School of Medicine
& Health Sciences

THE GEORGE WASHINGTON UNIVERSITY

Chronic Inflammatory Response Syndrome

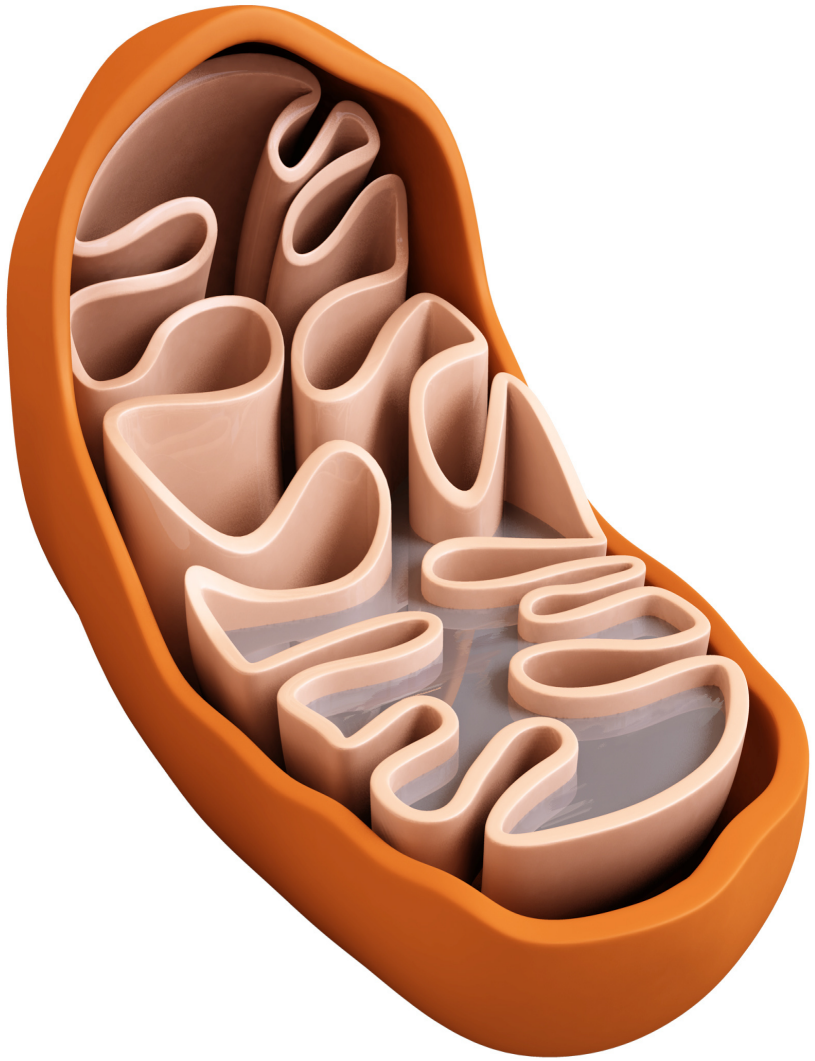
Andrew Heyman, MD MHSA
Medical Director of Integrative Medicine
Dept of Clinical Research and Leadership
George Washington University
Director of Academic Affairs
MMI and A4M
Ritchie Shoemaker, MD

Objectives

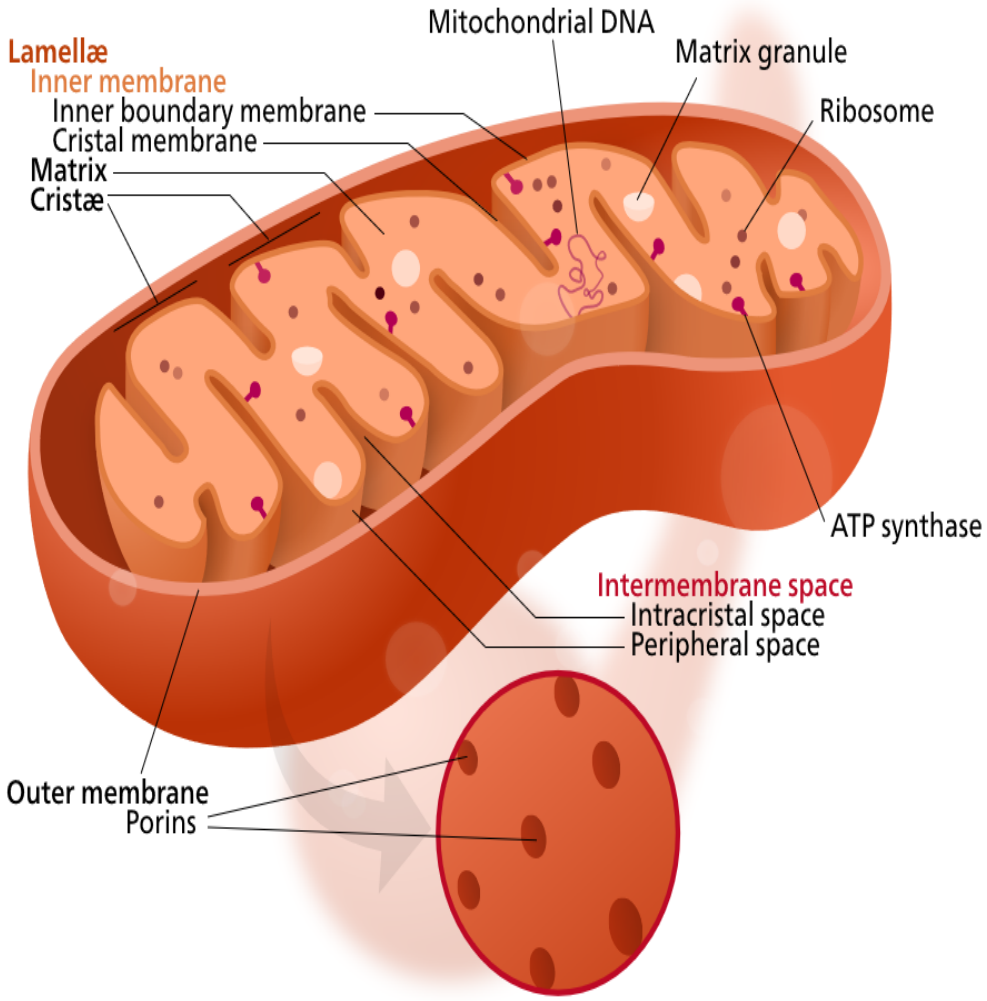
- Brief review of mitochondrial anatomy
- Discuss emerging model of mitochondrial metabolism
- Review transcriptomics of mtDNA in chronic inflammatory response

Energy Metabolism

- Mitochondria are about 0.5–1 mm in diameter and up to 7 mm long.
- Mitochondria is located in all cells but skeletal muscle, brain and kidney will have a larger number of mitochondria.
- Mitochondria has it own Genome and DNA
- Capable of self dividing when needed
- Responsible for making ATP to fuel cells, organs, muscles, and brain.



Mitochondria Structure



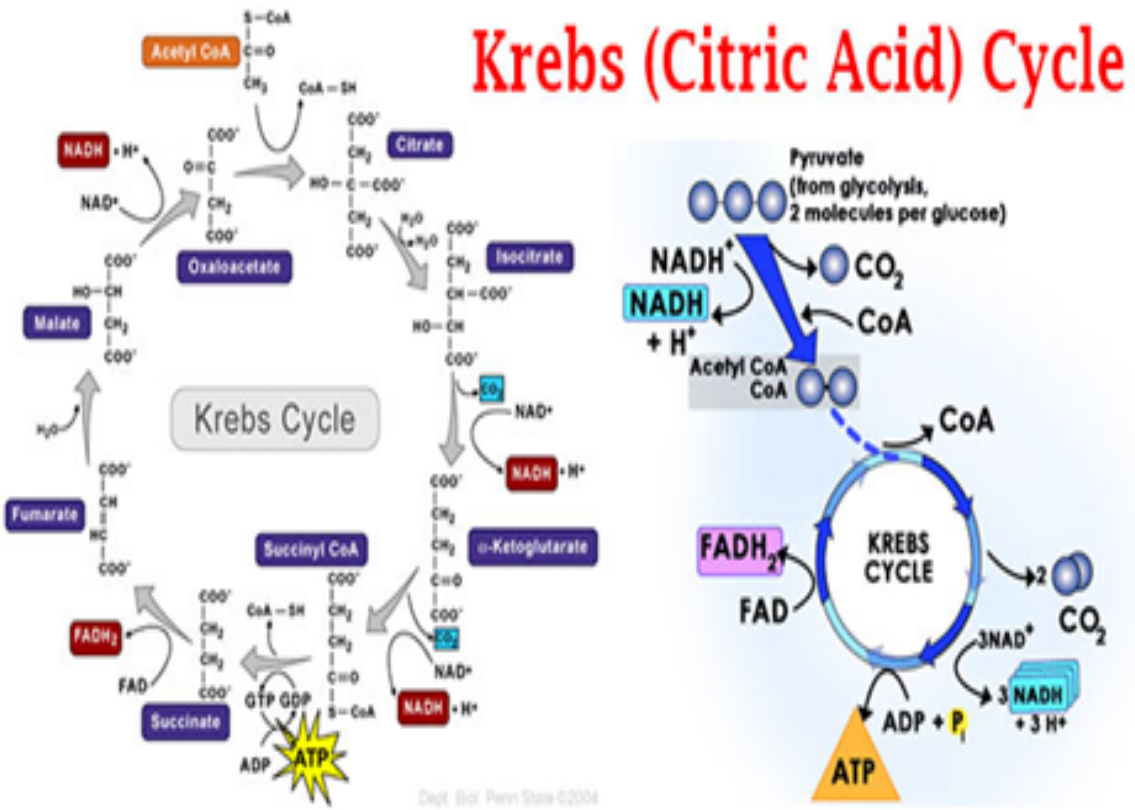
Mitochondria have two membranes, each composed of a phospholipid bilayer. The two membranes are quite distinct in appearance and in physio-chemical properties, thus determining the biochemical function of each membrane.

- **Outer membrane**
- **Intermembrane space**
- **Inner membrane**
- **Matrix**

Mitochondria Functions

- Synthesize ATP in a process called oxidative phosphorylation.
- Involved in calcium homeostasis in the cell
- Promote cell growth and also signal transmission
- Responsible for cell death in case of trauma
- Generate oxidative radicals during energy formation
- Support nerve conduction by helping neurotransmitter release

Mitochondria TCA Function



- Mitochondria synthesize adenine triphosphate or ATP from adenosine diphosphate ADP and inorganic phosphate in a process called oxidative phosphorylation.
- The citric acid cycle or krebs cycle breaks down pyruvate from glucose and the beta oxidation spiral breaks down fatty acids from fats.

Lehninger Principles of Biochemistry. 5th Edition. Chapter 15 : The Citric Acid Cycle

Additional Mitochondria Functions

- Signaling through mitochondrial reactive oxygen species
- Cellular Apoptosis-programmed cell death
- Calcium signaling (including calcium-evoked apoptosis)
- Certain heme synthesis reactions
- Steroid synthesis
- Hormonal signaling

Mitochondrial Imbalances

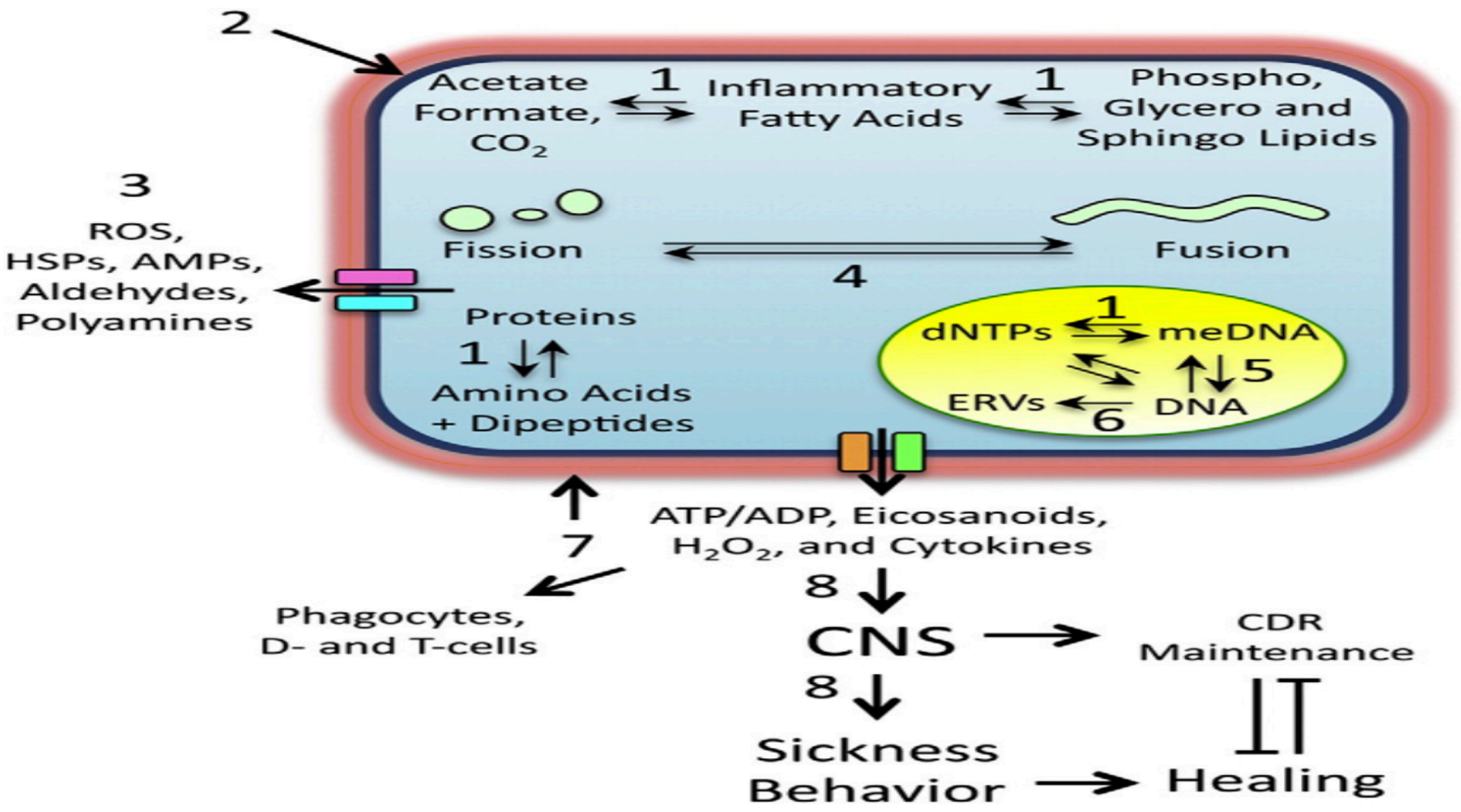
"Whether they appreciate mitochondrial disorders or not, practicing clinicians see patients with mitochondrial impairment virtually every day in their clinical practices."

As noted in the popular article by Pieczenik and Neustadt. Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007;83(1):84-92

"Clinical disorders associated with mitochondrial dysfunction include **schizophrenia, bipolar disease, dementia, Alzheimer's disease, epilepsy, migraine headaches, stroke, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, hypertension, diabetes mellitus, hepatitis C, and primary biliary cirrhosis.**"

Kozlov AV, Bahrami S, Calzia E, et al. Mitochondrial dysfunction and biogenesis: Do ICU patients die from mitochondrial failure? Ann Intensive Care. 2011;1(1):41.

More than Energy Production?



R.K. Naviaux / Mitochondrion 16 (2014) 7–17

CIRS in context of CDR

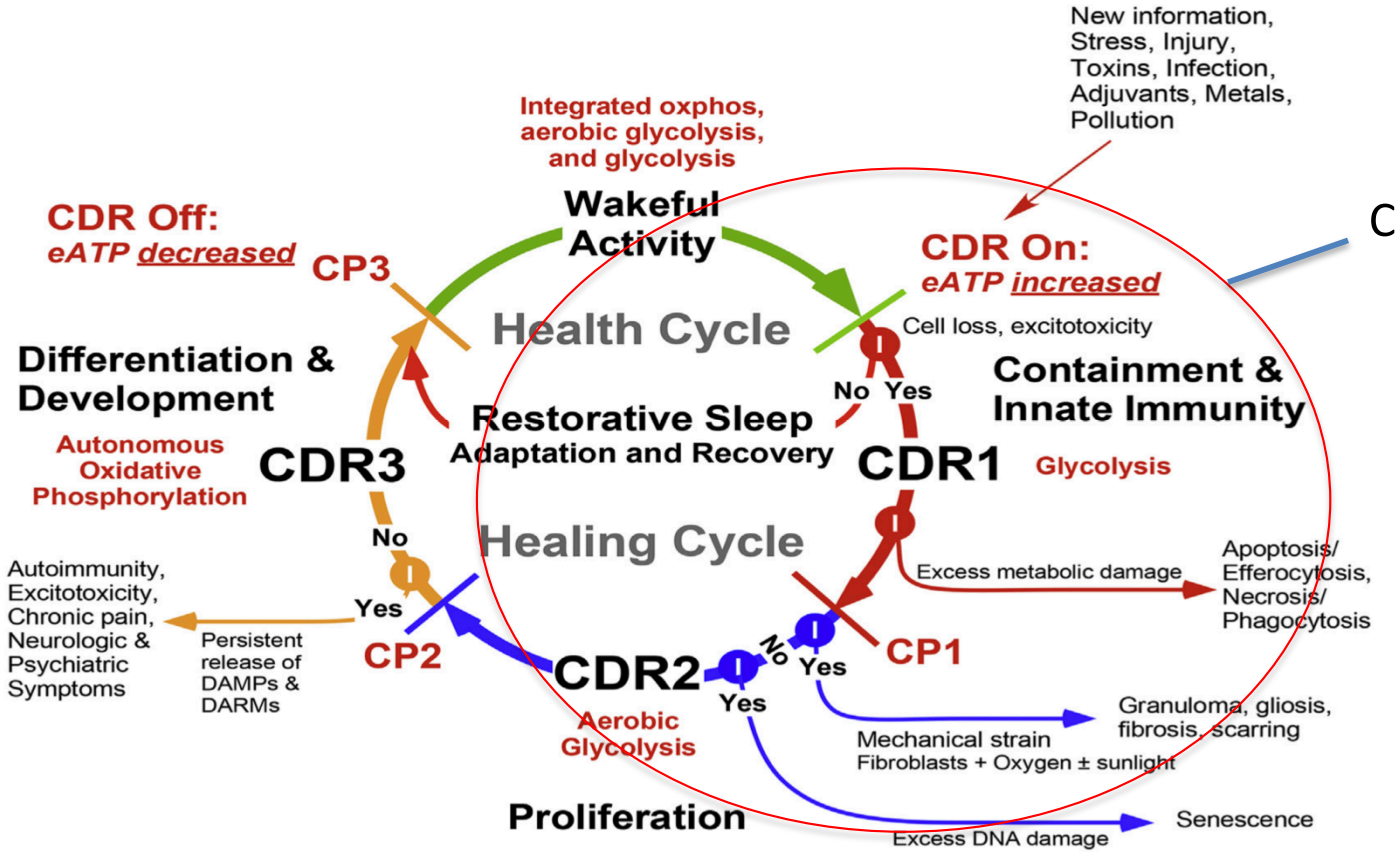
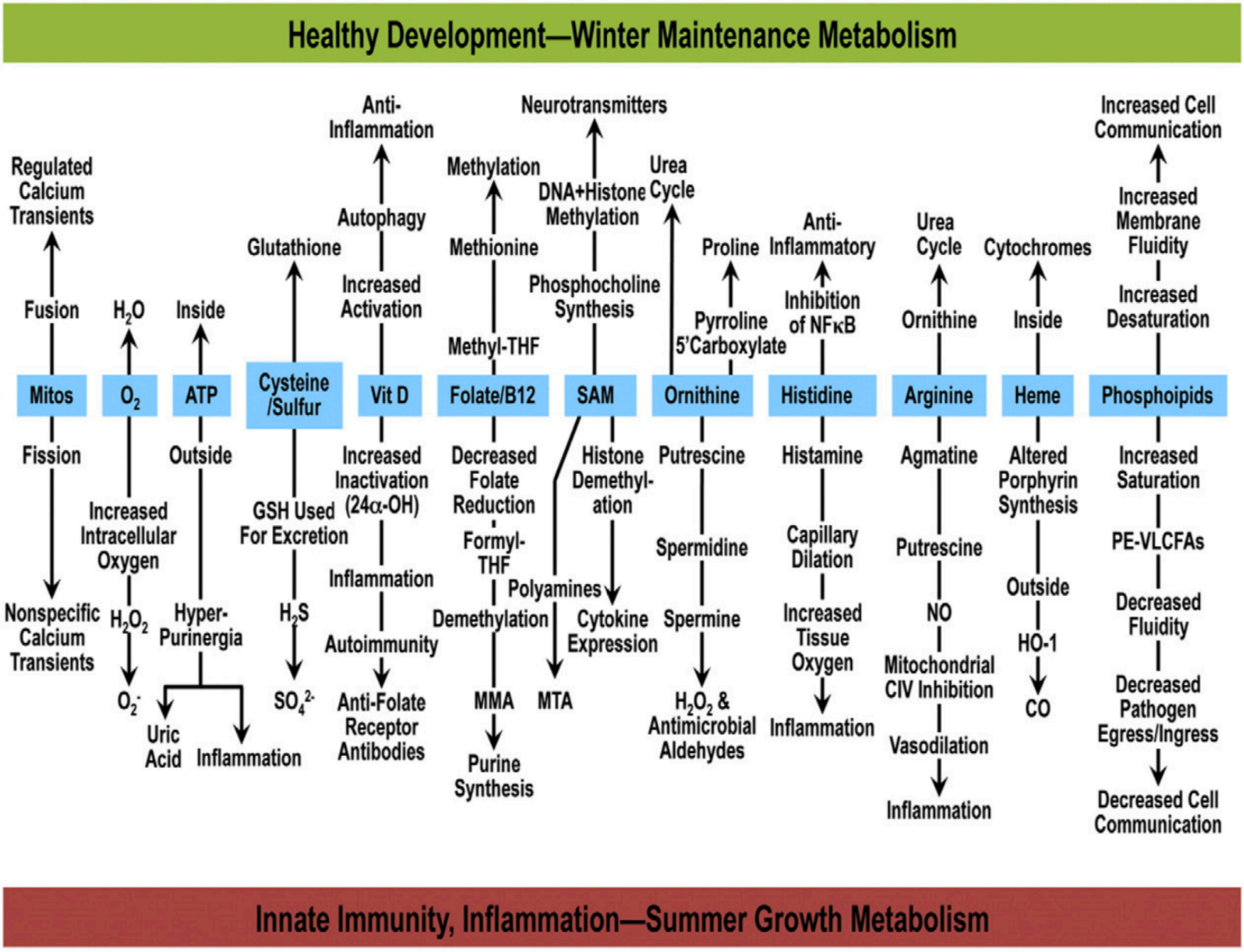


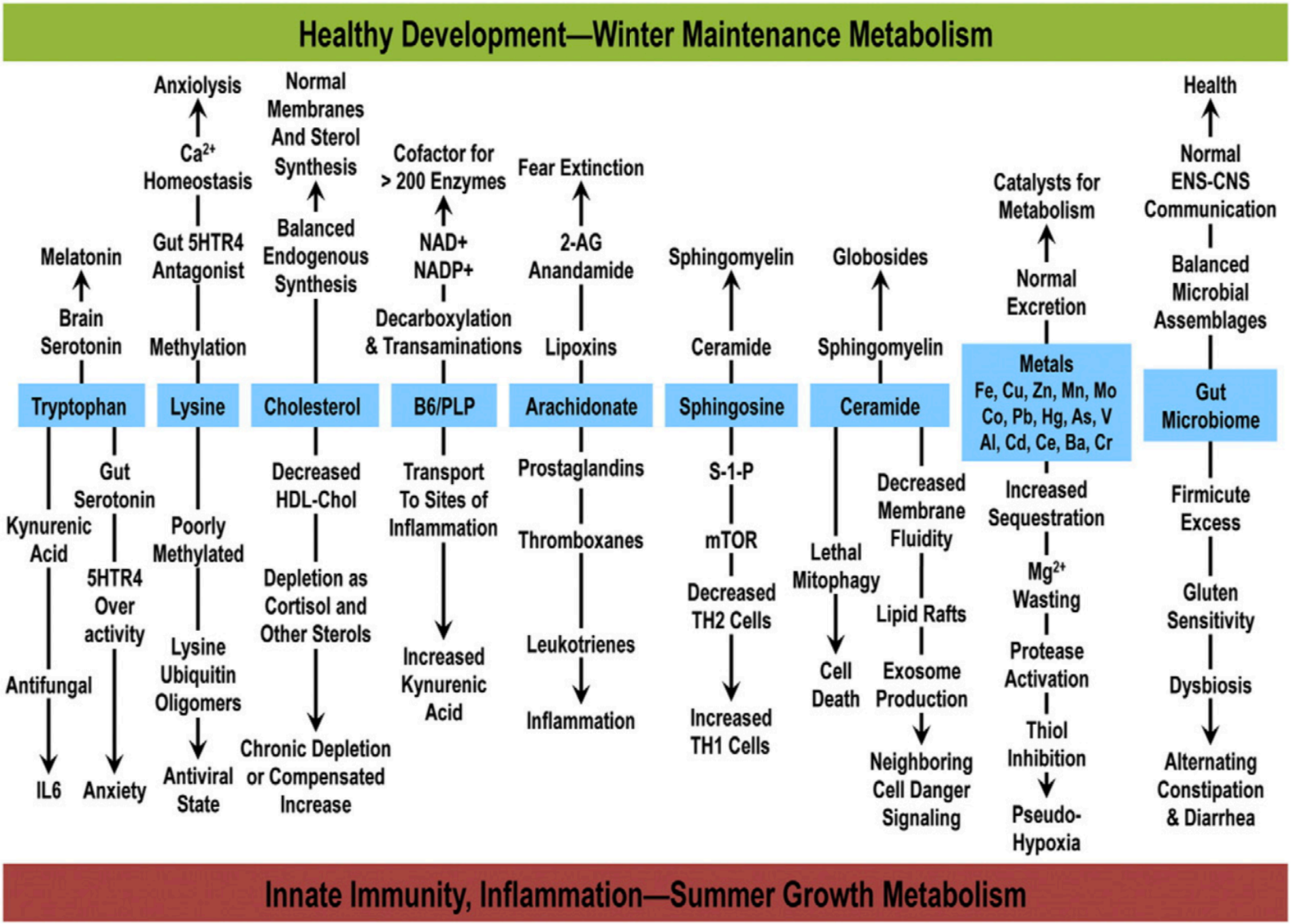
Fig. 1. A metabolic model of the health and healing cycles. Health is a dynamic process that requires regular cycling of wakeful activity and restorative sleep. The healing or damage cycle is activated when the cellular stress exceeds the capacity of restorative sleep to repair damage and restore normal cell-cell communication. CDR1 is devoted to damage control, innate immunity, inflammation, and clean up. CDR2 supports cell proliferation for biomass replacement, and blastema formation in tissues with augmented regeneration capacity. CDR3 begins when cell proliferation and migration have stopped, and recently mitotic cells can begin to differentiate and take on organ-specific functions. **Abbreviations**: eATP; extracelllular ATP; CP1–3: checkpoints 1–3; DAMPs: damage-associated molecular patterns; DARMs: damage-associated reactive metabolites.

Please cite this article as: Naviaux, R.K., Mitochondrion, https://doi.org/10.1016/j.mito.2018.08.001

A


Healthy Development—Winter Maintenance Metabolism
Regulated Calcium Transients
Fusion
Mitos
Fission
Nonspecific Calcium Transients
H_2O
O_2
Increased Intracellular Oxygen
H_2O_2
O_2^-
Uric Acid
Inside
ATP
Outside
Hyper-Purinergia
Inflammation
Glutathione
Cysteine /Sulfur
GSH Used For Excretion
H_2S
SO_4^{2-}
Anti-Inflammation
Autophagy
Increased Activation
Vit D
Increased Inactivation (24α-OH)
Inflammation
Autoimmunity
Anti-Folate Receptor Antibodies
Methylation
Methionine
Methyl-THF
Folate/B12
Decreased Folate Reduction
Formyl-THF
Demethylation
MMA
Purine Synthesis
Neurotransmitters
DNA+Histone Methylation
Phosphocholine Synthesis
SAM
Histone Demethyl-ation
Polyamines
Cytokine Expression
MTA
Urea Cycle
Proline
Pyrroline 5'Carboxylate
Ornithine
Putrescine
Spermidine
Spermine
H_2O_2 & Antimicrobial Aldehydes
Anti-Inflammatory
Inhibition of NFκB
Histidine
Histamine
Capillary Dilation
Increased Tissue Oxygen
Inflammation
Urea Cycle
Ornithine
Arginine
Agmatine
Putrescine
NO
Mitochondrial CIV Inhibition
Vasodilation
Inflammation
Cytochromes
Inside
Heme
Altered Porphyrin Synthesis
Outside
HO-1
CO
Increased Cell Communication
Increased Membrane Fluidity
Increased Desaturation
Phosphoipids
Increased Saturation
PE-VLCFAs
Decreased Fluidity
Decreased Pathogen Egress/Ingress
Decreased Cell Communication
Innate Immunity, Inflammation—Summer Growth Metabolism

B


Healthy Development—Winter Maintenance Metabolism
Tryptophan
Melatonin
Brain Serotonin
Kynurenic Acid
Antifungal
IL6
Gut Serotonin
5HTR4 Over activity
Anxiety
Lysine
Anxiolysis
Ca2+ Homeostasis
Gut 5HTR4 Antagonist
Methylation
Poorly Methylated
Lysine Ubiquitin Oligomers
Antiviral State
Cholesterol
Normal Membranes And Sterol Synthesis
Balanced Endogenous Synthesis
Decreased HDL-Chol
Depletion as Cortisol and Other Sterols
Chronic Depletion or Compensated Increase
B6/PLP
Cofactor for > 200 Enzymes
NAD+ NADP+
Decarboxylation & Transaminations
Transport To Sites of Inflammation
Increased Kynurenic Acid
Arachidonate
Fear Extinction
2-AG Anandamide
Lipoxins
Prostaglandins
Thromboxanes
Leukotrienes
Inflammation
Sphingosine
Sphingomyelin
Ceramide
S-1-P
mTOR
Decreased TH2 Cells
Increased TH1 Cells
Ceramide
Globosides
Sphingomyelin
Lethal Mitophagy
Cell Death
Decreased Membrane Fluidity
Lipid Rafts
Exosome Production
Neighboring Cell Danger Signaling
Metals
Fe, Cu, Zn, Mn, Mo
Co, Pb, Hg, As, V
Al, Cd, Ce, Ba, Cr
Catalysts for Metabolism
Normal Excretion
Increased Sequestration
Mg2+ Wasting
Protease Activation
Thiol Inhibition
Pseudo-Hypoxia
Gut Microbiome
Health
Normal ENS-CNS Communication
Balanced Microbial Assemblages
Firmicute Excess
Gluten Sensitivity
Dysbiosis
Alternating Constipation & Diarrhea
Innate Immunity, Inflammation—Summer Growth Metabolism

Final Thoughts: 'Omics and The Failure of Functional Medicine

- Mitochondria are the brains of the cell
- Predictable alterations in genomic and metabolomic expression occur in response to cellular threats
- Abnormal patterns become fixed despite resolution of threat
- Treating metabolomic shifts will not return mitochondria back to healthy state

Chronic Inflammatory Response Syndrome (CIRS): A Mitochondrial Based Disease

- Biotoxin based illness
- Chronic-lasts more than 6 months
- Innate immune response to antigen detection without presentation
- Multi-system, multi-system illness

CIRS

- Abnormal proteomics
- Abnormal transcriptomics
- Abnormal regulation of immune functions
- Abnormal regulation of hormonal function
- This disease is all around you!

At least 30 biotoxins induce CIRS: 80% Patients Suffer from WDB

- Beta glucans
- Mannans
- Spirocyclic drimanes
- LPS
- Actinomycetes
- Hyphal fragments
- Cell wall fragments
- Bioaerosols
- Endotoxins
- MVOCs

- Mycotoxins
- Mycolactones
- Hemolysins
- Proteinases
- Gram (+) and G (-) bacteria
- Particulates (small, fine, ultra)
- Conidia
- Protozoa
- (2015 SM Medical Consensus)

Note: All biotoxins target the Sarcin Ricin Loop in Ribosomes to disrupt proper protein formation

Who is At Risk? The 20%
Poor Antigen Presentation and Innate Immune Dysfunction

	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	4	3		53	
	11/12	3	52B		
	14	5	52B		
Mold	7	2/3		53	
	13	6	52A, B, C		
	17	2	52A		
	*18	4	52A		
Borrelia, post Lyme Syndrome	15	6			51
	16	5			51
Dinoflagellates	4	7/8		53	
Multi Antibiotic Resistant Staph epidermidis (MARCoNS)	11	7	52B		
Low MSH	1	5			
No recognized significance	8	3,4,6			
Low-risk Mold	7	9		53	
	12	7	52B		
	9	3/9		53	

CIRS- A wealth of biomarkers all confirmed

- About 25 papers; over 10,000 patients (peds too)
- Multi-site confirmation; 25 docs certified
  - About 100 in pipeline
- Ancillary data confirm; therapy adds needed weight: pulmonary HBP; restrictive lung disease, interstitial lung disease; volumetric CNS measurements; MR spectroscopy; transcriptomics; gastroparesis; T reg abnormalities in acquired and thymus derived; proteomics; HLA; VCS
- Protocols (ending with VIP) showing correction of proteomics, genomics and CNS atrophy
-

No difference in Clinical Presentation between CIRS-WDB and other biotoxin illnesses (PLS**)*

- Mold (think water-damaged buildings)
  - Don't ever forget endotoxin and actino
- Dinoflagellates (Pfiesteria, ciguatera, Chattonella, Karenina)
- Apicomplexans (Babesia, Sarcocystis and Eimeria); Lyme too
- Cyanobacteria (Microcystis, Lyngbya, cylindrospermopsis)

Return to CIRS: Tools you will need

- Symptoms-cluster analysis
- PFT, diffusion capacity; EKG and stress echo; VO2 max; VCS
- NeuroQuant
- Transcriptomics
- Interventions confirmed to work

Biotoxin symptoms clusters

- Fatigue, weak
- Headache
- Aches, cramps
- Unusual, sharp, claw, electrical
- Light sens, redness, blurring, tearing
- SOB, cough, sinus
- Abdominal pains, secretory diarrhea, constipation

- Joints, AM stiff
- Exec. cognitive memory concentration. Word assimilation, confusion, disorientation
- Mood, appetite, sweats, temp regulation, weight gain
- Thirst, pee, shocks
- Numbness, tingling, taste
- Vertigo, tremor, skin

Biotoxin Evaluation Process

Initial Screening

1. *Symptom Questionnaire*
2. *Laboratory Evaluation*
   a. *Proteomics*
   b. *Functional Labs*
   c. *HLA Sequences*
   d. Infectious Disease Markers
3. *Visual Contrast Study*
4. Complete History and Physical Exam
5. Exposure History

Verification

1. Tier 1: All 3
   a. Known Exposure
   b. Differential Diagnosis – Rule out other causes
   c. Positive symptoms in 8 of 13 clusters
2. Tier 2: 3 of 6
   a. Fail VCS
   b. Presence of HLA
   c. Elevated MMP 9
   d. ACTH/Cortisol imbalance
   e. ADH/Osmolality imbalance
   f. Low MSH
3. Tier 3: Confirmation 2 of 3
   a. Symptom improvement
   b. Pass VCS
   c. Resolution of laboratory values

Diagnostic Refinement

1. Lyme disease
   a. Nanotrap urine antigen test
   b. Two tier ELISA & Western Blot
2. *ERMI Home Mold Test*
3. CardioPulmonary Exercise Tolerance Test
4. Brain MRI NeuroQuant
5. Transcriptomics

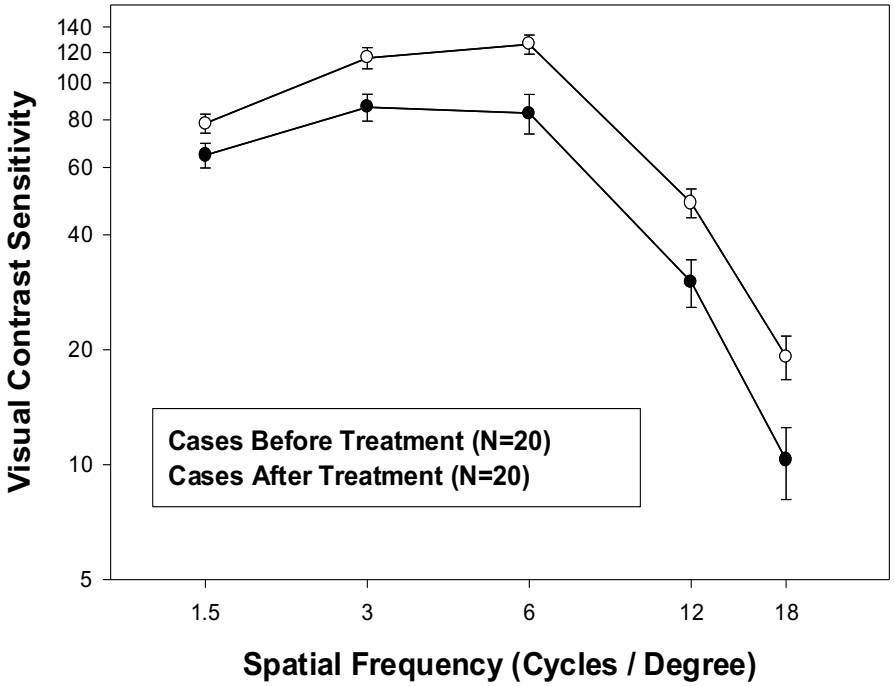
Objective Testing from Neurotoxicology

Visual Contrast Sensitivity (VCS)

- used over 40 years by US Air Force and in studies of non-biological toxicants
- Reproducible, reliable, portable, non-invasive, cheap!
- Just about the best marker beyond day 4 of biotoxin-associated/cytokine illness

With Permission from Ritchie Shoemaker, MD. 2014.

Acute Lyme: All Cases Before Any Treatment & After All Treatment



Visual Contrast Test

VCS Left Eye

	A	B	C	D	E
9	⊗	⊗	⊗	⊗	⊗
8	⊗	✓	✓	⊗	⊗
7	⊗	✓	⊗	⊗	✓
6	✓	✓	✓	✓	⊗
5	✓	✓	✓	✓	✓
4	✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓
2	✓	✓	✓	✓	✓
1	✓	✓	✓	✓	✓

VCS Right Eye

	A	B	C	D	E
9	⊗	⊗	⊗	⊗	⊗
8	✓	⊗	✓	⊗	⊗
7	✓	⊗	⊗	✓	⊗
6	✓	✓	✓	⊗	⊗
5	✓	✓	✓	✓	⊗
4	✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓
2	✓	✓	✓	✓	✓
1	✓	✓	✓	✓	✓

School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

Result: Fail

www.Survivingmold.com

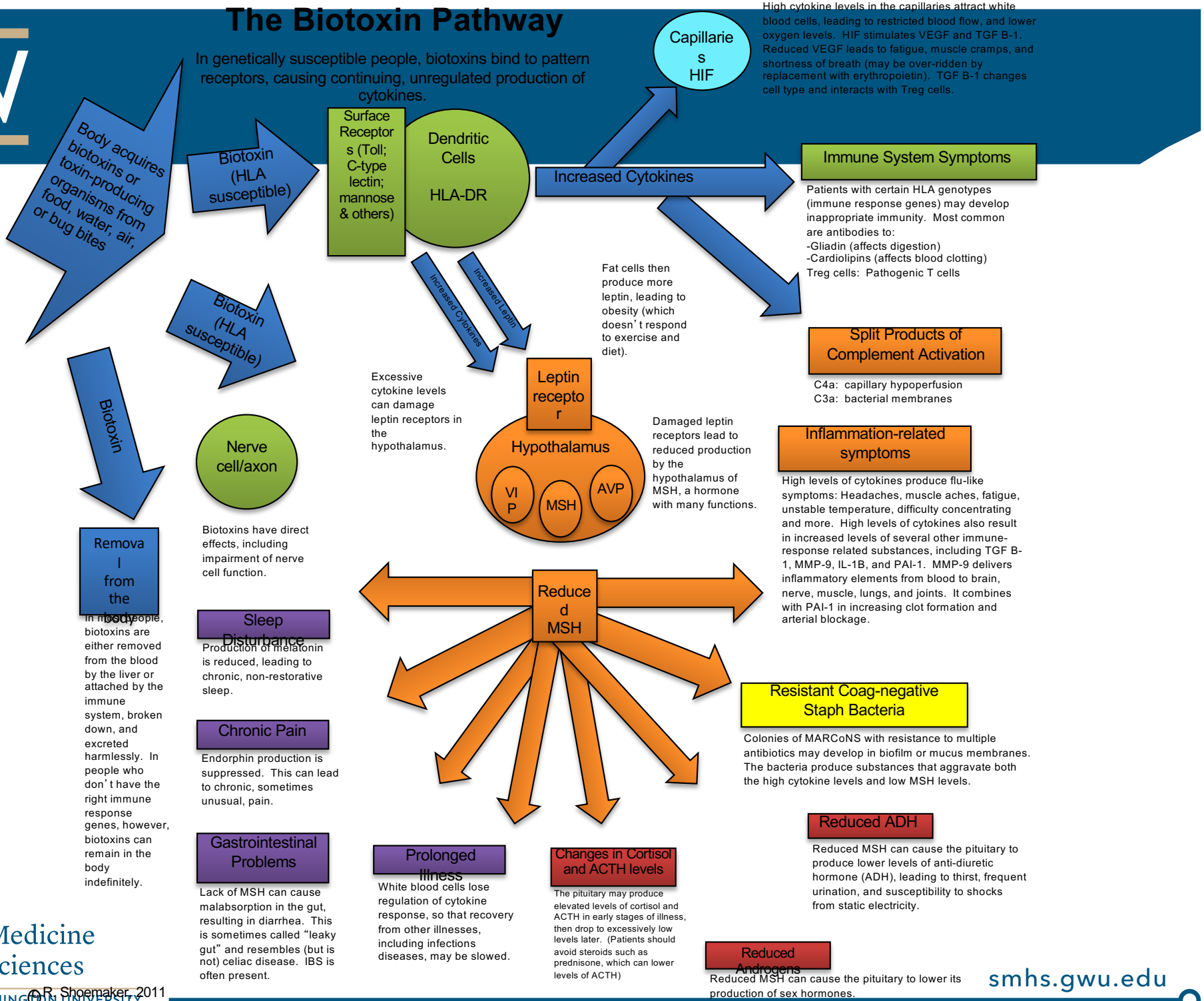
smhs.gwu.edu

Proteomics: The New Language of Inflammation

- Lowering levels of inflammagens: C3a, C4a, MMP9 and TGF beta-1
- Correct hormonal dysregulation
- Deal with auto-immunity
- Improve capillary hypoperfusion
- Eradicate commensal staphs
- Correct cellular immunity

The Biotoxin Pathway

In genetically susceptible people, biotoxins bind to pattern receptors, causing continuing, unregulated production of cytokines.



School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

VIP - Vasoactive Intestinal Polypeptide

Normal Range: 23-63 pg/mL

Vasoactive intestinal polypeptide (VIP) is a neuroregulatory hormone with receptors in the hypothalamus. This hormone/cytokine regulates peripheral cytokine responses, pulmonary artery pressures, and inflammatory responses throughout the body.

Low VIP levels are present in mold illness patients. This leads to unusual shortness of breath, especially in exercise. To date, every multiple chemical sensitivity patient Shoemaker has seen (over 500) have had low VIP. VIP plays a role similar to MSH in regulating inflammatory responses.

With respect to the digestive system, VIP seems to induce smooth muscle relaxation (lower esophageal sphincter, stomach, gallbladder), stimulate secretion of water into pancreatic juice and bile, and cause inhibition of gastric acid secretion and absorption from the intestinal lumen, which can lead to chronic, watery diarrhea.

VIP replacement, when used according to a strictly administered protocol, has proven to be fabulously effective in returning chronically fatigued patients back to a normal life. Do not use VIP if you are exposed to mold (with ERMI values greater than 2); if you fail a VCS test; or if you have a MARCoNS present in your nose.

MSH - Melanocyte Stimulating Hormone

Normal Range: 35-81 pg/mL

Alpha melanocyte stimulating hormone (MSH) has multiple anti-inflammatory and neurohormonal regulatory functions, exerting regulatory control on peripheral cytokine release, as well as on both anterior and posterior pituitary function.

In mold illness, MSH will be too low in over 95% of patients. This means increased susceptibility to mold illness, ongoing fatigue, pain, hormone abnormalities, mood swings, and much more. MSH is a hormone, called a regulatory neuropeptide, and it controls many other hormones, inflammation pathways, and basic defenses against invading microbes. Without MSH, bad things happen; chronic sleep disorders with non-restful sleep develop, and endorphin production is reduced, so chronic pain follows.

TGF Beta-1 - Transforming Growth Factor Beta-1

Normal Range: <2380 pg/ml

TGF Beta-1 is a protein that has important regulatory effects throughout innate immune pathways. This protein helps control the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (motility), and the self-destruction of cells (apoptosis). The TGF Beta-1 protein is found throughout the body and plays a role in development before birth, the formation of blood vessels, the regulation of muscle tissue and body fat development, wound healing, and immune system function (especially regulatory T-cells).

TGF Beta-1 can impair T-regulatory cell function, which in turn contributes to the activation of autoimmunity, yet TGF Beta-1 also plays a role in suppressing autoimmunity(!). TGF Beta-1 has become important in the exploding incidences of childhood asthma, raising the tantalizing issue of remodeling due to biotoxin exposure. The EPA says that 21% of all new cases of asthma are due to exposure to Water Damaged Buildings. If an individual develops wheezing after exposure to a water damaged building, look for remodeling to be the cause. Remodeling means "something" happens that the airway changes to be more reactive and in need of medications to reduce wheezing. Neurologic, autoimmune and many other systemmic problems also are found with high TGF Beta-1.

C4a

Normal Range: 0-2830 ng/ml

C4a has become the inflammatory marker of greatest significance looking at innate immune responses in those with exposure to Water Damaged Buildings (WDB).

The complement system is a group of proteins that move freely through your bloodstream. The proteins work with your immune system and play a role in the development of inflammation.

Each complement activates inflammatory responses, with spillover of effect from the innate immune response to acquired immune response and hematologic parameters.

These short-lived products are re-manufactured rapidly, such that an initial rise of plasma levels is seen within 12 hours of exposure to biotoxins, and sustained elevation is seen until definitive therapy is initiated.

AGA IgA/IgG

Normal Range: 0-19

Antigliadin (AGA) antibodies are produced in response to gliadin, a small protein that is part of gluten, biologically active of wheat, barley and rye. These antibodies were thought at one time to be specific for Celiac Disease.

Within 30 minutes of ingestion of gliadin, for those with antigliadin antibodies, there will be an inflammatory response. This inflammatory response can provide many symptoms, including some that mimic attention deficit disorder. We all know that some kids are labeled as having ADHD because of their abnormal behavior seen within 30 minutes of eating a cupcake. It is not the sugar in the icing, it is the gluten in the cake. Antigliadin antibodies are found in over 58% of children with biotoxin-associated illness.

ACTH/Cortisol

Normal Range: ACTH - 8-37 pg/mL; Cortisol - a.m. 4.3-22.4 / p.m. 3.1-16.7 ug/dL

ACTH is a hormone released from the anterior pituitary gland in the brain. Cortisol is a steroid hormone produced by the adrenal cortex, which is the outer part of the adrenal gland. The adrenal glands are located on top of both kidneys.

Early in the illness, as MSH begins to fall, high ACTH is associated with few symptoms; a marked increase in symptoms is associated with a fall in ACTH. Finding simultaneous high cortisol and high ACTH may prompt consideration of screening tumors, but the reality is that the dysregulation usually corrects with therapy.

VEGF

Normal Range: 31-86 pg/mL

Vascular endothelial growth factor (VEGF) is a substance made by cells that stimulates new blood vessel formation and increases blood flow in the capillary beds. VEGF is a polypeptide. Deficiency of VEGF is quite common and is a serious problem in biotoxin illness patients that must be corrected. If you don't have blood flow, cells begin starve and don't work properly.

ACLA IgA/IgG/IgM

Normal Range: IgA - 0-12; IgG 0-10; IgM 0-9

Anticardiolipins (ACLA) are autoantibodies. Antibodies are proteins in the blood that the body produces to fight off foreign agents. Antibodies do this by creating an immunity against unfamiliar microorganisms. Autoantibodies are antibodies that are directed against one's self. They interfere with the normal function of blood vessels and react with proteins in the blood that are bound to phospholipid, a type of fat molecule that is a part of the normal cell membrane.

IgA, IgM, and IgG are autoantibodies often identified in collagen vascular diseases such a lupus and scleroderma, and are often called anti-phospholipids.

An increased risk of spontaneous fetal loss in the first trimester of pregnancy is not uncommonly seen in women with the presence of these autoantibodies. They are found in over 33% of children with biotoxin-associated illnesses.

ADH/Osmolality

Normal Range: ADH - 1.0-13.3 pg/ml; Osmolality - 280-300 mosmol

Antidiuretic hormone (ADH), or vasopressin, is a substance produced naturally by the hypothalamus and released by the pituitary gland. The hormone controls the amount of water your body removes.

Osmolality is a test that measures the concentration of all chemical particles found in the fluid part of the blood.

Symptoms associated with dysregulation of ADH include dehydration, frequent urination, with urine showing low specific gravity; excessive thirst and sensitivity to static electrical shocks; as well as edema and rapid weight gain due to fluid retention during initial correction of ADH deficits.

MMP-9

Normal Range: 85-332 ng/mL

Matrix metallopeptidase 9 (MMP-9) is an enzyme that in humans, is encoded by the MMP9 gene. Proteins of the MMP9 family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes.

It has been implicated in pathogenesis COPD by destruction of lung elastin, in rheumatoid arthritis, astherosclerosis, cardiomyopathy, and abdominal aortic aneurysm.

MMP-9 delivers inflammatory elements of of blood into subintimal spaces, where further delivery into solid organs (brain, lung, muscle, peripheral nerve and joint) is initiated.

Leptin

Normal Range: Male: 0.5-13.8 ng/mL; Female: 1.1-27.5 ng/mL

Leptin turns on how tightly the body holds onto fatty acids. When Leptin is high, one holds onto fatty acids and stores them in fat. This leads to rapid weight gain, and because of the high Leptin, standard approches to weight loss like eating less and exercising more will fail. The inflammatory responses that causes Leptin levels to rise lead to patients who are chronically tired, in chronic pain, and forever overweight.

CBC and CD 57

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
HNK1 (CD57) Panel					
% CD8-/CD57+ Lymphs	6.3		%	2.0 - 17.0	01
This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.					
Abs.CD8-CD57+ Lymphs	101		/uL	60 - 360	
This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.					
WBC	5.5		x10E3/uL	3.4 - 10.8	01
RBC	5.04		x10E6/uL	4.14 - 5.80	01
Hemoglobin	15.9		g/dL	12.6 - 17.7	01
Hematocrit	44.3		%	37.5 - 51.0	01
MCV	88		fL	79 - 97	01
MCH	31.5		pg	26.6 - 33.0	01
MCHC	**35.9**	**High**	g/dL	31.5 - 35.7	01
RDW	14.4		%	12.3 - 15.4	01
Platelets	243		x10E3/uL	150 - 379	01
Neutrophils	52		%		01
Lymphs	30		%		01
Monocytes	14		%		01
Eos	3		%		01
Basos	1		%		01
Neutrophils (Absolute)	2.8		x10E3/uL	1.4 - 7.0	01
Lymphs (Absolute)	1.6		x10E3/uL	0.7 - 3.1	01
Monocytes(Absolute)	0.8		x10E3/uL	0.1 - 0.9	01
Eos (Absolute)	0.2		x10E3/uL	0.0 - 0.4	01
Baso (Absolute)	0.1		x10E3/uL	0.0 - 0.2	01
Immature Granulocytes	0		%		01
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1	01

Comp. Metabolic Panel (14)

Glucose, Serum	71	mg/dL	65 - 99	01
BUN	14	mg/dL	6 - 24	01
Creatinine, Serum	1.16	mg/dL	0.76 - 1.27	01
eGFR If NonAfricn Am	71	mL/min/1.73	>59	
eGFR If Africn Am	83	mL/min/1.73	>59	
BUN/Creatinine Ratio	12		9 - 20	
Sodium, Serum	141	mmol/L	134 - 144	01
Potassium, Serum	4.6	mmol/L	3.5 - 5.2	01
Chloride, Serum	102	mmol/L	97 - 108	01
Carbon Dioxide, Total	22	mmol/L	18 - 29	01
Calcium, Serum	9.4	mg/dL	8.7 - 10.2	01
Protein, Total, Serum	6.9	g/dL	6.0 - 8.5	01
Albumin, Serum	4.7	g/dL	3.5 - 5.5	01
Globulin, Total	2.2	g/dL	1.5 - 4.5	
A/G Ratio	2.1		1.1 - 2.5	
Bilirubin, Total	0.3	mg/dL	0.0 - 1.2	01
Alkaline Phosphatase, S	57	IU/L	39 - 117	01
AST (SGOT)	26	IU/L	0 - 40	01
ALT (SGPT)	35	IU/L	0 - 44	01

Antidiuretic Hormone Profile

ADH	0.8	pg/mL	0.0 - 4.7	01
Comment:				01

Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Osmolality	286	mOsmol/kg	275 - 295	01

Anticardiolipin Ab, IgG/M, Qn

Anticardiolipin Ab,IgG,Qn	<9	GPL U/mL	0 - 14	01
		Negative:	<15	
		Indeterminate:	15 - 20	
		Low-Med Positive:	>20 - 80	
		High Positive:	>80	
Anticardiolipin Ab,IgM,Qn	10	MPL U/mL	0 - 12	01
		Negative:	<13	
		Indeterminate:	13 - 20	
		Low-Med Positive:	>20 - 80	
		High Positive:	>80	

MMP-9 (Matrix metalloprot.-9)

MMP9	501	> 332 ng/mL		02
Reference Range: <984				

Proteomics

**Results of this test are for research purposes only per the assay manufacturer. The performance characteristics of this assay have not been established. The result should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Human Trans.Growth Fact.beta 1

TGF-b1	**7100**	**High**	pg/mL	344-2382	03

The performance characteristics of the listed assay was validated by Cambridge Biomedical Inc. The US FDA has not approved or cleared this test. The results of this assay can be used for clinical diagnosis without FDA approval. Cambridge Biomedical Inc. is a CLIA certified, CAP accredited laboratory for performing high complexity assays such as this one.

C6 B. burgdorferi (Lyme)

C6 Borrelia burgdorferi (Lyme)					
	<0.91		index	0.00 - 0.90	01
			Negative	<0.91	
			Equivocal	0.91 - 1.09	
			Positive	>1.09	
D-Dimer	0.24		mg/L FEU	0.00 - 0.49	01

In conjunction with a non-high clinical probability assessment, a normal (<0.50 mg/L FEU) result excludes deep vein thrombosis (DVT) and pulmonary embolism (PE) with high sensitivity.

Melanocyte Stimulating Hormone

20		pg/mL	0 - 40	01

Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Alternate Complement Pathway

Complement Component 4A SEE NOTE ARU

C4a LEVEL	H	17695 (NOTE)	[0-2830]	ng/mL

This test uses a kit/reagent designated by the manufacturer as "for research use, not for clinical use." The performance characteristics for this test have been validated by Advanced Diagnostic Laboratories at National Jewish Health. It has not been cleared or approved by the US Food and Drug Administration. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing.

Legend: H=High, L=Low, @=Critical
Performed at: National Jewish Center, Advanced Diag. Lab, 1400 Jackson St., Denver, CO 80206

Back to the brain

- Are executive symptoms telling us about abnormal brain structures?
- Brain physiology? Capillary!
- What we need is a dynamic imaging study that correlates with symptoms and physiology!
- And we have one: NeuroQuant

With Permission from Ritchie Shoemaker, MD. 2014.

Volumetric Brain Imaging

- Volumetric study of 11 brain regions
  - Can expand to 15
  - Changes over time key
- FDA cleared in 2007
- Software added to MRI of brain
- Takes 10 minutes ($96)
- Reproducibly reliable
- Controls data sets available

With Permission from Ritchie Shoemaker, MD. 2014.

What do changes from normal in VBI mean?

- Changes in volume
  - Interstitial edema; increase volume
  - Atrophy or pruning; decrease volume
- Analyzed sequentially
- Correlate with clinical studies
- Correlate with genomics! (GFAP mRNA)
- We can link mRNA to changes in brain volumes with changes in clinical status

With Permission from Ritchie Shoemaker, MD. 2014.

Atrophy

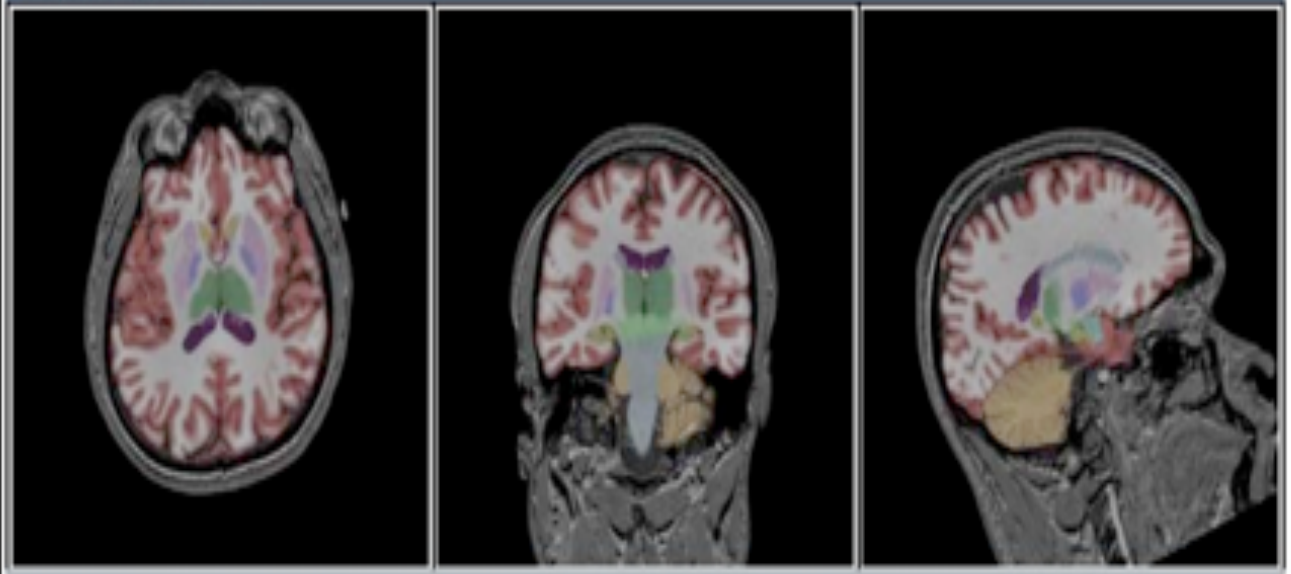
- Loss of neuronal tissue
- Atrophy is permanent unless it is actually dendritic pruning
- How can one tell?
- MRS, NAA and creatine help
- Often we know only after a therapeutic trial

With Permission from Ritchie Shoemaker, MD. 2014.

NeuroQuant® Standard Report

Page 2

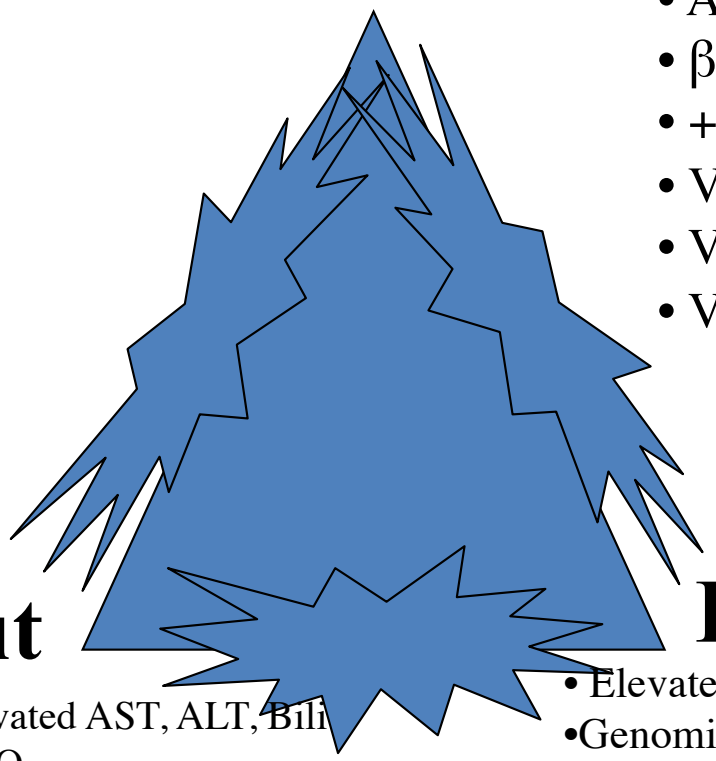
MORPHOMETRY RESULTS



Brain Structure	LH Volume (cm³)	LH Volume (% of ICV)	RH Volume (cm³)	RH Volume (% of ICV)	Asymmetry Index (%)*
Forebrain Parenchyma	530.42	33.41	544.54	34.30	-2.63
Cortical Gray Matter	238.78	15.04	239.66	15.10	-0.37
Lateral Ventricle	11.93	0.75	10.80	0.68	9.91
Inferior Lateral Ventricle	0.75	0.05	0.55	0.03	30.02
Hippocampus	3.98	0.25	4.02	0.25	-0.97
Amygdala	1.98	0.12	1.95	0.12	1.32
Caudate	4.07	0.26	3.67	0.23	10.33
Putamen	5.23	0.33	4.30	0.27	19.55
Pallidum	1.31	0.08	1.32	0.08	-0.83
Thalamus	7.66	0.48	6.95	0.44	9.70
Cerebellum	65.25	4.11	66.08	4.16	-1.25

*The Asymmetry Index is defined as the difference between left and right volumes, divided by their mean (in percent)

Gut-Immune-Brain Pathology



Brain

- Abnormal cortisol
- β2 microglobulin
- ++ MTHFR
- VIP, MSH, VEGF, TGFB1, C4a
- VBI
- VCS

Gut

- Elevated AST, ALT, Bili
- DAO
- LPS
- MSH
- IgG Food allergies
- Acetaldeyde

Immune

- Elevated CRP, ESR, IL-6, TNFα
- Genomics
- Markers of auto-immunity
- Measurable toxins, viruses
- MMP-9, C3a, C4a, TGFB1, CD4/25
- ACLA, VWf, D Dimer

CIRS

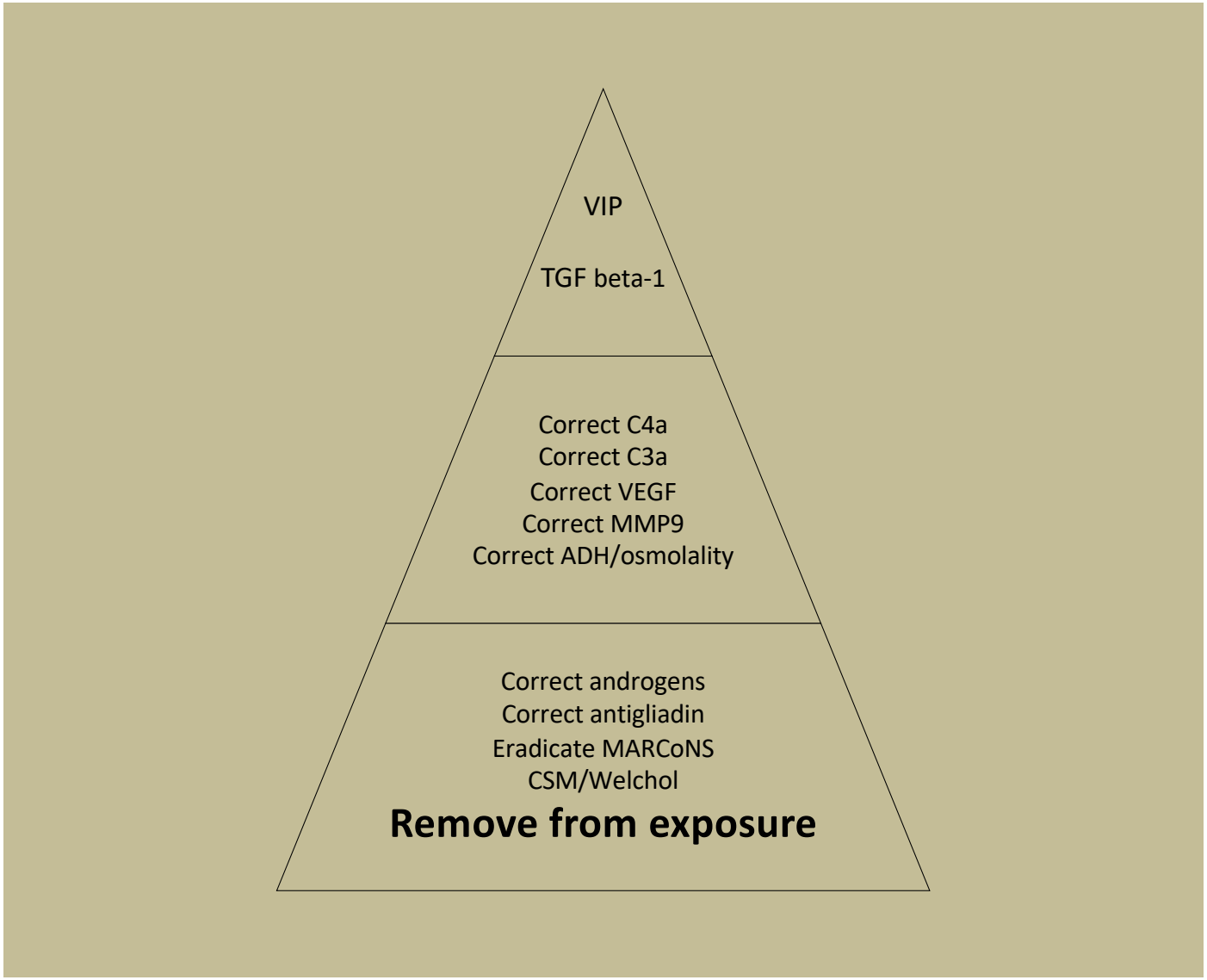
- Once you see it once your life as a physician will be changed forever
- Lack of regulation of inflammation
- Enhanced innate inflammatory parameters (C4a, TGF beta-1, MMP9 and more)
- Hormonal dysregulation
- Hypoxia from capillary hypoperfusion
- And now T regs too

With Permission from Ritchie Shoemaker, MD. 2014.

Treatment Challenges

- Eliminate the Exposure
- Correct Inflammatory Response (CIRS)
- Repair the Nervous System
- Restore normal Genomic activity

CIRS Treatment steps



With Permission from Ritchie Shoemaker, MD. 2014.

Biotoxin Treatment Process: Expanded

Foundations

1. *Low Inflammatory Low Mold Diet*
2. *Stress Management*
3. *Sleep support*
4. Lipid replacement
   a. Phosphatidylcholine
   b. Omega 6/Omega 3 and Resolvins
   c. Wheat Germ Oil
5. Reduce NeuroInflammation
   a. *RG3 2mg/NR 2 mg nasal spray BID*
   b. Curcumin
   c. BPC-157
   d. Magnesium
   e. L-Theanine
   f. Magnolia
   g. Flavonoids

Exposure Elimination

1. Lyme and Co Infections
   a. See *Lyme Protocol*
2. Mold remediation
   a. See *Tips for Mold Remediation Sheet*
   b. Maintaining cleanliness
      i. HEPA Vacuum cleaner
      ii. HEPA Units in trafficked rooms
      iii. Photocatalytic Air Purifier for home

Reduce Toxin Burden

Neurological	Respiratory	Gastrointestinal
VCS	MARCoNs	Nutrition

1. Biotoxin Management x 1-2 months
   a. *Cholestyramine 4 g QID or Okra*
   b. Soluble Fiber 11 g/d
   c. Multivitamin and minerals
   d. Oxbile 500 mg with meals
   e. N-acetyl Cysteine 1000 mg BID

Pass VCS

2. Upper Respiratory Tract
   a. MARCoNs Nasal Swab
   b. BE or BEG Spray x 6 weeks

3. GI Health
   a. IgG Food Panel
   b. Functional Digestive Test
   c. Ca/Mg/Butyrate 1.2 g BID

Clear MARCoNs

Metabolic Balance

Detox	Endocrine	Electrolytes
Chemicals/Metals	Hormones	Water Balance

1. Detoxification – pH above 6.5
   a. Chlorella 3 g BID/Clay/Okra
   b. Topical Glutathione

Wait 4 weeks
Before progressing

2. Hormone Balance
   a. Urine or Saliva Panel
   b. Block aromatase
      i. Chrysin 500 mg BID
      ii. Bilberry 6000 mg/d
   c. Balance Reproductive Hormones
      a. DHEA 25-50 mg daily
      b. BHRT

3. Electrolyte/Water balance
   a. Remeasure ADH/Osmolarity
   b. Desmopressin 0.2 mg qohs
   c. Ca/Mg/Butyrate 1.2 g BID

Resolution and Repair

Connective Tissue	Innate Immune	Genomic/CNS
Degrading Enzyme	Complement & TF	VIP

1. Manage Destructive Enzymes
   a. Remeasure MMP9
   b. Low Amylose Diet
   c. Boswellia 400 mg TID

MMP9<332

1. Reduce Complement Activation
   a. Remeasure C3a
      i. Red Yeast Rice 1200 mg BID
      ii. CoQ10 200 mg daily
   b. Remeasure C4a
      a. Fish oil 3:2 ratio 2 g BID
      b. Resolvins

C3a<780
C4a<2830

2. Reduce Transcription Factors Activation
   a. Remeasure TGFB1
      a. Losartan 25-50 mg BID
      i. Bilberry 6000 mg/d
      a. L carnitine 1000 mg BID

TGFB1<2380

3. VIP Nasal Spray Protocol

VIP Spray

- VIP = vasoactive intestinal Peptide
- It is a major hormone (neuro-polypeptide) made in the gut, pancreas, and the suprachiasmatic nuclei (SCN) located in the hypothalamus
- Vasoactive intestinal peptide (VIP) is a 28-amino acid neuropeptide that has been studied extensively since first isolated by Said in 1970
- In biotoxin illnesses, VIP supports healthy hormone levels, limits inflammation, regulates the immune system, and helps the brain heal
- Low VIP = < 25 pg/mL
  - 91% of people with CIRS have low VIP levels

Vasoactive intestinal peptide

- Administration causes changes in gene regulation found in ribosomal and mitochondrial activity.
- Microbial toxins cleave or modify ribosomal RNA at the conserved sarcin-ricin loop in the functional ribosome, rendering the ribosome useless.
- It is not known how VIP is acting to influence ribosomal or mitochondrial gene regulation, but several transcription factors were also shown to be differentially expressed after administration of VIP.
  - Ikaros, was shown to be the most highly up-regulated assemblage of genes
- Corrects areas of CNS interstitial edema and atrophy in CIRS

– VIP tx within 4-6 months can stop the caudate from shrinking due to its anti-inflammatory effects

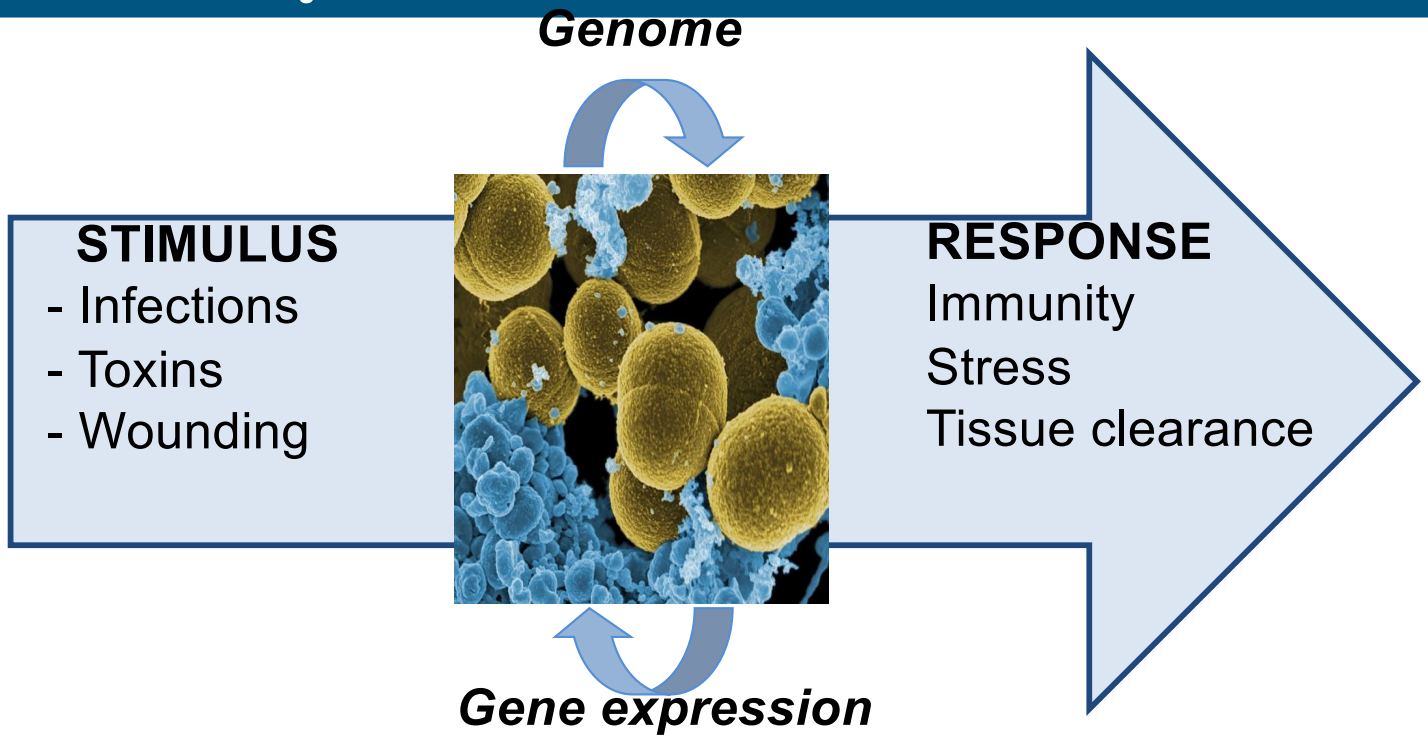
VIP Spray

- Without VIP, antidiuretic hormone and melanocyte stimulating hormone would be hard to correct with those with CIRS
- Low VIP causes the enzyme that converts hormone to female hormones (aromatase) to become overactive
  - Testosterone supplementation not recommended
  - 4 sprays VIP x 30 days helps to balance hormones

VIP Spray

- Dosage:
  - 50 mcg/ml -> 500 mcg/ml
  - Spray in each nostril 4 times daily 12 sprays daily
- Monitoring:
  - Check VCS, C4a, TGF beta -1, and fasting lipase e
  - If levels are improving, taper VIP to 2 doses over the next month

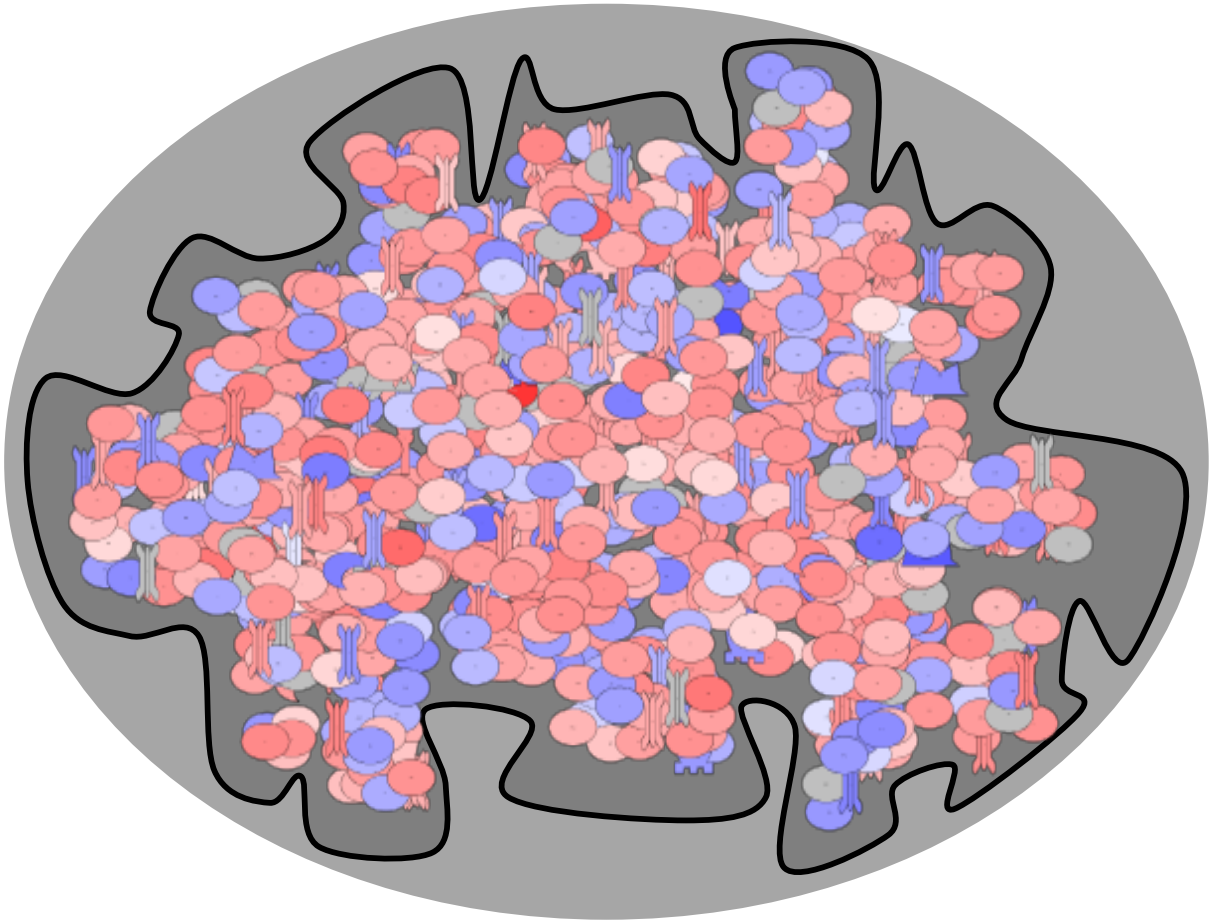
Functional Genomics:
Why do Patients Become Stuck?



- Monitor transcriptomic activity using RNA-Seq
  - ***Transcriptome*** = set of all RNA molecules produced by the genome at any one time

❖ **transcriptomes are sensitive indicators of both disease status and emerging health hazards**

Beyond Antigen Presentation Defects…..
Pre VIP Mitochondrial Gene Expression
(compared to controls)

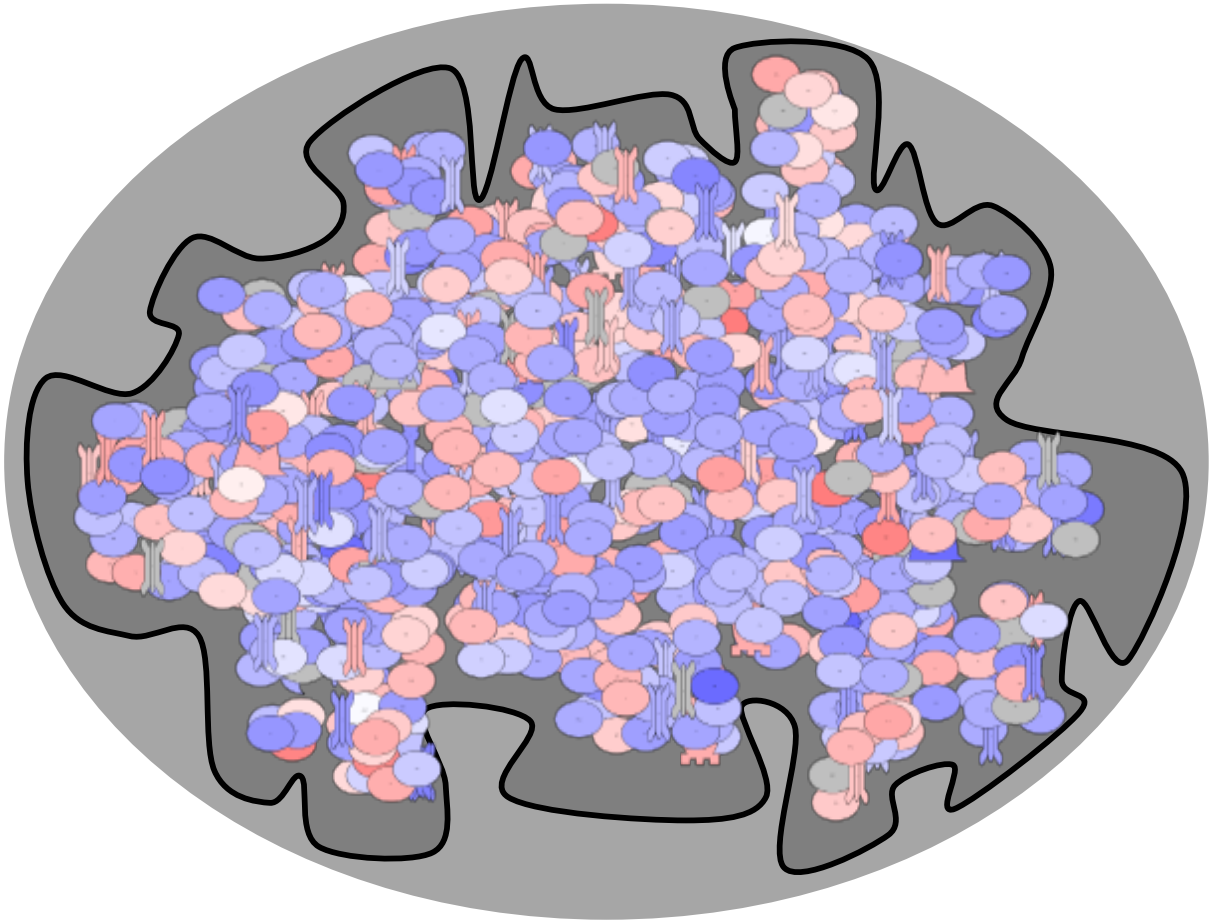


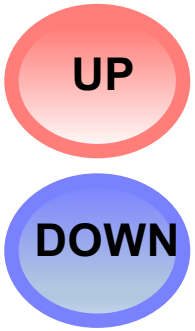
UP

DOWN

Post VIP Mitochondrial Gene Expression

(compared to controls)





Biotoxin Evaluation Process

Initial Screening

1. *Symptom Questionnaire*
2. *Laboratory Evaluation*
   a. *Proteomics*
   b. *Functional Labs*
   c. *HLA Sequences*
   d. Infectious Disease Markers
3. *Visual Contrast Study*
4. Complete History and Physical Exam
5. Exposure History

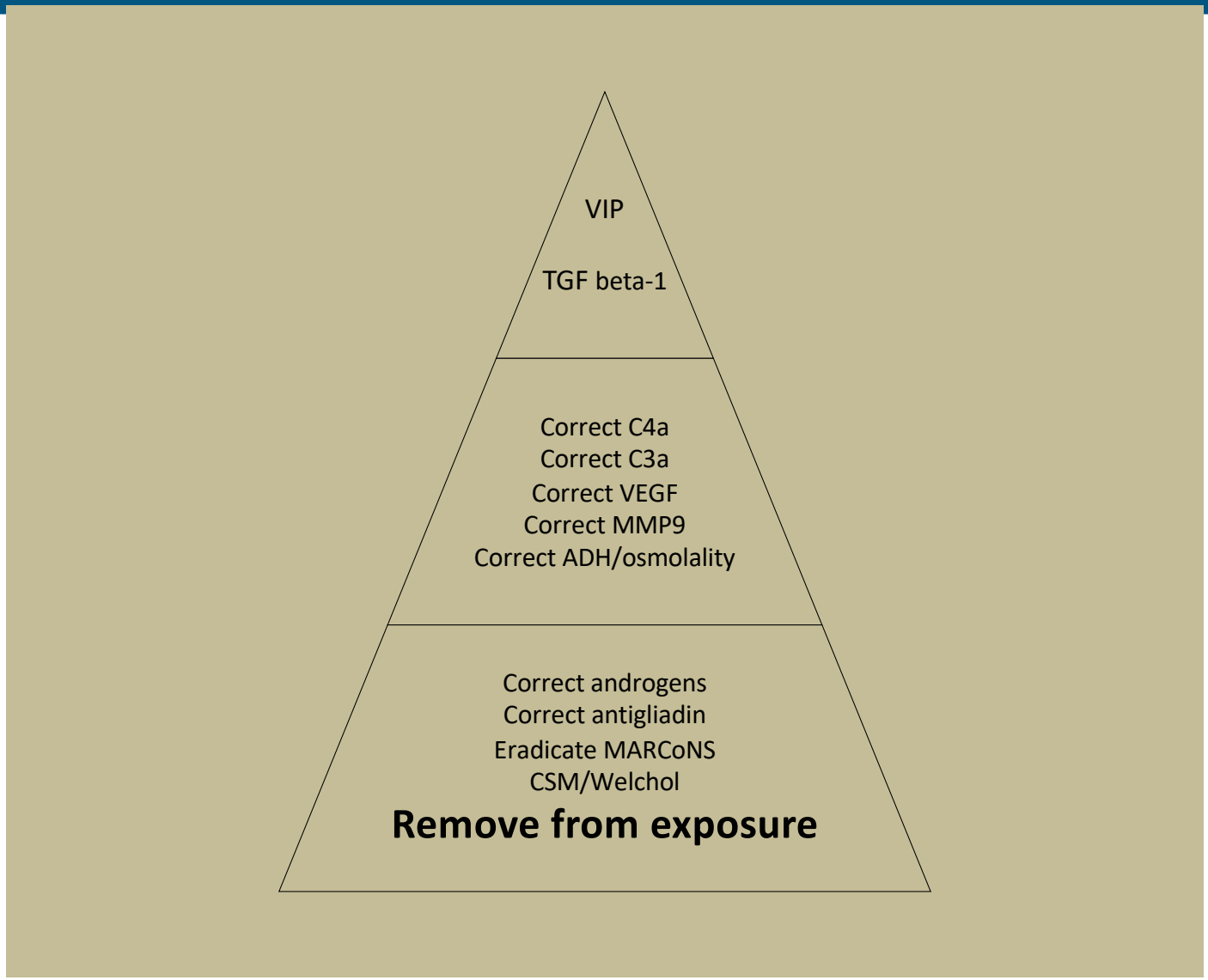
Verification

1. Tier 1: All 3
   a. Known Exposure
   b. Differential Diagnosis – Rule out other causes
   c. Positive symptoms in 8 of 13 clusters
2. Tier 2: 3 of 6
   a. Fail VCS
   b. Presence of HLA
   c. Elevated MMP 9
   d. ACTH/Cortisol imbalance
   e. ADH/Osmolality imbalance
   f. Low MSH
3. Tier 3: Confirmation 2 of 3
   a. Symptom improvement
   b. Pass VCS
   c. Resolution of laboratory values

Diagnostic Refinement

1. Lyme disease
   a. Nanotrap urine antigen test
   b. Two tier ELISA & Western Blot
2. *ERMI Home Mold Test*
3. CardioPulmonary Exercise Tolerance Test
4. Brain MRI NeuroQuant
5. Transcriptomics

CIRS Treatment steps



With Permission from Ritchie Shoemaker, MD. 2014.

Biotoxin Treatment Process: Expanded

Foundations

1. *Low Inflammatory Low Mold Diet*
2. *Stress Management*
3. *Sleep support*
4. Lipid replacement
   a. Phosphatidylcholine
   b. Omega 6/Omega 3 and Resolvins
   c. Wheat Germ Oil
5. Reduce NeuroInflammation
   a. *RG3 2mg/NR 2 mg nasal spray BID*
   b. Curcumin
   c. BPC-157
   d. Magnesium
   e. L-Theanine
   f. Magnolia
   g. Flavonoids

Exposure Elimination

1. Lyme and Co Infections
   a. See *Lyme Protocol*
2. Mold remediation
   a. See *Tips for Mold Remediation Sheet*
   b. Maintaining cleanliness
      i. HEPA Vacuum cleaner
      ii. HEPA Units in trafficked rooms
      iii. Photocatalytic Air Purifier for home

Reduce Toxin Burden

Neurological	Respiratory	Gastrointestinal
VCS	MARCoNs	Nutrition

1. Biotoxin Management x 1-2 months
   a. *Cholestyramine 4 g QID or Okra*
   b. Soluble Fiber 11 g/d
   c. Multivitamin and minerals
   d. Oxbile 500 mg with meals
   e. N-acetyl Cysteine 1000 mg BID
2. Upper Respiratory Tract
   a. MARCoNs Nasal Swab
   b. BE or BEG Spray x 6 weeks
3. GI Health
   a. IgG Food Panel
   b. Functional Digestive Test
   c. Ca/Mg/Butyrate 1.2 g BID

Pass VCS

Clear MARCoNs

Metabolic Balance

Detox	Endocrine	Electrolytes
Chemicals/Metals	Hormones	Water Balance

1. Detoxification – pH above 6.5
   a. Chlorella 3 g BID/Clay/Okra
   b. Topical Glutathione
2. Hormone Balance
   a. Urine or Saliva Panel
   b. Block aromatase
      i. Chrysin 500 mg BID
      ii. Bilberry 6000 mg/d
   c. Balance Reproductive Hormones
      a. DHEA 25-50 mg daily
      b. BHRT
3. Electrolyte/Water balance
   a. Remeasure ADH/Osmolarity
   b. Desmopressin 0.2 mg qohs
   c. Ca/Mg/Butyrate 1.2 g BID

Wait 4 weeks
Before progressing

Resolution and Repair

Connective Tissue	Innate Immune	Genomic/CNS
Degrading Enzyme	Complement & TF	VIP

1. Manage Destructive Enzymes
   a. Remeasure MMP9
   b. Low Amylose Diet
   c. Boswellia 400 mg TID
1. Reduce Complement Activation
   a. Remeasure C3a
      i. Red Yeast Rice 1200 mg BID
      ii. CoQ10 200 mg daily
   b. Remeasure C4a
      a. Fish oil 3:2 ratio 2 g BID
      b. Resolvins
2. Reduce Transcription Factors Activation
   a. Remeasure TGFB1
      a. Losartan 25-50 mg BID
      i. Bilberry 6000 mg/d
      a. L carnitine 1000 mg BID
3. *VIP Nasal Spray Protocol*

MMP9<332

C3a<780
C4a<2830

TGFB1<2380

Andrew Heyman, MD MHSA

Thank you!!!!!!!