The Science Behind
Infeperium
A Breakthrough Therapeutic in Immunotherapy

Marpe Holdings LLC

A Brief Description of INFEPERIUM™
In simple terms INFEPERIUM™ is a Biological Response Modifier (BRM) / Immunomodulator that helps reset the immune system so your body can heal itself. It addresses in an endogenous (from inside the body) way the majority causes of Chronic Disease and their effects on the body.

The active ingredient in INFEPERIUM™ modulates both the adaptive and innate immune systems (without negative side effects) and allows the body to eliminate chronic inflammation, a major cause in all diseases. INFEPERIUM™ restores proper cell signaling, pathogen recognition and proper cell energy, Adenosine Triphosphate production (ATP) endogenously.

INFEPERIUM™ is a major breakthrough in ImmunoTherapy. The action of INFEPERIUM™ is to modulate both the innate and adaptive immune systems that have been degraded and compromised due to disease, environmental, bacterial, viral etc. to normalization and homeostasis allowing the bodies own healing and defense mechanisms to restore proper cell signaling, proper cellular respiration versus fermentation, regulation of cellular transport, and healing. INFEPERIUM™ embodies the latest and most medically accepted theories and practices of immunotherapy, which is now at the forefront and becoming the standard of care for chronic diseases which include cancer, a wide range of autoimmune conditions, and most importantly addressing the growing concern of bacterial resistance.

What INFEPERIUM™'s breakthrough Immunotherapy can do, and why it is different.

INFEPERIUM™'s immunomodulator is one of the few molecules, if not the only one known today, that affects and modulates both the innate and adaptive immune systems without negative side effects.

The primary triggers for Chronic Disease are:

The establishment of a state of Chronic Inflammation (CI), which is now considered the main cause of the vast majority of disease.
Due to the prolonged state of CI, improper and aberrant cellular signaling begins which is the harbinger of most AutoImmune(AI) conditions.
This state of cellular "Misinformation" creates over and under reaction of the immune response and inhibits the bodies defense mechanisms from properly functioning. This includes but is not limited to depressed CD4 and CD8 counts.

Suppressed MHC I and MHC II, which Marshall the forces of T cells, B cells, NK cells and various Macrophages, that prevent pathogens from invading the bodies systems or once they have attacked them to consume and destroy them. Most importantly interfering with the Jak-Stat signaling pathway which controls immune deficiency syndromes and most Cancers.

These three states determine the vast majority of disease. However, if you can address these above states of disease from an Endogenous state, you are going to able to reverse a vast number of diverse conditions that are created by these altered states of health. As well as bringing the patient to Homeostasis.

INFEPERIUM™ addresses these altered states by the modulation of the bodies cytokine cascade from attacking healthy cells to reversing GI and inducing proper cell signaling and pathogen recognition. That it modulates and reestablishes proper function of the innate and adaptive immune systems and responses is the key to the unique effectiveness of INFEPERIUM™.

The Science

Why Biologics?
According to the United States Food & Drug Administration (FDA) Website(link is at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm)
Questions and Answers Section:

“Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.”

According to the FDA, how do biological products differ from conventional drugs?
“In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized. Biological products, including those manufactured by biotechnology, tend to be heat sensitive and susceptible to microbial contamination. Therefore, it is necessary to use aseptic principles from initial manufacturing steps, which is also in contrast to most conventional drugs.”

Again, according to the FDA, “Biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available.”

Therefore, Biologic response modifiers (BRMs) can improve or modify the body's natural response to infection and disease. BRMs, a drug class of their own, are the

newest medications which are based on compounds made by living cells, not synthetic drugs which the body naturally attempts to reject which frequently leads to injury of major organs like the liver and kidneys.

Biological response modifiers (BRMs) are substances that modify immune responses. They can be both endogenous (produced naturally within the body) and exogenous (from outside the body, as pharmaceutical drugs), and they can either enhance an immune response or suppress it.

Some of these substances arouse the body's response to an infection, and others can keep the response from becoming excessive. Thus they serve as immunomodulators in immunotherapy (therapy that makes use of immune responses), which can be helpful in treating many diseases, such as cancer (where targeted therapy often relies on the immune system being used to attack cancer cells) and in treating autoimmune diseases (in which the immune system attacks the self), such as some kinds of arthritis and dermatitis.

Most BRMs are biopharmaceuticals (biologics), including monoclonal antibodies, interleukin 2, interferons, and various types of colony-stimulating factors (e.g., CSF, GM-CSF, G-CSF). "Immunotherapy makes use of BRMs to enhance the activity of the immune system to increase the body's natural defense mechanisms against cancer", whereas BRMs for rheumatoid arthritis aim to reduce inflammation.

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Immunotherapy and Immunomodulators:

Immunotherapy

Immunotherapy is the treatment of disease by inducing, enhancing or suppressing an Immune Response. Jedd Wolchok MD summed up Immunotherapy just last year in response to Immunotherapy being Science Magazines 2013 ***Breakthrough of the Year***. "10 years ago Immunotherapy was almost in the category of snake oil. A few years ago it was stated that Immunotherapy can work. Now Immunotherapy has entered the main stream."

James T. Allison, PhD, professor and Chair of Immunology at the MD Anderson and the Cancer Research Institute (CRI) has received the prestigious Tang Prize, the Louisa Gross Horwitz Prize and the Harvey Prize, all in 2014 for his work on CTLA-4 as an antibody inhibitor in many treatment resistant cancers with amazing survival statistics. Work in CTLA-4 & PD-1 also called “immune check point therapies” are the only two presently approved FDA ImmunoTherapy agents so far.

Why Immunotherapy?
Specificity. T-cells recognize peptides, which are short chain biological molecules that are produced by every cell category including virus, bacteria, cancer/mutations. T-cells can recognize them and can destroy them, and most importantly they have the following two important elements.
First, Memory. As T-cells destroy pathogens, which are biological or environmental invaders which produce abnormal cells, they go through 3 phases: expansion, contraction and memory.

- Expansion is when the T-cells multiply to overwhelm the attacker, including cancers.
- Contraction is when they diminish due to program cell death after the attacker is neutralized.
- Memory is a multiplication of cells that remember the genetic code of the attacker. Memory cells proliferate and circulate through the body standing ready to attack.

Second, Adaptability. Cancerous tumors, viruses and bacteria, can mutate and alter themselves in order to evade various medical therapies. Cancer alone has 9 resistant mechanisms used to trick, hide and survive. So called present “Standard of Care Therapies” which use in large measure synthetically produced drugs frequently harmful to the body, but can’t adapt fast enough to counteract and destroy the mutation capabilities of cancer cells, bacteria and viruses. However, T-cell antigen receptors can. They adapt and respond as quickly as the pathogens, because they can combine and alter themselves as many 10 to the 15th power in different combinations. The stimulation of the T-cells is a natural response of the body’s immune system to the injection of Infeperium breakthrough therapies. This is the key to the why and how of immunotherapy.

Immunomodulators:
An immunomodulator is a substance that either suppresses or activates the body's immune response. These substances are separated into two groups: immunosuppressants and immune activators. Immunosuppressants inhibit the body’s natural immune response, while immune activators generally condition or reprogram it to target a specific disease-causing agent.

Immunomodulators can be produced in synthetic form or naturally in the body. Cytokines are examples of innate immune mediators. Synthetic versions are available in either immunosuppressant or immune activator forms. A suppressant immunomodulator works by inhibiting the activation of critical immune system agents such as calcineurin and the formation of thymus cells (T-cells) and antibodies. In comparison, an activating

immunomodulator uses the process of adaptive immunity to recondition lymphocytes and T-cells to kill known pathogens or tumor cells.

As an immunomodulator, Infeperium active ingredient is one of the few molecules that affects and modulates both the innate and adaptive immune systems without negative side effects, as well as modulating from either activation or suppression immunotherapy depending on what the body needs.

Cyclosporine and methotrexate are commonly used synthetic immunosuppressors. Methotrexate is used in patients with autoimmune ailments. Lupus and rheumatoid arthritis are examples of autoimmune disorders that cause the patient's body to attack his or her own cells. Eventually the targeted cells and tissue become damaged after repeated attacks.

The process of organ rejection is similar to autoimmune dysfunction, except the immune system targets the transplanted organ rather than the body's own cells. Organ transplant recipients take suppressant drugs such as cyclosporine, tacrolimus and sirolimus to prevent organ rejection. Nearly all transplant recipients, except a rare few, must adhere to a strict daily regime that involves taking these medications for life. Not taking the medications as prescribed will almost always induce organ rejection, which could lead to death. Due to the medication's toxic side effects, immuno-suppressors should only be used in cases of severe autoimmune dysfunction or organ transplantation. Our Breakthrough Therapeutic will be investigated in the near future for organ transplant anti-rejection and avoidance graft-versus-post disease (GvHD).

Immunomodulators that activate the immune system include vaccines and cancer immunotherapy. Vaccines work by exposing the patient to weakened or inactive forms of certain bacteria and viruses. The immune system then adapts by producing antibodies that are programmed to immediately kill the introduced pathogen once it re-enters the body, which is called adaptive immunity.

Cancer immunotherapy is very similar to pathogen vaccination. The difference between the two therapies is the agent in which adaptive immunity is induced. Vaccines use microorganisms, while cancer immunotherapy uses microorganisms and enhanced immune cells. Microorganism-based cancer immunotherapies are used to combat some forms of cervical and liver cancers caused by viruses. A cell-based immunomodulator, on the other hand, uses enhanced immune cells such as cytotoxic T lymphocytes (CTLs), dendritic cells (DC) and natural killer cells (NK cells) to target and destroy the patient's cancerous cells.

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What can Infeperium's breakthrough therapies do? Why are they different?
Infeperium active ingredient is one of the few molecules that affects and modulates both the innate and adaptive immune systems without negative side effects, as well as modulating from either activation or suppression immunotherapy depending on what the body needs.

Infeperium's breakthrough therapies can therapeutically treat the following conditions and more:
- Chronic Plaque Psoriasis; downstream complications of psoriatic arthritis and coronary heart disease
- Recalcitrant Diabetic Wounds; downstream complications of diabetic neuropathies, etc.
- Chronic Lyme Disease and its downstream complications.
- Primary Progressive MS (Multiple Sclerosis) and other Demyelinating Neuropathies and other Neurological conditions as Parkinson's and Alzheimers.
- Chronic Pain
- Chronic AutoImmune Diseases
- Crohn's, Irritable Bowel Syndrome (IBD) and Ulcerative Colitis
- Various Therapeutic Resistant Cancers
- Epstein barre and other viral overloads and their various complications

Actions addressed by Infeperium's breakthrough therapies:
I. Inflammation
- Preserving Acute inflammation which is necessary for healing, restoration and defense against invading pathogens.
- Reducing Chronic inflammation which is the beginning of the reversal of degenerative disease.

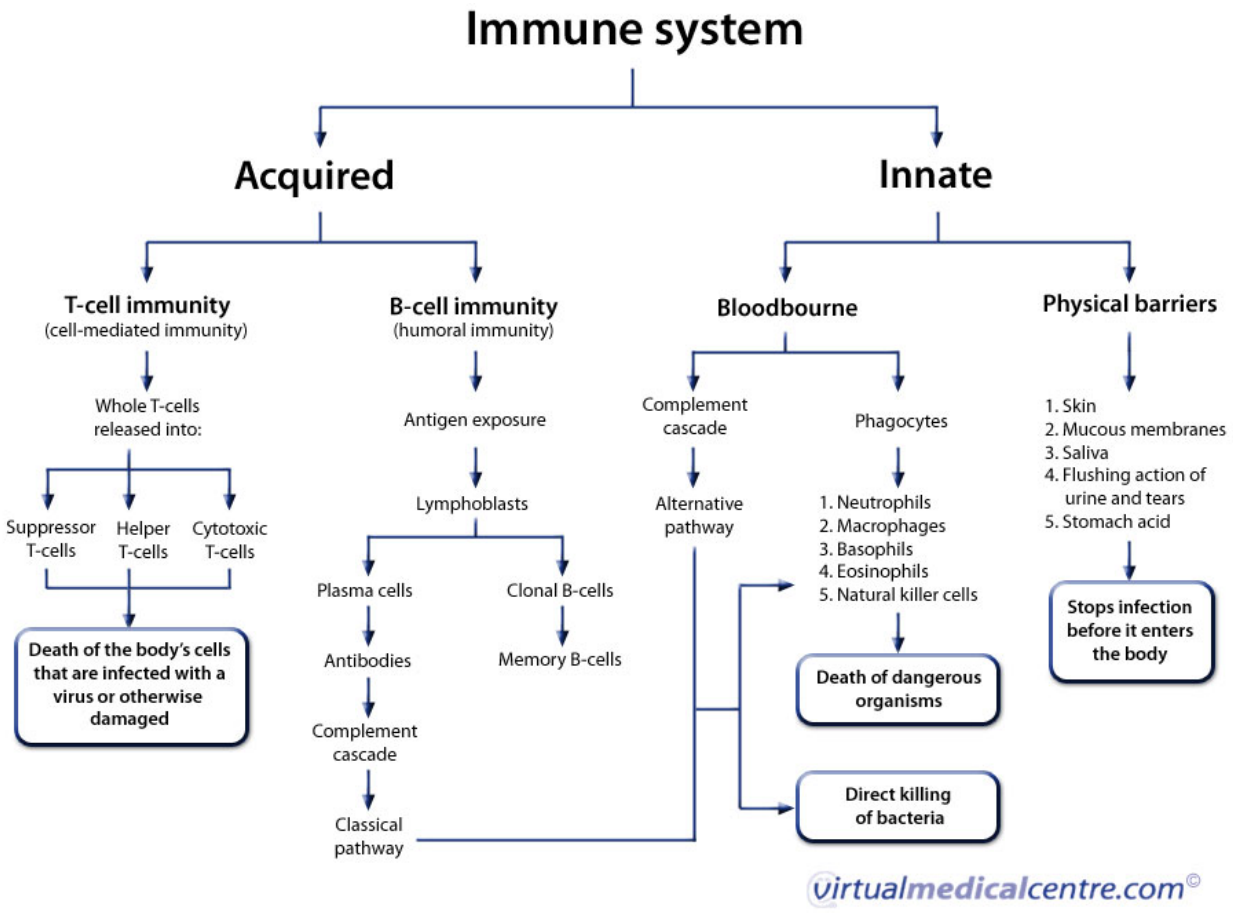
II. Restores proper Cell Signaling
- Through cytokines, cell messenger pathways, cellular communication and transduction, down-line to transcription and translation in the cell nucleus.
- Reverses aberrant, dysregulated, disrupted, error altered, confused and distracted communication.
- Aberrant signals and misinterpreted cell signaling is the initial cause and genesis of future degenerative conditions.

III. Acts as an Adjuvants or Adjunct

- Help regulate and restore the proper on/off switches of immune cascade proteins and cell activity, especially Apoptosis (programmed cell death).
- This will amplified proper cell activity, messaging and signal routing

The foundation of Infeperium's Breakthrough Therapies is that the therapeutic modulates both the Innate and Adaptive Immune System, making it unique in the field of Immunology.

The Immune System



The Adaptive Immune System

Adaptive immunity is a person's defense system built on specific cellular targeting. It takes time for the immune system to develop its weaponry (up to 96 hours after infection), but ultimately the adaptive response is far more effective because of its precision.

Once infection is identified, antigen is transported to lymphoid organs where it is recognized by naive B and T cells. Clonal expansion and differentiation of these cells occurs, and then the battle begins. The immune system can take several tacks, depending on the type of infection encountered. Ultimately, the goals of the adaptive response are two-fold: to produce neutralizing antibodies, and to “flag” infected cells for destruction. This annihilation can be carried out by the cells of both innate and adaptive immunity.

Actions of the Adaptive Immune System

Adaptive immunity is stimulated by the generic actions of innate immunity. Once a foreign organism is identified by the innate immune system, circulating T-cells begin interacting with foreign antigen. Based on their encounter, they can do one of three things: they can kill infected cells directly, they can boost the actions of macrophages to kill infected cells, or they can return to lymph tissue to incite a B cell response.

Stimulated B cells will proceed to produce antibodies, which can then circulate to fight the infection or pathogens.

Antigen Recognition

"Antigen" refers to the parts of a foreign organism recognizable by the adaptive immune system. Typically, these are structural proteins, such as the spike proteins of viruses. Antigens can be huge, and are more often identified by **epitopes**, or smaller fragments of the folded proteins. As such, a single antigen can be recognized by multiple antigen receptors. Antibody has evolved to recognize a dizzying array of antigen epitopes. Antigen can be picked up by lymphocytes in the lymph tissues (T cells and B cells) or the blood stream (T cells only).

T cell receptors (**TCR**) recognize **antigen fragments** (that is digestion products, known as phagocytosis) on the **surface of cells**, whereas B cell receptors (**BCR**) bind **whole antigens** in the **extracellular fluid**. T cells only "see" the antigens when they are presented by **MHC** (Major Histocompatibility Complex) on the cell surface. Antigen digestion and presentation is one of the major functions of the **dendritic cells** (circulating monocytes) and **macrophages**. These are referred to as **Antigen-Presenting Cells** (APCs).

Naive B-cells express IgD and IgM on their cell surfaces, which bind antigen as it is washed into lymph tissue with the afferent lymph fluid. Antigen is presented to B cells by **follicular dendritic cells** (FDCs), which are also classed as APCs. FDCs can endocytose antigen directly from the afferent lymph or receive them from CD4+ T-cells.

Cellular response: Proliferation and Differentiation

- *T cell response*

Once T cells recognize antigen presence in the tissues, they go into action. Their first response is always to recruit help, in the form of CD4+, which is accomplished by returning to the nearest lymph node to carry out clonal expansion. Daughter T cells are

created with identical TCRs in order to recognize the identified antigen. These daughter cells are then returned to the circulation via the efferent lymph.

T cells can differentiate three different ways, based on their **C**luster of **D**ifferentiation (CD) number. All T cells are CD3+, and naive circulating T cells will differentiate upon interaction with antigen to become either **CD8+ (cytotoxic)** or **CD4+ (helper)** T cells. CD4+ T-cells will initially become CD4-TH_0 cells, and must differentiate to TH_1 or TH_2 depending on the whim of the adaptive response. TH_1 and TH_2 cells carry out different types of responses: TH_1 is responsible for enhancing the macrophage response, whereas TH_2 cells enhance the B cell antibody production. Typically, animals produce a balanced response of TH_1 and TH_2 cells, though this can lead to pathology, as can a skewed response, depending on the nature of the foreign organism.

- *B cell response*

Naive B cells recognize antigen in the lymph tissue when it is presented to them by Follicular Dendritic Cells (FDCs). They also undergo clonal expansion, creating a **germinal center** in the follicle as they develop and mature into **plasma cells**. Once mature, plasma cells in the lymph node migrate to the medullary cords and begin secreting antibody into the efferent lymph. Antibody eventually reaches the circulation in order to wage war on the intruder.

Tools of the Adaptive Immune System

Antigen Presenting Cells

- Macrophages
- Interdigitating Dendritic Cells
    - Only IDCs can incite a primary response in naive T-cells
- CD4+ Tcells
- B-cells

Antigen Binding Molecules

- Immunoglobulins
- T-cell Receptor (TCR)
- Natural Killer (NK) Cells

Adaptive Immunity to Viruses

Humoral

- Production of **neutralizing antibody**
- **Antibody-dependent cell mediated cytotoxicity (ADCC)**

Antibody-labelled cells can be targeted by NK Cells as another defense against viral infection. Antibody produced against viral protein can attach to infected cells during their budding phase, which effectively labels them for NK targeting. NK cells express Fcγ receptors with which to detect such cells. Once activated, they release a host of enzymes to induce apoptosis of the budding cell.

Cell-Mediated

- CD8+ T-cell mediated killing of virus infected cells

- Main cells involved in the immune response to **intracellular** virus infection
- Recognition of MHC I-peptide complex
- Infected cells are killed by apoptosis
  - Perforin and granzymes activate the caspase cascade
  - Fas-ligand triggers the Fas-mediated apoptosis pathway
  - Cytotoxic cytokines (especially TNF-α & TNF-β lymphotoxin) act on TNF receptors to induce programmed cell death

Adaptive Immunity to Bacteria

- The adaptive and innate responses work together to destroy bacteria
- The adaptive response ensures the innate response is carried out efficiently

Humoral

- Complement activation of the classical pathway
  - Production of IgM and IgG makes the complement system more efficient

Cell-Mediated

- Help for macrophages
  - IgG production (T-helper type II cells and B cells) which improves phagocytosis by opsonisation
  - Infected macrophages are rescued by T-helper type I cells when phagocytosis and digestion mechanisms fail to eliminate the pathogen

Extracellular Infection

- Complement and phagocytosis
- B cell and T helper type II cell stimulation
- Production of IgM which activates the classical cascade
- Class switching of IgM to IgG which is a good opsonin and targets bacterial Fcγ receptor expressed by macrophages and neutrophils

Vesicular Infection

- The infected macrophage secretes IL-12
- IL-12 stimulates T-helper type I cells which release IFN-γ
- IFN-γ triggers the macrophages to kill the pathogens inside

The Innate Immune System

The innate immune system is the first barrier of defense to infection. It relies on an older, more generic, and faster acting set of tools than the adaptive system. While the adaptive system is essential for a specific response to infection, it is ultimately the innate system that conquers foreign attackers through means of phagocytosis.
Non-specific protective mechanisms include such innate factors as:

- **Physical barriers**
  - Skin
  - Ciliated mucous membranes
  - Commensal organisms
- **Humoral factors**
  - Lysozyme
  - Complement

    - Interferons
- **Cellular mechanisms**
    - Phagocytosis
- Factors which regulate **species specificity**
    - Membrane receptors for pathogens
    - Nutritional requirements
    - Temperature
    - pH
- Mechanisms of innate immunity are always present and generally unchanging
- Adaptive immunity is acquired only on contact with the infectious agent (antigen) and therefore does not function before first contact with the antigen

Actions of the Innate Immune System

Recognition of Microorganisms

- The innate immune system recognizes components of pathogens which are intrinsically foreign (i.e. not present on normal mammalian cells), such as:
    - Lipopolysaccharides of gram-negative bacteria
    - Peptidoglycans of gram-positive bacteria
    - Mannose sugars
    - D-isoform amino acids
- These are given away as foreign by expressing **pathogen-associated molecular patterns** (PAMPs)
- PAMPs are recognized by **pattern recognition receptors** (PRRs) expressed on mammalian cells
    - Pattern recognition receptors are expressed on many different cell types, not just on phagocytes
    - Not all are expressed by all cells: different cell types express a different range of PRRs
    - PRRs are either intracellular, membrane-associated or soluble:
        - Recognition of pathogens via the cellular PRRs results in phagocytosis and inflammation
        - Recognition of pathogens via the humoral PRRs results in various killing mechanisms
- Engagement of PRRs by PAMPs triggers:
    - **Phagocytosis**
    - The expression of **cytokines**, which brings about inflammation and other immune responses

Examples of Pattern Recognition Receptors

Receptor	Location	Ligands
TLR2 (*Toll-like receptor*)	Cell Membrane	Peptidoglycan of gram +ve bacteria

TLR3	Cell Membrane	dsRNA of RNA viruses (e.g. avian influenza)
TLR4	Cell Membrane	Lipoplysaccharide from gram-negative bacteria (e.g. E. coli, Salmonella)
TLR5	Cell Membrane	Bacterial flagellin
TLR9	Cell Membrane	Bacterial DNA (CpG DNA)
C-type lectins	Soluble	Carbohydrates, all bacteria, dead cells
fmlf	Soluble	Formyl peptides (i.e. all bacteria)
Complement receptors	Soluble	Fixed complement components (e.g. iC3b)
NOD2	Cytoplasm	Peptidoglycan of gram +ve bacteria
dsRNA-dependent Protein Kinase Receptor	Cytoplasm	ds RNA of RNA viruses

Phagocytosis

- Phagocytosis is a very primitive system of defense against infection
  - Even exists in invertebrates
- Phagocytosis is a form of endocytosis (cell eating), it is the method of removal of bacteria and dead cells by vesicular internalization
  - The internalized vesicle is referred to as the "phagosome"
  - **Lysosomes**, which contain a large range of enzymes, fuse with the phagosome, killing the microbes in an energy-dependent way
    - Oxygen-Dependent degradation utilizes Oxygen and chlorine free-radicals, Hydrogen peroxide, and Nitric oxide
    - Oxygen-Independent degradation depends on granules containing proteolytic enzymes such as Defensins, Lysozyme, and cationic proteins
      - In addition, these granules contain antimicrobial elements such as lactoferrin
  - Microbes are then digested by a number of different catabolic enzymes
    - Glycosidases: Digest carbohydrates
    - Lipases: Digest lipids
    - Proteases: Digest protein
  - Waste products of phagocytosis are either exocytosed or further degraded by the phagocyte
- **Neutrophils** and **macrophages** are phagocytic

- **Opsonins** promote and accelerate phagocytosis
- Phagocytic cells target pathogens by using cell membrane receptors (PRRs) that recognize intrinsically foreign components of microorganisms (pathogen-associated molecular patterns; PAMPs)

Tools of Innate Immunity

Barriers:

Physical Barriers

1. Skin

The simplest way to avoid infection is to prevent microorganisms gaining access to the body. The skin has an external coating of dead cells (cuticle) that, when intact, is impermeable to most infectious agents.

- Very few pathogens are capable of penetrating the thick stratified squamous epithelium of the skin.
    - Infection becomes a problem when there is:
        - Skin loss: e.g. burns
        - A break in the skin: e.g. wounds

2. Mucus Membranes

- Thin epithelial surfaces are necessary for the normal physiological functions of the body's mucus membranes (ie absorption and gas exchange).They are therefore more susceptible to infection
    - The body uses alternative protective mechanisms in these areas:
        - The **mucociliary escalator** of the respiratory tract (assisted by coughing and sneezing)
        - **Peristalsis, vomiting & diarrhea** when necessary removes microorganisms from the GIT

Biochemical Barriers

- **Lactic and fatty acids** in sweat and sebaceous secretions are directly bacteriocidal
- **Enzymes** e.g. lysozyme in saliva, sweat & tears and Gastric acid denature microorganisms
- Mucus itself is acidic, indigestible and traps microorganisms

Commensal Organisms

- Out-compete pathogens at mucosal and epithelial surfaces and produce natural antibiotics
- When commensals are disturbed, infection with opportunistic organisms is increased

Humoral Factors

Lysozyme

- Lysozyme is one of the major bactericidal agents in secretions

- Helps to protect vulnerable sites such as the eyes and nasal passages
- Exerts bactericidal effects by digesting bacterial cell walls
    - Gram-positive bacteria are more sensitive to lysozyme action than gram-negative bacteria
    - The outer membrane of gram-negative bacteria helps to protect them

Complement

- The Complement system is a group of about 30 proteins within the body fluids of all vertebrates and some invertebrates
- Complement promotes **phagocytosis** or causes lysis of an invading organism
- Complement acts as a cascade, like the blood clotting system
    - The early enzymes in the cascade are bound to invading bacteria and fungi
        - They have an affinity for components of microbial cell membranes
    - This binding initiates a cascade so that the binding of one molecule will eventually lead to the fixation of millions of later molecules
- The early components act as targets for phagocytes
- The later components punch holes in bacteria, causing their lysis

Interferons

- Lysozyme and complement have only marginal effects on virus infections because these are intracellular
    - The body has evolved non-specific mechanisms to protect against viruses
        - The most notable of these is the interferons
- Interferons are small polypeptides produced mainly by virus-infected cells
    - Interact with uninfected cells and render them resistant to infection
        - This resistance is mainly due to the production of enzymes that digest viral nucleic acids

Cellular responses

- If pathogens breach the barriers formed by the skin and mucus membranes, they must be detected and destroyed by cellular and humoral means
- The cells involved with innate protection are:
    - Blood granulocytes, or Polymorphonuclear Cells
        - Notable for their multi-lobed nuclei
        - **Neutrophils**: phagocytose bacteria
        - **Eosinophils**: kill parasites by the release of granules
        - **Basophils / mast cells**: kill parasites by the release of granules
    - Blood **monocytes**: phagocytose bacteria
    - Tissue mast cells and **macrophages**: phagocytose bacteria
- Effectively, innate cellular response seeks to hold off the infection until the adaptive response can back it up with a more specific attack

Macrophages

- The role of macrophages in Innate Immunity is to act as primary **phagocytes**

- Macrophages are present within tissues and take the form of distinct, tissue-specific populations:
    - Alveolar macrophages
    - Tissue histiocytes
    - Glomerular macrophages
    - Hepatic Küpffer cells
    - CNS microglia
    - Sinus-lining macrophages of the lymph nodes and spleen
- **Monocytes** (immature macrophages) are circulating phagocytes
    - Circulate for 6-8 hours
    - Can function as phagocytes within the blood and as newly migrated cells in tissues
    - Chiefly function to replace the various tissue macrophage populations

Neutrophils

- Neutrophils are the principal, highly active **phagocytes** in the blood
    - Comprise 30-70% of white blood cells depending on species
    - Kill and digest microbes in a similar way as macrophages
- Neutrophils can also cause extracellular bacterial killing by disrupting bacterial membranes
    - Secrete small antibacterial peptides
        - E.g. defensins and bactenecins
- Neutrophils produce vasoactive peptides
    - E.g. histamine and bradykinin
    - Cause a great increase in extravasation of blood granulocytes and monocytes and plasma proteins at the site of infection
- Neutrophils are the archetypal cell associated with acute inflammation
    - Are attracted to sites of inflammation by:
        - Complement activation
        - Cytokine production
        - Changes to vascular endothelium
    - Neutrophil activation in an inflammatory lesion results in the release of **prostaglandins**
        - Responsible for vasoactive changes and for pain
- The accumulation of dead and dying neutrophils at the site of infection is called **pus**
    - Their removal from the site after the removal of infection is an important step in the resolution of the lesion

Eosinophils

- Eosinophils are less common than neutrophils, and they are not phagocytic
    - Make up <5% of the leukocytes in normal blood
- Eosinophil numbers are increased:
    - Slightly during the resolution phase of inflammation
    - Many-fold in parasite-infected animals

        - The presence of a large proportion of eosinophils in a blood smear is highly indicative of parasitemia
- Mainly function by targeting the surface of parasites by means of specific antibody or complement
    - Release a large range of toxic molecules that break down the parasite integument
- Prominent in allergic (anaphylactic) reactions

Basophils / Mast Cells

- Basophils/mast cells are principally localized at epithelial surfaces
    - Very small numbers are present in blood
        - Less than 0.5% circulating leukocytes
- They have two principal functions:
    1. Induction of acute inflammation
        - Trauma and/ or bacterial infection causes the production of **cytokines** by the mast cells that induce a classical acute inflammatory response
    2. Response to parasite infection
        - Specific IgE binds cells
        - Subsequent contact with antigen causes the mast cells to degranulate
        - Release enzymes and vasoactive substances that can result in a high level of mucus secretion and smooth muscle contraction
- Also produce factors that influence local host cell physiology
    - Various mediators increase the ratio of phagocyte to microbe

Innate Immunity to Viruses

Because viruses invade host cells to take over a host's cellular machinery, the innate system has a more difficult time detecting viruses as foreign agents. However, there is a give-away element of the viral attack that the innate system can recognize: the **double-stranded RNA** (dsRNA) produced by a virus in its replication phase. Because mammalian cells only ever produce single-stranded RNA, the presence of dsRNA signals a foreign intruder. dsRNA can be detected by TLR-3R on the cell surface or intracellularly by the presence of dsRNA-dependent protein kinase.

The innate response to viral attack also depends on the presence of **Type-1 Interferons**, which are produced by all cells on recognition of a viral attack. Interferons serve to increase degradation of mRNA, inhibit protein synthesis, and increase the effectiveness of the adaptive response by increasing antigen presentation to antibody.

Lastly, the final line of defense for the innate response to viruses lies in the actions of **Natural Killer (NK) cells**]]. These warriors monitor the production of MHC (Major Histocompatibility Complex) on the surface of cells, which is produced as part of the adaptive response. A cell whose cellular machinery is compromised by viral infection will experience a drop in the amount of MHC it produces. When a cell's MHC production drops, NK cells are triggered to phagocytose these cells. As such, this is a non-specific targeting based simply on the ability of a cell to function normally, which also lends them to playing a role in targeting malignant cells. NK cells are incapable of directly targeting

viral infection.

Innate Immunity to Bacteria

The innate response to bacterial infection lies in its first-response role of detection of a foreign organism. By using the above described tools of Pattern-Recognition Receptors (PRRs), the innate response flags up problems while the adaptive response gets itself organized. Once a foreign organism is detected, the innate system responds by engaging in cell warfare via phagocytosis and triggering the inflammatory response. The release of inflammatory cytokines will cause an increase in vasodilation, vascular permeability and an influx of white blood cells. Neutrophils take on their primary role as phagocytes in this phase. In addition, systemic effects of inflammatory cytokines will sustain a rise in core temperature (fever), the release of acute phase proteins from the liver, and bone marrow mobilization as the need for white blood cells production is increased. Acute phase proteins will bind to bacterial cell walls, enhancing neutrophil, macrophage, and complement-initiated phagocytosis.

Inflammation

According to Dr. Andrew Weil, Chronic Inflammation is a disease. The system has gotten hung up, and instead of protecting the organism (our bodies) it starts to kill the organism, slowly but surely. Today modern medicine is starting to admit that chronic inflammation is the MAIN contributing factor to all chronic degenerative diseases and the real cause of the two greatest killers in America: Cancer and Heart Disease. Indeed, chronic inflammation might just be the real cause of all degenerative disease.

Some Facts:

- Chronic Inflammation depresses the immune system and helps promote the formation of cancerous tumors. The longer inflammation persists, the higher risk of associated carcinogenesis.
- Chronic inflammation destroys nerve cells in the brains, a primary cause of Alzheimers
- It is the real source of all autoimmune disorders with over 100 named conditions.

The chronic inflammation, misused or misread signaling pathways, and improper growth factors and apoptosis, creates the “perfect storm” for degenerative disease.

1. The Cancer Research Institute states that “Chronic Inflammation plays a multifaceted role in carcinogenesis”
2. Center for Disease Control and Prevention 2011 states “of the ten leading causes of mortality in the United States, Chronic low level inflammation contribute to the pathogenesis of at least seven. [heart disease/cancer/Chronic lower respiratory disease/stroke/Alzheimer/diabetes/nephritis]. Their findings conclude that Chronic Inflammation to be a major factor in the development of degenerative disease and loss of youthful functions — Aging—

3. Symptoms from Chronic Fatigue Syndrome, Epstein Barre and other conditions go undiagnosed and ignored because of lack of medical understanding of the destructive power of Chronic Inflammation.
4. Chronic Inflammation, allowed to persist, leads to deregulation, altered, and distorted cell communication and specific growth and survival—related pathways. This results in:
   - Aberrant IFN expression is associated with a large number of auto-inflammatory, autoimmune diseases.
   - Disrupted JAK-STAT functionality can result in immune deficiency syndromes and cancers
   - Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity and diabetes.
   - When you combine Chronic Inflammation, misread and distorted signaling pathways, as well as overgrowth and deregulated apoptosis, you get cancer that is immortalized and degenerative conditions that are unalterable.

Cell Signaling

Cytokines are small proteins that are essential for cell signaling and communication. They are released by cells and effect the behavior of other cells. They modulate the balance between immune responses.

- Chemokines
- Interferons
- Interleukins
- Lymphokines
- Tumor necrosis factor (TNF)

Primary & Signaling Pathways - JAK STAT (Janus Kinase Signal Transducer and Activator of Transcription) signaling pathway transmits information from chemical signals outside a cell (Cytokines), through the cell membrane to the DNA & mRNA transcription in the activity in a cell nucleus. This is called Transduction and is a major actuator of on/off switching of proteins. Since JAK-STAT signaling pathways are expressed through white blood cells (source of all immune cellular activity). They are central & crucial to regulation of the immune system.

Secondary Message System

- cAMP — cyclic adenosine monophosphate
- cGMP — cyclic guanosine monophosphate
- Calcium signaling
- Mitochondrion - is the powerhouse within the cell producing, ATP (Adenosine triphosphate) the energy currency of all cell activity.

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Acute Inflammation

Acute Inflammation (Latin, inflammatio) is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.

The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.

Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (e.g. bacteria) and compromise the survival of the organism. In contrast, chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

Inflammation is not a synonym for infection. Infection describes the interaction between the action of microbial invasion and the reaction of the body's inflammatory defensive response — the two components are considered together when discussing an infection, and the word is used to imply a microbial invasive cause for the observed inflammatory reaction. Inflammation on the other hand describes purely the body's immunovascular response, whatever the cause may be. But because of how often the two are correlated, words ending in the suffix -itis (which refers to inflammation) are sometimes informally described as referring to infection. For example, the word urethritis strictly means only "urethral inflammation", but clinical health care providers usually discuss urethritis as a urethral infection because urethral microbial invasion is the most common cause of urethritis.

It is useful to differentiate inflammation and infection as there are many pathological situations where inflammation is not driven by microbial invasion - for example, atherosclerosis, type III hypersensitivity, trauma, ischaemia. There are also pathological situations where microbial invasion does not result in classic inflammatory response— for example, parasitosis, eosinophilia.

The connection between Chronic Disease and Chronic Inflammation

Some diseases caused by Chronic inflammation happen fairly soon. Many take a long time, often ten to twenty years or more. Reducing inflammation can delay or even prevent many chronic diseases! Most of these diseases are far more preventable than curable – so it makes a lot of sense to make some effort to reduce chronic inflammation.

Diseases with strong evidence currently being researched.

Alzheimer’s	Dermatitis	Multiple Sclerosis
Arthritis	Diabetes Insipidus	Myalgias
Arthritis, Rheumatoid	Eczema	Nephritis
Asthma, Allergies	Fibromyalgia (FM)	Osteoarthritis
Atherosclerosis	Inflammatory Bowel	Parkinson's
Autoimmune	Interstitial Cystitis	Psoriasis
Cardiovascular	Irritable Bowel Syn.	Sarcoidois
Cancers	Joint pain	Sjögren's Syndrome
Colitis	Lupus Erythematous	Ulcerative Colitis
Crohn's	Lyme Disease	

Alzheimer's, Dementia, Cognitive Decline

Medical specialists are becoming interested in Alzheimer's and inflammation these days. In the journal Neurology in 1997, neurologists presented research that people who had been regularly taking anti-inflammatory medicine like Ibuprofen had much lower rates of Alzheimer's disease. In the New England Journal of Medicine in 2001, a study showed an 80% reduction in risk of Alzheimer's among those taking anti-inflammatory medicines daily for two years.

Linda Van Eldik, neurobiologist at Northwestern University School of Medicine, explains that whenever the brain is injured or irritated, glial cells pump out cytokines. These are chemical signals to begin the inflammatory process. However, "in chronic neurodegenerative diseases like Alzheimer's, these glial cells are activated too high or too long or both," says Van Eldik.

Now, the path to Alzheimer's disease is being strongly linked to discrete inflammation in the area of the brain Alzheimer's affects. Inflammation begins with an immune response to a very specific threat (insoluble amyloid beta fibrils). However, new research suggests delay or prevention of Alzheimer's may be possible with anti-inflammatory treatments.

Several observational studies have linked chronic low-level inflammation in older adults to cognitive decline and dementia, including vascular dementia and Alzheimer’s disease (Singh et al. 2011). One study found that people with the highest CRP and IL-6 levels (> 2.4 pg/mL) had a ~30-40% increased risk of cognitive decline compared to those with the lowest levels (< 1.4 pg/mL). (Yaffe et al. 2003). Inflammatory markers can be elevated before the onset of cognitive dysfunction, indicating their potential relevance as a prognostic tool in high-risk individuals (Singh et al. 2011).

Not surprisingly, chronic inflammation has also been linked to depression with higher circulating levels of IL-6 and CRP. Whether inflammation leads to depression or whether depression leads to inflammation is still being debated.

Autoimmune Disorders

Among the best-known autoimmune diseases are: rheumatoid arthritis, lupus, multiple sclerosis, insulin-dependent (type 1) diabetes, Crohn's disease, and ulcerative colitis. Rheumatoid arthritis, in particular, has been studied closely for links with chronic inflammation and its characteristic biomarkers. Both TNFa and IL-6 are elevated in patients with rheumatoid arthritis.

People with systemic lupus erythematosus also show elevated levels of IL-6 and TNFa, making it is clear that inflammation has a role.

Inflammatory Bowel Diseases, such as Crohn's disease or ulcerative colitis, are another example of autoimmune disorders where inflammation plays a key role. In fact, doctors are debating about whether IBDs are really autoimmune diseases or whether they should be put in another, relatively new category known as “auto-inflammatory” diseases. In both cases, blocking TNFa or IL-6 can be an effective treatment for patients who do not respond to more conventional treatments.

Cancer

Several studies have established links between chronic low-level inflammation and many types of cancer, including lymphoma, prostate, ovarian, pancreatic, colorectal and lung (Aggarwal et al. 2006).(Kundu et al. 2008) There are several mechanisms by which inflammation may contribute to carcinogenesis, including alterations in gene expression, DNA mutation, epigenetic alterations, promotion of tumor vascularization, and the expression of pro-inflammatory cytokines that have roles in cancer cell proliferation (Kundu et al. 2008, Balkwill 2009)

Researchers in the journal Cell presented their findings about what could be the long-elusive mechanism through which inflammation can promote cancer. "There is plenty of evidence that chronic inflammation can promote cancer" says Alexander Hoffmann, at U.C. San Diego, who led a study. "We have identified a basic cellular mechanism that we think may be linking chronic inflammation and cancer."

Cancer is much like Alzheimer's in that it does not necessarily begin with inflammation. However, inflammation can greatly accelerate the development of cancer once it has begun. NFkB helps cells, which have gone through DNA transformation (cancerous cells, in this case), avoid death. This allows them to continue to proliferate.

In addition, NFkB plays a role in the angiogenesis of cancerous tumors. (This is when they develop their own blood supply, and the metastasis of cancer.) NFkB activity is turned up by the pro-inflammatory messengers, including TNFa and IL-6. In people suffering from chronic inflammation, the risk of certain cancers can be much higher.

"Studies with animals have shown that a little inflammation is necessary for the normal development of the immune system and other organ systems," explains Hoffmann. "But

there can be too much of a good thing. In the case of chronic inflammation, the presence of too much p100 may over activate the developmental pathway, resulting in cancer."

Heart, Coronary & Cardiovascular Disease

Inflammation also plays a role in heart disease! In fact, inflammation is so closely associated with heart disease that many doctors now use a test for inflammation called CRP (C-reactive protein) to assess a person's risk of heart attack. Research shows that CRP can predict the risk of heart attack and stroke as well or better than cholesterol levels.

This is because the immune system attacks LDL "bad" cholesterol that has been embedded in arterial walls. Also, studies have shown that chronic inflammation directly leads to a damaged endothelium (the lining of our blood vessels). The ongoing inflammation eventually damages the arteries - which can cause them to burst. This, in turn, causes another round of plaque patching build-up.

Inflammation is an integral part of atherosclerosis (oxidized low-density lipoprotein cholesterol stimulates the inflammatory response). It is these circulating inflammatory cytokines that are predictive of peripheral arterial disease, heart failure, atrial fibrillation, stroke, and coronary heart disease (Singh et al. 2011, Emerging Risk Factors Collaboration et al. 2010).

That is why researchers have found that CRP is a moderate indicator of coronary heart disease. Total cholesterol levels, blood pressure and smoking still rules but CRP may play a role in their onset.

Inflammation is the match that starts the blaze in the development of heart diseases. Without an elevated level of CRP damaging the blood vessels, much less plaque would formed - even if all other factors were present.

Diabetes

Recent research has linked inflammation, caused by increased fat tissue, with insulin resistance. In type 1 diabetes, the immune system attacks the cells that make insulin. As circulating pro-inflammatory messengers and macrophages increase, insulin resistance follows. While other factors can contribute to insulin resistance and diabetes, the link between chronic inflammation caused by obesity and diabetes is very strong.

The infiltration of macrophages into fat tissue and their subsequent release of pro-inflammatory cytokines into circulation occur at a greater rate in type II diabetics than in non-diabetics (Pickup et al. 2000, Nappo et al. 2002, Ortega Martinez de Victoria et al. 2009). Pro-inflammatory cytokines clearly decrease insulin sensitivity (Bastard et al. 2006).

Children who have allergies are less likely to develop type 1 diabetes. "Children with type 1 diabetes are less likely to get asthma, eczema, or hay fever," says pediatrician Dr. Alan Greene, MD. "And the reverse is true, that those with asthma, eczema, or hay fever are less likely to get type 1 diabetes."

"One possible explanation for this is the imbalance between two types of immune cells, T-helper 1 cells and T-helper 2 cells. In children with diabetes, the balance tends to favor T-helper 1 cells; in those with asthma, T-helper 2 cells. It's difficult for one child to have both."

Type II diabetes is also linked to inflammation, as chronic inflammation releases TNF (tumor necrosis factor), which makes cells more resistant to insulin. "No one would have thought these things were related, but they are" says Dr. Walter Willett, chairman of the department of nutrition at the Harvard School of Public Health.

Chronic Lyme Disease

Increasing evidence points to inflammation as source of nervous system manifestations of Lyme disease. About 15% of patients with Lyme disease develop peripheral and central nervous system involvement, often accompanied by debilitating and painful symptoms. New research indicates that inflammation plays a causal role in the array of neurologic changes associated with Lyme disease, according to a study published in The American Journal of Pathology. The investigators at the Tulane National Primate Research Center and Louisiana State University Health Sciences Center also showed that the anti-inflammatory drug dexamethasone prevents many of these reactions.

"These results suggest that inflammation has a causal role in the pathogenesis of acute Lyme neuroborreliosis," explained Mario T. Philipp, PhD, Professor of Microbiology and Immunology and chair of the Division of Bacteriology and Parasitology at Tulane National Primate Research Center (Covington, LA).

Lyme disease in humans results from the bite of a tick infected with the spirochete Borrelia burgdorferi (Bb). As Bb disseminates throughout the body, it can cause arthritis, carditis, and neurologic deficits. When the nervous system is involved, it is called Lyme neuroborreliosis (LNB). Clinical symptoms of LNB of the peripheral nervous system may include facial nerve palsy, neurogenic pain radiating along the back into the legs and feet, limb pain, sensory loss, or muscle weakness. Central nervous system involvement can manifest as headache, fatigue, memory loss, learning disability, depression, meningitis, and encephalopathy.

To understand further the neuropathologic effects of Bb infection, researchers infected 12 rhesus macaques with live B. burgdorferi; two animals were left uninfected as controls. Of the 12 Bb-inoculated animals, four were treated with the anti-inflammatory steroid dexamethasone, four with the non-steroidal anti-inflammatory drug (NSAID) meloxicam, and four remained untreated. Half of each group was studied for eight

weeks postinoculation and the other half for 14 weeks.

The researchers examined the role of inflammation in the nervous systems of Bb-infected animals. Significantly elevated levels of the inflammatory mediators interleukin-6 (IL-6), IL-8, CCL2, and CXCL13 were observed, as well as pleocytosis (increased cell counts, primarily white blood cells) in the cerebrospinal fluid of all infected animals -- except in those treated with dexamethasone. "Chemokines such as IL-8 and CCL2 are known to mediate the influx of immune cells in the central nervous system compartment during bacterial meningitis, and CXCL13 is the major determinant of B cell recruitment into the cerebrospinal fluid during neuroinflammation," explained Dr. Philipp.

Infection with Bb led to many histopathologic findings in infected animals not treated with dexamethasone, such as leptomeningitis, vasculitis, focal inflammation in the brain and spinal cord, and necrotizing focal neurodegeneration and demyelination in the cervical spinal cord. Evaluation of the dorsal root ganglia showed inflammation with neurodegeneration, along with significant apoptosis of neuronal and satellite glial cells (which surround sensory neurons), in all infected animals with the exception of those treated with dexamethasone. Researchers were able to quantify the protective effect of dexamethasone treatment in protecting both satellite glial cell and neuronal apoptosis; in contrast, meloxicam treatment was only effective in protecting against satellite glial cell apoptosis and only after prolonged administration.

The dorsal roots of animals infected with live Bb (but not treated with dexamethasone) showed the presence of abundant lymphocytes and monocytes. Interestingly, reactions near the injection sites were histologically different from the more diffuse inflammation found along the spinal cord. The pathology found in the dorsal root ganglia and sensory nerves may explain the localized pain and motor deficits that Lyme disease patients experience close to the origin of the tick bite.

Some patients with Lyme disease also show evidence of demyelinating neuropathy and slowing nerve conduction. Nerve conduction studies in motor and sensory nerves of the macaques showed that the Bb infection resulted in specific electrophysiological abnormalities (increased F wave latencies and chronodispersion) that could be prevented with dexamethasone.

Although antibiotics are the standard and necessary first-line treatment for Lyme disease, the results show the potential therapeutic impact of anti-inflammatory or immune-modulatory agents for Lyme-related neuroborreliosis. Most of the neuropathological changes produced by Bb infection were prevented by dexamethasone, a broad-spectrum steroidal anti-inflammatory drug, whereas the non-steroidal anti-inflammatory drug meloxicam was generally ineffective or only partially effective. Analyses of the differences in the mechanisms of action of both drugs may provide a blueprint for the development of new adjuvant treatments for LNB.

"Importantly, we found necrotizing myelitis and degeneration in the spinal cord, neurodegeneration in the dorsal root ganglia, and demyelination in the nerve roots only when lymphocytic inflammatory lesions were also observed in both the central nervous system and peripheral nervous system," stated Dr. Philipp. "Our results suggest that ongoing cytokine activation in the nervous system can contribute to the persistent symptoms of fatigue, pain, and cognitive dysfunction that patients sometimes experience despite having been treated for Lyme disease."

Chronic Kidney Disease (CKD)

The chronic, low-grade inflammation in CKD can lead to the retention of several pro-inflammatory molecules in the blood (including cytokines, AGEs, and homocysteine) (Glorieux et al. 2009). The reduced excretion of pro-inflammatory factors by the diseased kidney can accelerate the progression of chronic inflammatory disturbances elsewhere in the body, such as the cardiovascular system.

Osteoporosis

Inflammatory cytokines (TNF-α, IL-1β, IL-6) are involved in normal bone metabolism. Osteoclasts, the cells that break down (resorb) bone tissue, are a type of macrophage and can be stimulated by pro-inflammatory factors. Systemic elevations in pro-inflammatory cytokines push bone metabolism towards resorption, and have been observed to induce bone loss in persons with periodontal disease, pancreatitis, inflammatory bowel disease, and rheumatoid arthritis (Cao 2011).

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Reactive Oxygen Species and Oxidative Stress

Oxidative stress reflects an imbalance between the systemic manifestation of Reactive Oxygen Species (ROS) and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative

stress from oxidative metabolism causes base damage, as well as strand breaks in DNA. Base damage is mostly indirect and caused by reactive oxygen species (ROS) generated, e.g. O2– (superoxide radical), OH (hydroxyl radical) and H2O2 (hydrogen peroxide). Further, some reactive oxidative species act as cellular messengers in redox signaling. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling.

In humans, oxidative stress is thought to be involved in the development of Asperger syndrome, ADHD, cancer, Parkinson's disease, Lafora disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction, fragile X syndrome, Sickle Cell Disease, lichen planus, vitiligo, autism, infection, and chronic fatigue syndrome. However, reactive oxygen species can be beneficial, as they are used by the immune system as a way to attack and kill pathogens.[20] Short-term oxidative stress may also be important in prevention of aging by induction of a process named mitohormesis.

Chemical and biological effects

Chemically, oxidative stress is associated with increased production of oxidizing species or a significant decrease in the effectiveness of antioxidant defenses, such as glutathione. The effects of oxidative stress depend upon the size of these changes, with a cell being able to overcome small perturbations and regain its original state. However, more severe oxidative stress can cause cell death and even moderate oxidation can trigger apoptosis, while more intense stresses may cause necrosis.

Production of reactive oxygen species is a particularly destructive aspect of oxidative* stress. Such species include free radicals and peroxides. Some of the less reactive of these species (such as superoxide) can be converted by oxidoreduction reactions with transition metals or other redox cycling compounds (including quinones) into more aggressive radical species that can cause extensive cellular damage. Most long-term effects are caused by damage to DNA. DNA damage induced by ionizing radiation is similar to oxidative stress, and these lesions have been implicated in aging and cancer. Biological effects of single-base damage by radiation or oxidation, such as 8-oxoguanine and thymine glycol, have been extensively studied. Recently the focus has shifted to some of the more complex lesions. Tandem DNA lesions are formed at substantial frequency by ionizing radiation and metal-catalyzed H2O2 reactions. Under anoxic conditions, the predominant double-base lesion is a species in which C8 of guanine is linked to the 5-methyl group of an adjacent 3'-thymine (G[8,5- Me]T). Most of these oxygen-derived species are produced at a low level by normal aerobic metabolism. Normal cellular defense mechanisms destroy most of these. Likewise, any damage to cells is constantly repaired. However, under the severe levels of oxidative stress that cause necrosis, the damage causes ATP depletion, preventing controlled apoptotic death and causing the cell to simply fall apart.

Polyunsaturated fatty acids, particularly arachidonic acid and linoleic acid, are primary targets for free radical and singlet oxygen oxidations. For example, in tissues and cells, the free radical oxidation of linoleic acid produces racemic mixtures of 13-hydroxy-9Z, 11E-octadecadienoic acid, 13-hydroxy-9E,11E-octadecadienoic acid, 9-hydroxy-10E,12-

E-octadecadienoic acid, and 11-hydroxy-9Z,12-Z-octadecadienoic acid as well as 4-Hydroxynonenal while singlet oxygen attacks linoleic acid to produce (presumed but not yet proven to be racemic mixtures of) 13-hydroxy-9Z,11E-octadecadienoic acid, 9-hydroxy-10E,12-Z-octadecadienoic acid, 10-hydroxy-8E,12Z-octadecadienoic acid, and 12-hydroxy-9Z-13-E-octadecadienoic (see 13-Hydroxyoctadecadienoic acid and 9-Hydroxyoctadecadienoic acid). Similar attacks on arachidonic acid produce a far larger set of products including various isoprostanes, hydroperoxy- and hydroxy-eicosatetraenoates, and 4-hydroxyalkenals. Many of these products are markers of oxidative stress, contribute to tissue and/or DNA damage, and/or serve as signals to activate pathways that combat oxidative stress.

Production and consumption of oxidants

One source of reactive oxygen under normal conditions in humans is the leakage of activated oxygen from mitochondria during oxidative phosphorylation. However, E. coli mutants that lack an active electron transport chain produced as much hydrogen peroxide as wild-type cells, indicating that other enzymes contribute the bulk of oxidants in these organisms.[40] One possibility is that multiple redox-active flavoproteins all contribute a small portion to the overall production of oxidants under normal conditions. Other enzymes capable of producing superoxide are xanthine oxidase, NADPH oxidases and cytochromes P450. Hydrogen peroxide is produced by a wide variety of enzymes including several oxidases. Reactive oxygen species play important roles in cell signaling, a process termed redox signaling. Thus, to maintain proper cellular homeostasis, a balance must be struck between reactive oxygen production and consumption.

The best studied cellular antioxidants are the enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase. Less well studied (but probably just as important) enzymatic antioxidants are the peroxiredoxins and the recently discovered sulfiredoxin. Other enzymes that have antioxidant properties (though this is not their primary role) include paraoxonase, glutathione-S transferases, and aldehyde dehydrogenases. The amino acid methionine is prone to oxidation, but oxidized methionine can be reversible. Oxidation of methionine is shown to inhibit the phosphorylation of adjacent Ser/Thr/Tyr sites in proteins. This gives a plausible mechanism for cells to couple oxidative stress signals with cellular mainstream signaling such as phosphorylation.

Oxidative stress and diseases

Oxidative stress is suspected to be important in neurodegenerative diseases including Lou Gehrig's disease (aka MND or ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, and Multiple sclerosis. Indirect evidence via monitoring biomarkers such as reactive oxygen species, and reactive nitrogen species production, antioxidant defense indicates oxidative damage may be involved in the pathogenesis of these diseases, while cumulative oxidative stress with disrupted mitochondrial respiration and mitochondrial damage are related with Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases.

Oxidative stress is thought to be linked to certain cardiovascular disease, since oxidation of LDL in the vascular endothelium is a precursor to plaque formation. Oxidative stress also plays a role in the ischemic cascade due to oxygen reperfusion injury following hypoxia. This cascade includes both strokes and heart attacks. Oxidative stress has also been implicated in chronic fatigue syndrome. Oxidative stress also contributes to tissue injury following irradiation and hyperoxia, as well as in diabetes.

Oxidative stress is likely to be involved in age-related development of cancer. The reactive species produced in oxidative stress can cause direct damage to the DNA and are therefore mutagenic, and it may also suppress apoptosis and promote proliferation, invasiveness and metastasis. Infection by Helicobacter pylori which increases the production of reactive oxygen and nitrogen species in human stomach is also thought to be important in the development of gastric cancer.

Antioxidants as supplements

The use of antioxidants to prevent some diseases is controversial. In a high-risk group like smokers, high doses of synthetic beta carotene increased the rate of lung cancer. In less high-risk groups, the use of vitamin E appears to reduce the risk of heart disease, although more recent evidence may in fact suggest the opposite. In other diseases, such as Alzheimer's, the evidence on vitamin E supplementation is mixed. Since dietary sources contain a wider range of carotenoids and vitamin E tocopherols and tocotrienols from whole foods, ex post facto epidemiological studies can have differing conclusions than artificial experiments using isolated compounds. However, AstraZeneca's radical scavenging nitrone drug NXY-059 shows some efficacy in the treatment of stroke.

Oxidative stress (as formulated in Harman's free radical theory of aging) is also thought to contribute to the aging process. While there is good evidence to support this idea in model organisms such as Drosophila melanogaster and Caenorhabditis elegans, recent evidence from Michael Ristow's laboratory suggests that oxidative stress may also promote life expectancy of Caenorhabditis elegans by inducing a secondary response to initially increased levels of reactive oxygen species. This process was previously named mitohormesis or mitochondrial hormesis on a purely hypothetical basis. The situation in mammals is even less clear. Recent epidemiological findings support the process of mitohormesis, with a 2007 meta-analysis indicating studies with a low risk of bias (randomization, blinding, follow-up) find that some popular antioxidant supplements (Vitamin A, Beta Carotene, and Vitamin E) may increase mortality risk (although studies more prone to bias reported the reverse).

Metal catalysts

Metals such as iron, copper, chromium, vanadium, and cobalt are capable of redox cycling in which a single electron may be accepted or donated by the metal. This action catalyzes production of reactive radicals and reactive oxygen species.[65] The presence of such metals in biological systems in an uncomplexed form (not in a protein or other protective metal complex) can significantly increase the level of oxidative stress. These

metals are thought to induce Fenton reactions and the Haber-Weiss reaction, in which hydroxyl radical is generated from hydrogen peroxide. The hydroxyl radical then can modify amino acids. For example meta-tyrosine and ortho-tyrosine form by hydroxylation of phenylalanine. Other reactions include lipid peroxidation and oxidation of nucleobases. Metal catalyzed oxidations also lead to irreversible modification of R (Arg), K (Lys), P (Pro) and T (Thr) Excessive oxidative-damage leads to protein degradation or aggregation.

The reaction of transition metals with proteins oxidated by Reactive Oxygen Species or Reactive Nitrogen Species can yield reactive products that accumulate and contribute to aging and disease. For example, in Alzheimer's patients, peroxidized lipids and proteins accumulate in lysosomes of the brain cells.

Non-metal redox catalysts
Certain organic compounds in addition to metal redox catalyst can also produce reactive oxygen species. One of the most important classes of these are the quinones. Quinones can redox cycle with their conjugate semiquinones and hydroquinones, in some cases catalyzing the production of superoxide from dioxygen or hydrogen peroxide from superoxide.

Immune defense
The immune system uses the lethal effects of oxidants by making production of oxidizing species a central part of its mechanism of killing pathogens; with activated phagocytes producing both ROS and reactive nitrogen species. These include superoxide ($\bullet O_2$), nitric oxide ($\bullet NO$) and their particularly reactive product, peroxynitrite (ONOO-). Although the use of these highly reactive compounds in the cytotoxic response of phagocytes causes damage to host tissues, the non-specificity of these oxidants is an advantage since they will damage almost every part of their target cell. This prevents a pathogen from escaping this part of immune response by mutation of a single molecular target.

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Medical Treatment Built on a Different Philosophy

Why A Gastroenterologist?

What distinguishes the immune therapy employed by Infeperium is that it relies first on the gastroenterologist. Gastroenterology is the branch of medicine that is focused on the entire digestive system and its disorders. In the United States, it focuses on the diseases of the gastrointestinal tract. With the recent explosion of data in interest in the study and practice of immunology, it is important to understand that 70% of the immune system is based in the gut and 60% of all immune cells are housed in the tissue in the gut.

These amazing statistics help us understand how important diet, nutrition, and the diseases and pathogens that are daily being identified, sorted and attacked by our own immune system are in our digestive tract. There are only three ways for a pathogen to attack the human body. Either through the skin, which is the largest barrier of all, through a cut or bruise, through our airways and lungs, or through our stomach. It's interesting to note that the surface area of the average human lung is 75 m². Where the average surface area of the gut in humans is 520 m/sq (or 2 tennis courts), almost 8 times the volume of area is involved in the gut as in the lung.

Since the majority of pathogens get into our body through the digestive track it is here that the toll like receptors (TLR's) do their wonderful work. These toll like receptors or TLR's communicate through dendritic cells and they are constantly in surveillance of the lumen, or all the things that we eat and digest and their responsibility is to to determine what we referred to in the medical community as self versus non self.

These cellular surveillance mechanisms determine what is good for us and what is bad for us through the process of elimination through the liver, through the kidneys, through urine, and through the colon, rid the body as quickly as possible. When a pathogen is discovered it provokes an immune response T cells and B cells macrophages and all the other tools that are part of the immune system quickly going to action to eradicate and destroy any bacteria or any virus, any fungus, or any parasite as quickly as possible. The innate immune system reacts immediately and the holds those pathogens at bay until the adaptive immune response can engage a more selective and a more perfected mechanism to eradicate and destroy the attacker.

Toll Like Receptors are single membrane spanning non-catalytic receptors usually expressed in sentinel cells(cell that are in surveillance) in the cell lining of the digestive system, such as macrophages and dendritic cells, they recognize structurally conserve molecules derived from microbes or bacteria. Once these microbes have breached the physical barriers such as the skin or the intestinal tract, there recognized by the TLR's which then activates the immune cell responses. TLR's are a type of pattern recognition

receptors or (PRR) and recognize molecules that are broadly shared by pathogens(non-self) but distinguishable from host(self) molecules collectively referred to as pathogen associated molecular patterns or camps PAMPS. TLR's together with interleukin one receptors form a receptor superfamily that continues to daily ,at every moment, help distinguish between self which helps and absorbs nutrients, and non self which they try to destroy.

Cell Like Receptors are now counted among the very keen and powerful molecules that alert the immune system to the presence of microbial infections, bacteria's, fungus, viruses, mutations(cancer), or parasites .When a parasite or a pathogen alerts the TLR's, they and the cells of the immune system provoke an innate a immune response this is good. This is what the body is meant to do. However, the same responses can be detrimental if they are excessively prolonged or intense.

When the innate immune system is activated because the toll like receptors have found the presence of pathogens, these toll like receptors begin a signaling cascade to other cells, they begin to engage signaling factors called Cytokines, which trigger inflammation at the site of the bacterial, viral, mutation, or fungus area. Once the pathogens are digested and its' Antigens presented to CD4 and T cells, the infected cells shut off their protein synthesis and undergo program cell death known as apoptosis.

When this process is finished, that immune response subsides, and those cells die. This is where degenerative disease has its foothold, for reasons we don't yet know, inflammation continues and those cells continue to signal, and chronic inflammation begins. Since chronic inflammation is the source of all disease, the gastroenterologist will find out what your baseline is so the therapies that are employed bring immediately relief, can be then assisted by nutritional and supplemental therapies that will begin to bring the body to homeostasis and the immune cells and immune system to its original set-point, thus finding out what the original cause of your debilitating condition was.

Our's proprietary and novel BRM (Biological Response Modifiers) therapeutics will put out the flame of chronic inflammation, but proper nutrition and supplements, as well as nutrient rich anti-inflammatory green drinks need to address the original state of dysbiosis, leaky gut syndrome, and restoration of the immune surveillance mechanisms bringing the body back to homeostasis. Correctly identifying "Self "which are good cells, from "Non-Self" which are bad cells.

The vast majority of peer-reviewed, confirmed research, as to the origins of disease, and their prevention being observed in the mechanism of intestinal immune cells and GUT homeostasis and immune surveillance are from 2012 to the present time. This is "Cutting Edge" science! These combined therapies of BRM's, customized nutrition rich and anti-inflammatory diets and juices, and organic targeted supplements,is rapidly changing the direction of medicine from being disease and symptom centered as to treatment,------ to origin, system, cause identification, and treatment centered, bringing the patient to homeostasis.

Chronic symptoms from an autoimmune reaction, explain why some symptoms persist even after the original cause from a pathogen was eliminated! Once the autoimmune trigger is pulled, the original cause is no longer essential! This is why many people with Lyme disease are NOT effectively treated, because the bacteria has provoked an autoimmune response. The antibiotics have killed the bacteria, but that therapy has no effect on the autoimmune response that continues. That, once again is the reason for a therapy that is based upon Biological Response Modifiers, with additional targeted nutritional and supplement protocols, to not only eliminate the cause, but to treat and modulate the ongoing effect! Overloads of Epstein Barr Virus have now been proven to be the genesis of many acute and chronic conditions from MS to Cancer. Again, once the autoimmune response is triggered, just lowering the Viral load won't usually be enough. Many a patient has been told by their Doctor, that their condition is "in their head" or something similar, because their bacteria or virus is now "undetectable"! That is the difference between traditional medicine and immunotherapy and functional medicine.

This is the holistic approach to Our's therapy and Functional Medicine! Immediate therapeutics that work as immunomodulators begin to immediately reverse your condition, and the nutritional and supplemental guidance and counseling in order to eradicate the original source of your problem, and bring your body to homeostasis so you can actually get on with your life. That is the philosophy of immunotherapy, Functional Medicine and Our's Breakthrough Therapies, where the whole person is treated, and not just the symptom and the disease.

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Additional reading resources:

Books:

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Contraindications

Infeperium **breakthrough therapies** work as a positive adjunct for antibiotic, antiviral, and chemotherapeutic therapies. **However, Corticosteroids and any other steroid therapy will immediately cause the biologic modification and immunomodulating effectiveness to cease.** Therefore, all steroid therapies must cease 30 days prior to the start of any Infeperium immunomodulators and biological response modifiers protocol. There are no other known pharmaceutical contradictions experienced in over 10 years.

Safety Study for Infeperium breakthrough therapies:

Brief description
Infeperium immunomodulators and biological response modifiers are presently made according to the most rigid standards of Current Good Manufacturing Practices (cGMP). The active ingredient in Infeperium breakthrough therapies has already met the rigorous standards for Veterinary use and it is approved for animal prescription under the USDA!

We believe Infeperium breakthrough therapies to be a new category of drug that may be characterized as a Biological Response Modifier and an "Immunomodulator." We believe that many disease pathologies that affect individuals are the result of an over-active immune system. Specifically, when a viral agent begins to adversely affect an individual's cells, the immune system frequently becomes overactive, which destroys the viral agent but also injures surrounding healthy cell structures. We believe other disease pathologies suppress an individual's immune system, which allows other diseases and agents to kill healthy cells. Although research is always ongoing, the product in its present form is complete. Research has concluded that Infeperium breakthrough therapies regulate the bodies immune system to prevent it from both over-reacting and under-reacting to a viral invasion of an individual's body systems. We believe that Infeperium breakthrough therapies contains a number of unique peptide or lipopeptide molecules which may neutralize viral pathogens and their inhibitory properties by activation of a cytokine system. This, in turn, will enhance an individual's cell mediated immunity and augment the individual's humoral immune system possibly by eliminating negative inhibitory cytokine factors and pathogenic free-floating organisms, while simultaneously sparing normal and healthy cells.

Our objective is the continued development of Infeperium breakthrough therapies and there cognates and variants for treatment of multiple medical conditions.

Safety and Toxicity
Infeperium immunomodulators and biological response modifiers were not pyrogenic (endotoxin < 0.08 EU/mg).

They (≤ 1mg/mL) did not affect cell viability or inhibit protein translation as assessed in human diploid fibroblasts,

They (≤ 1mg/mL) did not induce the hemolysis of red blood cells, and

They did not promote a "Delayed Type Hypersensitivity Reaction": wheals did not form when 0.1 mL they (20mg/mL) was introduced by intradermal injection into New Zealand White rabbits previously exposed to Infeperium breakthrough therapies at a dose ten times a therapeutic amount.

Safety Studies with the Active Ingredient Infeperium immunomodulators and biological response modifiers
Pyrogenicity of Infeperium breakthrough therapies. *Pyrogenicity*. The standardized endotoxic activity for two independent preparations of Infeperium breakthrough

therapies was determined by an independent lab using an LAL gel clot assay (Test Date 12/6/2000 - see Unit 2B). The threshold sensitivity of the reaction was 0.03 endotoxic unit (EU) per ml. Two separate preparations of Infeperium breakthrough therapies were analyzed for endotoxic activity. Each preparation had equivalent endotoxin levels of 0.08 EU/mg. Therefore Infeperium breakthrough therapies does not contain a level of endotoxin sufficient to promote a pyrogenic response.

Hemolysis of Red Blood Cells was not Induced by Infeperium breakthrough therapies

The BRM-induced hemolytic activity in a 5% suspension of human red blood cells was measured by reading the absorbance of the hemolysate at 415 nm as described by Yoshida *et al*. (1994).

Study performed: The toxicity of Infeperium breakthrough therapies was tested by determining its ability to lyse human erythrocytes. Freshly collected blood (~4ml) was placed in a 15ml centrifuge tube and PBS added to bring the volume to 10ml. After centrifuging for 2-3 minutes at 2000g, the sample contained three layers: bottom layer of RBC, middle interphase of WBC, and the top supernatant layer. The supernatant and interphase layers were removed and the volume brought to 10mls and centrifuged and washed as above four more times. PBS was then added to the RBC's to make approximately a 10% (v/v) suspension. Infeperium breakthrough therapies concentrates ranging from 1ug/ml to 1mg/ml were incubated with a 5% suspension of red blood cells and incubated for 30 minutes. Absorbance was monitored at 400 nm and hemolysis determined by comparison to control the wells that had undergone complete hemolysis by the addition of 0.2% Triton X-100 as a positive control.

The values obtained from the hemolysis assay are presented in Table 1.

Sample	1	2	3	Avg	Hemolysis
Positive Control	0.135	0.131	0.134	0.133	100
Negative Control	0.002	0.003	0.002	0.002	0
1 ug/ml BRM	-0.001	-0.001	-0.002	-0.001	0
10 ug/ml BRM	-0.001	-0.002	-0.002	-0.002	0
100 ug/ml BRM	-0.003	-0.002	-0.002	-0.003	0
1 mg/ml BRM	-0.002	-0.002	-0.003	-0.002	0

Table 1. Percent hemolysis was calculated using the equation:
(Sample — Neg. Control)(Pos. Control — Neg. Control)*100%

None of the concentrates of Infeperium breakthrough therapies exhibited any degree of red blood cell hemolysis

Assessment of Cell Viability and Inhibition of Protein Translation in the Presence of Infeperium breakthrough therapies

Cell Viability/Fibroblast Toxicity. Infeperium breakthrough therapies weres used as the test article. The test article was prepared as a 1 mg/ml stock solution in media and was serially diluted in a decade series to give 1, 10, 100, and 1000 ug/ml test solutions. Test solutions thus prepared were used within one hour.

- Infeperium breakthrough therapies-induced damage and inhibition of cellular replication in normal fibroblast and epithelial cell lines was monitored and found negative.

- *Cell Viability Assay*: Human diploid fibroblasts cultures were established from skin tissue obtained from O'Bleness Medical Center, Athens, OH. Cells were maintained in Dulbecco's modified Eagle's media (DMEM). DMEM was prepared with L-glutamine, pyridoxine hydrochloride and without sodium pyruvate and sodium bicarbonate (Gibco^{R}, Invitrogen, Carlsbad, CA) supplemented to a final concentration of 100 units/ml of penicillin and 100 micrograms/ml of streptomycin (penicillin-streptomycin, Gibco^{R}, Invitrogen, Carlsbad, CA), and adjusted to contain 10% NuSerum I (Collaborative Research Products, Bedford, MA).

- The cells were transferred into 12-well culture plates at a concentration of $5X10^{4}$ cells/cm^{2} (in 2 ml media) and incubated for 24 hours at 37 degrees C with 5% CO_{2}. After the cells were incubated for 36 hours, the media was removed and replaced with 2ml of the test article Infeperium breakthrough therapies at concentrations from 1ug/ml to 1mg/ml dissolved in DMEM media. Three wells at each concentration of test article were prepared on two separate plates to provide triplicate measurements at 24 hours. A control plate was established with three wells of cells to which DMEM media (2ml) only was added in place of the test article. The control plate was incubated as described above. Three control wells were read at 24 hours.

- When the test or control plate was removed from the incubator (24 hours), the supernatant was aspirated with 50ul of 0.05% trypsin/EDTA (Invitrogen) added to each well. The plate was incubated at 37 C for two hours. Then, 950ul fresh DMEM was added to each well and cells responded. After mixing to ensure homogeneity, the cells were counted by the trypan blue dye exclusion method: to each 100ul of cell volume, 100ul of 0.4% trypan blue is added. After mixing, the hemocytometer was loaded and the number of live cells (those that had excluded trypan blue) counted in the four counting fields. The number of cell/ml was calculated by the following formula: Cells/ml=average of total cells counted *dilution factor* volume hemocytometer.

- Results: Incubation of cells with concentrates of Infeperium's breakthrough therapies up to 1 mg/ml did not decrease cell viability.

A similar test was performed by **Viromed**, as part of the Infeperium's breakthrough therapies assessment study for which they were contracted. Using the A-72 canine fibroblast cell line they determined that Infeperium breakthrough therapies was not cytotoxic (cellular proliferation was not impaired). These results can be found in the

Viromed documentation provided (project numbers: 10295 and 10296, following the assigned protocol numbers: MS121200-AV and MS121200-V).

- *Translation Inhibition Assay*: After fibroblast cells were incubated for 24 hours as described above, the media was aspirated and the cells washed twice with fresh met-cya-media. The test article at concentrations of 0.001, 0.01, 0.1, and 1 mg/ml in [^{35}S]met-cys-media (Gibco^{R}, Invitrogen, Carlsbad, CA) to give a final specific activity of 20uCi/ml were prepared. Each test article concentration (0.5ml for 1 hr, 1.0ml for 24 hr) was added to each of three wells (n=3) on each of two culture plates as described above. The plates were incubated for either 1 hour or 24 hours. After incubation, the media from each of the wells was discarded and the wells washed twice with PBS. Trichloroacetic acid (0.5ml) was added to each well and the cells removed with a rubber policeman, transferred to microcentrifuge tubes, and incubated for 30 minutes on ice. The incorporation of [^{35}S]methionine was measured by liquid scintillation counting.

- **Results**: At 1 hour after addition of Infeperium's breakthrough therapies, significant translation inhibition was only noted at a test concentration of 1mg/ml. However 24 hours after addition of Infeperium's breakthrough therapies, translation inhibition was not noted at any of the test concentrations of Infeperium immunomodulators and biological response modifiers. At 1 hour after addition of test sample, the high concentration of Infeperium's breakthrough therapies may have swamped the ability of the cell to incorporate radiolabel. However, as noted at 24 hours, equilibrium was established over time, thus demonstrating that Infeperium's breakthrough therapies has no effect on protein translation over time.

- **Discussion**: Cell viability was chosen as a study parameter as it provides an easily visualized and understood answer for a drug's toxicity to a cell line. Since cell viability can show a degree of variance, an additional parameter was chosen to be assessed —inhibition of protein translation. Using this method we would be able to detect subtle, sub-lethal changes in cell viability. By performing both of these studies, we were able to demonstrate that Infeperium's breakthrough therapies has no effect on cell viability or on translation of human fibroblast cells.

Delayed Type Hypersensitivity

Delayed Type Hypersensitivity. Six New Zealand White rabbits (3 animals per group) received either 5mg of Infeperium's breakthrough therapies in 0.25ml Freund's Complete Adjuvant (FCA) or 0.25ml FCA by subcutaneous injection. On days 4, 11, and 21 one rabbit from each group was selected to receive an intradermal injection of 0.1ml (200ug) of Infeperium breakthrough therapies and sterile water (negative control) on the exposed lateral thorax. After 15-30 minutes the injections sites were observed for raised erythematous lesions (wheals) at the injection site. No wheal development was observed indicating the absence of a delayed type hypersensitivity reaction to Infeperium's breakthrough therapies.

Safety Testing of USDA approved product which contains the same active ingredient of Infeperium's breakthrough therapies.
Over 100,000 animals were tested, species ranging from horses, pigs, sheep and cows, without any negative events recorded including no systemic anaphylactic reactions.

A range finding safety study in rats and guinea pigs was performed lasting two weeks after dosage, the following tissues were examined and submitted for histopathologic examinations.

The following tissues were taken at necropsy:

Brain	Eye	Trachea	Esphagus
Thymus	Lung	Heart	Diaphragm
Liver	Kidney	Spleen	Adrenal
Urinary Bladder	Ovaries and Uterus	Testes	Stomach
Duodenum	Jejunum	Colon	Pancreas
Biceps Muscle	Skin and SubQ tissue at injection site	Ischiatic nerve	Femur with bone marrow

Gross Pathology Results
No gross lesions were seen.

Histopathology Results
No lesions considered to be treatment related were seen.

Discussion and Conclusions
Three doses were chosen for this study—half (0.75ml), double (3.0ml), and the standard human clinical dose (1.5ml) into rats and guinea pigs.

By contrast, a 60kg human receiving a standard clinical dose of Infeperium breakthrough therapies (1.5ml) would be receiving a dose of 0.025ml Infeperium breakthrough therapies/kg, a dose 700 times lower than the top dose used in rats and guinea pigs in this study. This indicates a potentially very favorable safety profile for this agent.

Clinical Assessment of Safety

Clinical Assessment of Our's immunomodulator safety and efficacy involved the treatment of patients on an informed consent basis.

The assessment included treatment and clinical management of approximately 200 patients over a 30 month period. The greater majority of whom, received the 'Product' for the entire duration of that time period.

During that time clinical data was collated as well as from patients' diaries which were self-recorded on a daily basis.

Treatment Regimen

The 'Product' was administered by sub-cutaneous injection in variable dosages, according to response.

Initially a test dose of 0.1mls was administered. The reason for the test dose was to ascertain that there was no allergic response or in its severest form, anaphylactic shock.

Thirty minutes after administration of the test dose a further 0.9ml was given again by sub-cutaneous injection. Patients remained in the waiting area for an additional 30 minutes, in order to ascertain that there were no adverse side-effects which required recording and/or addressing.

Subsequently all patients attended weekly or bi-weekly for treatment. The dose given varied from 1ml to 4mls - according to the clinical response of the patient.

All patients were instructed to keep a daily diary of their condition, either written or taped.

Clinician's Summary

Firstly, the product itself is extremely well tolerated, except for a reasonable proportion of patients who have a mild localized reaction at the site of injection, this reaction is akin to an "insect bite", and attenuated by the use of antihistamines.

Secondly, in two and a half years, no patient has exhibited any adverse reactions of note. The apparent lack of side effects is quite amazing and totally unexpected. This is supported by the observations of the two clinical trials that were undertaken in the UK.

In a number of patient's blood samples were taken for routine testing, and in all cases the parameters were entirely normal (Renal Function, Liver Function, Full blood Count, etc.).

It must be noted that all the above held true across the dosage range of 1ml to 8ml per week.

Conclusion

This novel biological product appears to be a safe and effective, beneficial treatment and free from major side effects. To date no individual has reported any side effect of note.

