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I am a traditionally-trained osteopathic physician (DO) who is also board certified in Holistic Medicine and a co-founder of the American Board of Holistic Medicine. The **goals** of our 25,000+ board-certified MD and DO members is, *first and foremost*, to be true to our Hippocratic oath of "**do no harm**." Our 2nd goal is to **treat the medical *problem* and not just the symptoms** of any illness. As a result, we do all we can in the healing process *before* using pharmaceutical medications and/or surgery. ***Treating CoVID-19 is no exception***, and **THE MOST VIABLE HOLISTIC TREATMENT OPTION *CURRENTLY* AVAILABLE** for this pandemic ***can be on the front lines within 24 hours***!

Please find **attached** a "**white paper**" explaining this **safe** and **cost-effective** treatment, the methodology for which has over 25 years of science and proven efficacy behind it. **The 3 medicines** described and explained in this white paper **can save lives** and help end this pandemic sooner vs later and, likely, help prevent a significant 2nd wave of CoVID-19. The sooner our citizens and patients can get back to work, the sooner the health of our economy can also recover.

PLEASE READ THIS WHITE PAPER and then call me to arrange getting these medicines to the people on the front lines *immediately* for the **prophylactic benefit** of those who are currently **asymptomatic** and to avoid progression of CoVID-19 into the hospital setting for the currently infected who are ***mildly* symptomatic**. The savings could be into the millions of dollars alone just by decreasing the need for ventilators and segregated facilities! Using the medicine formulated for ***severely* symptomatic** people, *along with either of the two following protocols*, could rapidly save even more lives:

• https://articles.mercola.com/sites/articles/archive/2020/04/20/zinc-dosage-for-immune-system.aspx?cid_medium=etaf&cid=share (documenting a New York doctor who treated 699 consecutive CoVID-19 cases with 100% success); and

• https://covid19criticalcare.com/wp-content/uploads/2020/04/PressReleaseTreating-Covid-19-in-ER-April-15-2030_3.pdf (documenting the *independent* **Front Line COVID-19 Critical Care Working Group**'s *Early Intervention Protocol for Any ER or Hospitalized Patient Developing Breathing Difficulty* that is outlined and referenced in detail; for updated versions of this release, go to: https://covid19criticalcare.com).

Thank you.
I look forward to hearing from you.

Ann McCombs, DO/DABHM/DNM

Coronavirus Infection Analysis

Research and Hypotheses behind Creating a Multifactorial Set of Three Coronavirus Relief Signaling Formulas

(Prophylactic, Symptomatic, Severe)

Exposure – Infection – Inflammation – Pneumonia – Pulmonary Failure – Mortality

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Abstract

There is currently no effective pharmaceutical or vaccine therapy yet available to deal with the CoVID-19 pandemic. Even the seasonal Influenza Type A (IAV) vaccine was only 29% *overall* effective in 2019, per the CDC. Numerous researchers have concluded that ***any and all potentially viable therapeutic modalities must be considered*** when dealing with highly pathogenic viral infections. It was to address this urgent need that **Leptica Research did this analysis** on coronavirus, especially ***to determine if cell signaling factors (CSFs) might play a role*** in creating potentially effective *isoenergetic cell signaling™* Cell Function Activator™ medicine(s) to use ***with exposure to CoVID-19***. That question has been answered in this white paper, and Leptica Research has accomplished the task of creating ***three* safe** *(no side effects) and* **cost-effective** *formulas* (**Prophylactic**, **Symptomatic** and **Severe**, which cost 17¢, $1.75 and $3.00 *per person per day*, respectively) that have a high probability of being clinically effective. *Collaborator Comments and Clinical Experiences* with isoenergetic cell signaling™ Cell Function Activator™ medicines *follow the author's Epilogue* at the end of this paper, as do brief *biographical sketches* of both the author and collaborator.

Introduction and Historical Context

Barbara A. Brewitt, PhD, MDiv (1948-2009) is the original researcher of the ***isoenergetic cell signaling™*** approach to healing. Through her doctoral research in Biological Structure (1989) at the University of Washington School of Medicine, as well as her post-doctoral studies as an NIH Fellow, Barbara became recognized as *an international expert on cell-to-cell communication* and broadened the understanding that ***growth factors*** (a type of cell signal) ***are related to health and healing***. Her research was translated into 8 languages. Like all pioneers, however, Barbara was maligned by some colleagues who did not fully comprehend her research and attempted to discredit both her and her work. Nevertheless, by combining the principles of *molecular biology* and *biophysics* with those gleaned from *homeopathy* over a 250-year period, Barbara and I (as her Research Associate and principal investor) created nine different cell signaling formulas that were *safe*, *clinically-proven* and *orally-delivered* to address symptoms associated with such ailments as HIV, Autism and PTSD, as well as hormone and age-related imbalances, that have stood the test of time. **Nine** national and international **patents** were held by our company (Biomed Comm, Inc. in Seattle, WA). **Homeopathic provings** (or "proving trials", where a homeopathically prepared substance is tested on healthy volunteers – "provers" – in order to reveal, through recording the effects, the state of health-disturbance that the substance induces) were done on human Growth Hormone (**hGH**) and Insulin-like Growth Factor-1 (**IGF-1**). Our first ***double-blind, placebo-controlled clinical study***, published in 1995, proved that a set of non-molecular isopathic growth factors could prevent HIV-positive adults from losing lean body mass and experiencing opportunistic infections over a 6-month period. Our **second clinical study** was a *blinded, placebo-controlled* one with orphaned children in South Africa. It "unblinded" itself, however, when half of the

children became more energetic and engaged. Our **third** most notable **research study** was on anti-aging, using homeopathic Human Growth Hormone (hGH). These studies were ***peer-reviewed*** and published in *The Townsend Newsletter* (now known as *The Townsend Letter for Doctors*) and the *Journal of Complementary and Alternative Medicine*. Multiple **proof-of-hypothesis case studies** conducted since 1995 (on Parkinson's, leptin – for cravings and weight issues – PMS, menopause, chronic alcohol addiction, psoriasis, chronic Lyme Disease, Chronic Fatigue Syndrome and, currently, on latent HIV reactivation), as well as **hundreds of anecdotal reports** from medical practitioners around the world have repeatedly validated the effectiveness of these formulas. Subsequent to Barbara's untimely death in 2009, I inherited the patents and proprietary information. Since then, I have researched and developed many other medicinal formulas for both chronic and acute conditions which are ***safe, cost-effective*** and have ***proven efficacy*** with ***no adverse side effects*** (see the complete list on my website: www.LepticaMedical.com – access is user-name and password-restricted for physicians).

The Purpose of this White Paper

A white paper is an authoritative report or guide that addresses issues and how to solve them. Its purpose is to inform readers concisely about a complex issue and present the author's philosophy on the matter, as well as his/her specific solution(s) to resolve it. In this white paper, the complex issue is how to treat a pandemic infection such as CoVID-19 *safely*, *effectively* and *cost-effectively*. To understand my philosophy and the solution that, I believe, could achieve these goals, the reader will be introduced to:

(1) the nature and complexity of ***cell signaling factors*** (CSFs) – the molecules that are responsible for transmitting information between the cells of the body – and how they play a role in the way the body responds to a highly pathogenic coronavirus infection;

(2) how the evolution of CoVID-19 symptoms reflecting the difference in one's state of health is, in part, dependent upon the change in ratios of various CSFs – for example, the presence of fever reflects the levels of *specific* pro-inflammatory CSFs (IL-1β, IL-6, TNF-α);

(3) the concept that the variety and degree of CoVID-19 symptoms directly affects the choice and strength of the energetic frequencies of the CSFs used in the different formulas;

(4) the nature of ***isoenergetic cell signaling*™ medicines** and how they differ from homeopathic and pharmaceutical preparations; and how multiple CSFs can be uniquely combined in a ***Cell Function Activator*™ medicine** to effectively and safely complement diverse treatment protocols to accelerate the healing process of highly pathogenic coronavirus infections, e.g. CoVID-19.

Pandemics Past and Present – A Brief Overview

Pandemic viral infections are an on-going scourge sometimes faced by humankind as well as animals (e.g. swine flu). Highly pathogenic viruses create fever, viral pneumonia, encephalitis and acute respiratory distress syndrome (ARDS) as a result of excessive pro-inflammatory cytokine (a type of cell signaling molecule) and chemokine (small cytokines that attract white blood cells - WBC's - to sites of infection) reactions that the body initiates in response to being exposed to virulent viral infections (Klein, 2012). Every year over 10,000 people in the United States alone die from influenza – primarily from Influenza Type A (IAV) viruses – *including those who were immunized*. **Those who are severely afflicted with a sepsis-like response to the "cytokine storm" of these highly pathogenic viruses**

can be left with a *compromised immune system* that increases their susceptibility to future infections.

To reduce the risk of mortality from these pandemic viral infections, it is crucial to address virus-induced pulmonary failure, especially due to those infections affecting the *lower* respiratory tract. Current vaccines are not completely protective against infections with seasonal influenza strains and are ineffective at protecting against emerging new or pandemic strains (Osterholm, 2012), including CoVID-19. **To date, there are no vaccines – nor any safe and effective pharmacological means – that *adequately* address and *effectively* treat the CoVID-19 pandemic**. Therefore, to minimize morbidity, mortality and reduce the economic burden on society, *especially* in the case of pandemic infections like CoVID-19, ***all* plausible approaches having the potential to be effective against such viral exposures *must be considered***. In the past, in the United States alone, the cost of these highly pathogenic influenza virus outbreaks was more than $85 billion (Molinari, 2007). The potentially devastating health and economic effects of this CoVID-19 pandemic is no different and will likely have an even greater economic impact, possibly into the *trillions* of dollars.

Our Focus is *only* on the Coronavirus Family in this Analysis

It is beyond the scope or intention of this paper to do an analysis of *all* the various viral afflictions most common to humans. Even though the research for these three formulas was restricted to the Coronavirus family, it would not be surprising if there were overlap with other highly pathogenic viral infections (such as Influenza Type A Virus) with respect to the body's antiviral responses to them, especially in the way they reproduce, proliferate and migrate in various organs and tissues.

A very brief overview follows of the order, genus and species of some of the more well-known viruses – divided by phylogenetic clustering (Fehr, 2015) – to show where CoVID-19 fits into the coronavirus viral hierarchy:

Nidovirales order – all viruses in this order are RNA viruses and share an enveloped, non-segmented, positive-sense (polarity), single-stranded genetic structure.

- *Coronaviridae* (CoV) family – first identified in the mid-1960s and named for the crown-like spikes on their surface, seven of which can infect humans.
  - Alpha group of coronaviruses
    - HCoV-229E – associated with the common cold
    - HCoV-NL63 – associated with acute laryngotracheitis (croup)
  - Beta group of coronaviruses
    - HCoV-HKU1 – associated with the common cold
    - HCoV-OC43 – associated with the common cold
    - MERS-CoV – causes Middle East Respiratory Syndrome (or MERS)
    - SARS-CoV – causes Severe Acute Respiratory syndrome (or SARS)
    - SARS-CoV-2 – causes coronavirus disease 2019 (or CoVID-19)
  - Delta group of coronaviruses – not a human contagion
  - Gamma group of coronaviruses – not a human contagion
- *Orthomyxoviridae* family – includes the Influenza A (IAV) viruses
- *Arteriviridae* family
  - Equine arteritis virus (EAV)
  - Lactate dehydrogenase-elevating virus (LDV)
  - Porcine respiratory and reproductive syndrome virus (PRRSV)
  - Simian hemorrhagic fever virus (SHFV)
- *Roniviridae* family – includes the yellow head virus (YHV) in shrimp

Other virus families in this order which also have well-known members:

Flaviviridae family – includes the dengue viruses

Bunyaviridae family – includes the oropouche virus

Togaviridae family – includes the following more-well-known examples:

Chikungunya virus (CHIKV)

O'nyong-nyong virus (ONNV)

Frequency and Prevalence

CoVs are endemic in the human population, causing 15-30% of respiratory tract infections each year. Severity comes with those that cause a greater incidence of *lower* respiratory tract infections, e.g. SARS-CoV and MERS-CoV. CoVID-19 now joins these two highly pathogenic CoVs exhibiting this same characteristic.

Susceptibility

Though not exclusively, the most susceptible people manifesting severe reactions are neonates, the elderly and individuals with underlying illnesses (Fehr, 2015). It is not surprising that those with undeveloped immune systems, those over age 65 and the significantly immunocompromised ("survivors" of sepsis or those who have other immune-compromising afflictions, e.g. organ transplant, HIV and COPD) are the *most* susceptible to these CoVs, as well as the secondary infections, complications and morbidity that come from these highly pathogenic viral influenza infections. Unknown genetic factors that compromise the immune response can also cause healthy adults *and* youth to be at risk. In addition, Immunosenescence (the gradual decline in immune functioning due to natural aging) enhances one's susceptibility to viral infection and also renders vaccination less effective (Hernandez-Vargas, 2014).

It is also possible that one's previous antibiotic usage (which compromises the gut biome) can adversely impact macrophage responsiveness to Types I and II interferons. This antibiotic use causes a reduced capacity *early-on* of these INFs to recognize viral pathogens, control viral replication and limit the inflammatory response. This reduction in macrophage responsiveness also includes less efficient production of multiple effector molecules (those which directly affect cell pathway responses): IFN-γ, TNF-α, IL-2, MIP-1α and CD107a (Abt, 2012), which could subsequently create a degree of T-cell exhaustion. Because antibiotic usage *also* affects the aerobic *and* anaerobic commensal bacteria in the *upper* respiratory tract, an impaired beneficial bacterial presence due to their use could likewise result in impaired anti-viral actions, which could further result in the following (Abt, 2012):

- Greater epithelial cell necrosis and, in severe cases, loss of the bronchiole epithelial layer
- Increased exudate and dead cells in the bronchiolar lumen
- Reduced blood oxygenation saturation
- Impaired viral clearance
- Reduced virus-specific antibodies
- Peribronchiolar inflammation
- Weight loss

Abt and associates then conclude (bold is author's emphasis): ***these data indicate that commensal-derived signals are critical in promoting optimal immunity against multiple viral infections at sites distinct from the gastrointestinal tract, and signals derived from commensal bacteria calibrate the activation threshold of antiviral immune response pathways in macrophages. This indicates an inherent* in*ability to respond to viral infection****.*** They further state that**: *for rapidly replicating viruses, such a delay in initiating antiviral pathways (expression of anti-viral defense genes and***

interferon-responsive pathways) and activating downstream events [such as humoral and cell-mediated adaptive immune responses] can have dramatic consequences, leading to failure to control infection, increased host morbidity and mortality. The consequences to which Abt and associates refer are cytokine storm and sepsis. De Vrese and associate further note (bold, caps and parenthesis are author's emphasis): ***prophylactic probiotic [NOT antibiotic] administration can limit the duration and severity of respiratory viral infections in human subjects***, especially when enhanced by corrective cell signaling and when antibiotics are used *only* to preserve life.

CoVID-19 Symptoms (those in amber are the most common)

- Chills / Hypothermia
- Dehydration
- Diarrhea
- Difficulty moving
- Joint pain / arthritis
- Labored breathing / difficulty breathing
- Decrease or loss of smell (anosmia)
- Decrease or loss of taste (hypogeusia / ageusia)
- *Persistent* dry cough
- *Persistent* muscular weakness
- *Persistent* myalgia (muscle pain)
- Pyrexia (fever) – macrophages produce IL-1β, IL-6 and TNF-α, which induce fever (Tamura, 2004).
- Shortness of breath

Lung Damage

IL-17 is important in inducing the neutrophil response. Excessive neutrophil production, which rapidly infiltrates the lung and is an important source of pro-inflammatory cytokines (IL-1β, TNF-α), correlates with worsening lung injury (Crowe, 2013). This is shown in:

- increased perivascular inflammatory infiltrates
- inflammation extending from the perivascular bed into the parenchyma
- capillary leaks
- lung epithelial apoptosis

Mortality Rates

MERS-CoV and SARS-CoV, both severe infections of the *lower* respiratory tract, have overall mortality rates of 35% and 10% respectively. In populations which have weak immune systems (infants, elderly) or are immunosuppressed (HIV+), the mortality rates **can be greater than 50%** (Gralinski, 2015). From early clinical reporting, *CoVID-19 may have a similar severity*.

A Complex Challenge Requires a Comprehensive Solution

Late-term symptom progression is less related to viremia and more likely to be associated with immunopathological damages resulting *from excessive and inadequate cell signaling responses*, such as:

- excessive pro-inflammatory interleukins, which can damage paracrine (nearby) healthy cells;
- inadequate interferon lambda signaling, which is *only* exhibited by epithelial cells, due to viral suppression of its expression; or
- overexpression of interferon alpha and beta signaling, which is also expressed on endothelial cells, and can result in systemic inflammation.

In the alveolar airspace we need to:

- reverse the loss of barrier function – there is functional and structural impairment of the tight AEC layer; thus, the alveolar-capillary barrier results in fluid leakage from the vascular compartment into the alveolar space, and persistent edema results (Peteranderl, 2016; Wolk, 2008)
- decrease inflammation
- repair the damaged epithelium
- improve edema fluid clearance

Introduction to My Research on Coronavirus

In 2016, with news of the zika, dengue and chikungunya viruses following warming trends northward to Florida, I became concerned about the potential dangers of these viruses to children and adults. I started looking at the scientific data then and, at the request of a doctor in Phoenix, I completed a formula to address the issue of cytokine storm and sepsis. (The current *Coronavirus* ***Severe*** *Relief Signaling Formula* is related to that formula and should help speed recovery from life-threatening CoVID-19 symptoms, leaving the body with enhanced and balanced immunity, as well as improved GI functioning.)

In December 2019, upon hearing of the outbreak of CoVID-19 in Wuhan, China, my thoughts turned to my graduate school classmates in Taiwan and Japan, so I returned to my 2016 research with a focus on highly pathogenic coronaviruses. My analysis came to fruition and concluded on March 15, 2020 with the realization that **3 *distinctly individual* formulas would work best** to address the ***3 phases of symptom development*** of highly pathogenic coronavirus infections:

Prophylactic (pre-symptomatic)
Symptomatic (*or* infected and asymptomatic)
Severe

My reason for this conclusion is this: during the course of symptom development, **the body activates a *variety* of antiviral responses that are related to *specific* CSFs** (primarily interleukins and interferons), which form the basis of our innate immune response to pathogens. Due to the fact that **the ratios of these CSFs change**, maintaining a cell signaling balance of these factors **to avoid a "cytokine storm"** is both *critical* to the success of using **these formulas** to **counter** this **CoVID-19** outbreak effectively and *crucial* for people **start using them ASAP**. More specifically, ***to avoid this event*** (also known as hypercytokinemia), ***maintaining the ratios of Th1/Th2/Th17*** – innate immune T-cell responses governed by pro- and anti-inflammatory cell signaling factors (such as Type I, II and III interferons and interleukins 2,4,10,13 and 17) – ***is critical***. *To accomplish this goal*, I saw that I not only had to modify these formulas to reflect the *specific* cell signaling changes that occur *with exposure* to highly pathogenic coronavirus infections, I also had to modify them to reflect the specific cell signaling changes that occur *during the course of* the body's antiviral responses to *and recovery from* them.

Our Medicines: Unique + Anecdotally and Clinically Proven since 1995

Based on my research, the same approach I have seen work so well for the past 25 years (***isoenergetic cell signaling™* formulas** that have been isopathically-derived and homeopathically-

prepared) **can be employed to address** the current coronavirus pandemic, specifically to stimulate and balance the body's immune response to **CoVID-19**. I call these formulas ***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 homeopathic sequential kinetic preparation; and, through the addition of neuro-energetic signaling, they truly represent ***a different class of medicine***. They are derived from recombinant DNA human proteins (polypeptides), acquired from established FDA-approved laboratories, which also produce bio-identical hormones. **Through this derivative process, *pure* molecules are produced that are *identical* to what the body itself produces**. This is accomplished by taking the human gene that produces each *specific* CSF and splicing it into laboratory yeast, which are then fed the foods (usually sugars) that make them multiply, after which they are *separated*. What results are *pure* CSF molecules *exactly like* those that the human body makes. The bio-electrical energy of these *pure* CSF molecules is *identical* to what the body produces, so it can *recognize* it 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 past 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, which is why I have called them ***isoenergetic cell signaling*™ medicines**. **Like homeopathic remedies**, the different *signaling* frequencies (energies) each elicit *different* signaling responses. For example, IGF-1 (Insulin-like Growth Factor-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, my collaborator and I 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.

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 us 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, producing an instantaneous recall of time, space and events, as well as an awakening of the senses. (For additional insights into the research on this topic, I 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.*

Our goals in addressing the current coronavirus pandemic with this isoenergetic cell signaling™ approach are, *first and foremost*, to safely and effectively ***strengthen the body's own innate antiviral immune response*** to resist initial exposure to the virus. An *equally* important goal is to ***reduce migration*** of this virus **to the *lower* respiratory tract**, primarily to significantly decrease the risk of mortality due to increased susceptibility and potential adverse responses of a compromised immune system to viral and bacterial pneumonia.

Challenges – Balancing Virus Elimination and Immune Pathology for a Safe Recovery

Our *primary challenge* is how to minimize the severity of the body's antiviral responses to promote recovery and thereby reduce hospitalizations and mortality. To accomplish this task, we must figure out **how to *control* the cytokine storm and neutrophil-driven inflammation** during catastrophic viral pneumonia (Ito, 2015). For effective host protection from excessive, life-threatening immunopathology, research shows a need to inhibit systemic cytokine and chemokine over-production and *still* stimulate sufficient innate immune cell recruitment.

Our *next challenge* is to figure out **how to *optimize* the bone marrow response** to signals from infected lungs to generate the correct number of leukocytes to attack respiratory viral infections.

Our *final challenge*: **how can we solve *both* of these challenges in a highly effective manner, free of adverse side effects, and still be *extremely* cost effective?** As we had already experienced with the success of our formulas for Parkinson's, COPD, PTSD and CTE (just to name a few), it seems to me that **the *right* combination of cell-signaling factors at the *right* frequencies should be able to meet all of these challenges**.

From my research, I determined that we must **focus on stimulating and balancing Type I, II and III interferons (IFN-α/β/ω, gamma and lambda, respectively) and the interactions of *specific* interleukins**. When the expression of these cytokines and chemokines is inhibited and imbalanced, these CSF's can promote morbidity and mortality. Through the induction of aberrant inflammatory responses during viral infection, these factors can support immune suppression and balance lymphoid tissue disorganization and CD4 T-cell dysfunction (Teijaro, 2016).

Advantages of a *Cell Function Activator*™ Medicine

- *Repeated administration* is possible.
  Due to the transient effectiveness of some medications (TLR-4 antagonists, for example), repeated treatments can be difficult.
- These medicines are *highly cost-effective* – **each 2-oz formula costs only US$120.**
  The **Prophylactic** formula **lasts 102 weeks** (almost 2 years)
  … youth & adults need 2 sprays (sub-lingual) twice/week spaced evenly during the week
  The **Symptomatic** formula **lasts just over 68 days** (2.3 months)
  … youth & adults need 2 sprays (sub-lingual) 3 times a day (upon arising, mid-afternoon and before bedtime or approximately every 8 hrs)
  The **Severe** formula **lasts 40 days** (1.3 months)
  … youth & adults need 2 sprays 5 times a day (approximately every 5 hrs)
- Since 1995, there have been *no adverse side effects* reported from taking this type of medicine, and it has been proven to be *safe* and *clinically effective* over time.
- It is *not a pharmaceutical* drug or drug derivative.
  It is derived from isopathic recombinant DNA human proteins and homeopathically prepared to a non-molecular strength beyond Avogadro's number (6.0221×10^{-23}).

- It is *non-prescription*.
- Because it is prepared by sequential kinetic succussing (diluting) to specific frequencies, it falls under a homeopathic classification, though *it is* technically *an isopathic Cell Function Activator™ medicine* and *not* a homeopathic remedy.

How to Select Which Formula to Use

The correct application of these 3 formulas depends *first* on the body's current state of being: symptomatic or asymptomatic. When asymptomatic, the **Prophylactic** formula should be taken to stimulate certain CSFs in the body (*specific* interferons and interleukins) to respond appropriately if exposed to a potential coronavirus. If you become symptomatic, use the following *Self-Assessment of Symptoms* form to help determine which formula to use next: **Symptomatic** or **Severe**.

Self-Assessment of Symptoms (SAS) Form – for Medical Practitioners and/or Patients

The SAS form is meant to be used **to evaluate one's *current* state of health** to assist in determining which formula to use **if exposure to** a highly pathogenic coronavirus (e.g. **CoVID-19**) **has happened or is suspected**. This form does *not* replace the need to consult with a licensed medical practitioner once awareness of such an exposure has occurred. **NOTE**: not one (or even several) symptoms on this form can determine the presence or absence of a coronavirus infection or antibodies – *only* a reliable test from a reputable medical professional, clinic or hospital can do that or determine if it needs to be done.

Before* starting any of the 3 formulas, complete the SAS form *first, so that a *baseline* state of *current* health can be established. Chronic or frequent presence of symptoms when *not* feeling symptomatic will help to identify when becoming symptomatic has begun, especially with *concurrent* symptoms listed in amber on this form. Specific instructions follow on how to use the SAS form. Note that it is color-coded to help the user determine which formula to use.

- If exposure to a highly pathogenic coronavirus *has* occurred OR is even *a possibility*, fill out the SAS form and start the **Prophylactic** (pre-symptomatic) formula *immediately*.
- If any symptoms listed on the SAS form begin to occur, fill out the SAS form *again*, start the **Symptomatic** formula *immediately* AND consult with a licensed medical professional as soon as possible. **Note** that the "incubation" (or asymptomatic) period for these viruses can be up to 14 days, so there could be some overlap between a possible exposure and onset of symptoms.
- If symptoms become progressively worse, *immediately* seek emergency medical help *AND* start the **Severe** formula.

Oral – Gastrointestinal

	Score 0 = not an issue			1 = very mild or hardly noticeable						10 = very severe
Decrease in sense of smell	0	1	2	3	4	5	6	7	8	9	10
Decrease in sense of taste	0	1	2	3	4	5	6	7	8	9	10
Loss of appetite	0	1	2	3	4	5	6	7	8	9	10
Sore throat	0	1	2	3	4	5	6	7	8	9	10
Vomiting	0	1	2	3	4	5	6	7	8	9	10
Diarrhea	0	1	2	3	4	5	6	7	8	9	10
Dehydration (yellow urine)	0	1	2	3	4	5	6	7	8	9	10

Respiratory

	Score 0 = not an issue									10 = very severe
				1 = very mild or hardly noticeable						
Labored breathing	0	1	2	3	4	5	6	7	8	9	10
Persistent dry cough	0	1	2	3	4	5	6	7	8	9	10
Shortness of breath	0	1	2	3	4	5	6	7	8	9	10
Feeling chest is compressed	0	1	2	3	4	5	6	7	8	9	10
Congested lungs	0	1	2	3	4	5	6	7	8	9	10

Physiological

	Score 0 = not an issue									10 = very severe
				1 = very mild or hardly noticeable						
New headaches	0	1	2	3	4	5	6	7	8	9	10
Excessive fatigue	0	1	2	3	4	5	6	7	8	9	10
New Joint pain / arthritis	0	1	2	3	4	5	6	7	8	9	10
Difficulty moving	0	1	2	3	4	5	6	7	8	9	10
Chills / feel cold	0	1	2	3	4	5	6	7	8	9	10
Fever, esp >100.8° F	0	1	2	3	4	5	6	7	8	9	10
Profuse sweating (w/o exertion)	0	1	2	3	4	5	6	7	8	9	10
Persistent muscular pain	0	1	2	3	4	5	6	7	8	9	10
Persistent muscular weakness	0	1	2	3	4	5	6	7	8	9	10
Strange or odd body Sensations	0	1	2	3	4	5	6	7	8	9	10

Summary

As has been frequently stated in many of the references that were researched in preparing this white paper, **there is currently no effective pharmaceutical or vaccine therapy yet available to deal with the CoVID-19 pandemic**. Even if a vaccine were available, it should be noted that the seasonal Influenza Type A (IAV) vaccine has *never* been shown to prevent transmission of the flu; the best it can do is to limit the symptoms in an infected person (https://www.drbrownstein.com/should-you-get-the-flu-shot/, 2019) and https://www.drbrownstein.com/wsj-article-on-flu-shots:-perfect-example-of-fake-news!/, 2019). It is to the credit of numerous researchers cited in the References section who have concluded that **any and all potentially viable therapeutic modalities must be considered when dealing with highly pathogenic viral infections**. It was to address this urgent need that *I did this research* on coronavirus, especially *to determine if CSFs might play a role in creating* potentially effective *isoenergetic cell signaling™ Cell Function Activator™ medicines to use with exposure to CoVID-19*. As previously outlined in this white paper in detail, *I believe I have answered that question and accomplished that task*. **All that remains now is to apply the three formulas that emerged from my research to see if they will prove to be as effective as it seems they have the potential to be**, knowing that no harm will likely come from using this approach, based upon the results obtained from using it successfully for many other medical conditions over the past 25 years.

Overview of the Remainder of this White Paper

What follows next reflects my thought process and the research I did to determine which CSFs needed to be *specifically* considered to correct the imbalance in the human cell signaling system that can occur when exposed to a highly pathogenic coronavirus like CoVID-19.

To enable the reader to understand this complex research effort, I have included many **terms** (and their **abbreviations** and ***relevant* definitions**) to provide a context for the discussion of the *specific* CSFs that were taken into consideration to accomplish this task**. A list of the CSF's** (including *their* abbreviations and definitions) **involved in understanding their interaction with and impact upon** highly pathogenic viruses in general, and **CoVID-19** in particular, **follows *these* terms and abbreviations**. All the research that I did has been included in the References section.

Terms and Abbreviations

AEC	Airway epithelial cells
ALI	Acute lung injury: non-cardiogenic pulmonary edema, capillary leak, hypoxemia (Crowe, 2009)
AM	Alveolar macrophage
Apoptosis	*Programmed* cell death through pathways governed by cell signaling factors
ARDS	Acute respiratory distress syndrome – most severe form of ALI
AT2	Alveolar type II (epithelial) cells
Autophagy	The breakdown and recycling or elimination of cells
BAL	Bronchoalveolar lavage (fluid) – also known as BALF
CARD	Caspase activation and recruitment domain – a caspase is a protease enzyme that plays an essential role in programmed cell death and inflammation.
CD4+ T-cells	CD4+ T-cells – one of the 4 types of T-cells (lymphocyte WBCs that protect the body from pathogens and cancer cells). CD4+ cells are essential in the formation of protective memory CD8+ T-cells, which are activated following infection or immunization to support memory CD8+ T-cell development (Laidlaw, 2016).
CD8+ T-cells	CD8+ T-cells – one of the 4 types of T-cells, also known as tissue-resident memory cells. These memory CD8+ T-cells adapt to the local tissue microenvironment and interact with other immune cells during their development to maintain, as well as confer, immune protection (Rosato, 2017).
CD14	CD14 – a lipopolysaccharide-binding protein which functions as an endotoxin receptor. This CSF is anchored to and expressed at the cell surface (mainly in monocytes, macrophages and neutrophils). It is also a co-receptor and amplifies TLR-mediated pro-inflammatory and immunomodulatory responses (Raby, 2016).
CD69	CD69 – a membrane-bound, C-Type II lectin protein receptor encoded by the CD69 gene. This CSF regulates the differentiation of regulatory T-cells (T_{reg}), formerly known as suppressor T-cells, as well as the secretion of IFN-γ, IL-17 and IL-22 (Cibrian, 2017).
cDCs	Conventional dendritic cells – innate immune cells that reside in tissues which, following tissue infection or injury become activated and migrate to draining lymph nodes to promote adaptive immune responses (https://rdcu.be/b3j8N, 2020).
CSFs	Cell signaling factors – the molecules that are responsible for transmitting information between the cells of the body, which include hormones, cytokines, chemokines, adipokines, growth factors and neurotrophic factors.
CoV	Coronavirus
DAD	Diffuse alveolar damage
DLN	Draining lymph node
ENaC	Epithelial sodium channel
H_N_	Hemagglutinin ___ Neuraminidase ___ : there are 16 different hemagglutinins (HA) and 9 different neuraminidases (NA), and re-assortment of these two antigens determines the influenza A virus subtype (Hale, 2010).
H1N1	Highly pathogenic avian (swine flu) influenza strain: 1918 and 2009 (pandemic strains)
H5N1	Highly pathogenic avian (bird flu) influenza strain
H7N9	Highly pathogenic avian (bird) influenza strain
HPAI	Highly pathogenic avian (bird) influenza
IAV	Influenza A Virus: e.g. H1N1, H5N1, 1918 Spanish flu

ILD	Interstitial lung disease – an umbrella term for a large group of disorders that cause scarring (fibrosis) of the lungs, which then causes stiffness, making it difficult to breathe. Characterized by a dry, hacking cough. Examples are: scleroderma, pulmonary fibrosis, hypersensitivity pneumonitis and sarcoidosis (www.WebMD.com>lung>interstitial-lung-disease, 2019).
IPF	Idiopathic pulmonary fibrosis – the most common type of ILD. It is most often caused by the *Mycoplasma pneumoniae*, characterized by inflammation of the air sacs or the web of tissue surrounding the air sacs (interstitium), causing alveolar epithelial cell injury/cell activation, expansion of the fibroblast/myofibroblast population and exaggerated accumulation of extracellular matrix (ECM) components, which ultimately results in the destruction of the lung parenchyma (Pardo, 2012).
ISGs	Interferon-stimulated genes – genes which direct antiviral and immunomodulatory actions that can limit infection (Takaoka, 2006).
MAIT	Mucosal-associated invariant T-cells
MAVS	Mitochondrial antiviral signaling protein
MDA5	Melanoma differentiation-associated gene 5
MERS	Middle East respiratory syndrome - caused by one of the viruses in the CoV family
MMP	Matrix metalloprotease – in humans, a diverse group of 23 signaling proteins
MODS	Multiple organ dysfunction syndrome - occurs when there is excessive inflammatory cytokine response (cytokine storm) that can result in tissue damage and apoptosis.
NF-$_K$B	Nuclear factor kappa B – a protein complex that controls the transcription of DNA, cytokine production and cell survival/apoptosis
pDCs	Plasmacytoid dendritic cells – cells which play a critical role in regulating pulmonary function by suppressing inflammation (Kang, 2017).
RAS	Renin-angiotensin system – a hormone system that regulates blood pressure, as well as fluid and electrolyte balance and systemic vascular resistance.
RIG-I	Retinoic acid-inducible gene I
RSV	Respiratory syncytial virus – a member of the family Paramyxoviridae, which preferentially infects lung epithelial cells (Monick, 2005)
SARS	Severe acute respiratory syndrome **-** caused by one of the viruses in the CoV family
SIRS	Systemic inflammatory response syndrome – caused by an overexpression of inflammatory CSFs which are expressed on numerous cells in tissues and organs throughout the body.
TRAIL	TNF-related apoptosis-inducing ligand – may play a distinct role in pathogenesis and pathogen elimination (Gyukovska, 2016)
Zoonotic	Of wild or domestic animal origin

Cell Signaling Factors

CSFs play a significant role in determining molecular pathways which influence cell functioning, and they have differing functions. Some initiate signaling pathways, some are involved in pathway progression and others are expressed as a result of the pathway's actions. Some CSFs are pro-inflammatory, and others are anti-inflammatory. Some CSFs can also be *both*, depending on whether they are over- or under-expressed. ***With symptom progression during a CoV infection, the expression and ratios of these signaling factors vary*****.** *Thus, it is necessary for the formulas to vary*, depending upon which CSFs from the following list are used. The *specific* CSFs used in each formula I make, as well as the specific potencies used in each formula, are proprietary.

Research has demonstrated that **the following CSFs are involved in acute viral respiratory issues**. They may be either (or both) over- and under-expressed, and even exert pro- *and* anti-inflammatory actions. It is beyond the scope of this paper to present a comprehensive explanation detailing each of their interactions; instead, I 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.

ACE Angiotensin-converting enzyme

ACE2 ACE2 is a homolog of ACE and cleaves a single amino acid from Angiotensin II. ACE2 appears to play a protective role in ARDS, as ACE2 is a receptor for the SARS-CoV (Kaparianos, 2011).

ACTH Adrenocorticotrophic hormone – an important component of the hypothalamic-pituitary-adrenal axis is secreted by the anterior pituitary gland. It is often produced by biological stress, though can be inhibited by excessive infection and the presence of a high concentration of persistent organic pollutants and mycotoxins (Gray, 2015 unpub).This inhibition results in extreme sensitivity to bacterial infection and endotoxic shock due to its suppression of pro-inflammatory mediators (Bucala, 1996).

ATG5 Autophagy-related 5 gene **–** Autophagy and apoptosis are two major and interconnected host cell responses to viral infection, including Influenza A Virus (IAV). Inhibition of autophagy induction blocks both virus replication and apoptosis pathways. IAV can inhibit autophagic formation via interaction with the autophagy-related genes (ATGs), such as ATG5 and other cell signaling pathways (Zhang, 2014).

CCL2 Chemokine ligand 2 (also known as MCP-1) **–** elevated levels are associated with a hyper-inflammatory response.

CTGF Connective tissue growth factor **–** located on the TGFβ1-CTGF axis, overexpression of this CSF contributes to fibrogenesis (Gralinski, 2013).

E2 Estrogen 2 **–** one of the three estrogen reproductive hormones, predominantly found in females. In higher doses, E2 suppresses inflammatory cytokines and chemokines (including TNF-α and CCL2) and is also mediated, in part, by the inhibition of $NF\text{-}_KB$ transcriptional activity (Klein, 2012).

EGF Epidermal growth factor – the elevated host response of this CSF's receptor signaling can lead to pulmonary fibrosis. After the SARS-CoV outbreak in 2003, many older survivors developed residual pulmonary fibrosis (Venkataraman, 2017).

FGF-2 Fibroblast growth factor 2, also known as basic fibroblast growth factor (bFGF) **–** a growth factor and signaling protein encoded by the FGF2 gene that is required for lung epithelial recovery. FGF-2 promotes myofibroblast differentiation and proliferation, in cooperation with the profibrotic growth factor TGF-β1 (Guzy, 2015). Care must be taken, however, not to create a signaling imbalance, which could lead to pulmonary fibrosis.

GAL-1 Galectin-1 **–** a ubiquitously expressed lectin (carbohydrate-binding proteins) which can reduce influenza viral loads and decrease inflammation and apoptosis through binding to the influenza envelope of glycoproteins (Yang, 2011).

G-CSF Granulocyte-colony stimulating factor **–** a glycoprotein that stimulates the bone marrow to produce granulocytes (WBCs that contain secretory granules in their cytoplasm, i.e. a neutrophil, basophil, or eosinophil) and stem cells and release them into the bloodstream. In the H1N1 pandemic, excess production of G-CSF contributed to severe immunopathology, including excessive recruitment of neutrophils and mononuclear cells in the lungs (To, 2016).

GM-CSF Granulocyte-macrophage colony-stimulating factor **–** a glycoprotein that confers viral resistance by enhancing innate immune mechanisms that depend on alveolar macrophages (Huang, 2011).

HGF Hepatocyte growth factor **–** a CSF that has multiple biological effects on stem cells, epithelial proliferation and wound healing, including the ability to ameliorate the

enlargement of airspaces and alveolar wall destruction (Hegab, 2008). HGF also inhibits the production of MCP-1/CCL2 in response to TNF-α.

HIF-1α Hypoxia inducible factor 1-alpha **–** a CSF that plays an important role in the evolution and propagation of the inflammatory process. Humans infected with H1N1 influenza develop large areas virtually devoid of alveolar epithelial cells, requiring both expansion and migration of surviving AEC2s and more undifferentiated progenitors to restore alveolar epithelial barriers. HIF-1α inhibition can improve lung function by re-directing airway progenitor responses toward rapid AEC2 expansion and migration (Xi, 2018).

HSP-70 Heat shock protein-70 **–** one of the HSPs, a family of proteins that are produced by cells in response to stressful conditions. HSP-70 may contribute to the avoidance of excessive inflammation (Takashima, 2018).

INF-α Interferon alpha **–** a member of the Type I Interferons. IFN-α treatment restricts IAV replication but exacerbates disease, thus increasing pulmonary proinflammatory cytokine secretion by pDCs and cDCs, innate cell recruitment and epithelial cell death, unlike IFN-λ treatment (Davidson, 2016). IFN-α is essential for curbing viral propagation and restricting viral pathogenesis (Teijaro, 2016; Sheehan, 2015).

INF-β Interferon beta **–** also a member of the Type I Interferons. This CSF can be expressed within the first 2-4 hours of post-infection pathogen recognition. Alphavirus-infected cells induce a viral-protective response and become unable to response to IFN-β treatment. Very low sub-protective doses of IFN-β, which *do not* induce the antiviral response in *un*infected cells, have a very strong stimulatory effect on the cell's ability to express Type I IFNs and activate interferon-stimulated genes during subsequent infection (Frolov, 2012).

IFN-γ Interferon gamma **–** the only one in the Type II Interferon family. IFN-γ is mainly produced by immune cells (activated T-cells, natural killer cells and macrophages) and shows a response against viruses, bacteria and pathogens (Stanifer, 2019). The natural killer (NK) cells that appear in pulmonary lymphocytes after influenza virus infection produce IFN-γ and limit viral spread by virus-infected cell lysis (Tamura, 2004).

IFN-λ1 Interferon lambda 1 (also known as IL-29) **–** this CSF effectively limits the spread of respiratory viruses in a contact transmission setting, in part due to its inhibition of viral replication in the upper airways (Klinkhammer, 2018). IFN-λ1 signaling is necessary for the negative regulation of IL-10 and its immunoregulatory network, which links with aberrant CD8+ T cell responses during IAV infections (Hemann, 2019). IFN-λ1 also lowers the frequency of AEC apoptosis, as compared to IFN-α (Davidson, 2016).

IFN-λ2 Interferon lambda-2 (also known as IL-28A) **–** like the other IFN-lambdas, this CSF is produced by AECs and shares its mucosal antiviral immune response with IFNλ1 and IFNλ3 (Ueki, 2013). ***When AECs are virally infected, IL-8 is produced and IFN-λ production is inhibited.***

IFN-λ3 Interferon lambda-3 (also known as IL-28B) **–** this CSF shares similar antiviral functions with IFN-λ1 and IFN-λ2.

IFN-ω Interferon omega **–** a member of the Type I Interferon group (which includes IFNα and INFβ) that possesses similar Type I Interferon antiviral properties.

IL-1β Interleukin 1-beta **–** elevates inflammation level.

IL-2 Interleukin-2 **–** enhances the production of regulatory T (T_{reg}) cells.

IL-4 Interleukin-4 **–** an anti-inflammatory signaling protein that drives Th2 polarization, resulting in the inhibition of IL-12 and IFNγ-driven Th1 differentiation (Tanaka, 2008). IL-4 is crucial to help balance pro-inflammatory over-expression.

IL-6 Interleukin-6 **–** elevates inflammation level and is significantly over-produced in individuals with SARS (Chien, 2006). In the H1N1 pandemic, excess production of IL-6 contributed in the same way that G-CSF did - see details in G-CSF description, above (To, 2016).

IL-7 Interleukin-7 **–** down-regulates SOCS-3 and promotes production of cytoprotective IL-22, which attenuates (reduces the effects of) liver pathology (Pellegrini, 2011).

IL-8 Interleukin-8 **–** was over-expressed in the H1N1 pandemic. Excess production of IL-8 contributed in the same way that G-CSF and IL-6 did - see details in G-CSF description, above (To, 2016).

IL-10 Interleukin-10 **–** a Th2 T-cell promoting protein, which is under-produced in patients with SARS (Chien, 2006), and can result in excessive inflammation. In the H1N1 pandemic, excess production of IL-10 contributed in the same way that G-CSF, IL-6 and 8 did - see details in G-CSF description, above (To, 2016).

IL-12 Interleukin-12 **–** an inflammatory protein and an anti-viral cytokine that is under-expressed with SARS. It is important for the development of Th-1 cells, which have potent antiviral activities (Trinchieri, 2003).

IL-13 Interleukin-13 **–** a Th2 anti-inflammatory cytokine that induces macrophage activation (Mantovani, 2013).

IL-15 Interleukin-15 **–** controls release of the proinflammatory IL-18 from human monocytes, which induces the antiviral protein IFN-γ (Sattler, 2015).

IL-17 Interleukin 17 **–** this CSF's receptor is activated by IL-17A and IL-17F. Signaling may be detrimental in the response to an influenza virus challenge (Crowe, 2013).

IL-18 Interleukin-18 **–** a potent pro-inflammatory cytokine that is induced by IL-15 which, in turn, induces MAIT (Loh, 2016).

IL-22 Interleukin-22 **–** has been shown to act in a synergistic manner with Type III IFNs, leading to an increase in STAT1 (the primary transcription factor activated by interferons) activation, which then leads to an increase in the Type III IFN-dependent expression of interferon-stimulated genes (ISGs) (Stanifer, 2019).

IL-25 nterleukin-25 **–** this CSF's receptor is highly expressed by CD14+ cells in human blood and, in response to IL-25, can down-regulate the expression of inflammatory cytokines induced by TLR ligands, including TNF-α and IFN-γ (Caruso, 2009).

IL-27 Interleukin-27 **–** exhibits broad anti-inflammatory activity via suppression of Th1/Th2/Th17 effector CD4+ T cells and the stimulation of IL-10. It also antagonizes IL-2, and its upregulation during inflammation may limit T_{reg} cells at sites of infection, which shows that it may be necessary for optimal/balanced regulatory functions under inflammatory conditions (de Aquino, 2014).

IP-10 Interferon-gamma-inducible protein 10 (also known as CXCL10) **–** a chemokine produced by T-cells, monocytes, endothelial cells and keratinocytes after stimulation with IFN-γ, whose levels are significantly elevated during SARS infection (Chien, 2006). In the H1N1 pandemic, excess production of IP-10 contributed in the same way that G-CSF, IL-6, IL-8 and IL-10 did - see details in G-CSF description, above (To, 2010).

LEP Leptin **–** a hormone made predominantly by fat cells and enterocytes in the small intestine that helps to regulate energy balance by inhibiting hunger which, in turn, diminishes fat storage in adipocytes. LEP has been found to delay the cleavage of Bid and the migration of Bax in the mitochondrial release of Cytochrome c in the pro-apoptotic cascade. In addition, LEP also delays the mitochondria-derived activator of caspase, as well as the activator of both caspase-8 and caspase-3, *thus delaying cell death activation*. Leptin also activates both the PI3K and MAPK signaling pathways, resulting in the inhibition of

the mitochondrial death pathway. *These functions make leptin* ***a critical cytokine*** *in the survival of neutrophils by blocking apoptosis*, similar to G-CSF (Bruno, 2005). It is the infection itself, as well as its replication within cells, the progression to cell death and the subsequent release of the cell's contents that *must* happen before the virus can be released from the body. Thus, ***delaying cell death is one way in which the body is able to reduce viral replication and viral load***.

MCP-1 Monocyte chemo-attractant protein-1 (also known as CCL2) **–** contributes to protection against influenza. However, if this CSF is in excess, it can be inflammatory, as seen in the H1N1 pandemic, when excess production of MCP-1 contributed in the same way that G-CSF, IL- 6,8,10 and IP-10 did - see details in G-CSF description, above (To, 2016). This dichotomous effect is similar to TNF-α.

MDA5 Melanoma differentiation-associated gene-5 **–** a pattern recognition receptor protein that recognizes cytoplasmic viral double-stranded RNA and initiates rapid innate antiviral responses (Takashima, 2018). MDA5 also recognizes measles virus and picornavirus which includes poliovirus and encephalomyocarditis virus) (Gitlin, 2006).

MIF Macrophage migration inhibitory factor **–** a pro-inflammatory cytokine that acts within the cytokine cascade in concert with glucocorticoids to control the "set point" of the immune and inflammatory response. As an important regulator of innate immunity, MIF can promote the following pro-inflammatory protein expressions: TNF-α, IL-1β, IL-2, IL-6, IL-8 and IFN-γ (Baugh, 2003). In the case of ARDS, the pro-inflammatory nature of MIF may counter-regulate the anti-inflammatory effects of glucocorticoids on cytokines expression from alveolar macrophages. This increased MIF expression correlates with the development of ARDS in septic patients (Beishuizen, 2001). The role MIF plays in ARDS may be due to its ability to upregulate the neutrophil chemo-attractant MIP-2 (Makita, 1998).

Perforin Perforin **–** one of the primary T-cell-mediated antiviral effectors, along with IFN-γ (de Aquino, 2014).

S1P Sphingosine 1 phosphate **–** a protein that modulates IFN-α signaling through CD69 (Teijaro, 2016; Shiow, 2006).

SOCS-3 Suppressor of cytokine signaling-3 **–** a feedback inhibitor of the JAK/STAT3 pathway (a chain of interactions between proteins in a cell). The STAT3 pathway triggers a variety of gene responses, depending on stimulation by proteins such as IL-6, IL-10 and other growth factors, resulting in pro- *and* anti-inflammatory responses (Gao, 2018). The STAT3/SOCS3 expression level and responses can activate *or* inhibit (respectively) IL-27, LEP, IL-10, G-CSF, IL-6 and others in the IL-6 family of signaling proteins (Gao, 2018).

TEST Testosterone **–** a predominantly male reproductive hormone. TEST declines with age as well as with increased toxic load (Gray, 2015 unpub). and may contribute to increased morbidity in males. In an experiment, a murine animal model inoculated with Influenza A Virus showed greater morbidity, clinical disease and pulmonary inflammation, as well as reduced antibody responses, in older males than in younger males (vom Steeg, 2016).

TGF-β1 Transforming Growth Factor-beta 1 **–** an anti-inflammatory CSF that promotes CTGF and inhibits the expression of IFN-γ.

TLR3, 7/8, 9 Toll-like receptors 3, 7/8, and 9 **–** CSF's that recognize viral nucleic acids. Their sensors scan the extracellular and endosomal (cytoplasmic) spaces looking for RNA and DNA viral genomes that have been lysed from virus particles outside the cell. When they detect them, they then initiate a signaling sequence leading to the secretion of interferons and other pro-inflammatory molecules (Garcia-Sastre, 2017). These TLR ligands induce Type III interferons (Odendall, 2015), which viruses are able to suppress.

TLR-4 Toll-like receptor 4 **–** a TLR ligand which has sensors that recognize *molecular* patterns of viruses, bacteria and fungi that initiate innate immune responses to invading pathogens. TLR-4 is involved in promoting viral recognition (Totura, 2015).

TSLP Thymic stromal lymphopoietin **–** a cytokine that activates immune cells after being activated by IFN-λ (Ye, 2019).

TNF-α Tumor necrosis factor alpha **–** a cell signaling protein (cytokine) involved in systemic inflammation that makes up part of the *acute* phase reaction. TNF-α elevates inflammation and has stronger anti-viral activity against the influenza virus than IFN-α/β or IFN-γ do (Hernandez-Vargas, 2014).

VEGF Vascular endothelial growth factor **–** induced by HIF-1α and promotes AT2 cell proliferation after lung injury (McClendon, 2017).

Epilogue

After a thorough analysis of the information gleaned from my references, the three formulas previously outlined and discussed were conceptualized and then derived in the manner previously described. Only time will tell if I accomplished my task well enough or not. However, based upon my research efforts and experiences of the past 25 years in determining *which* CSF's seem to play *specific* roles in *specific* "disease" states (or imbalanced cell signaling states), and at which potencies they must be used to reverse that imbalance, **I feel quite confident that these *three formulas* will be at least as effective as my previous ones have been**. *Most* importantly, however, I deeply believe that the people who choose to include these formulas, along with whatever other treatment protocols they may elect to use during the current CoVID-19 pandemic, have **nothing to lose** (especially their mortality) and - potentially - **everything to gain**, including the possibility of having an even *healthier* immune system than when they were first exposed to this highly pathogenic coronavirus.

References - articles in **amber** are highly recommended

I wish to profoundly thank the hundreds of researchers who have dedicated their lives to researching the myriad complexities of how cell signaling factors and pathways influence each other over the course of viral infection. Without their targeted focus and the insights they presented in the following papers, my analysis would not have been possible.

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Collaborator's Comments and Clinical Experiences with these Medicines

As a physician in private practice for over 30 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 until the fall of 2019 when I met *the author of this white paper* (**Paul Opheim**, 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 been finding significant relief from both of these conditions since starting the CTE and Anxiety and Depression formulas. **I now use these formulas in conjunction with any and all other therapeutic modalities**, in an effort to help patients reach their treatment goals sooner and more cost-effectively.

Mr. Opheim and I are also currently co-conducting a small **clinical trial with veterans** using his **PTSD 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 **now** feels **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). To date, overall results of this study lie all along the 0-10 continuum, and 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 am so encouraged with the results I have seen with the veterans in our PTSD study, as soon as Mr. Opheim completed his coronavirus research, I immediately sought funds to help them be able to participate in **another clinical trial using the formulas outlined in this white paper**. 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), as well as ***severe* symptoms** ($3.00 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, *as of 4-16-20, more than 90% our PTSD Study veterans (and their families) have started the* ***Prophylactic*** *formula*, and **Mr. Opheim and I are committed to making this cost-effective option available to as many people as we can - as soon as possible** - *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 importance 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. The results were published in the *Townsend Newsletter*. 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 to bringing these exclusive ***isoenergetic cell signaling*™ Cell Function Activator™** formulas into the world of medicine, health and healing.

Paul E Opheim, MIM, MA
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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 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-present). 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 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 (both of which she expects will be published in 2020), 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 has been doing *pro bono* work in Benson, AZ 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 and Dr. Gray have also been hired to share the Medical Director position for the new Sierra Vista-based Eden Health Hospice program, which will begin as soon as it is safe to do so following the CoVID-19 pandemic.

Dr. McCombs' **professional goals** are: to be a part of creating a global health care system, including the best of both traditional and non-traditional medicine, that works for everyone (patients/clients, physicians and insurance companies); 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 being implemented in Scottsdale, AZ sometime in 2020 and in Colonel Tim Kirk (USAF, Ret)'s Warrior Healing Center in Sierra Vista, AZ since Dec 2018). 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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