anterior cingulate and ventral prefrontal areas (including the orbital frontal cortex), inferior frontal gyrus and ventral-medial PFC (Morey, 2008). The amygdala and insula show hyperactive responses to trauma-related emotional information in PTSD (Simmons, 2008).

Certain Brain Regions Experience Trauma-related Hormonal-signaling **Hypoactivity**

Offsetting the hyperactivation, there is reduced activity in the dorsolateral and dorsomedial PFC, as well as the hippocampus. The result of dysfunctional processing of cognitive inputs can lead to problems with:

- memory processing, including dissociation of past events with present stimuli, e.g. gunfire vs fireworks
- stimulus overload, e.g. agoraphobia
- sustained attention and mental clarity
- memory recall (Vasterling, 2002), forgetfulness

The Axis Imbalance Hypothesis: Cell Signaling Imbalances Underlie PTSD Symptoms

No hormones, growth factors or neurotrophic factors function independently of each other. They are all involved in overlapping pathways and what are called axes. People with PTSD have been found to exhibit alterations in hypothalamic-pituitary-adrenal (HPA) axis function (Charney, 1993). PTSD individuals also display an inability to suppress fear or feel safe, and this was found to significantly correlate with both cortisol and adrenocorticotrophic hormone (ACTH). From this research, we can see that alterations in hormonal axes are implicated in PTSD, especially those relating to activation of the autonomic / SNS (fight or flight, freeze - survival) nervous system.

Several Axes that are Determined by Brain Regions

- **Hypothalamus – Pituitary – Adrenal (HPA) axis:** mediates many of the body's responses to stressors. Disruption can lead initially to hypercortisolism and, over time, to hypocortisolism (urine and serum) and increased levels of corticotropin-releasing hormone (CRH), which blunts ACTH responses and can lead to adrenal fatigue and hippocampal atrophy.
- **Brain stem – Thalamus – Cortex axis:** compromises the sleep-wake cycle, especially by disrupting the natural progression from wake to sleep.
- **Locus coeruleus – Raphe – Tuberomammillary:** influences the various sleep and arousal states in the mind, thus altering the sleep phases.
- **Hypothalamus – Pituitary – Adrenal - Thyroid axis:** disruption can lead to an abnormal T3-T4 ratio (both were elevated and T3 was higher in the Prang study), which can manifest as increased anxiety (Prang, 1999). Importantly, this axis directly mediates metabolism.

Several Axes that are Determined by Cell Signaling Factors

- **Ghrelin – GH – IGF-1 axis:** related to fear learning. Following chronic stress, ghrelin requires GH in the amygdala to exert fear-enhancing effects (Meyer, 2013).
- **LEP – NPY – GH – STT axis:** LEP suppresses NPY neurons. GH acts on the NPY neurons in the ARC and STT neurons in the PeV through the GH receptor, which activate STT release and inhibit GH secretion (Minami, 1998).

- **NE (norepinephrine) – 5-HT (serotonin) axis:** active while awake; decreases during slow wave sleep and further decreases during REM sleep.
- **BDNF – LEP axis:** within the PFC and hippocampal cortical area 1 (CA1 region), BDNF levels may be a critical mediator of PFC-dependent regulation of emotional reactivity and CA1-related anxiety (Rakofsky, 2013).
- **CRF – ACTH – CORTISOL axis:** CRF is released in response to stress and stimulates increased secretion of ACTH from the anterior pituitary (also the location for GH secretion), which then stimulates the release of cortisol from the adrenal gland (Flanagan, 1997). Notice that prolonged stress stimulates sustained adrenal stimulation (hypercortisolism), which can lead to adrenal fatigue.

Several Axes that are Determined by Symptomology

Depression

Somatostatin – Growth Hormone – Insulin-like Growth Factor-1 axis

Growth Hormone – Leptin – Brain-derived Neurotrophic Factor axis (Ge, 2018).

Anxiety

Ghrelin – Growth Hormone – IGF-1 axis (Meyer, 2013)

Depression – Stress - Anxiety

Leptin – Neuropeptide Y Axis (Morales-Medina, 2010)

Sleep – Wake – Alertness

Hypothalamus – Pituitary – Adrenal axis

The sleep-wake state includes both wakefulness-promoting and sleep-promoting components. The structural systems involved include: the hypothalamus (tuberomammillary histaminergic projections and preoptic nuclei); the serotonin projection system from the raphe nuclei; the norepinephrine projection system from the locus coeruleus; the cholinergic system, including both thalamic projections from the midbrain and cortical projections from basal forebrain regions and several thalamic nuclei (Oken, 2010). Diverse and over-lapping cell-signaling factors are involved in each of these systems. Even nicotine functions as a cell-signaling factor by its influence on increasing sustained attention and alertness (Oken, 2010). Additionally, nicotine suppress NPY expression, which reduces appetite.

Amygdala – Nucleus accumbens axis

Motivation

Striatum - Nucleus accumbens - Amygdala axis

Much of the dopaminergic system functions along this axis (Robbins, 1996).

Fear-extinction memories

FGF-2 affects the molecular cascade involved in learning and memory. FGF-2 has been shown to both facilitate long-term extinction of fear and reduce stress-precipitate relapse (Graham, 2010). Reduced volume in PFC, including nucleus accumbens, ventromedial prefrontal cortex, grey matter in the anterior cingulate cortex (ACC) and white matter in the orbito-frontal cortex (OFC) (Rakofsky, 2013).

Brain Regions can Experience Atrophy with PTSD – a Potential Long-term Challenge which must be Addressed

Brain regions interact with each other. For example, from the basal forebrain (BF) there are reciprocal information exchanges with the hippocampus and amygdala, which are key structures of the limbic system. The afferents and efferents which project between these neurons involve cell signaling factors. Somatostatin, calbindin and neuropeptide Y are expressed in the neurons of the aforementioned structures (McDonald, 2012).

Several brain areas which display altered hormonal signaling axes and disrupted homeostatic feedback loops can experience atrophy. Studies have demonstrated hyperactivation of the amygdala and hypoactivation of the PFC. The degree of atrophy would depend on age, severity, medications and gender. Atrophy can occur in the hippocampus, amygdala, PFC and ACC and show reduced tissue volume with PTSD (Yamasue, 2003). As symptoms increase over time, Cardenas reported accelerated atrophy, particularly in the brainstem and in the frontal and temporal lobes. This atrophy was associated with greater rates of decline in verbal memory, attention and mental processing as seen in delayed facial recognition (Cardenas, 2011).

Pre-Clinical Study

Goals

Primary Goals

- To quantify a significant improvement in the quality of life for veterans with PTSD
- To statistically prove that a non-molecular *isoenergetic cell signaling*[™] *Post Traumatic Vets Defense*[™] (PTVD) formula can be highly efficacious as demonstrated anecdotally
- To quantify a significant reduction in suicidal ideation

Secondary Goal

- To reduce the need for drugs prescribed for anxiety and depression, many of which have significant adverse side effects

Pre-clinical Study Design

- There was purposefully no placebo/control group design. Our firm belief is that it is unconscionable for anyone to have a clinical diagnosis of PTSD and then be put into a control group. This is especially true when quality of life is compromised and major symptoms include recurrent nightmares and suicidal ideation.
- PTSD is an established affliction with a clear set of definable symptoms. From the initial interview of all participants by the collaborator and the evaluation of the “baseline” SAS questionnaire each participant filled out prior to starting the *PTVD* formula, we were able to ascertain the existence and degree of PTSD that each participant was experiencing. We were even able to validate the existence of PTSD in two participants who had been repeatedly unable to receive an accurate assessment of their symptoms at the VA hospital. They had faced years of diagnosis for anxiety, depression, personality disorders, etc and were prescribed multiple pharmaceuticals for these conditions, most of which had not proven to be of any long-term or normalizing benefit for those with PTSD.
- Budget limitations restricted us to working with a nearby veterans center: The Warrior Healing Center (WHC) in Sierra Vista, AZ. We are indebted its Director (Dr Tim Kirk) and to each veteran’s (and, where appropriate, their respective partner’s) willingness to participate in and support this study, as well as for the veteran donor who helped fund the study.
- Along with our in-depth PTSD research starting in 2008 and making notations of PTSD-associated symptoms, as well as interviews with individuals with PTSD along the way who acquired these symptoms from childhood trauma(s) and/or and trauma experienced in the military, a comprehensive questionnaire was designed to serve as a basis from which to do targeted studies. This comprehensive symptoms list included 97 entries. Through consulting with Dr McCombs and her consults with Dr. Kirk and two other veteran providers at the WHC, the number of self-assessment entries that was deemed necessary and important was narrowed down to 91.

Formula Challenge – Creating an Integrated Cell-signaling Formula

An accurate PTSD diagnosis is a composite of several symptoms (e.g. depression, anxiety, hypervigilance, insomnia, unpleasant/recurring nightmares, impromptu/irrational mood swings and flashback triggers). We believe it is possible to assess the PTSD-associated symptoms, identify the affected pathways and brain regions and then identify the involved cell-signaling factors (CSFs). Following this methodology, we determined which CSFs could be causative, resultative (or both), which are over- and under-expressed and which are major CSFs (e.g. BDNF, OXT, STT and GH). The result was a combined *isoenergetic cell signaling*[™] formula designed to help the body return from being “stuck” in an imbalanced state to a balanced, healthy state of homeostasis. **We believe that it is only through the stimulation, inhibition and ultimate rebalancing of these CSFs that the symptoms associated with PTSD can be resolved.**

Formula Goals

- To offer an immediate, safe and effective option to eliminate the 22 military veteran suicides/day
- To be extremely affordable (currently, the cost is ~\$1.50/day)
- To be available for veterans and first responders *immediately* after completing the Self-assessment of Symptoms (SAS) questionnaire – which one can take by oneself – thus allowing the formula to be used without having the “stigma” of a PTSD diagnosis in one’s medical record
- To enable military veterans and first responders initiate cell-signaling corrections *immediately* after a trauma occurs, to avoid the “slippery slope” of developing *chronic* PTSD (a prophylactic goal)
- To demonstrate quality-of-life improvements that start within the first weeks of taking the formula and observe a steady progression of symptom improvements
- To create a formula which is safe for children who are exposed to traumatic events

Formula Benefits

- **Previously-proven efficacy** of *isoenergetic cell signaling*[™] medicine – the first published placebo-controlled, multi-site clinical study in 1995 proved that a combination of 4 CSFs over a 6-month period could prevent loss of lean body mass and help patients avoid opportunistic infections and hospitalizations in an AIDS population
- **No recorded adverse side effects** with any of the *isoenergetic cell signaling*[™] medicines – care must be taken, however, to monitor patients who are concurrently on pharmacological drugs, as current dosages of their prescription medications might manifest as adverse side effects due to normalization of the body’s cell-signaling pathways. This possibility may particularly apply to medications that are being prescribed for anxiety, depression and sleep issues.
- The formula is **available as a non-prescription, over-the-counter medicine** – the PTSD formula, like all of our *isoenergetic cell signaling*[™] medicines, meets FDA mandates that medicines prepared in a sequential kinetic fashion by succussion (homeopathic medicines) must be proven both effective and safe. Also per FDA and FTC guidelines, discussion of benefits of these medicines must be based on symptoms that are self-diagnosed. The SAS Questionnaire *only* includes self-diagnosing entries.
- This formula, by its design, **should complement and enhance the efficacy of any PTSD “talk therapies,”** which it does.

The Formula – *Post Traumatic Vets Defense*[™]

Based on our research, we believe that the same approach the primary author has seen work so well for the past 25 years (***isoenergetic cell signaling*[™]**) **can be employed to address PTSD**, specifically to stimulate and balance the body's altered cell-signaling pathways. These formulas are called ***Cell Function Activator*[™]** **medicines**. They are *not pharmaceutical drugs*, nor are they *traditional* homeopathic remedies. They incorporate the best of scientific research, as well as safe and accurate sequential kinetic preparation; and, through the addition of neuro-energetic cell-signaling frequencies, they truly represent ***a different class of medicine***. They are derived from recombinant DNA human proteins (polypeptides) acquired from established FDA-approved laboratories that also produce bio-identical hormones. Through this derivative process, *pure* molecules are produced that are *identical* to what the body itself produces. This process is accomplished by taking the human gene that produces each *specific* CSF and splicing it into laboratory yeast, which are then fed the foods (sugars) that make them multiply, after which they are *separated*. What results are *pure* CSF molecules that are *exactly like* those that the human body makes. Because the bio-electrical energy of these *pure* CSF molecules is *identical* to what the body itself naturally produces, it can *recognize* these molecules as “self.”

Unlike homeopathic remedies, whose components come from the *Homeopathic Pharmacopoeia of the United States* and the concept of “like treats like”, **our medicinal formulas are technically isopathic** and should be thought of, distinguished from, and most accurately described as “identical treats identical”. The method of development of *both* kinds of medicines, however, is the same: sequential kinetic succussing (diluting) to specific frequencies (Vithoulkas, 1980). Because these frequencies can be detected beyond Avogadro's number – the number of atoms or molecules in one mole of a substance equal to 6.0221×10^{23} (Beauvais, 2018) – they are *technically* defined as non-molecular and are thought to exist only in ***energetic*** form. This is why we call them ***isoenergetic cell signaling*[™]** **medicines**. **Like homeopathic remedies**, the different *signaling* frequencies (energies) of these isopathic molecules each elicit *different* signaling responses. For example, IGF-1 at a homeopathic frequency of 12C can often relieve cramps associated with PMS within 10 minutes, whereas a 1M frequency of IGF-1 is a very powerful anti-depressant. For additional insights into the research on this topic, we highly recommend Richard Gerber, MD's book *Vibrational Medicine: the #1 Handbook of Subtle Energy Therapies* (3rd edition, 2009).

Unlike pharmacological drugs (which are *derivatives* of molecules or *synthetic* creations and *not identical to what the body produces*), our medicinal formulas do *not* come with the potential for adverse side effects, nor must they undergo Phase I, II and III clinical trials to establish sufficient safety and efficacy. Another very important difference between our medicines and pharmacological drugs is that the latter rely primarily on a *monotherapy* approach, whereas **our formulas are composed of multiple CSFs at specific signaling frequencies**, allowing them to respond promptly *and* simultaneously to *multiple* cell-signaling pathways. **The *Post Traumatic Vets Defense*[™] formula** used in this pre-clinical study was derived from input, analysis and research on GH, IGF-1, BDNF and other human cell-signaling factors related to PTSD.

It is sometimes difficult to conceptualize this type of non-molecular medicine, so perhaps **an example** would better illustrate the ability of our *Cell Function Activator*[™] formulas to elicit such a powerful effect. Let's say you get a whiff of something that instantly reminds you of an experience in the past, e.g. a summer family barbecue at the lake. Since large aromatic molecules cannot get past your olfactory lobe, how did that memory happen? Based on the premise in physics that all identical molecules uniquely possess a specific “electrical” energy or *resonance*, your olfactory nerve endings were able to sense that energy and produce an *instantaneous* recall of time, space and events as well as an awakening of your senses. (For additional insights into the research on this topic, we highly recommend Chandler Burr's book *The Emperor of Scent*, 2004.) **Another example**: how do specific smells or sounds immediately elicit responses to past trauma, even if the trauma was *consciously*

forgotten? Both examples graphically illustrate the power of our *neuro-energetic* system. **Merging the concepts of energy medicine, neurology and endocrinology with structural biochemistry and cellular/systems biology provides the basis to understand our medicines and how they can work so effectively.**

Possible Post Traumatic Vets Defense™ Formula Modifications

- We learned that one participant in the pre-clinical study has **fibromyalgia**. Though the mechanism is still not known regarding how or why even a non-molecular isopathic GH CSF can increase the frequency of discomfort from fibromyalgia *in some individuals*, we have observed that it does. For this reason, we substituted IGF-1 signaling for GH signaling in the formula for this participant. This substitution was made for three reasons: (1) because IGF-1 signaling is not known to increase fibromyalgia discomfort; (2) there is a very close relationship between GH and IGF-1, so their benefits and actions have significant overlap; and (3) the primary author suspected that the main CSF “workhorse” providing symptomatic relief for PTSD is IGF-1, because this is what the last 15 years of anecdotal observation has shown.
- Increasingly, people who have **EMF-EHS** (electromagnetic field/hypersensitivity syndrome) issues have been observed to also have medication sensitivities. We anticipated that one or two participants in this pre-clinical study might have such issues and, indeed, this was the case with one individual. We began his administration of the formula with the recommended 3 sprays 3 times a day. After the second week on the formula, one of his PTSD symptoms became worse. He was then asked to stop the formula for two days, which immediately reversed his symptom that had gotten worse. He then restarted the formula at 1 spray once/day and was able to increase his dosage to 1 spray 2 times a day to improve that particular PTSD symptom. In such a case, our formulas are able to be taken in reduced amounts. Even a partial spray just once a day is the optimal dosage for some people, as was the case for one of the collaborator’s patients who was not part of this study and had been suffering from both PTSD and EMF-EHS for many years.
- Though not common, **fluoroquinolone** (e.g. Cipro) **toxicity** or FQ toxicity is a serious, debilitating issue for some individuals. If a person with FQ toxicity also has PTSD, we believe that normalizing dysfunctional cell signaling pathways due to the damage from this type of antibiotic should be addressed *first*. In this case, our *FQ Toxicity Relief Signaling* formula is recommended until symptoms from that condition are deemed sufficiently decreased.

Pre-clinical Study Participants

Participant Selection

A spectrum of qualified veterans were invited to participate in this study. The *primary* goal was to match a complex cell-signaling formula with a diverse population of veterans based on 3 specific variables – age, gender and affliction duration – to see if a small, formalized study would validate what had already been observed and demonstrated anecdotally with veterans and state highway patrol troopers over many years. A strong *secondary* goal, however, was to assess if the changes experienced by the veterans were also observed by their partners. Twelve veterans were invited to participate in this pre-clinical study, and 11 of them completed it. Four partners were invited to participate, and 3 of them completed it.

Participant Exclusions

The following conditions were exclusion factors due to potential for non-compliance or conflicting interactions of cell-signaling pathways:

- Current alcohol addiction or in treatment for same
- Current opioid addiction or in treatment for same

The following conditions were also declared on the Consent to Participate form as having the potential to be affected by the *PTVD* formula: ALS, Atopic Dermatitis, Cancer, Chronic Fatigue, Chronic Lyme, Crohn's/IBS,* Epstein Barr, Fibromyalgia,** Hepatitis C, Lupus, Multiple Sclerosis, Overweight, Psoriasis, Rheumatoid Arthritis and Shingles.

* One participant had both fibromyalgia and IBS. After the 4-month pre-clinical study period was complete, he began our Crohn's/IBS formula which began to resolve his IBS symptoms within 2 weeks (following evaluation and implementation of lifestyle changes - including nutritional - by Dr. McCombs), which did not fully resolve during the study period.

** The participant with fibromyalgia is the one discussed in the Possible *PTVD* Modifications section.

Pre-clinical Study: Self-assessment of Symptoms

Symptoms oftentimes appear in clusters. In PTSD, three different symptom clusters have been identified (Ravindran, 2009):

- Consistent re-experiencing of the trauma
- Numbing/avoidance behavior
- Persistent hyperarousal

These clusters of symptoms were significantly expanded upon in the SAS Questionnaire, which was first devised in 2008. There had subsequently been minor edits on this questionnaire through the years, after doing extensive research of the literature on the subject, as well as from the feedback given to us from people who were sexually molested as children, in addition to those who experienced trauma from serving in the military.

Entry Selection

PTSD is an aggregate of conditions manifesting diverse symptoms. We grouped the final 91 entries into the following 11 categories:

- | | |
|-------------------------|----|
| • Quality of Life | 5 |
| • Physical Constitution | 8 |
| • Oral | 1 |
| • Musculoskeletal | 2 |
| • Abdominal/GI | 5 |
| • Respiratory | 5 |
| • Neurological | 8 |
| • Sleep | 6 |
| • Skin | 1 |
| • Social Interactions | 18 |
| • Psychological | 33 |

The following comprehensive self-assessment questionnaire was used in our pre-clinical study with 11 veterans from the Warrior Healing Center in Sierra Vista, Arizona and the partners of 3 of them.

Self-Assessment of Symptoms Questionnaire (SASQ) for PTSD

Post Traumatic Vets Defense[™] - A Cell Function Activator[™] Formula as part of a PTSD Solution Protocol

The Cell Function Activator[™] *Post Traumatic Vets Defense* is a non-molecular, non-prescription formula based on recombinant DNA and isopathically-formulated human cell signaling factors, such as hGH (human Growth Hormone) and Leptin. It is not a pharmaceutical drug, nor is it derived from a drug. Symptom changes may be noticed within days to the first few weeks after starting this formula.

Prior to starting this formula, please complete this **Self-Assessment Symptom Questionnaire**, so that we will have baseline information. Then complete it again after the:

1st 2 weeks _____
4th week _____
8th week _____

and every 3 months thereafter, if you are still taking the formula.

It is very important for ALL questions to be answered, even if the answer is 0.

Name: _____ Date: _____

Current therapy, if any (please describe): _____

_____ On a scale of 1-10, rate your **overall stress level**, where 1 = none and 10 = extremely stressed

_____ On a scale of 1-10, rate your **overall quality of life**, where 1 = great and 10 = horrible

PTSD covers a wide range of symptoms. Some symptoms apply to certain people and not to others. The following **Self-Assessment of Symptoms Questionnaire** has been developed over the past 9 years. Its contents are based on interviews with individuals diagnosed with PTSD, as well as known growth factor and neurotrophic factor deficiencies and incorporates recognized PTSD symptoms from numerous clinical study protocols.

Circle “0” if you do **not** currently have/see/experience the symptom listed **or** if it is not applicable to you.

Circle a number from “1 to 10” if you **currently** have or notice the symptom listed to indicate the *degree* you are experiencing or noticing that specific symptom, where: **1** = very mild, very decreased or reduced and **10** = very severe or very increased.

Physical Constitution 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Fatigue	0	1	2	3	4	5	6	7	8	9	10
Unwanted weight loss / gain	0	1	2	3	4	5	6	7	8	9	10
Chest tightness or pain	0	1	2	3	4	5	6	7	8	9	10
Blood pressure concerns	0	1	2	3	4	5	6	7	8	9	10
Ignore pain / insensitive to pain	0	1	2	3	4	5	6	7	8	9	10
Overly sensitive to pain	0	1	2	3	4	5	6	7	8	9	10

Oral 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Teeth grinding / jaw tightness (daytime or while sleeping)	0	1	2	3	4	5	6	7	8	9	10
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Musculoskeletal 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Joint pain	0	1	2	3	4	5	6	7	8	9	10
Muscle tension or tightness	0	1	2	3	4	5	6	7	8	9	10
Other: _____	0	1	2	3	4	5	6	7	8	9	10

Abdominal / GI 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Nausea / Vomiting	0	1	2	3	4	5	6	7	8	9	10
Abdominal bloating after eating	0	1	2	3	4	5	6	7	8	9	10
Burning/cramping or gas	0	1	2	3	4	5	6	7	8	9	10
Diarrhea or constipation	0	1	2	3	4	5	6	7	8	9	10
Food cravings when stressed	0	1	2	3	4	5	6	7	8	9	10

Respiratory 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Shortness of breath	0	1	2	3	4	5	6	7	8	9	10
Other breathing difficulties	0	1	2	3	4	5	6	7	8	9	10
Anxiety/panic attacks in public	0	1	2	3	4	5	6	7	8	9	10
Anxiety/panic attacks at home	0	1	2	3	4	5	6	7	8	9	10
Frequent use of asthma meds	0	1	2	3	4	5	6	7	8	9	10

Neurological 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Headaches	0	1	2	3	4	5	6	7	8	9	10
Confusion	0	1	2	3	4	5	6	7	8	9	10
Dizziness	0	1	2	3	4	5	6	7	8	9	10
Difficulty remembering things	0	1	2	3	4	5	6	7	8	9	10
“Black Outs” or suddenly feel disoriented to time or place	0	1	2	3	4	5	6	7	8	9	10
Adverse reaction to common sounds	0	1	2	3	4	5	6	7	8	9	10
Exaggerated “startle” response	0	1	2	3	4	5	6	7	8	9	10
Unanticipated response to laugh or cry	0	1	2	3	4	5	6	7	8	9	10

Sleep 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Unpleasant dreams / nightmares	0	1	2	3	4	5	6	7	8	9	10
Recurring dreams / nightmares	0	1	2	3	4	5	6	7	8	9	10
Night sweats or cold sweats	0	1	2	3	4	5	6	7	8	9	10

Need to sleep with weapon	0	1	2	3	4	5	6	7	8	9	10
Late night TV watching	0	1	2	3	4	5	6	7	8	9	10
Unable to go to sleep (insomnia)	0	1	2	3	4	5	6	7	8	9	10

Skin 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Itching or skin irritation	0	1	2	3	4	5	6	7	8	9	10
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Social Interactions 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Lack of compassion for self	0	1	2	3	4	5	6	7	8	9	10
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Lack of compassion for others	0	1	2	3	4	5	6	7	8	9	10
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Trouble initiating social interactions	0	1	2	3	4	5	6	7	8	9	10
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“Stress sweat” (social situations)	0	1	2	3	4	5	6	7	8	9	10
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Difficulty sharing my feelings with others	0	1	2	3	4	5	6	7	8	9	10
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Don’t like to be touched or held	0	1	2	3	4	5	6	7	8	9	10
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Don’t like people to invade my personal space	0	1	2	3	4	5	6	7	8	9	10
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Uncomfortable in crowds	0	1	2	3	4	5	6	7	8	9	10
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If yes, why? _____											
Prefer to sit with my back against the wall	0	1	2	3	4	5	6	7	8	9	10

Sudden, irrational, unprovoked violent behavior	0	1	2	3	4	5	6	7	8	9	10
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Unexpected or unexplainable irritability towards others (“for no reason”)	0	1	2	3	4	5	6	7	8	9	10
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Internal struggle with intrusive thoughts which may or may not result in loss of impulse control	0	1	2	3	4	5	6	7	8	9	10
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Hostility towards authority figures	0	1	2	3	4	5	6	7	8	9	10
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Mistrust or distrust of authority figures	0	1	2	3	4	5	6	7	8	9	10
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Increased alcohol consumption or “comfort drinking” when stressed	0	1	2	3	4	5	6	7	8	9	10
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Frequent difficulties with people I live with	0	1	2	3	4	5	6	7	8	9	10
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Feeling that your pet “gets” you better than people do	0	1	2	3	4	5	6	7	8	9	10
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Would rather play video games or spend time on my cell phone, the internet or social media than interact with others	0	1	2	3	4	5	6	7	8	9	10
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Psychological 0 = not an issue 1 = very mild or hardly noticeable 10 = very severe

Repetitive behaviors	0	1	2	3	4	5	6	7	8	9	10
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Feel emotionally numb	0	1	2	3	4	5	6	7	8	9	10
Extreme mood swings	0	1	2	3	4	5	6	7	8	9	10
Frequently feel sad	0	1	2	3	4	5	6	7	8	9	10
Frequently feel depressed	0	1	2	3	4	5	6	7	8	9	10
Feel rejected	0	1	2	3	4	5	6	7	8	9	10
General feelings of shame / guilt	0	1	2	3	4	5	6	7	8	9	10
Feel guilty for being a “problem child” or “problem partner” (like I’m a burden, bother or inconvenience)	0	1	2	3	4	5	6	7	8	9	10
Thoughts of suicide	0	1	2	3	4	5	6	7	8	9	10
Feelings of “survival guilt”	0	1	2	3	4	5	6	7	8	9	10
Unexplained feelings of anger	0	1	2	3	4	5	6	7	8	9	10
Low self-esteem	0	1	2	3	4	5	6	7	8	9	10
Self-loathing	0	1	2	3	4	5	6	7	8	9	10
Self-wounding	0	1	2	3	4	5	6	7	8	9	10
Constant feeling of being “on guard” (hypervigilant)	0	1	2	3	4	5	6	7	8	9	10
Flashbacks triggered by sounds or smells	0	1	2	3	4	5	6	7	8	9	10
Feeling used or exploited	0	1	2	3	4	5	6	7	8	9	10
Prone to feelings of “road rage”	0	1	2	3	4	5	6	7	8	9	10
Unsure of who I really am	0	1	2	3	4	5	6	7	8	9	10
Feelings of frustration	0	1	2	3	4	5	6	7	8	9	10
Little to no interest in being sexually intimate with anyone	0	1	2	3	4	5	6	7	8	9	10
Prefer masturbation or sex with a stranger instead of my partner	0	1	2	3	4	5	6	7	8	9	10
Feelings of isolation	0	1	2	3	4	5	6	7	8	9	10
Prefer to be alone	0	1	2	3	4	5	6	7	8	9	10
Inability to concentrate	0	1	2	3	4	5	6	7	8	9	10
Often feel fearful / anxious or scared	0	1	2	3	4	5	6	7	8	9	10
Feelings of being betrayed	0	1	2	3	4	5	6	7	8	9	10
Feelings of helplessness	0	1	2	3	4	5	6	7	8	9	10
Feelings of hopelessness (“why even bother?”)	0	1	2	3	4	5	6	7	8	9	10
Frequently argue with myself out loud	0	1	2	3	4	5	6	7	8	9	10
Unsure about my future	0	1	2	3	4	5	6	7	8	9	10
Use of mind-altering or pain-numbing drugs	0	1	2	3	4	5	6	7	8	9	10
Smoke or chew tobacco to relax	0	1	2	3	4	5	6	7	8	9	10

Quality of Life

Currently feeling **positive or optimistic** (in general), where **1** = always and **10** = never, not at all

	1	2	3	4	5	6	7	8	9	10
Currently feeling a sense of peace or calm , where 1 = always and 10 = never, not at all										
	1	2	3	4	5	6	7	8	9	10
Currently feeling optimistic about my future plans , where 1 = exceedingly optimistic and 10 = not optimistic at all										
	1	2	3	4	5	6	7	8	9	10

Other Symptoms – please add additional observances, thoughts or feelings and rate each one 1-10, as follows:
1 = very mild or hardly noticeable and **10** = very severe

Prescription Drug use? (please list) _____

Amount of Daily or Weekly Exercise (Exercise promotes hormonal release, such as hGH and BDNF – brain derived neurotrophic factor – both of which enhance quality of life.)

Additional Comments, if any: _____

Please return your completed questionnaire to Dr. Ann McCombs.
 If you have any questions or concerns, please call Dr. McCombs at 206-718-4343.
 Your participation is most appreciated. Thank you!

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Leptica Research, LLC	The Center for Optimal Health

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Pre-clinical Study Formula Application

Eleven adults were each given one 2-oz bottle of the formula with a spray nozzle. For the first 5 days, they were instructed to take 3 sprays under the tongue twice daily: (AM) upon rising and (PM) in the late afternoon. Starting the 6th day, they were to take it an additional time: (EV) nearing bedtime. The reason for this dosing schedule is because, over the past 20 years, it has been occasionally observed that, some individuals (including the primary author) who first took GH prior to bedtime would experience alertness and an inability to sleep. Even though our 1999 GH clinical study proved that overall sleep improved and dreams were enhanced, we thought it best to have the *PTVD* formula application standardized for everyone to avoid this rare, though potential, risk factor.

As this is a non-molecular *isoenergetic cell signaling*TM formula, it relies on energetic conveyance via the nerve endings. Consequently, the mouth must be clear of other interfering signals (e.g. foods, beverages, gum, tobacco – especially chewing tobacco – toothpaste and mouth rinses). We recommend taking the sprays 5 minutes prior to ingesting any of the aforementioned items OR waiting at least 20 minutes after using or ingesting them to take the formula dose.

Each participant was given a *Chart Your Use* form which we developed for our formulas to help with compliance. For this study, using this form also documented participants' compliance as well as efficacy, if occasional dosages were missed.

Pre-clinical Study Results

Cross-supporting Entries

Fifty-five of the 91 entries on the SAS Questionnaire showed statistical significance ($p < .05$) and 10 others demonstrated *trending* significance ($p < .095$). Post study, we grouped these 65 entries into 5 categories. It is beyond the scope of this paper to explain which hormonal, neurotrophic and growth factors might be assigned to each entry to demonstrate a cell-signaling relationship.

Just as there is overlap between cell-signaling pathways (e.g. anxiety and depression), there can also be overlap with moods and perceptions. This interconnectedness of symptoms demonstrates the “cross-talk” of the cell-signaling factors which modulate cell-signaling pathways. Reflecting the complexity of the ***Post Traumatic Vets Defense***TM formula, these entries were grouped to validate the efficacy of this formula with multiple related entries, not just isolated symptoms.

- **Physically-compromising symptoms due to anxiety, stress and tension**

Food cravings when stressed	.015
Ignore pain / insensitive to pain	.016
Shortness of breath	.019
Headaches	.020
Overall stress level	.021
Teeth grinding / jaw tightness	.024
Burning/cramping or gas	.026
Diarrhea or constipation	.039
Anxiety/panic attacks at home	.044
Chest tightness or pain	.051 - trending
Muscle tension or tightness	.055 - trending
Nausea or vomiting	.061 - trending
“Black outs” or suddenly feel disoriented to time or place	.083 - trending

- **Social interactions**

Feelings of being betrayed	.005
Don't like people to invade my personal space	.006
Frequent difficulties with people I live with	.007
Prefer to be alone	.011
Mistrust or distrust of authority figures	.013
Anxiety / panic attacks in public	.014
Difficulty sharing my feelings with others	.018
Don't like to be touched or held	.020
Feel your pet “gets” you better than people do	.022

Prone to feelings of “road rage”	.024
“Stress sweat” (social situations)	.032
Uncomfortable in crowds	.083 - trending *
Trouble initiating social interactions	.089 - trending

* voluntary comments on SAS questionnaires after March 2020 mention the CoVid-19 pandemic as an important contributing factor to crowd aversion

- **Sense of personal self**

Frequently feel sad	.000
Frequently feel depressed	.000
Feelings of helplessness	.001
Feelings of hopelessness (“why even bother?”)	.001
Feel emotionally numb	.002
Feel rejected	.002
Low self-esteem	.004
Currently feeling a sense of peace or calm	.004
Lack of compassion for self	.007
Unsure about my future	.010
Thoughts of suicide	.018
Self-loathing	.020
Currently feeling positive or optimistic (in general)	.024
Feelings of “survival guilt”	.069 - trending

- **Behavior, mental state, mood swings and emotional control**

Extreme mood swings	.001
Inability to concentrate	.002
Often feel fearful / anxious / scared	.002
Adverse reaction to common sounds	.002
Repetitive behaviors	.003
Unexplained feelings of anger	.003
Flashbacks triggered by sounds or smells	.003
Unexpected or unexplainable irritability towards others (“for no reason”)	.003
Exaggerated “startle” response	.005
Internal struggle with intrusive thoughts which may or may not result in loss of impulse control	.005
Constant feeling of being “on guard” / hypervigilant	.007
Sudden, irrational, unprovoked violent behavior	.010
Prefer to sit with my back against the wall	.014
Difficulty remembering things	.018
Feelings of frustration	.021
Dizziness	.026
Frequently argue with myself out loud	.030
Confusion	.088 - trending
Unanticipated response to laugh or cry	.092 - trending

• Sleep	
Recurring dreams / nightmares	.002
Unpleasant dreams / nightmares	.011
Night sweats or cold sweats	.018
Unable to go to sleep (insomnia)	.061 - trending
Late night TV watching	.077 - trending

Discussion of Pre-clinical Study Findings

Definitive Benefits Demonstrated

The PTSD formula conclusively demonstrated the efficacy and safety of a complex *isoenergetic cell signalingTM* formula to significantly reduce a majority of the symptoms associated with PTSD, **including suicidal thoughts**.

Participant Partner Findings

Individuals who live with people who have PTSD are directly affected by PTSD-related attitudes and behaviors. We had no idea if partner perceptions and observations would be different from or similar to the degree of symptom severity perceived by the participants themselves. What we sought to ascertain was whether or not the partner would observe *quantifiable* changes over a 4-month period. Partner analysis of SASQ forms demonstrated a dramatic concurrence that the formula had worked, with partner p values of <0.001, <0.001 and <0.003. These partnership p values manifested as reported improvements in the areas of relationship and quality of life. However, it was clinically reported to Dr. McCombs from some of the participants, as well as some of the partners, that there may be secondary issues at play in their relationships in addition to PTSD that especially impact partners. In the literature, this impact is sometimes referred to as *complex PTSD* (Tanasugarn, 2020).

Complexity of Cell Signaling Pathways to Consider

PTSD is not a disease as much as it is a disruption of numerous inter-related cell-signaling pathways whereby cell signaling factors become under- and over-expressed. To understand these brain processes, such as memory, it is essential to understand the macromolecular interactions *as well as* the intra- and intercellular mechanisms that allow circuits to process, store, retrieve and edit behaviorally-relevant information (Silva, 2003). The allostatic state of dysfunctional cell signaling gives rise to the symptoms. As this formula was created, the following pathways or axes had to be considered, along with the cell signaling factors which (1) initiate, (2) drive and (3) result from activation of these pathways. Note that a specific cell signaling factor could be involved in multiple steps and concurrently influence multiple sites in the brain as well as the body.

- Anxiolytic pathway – to reduce *inappropriate* anxiety
- Depressolytic pathway – to reduce *inappropriate* feelings of depression
- Dopaminergic pathway – to reduce conditioned rewards, e.g. the “thrill of battle and camaraderie”
- Neurogenic pathway – to extinguish *inappropriate* fear
- Sleep-Wake Cycle – to improve sleep quality

Study Limitations

- **Low “n” Number** – only 11 participants began and completed the study. The diversity of gender, age, and duration of PTSD could have been problematic. Instead, we found that the *PTVD* formula had a broad enough application to have relevance and benefit to all participants.
- **Duration / Degree of Trauma** – we were unable to assess the potential link between the duration and/or degree of trauma leading to each participant’s reduction of PTSD symptoms, either in quality or quantity, with being on the *PTVD* formula for only 4 months.
- **Time since Trauma** – for the same reason as above, we were unable to assess the potential link between the duration of time from having PTSD with the duration of time for reduction of PTSD symptoms.
- **Headaches / Migraines** – our study included an entry for headaches ($p = 0.020$), but we did not have a specific entry for *migraine* headaches. As the study progressed, we learned that some participants who suffered from migraines had found near-total relief. This finding indicates that a specific entry for migraines, even though they may be of diverse causes, should be included in future, on-going studies. [Note: the cessation of migraines was also unexpectedly anecdotally reported for our *Chronic Lyme Relief Signaling* formula.]
- **TBI / CTE** – comorbidity with TBI or unresolved TBI leading to CTE as contributing factors to PTSD was not included in this study. Pituitary injury is not associated with PTSD, though it is often associated with TBI/CTE, which also involves dendritic branch and axonal shearing. Note that GH is secreted from the anterior pituitary, as it is with TBI/CTE. Thus, the GH – SST axis is closely involved with all 3 conditions. Additionally, there is overlap of other cell-signaling factors involved with both TBI / CTE and PTSD (e.g. BDNF). However, the formulas designed for TBI and CTE are unique unto themselves and can thus be taken concurrently with the formula for PTSD, if indicated.
- **Wake-to-Sleep Cycle** – we believe that the major issue of insomnia can be better addressed, especially for people with difficulty transitioning from wake-to-sleep *independent of or in addition to* maintaining sleep, as these are two *separate* parts of the sleep cycle. These two patterns involve cell signaling factors (e.g. adenosine) which exert controls outside of the tryptophan-serotonin-melatonin axis. We currently have a formula for the wake-to-sleep cycle issue (*Circadian Insomnia Relief Signaling Formula*), which several doctors have anecdotally informed us is slowly but progressively effective. It is possible that for individuals with a wake-to-sleep imbalance, including the *Circadian Insomnia Relief Signaling Formula* might be of benefit.
- **Detoxification** – while in military service, many veterans are exposed to a significant number of toxic substances which have now been proven to have detrimental epigenetic effects on cell-signaling pathways. The addition of adjuvants (e.g. formaldehyde, mercury and aluminum) in vaccines are another source of toxic epigenetic effects on hormonal and neurotrophic factor functioning. Ideally, individuals with PTSD should all have toxicity testing done to ascertain the need for detoxification, which is being done by a local environmental toxicologist for the participants in our study as Dr. McCombs ascertains if that is needed in her follow-up visits. A possible rationale to explain the need for detoxification is: when growth hormone is released from the anterior pituitary, it goes to the liver, where it stimulates the release of the all-important IGF-1 growth factor. Liver toxicity could compromise this action which, in turn, could compromise and give rise to a broad array of dysfunctional IGF-1 signaling actions.
- **Manual Data Collection** – given the significant number of entries in the SASQ, we observed no negative feedback with respect to its length. However, we did notice that entries were sometimes left incomplete. Ideally, the next SASQ would be computerized, so that completing it would be sequential, thus requiring completeness of *all* entries before it could be submitted. Making this one

change alone would also enable us to have multi-site participation with a much larger participant pool from which to draw.

- **Duration of Study** – while we began to see significant benefits as early as the 2nd week of the study with some participants, from experience we believe that a longitudinal study would be of the greatest value to determine if and how the *PTVD* formula might lead to significant improvements in the formula. For example, it could be that this formula might not need to be taken on a regular basis, once a patient's major PTSD symptoms are mostly or completely controlled. It might also be that periodic use is best at that point, or that the formula may also no longer be needed at all. *Continuing this study for the purpose of seeking evidence of a significantly improved, sustainable, effect on these 55-65 clinical, statistically-significant measures alone could prove to be groundbreakingly impactful on decreasing the current number of veteran suicides per day.*
- **Empathy Fatigue** – are empathys more susceptible to acquiring PTSD? Might that idea be a possibility due to these patients' heightened sensitivity to the feelings of others? If so, might that continuous empathic activation lead to an emotional exhaustion that might be reflected in a downregulation of oxytocin production or receptor site activation?
- **CoVid-19** – we began the study in early February 2020, when CoVid-19 was just beginning to surface as a global pandemic. While none of the participants in the study contracted CoVid-19, the pandemic had a profound impact on several of the SASQ entries, including:
 - Uncomfortable in crowds ($p = 0.083$)
 - Prefer to be alone ($p = 0.011$) – shows a *significant* decrease in preferring to be alone
 - Unsure about my future ($p = 0.010$) – shows a significant decrease in future uncertainty
 - Mistrust or distrust of authority figures ($p = 0.13$)
 - Feelings of isolation ($p =$ non-trending or significant) – many participants noted that they wanted to avoid potential CoVid-19 exposure
 - Currently feeling optimistic about my future plans ($p =$ non-trending or significant)

[**Note:** All but one of the study participants volunteered to be part of the *Coronavirus Relief Signaling Prophylactic* formula study that we started in mid-April 2020 at the WHC. A set of 3 CoVid formulas (Prophylactic, Symptomatic, Severe) was completed in mid-March 2020, after the primary author initiated research on a viral pandemic at the beginning of 2016. Details regarding this research and formulas can be found in the Coronavirus “white paper” on this subject at www.LepticaMedical.com.]

- **Reliable Biomarkers** – It is important to note that *there is no single definitive biomarker which proves the existence of PTSD*, as you would find with a viral, fungal, or bacterial pathogen-based affliction. Therefore, with PTSD, it is crucial to look at symptoms. The primary ones are depression, anxiety, hypervigilance, insomnia and uncontrolled moods. A biomarker is defined as a “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention” (Kang, 2015). Changes in cell-signaling factor levels reflect imbalance in signaling axes and, while it may be hard to see them as a “characteristic,” they nevertheless provide definitive direction in defining the degree of PTSD. One biomarker which research supports as being over-expressed in PTSD is urine norepinephrine (NE) levels as well as cerebrospinal fluid NE levels (Geraciotti, 2001). It should also be pointed out that urine levels and serum levels are *not* interchangeable for a variety of reasons. In addition, baseline plasma NE levels fail to show a difference between individuals with and without PTSD (Yehuda, 1992). Another crucial “biomarker” is BDNF, which is under-expressed in patients with PTSD. When looking at biomarkers (e.g. oxytocin), some tests measure plasma

levels and some tests measure salivary levels. That is why the reliability of these biomarkers can be questionable.

This Study Did Not Assess:

- Multiple formula applications for co-morbid issues, such as PTSD - Alcoholism, PTSD - Opioid Addiction and PTSD - Nicotine Addiction.
- The very close cell-signaling pathway relationships between depression, anxiety and PTSD. It should be noted that stress, anxiety and depression all showed a very significant decline in this study.
- Duration and severity of the trauma and its relationship to the duration and improvement in recovery from PTSD.
- Influence of time lapse since the PTSD trauma occurrence(s) on the length of time for recovery from PTSD.
- Gender differences – meaning, potentially, that the formula might ideally need to be gender specific in order to be more optimal.
- Life circumstances pre-PTSD trauma(s), which might lower the threshold of PTSD susceptibility.
- Combination of exercise and *PTVD* formula to enhance recovery.

Unanswered Questions

A study of 4 months to assess a chronic affliction has its limitations. However, The *Post Traumatic Vets Defense™* formula conclusively demonstrated the efficacy and safety of a complex *isoenergetic cell signaling™* formula in reducing a majority of the symptoms associated with PTSD, including traumatic, repetitive nightmares – which one participant had experienced for decades – and suicidal thoughts. Yet, this study raises numerous questions associated with the promise of resolving the issue of PTSD symptoms. We plan to continue this small study longitudinally as long as the current participants are willing and available to see what additional solutions might present themselves over time. Some of the questions to which we seek answers are listed below. In addition, we welcome the readers' specific questions as well.

- Over time, given the “nudge” from *isoenergetic cell signaling™*, will the body's own BDNF, GH, etc. neurotrophic factor production increase to normal, homeostatic-functioning levels?
 - If yes, what factors will govern its normalization? e.g. time for neurogenesis, duration of PTSD symptoms, amount of atrophy to overcome (e.g. prefrontal cortex), amount of exercise, sleep, gender specific gonadotropin-related issues, partnership support, physical intimacy?
- Will the overexpression of SST in response to mesolimbic system dominance decrease and return to healthy homeostatic expression and signaling?
- All cells have “memory” for experiences. So, once cell signaling pathways return to a healthy, balanced state, will the PTSD-associated memories “fade” sufficiently with time and no longer have a debilitating effect?
- In the event of *new* traumatic or challenging events, will it be useful to take the *PTVD* formula to help avoid a recurrence of dysfunctional signaling imbalances, sort of like preventing the recurrence of food cravings by taking the *Naturally Leptin Signaling formula* to curb those cravings should one find oneself in a food-tempting situation or have issues with stress eating or addictive eating?
- For participants whose wake-to-sleep cycle was not sufficiently normalized with the *PTVD* formula, would the addition of our *Circadian Insomnia Relief Formula™* be beneficial in normalizing sleep patterns?

What Comes Next

The extraordinary validation of the benefits of the PTVD formula for both participants and their partners demonstrates the need for immediate implementation of this formula in patient protocols and calls for an expanded, nationwide study to evaluate the use of this formula to lessen the suffering and impact of PTSD on veterans, their partners and/or their families as well as improve their quality of life in general.

The following goals for future studies include:

- review the exclusions
- assess the potential for multiple arms
- expand the study to multiple sites
- increase the participant numbers up to 200
- computerize the SASQ for enhanced completion and convenience

Potential Formula Improvements

As we assess the PTVD formula and review symptoms changes, the following issues also need to be addressed as cell signaling improvements are considered for the formula:

- Is the cell signaling factor causative or resultative?
- If a cell-signaling factor is measured that is over-expressed, what measurements should be taken so that some other cell-signaling factors are under-expressed?
- Normal weight vs overweight subjects will have differing levels of cell signaling factors. Leptin is released primarily by adipose cells. Yet, due to the blood brain barrier (BBB), there can be *hyperleptinemia* in the body and inadequate leptin signaling in the brain, due to inadequate and/or dysfunctional transport across the BBB. Note that, being non-molecular, *isoenergetic cell-signaling*TM does *not* increase leptin or other cell signaling levels.
- Gender plays a role also, because many cell-signaling factors that influence stress, anxiety and depression also are gonadotropic.
- What is a healthy cell-signaling balance? Each individual is unique, so balanced signaling levels could vary significantly. To look at one's hormonal levels and measure them against the "norm" could greatly miss the mark and be completely inaccurate in assessing what healing measures to take.

We welcome practitioners from around the country to contact us for a prospective 200-person, multi-site clinical study, which *will* have a computerized assessment component.

Cell Signaling Factors

Numerous Trophic Factors Play a Role in PTSD - Review of Hormones, Growth and Trophic Factors Researchers Consider to Have Therapeutic Potential with PTSD

CSFs play a significant role in determining molecular pathways which influence cell functioning, and they each have differing mechanisms by which they do that. Some initiate cell-signaling pathways, some are involved in pathway progression and others are expressed as a result of the pathway's actions. These mechanisms include neuroprotective, neuroregenerative, pro-inflammatory and anti-inflammatory functions. Some CSFs can also do *both*, depending on whether they are over- or under-expressed and what influences they receive from other cell-signaling factors. *With symptom progression during PTSD, the expression and ratios of these cell-signaling*

factors vary. The *specific* CSFs used in each formula, as well as the specific potencies (frequencies) used in each formula, are proprietary.

Chronic stressors, repeatedly or maintained over time, can lead to both an increase and decrease in various neuroendocrine responses, which – ultimately – have an adverse effect on the body by creating an allostatic (unhealthy) imbalance, as opposed to a homeostatic (healthy) balance. The actions of neurotrophic factors may activate both common and different pathways, resulting in individual and synergistic effects. Presented in this section are their PTSD-related functions.

Research has demonstrated that **the following important CSFs are involved in PTSD**. It is beyond the scope of this paper to present a comprehensive explanation detailing each of their interactions; instead, we will present some of their *most relevant* functions. Please refer to the References section for a more detailed presentation of the research to explain each of these CSFs many functions.

ACTH Adrenocorticotropin hormone

ACTH plays a prominent role in the stress response which is associated with the HPA (hypothalamic-pituitary-adrenal) axis. Persons with PTSD have been found to exhibit alterations in HPA axis function (Bremner, 1997). ACTH is released from the pituitary and, with CRF released from the hypothalamus, cortisol (glucocorticoid) is released from the adrenal gland (Bremer, 2006). Oxytocin as a stress-inhibiting hormone inhibits ACTH release (Burmeister, 2019).

ALLO Allopregnanolone

ALLO has an effect on GABA neurotransmitters, which is thought to give them antidepressant, anxiolytic and sleep-promoting benefits (Liang, 2018). In a similar manner as some neurotransmitters involved with depression, ALLO exerts its antidepressant role through pathways associated with the limbic system, likely acting on all the main brain sites responsible for the balance that promotes depressive/anti-depressive regulation (Almeida, 2020). *Social isolation has consistently been associated with a significant decrease in allopregnanolone* (Serra, 2000). Neurosteroidogenic enzymes involved in the biosynthesis of brain ALLO (including 3 α -HSD, 3 β -HSD and 5 α -reductase) are down-regulated in the hippocampus and amygdala (Guo, 2017). For anxiolytic and depressolytic effects, the goal is to increase ALLO signaling in the PFC and hippocampus.

AVP Arginine Vasopressin

AVP is synthesized in the hypothalamus and has a controlling influence on anxiety, stress-coping and sociality (Neumann, 2012). AVP and OXT have been associated with regulating fear, neuroendocrine stress responsiveness and social behavior. However, salivary AVP levels have not been shown to differ between healthy controls in male and female police officers with PTSD (Friling, 2015).

BDNF Brain-derived Neurotrophic Factor

BDNF is a crucial mediator of neuronal plasticity, which regulates synaptic composition, neuronal maturation and neurotransmitter release, survival and excitability in the adult nervous system (Almeida, 2020; Huang, 2001). Pre-clinical studies suggest a role of the hippocampal BDNF system in *fear extinction* (Heldt, 2007). The potential role of BDNF in *mood disorders* is also associated with anxious/depressed patients (Montag, 2010). Stress and depression are documented as showing a reductive effect on the expression of BDNF. In addition, the BDNF pathway has been implicated in several psychiatric disorders, including PTSD, phobia and panic disorder (Ander, 2014). BDNF not only protects CA3 (sub-region of the hippocampus) pyramidal neurons, which can atrophy from repeated stress (McEwen, 2001); it also assists in the sprouting of 5-HT axons, which confirm that BDNF is involved in neuritogenesis (the sprouting of neurites from a cell) of hippocampal cells (Mamounas, 1995). Stress reduces BDNF expression showing in the lower hippocampal CA1 region, which relates to more extreme anxiety responses to stress (Rakofsky, 2013). In the CNS, BDNF modulates the activity of serotonin, dopamine and glutamate – which are all neurotransmitters involved in the mood-related circuits – including neurogenesis (Mossner, 2000; Carvalho, 2008).

Impaired BDNF signaling has been found in patients with depression and Alzheimer's (Byers, 2014). Thus, *chronically-impaired BDNF signaling implicates a progression from depression and PTSD disorders to dementia and Alzheimer's*. When PTSD is comorbid with bipolar disorder (BD), it is associated with the worsening of BD symptoms which - in turn - leads to a higher rate of substance abuse, hospitalization and suicide. This example, illustrating the difficulty of "conventional treatment" of PTSD in patients with BD, shows there is a heightened risk of manic induction when antidepressants are used in treatment (Leverich, 2006).

CRF Corticotropin-releasing Factor

CRF (aka corticotropin-releasing hormone, CRH) and STT both play important roles in *mediating responses to acute and chronic stress* (Bremner, 1997). CRF, which is released during stress from nerve terminals originating in the paraventricular nucleus of the hypothalamus, increases the secretion of ACTH from the anterior pituitary, which in turn stimulates release of cortisol from the adrenal gland (Owens, 1991). The change in CRF thus affects CRF-expressing neurons, which are distributed in a variety of ex-hypothalamic locations (including the amygdala, central gray area, locus coeruleus and bed nucleus of the stria terminalis (BNST) and the dorsal vagus complex). This change results in a direct influence on how stress and alertness is mediated (Valentino, 1992). With PTSD and secondary psychotic symptoms, subjects in this study had significantly higher mean levels of CRF than control subjects, though they shared similar somatotropin-release-inhibiting hormone (Sautter, 2003). Research also shows that leptin administration decreases CRF (CRH) expression.

E2 Estrogen

Natural fluctuations in estradiol, progesterone and its metabolite allopregnanolone, the primary endogenous female steroid hormones, over the ovarian cycle of women are associated with changes in PTSD symptoms (Ravi, 2019). Estrogen enhances NMDA (a glutamate receptor and ion channel protein found in nerve cells) function and LTP (long-term potentiation) in hippocampal neurons via activation of Src (a proto-oncogene), tyrosine kinases and MAPK (mitogen-activated protein kinase) pathways, which is associated with the ability of leptin to facilitate NMDA-induced Ca^{2+} increases (Bi, 2000). An emerging hypothesis is that fluctuating gonadal hormones, especially estrogen, in the menstrual cycle may play a critical role in fear extinction and, hence, PTSD vulnerability and symptom severity in women (Glover, 2015).

FGF-2 Fibroblast Growth Factor-2

FGF-2 is a growth factor involved in brain development and regeneration through its effects on molecular signaling cascades involved in learning and memory. In addition, it has been shown to facilitate long-term *extinction of fear* and reduce stress-precipitated relapse in rats. (Graham, 2010).

GAL Galanin

Galanin receptors are expressed in the frontal cortex and hippocampus and is shown to be down-regulated by stress and trauma. Galanin is co-expressed with and modulates noradrenaline and serotonin systems, which are both expressed in depression (Kuteeva, 2008). Galanin recruitment during extreme behavioral and physiological provocations (i.e. stress) may serve to *attenuate negative emotional states* caused by noradrenergic hyperactivation (Karlsson, 2006). Administration of galanin was found to reduce corticosterone over-expression and increase hippocampal CA1 expression of 5HT-1A and BDNF mRNA (Kozlovsky, 2009).

GH Growth Hormone

During the heightened mesolimbic response, the release of SST inhibits GH release which, depending on severity or duration, can result in a prolonged imbalance. Evidence of the influence of NPY and SST on GH is suggested by GH acting on NPY neurons in the hypothalamic arcuate nucleus (ARC) and SST neurons in the periventricular nucleus (PeV) through the influence of the GH receptor also found on these neurons

(Minami, 1998). In patients with GH deficiency, considerable *improvements of cognition* (enhanced attention and memory, as well as psychological parameters) have been reported after GH administration (Stabler, 2001).

GABA Gamma-Aminobutyric acid

GABA is the primary inhibitory neurotransmitter in the brain. Reduced GABA inhibitory tone contributes to stress-induced neuroadaptations associated with PTSD symptoms (Roozendaal, 2009).

GLU Glucocorticoids

Chronic stress results in sustained increases in plasma glucocorticoid levels (Ottewiller, 1989). Chronically elevated glucocorticoids are associated with damage to the hippocampus, a brain region involved in memory that has been suggested to have an inhibitory effect on glucocorticoid release from the hypothalamus (McEwen, 1992). Excessive exposure to glucocorticoids can cause the HPA axis to remain unstable, hypersensitive or dysfunctional, thus adversely affecting the body's ability to physically and mentally handle stressors (Donadon, 2018).

GRE Ghrelin

Stress-related increases in circulating ghrelin are necessary and sufficient for stress-associated vulnerability to exacerbated fear learning, and these actions of ghrelin occur in the amygdala (Meyer, 2013). Ghrelin is increased by repeated stress, and growth hormone is upregulated in the amygdala and released following chronic stress due to ghrelin receptor stimulation (Meyer, 2013). Human data and adolescent rat data suggest that chronic stress exposure increases the risk of PTSD by elevating ghrelin for an extensive period following the initial occurrence of the primary stressor (Yousufzai, 2018). Malik's study of human adolescents observed an association between elevated ghrelin and PTSD symptom severity (Malik, 2020).

5-HT 5-Hydroxytryptophan

5-HT is an amino acid that the body naturally produces and uses to produce the neurotransmitter *serotonin*. It plays a role in regulating sleep, appetite, sexual behavior, aggression/impulsivity, motor function, analgesia and neuroendocrine function (Sherin, 2011). 5-HT also has a role in the stress response, so it indirectly affects depression and suicidality.

IGF-1 Insulin-like Growth Factor-1

Chronic stress can increase anxiety-like behavior and imbalance HPA axis functioning. IGF-1 attenuates spatial learning deficits in aged rats and promotes neurogenesis in the dentate gyrus of the hippocampus. IGF-1 treatment restores spatial abilities, reduces HPA axis dysfunction and increases plasma estradiol levels (Darnaudery, 2006). In a study with military personnel, paired t-tests of the sleep-improved group revealed significant declines in depression ($p = 0.005$) and posttraumatic arousal ($p = 0.006$) symptoms, as well as a significant increase in concentrations of IGF-1 ($p = 0.009$) (Rusch, 2015). In relation to improvements in cognitive function, a possible mechanism is that IGF-1 interfaces with BDNF to mediate exercise-induced synaptic and cognitive plasticity (Ding, 2006).

IL-1 β Interleukin 1 β

IL-1 β is one of the three major inflammatory cytokines with increased expression in conjunction with increase severity of PTSD (von Kanel, 2010; Passos, 2015).

IL-4 Interleukin 4

IL-4 levels reflect a state of inflammation which, as an anti-inflammatory cytokine, is shown to be decreased with PTSD (von Kanel, 2010) due to generally increased inflammatory cytokine expression.

IL-6 **Interleukin 6**

Overexpressed IL-6 functions and serves as an inflammatory biomarker. After controlling for depressive symptoms, PTSD patients had higher IL-6 levels (von Kanel, 2010). The research by Kim revealed a positive association between PTSD severity and CSF (cerebral spinal fluid) IL-6 levels (Kim, 2020). PTSD severity is associated with increased levels of IL-6 (Passos, 2015).

LEP **Leptin**

The leptin receptor is highly expressed in many brain regions that regulate synaptic plasticity. Deprivation of rapid eye movement (REMD) impairs cue and contextual fear memory and negatively affects pre- and post-synaptic functions of the thalamus – lateral amygdala pathway. Leptin treatment *reversed REMD-induced memory deficits* by a postsynaptic action (Chang, 2013).

Leptin also has pluripotent effects on neuroprotection and neuroregeneration. In extra hypothalamic sites, leptin has remarkable effects on neurogenesis, axon growth synaptogenesis, dendritic morphology, development of oligodendroglial cells and neuron excitability, as well as neuroprotection and regulation of beta-amyloid levels (Paz-Filho, 2010). The neuroregenerative abilities make leptin important for the establishment of hypothalamic, hippocampal and cortical pathways (Bouret, 2010). Leptin's neuroprotective actions include inhibiting apoptotic cell death, attenuating cell death, improving cell survival, protecting against glutamatergic cytotoxicity and oxidative stress, as well as and promoting the proliferation of hippocampal progenitor cells.

Leptin also directly modulates the anxiety pathway. Memory may also be improved by leptin, including spatial learning, memory performance and long-term potentiation in the hippocampus (Paz-Filho, 2010). In the hippocampus, NMDA receptors are necessary for the induction of LTP. Src tyrosine kinases can enhance NMDA receptor function, and leptin can activate a number of signaling pathways associated with hippocampal LTP (Shanley, 2001). Effects of leptin on axonal growth are evident in the hippocampus as well as the cortex (Valerio, 2006). Low leptin levels have been implicated as a direct cause of cognitive impairments, particularly Alzheimer's disease (AD) (Power, 2001). High leptin levels were associated with a lower risk of dementia and Alzheimer's. It is important to note that the positive effect of leptin against the development of AD was only observed among *lean* individuals, whereas *obese* humans – who often have hyperleptinemia – are not shown to exhibit the protective benefits of leptin, probably due to disrupted leptin transport to the brain, along with dysfunctional signaling (i.e. "leptin resistance").

NPY **Neuropeptide Y**

Cerebrospinal fluid (CSF) NPY is positively associated with PTSD severity (Kim, 2020). Depression is often comorbid with PTSD. NPY receptors are highly expressed in the cortex, hippocampus and amygdala, which are regions in the brain associated with mood disorders, stress responses and memory processing. Studies show that NPY receptors mediate some aspects of depression-like disorders, anxiety and stress responses (Eaton, 2007), fear learning and memory, blood pressure control (Chen, 1988) and sympathetic activity (Morales-Medina, 2010). NPY and two of its four known receptors, Y(1) and Y(2), are known to be involved in regulating mood disorders, stress responses and memory processing (Morales-Medina, 2010). *NPY expression is directly related to leptin expression*. NPY feeds back to leptin which – in turn – stimulates BDNF. NPY is known to act within the hypothalamus and inhibit GH secretion via SST. The NPY neurons in the arcuate nucleus (ARC) have been shown to project to SST neurons in the hypothalamic periventricular nucleus (PeV). The feedback effect of GH on the hypothalamus is mediated not only by SST neurons in the PeV, but also by NPY neurons in the ARC (Kamegai, 1994).

OXT Oxytocin

OXT promotes pro-social behaviors, including self-confidence, social interactions and positive social memories. The presence of emotional trauma (ET) and PTSD is strongly associated with reductions in endogenous OXT levels (Donadon, 2018). Trauma-exposed veterans showed higher resting-state alpha (8-13Hz) activity compared to controls in the left dorsolateral PFC, which is involved with working memory and cognitive control that are disrupted with PTSD. OXT is involved as it mediates cortical synaptic plasticity that accompanies sensory enrichment (Zheng, 2014). This higher-level activity was “normalized” following OXT administration, so increased resting-state alpha was associated with lower baseline plasma OXT, reduced salivary OXT activity and increased re-experiencing of symptoms (Eidelman-Rothman, 2015). OXT reduces the stress hormone ACTH and cortisol. Research demonstrates that OXT directly promotes the formulation of stronger synaptic connections, which mediate memory-related behaviors. This includes OXT’s important role in enhancing excitatory connections within the hippocampus to mediate LTP and social memory formation, in addition to mediating aspects of adult neurogenesis in the hippocampus (Pekarek, 2020).

STT Somatostatin

STT concentrations in PTSD patients are higher than those of control subjects (Bremner, 1997). It is vitally important to note that on the STT – GH – GHRH – IGF1 axis, STT inhibits GH secretion (Rivier, 1985; Minami, 1998).

TNF- α Tumor Necrosis Factor alpha

TNF- α , along with IL-1 β and IL-6, are commonly overexpressed with low-grade systemic inflammation. TNF- α is found to have elevated expression, along with IL-1 β and IL-6, in PTSD (von Kanel, 2010).

VGF VGF (non-acronymic)

VGF (a protein coding gene) enhances hippocampal synaptic plasticity and has antidepressant-like actions. Its actions are implicated in energy balance, seizures, and long-term potentiation (LTP) (Thakker-Varia, 2010).

Conflict of Interest

The primary author is the founder and CEO of Leptica Research, LLC and, as such, owns the proprietary non-molecular *isoenergetic cell-signaling Post Traumatic Vets Defense* formula used in this study. We do not consider it a “conflict of interest” to conduct an objective pre-clinical study with this formula to analyze and validate its potential benefits and short-comings in relieving symptoms of PTSD with this unique type of *isoenergetic cell-signalingTM* medicine. It should be noted that the only monetary gain to the author was from the veteran donor who contributed the funds to cover the actual cost only (not the primary author’s labor) to make the bottles of this formula that the primary author provided to the participants in the study.

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Co-investigator's Comments/Clinical Experiences with *Isoenergetic Cell-signaling™* Medicines

As a physician in private practice for over 31 years, I have been aware of *isoenergetic cell signaling™* medicines for over 25 of those years, having been introduced to them by the original researcher of this approach to healing (**Barbara Brewitt**, PhD, MDiv) in Seattle, WA who provided me with some of her first formulas to use with my patients. After Barbara died in 2009, I thought the formulas were no longer available, so I was unable to include them as part of my overall treatment approach again until the fall of 2019 when I met *the primary author of this white paper* (**Paul Ophem**, MIM, MA and CEO/Research Director of Leptica Research, LLC).

Since then, I have been able to re-introduce this **highly-effective holistic medical therapy** back into my practice, which has helped my patients tremendously on their journeys to optimal health. In addition, Mr. Opheim and I have also been able to collaborate together on some of my **most complicated cases** that were either minimally or unresponsive to other forms of therapy that I had tried with them. One patient in particular, whom I have been treating since 2006 for myriad chronic conditions - including breast cancer - is now **finally starting to respond** with the use of Paul's formulas as part of her overall treatment protocol. Another patient, who had a TBI over 20 years ago, in addition to life-long anxiety and depression since childhood, has found significant relief from both of these conditions since taking the CTE and Anxiety and Depression formulas. **I now use these formulas in conjunction with any and all other therapeutic modalities** in my practice, in an effort to help patients reach their treatment goals sooner and more cost-effectively.

Mr. Opheim and I co-conducted this small clinical trial with veterans using his **PTVD formula**. Some of these vets have been suffering with this condition for more than 50 years. After just a short time on this formula, many of these vets' longstanding symptoms began to ease and, for some, even dissipate (including horrific nightmares for one vet that had been a nightly occurrence for 40 years, after only *two days* on this formula). Within just 6 weeks, that same vet stated he felt that **80% of his PTSD symptoms** were **gone**, which his wife corroborated; and, after 10 weeks on this formula, he stated that he felt **93% recovered** from the initial trauma he experienced in the Marine Corps that caused him to attempt suicide 30 times before his PTSD diagnosis was finally made in 2014. It took another vet in the study 8-10 weeks to reach **80-85% relief**, after more than 50 years of debilitating nightmares and at least a 30-year loss of mental clarity. For me, as a physician caregiver, this kind and degree of clinical results is rare (though "miraculous" is the word *both* of these men have used to describe their results). As of this writing, the results of this 4-mo pre-clinical study show great promise and are corroborated by my clinical observations as I met with each participant on a weekly-to-monthly basis as the Co-investigator on this study. I know that the resolution of such deeply-entrenched trauma patterns in chronic conditions like PTSD takes time. However, **I feel hopeful** for the vets in our study in a way that I haven't felt hopeful for patients in a long time, and it often brings me to tears when I sit in their presence and witness their progress. They truly inspire me every day.

Because I was so encouraged with the results I have seen with the veterans in our pre-clinical PTSD study, as soon as Mr. Opheim completed his coronavirus research I immediately sought funds to help our vets be able to participate in **another clinical trial using the formulas outlined in the Coronavirus "white paper"** (available on both of our websites). I did so mostly because I don't want to lose *any* of them to this current pandemic, and also because **prevention** is **EXTREMELY cost-effective** (~17¢ per person per day), as is **treatment** for **mild symptoms** (~\$1.75 per person per day) and **severe symptoms** (\$3 per person per day). Mr. Opheim and I both feel that our veteran participants have **NOTHING TO LOSE AND EVERYTHING TO GAIN** (as do we ALL) by taking these *Coronavirus Relief Signaling* Formulas during this eerily quiet, sometimes chaotic and often surreal experience of being asked to home-quarantine and practice social distancing at a time when we really need each other the most. I am happy to say that *more than 90% our PTSD Study veterans (and their families) have started the Prophylactic formula*. **Mr. Opheim and I are committed to making these cost-effective formulas available to as many people as we can, especially** to those who are currently on the front lines, risking their lives 24/7 to take care of all who have already fallen prey to CoVID-19.

Ann B. McCombs DO, DABHM, DNM

American Board of Holistic Medicine Co-founder and Founding Diplomate

Leptica Research – *the Founder's Story*

My name is Paul Opheim. I have always had an interest in health and wellness, so I became a pre-med student in my early college years. However, I couldn't quite reconcile the allopathic approach to medicine and its primarily pharmacological focus without also including a holistic, integrative approach, so I did not apply to medical school and instead finished a BS degree in botany.

I sensed what I was looking for was out there, but where? In the late 1970s, I went to Taiwan where I became fluent in written and spoken Mandarin and later finished a master's degree in Chinese Literature with a minor in Japanese. After Taiwan, I also did graduate studies in China and Japan. Equally important to me was the introduction and exposure I had to the various practices of Chinese Medicine, including acupuncture, and the understanding of the body's *qi* (*ki* or *chi*) energy system as used in martial arts. I also decided to get another master's degree in International Management (Thunderbird Graduate School of Global Management).

After coming back to the United States, I had the opportunity to work for a company that unified the western disciplines of endocrine research and isopathy with the eastern concepts of energy and wellness with its development of homeopathic Insulin-like Growth Factor-1 (IGF-1) and human Growth Hormone (hGH). Our first clinical study, using a set of growth factors for HIV, proved that loss of lean body mass could be prevented with these medicines. The results were published in the *Townsend Newsletter for Doctors*. After the passing of my mentor (Barbara Brewitt PhD, MDiv) in 2009, I acquired the company (including its patents and proprietary information) and began researching the cell signaling factors and pathways involved in the neurodegenerative afflictions of PTSD, Parkinson's and dementia.

When doctors learned I was including the cell signaling factor called leptin for its neuroprotective attributes in my formulas, they asked that I create a formula for satiety, cravings and addictive eating. I agreed and, in December 2012, I finished the formula **Naturally Leptin Signaling Complex** and, in January 2013, I started doing the case studies. Now I'm happy to report that, after years of use by practitioners in their weight loss and weight management programs, this formula has proven to be safe and very effective - especially for controlling cravings - as it circumvents the issue of leptin impedance (resistance) at the blood brain barrier.

I am a member of The Endocrine Society and an invited member of the Society for Neuroscience, where cutting edge discoveries and research are presented every year. My fascination and passion for understanding how the cell signaling pathways in the body govern health motivates me to continue to develop additional isopathic formulas to address cell signaling challenges (including women's health issues, healthy aging, addictions, immune suppression, anxiety & depression, dementia and Parkinson's. These unique, highly effective and affordable formulas are now available to physicians for their patients through www.LepticaMedical.com (access is user-name and password-restricted for physicians).

Thank you for your time and interest in hearing a little about how I got into the fascinating world of neuroendocrine research and analysis, and how it has led me to bringing these exclusive **isoenergetic cell signaling™ Cell Function Activator™** formulas into the world of medicine, health and healing.

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Ann B. McCombs DO, DABHM, DNM

Ann McCombs is an osteopathic and naturopathic physician (DO, DNM) who has been practicing Holistic Family Medicine as a General Practitioner and Holistic Medicine specialist in WA state since 7-31-89. She is the Co-founder, Medical Director, CEO and President of the Center for Optimal Health, practicing in Bellevue, WA (1994-present), Sierra Vista, AZ (2018-present) and Benson, AZ (2019). She had successful careers in both teaching and marriage and family counseling before pursuing her first love: Holistic Medicine! Dr. McCombs served as a member of the Board of Trustees of the American Holistic Medical Association for 10 years (1992-2002) and the American Board of Holistic Medicine during its first 3 years (2000-2003), of which she was also a co-founder in 1995. She served on the Board of Directors for Dr. Devi Nambudripad's Allergy Research Foundation (1995-2005) and has served as a consultant with Carbon-based Corporation/Lab Interpretation (a company specializing in the multi-variant analysis of biochemical, metabolic and environmental tests) since 1995.

Dr. McCombs was board-certified in Pain Management (1992) and now holds Diplomate status in Integrative Pain Management (2012) and Nutritional Pain Management (2018). She was also the first certified Neural Therapy/Neural Kinesiology Practitioner in the U.S. (1995). In addition, she has acquired post-graduate certifications from the American Boards of Neural Therapy (1996), Holistic Medicine (2000), Chelation Therapy (2003), Oxidative Medicine (2004), Heavy Metal Toxicology (2005) and Drugless Practitioners (2012), as well as certification in T3 Therapy (2013), Stem Cell Therapy (2018) and Emotional Freedom Technique (EFT Intermediate Practitioner 1) in 2019. Reiki (all levels), Nambudripad's Allergy Elimination Technique (N.A.E.T.), Hellinger work (Systemic Family Therapy), Hendricks work (Body-centered Psychotherapy and Brief Relationship Therapy), Tennant Biomodulator treatment and HALO Biophotonic Light Therapy are some of Dr. McCombs' other **therapeutic skills and certifications**.

As an educationally based, holistic medical practitioner, Dr. McCombs is actively engaged in clinical practice, teaching and mentoring. Her unique approach, utilizing **Non-Protocol Diagnosis and Treatment**, puts her on the cutting edge of those physicians who assist clients to achieve optimal health and healing. She has lectured both nationally and internationally on the use of this approach in treating both chronic pain (using a medical-dental-podiatry model without drugs and surgery) and chronic illness. She is currently co-authoring two books about these principles (one of which became available on Amazon in Jan 2021), where she and her two colleagues share personal and professional experiences from their own unique journeys towards optimal health as they assist their patients/clients to do the same. In addition, Dr. McCombs did *pro bono* work in Benson, AZ during the first 7 months of 2020 (interrupted by the second wave of the CoVID pandemic) as a Holistic Medicine Consultant, Medical Service Provider and Clinical Administrator with nationally-recognized Environmental Medicine specialist and Research Toxicologist, Dr. Michael Gray (MD, MPH, CIME). Through his not-for-profit Progressive Healthcare Group, they are exploring how to collaborate and navigate through our currently very broken disease care system to bring their combined approaches together to help patients heal more quickly from environmental illness caused by hypertoxicity and regain enough of their health to function effectively once again in their lives.

Dr. McCombs' **professional goals** are: to be a part of creating a global health care system that works for everyone (patients/clients, physicians and insurance companies), including the best of both traditional and non-traditional medicine; to provide a healing opportunity and environment for health care providers to heal themselves; to create an effective model of clinical practice that includes the physician-dentist team which can be duplicated locally, nationally and internationally; to create and teach a Living Medicine medical curriculum with Dr. Gladys McGarey that will include Non-Protocol Medicine; and, ultimately, to assist in founding clinical training, research and education at both the graduate and undergraduate levels which will utilize and train others

to use this approach skillfully and with integrity (currently embodied in Dr. Gladys' Village for Living Medicine concept and being implemented in Colonel Tim Kirk (USAF, Ret)'s Warrior Healing Center in Sierra Vista, AZ since Dec 2018 and will be implemented in or near Scottsdale, AZ pending the resolution of the CoVID-19 pandemic). Not-for-profit status was granted December 11, 2002 for Dr. McCombs' own educational and research interests (the Optimal Health Foundation, founded in 1998), which was active until 2012.

Dr. McCombs **currently** serves on the Advisory Board of the Foundation for Living Medicine (2018-present) and as the On-site/On-call Urgent Care Service Provider and Medical Director for the Warrior Healing Center (2019-present) to assist her professional goals to come to fruition. In addition, Dr. McCombs is the Research Co-director (with Paul Opheim, Research Director/CEO of Leptica Research, LLC) of the PTSD and CoVID-19 clinical studies currently being conducted in Sierra Vista at the WHC (2020-present). She is also currently in partnership with Dr. Gladys and Colonel Kirk to do whatever it takes to bring into being *their* individual global visions for *whole-person healing*, an idea whose time has more than come. (For details of their individual visions, see www.thefoundationforlivingmedicine.org and www.visionheals.org.)

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Robert F. Waters, PhD

- Director of International Research: (Zon International Ltd., Jamaica)
- Senior Collaborative Research Scientist: Arizona State University Biodesign Institute
- Retired Medical School Professor: Medical Biochemistry and Medical Genetics
- Elected Emeritus Status in the American College of Medical Genetics (2019)
- Current owner/operator of a farm and ranch in Montana (Agribusiness for over 30 years)
- Cancer Research Director
- Biostatistician
- Co-developer of many successful anti-cancer and anti-viral treatments.

Professor Waters earned a Ph.D. in Molecular Genetics from Montana State University Genetics Institute (1975) with minor emphasis in Biochemistry and Mathematical Statistics, thesis: *A Modified Microbiological Assay of Amino Acids in Hordeum spp.*, with patent (published). His post-doctoral research and faculty appointment was at Kansas State University working on DNA Hybridization techniques and worked with CYMMYT (Mexico) under the auspices of Nobel Prize Laureate, Prof. Norman E. Borlaug, in Mexico (1975-1977) (with publications). Studied CIS WAN communications and became a specialist working with CAPLAMAR (Mexico City), CIA (Langley), British Petroleum (London) and Tyndall AFB (Florida) in the late 1970's to early 80's. In the late 80's, he had extensive CSE training with IBM, DEC, Data General, CDC, etc, and developed high volume billing system for emergency room use, and mathematical statistical modeling in predictive systems. He helped in the successful rewriting of the national EMT-Basic curriculum for DOT/NHTSA, a multi-million dollar grant with Samaritan Health Systems approved by all 50 states. Dr. Waters' research interests include focus in genomics, anti-virals, diabetes, cancer, artificial intelligence mathematics and continues to publish in major journals.