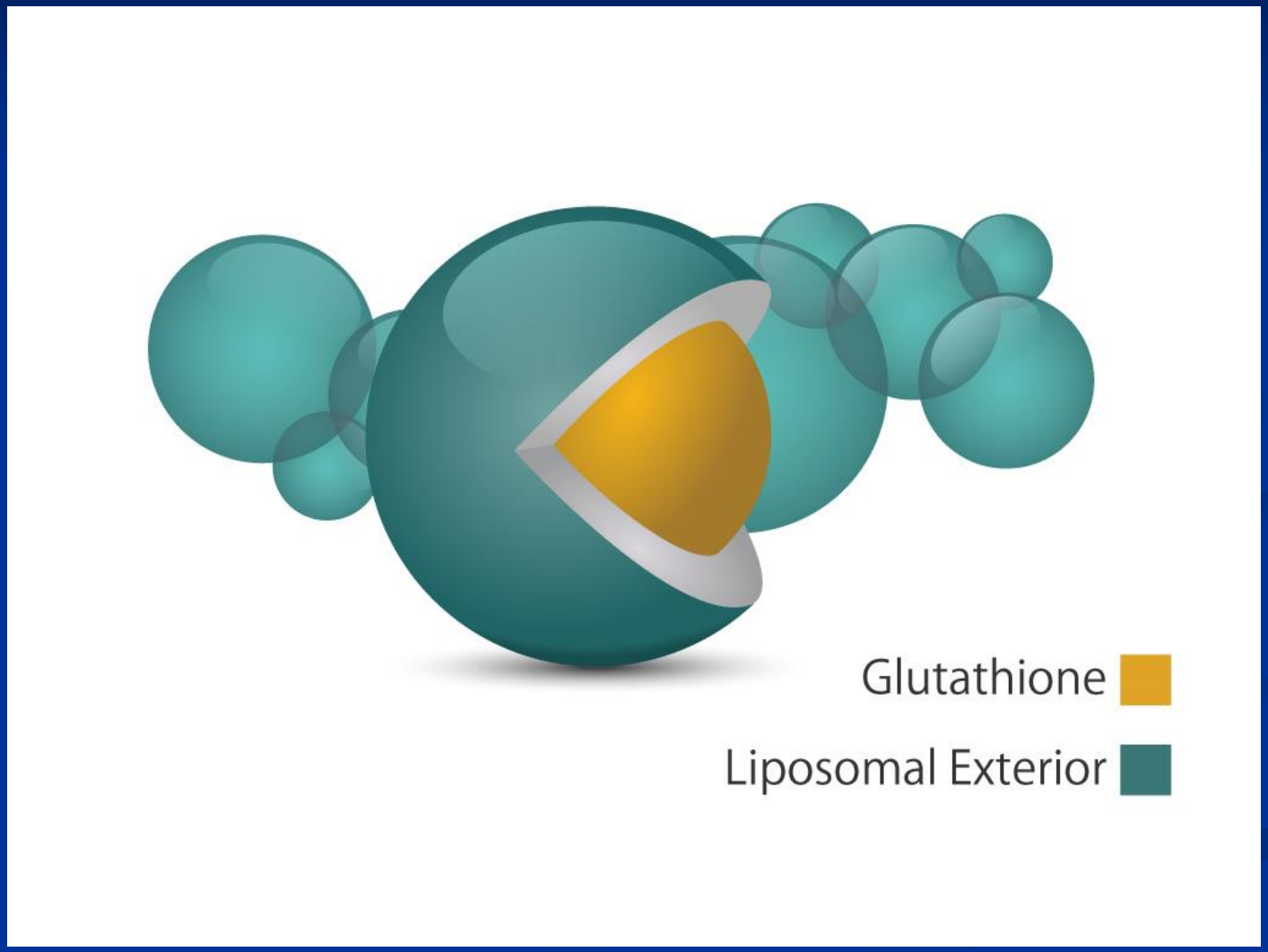
Mycotoxin and Glutathione

Tim Guilford, MD
Your Energy Systems, LLC
DrGuilford.com/publications or research
Email: Drg@readisorb.com
Office Phone: 650-323-3238

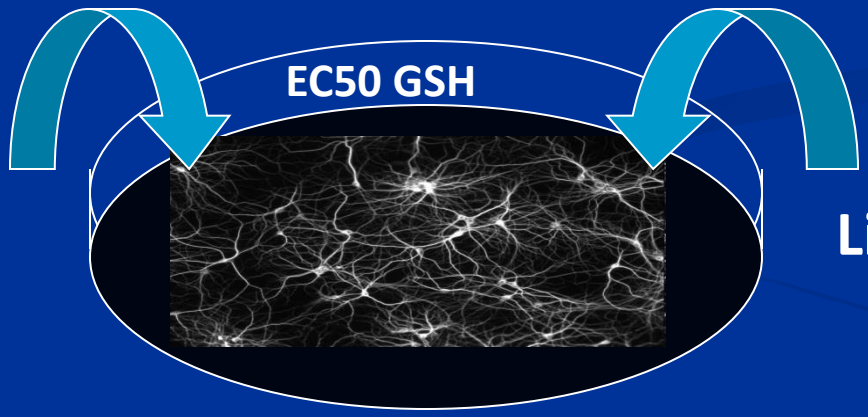
ReadiSorb® Liposomal Glutathione



Can L-GSH Improve GSH Concentration across Membranes?

- Neuron cell culture depleted of GSH by DEM (diethyl maleate)
- L-GSH was > 100-fold more potent than plain GSH in solution (non-L-GSH) in replenishing intracellular GSH

Mol Wt. GSH - 304



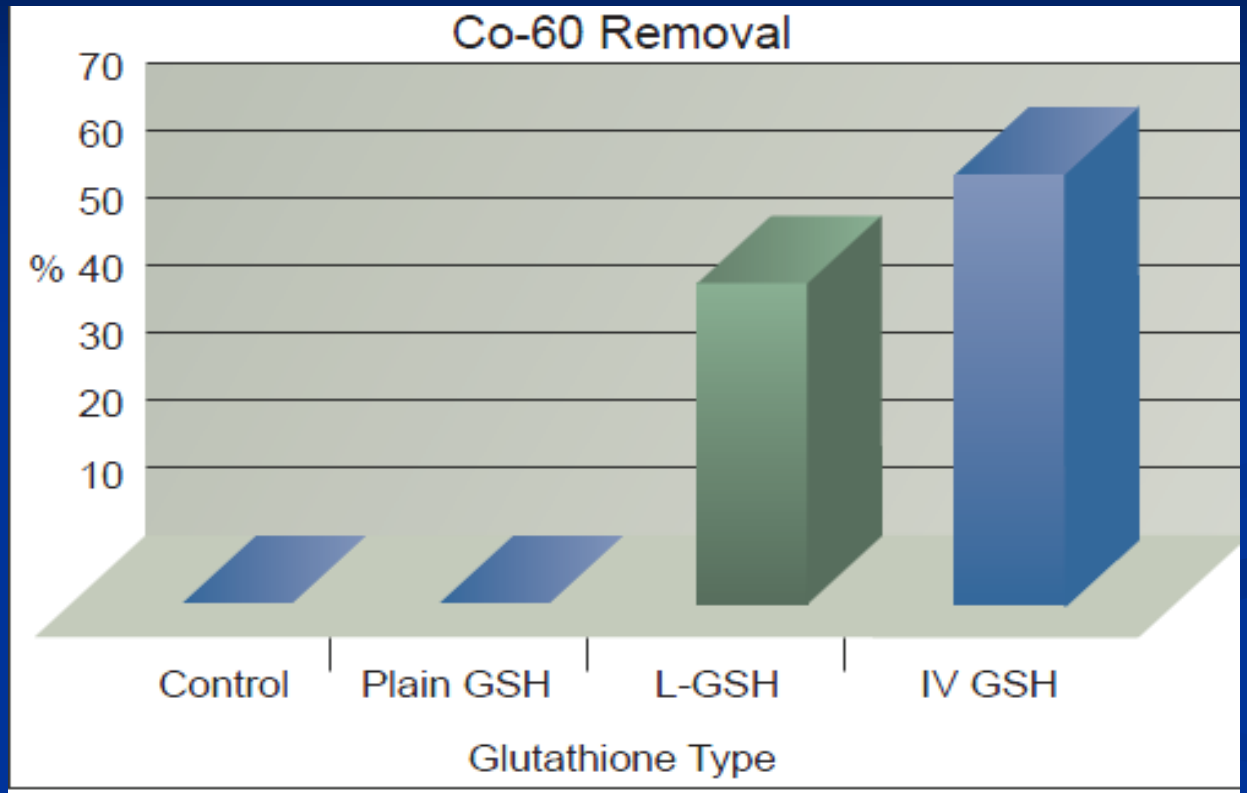
Plain GSH
575 µM

Liposomal GSH
4.75 µM

Zeevalk GD, Bernard LP, Guilford FT. Liposomal-glutathione provides maintenance of intracellular glutathione and neuroprotection in mesencephalic neuronal cells. Neurochem Res. 2010;35(10):1575-87.

Level of Evidence: B

L-GSH absorption and function in tissue



Removal of Co-60 from the liver of rats infused with Co-60. Oral lipsomal GSH has 75% of the function of IV GSH. IV GSH removed 64%. Liposomal GSH given orally removed 47% and plain glutathione given orally removed 0%.

Levitskaia TG, et al. Aminothiol receptors for decorporation of intravenously administered (60)Co in the rat. Health Phys. 2010;98(1):53-60.

Level of Evidence: B
FT Guilford 2016

Cell Studies Document Absorption

- 1,000 times more efficient in replenishing GSH (and supporting immune function) than NAC
- In human cells with depleted GSH

- Because of this observation, ReadiSorb Glutathione was then used in a Human Randomized Clinical Trial (Ly 2015)

Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione Supplementation Improves Macrophage Functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. PMID: 23409922

Clinical Study documents human repletion of GSH

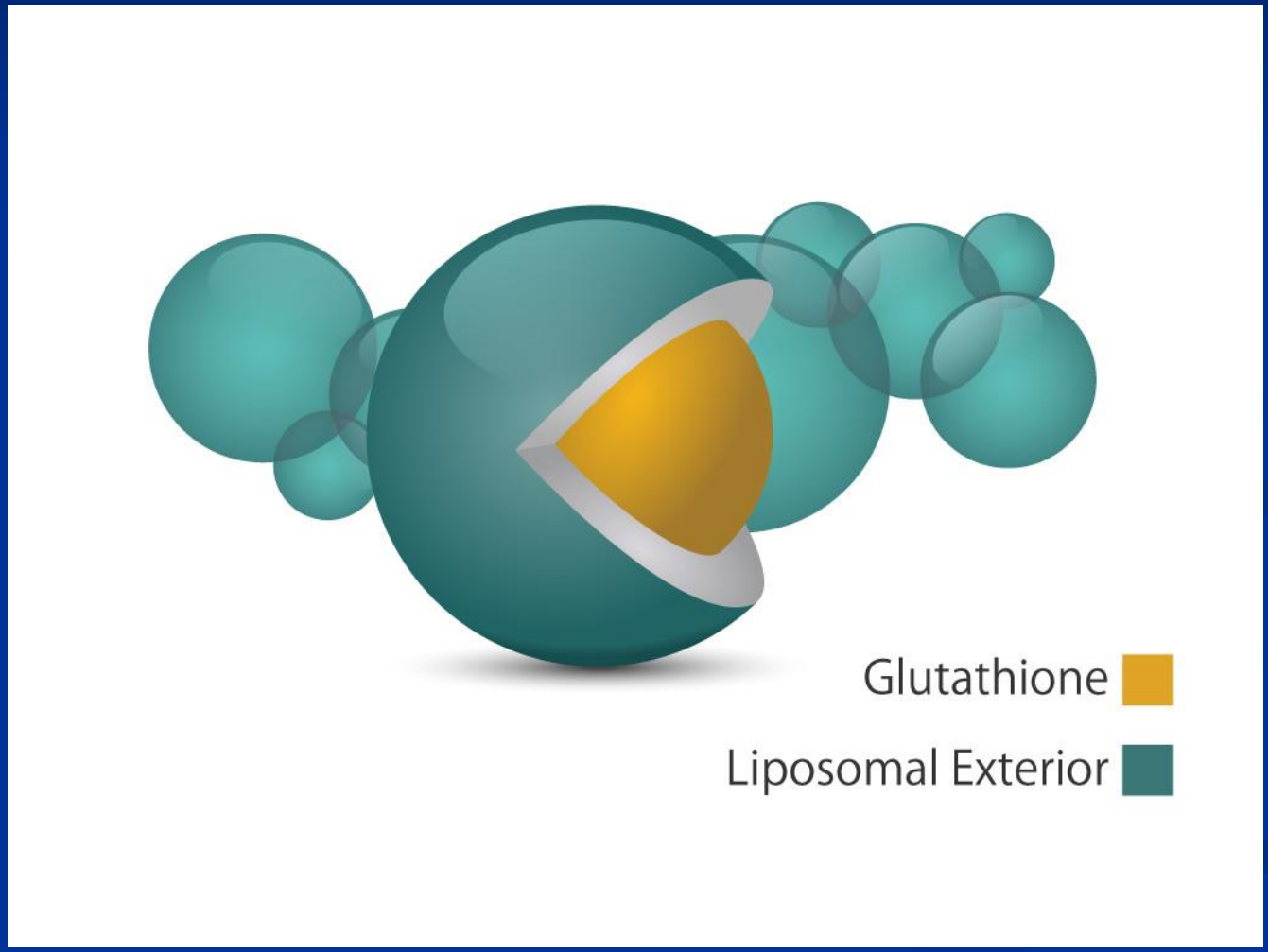
- Liposomal Glutathione Supplementation Restores TH1 Cytokine Response to Mycobacterium tuberculosis Infection in HIV-Infected Individuals.

- Ly J, Lagman M, Saing T, Singh MK, Tudela EV, Morris D, Anderson J, Daliva J, Ochoa C, Patel N, Pearce D, Venketaraman V.

- J Interferon Cytokine Res. 2015 Nov;35(11):875-87.
  doi: 10.1089/jir.2014.0210. PMID: 26133750
  http://www.ncbi.nlm.nih.gov/pubmed/26133750

Level of Evidence: A

ReadiSorb.com – References for the complete list of studies



Level of Evidence: A

2016 International Summit on Mycotoxin Treatments

Frederick T. Guilford, M.D.
Clinical physician and
Science Officer for
Your Energy Systems, LLC
DrGuilford.com/publications or research

Email: Drg@readisorb.com
Office Phone: 650-323-3238

Rationale for the use of liposomal glutathione in the management of mycotoxin- related conditions.

“Biologic Agents”

- Biological agents are those that depend for their effects on multiplication within the target organism while “toxins are poisonous products of organisms.”
- Unlike biological agents, “toxins are inanimate and not capable of reproducing themselves.”

World Health Organization in a 1970 report discussed in Bennett JW, Toxins (Basel). 2015 Sep 22;7(9):3785-804. Review. PMID: 26402705

Level of Evidence: A

“poisoning by natural means”

- In contrast to mycoses, mycotoxicoses are examples of “poisoning by natural means” and thus are analogous to the pathologies caused by exposure to pesticides or heavy metal residues.
- mycotoxin poisoning can be compounded by factors such as vitamin deficiency, caloric deprivation, alcohol abuse, and infectious disease status. In turn, mycotoxicoses can heighten vulnerability to microbial diseases, worsen the effects of malnutrition, and interact synergistically with other toxins.

Bennett JW, Klich M. Mycotoxins. Clinical Microbiology Reviews. 2003;16(3):497-516. PMCID: 164220. http://www.ncbi.nlm.nih.gov/pubmed/12857779

Level of Evidence: B

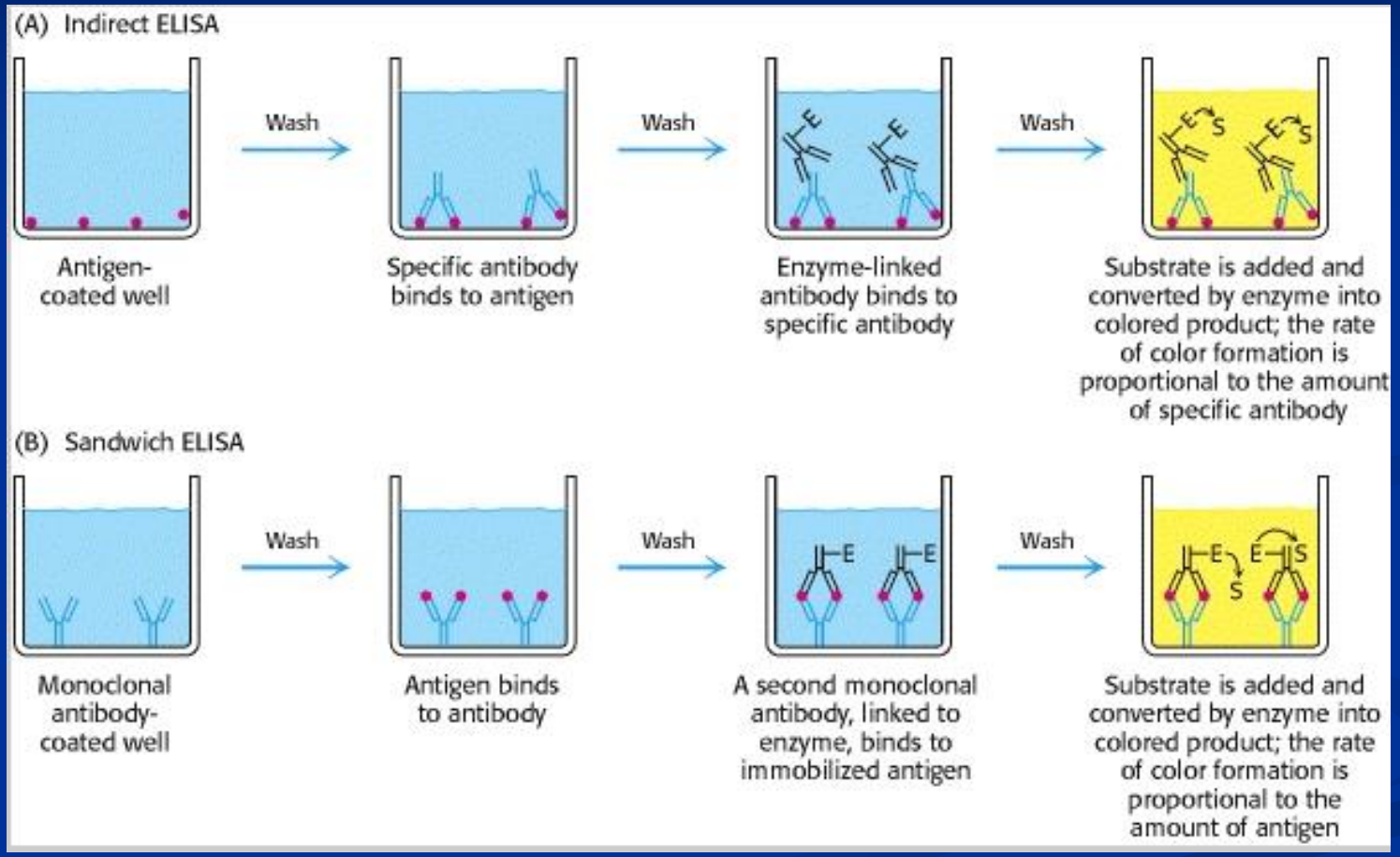
Hooper

- **Mycotoxin detection in human samples from patients exposed to environmental molds.**
- Hooper DG, Bolton VE, Guilford FT, Straus DC.
- Int J Mol Sci. 2009 Apr 1;10(4):1465-75
- PMID: 19468319

- RealTime Lab (Realtimelab.com) (972) 492-0419

Level of Evidence: A

Sandwhich Assay



Level of Evidence: A

Brewer

- Detection of **mycotoxins** in patients with chronic fatigue syndrome.
- Brewer JH, Thrasher JD, Straus DC, Madison RA, Hooper D.
- Toxins (Basel). 2013 Apr 11;5(4):605-17. doi: 10.3390/toxins5040605.
- PMID: 23580077

Level of Evidence: A

- 112 pts with Chronic Fatigue syndrome (CFS)
- Duration 2 – 36 years
- Severity: 68% of the patients were either unable to work, receiving disability or unable to attend school.
- History of mold allergy and/or chronic sinusitis in 48%
- 90% of the 112 patients confirmed exposure to a WDB and frequently the presence of a moldy environments in the home, workplace or both.

Level of Evidence: A

Brewer Paper

- Urine was tested for aflatoxins (AT), ochratoxin A (OTA) and macrocyclic trichothecenes (MT) using Enzyme Linked Immunosorbent Assays (ELISA)
- **Urine specimens from 104 of 112 patients (93%) were positive for at least one mycotoxin**
- Exposure histories indicated current and/or past exposure to WDB in over 90% of cases.
- Environmental testing in a subset of these patients confirmed mold and mycotoxin exposure.

Level of Evidence: A

- Common symptoms in this patient population included fatigue, headache, flu-like symptoms, cognitive complaints, myalgia, arthralgia, gastrointestinal problems and various neurologic symptoms. Other previous diagnoses included fibromyalgia, Lyme disease, peripheral neuropathy, orthostatic intolerance (including postural orthostatic tachycardia syndrome and neural-mediated hypotension), migraine, chronic dermatitis, gastroparesis, chronic abdominal pain, irritable bowel syndrome, interstitial cystitis, anxiety, depression, chemical sensitivity, vertigo, chronic sinusitis, gluten intolerance, tremor, myoclonus and cognitive dysfunction.

Level of Evidence: A

Brewer Paper

- OTA was the most common mycotoxin detected in 83% of subjects followed by
- MT (44%) and
- AT (13%).

- At that time Gliotoxin testing was not available

Level of Evidence: A

Guilford

- Deficient Glutathione in the Pathophysiology of Mycotoxin-Related Illness
- F. T. Guilford and Janette Hope
- Toxins 2014, 6, 608-623
- PMID: 24517907

Level of Evidence: B

Mycotoxins Deplete GSH

- oxidative stress associated with mycotoxins
- direct suppression of GCLC gene function,
- post-translational modification of Nrf2
- excess TGF-β
- Decreased function of the enzymes of glutathione production results in a microenvironment depleted of glutathione on a chronic basis.

Level of Evidence: B

Deficient Glutathione in the Pathophysiology of Mycotoxin-Related Illness F. T. Guilford and Janette Hope
Toxins 2014, 6, 608-623 PMID: 24517907

Mycotoxins

- **mycotoxicoses can heighten vulnerability to microbial diseases**

Are Some Fungal Volatile Organic Compounds (VOCs) Mycotoxins?
Bennett JW, Inamdar AA.
Toxins (Basel). 2015 Sep 22;7(9):3785-804. Review. PMID: 26402705

Overview

- Intro to GSH and mycotoxins
- Is Candida albicans an example of mycosis and possible mycotoxin
- GSH origins in normal cells (Nrf2)
- Mycotoxins and allergies
- Liposomal glutathione advantages

Level of Evidence: B

Mycotoxins and Human Disease: a largely ignored (unknown) global health issue

- Toxins from molds
- Aspergillus → Aflatoxin (AFB1),
- Ochractoxin (OTA)
- Gliotoxin (Gt)
- Penicillium → OTA & Gt
- Stachybotris → Trichothecene

Mycotoxins and human disease: a largely ignored global health issue

Christopher P. Wild, Yun Yun Gong

Carcinogenesis. 2010 January; 31(1): 71–82. PMCID: PMC2802673

Level of Evidence: B

OxStress a Common Pathway of Mycotoxin Toxicity

- Mycotoxins exert their toxicities with different mechanisms. For example, aflatoxins intercalate with DNA, fumonisin is an inhibitor of sphingolipid biosynthesis, and trichothecenes interfere with protein synthesis PMID: 26402705
- We are discussing a common pathway of toxicity from mycotoxins: Oxidative Stress and glutathione depletion. PMID: 24517907

Level of Evidence: B

Are Some Fungal Volatile Organic Compounds (VOCs) Mycotoxins? Bennett JW, Toxins (Basel). 2015 Sep 22;7(9):3785-804. PMID: 26402705

Oxidative Stress (OxStress)

- OxStress occurs when the production of ROS exceeds the body's natural antioxidant defense mechanisms, causing damage to macromolecules such as DNA, proteins, and lipids.
- Measurements of oxStress generally refer to the level of reduced glutathione (GSH) vs. oxidized glutathione (GSSG).
- GSH can inhibit peroxidation, scavenge free radicals, protect cell membranes

Glutathione homeostasis and functions: potential targets for medical interventions. Lushchak VI. J Amino Acids. 2012;2012:736837. PMID: 22500213

Level of Evidence: B

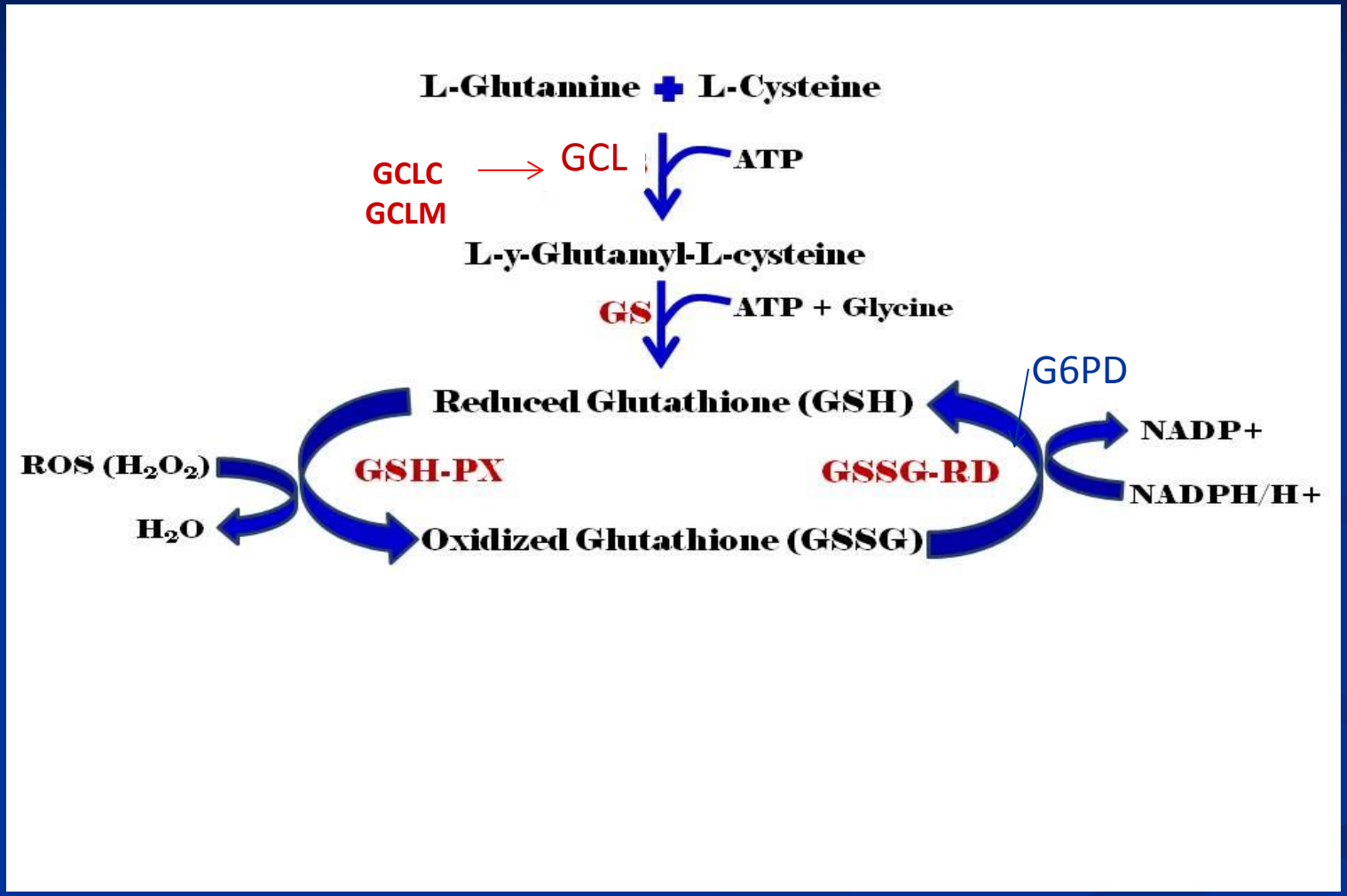
Mycotoxins and OxStress

- Ochratoxin ↓ GCLC
- Alfatoxin - PMID 6818882 “intact GSH molecule needed for therapy”
- Trichothcene - PMID 18520041, 22245378: ↓GSH
- Gliotoxin - PMID: 17161924 decreased epithelial GSH and ↑ TGFβ1 levels + ↑ IL-6 and IL-8
- Cause problems by increasing oxidative stress and decreasing GSH

Guilford FT, Hope J. Deficient glutathione in the pathophysiology of mycotoxin-related illness. Toxins (Basel). 2014;6(2):608-23. http://www.ncbi.nlm.nih.gov/pubmed/24517907

Level of Evidence: B

Glutathione Formation and Recycling



Level of Evidence: A

Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione Supplementation Improves Macrophage Functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. PMID: 23409922

Mycotoxin Pathology

- increase oxidative stress and deplete glutathione
- **Cytotoxicity and ROS generation**

are mechanisms of mycotoxins mediated toxicity.

Omar, Chapter 3 "Mycotoxins-Induced Oxidative Stress and Disease"

open access 2013 http://www.intechopen.com/books/mycotoxin-and-food-safety-in-developing-countries/mycotoxins-induced-oxidative-stress-and-disease

Guilford FT, Hope J. Deficient glutathione in the pathophysiology of mycotoxin-related illness. Toxins (Basel). 2014;6(2):608-23. http://www.ncbi.nlm.nih.gov/pubmed/24517907

Level of Evidence: B

Mold producing toxins found in wall board!

- Gypsum wallboard is a popular building material, but is also very frequently overgrown by Stachybotrys chartarum after severe and/or undetected water damage.
- Aspergillus was the most dominant fungus on the gypsum wallboard followed by Chaetomium globosum (chaetoglobosins) and Stachybotrys chartarum (trichothecene) PMID: 16238166)

Pre-contamination of new gypsum wallboard with potentially harmful fungal species.
Andersen B, Dosen I, Lewinska AM, Nielsen KF.
Indoor Air. 2016 Mar 11.. PMID: 26970063

Level of Evidence: A

GSH & Trichothecenes

- "GSH has been shown to decrease the oxidative stress induced by many toxins including trichothecenes".
- "GSH attenuated satratoxin H-induced generation of ROS and lipid peroxidates".

Satratoxin H generates reactive oxygen species and lipid peroxides in PC12 cells. Nusuetrong P, et al, Yoshida M. Biol Pharm Bull. 2008 Jun;31(6):1115-20. PMID: 18520041 Free Article

Level of Evidence: B

GST, A "Matchmaker" Enzyme Introduces Toxins to GSH

- mu, pi, theta, alpha, sigma, omega and zeta
- GSTM, P, T, etc. - functional polymorphisms known as SNP's
- SNP's Single nucleotide polymorphisms contribute to inter-individual differences in response to xenobiotics and clearance of oxidative stress products and, therefore, may determine susceptibility to various inflammatory pathologies including cancer, and cardiovascular and respiratory diseases .

Level of Evidence: A

Glutathione transferases. Hayes JD, Flanagan JU, Jowsey IR. Annu Rev Pharmacol Toxicol. 2005;45:51-88. Review. PMID: 15822171

Binding of mycotoxin - GST

- Binding to GSH Spontaneously catalyzed by Glutathione S-tranferases (GST)
- GST M binds mycotoxin (1)
- GSTM1 missing in up to 40% of population (2)

1. GST-M1 is transcribed moreso than AKR7A2 in AFB_1-exposed human monocytes and lymphocytes. Bahari A, et al, Dehghani H. J Immunotoxicol. 2015 Apr-Jun;12(2):194-8. PMID: 25027672

2. Identification of the GST-T1 and GST-M1 null genotypes using high resolution melting analysis. Drobná Z et al, Stýblo M. Chem Res Toxicol. 2012 Jan 13;25(1):216-24. PMID: 22136492

Level of Evidence: B

GST, The Matchmaker facilitates removal of metals and mycotoxin

- AFB1 Inactivated and excreted by GSH
- Reaction catalyzed by GSH S-Transferase to form

J Dairy Science 1993;76(3):880-90
& The Significance of Glutathione Conjugation in Aflatoxin Metabolism 2013 Ziglari T & Allameh A in Aflatoxins – In Recent Advances and Future Prospects http://cdn.intechopen.com/pdfs-wm/41614.pdf

Level of Evidence: B

Metals deplete GSH

- redox active metals like iron (Fe), copper (Cu), chromium (Cr), cobalt (Co) mercury (Hg) and other metals undergo redox cycling reactions → reactive radicals such as superoxide • O_2^-, and peroxynitrite •$ONOO^-$, H_2O_2, •OH
- cadmium (Cd), arsenic (As) and lead (Pb) show their toxic effects via bonding to sulphydryl groups of proteins and depletion of glutathione.

Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. Toxicology. 2011;283(2-3):65-87.

Pb and Allergies

- Environmental exposure to Pb has been reported to promote IgE production in children and to be an influence on asthma incidence (Lutz *et al.*, 1999b), which has been suggested to be related to Pb-enhancement of Th2 responses (Lawrence and McCabe, 2002).
- A statistically significant relationship of IgE and blood lead level was found in this population; as blood lead (PbB) level increases, IgE level increases. (Lutz *et al.*, 1999b)

Lead effects on development and function of bone marrow-derived dendritic cells promote Th2 immune responses.
Gao D, Mondal TK, Lawrence DA. Toxicol Appl Pharmacol. 2007 Jul 1;222(1):69-79. PMID: 17512567

LOE: B

As, Cd, Ni, and Pb elevated in HIV+ vs. Control

- Significantly higher levels of As, Cd, Ni, and Pb in the biological samples (scalp hair, blood, and urine) of male HIV-1 patients, compared with control subjects
- The high levels of these toxic elements may be predictors for secondary infections in HIV-1 patients

Evaluation of arsenic, cadmium, lead, nickel, and zinc in biological samples (scalp hair, blood, and urine) of tuberculosis and diarrhea male human immunodeficiency virus patients.
Afridi HI, et al Clin Lab. 2011;57(11-12):867-78. PMID: 22239016

LOE: B

Metal Chelation to improve oxidative stress - Cadmium

- EDTA + GSH IV removes cadmium more efficiently than EDTA alone
- 500 mg of Ca-EDTA and 50 mg/kg of glutathione alone or in 1 L of normal saline 24 hours and repeated over 12 consecutive days.
- blood Cd level
- EDTA Alone: 4.6 mcg/L
- → EDTA + GSH 7.4 mcg/L, $p < 0.01$
- Renal Cd excretion: basal 23.4 +/- 15.81 mcg/g creatinine → 89.23 $p < 0.01$) mcg/g cr.
- No sign of renal toxicity

Effect of glutathione on the cadmium chelation of EDTA in a patient with cadmium intoxication. Gil HW, et al Hum Exp Toxicol. 2010 Apr 22. PMID: 20413561

LOE: A

Gliotoxin

- Gliotoxin produced by Asp and Pen
- Candida albicans PMCID: 1784797, PMID: 20431851, 16893972

Clinical isolates of yeast produce a gliotoxin-like substance Yes: Shah, Larsen 1991 PMID: 1724551

No: Kupfahl el al 2007 PMID: 17537180

- Increased ROS appear to mediate cyto-toxicity

Gliotoxin-induced cytotoxicity proceeds via apoptosis and is mediated by caspases and reactive oxygen species in LLC-PK1 cells. Zhou X, Zhao A, Goping G, Hirszel P. Toxicol Sci. 2000 Mar;54(1):194-202. PMID: 10746946

Level of Evidence: B

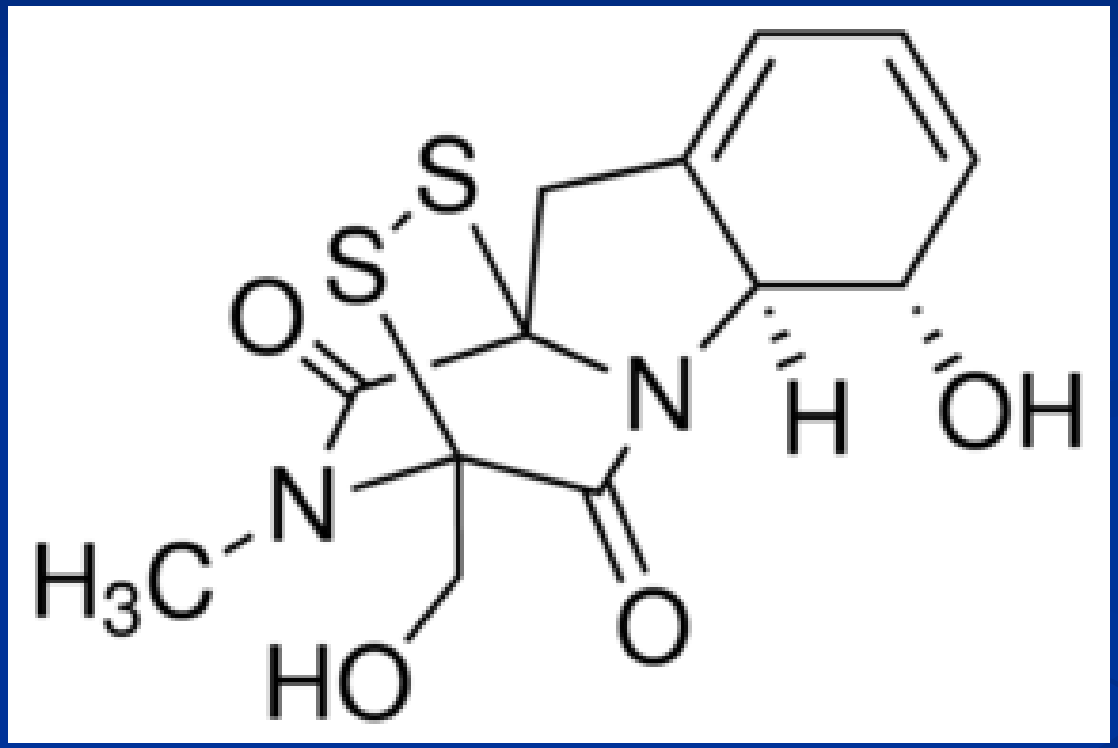
Gliotoxin active in disufide bridge form (oxidized)

- Gliotoxin is an epipolythiodioxopiperazine (ETP) class fungal toxin containing
- a disulfide bridge responsible for the deleterious effects of this toxin - occurs with oxidation PMID 1868908 in 25126990
- Antioxidant and S-methylation significantly depletes the bioactivity of this metabolite 4670497.

Mechanism of action of gliotoxin: elimination of activity by sulfhydryl compounds. Trown PW, Bilello JA. Antimicrob Agents Chemother. 1972 Oct;2(4):261-6. PMID: 4670497

Level of Evidence: B

Gliotoxin disulfide bridge



http://www.sigmaaldrich.com/catalog/product/sigma/g9893?lang=en&region=US

Level of Evidence: B

Gliotoxin neutralized by GSH

- Remarkably, addition of reduced glutathione (GSH; 20 mM) to test plates completely abolished the cytotoxic effects of exogenous Gt
- The gene GliT, a gliotoxin reductase , prevents Aspergillus from gliotoxin self-toxicity - 20593880

Self-protection against gliotoxin--a component of the gliotoxin biosynthetic cluster, GliT, completely protects Aspergillus fumigatus against exogenous gliotoxin.
Schrettl Met al, Doyle S.
PLoS Pathog. 2010 Jun 10;6(6):e1000952. PMID: 20548963
http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1000952

Level of Evidence: B

Gliotoxin Suppresses Macrophage Immune Function

- by Subverting Phosphatidylinositol 3,4,5-Trisphosphate Homeostasis.
- In healthy humans, alveolar macrophages can ingest and eliminate fungal spores, thus limiting their germination into mycotoxin-producing hyphae.

Schlam D[1], et a; , Fairn GD[4].
Gliotoxin Suppresses Macrophage Immune Function by Subverting Phosphatidylinositol 3,4,5-Trisphosphate Homeostasis.
MBio. 2016 Apr 5;7(2):e02242.

Level of Evidence: B

- in response to Gt toxin, macrophages cease to ruffle, undergo abrupt membrane retraction, and fail to phagocytose large targets effectively.

Schlam D[1], et a; , Fairn GD[4].
Gliotoxin Suppresses Macrophage Immune Function by Subverting Phosphatidylinositol 3,4,5-Trisphosphate Homeostasis.
MBio. 2016 Apr 5;7(2):e02242.

Level of Evidence: B

Candida albicans - Gliotoxin

- 2010 Article:
- "Candida albicans is known to produce gliotoxin, which has several prominent biological effects, including immunosuppression"

Shah DT, et al, Larsen B. Effect of gliotoxin on human polymorphonuclear neutrophils. Infect Dis Obstet Gynecol. 1998;6(4):168-75. PMCID: 1784797.
http://www.ncbi.nlm.nih.gov/pubmed/9812249

Candida albicans and its metabolite gliotoxin inhibit platelet function via interaction with thiols.
Bertling A, et al , Kehrel BE.
Thromb Haemost. 2010 Aug;104(2):270-8.
PMID: 20431851

Level of Evidence: B

Journal of Advancement in Medicine
Volume 1, Number 1, Spring 1988

Human Serum Immunoglobulin G,A,M Levels in Low Grade Chronic Candidiasis

James R. Bunting, PhD, George DerBalian, PhD, F. Timothy Guilford, MD, Joanne Riccomini, BS

ABSTRACT: Amounts of Candida albicans specific human antibodies of classes IgG, IgM, and IgA were correlated with responsiveness to therapy for presumptive chronic low grade candidiasis (LGCC). 59 patients with apparent clinical manifestations of LGCC were given treatment of diet and oral antifungiside. 41 responded positively while 18 showed no response. Scores for specific antibody in the responders as determined by enzyme linked immunosorbant assay, was 21.2 ± 11.6, 61.9 ± 55.2, and 37.9 ± 38.7 ug/mL for IgG, IgM, and IgA, respectively. For the nonresponders the levels were 2.5 ± 2.0, 32.8 ± 40.5 and 8.3 ± 8.2 for IgG, IgM and IgA, respectively. The differences are statistically significant suggesting a use for candida specific antibody measurements as a diagnostic aid.

Introduction

Bunting J, DerBalian G, Guilford F, Riccomini J. Human Serun Immunoglobulin G, A, M levels in Low Grade Chronic Candidiasis. Journal of Advancement in Medicine. 1988;1(1):12-30.

Level of Evidence: A

Antibody Response to Strep Vaccination

- As a measure of immune dysfunction - defined as a 4-fold or greater increase over baseline (ratio of post-immunization titer to preimmunization titer) or a post-immunization titer value of 1.3 µg/mL or greater.[1]

Hare ND, Smith BJ, Ballas ZK. Antibody response to pneumococcal vaccination as a function of preimmunization titer. J Allergy Clin Immunol. 2009;123(1):195-200. PMCID: 3613280.

Level of Evidence: A

TABLE 3

Summary of candida specific immunoglobulin levels correlated with effectiveness of therapy

Nystatin

THERAPEUTIC OUTCOME		ORIGINAL IMMUNOGLOBULIN LEVELS (ug/ml) IgG	IgM	IgA
IMPROVED	N = 41	21.2 ± 11.6	61.9 ± 55.2	37.9 ± 38.7
NOT IMPROVED	N = 18	2.5 ± 2.0	32.8 ± 40.5	8.3 ± 8.2
STATISTICAL* SIGNIFICANCE		P < 0.01	P < 0.05	P < 0.01

*As determined by Students t analysis, see text.

Level of Evidence: A

Bunting J, DerBalian G, Guilford F, Riccomini J. Human Serum Immunoglobulin G, A, M levels in Low Grade Chronic Candidiasis. Journal of Advancedment in Medicine. 1988;1(1):12-30.

Symptoms of Early Response

TABLE 4

Summary of candida specific immunoglobulin levels correlated with symptoms of early response to therapy

SYMPTOMS		ORIGINAL IMMUNOGLOBULIN LEVELS IgG	IgM (ug/ml)	IgA
ADVERSE	N = 18	26.6 ± 9.9	60.1 ± 59.0	54.3 ± 50.2
NOT ADVERSE	N = 18	18.0 ± 11.3	69.0 ± 53.0	31.7 ± 4.7
STATISTICAL* SIGNIFICANCE		P<0.02	NONE	NONE

*As determined by student's t analysis, see text.

Bunting J, DerBalian G, Guilford F, Riccomini J. Human Serun Immunoglobulin G, A, M levels in Low Grade Chronic Candidiasis. Journal of Advancedment in Medicine. 1988;1(1):12-30.

Level of Evidence: A

TABLE 5

Change in immunoblobulin levels upon treatment

SAMPLE (N = 15)	MEAN IMMUNOGLOBULIN LEVELS IgG (ug/ml)	IgM (ug/ml)	IgA (ug/ml)
BEFORE TREATMENT	16.9 ± 9.2	92.6 ± 128.5	43.4 ± 32.8
AFTER TREATMENT	8.8 ± 5.6	30.5 ± 32.3	15.3 ± 19.8
STATISTICAL* SIGNIFICANCE	P <0.005	P <0.05	P <0.01
AVERAGE NUMBER OF DAYS BETWEEN SAMPLING = 84 ± 29			

*As determined by student's t analysis, see text.

Bunting J, DerBalian G, Guilford F, Riccomini J. Human Serun Immunoglobulin G, A, M levels in Low Grade Chronic Candidiasis. Journal of Advancedment in Medicine. 1988;1(1):12-30.

Level of Evidence: A

Case example

- 19 y.o. woman dropped out of college due to diffuse pain and fatigue. Hx of chronic sinusitis treated with repeated antibiotic.
- IgG candida score class IV/IV.
- Symptoms had defied eval. and treatment by 1^{o} Phys, neurologist, allergist, pulmonologist, ENT, gastroenterologist
- "Herxheimer" reaction after initiating nystatin
- Nystatin related symptoms improved with charcoal ingestion

Level of Evidence: A

- After adding intranasal itraconazole 1/2%%
- Sx's significantly improved.

Level of Evidence: A

Gliotoxin down regulates Vit D receptor in CF patients

- Secreted by the hyphal form of A. Fumigatus, gliotoxin (Gt) is the causative agent in VDR down regulation.
- VDR gene expression was significantly down-regulated by approximately 80% in CF tracheal epithelial (CFTE) cells($P<0.001$) treated with Gt
- In CF, Gliotoxin Enhances the Production of Th2 Cytokines, which Are Decreased after Itraconazole Treatment

The effect of Aspergillus fumigatus infection on vitamin D receptor expression in cystic fibrosis.
Coughlan CA, et al, McElvaney NG.
Am J Respir Crit Care Med. 2012 Nov 15;186(10):999-1007.
PMID: 22904183

Level of Evidence: A

Allergic Bronchopumonary Aspergillosis

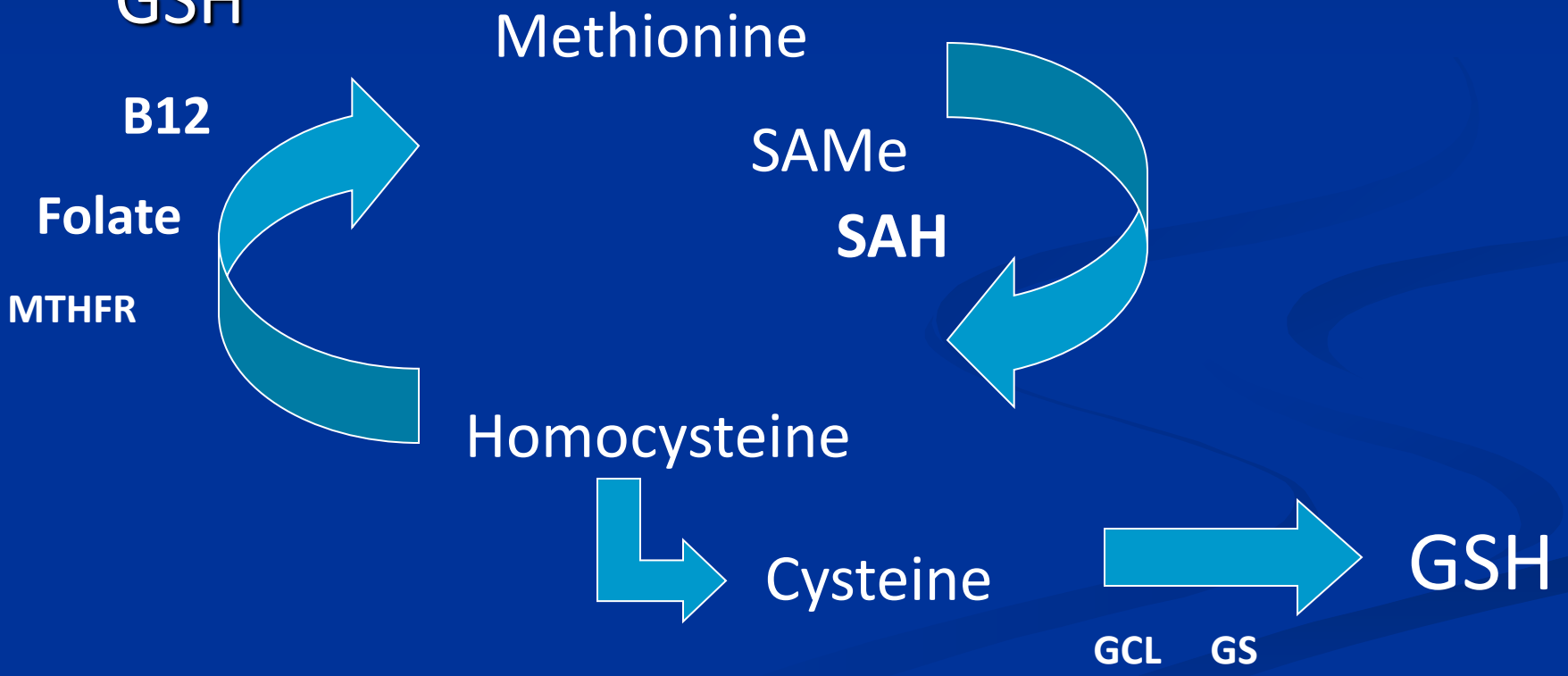
- Potential for Vit D in ABPA PMID: 22904183
  - Decreases TH2 in CF 27011794
  - Merck Manual Rx approach: pred, itraconazole
- My experience using intradermal Skin test, Sublingual immunotherapy (SLIT), adequate Vit D &
- mycotoxin treatment for Aspergillus including
- liposomal glutathione
- May be able to avoid Steroids & systemic itraconazole with this approach

Merck manual on Allergic Bronchopulmonary Aspergilloisis Aspergillosishttp://www.merckmanuals.com/professional/pulmonary-disorders/asthma-and-related-disorders/allergic-bronchopulmonary-aspergillosis-(abpa)

Level of Evidence: A

Methionine cycle
Source of Cysteine for GSH

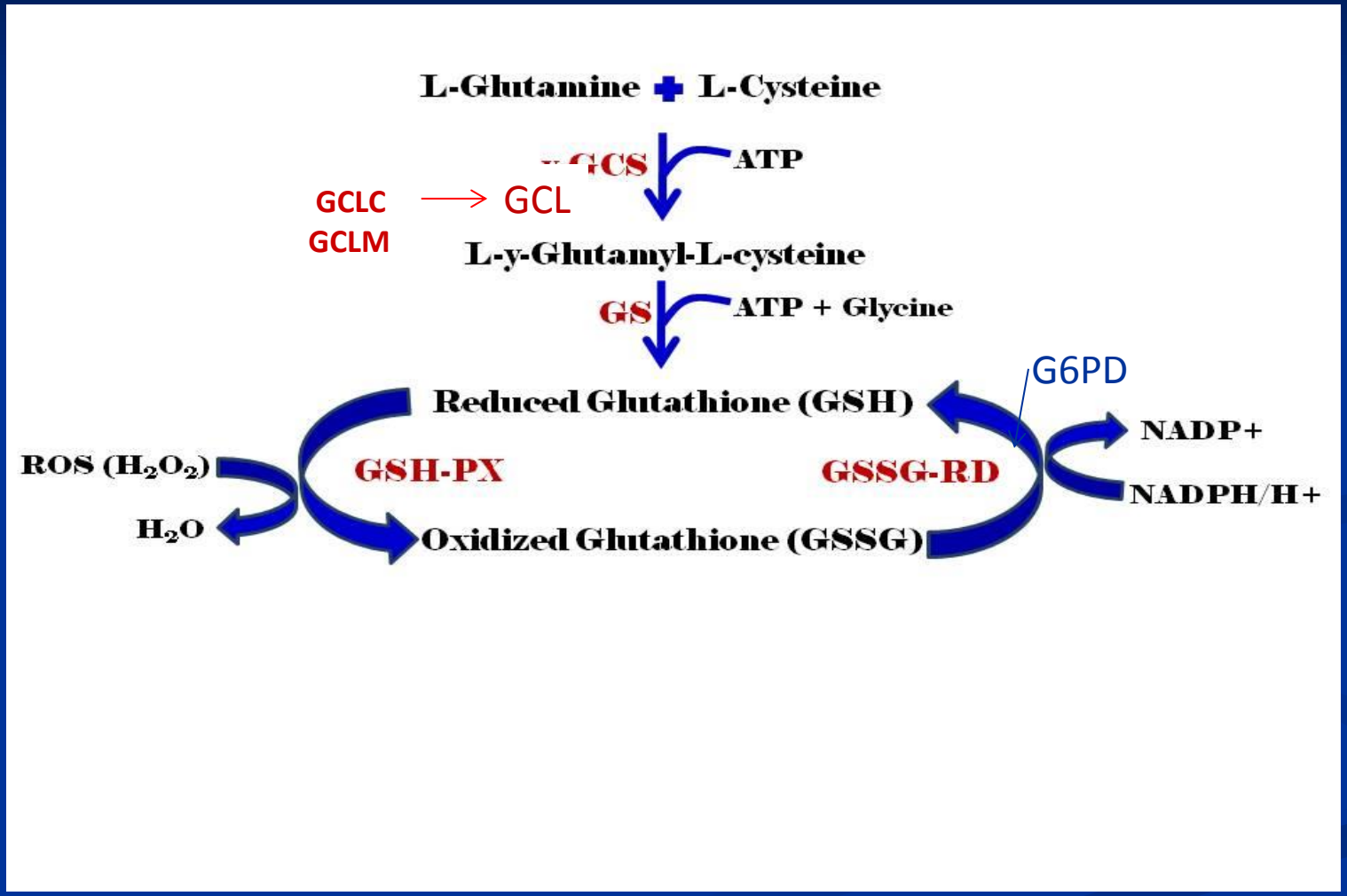
Methylation cycle produces cysteine to build GSH



James SJ, et al. Am J Clin Nutr. 2004 2004;80(6):1611-7. 40/90

Level of Evidence: A

Glutathione Formation and Recycling



Level of Evidence: A

Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione Supplementation Improves Macrophage Functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. PMID: 23409922

4 Million •OH radicals formed per cell per day

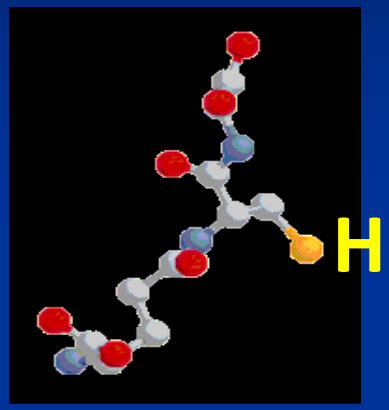
- It is estimated that we produce around 50 hydroxyl radicals in each cell every second
- Or
- 4 million OH radicals per day in each cell

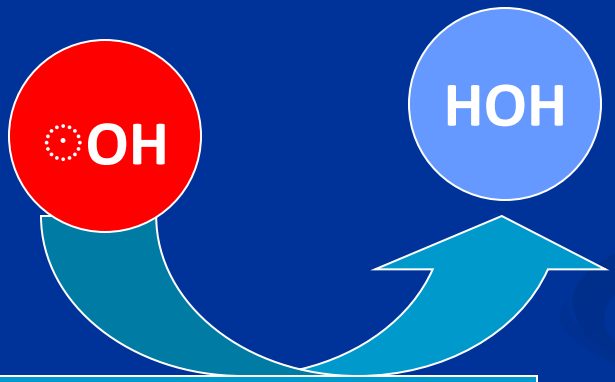
Stohs SJ, Bagchi D. Oxidative mechanisms in the toxicity of metal ions. Free Radic Biol Med. 1995;18(2):321-36.

Lane N. Oxygen—the Molecule that made the World. Oxford: Oxford: Oxford University Press; 2002, pg 124

Level of Evidence: A

Glutathione the key player in removing free radicals in human cells





GSH Peroxidase

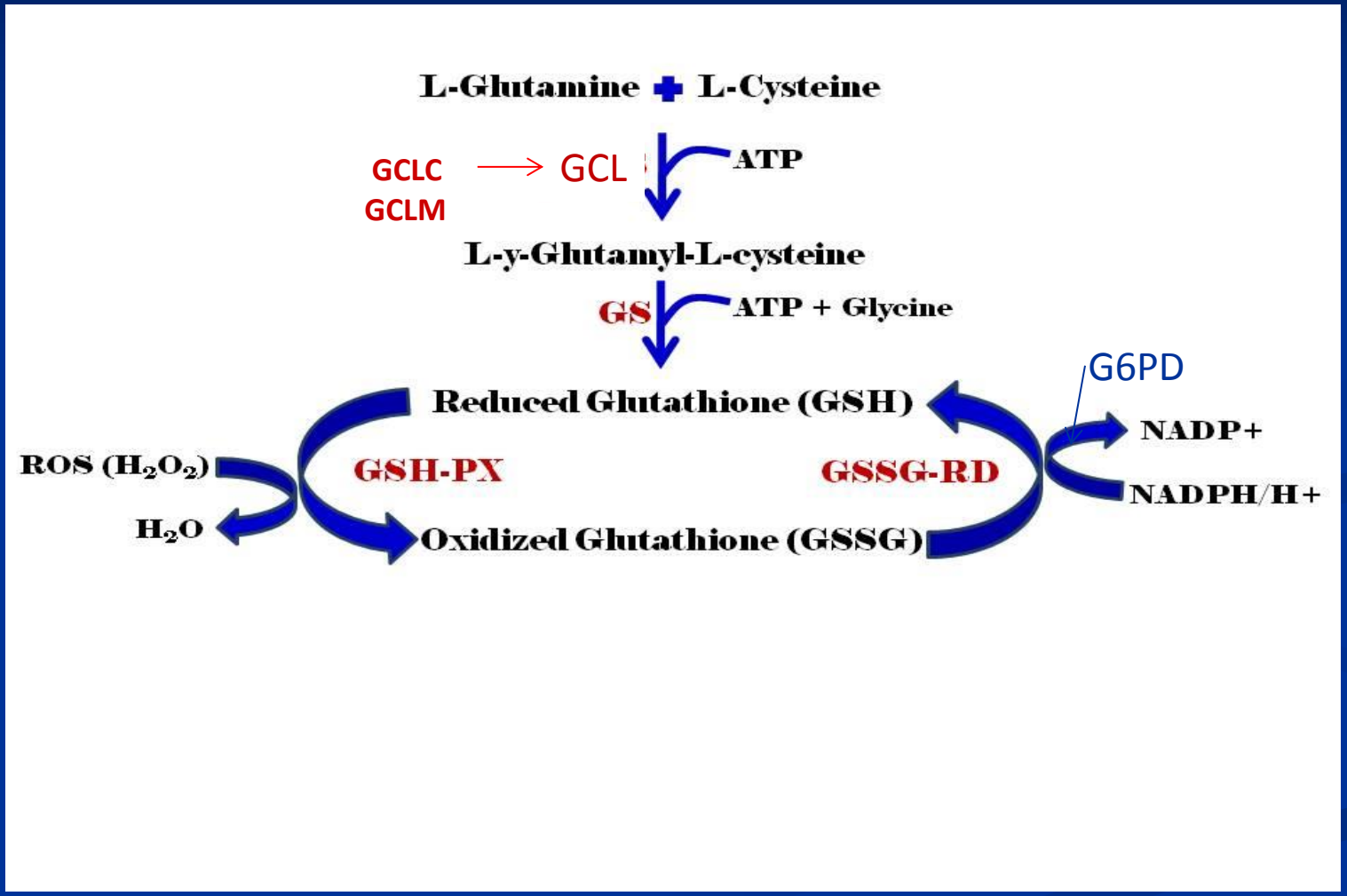
GSH → GSSG

GPx 1-4
GPx1 in Mt
GPx3 for membranes

Level of Evidence: A

Wu D, Cederbaum AI. Alcohol, oxidative stress, and free radical damage. Alcohol Res Health. 2003;27(4):277-84. http://pubs.niaaa.nih.gov/publications/arh27-4/277-284.pdf

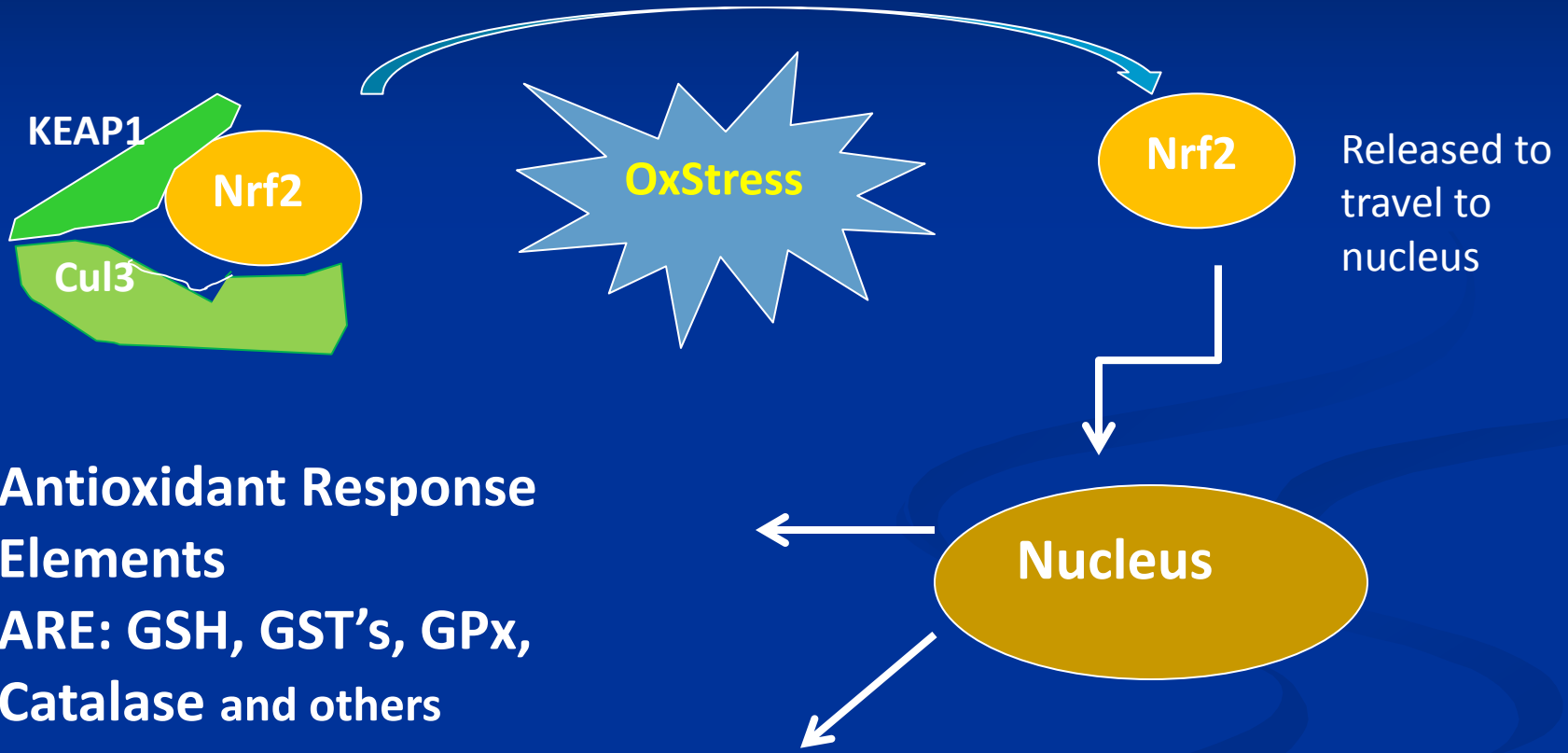
Glutathione Formation and Recycling – subunits control production



Level of Evidence: A

Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione Supplementation Improves Macrophage Functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. PMID: 23409922

Nrf2, the Oxidant 'Thermostat' of the Cell: The 'Oxidant-stat'



Thiol redox disturbances in children with severe asthma are associated with posttranslational modification of Nrf2. Fitzpatrick AM, et al J Allergy Clin Immunol. 2011 Apr 21. PMID: 21514635

Level of Evidence: A

OTA Inhibits NRF2

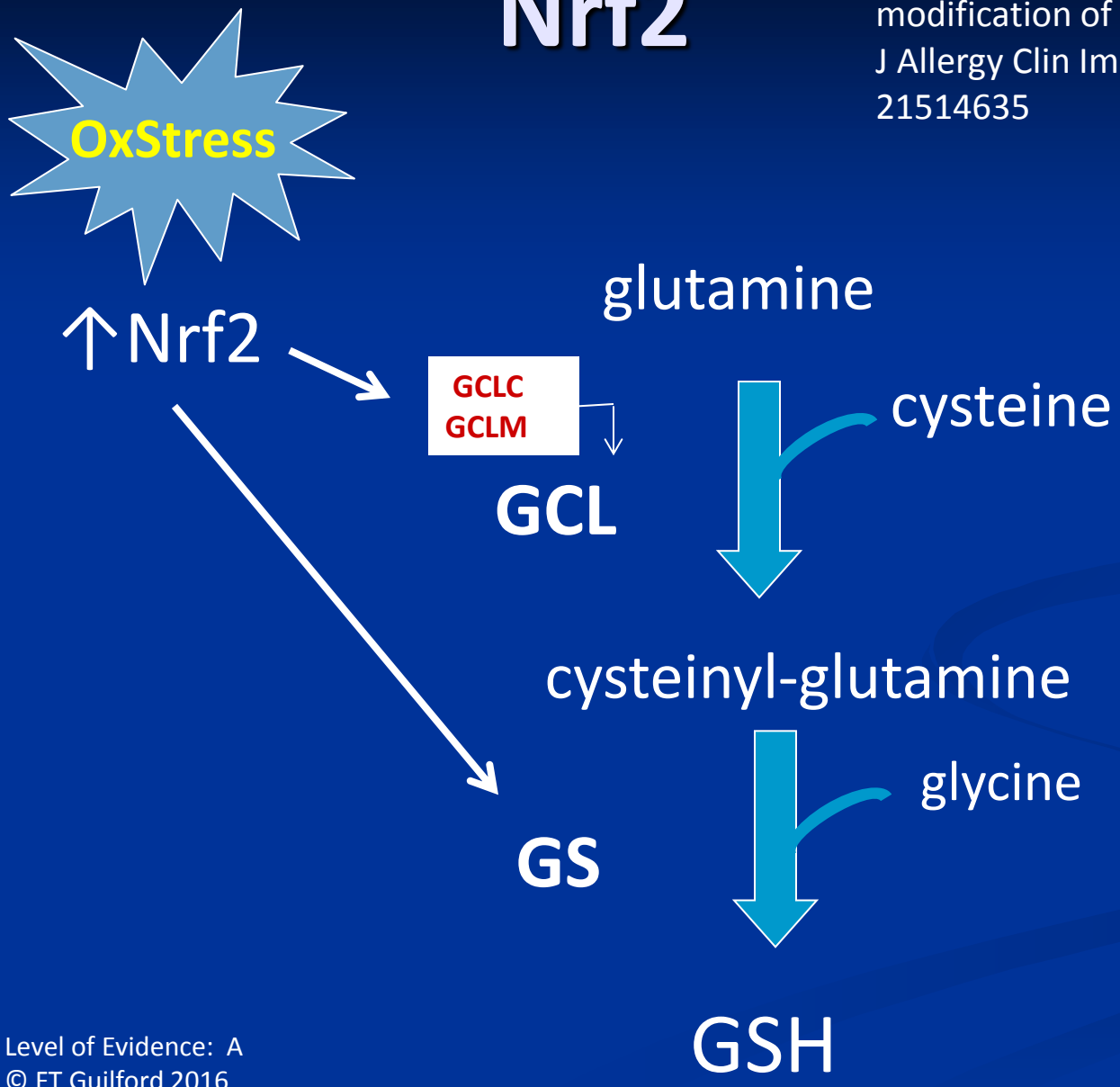
- Several studies have demonstrated that ochratoxin A (OTA) inhibits the nuclear factor, erythroid 2-like 2 (Nrf2) oxidative stress response pathway. At the cellular level (microenvironment) this would attenuate (i) glutathione synthesis; (ii) recycling of oxidized glutathione; (iii) activity of oxidoreductases; and (iv) phase II metabolism inducibility.
- genes affected included GCLC, GCLM, glutathione synthetase (GSS), UGT3B5 and multiple GST isoforms.

Limonciel A, Jennings P. A review of the evidence that ochratoxin A is an Nrf2 inhibitor: implications for nephrotoxicity and renal carcinogenicity. Toxins (Basel). 2014;6(1):371-9. PMCID: 3920267. http://www.ncbi.nlm.nih.gov/pubmed/24448208

Level of Evidence: A

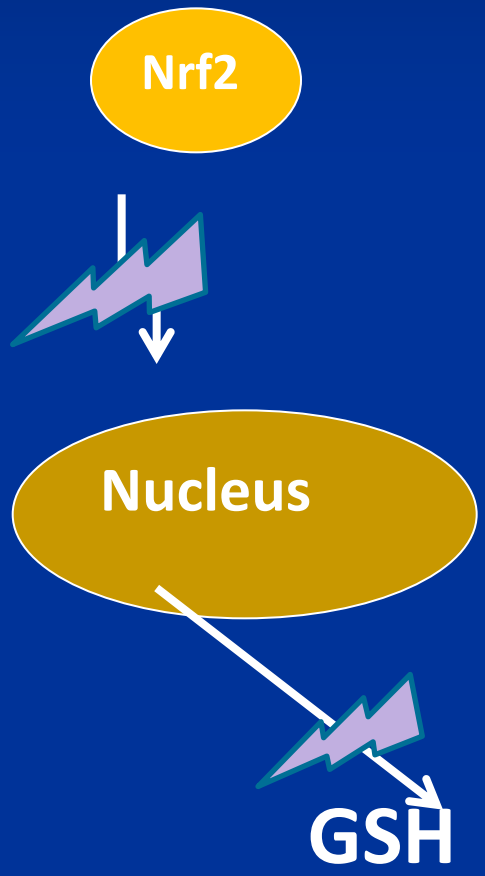
Nrf2

Thiol redox disturbances in children with severe asthma are associated with posttranslational modification of Nrf2. Fitzpatrick AM, et al J Allergy Clin Immunol. 2011 Apr 21. PMID: 21514635

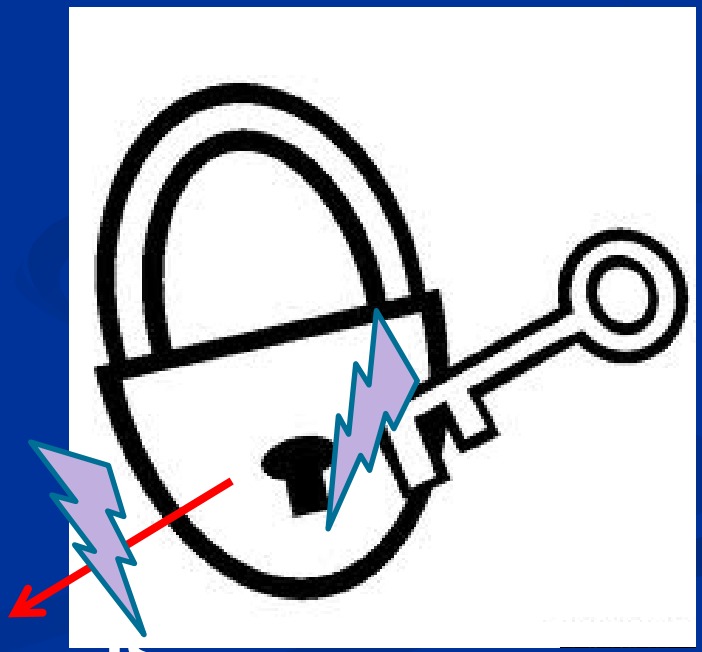


Level of Evidence: A

Nrf2 Function Blocked by Severe Oxidant Stress

- 

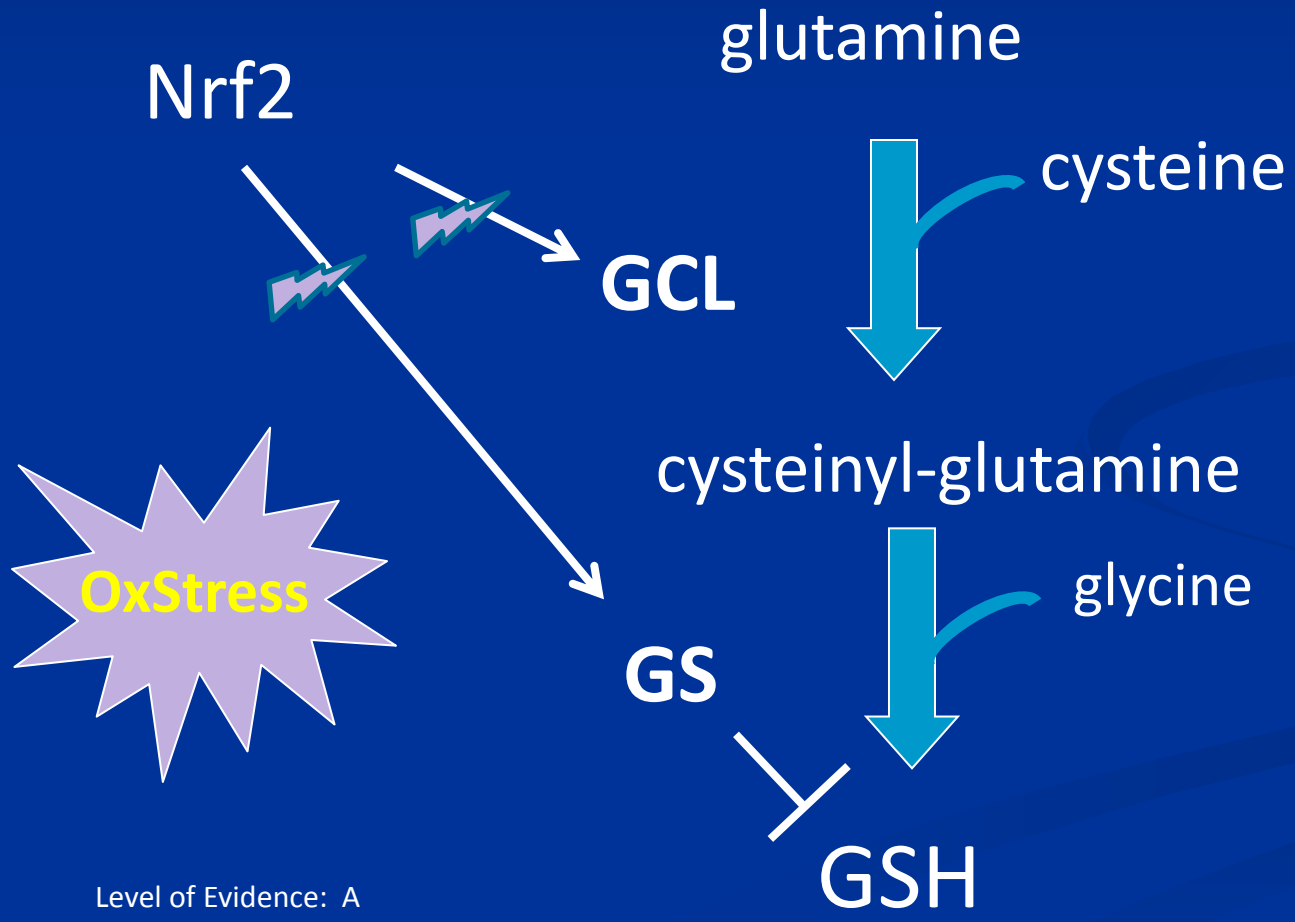
- The Nrf2 “key” no longer fits in the “lock” of the Nucleus



Is not produced

Level of Evidence: A

Nrf2 Subject to post translational modification – doesn't "turn on" nuclear response



Level of Evidence: A

Fitzpatrick 2011 PMID: 21514635

Nrf2

- Post translational modification has been reported in
- severe asthma
- COPD
- Neurodegenerative diseases
- Age related vascular disease in rats & monkey
  PMID: 21602469, 21622983

Thiol redox disturbances in children with severe asthma are associated with posttranslational modification of Nrf2.
Fitzpatrick AM, et al
J Allergy Clin Immunol. 2011 Apr 21. PMID: 21514635

Level of Evidence: A

OTA, induces OxStress (ROS) also blocks response by Nrf2

- OTA-induced inhibition of Nrf2 activation and Nrf2 gene transcription together with OTA-induced Nrf2 protein depletion would
- render the cell defenseless to oxidative stress.

Limonciel A, Jennings P. A review of the evidence that ochratoxin A is an Nrf2 inhibitor: implications for nephrotoxicity and renal carcinogenicity. Toxins (Basel). 2014;6(1):371-9. PMCID: 3920267. http://www.ncbi.nlm.nih.gov/pubmed/24448208

Level of Evidence: A

Nrf2 activates Mrp2

- Mrp2 (multidrug-resistance protein 2) pump mediates the excretion of GSH and GSSG excretion (as part of detoxification) as well as endo- and xeno-biotics that are conjugated with GSH, glucuronate or sulphate

Role of Nrf2 in the regulation of the Mrp2 (ABCC2) gene.
Vollrath V, Wielandt AM, Iruretagoyena M, Chianale J.
Biochem J. 2006 May 1;395(3):599-609. PMID: 16426233

Level of Evidence: A

OTA and Cancer

- “Nrf2 inhibition and subsequent increase in ROS would lead to lipid peroxidation, proteotoxic stress and oxidative DNA damage.
- Other protective pathways would inevitably be activated, such as p53, to prevent the cell replicating by initiating cell cycle blockade and promoting apoptosis. However, over a chronic time course such a situation will create a selective pressure leading to escape from p53 activity and thus promotion of a cancerous phenotype.”

Limonciel A, Jennings P. A review of the evidence that ochratoxin A is an Nrf2 inhibitor: implications for nephrotoxicity and renal carcinogenicity. Toxins (Basel). 2014;6(1):371-9. PMCID: 3920267.

Level of Evidence: A

OTA's inhibition of Nrf2 → Nephrotoxicity and carcinogenicity

- Additionally, Nrf2 inhibition alone may select for cells with somatic mutations in Nrf2 or Keap-1, leading to a constitutive activation of the pathway. A cell without p53 control (of replication) and with a constitutively active Nrf2 system would have a massive survival advantage and would also be very resistant to chemotherapeutics.
- Compelling evidence that OTA's inhibition of Nrf2 is the mechanism for both its nephrotoxicity and carcinogenicity.

Level of Evidence: A

Limonciel A, Jennings P. A review of the evidence that ochratoxin A is an Nrf2 inhibitor: implications for nephrotoxicity and renal carcinogenicity. Toxins (Basel). 2014;6(1):371-9. PMCID: 3920267.

Mycotoxin also have direct effect against GCLC and GST

- Trichothecene and OTA (Ochratoxin A) - ↓ GCL and glutathione-S-transferase (GST) in cell culture

Boesch-Saadatmandi C, Wagner AE, Graeser AC, Hundhausen C, Wolffram S, Rimbach G. Ochratoxin A impairs Nrf2-dependent gene expression in porcine kidney tubulus cells. J Anim Physiol Anim Nutr (Berl). 2009;93(5):547-54.

Level of Evidence: A

Speculation

- Can mycotoxins, which deplete GSH, skew the immune response to TH2 and antibody formation.
- Evidence?

Level of Evidence: A

Mold Extracts & Toxin increase allergic (IgE) response to a 2° Antigen

- Mould extracts increase the allergic response to ovalbumin in mice.
  - Instanes C, et al. Clin Exp Allergy. 2004 Oct;34(10):1634-41.PMID: 15479281

- Exposure to mycotoxins (in airway and GI) increases the allergic immune response in a murine asthma model.
  - Schütze N, et al. J Respir Crit Care Med. 2010 Jun 1;181(11):1188-99. Epub 2010 Mar 1.PMID: 20194814

Level of Evidence: A

Mycotoxin exposure increases allergic asthma to a different antigen

- Inc'd Th2 cytokine levels.
  - Decreased IFN-γ production in T cells.
  - Inhibited IL-12 production in maturing DCs
- Enhanced OVA-induced lung lipid peroxidation
- Acts like an adjuvant to increase response to other ag's – ↑ IgE to OVA
- moderately increased isoprostane levels in naive mice – <u>mycotoxin has a direct oxidative effect</u>

Exposure to mycotoxins increases the allergic immune response in a murine asthma model. Schütze N, et al, Am J Respir Crit Care Med. 2010 Jun 1;181(11):1188-99. PMID: 20194814

Level of Evidence: A

Mycotoxin DON and allergy to whey in mice

- Together, these results demonstrate that DON facilitates allergic sensitization to food proteins and that development of sensitization can be induced by different molecular mechanisms and local immune responses.

The **mycotoxin** deoxynivalenol facilitates allergic sensitization to whey in mice.

Bol-Schoenmakers M, Braber S, Akbari P, de Graaff P, van Roest M, Kruijssen L, Smit JJ, van Esch BC, Jeurink PV, Garssen J, Fink-Gremmels J, Pieters RH.

Mucosal Immunol. 2016 Feb 17. PMID: 26883726

Level of Evidence: A

Low GSH leads to Th2 (Ig production like IgG or IgE)

- Low GSH leads to Th2 cytokine release from Antigen presenting cells (dendritic) cells
- PMID: 9501217 (Peterson 1996)
- Argawal using Thimerosal to lower APC GSH

Thimerosal induces TH2 responses via influencing cytokine secretion by human dendritic cells.
Agrawal A, Kaushal P, Agrawal S, Gollapudi S, Gupta S.
J Leukoc Biol. 2007 Feb;81(2):474-82. PMID: 17079650

Level of Evidence: A

Pollen and Ox Stress

- pollen exposure-induced oxidative stress may contribute to local innate immunity and participate in the initiation of adaptive immune responses to pollen Ags
- modulate dendritic cell function and
- induce Th2 polarization

Innate responses to pollen allergens.
Hosoki K, Boldogh I, Sur S.
Curr Opin Allergy Clin Immunol. 2015 Feb;15(1):79-88..
Review. PMID: 25546327

Level of Evidence: A

Pollen and OxStress

- ROS generated by
- NAD(P)H oxidases found in pollen grains intensify immediate allergic reactions and recruitment of inflammatory (neutrophils) cells

Effect of pollen-mediated oxidative stress on immediate hypersensitivity reactions and late-phase inflammation in allergic conjunctivitis.
Bacsi A, Dharajiya N, Choudhury BK, Sur S, Boldogh I.
J Allergy Clin Immunol. 2005 Oct;116(4):836-43. Epub 2005 Aug 19.
PMID: 16210058

Level of Evidence: B

Pollen Allergy Assoc with

- allergists know why pollen makes people sneeze: the body's immune system is releasing a lot of inflammatory cells, including neutrophils and eosinophils, in response to the invading pollen proteins.
- pollen extracts from weeds, trees, and grasses have intrinsic NADPH oxidase activity that induces ROS in airway epithelium within minutes

Adler T. The radical theory of sneezing. Environ Health Perspect. 2005;113(11):A736. PMCID: 1310958. http://www.ncbi.nlm.nih.gov/pubmed/16276649

Level of Evidence: B

radical theory of sneezing

- "antioxidants available now clear from the lungs too quickly to be effective in people" (Adler)

- ReadiSorb Glutathione providing maximal scavenging for Free Radicals can be taken several times a day [Ed]

Adler T. The radical theory of sneezing. Environ Health Perspect. 2005;113(11):A736. PMCID: 1310958. http://www.ncbi.nlm.nih.gov/pubmed/16276649

Level of Evidence: A

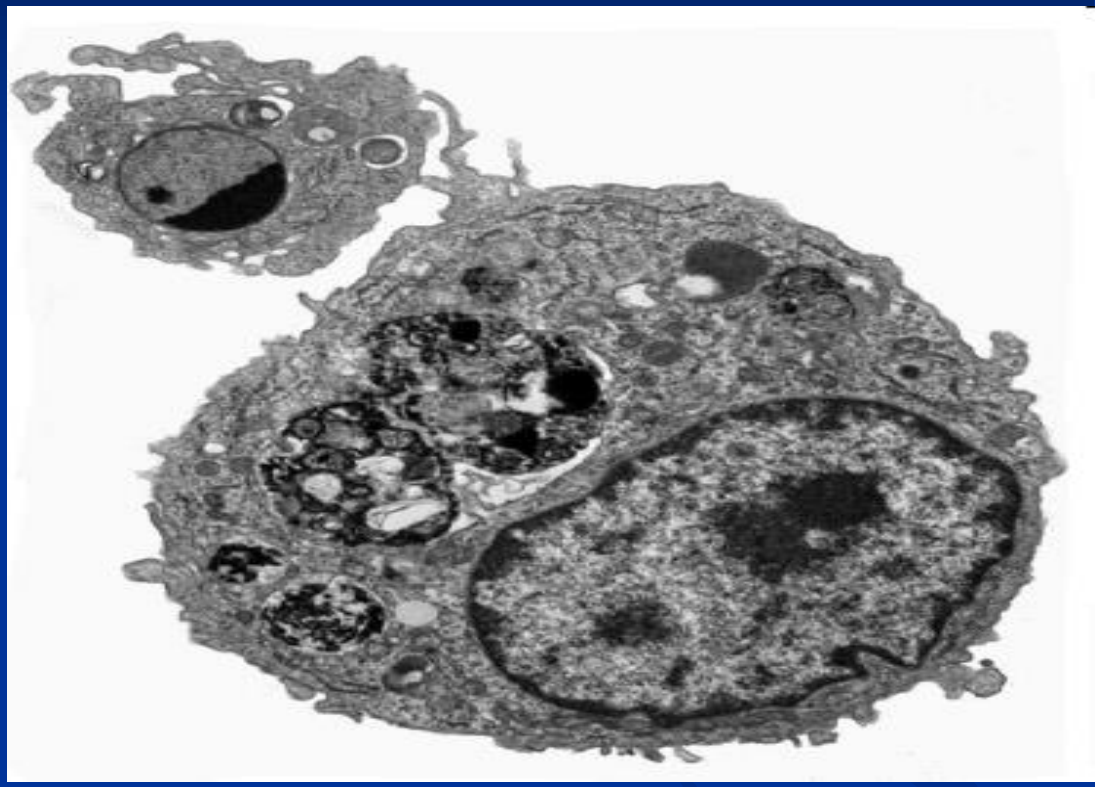
MΦ eliminates fungal conidia

- In the lung of In healthy individuals,
- macrophages are responsible for rapidly phagocytose and eliminate these conidia, effectively curbing their germination and consequent invasion of pulmonary tissue.
- This function suppressed by Gt

Schlam D, Canton J, Carreno M, Kopinski H, Freeman SA, Grinstein S, et al. Gliotoxin Suppresses Macrophage Immune Function by Subverting Phosphatidylinositol 3,4,5-Trisphosphate Homeostasis. MBio. 2016;7(2):e02242. PMCID: 4817266.
http://www.ncbi.nlm.nih.gov/pubmed/27048806

Level of Evidence: B

GSH maintains Efferocytosis

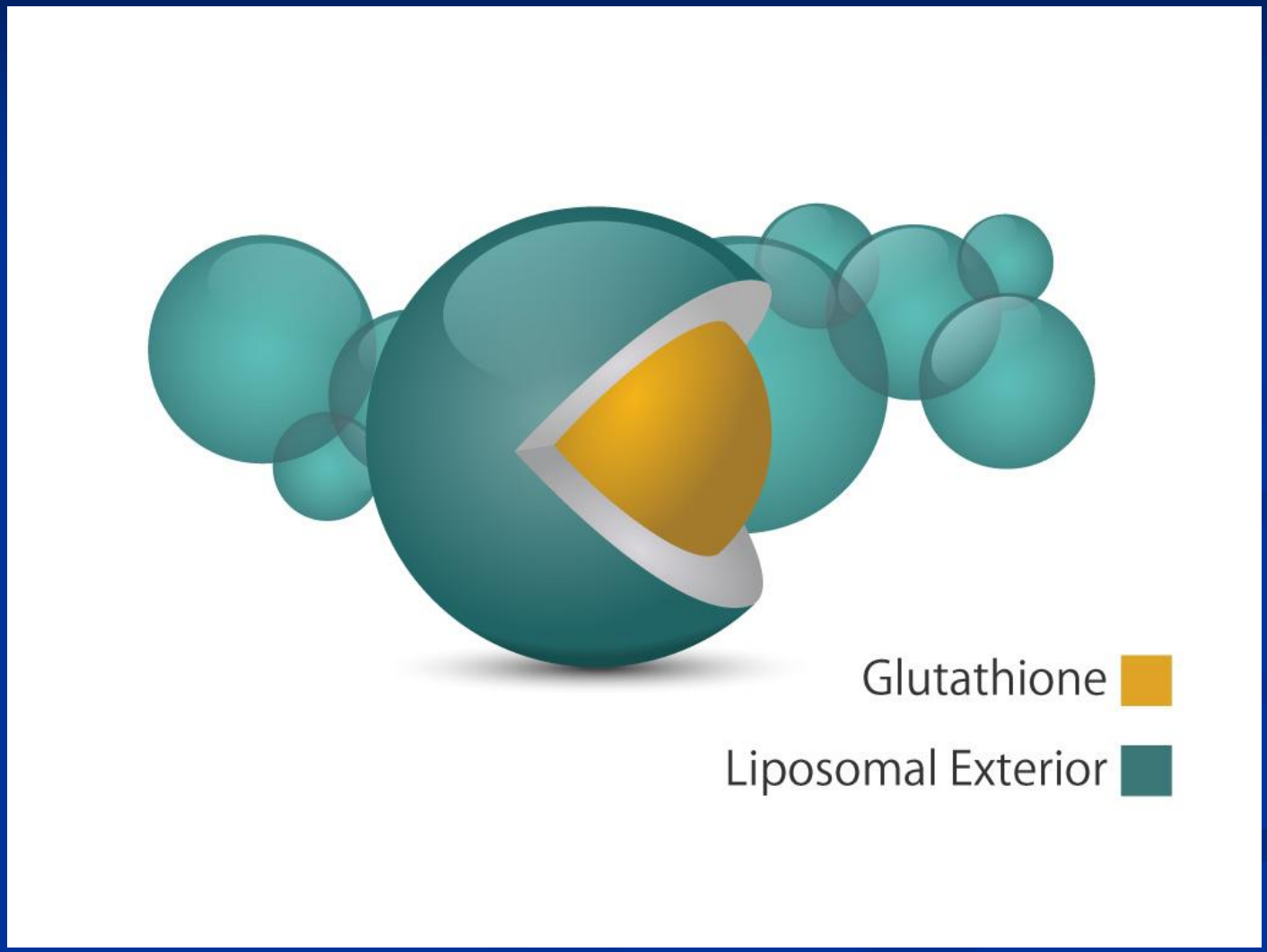


Glutathione oxidation is associated with airway macrophage functional impairment in children with severe asthma.
GSH supplementation rescued AM phagocytosis and intracellular killing of S. aureus in children with severe asthma:
Fitzpatrick AM, Teague WG, Burwell L, Brown MS, Brown LA; Pediatr Res. 2011 Feb;69(2):154-9.
PMID: 20975618

Macrophage engulfment of apoptotic neutrophils contributes to the resolution of acute pulmonary inflammation in vivo.
Cox G, Crossley J, Xing Z.
Am J Respir Cell Mol Biol. 1995 Feb;12(2):232-7.
PMID: 7865221

Level of Evidence: A

ReadiSorb® Liposomal Glutathione

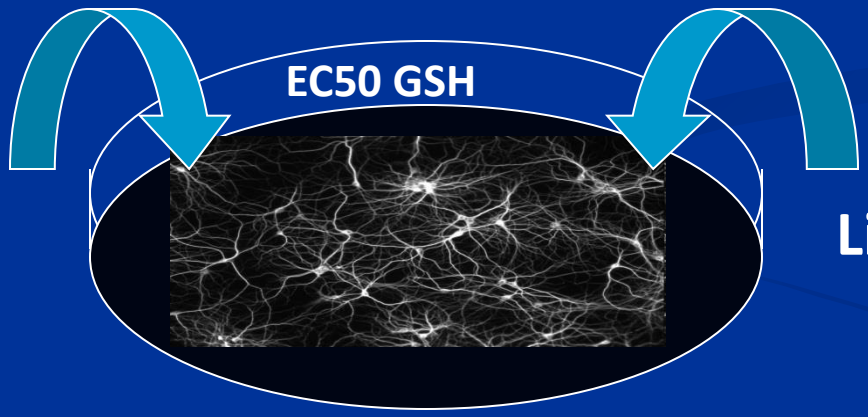


Level of Evidence: A

Can L-GSH Improve GSH Concentration across Membranes?

- **Neuron cell culture depleted of GSH by DEM (diethyl maleate)**
- **L-GSH was > 100-fold more potent than plain GSH in solution (non-L-GSH) in replenishing intracellular GSH**

Mol Wt. GSH - 304



Plain GSH 575 µM

Liposomal GSH 4.75 µM

Zeevalk GD, Bernard LP, Guilford FT. Liposomal-glutathione provides maintenance of intracellular glutathione and neuroprotection in mesencephalic neuronal cells. Neurochem Res. 2010;35(10):1575-87.

Level of Evidence: B

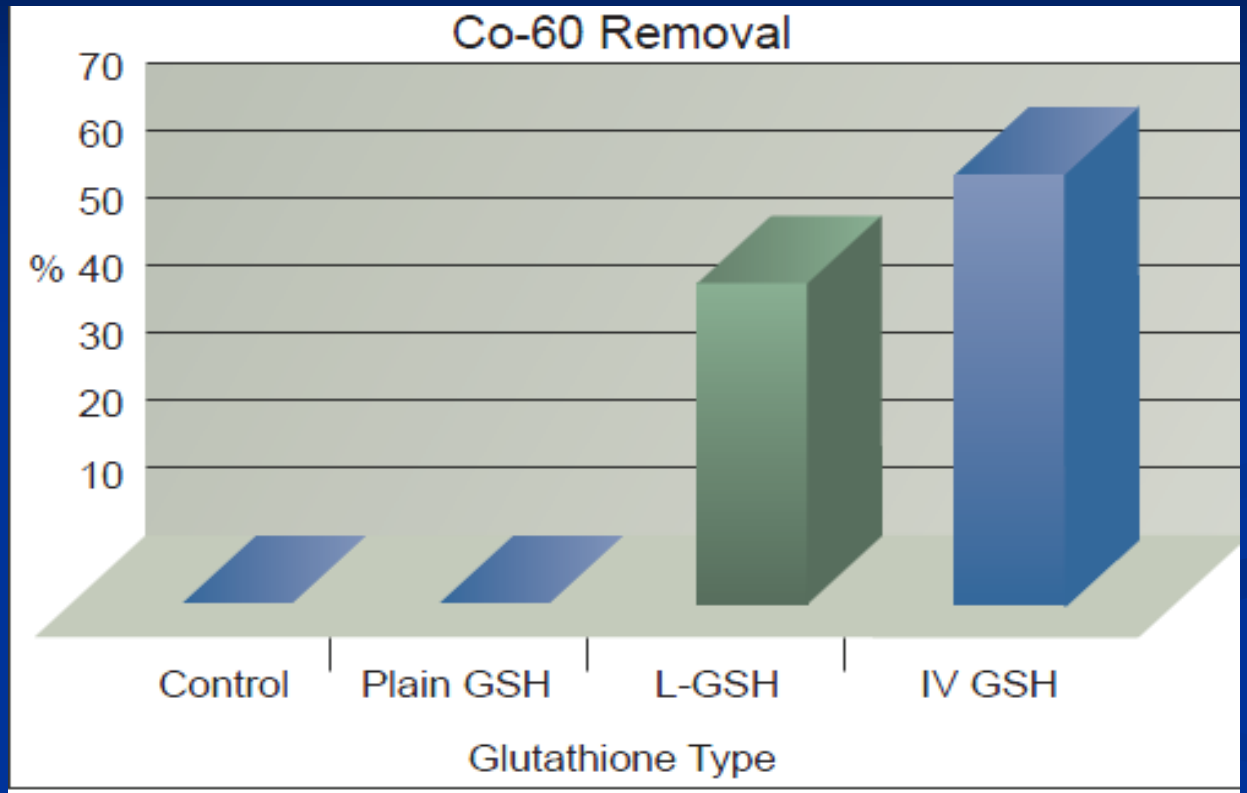
Plain, non-liposomal GSH

- Plain, oral glutathione has few positive studies and
- A two month study showed no effect

Allen J, Bradley RD. Effects of oral glutathione supplementation on systemic oxidative stress biomarkers in human volunteers. J Altern Complement Med. 2011;17(9):827-33. PMCID: 3162377.

Level of Evidence: A

L-GSH absorption and function in tissue



Removal of Co-60 from the liver of rats infused with Co-60. Oral lipsomal GSH has 75% of the function of IV GSH. IV GSH removed 64%. Liposomal GSH given orally removed 47% and plain glutathione given orally removed 0%.

Levitskaia TG, et al. Aminothiol receptors for decorporation of intravenously administered (60)Co in the rat. Health Phys. 2010;98(1):53-60.

Level of Evidence: A

TGF-β

- decreases GSH in various types of cells *in vitro* while GSH replenishment suppresses TGF-β's PMID: 19800967

1. Ly J, et al, Venketaraman V. Liposomal Glutathione Supplementation Restores TH1 Cytokine Response to Mycobacterium tuberculosis Infection in HIV-Infected Individuals. J Interferon Cytokine Res. 2015;35(11):875-87. PMCID: 4642835. http://www.ncbi.nlm.nih.gov/pubmed/26133750
2. Liu RM, Pravia KA. Oxidative stress and glutathione in TGF-beta-mediated fibrogenesis. Free Radic Biol Med. 2010;48(1):1-15. PMCID: 2818240. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2818240/?tool=pubmed

Level of Evidence: A

Immune Dysfunction in HIV

- Low GSH – HIV a low GSH disease
- ↓GCL in HIV → Low GSH
- Decreased intracellular killing of bacteria (MTb)
- Increased inflammatory cytokine production
- In this setting a specific liposomal glutathione has been shown to be 1,000 times more efficient than NAC in repleting GSH and restoring macrophage function *in vitro*

Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione Supplementation Improves Macrophage Functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. PMID: 23409922

Level of Evidence: A

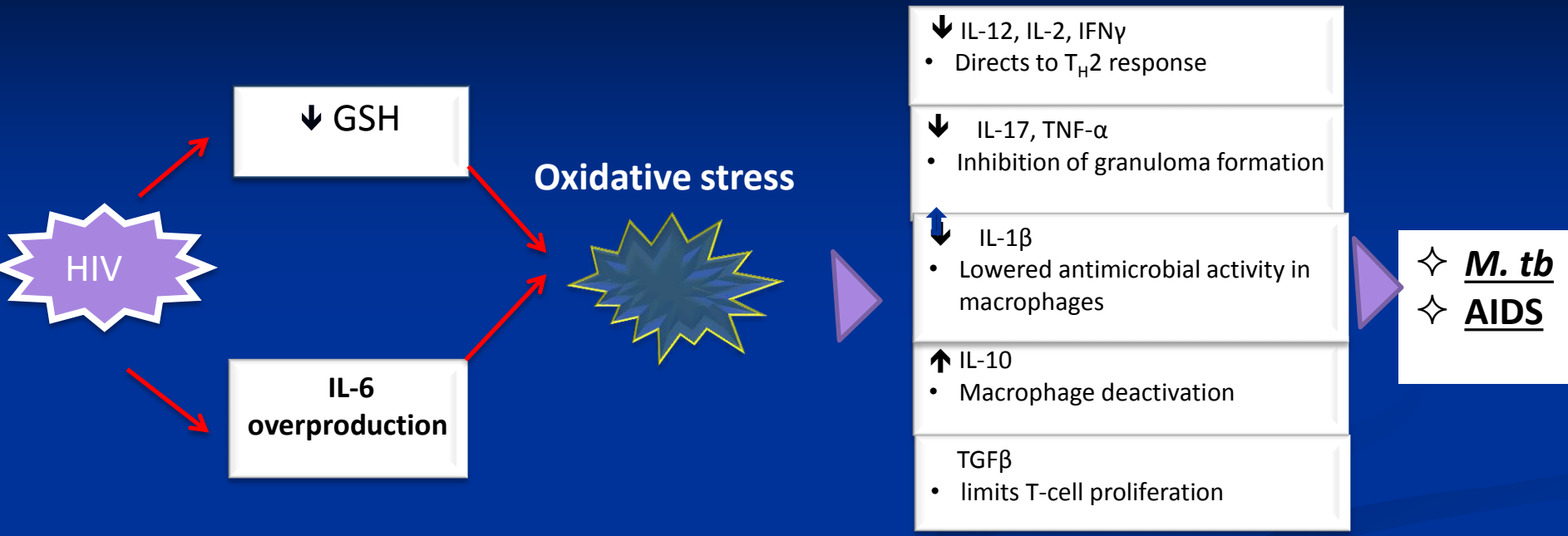
The slide to follow refers to:

- Liposomal Glutathione Supplementation Restores TH1 Cytokine Response to Mycobacterium tuberculosis Infection in HIV-Infected Individuals.

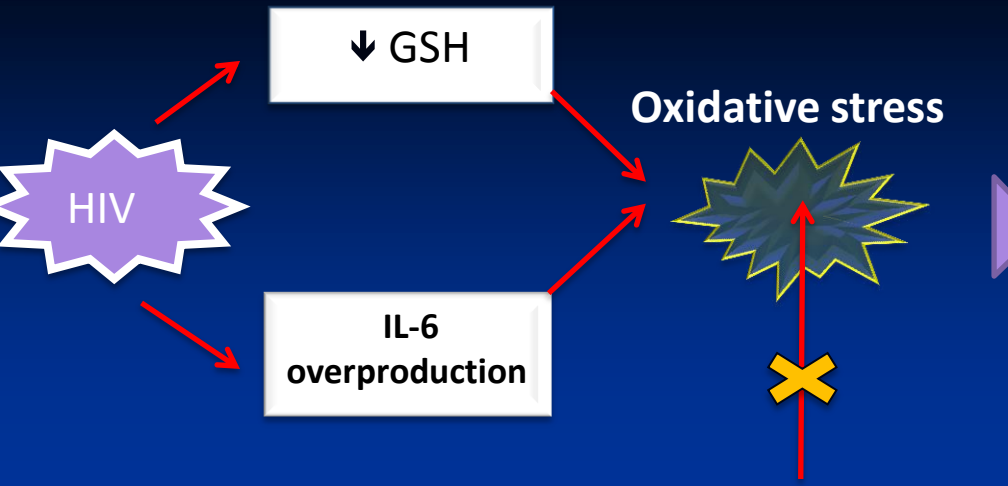
- Ly J, Lagman M, Saing T, Singh MK, Tudela EV, Morris D, Anderson J, Daliva J, Ochoa C, Patel N, Pearce D, Venketaraman V.

- J Interferon Cytokine Res. 2015 Nov;35(11):875-87.
  doi: 10.1089/jir.2014.0210. PMID: 26133750
  http://www.ncbi.nlm.nih.gov/pubmed/26133750

Level of Evidence: A



Ly 2015 PMID: 26133750



- ↓ IL-12, IL-2, IFNγ
  - Directs to T_H2 response
- ↓ IL-17, TNF-α
  - Inhibition of granuloma formation
- ↓ IL-1β
  - Lowered antimicrobial activity in macrophages
- ↑ IL-10
  - Macrophage deactivation
- ↑ TGFβ
  - limits T-cell proliferation

✧ ***M. tb***
✧ **AIDS**

Liposomal Glutathione

- ↓ IL-6
  - Decreased ROS production
- ↑ IL-12, IL-2, IFNγ
  - Directs to T_H1 response
- ↑ IL-17, TNF-α
  - Granuloma formation
- ↑ IL-1 β
  - Antimicrobial activity in macrophages
- ↓ IL-10
  - Macrophage activation
- ↓ TGFβ
  - T-cell proliferation

✧ Control of *M. tb* infection.
✧ Control of AIDS progression.

Ly 2015 PMID: 26133750

T_H 1 vs T_H 2

T_H	Cytokine (plasma)	HIV Pre-RLG vs. NL	HIV Post vs. Pre-RLG
T_H 1	IL-1	12 X ↓	10 X ↑
1	IL-2	2 X ↓	--
1	IL-12	8 X ↓	3 X ↑
1	IFN-	3 X ↓	2 X ↑
1	TNF-	11 X ↓	2.5X ↑
1	IL-17	3 X ↓	↑
T_H2	TGF-	2 X ↑	3 X ↓
2	IL-6	16 X ↑	2 X ↓
2	IL-10	6 X↑	6 X ↓

Level of Evidence: A

Ly 2015 PMID: 26133750

TH2 cytokines

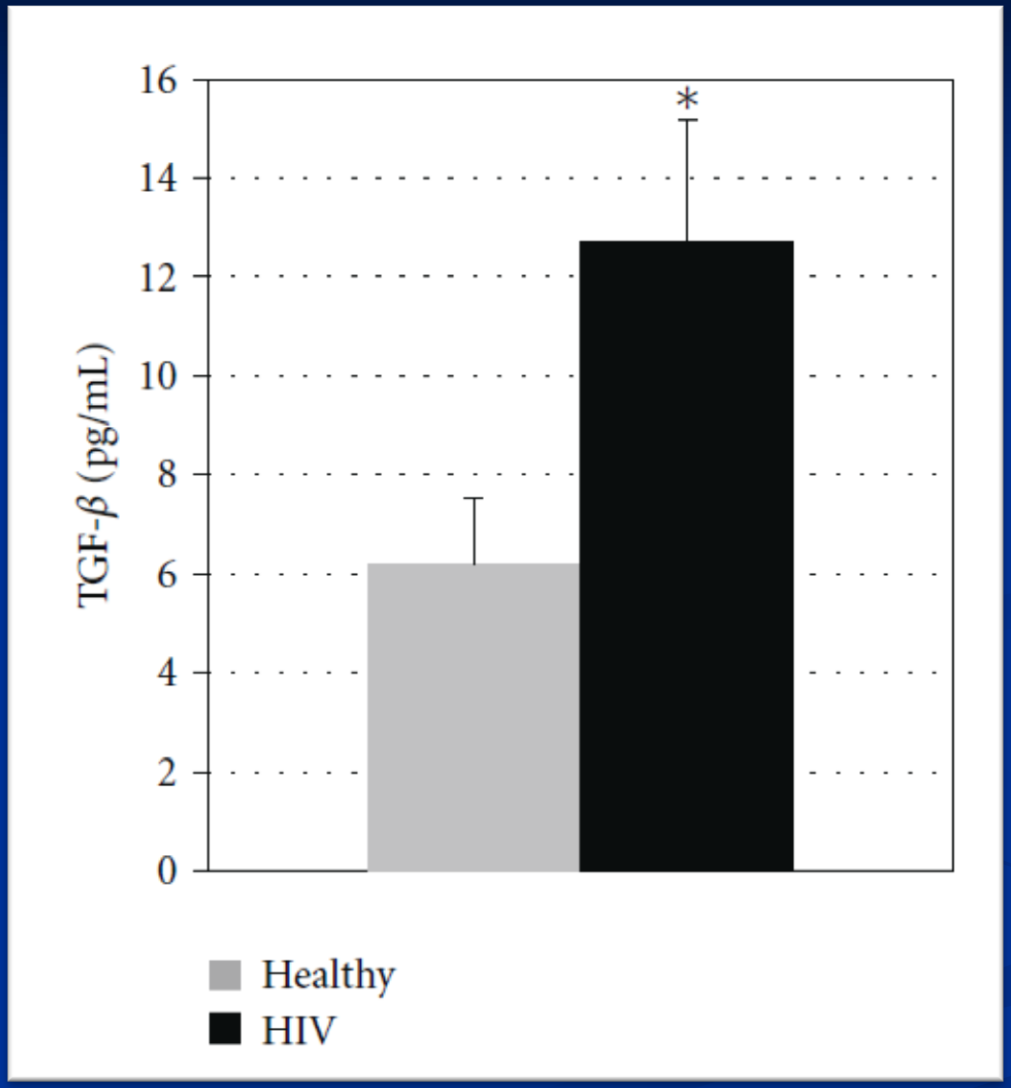
- ↑ IL-6 – associated with oxidative stress
- ↑ IL-10 – immunosuppressive
- ↑ TGF-β – blocks formation of GCLC
- = ↓GSH

Liposomal Glutathione Supplementation Restores TH1 Cytokine Response to Mycobacterium tuberculosis Infection in HIV-Infected Individuals.

Ly J, Lagman M, Saing T, Singh MK, Tudela EV, Morris D, Anderson J, Daliva J, Ochoa C, Patel N, Pearce D, Venketaraman V.
J Interferon Cytokine Res. 2015 Nov;35(11):875-87. doi: 10.1089/jir.2014.0210. Epub 2015 Jul 2.
PMID: 26133750
http://www.ncbi.nlm.nih.gov/pubmed/26133750

Level of Evidence: A

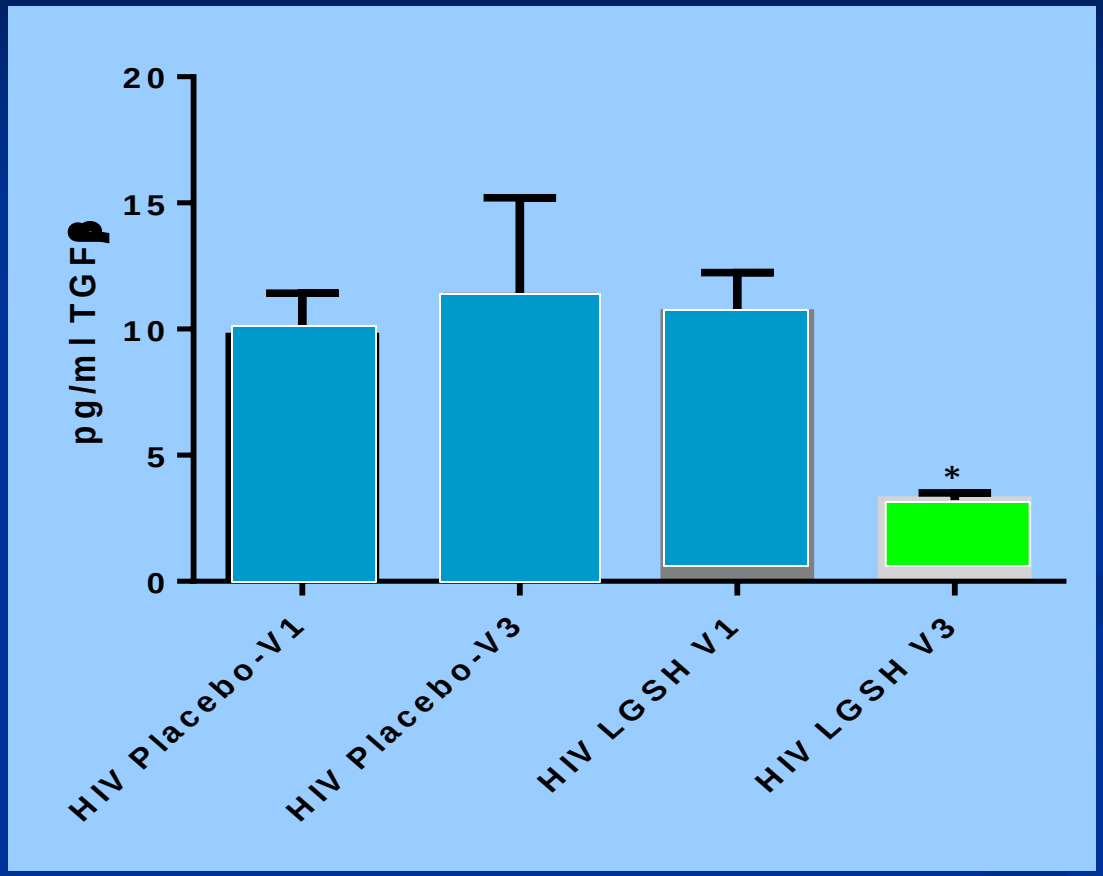
TGF-β Elevated in HIV - Related to decrease in GSH



Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione Supplementation Improves Macrophage Functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. PMID: 23409922

Level of Evidence: A

TGFβ Post RLG



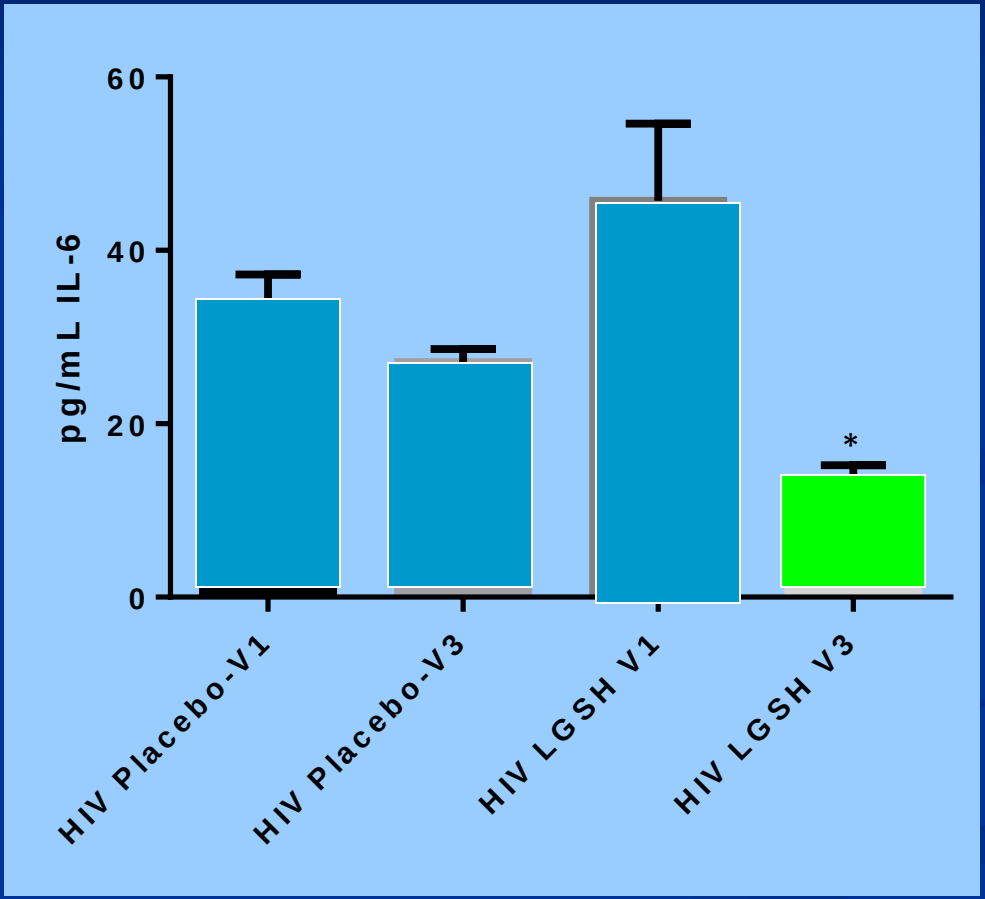
Liposomal Glutathione Supplementation Restores TH1 Cytokine Response to Mycobacterium tuberculosis Infection in HIV-Infected Individuals.

Ly J et al, Venketaraman V.

J Interferon Cytokine Res. 2015 Nov;35(11):875-87 PMID: 26133750

Level of Evidence: A

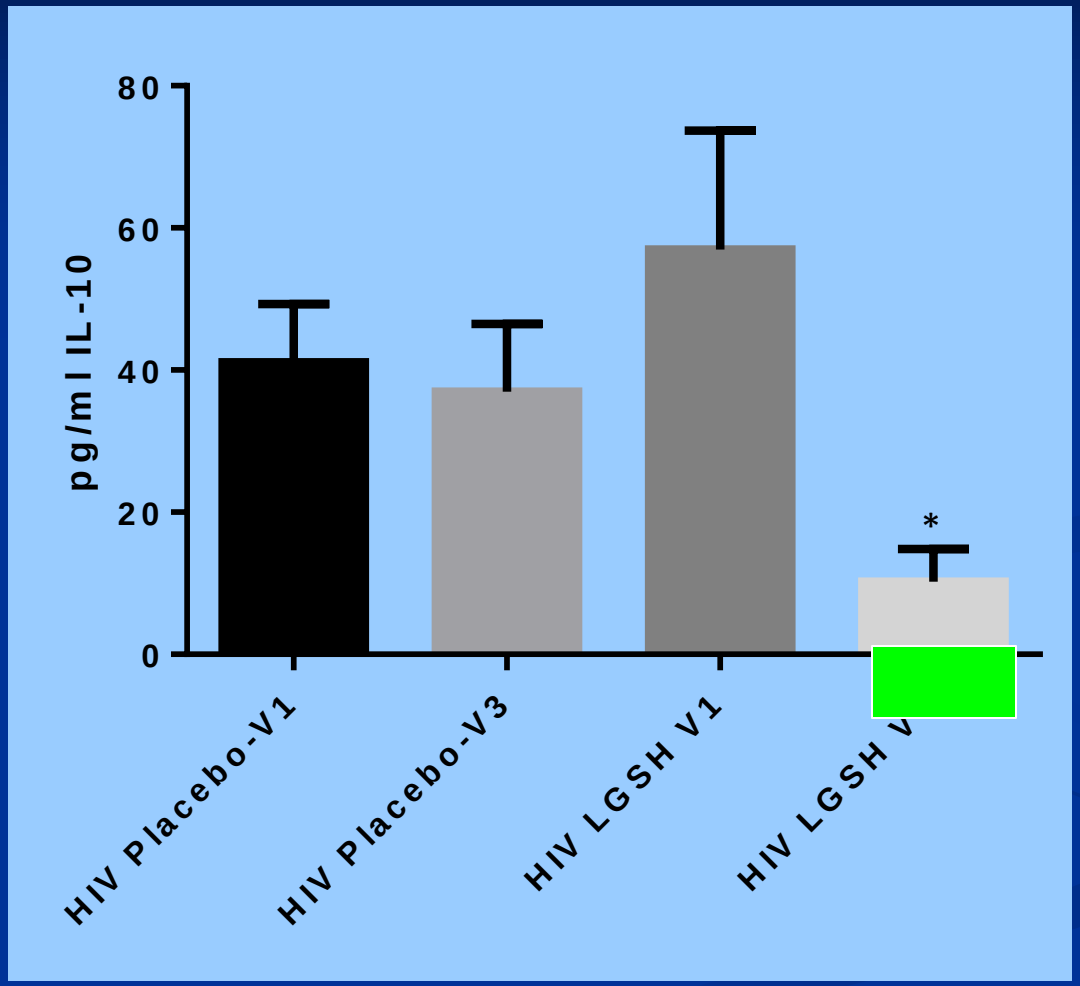
IL-6 Post RLG



Ly J et al, Venketaraman V.
J Interferon Cytokine Res. 2015 Nov;35(11):875-87 PMID: 26133750

Level of Evidence: A

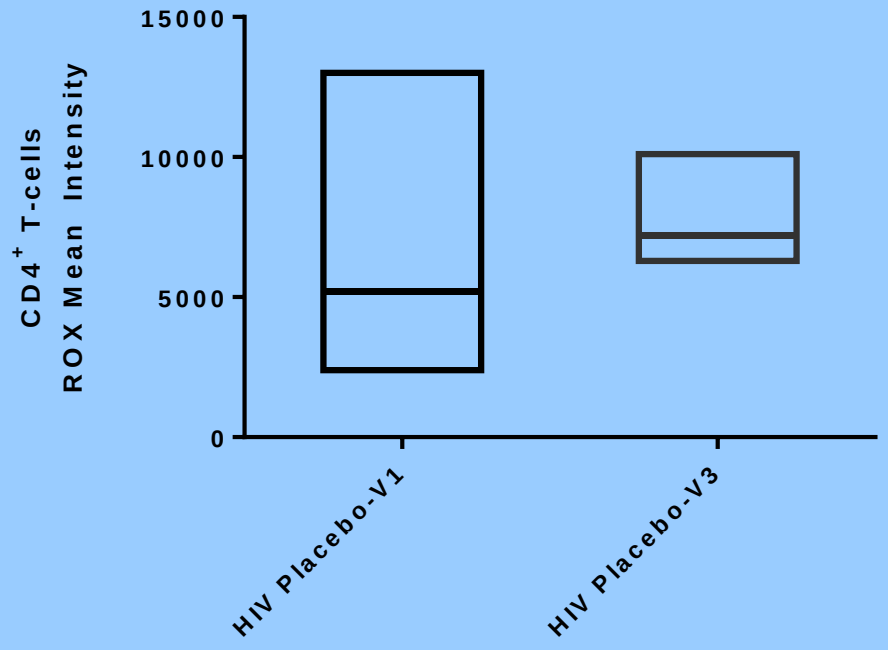
IL-10 suppressed by RLG

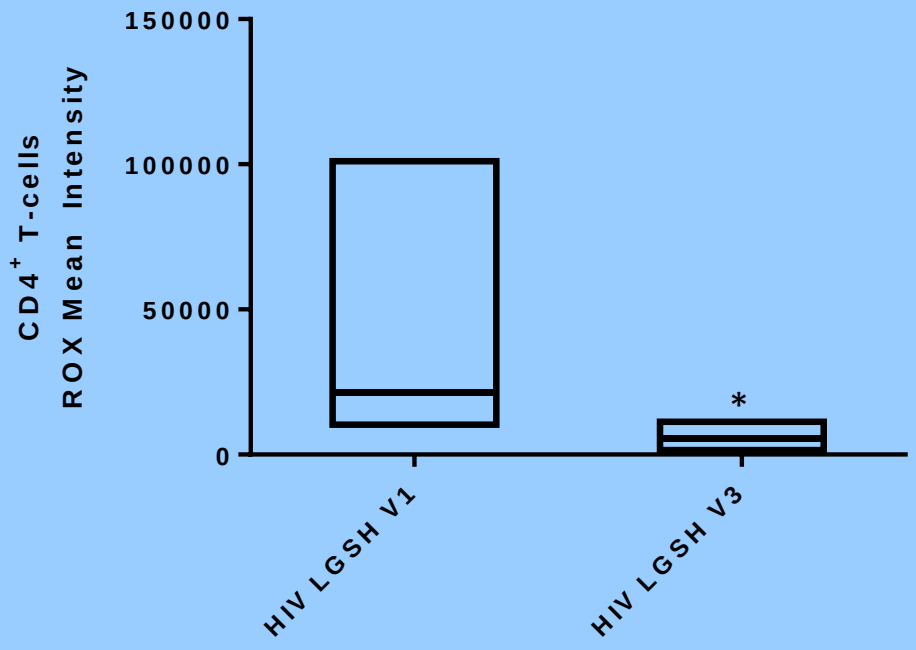


Ly J et al, Venketaraman V.
J Interferon Cytokine Res. 2015 Nov;35(11):875-87 PMID: 26133750

Level of Evidence: A

ROX, a measure of ROS in CD4 T cells

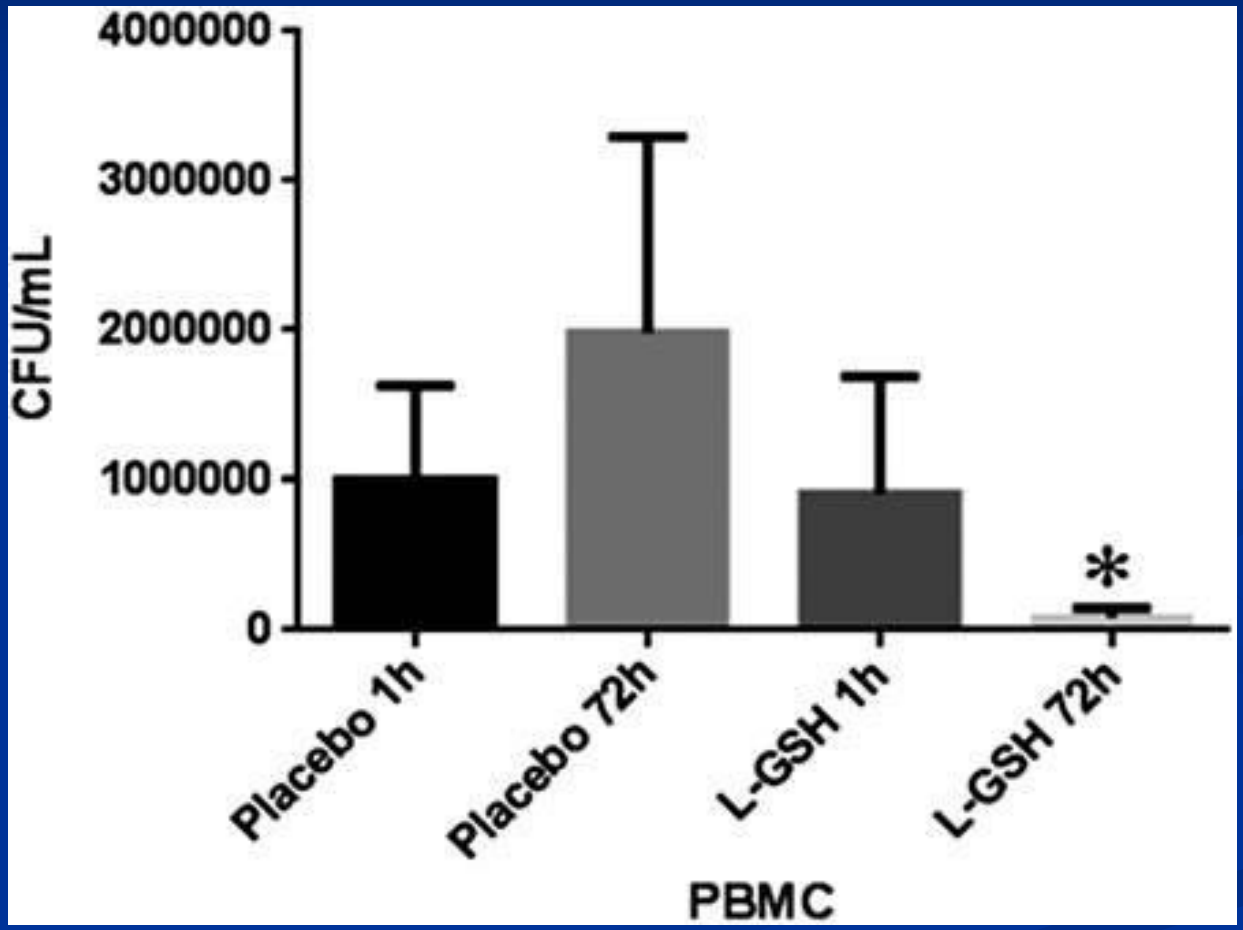




Ly J et al, Venketaraman V.
J Interferon Cytokine Res. 2015 Nov;35(11):875-87 PMID: 26133750

Level of Evidence: A

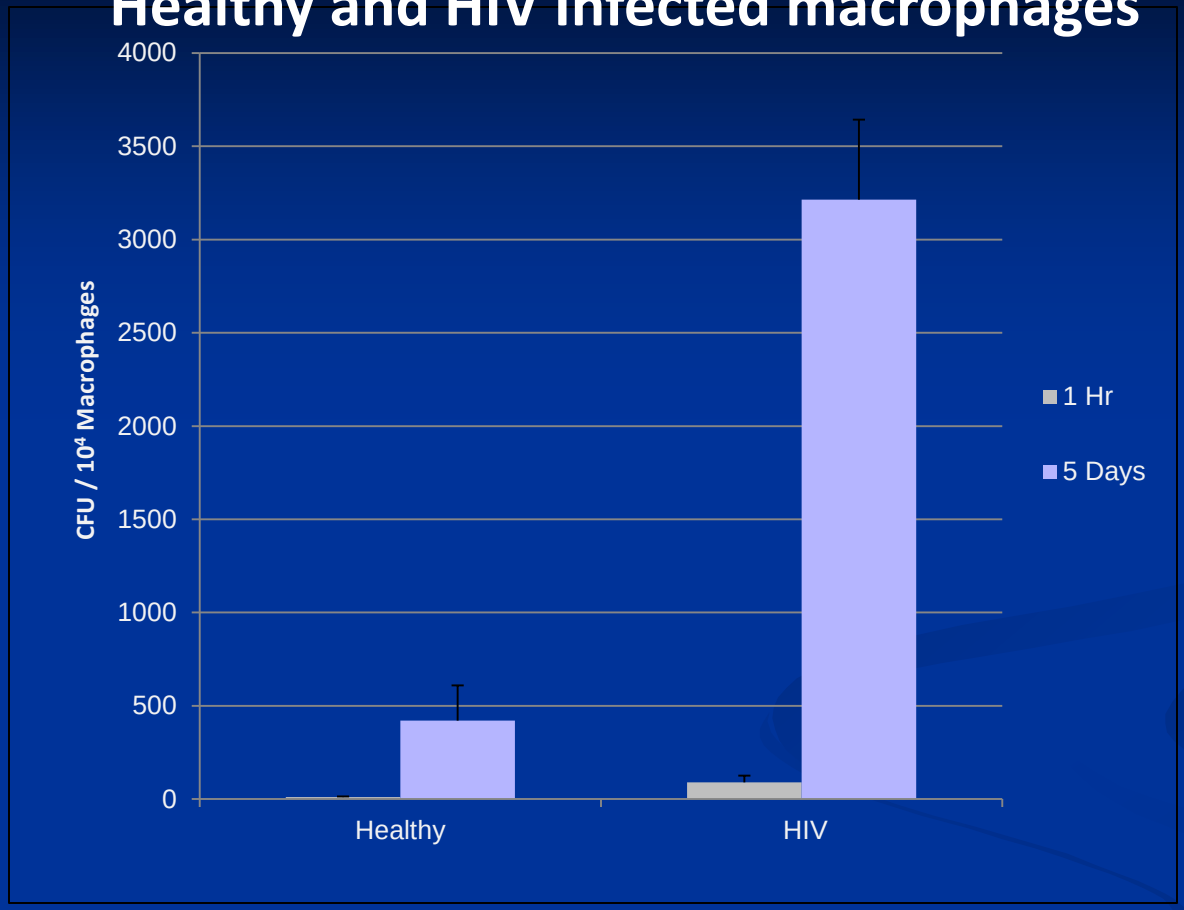
Colony forming units decreased by LRG



Level of Evidence: A

Ly J, Venketaraman V, **Liposomal Glutathione Supplementation in HIV-Infected Individuals.** J Interferon Cytokine Res. 2015. _PMID: 26133750

A Comparison of Intracellular Survival of *M. tb* in Healthy and HIV Infected macrophages

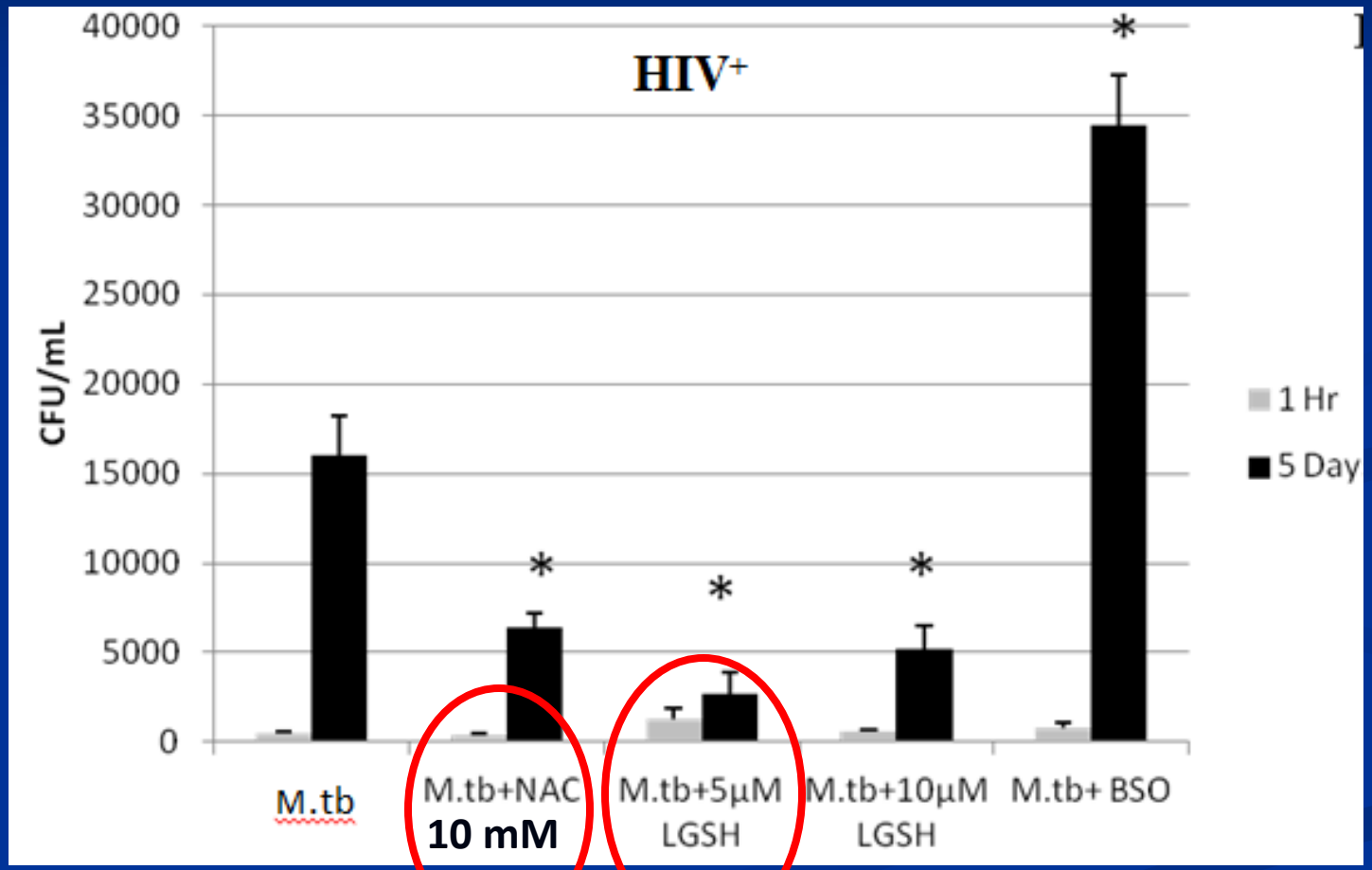


Intracellular survival of *M.tb* is an order of magnitude lower in healthy macrophages compared to HIV⁺ macrophages

Morris D, et al, Venketaraman V. Unveiling the Mechanisms for Decreased Glutathione in Individuals with HIV Infection. Clin Dev Immunol. 2012;2012:734125. PMCID: 3254057.

Level of Evidence: A

Intracellular survival assay of *M.tb* in macrophages from HIV+ subjects.



Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione Supplementation Improves Macrophage Functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. PMID: 23409922

Level of Evidence: A

LG supports TNF-α defense in neutrophils

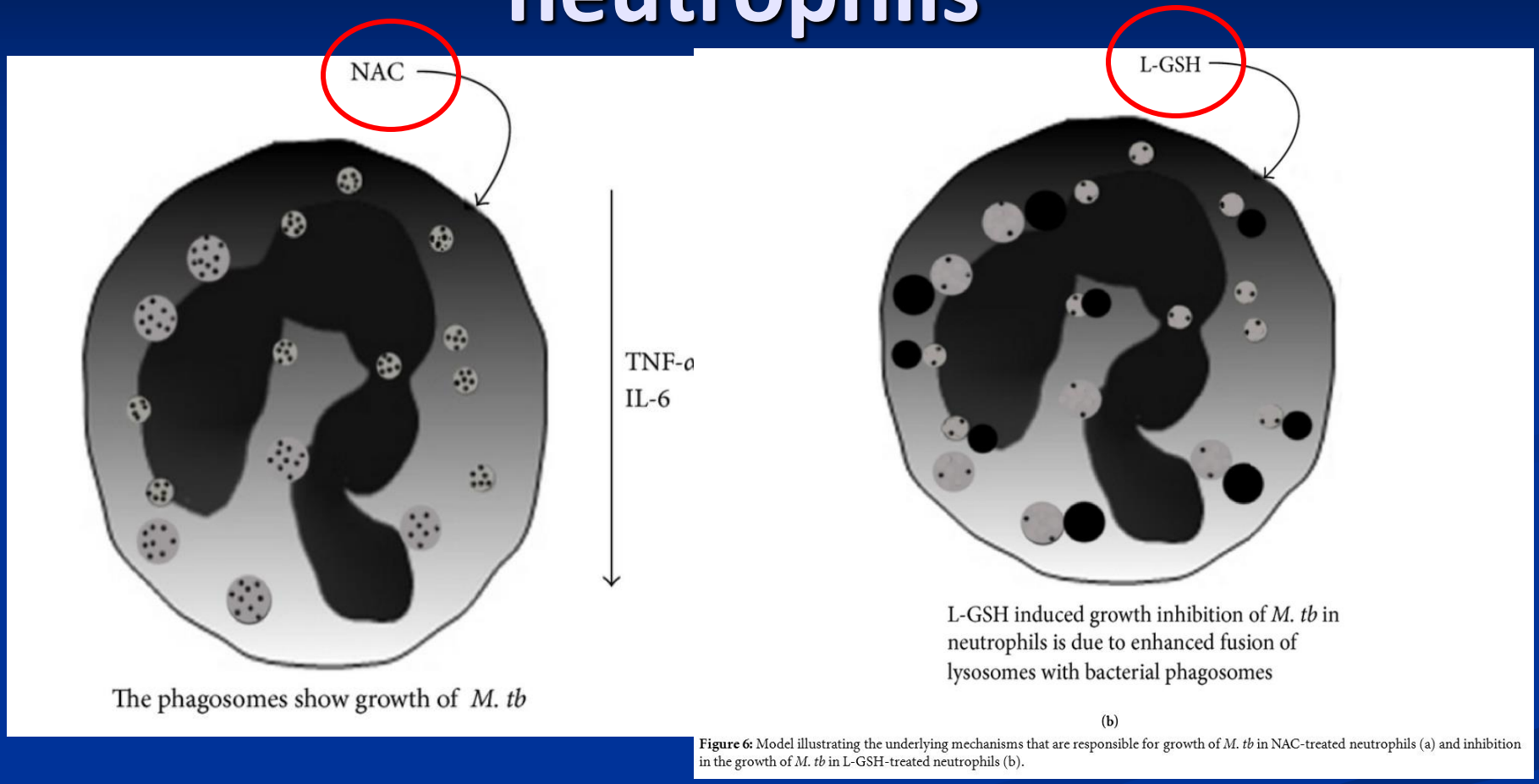


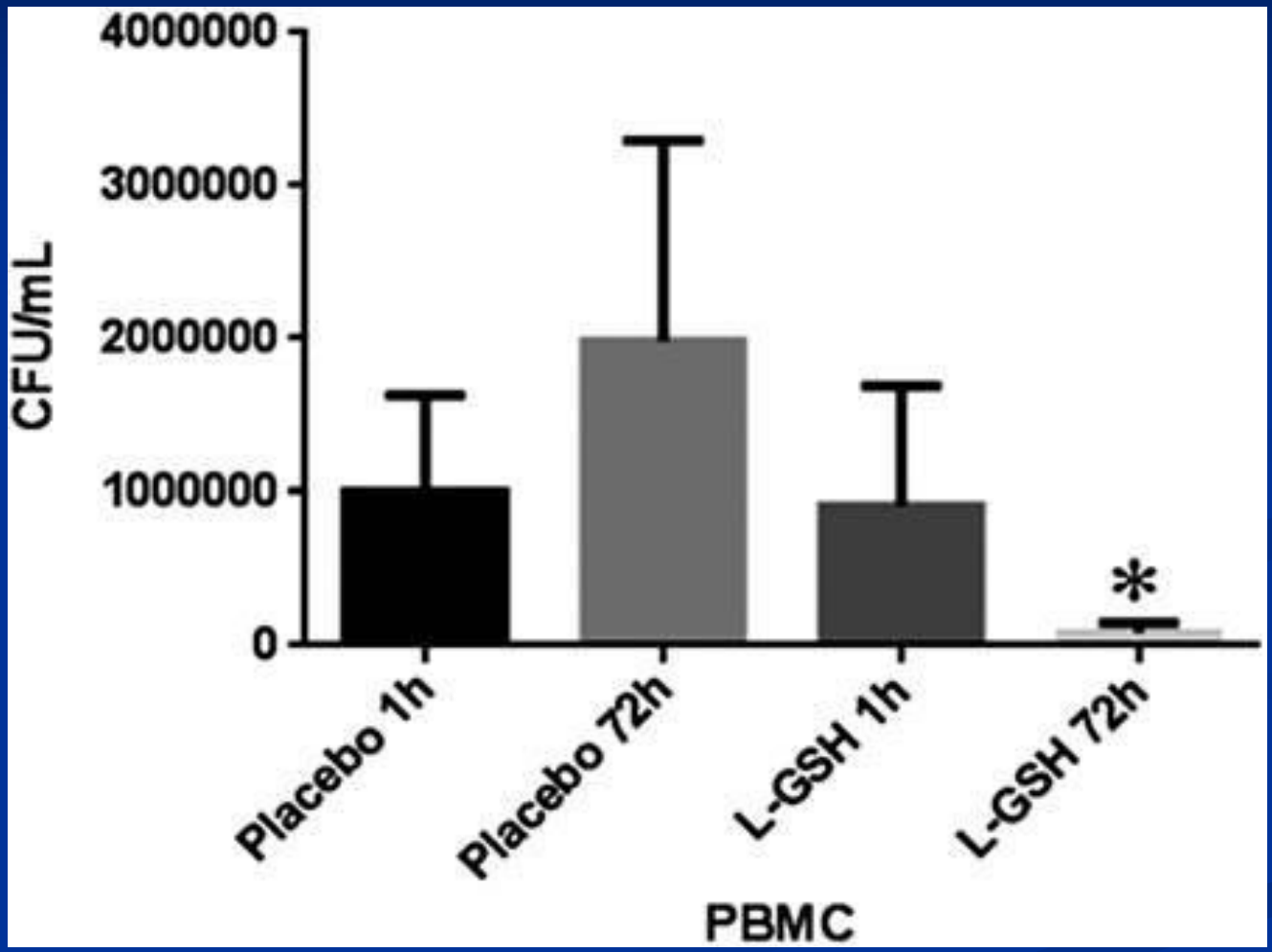
Figure 6: Model illustrating the underlying mechanisms that are responsible for growth of *M. tb* in NAC-treated neutrophils (a) and inhibition in the growth of *M. tb* in L-GSH-treated neutrophils (b).

Fig 6

Morris D, Nguyen T, Kim J, Kassissa C, Khurasany M, Luong J, et al. An Elucidation of Neutrophil Functions against Mycobacterium tuberculosis Infection. Clinical and Developmental Immunology. 2013;Volume 2013 (2013):11. http://www.hindawi.com/journals/cdi/2013/959650/

Level of Evidence: A

LRG support Antibacterial Defense



Level of Evidence: A

Ly J, Venketaraman V, **Liposomal Glutathione Supplementation in HIV-Infected Individuals.** J Interferon Cytokine Res. 2015. _PMID: 26133750

Mycotoxins

- **mycotoxicoses can heighten vulnerability to microbial diseases**

Are Some Fungal Volatile Organic Compounds (VOCs) Mycotoxins?
Bennett JW, Inamdar AA.
Toxins (Basel). 2015 Sep 22;7(9):3785-804. Review. PMID: 26402705

Level of Evidence: A

Mycotoxins and OxStress

- Ochratoxin ↓ GCLC
- Alfatoxin - PMID 6818882 “intact GSH molecule needed for therapy”
- Trichothcene - PMID 18520041, 22245378: ↓GSH
- Gliotoxin - PMID: 17161924 decreased epithelial GSH and ↑ TGFβ1 levels + ↑ IL-6 and IL-8
- Cause problems by increasing oxidative stress and decreasing GSH

Guilford FT, Hope J. Deficient glutathione in the pathophysiology of mycotoxin-related illness. Toxins (Basel). 2014;6(2):608-23. http://www.ncbi.nlm.nih.gov/pubmed/24517907

Level of Evidence: A

Conclusion and Clinical Pearls

- Oxidative Stress and Deficient Glutathione is a critical component of the Pathophysiology of Mycotoxin-Related Illness
- Due to the loss of GSH-producing enzyme function, more efficient resolution of the effects of glutathione depletion may be obtained with the administration of the complete molecule of GSH as demonstrated *in vitro* and in a human randomized clinical trial in HIV+ individuals, whose immune cells are deficient of GSH.

Level of Evidence: A

Rationale for the use of liposomal glutathione in the management of mycotoxin-related conditions.

Tim Guilford, MD

DrGuilford.com - publications or research

GuilfordMD@gmail.com

650-323-3238