Casual Friday Series

The Layers of Liver Disease Part 3

A Biogenetix Clinical Presentation

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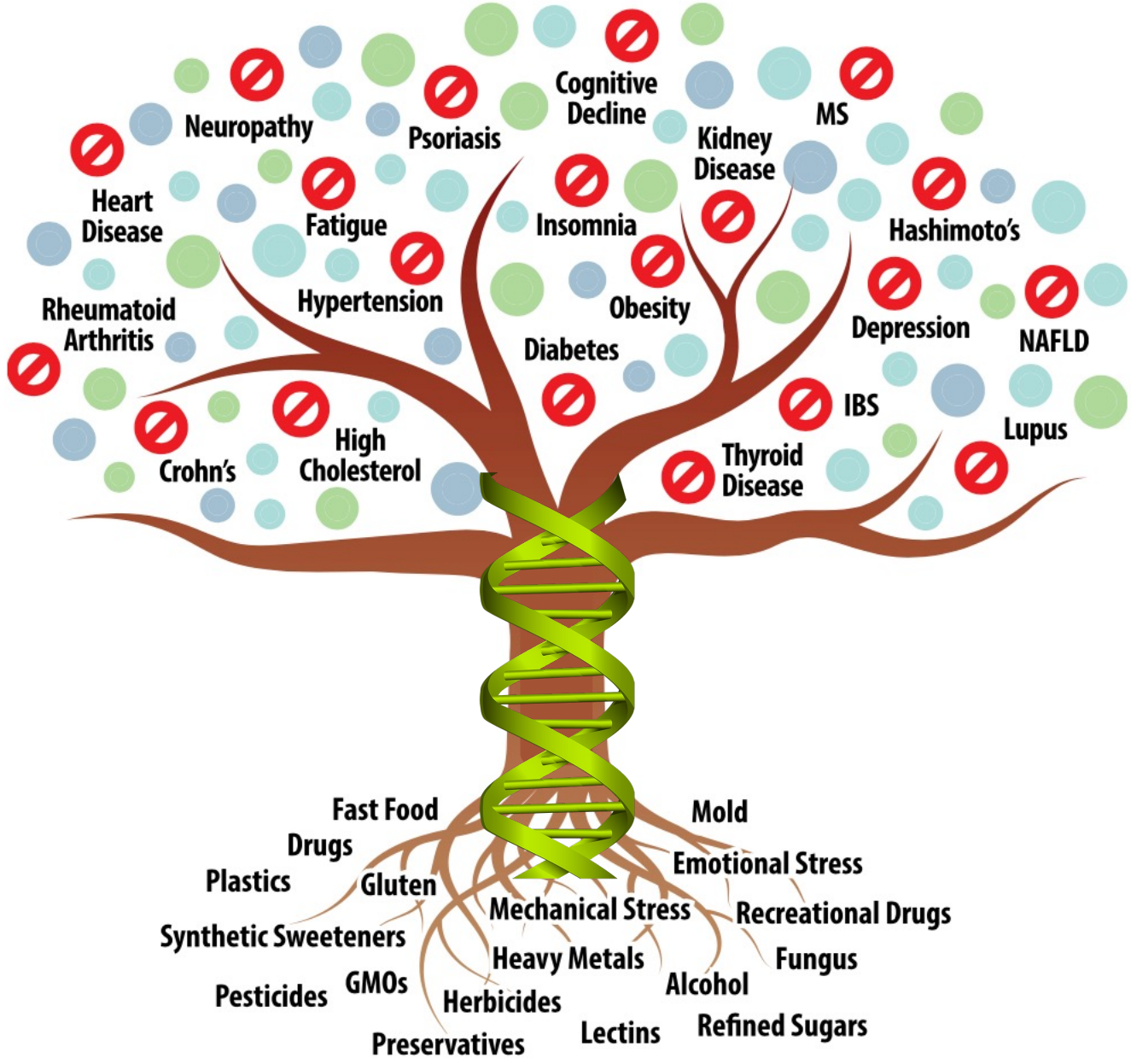
Disclaimer

- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*


Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Lectins
Refined Sugars
Preservatives

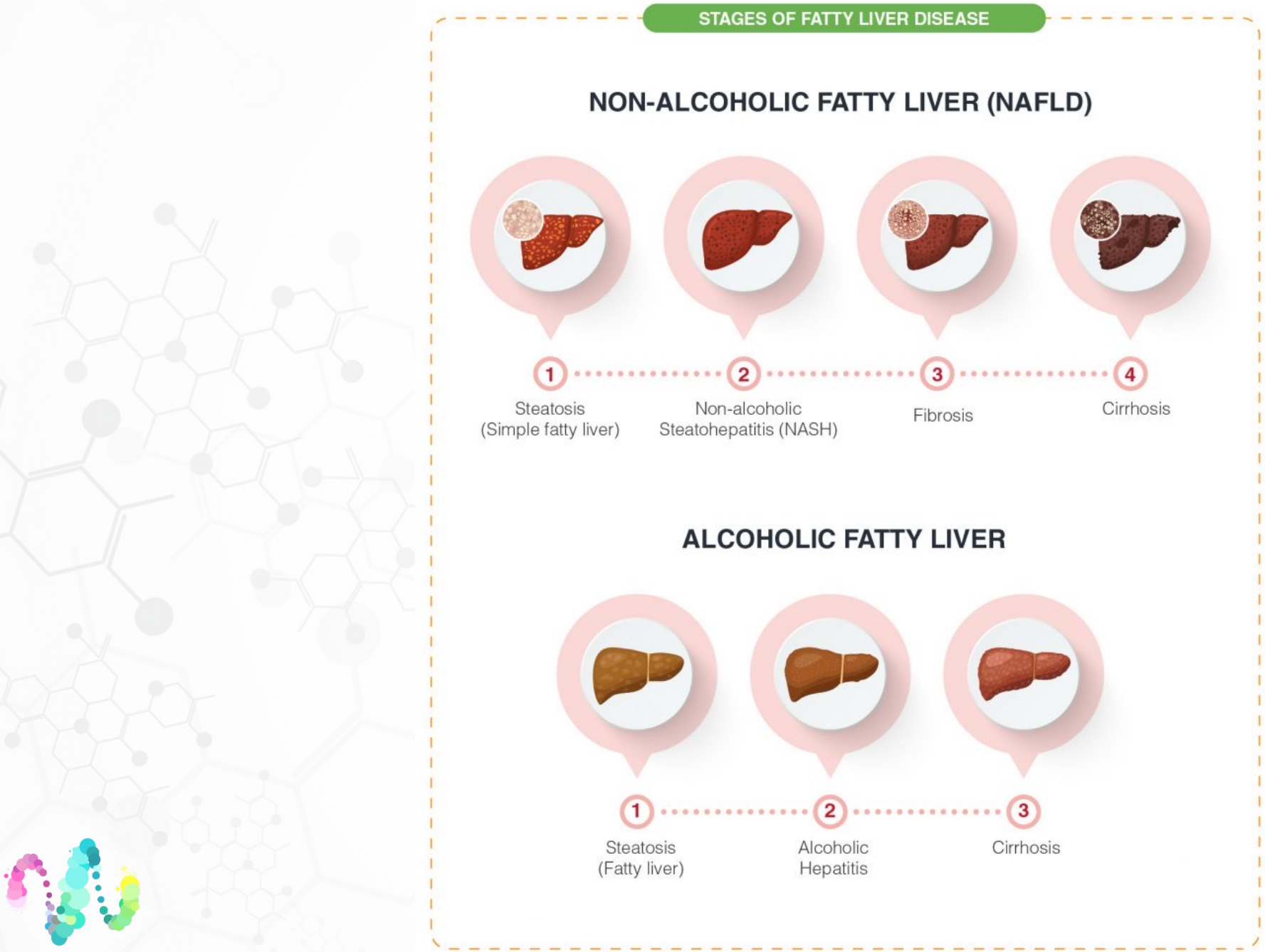
Functional Lab Ranges

- Alanine transaminase: 10-26 IU/L
- Aspartate transaminase: 10-26 IU/L
- Alkaline phosphatase: 65-90 IU/L
- Gamma-glutamyltransferase: 10-26 IU/L
- Bilirubin: .5-.8 mg/dL
- Prothrombin time: 10.9 to 12.5 seconds
- Albumin: 4.2-4.7 g/dL

https://www.ncbi.nlm.nih.gov/books/NBK482489/

Functional Lab Patterns

Alcohol Induced Pattern:	AST:ALT 2:1 GGT Elevated Bilirubin +/-
Cholestatic Pattern:	Alk. Phos. Elevated GGT Elevated Bilirubin Elevated



https://www.lalpathlabs.com/blog/wp-content/uploads/2020/04/3-4-870x1024.jpg

Supplement Facts

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Servings per Container: 90

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Vitamin C (as ascorbic acid)	17 mg	29%
Thiamine (as thiamine HCl)	12 mg	851%
Riboflavin (as Riboflavin-5-Phosphate)	8 mg	500%
Niacin (as niacin)	12 mg	64%
Vitamin B6 (as Pyridoxal-5-Phosphate)	7 mg	383%
Pantothenic Acid (as calcium pantothenate)	12 mg	128%
Magnesium (as magnesium citrate)	12 mg	3%
Zinc (as Zinc L-Monomethionine)	8 mg	55%
Copper (as copper gluconate)	170 mcg	9%
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Dandelion extract (root)	63 mg	**
DL-Methionine	68 mg	**
Ginger Root	42 mg	**
N-Acetyl L-Cysteine	46 mg	**
Glycine	38 mg	**
R alpha Lipoic acid (thioctic acid)	8 mg	**
Watercress leaf powder	17 mg	**
S-Acetyl L-Glutathione	8 mg	**
Trimethylglycine (TMG)	17 mg	**
Betaine HCL	17 mg	**
Ginseng root (Panax)	12 mg	**
Taurine	21 mg	**
Protease	4 mg	**
Bromelain	297,700 FCC	**

** Daily Value (DV) not established.

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NIHMSID: NIHMS1677611
PMID: 33268508

Glycine-based treatment ameliorates NAFLD by modulating fatty acid oxidation, glutathione synthesis, and the gut microbiome

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Nonalcoholic fatty liver disease (NAFLD) including nonalcoholic steatohepatitis (NASH) has reached epidemic proportions with no pharmacological therapy approved. Lower circulating glycine is consistently reported in patients with NAFLD, but the causes for reduced glycine, its role as a causative factor, and its therapeutic potential remain unclear. We performed transcriptomics in livers from humans and mice with NAFLD and found suppression of glycine biosynthetic genes, primarily alanine-glyoxylate aminotransferase 1 (*AGXT1*). Genetic (*Agxt1*$^{-/-}$ mice) and dietary approaches to limit glycine availability resulted in exacerbated diet-induced hyperlipidemia and steatohepatitis, with suppressed mitochondrial/peroxisomal fatty acid β-oxidation (FAO) and enhanced inflammation as the underlying pathways. We explored glycine-based compounds with dual lipid/glucose-lowering properties as potential

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Glycine-ba
glutathione

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Hepatic overload of free fatty acids is central to the pathogenesis of NASH. When free fatty acids are supplied to the liver in excess or their disposal via FAO is impaired, they are used as substrates for lipotoxic species that induce oxidant stress and pro-inflammatory/pro-fibrogenic pathways, promoting steatohepatitis and fibrosis (2). Our transcriptomics analysis showed that FAO was among the most suppressed pathways in livers from mice with NASH, which was reversed by DT-109 with subsequent reduction in HS and lipotoxicity. Unlike the gut microbiome, the effects of DT-109 on FAO were found to be independent of NASH, as liver TGs were reduced and FAO-related genes were upregulated also in *Apoe*$^{-/-}$ mice on WD and in wild-type mice on CD. In support, glycine intake was previously reported to increase FAO indices in livers from sucrose-fed rats (22). The *in vivo* evidence together with the metabolic assays using Seahorse indicate increased FAO as a central mechanism by which glycine-based treatment protects against NASH.

Enhancing FAO together with increasing GSH availability has been proposed as a potential strategy for NAFLD treatment (8). Glycine is the final amino acid precursor necessary for GSH synthesis (16). Both in NAFLD and T2D, GSH synthesis is diminished due to limited glycine availability and is restored following dietary supplementation (8, 56). Herein, transcriptomics showed that GSH metabolism was suppressed in NASH and was restored by glycine-based treatment that reduced hepatic lipid peroxidation. Appling metabolomics *in vivo* and *in vitro*, we found that DT-109 directly contributed to *de novo* GSH synthesis. Unlike its effects on the microbiome, the effects of DT-109 on FAO and GSH were independent of NASH. Thus, our studies indicate that glycine-based treatment induces hepatic FAO and stimulates GSH synthesis, lowering HS and lipotoxicity, which in turn attenuates NASH progression (2). Indeed, using our model, we found that glycine-based treatment attenuated NASH-diet-induced hepatic/systemic inflammation and fibrosis as evident by histological, transcriptomics, and plasma analyses.

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> Eur J Pharmacol. 2012 Oct 5;692(1-3):10-8. doi: 10.1016/j.ejphar.2012.07.028. Epub 2012 Jul 20.

Alpha-lipoic acid induces adipose triglyceride lipase expression and decreases intracellular lipid accumulation in HepG2 cells

In the present study, we established a fatty liver cell model by incubating HepG2 cells in a high glucose (30mM glucose) and high fat (0.1mM palmitate) medium. We found that the activation of the AMPK signalling pathway induced ATGL protein expression and enhanced lipid hydrolysis. Similarly, treatment of the fatty liver cell model with alpha-lipoic acid reduced intracellular lipid accumulation in HepG2 cells, increased AMPK phosphorylation, and induced ATGL expression. We showed that insulin phosphorylates the transcription factor forkhead box O1 (FOXO1), which regulates ATGL expression and inhibits FOXO1 translocation into the nucleus. In contrast, alpha-lipoic acid dephosphorylated FOXO1 and reversed the nuclear exclusion of FOXO1. These data suggest that alpha-lipoic acid can effectively ameliorate intracellular lipid accumulation and induce ATGL expression through the FOXO1/ATGL pathway in liver cells. Thus, alpha-lipoic acid may be a potential therapeutic agent for treating fatty liver disease.

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PMCID: PMC4269824
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In Vivo Efficacy Study of Milk Thistle Extract (ETHIS-094™) in STAM™ Model of Nonalcoholic Steatohepatitis

Pilar Pais[1] and Massimo D'Amato[2]

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Silymarin has been shown to exert (1) antioxidant activity (silymarin is an ROS scavenger and also reduces the loss of endogenous antioxidant enzymes such as glutathione reductase and peroxidase, catalase and superoxide dismutase [7, 11]); (2) anti-inflammatory activity (silymarin interferes with the NF-κB-induced inflammatory cascade, namely, on the leukotrienes release by Kupffer cells [12]); and (3) antifibrotic activity (silymarin has been shown to reduce liver collagen deposition in vivo in models of chronic toxic liver damage [8] and in a primate model of chronic alcoholic liver damage [13]). The same antifibrotic activity has also been recently demonstrated in a dietary model of NASH [14].

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The MT extract used in the present study induced a decreasing trend in NAS compared with the vehicle group. Among the three items of the NAS, MT decreased the steatosis score compared with the vehicle group. The lack of power resulting from the small sample size was the most likely reason that this comparison failed to detect a statistical difference between treatments.

The reduction in steatosis score was accompanied by a statistically significant decrease in liver weight and the liver-to-body weight ratio, which implies a potential anti-steatosis effect of MT. The decrease in steatosis correlated well with reduced liver weights, indicating less accumulation of fat in the hepatocytes of animals treated with MT compared with controls. The lack of improvement in hepatocellular ballooning and inflammation should be explored in future studies of longer duration, possibly also in combination with anti-inflammatory/fibrotic agents that lack an anti-steatosis effect.

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Research article | Open Access | Published: 08 August 2017

Efficacy of glutathione for the treatment of nonalcoholic fatty liver disease: an open-label, single-arm, multicenter, pilot study

Yasushi Honda, Takaomi Kessoku, Yoshio Sumida, Takashi Kobayashi, Takayuki Kato, Yuji Ogawa, Wataru Tomeno, Kento Imajo, Koji Fujita, Masato Yoneda, Koshi Kataoka, Masataka Taguri, Takeharu Yamanaka, Yuya Seko, Saiyu Tanaka, Satoru Saito, Masafumi Ono, Satoshi Oeda, Yuichiro Eguchi, Wataru Aoi, Kenji Sato, Yoshito Itoh & Atsushi Nakajima

Glutathione plays crucial roles in the detoxification and antioxidant systems of cells and has been used to treat acute poisoning and chronic liver diseases by intravenous injection. This is a first study examining the therapeutic effects of oral administration of glutathione in patients with nonalcoholic fatty liver disease (NAFLD).

Research article | Open Access | Published: 08 August 2017

Efficacy of glutathione for the treatment of nonalcoholic fatty liver disease: an open-label, single-arm, multicenter, pilot study

Yasushi Honda, Takaomi Kessoku, Yoshio Sumida, Takashi Kobayashi, Takayuki Kato, Yuji Ogawa,

The levels of protein-bound glutathione were reported to return to baseline levels after an overnight fast [12]. In the current study, we found that the baseline level of the protein-bound form of glutathione significantly decreased after an overnight fast following 4 months of glutathione administration, especially in ALT responders. The levels of protein-bound glutathione in patients in the current study were considerably higher than those of healthy volunteers in previous studies [12] estimated using the same method. Glutathione treatment also decreased protein-bound glutathione to normal baseline levels. These findings suggest that oral administration of glutathione may increase the incorporation of protein-bound glutathione into the liver or decrease the pathological excretion of glutathione from the liver.

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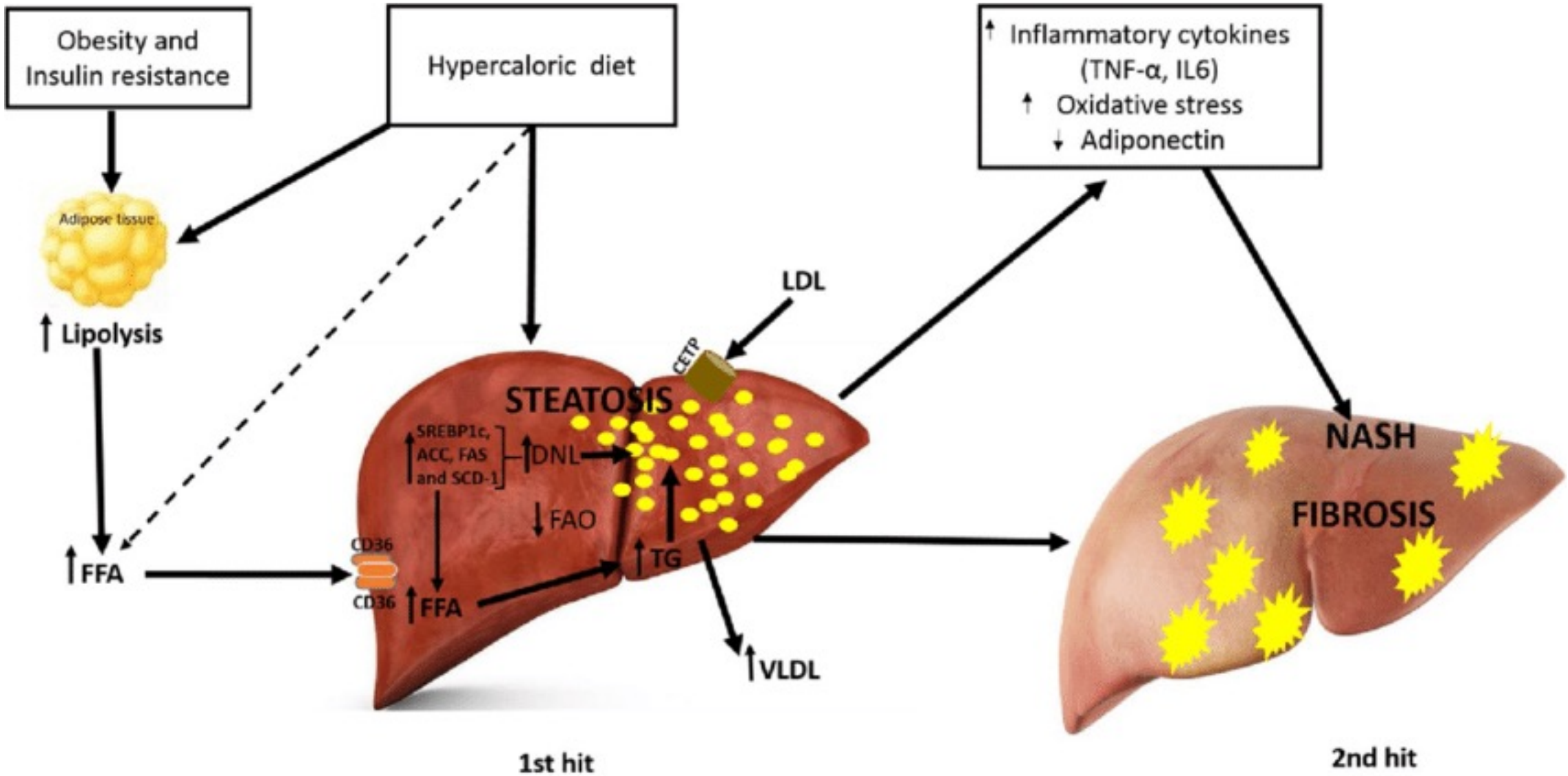
Efficacy of glutathione for the treatment of nonalcoholic fatty liver disease: an open-label, single-arm, multicenter, pilot study

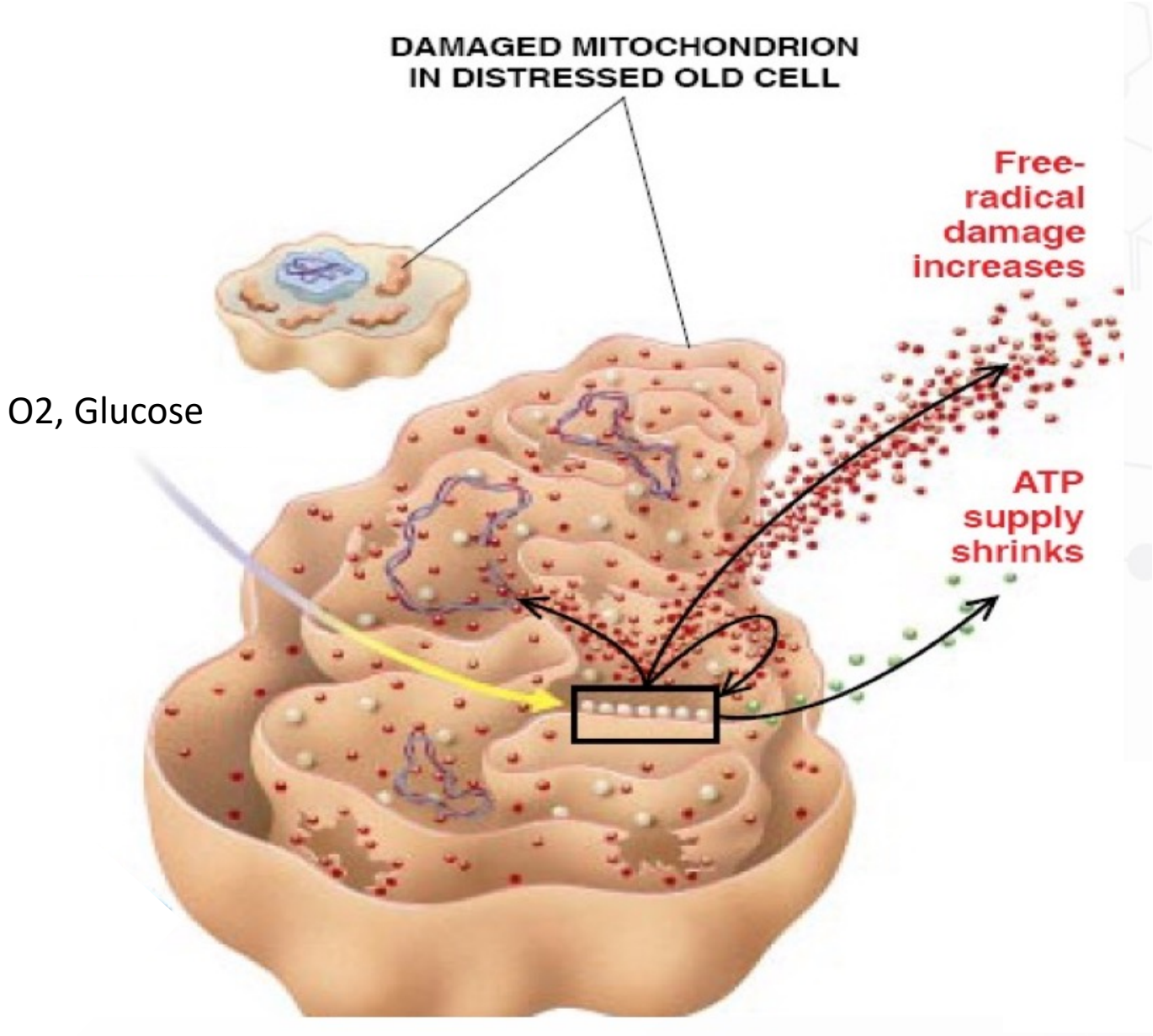
Yasushi Honda, Takaomi Kessoku, Yoshio Sumida, Takashi Kobayashi, Takayuki Kato, Yuji Ogawa, Wataru Tomeno, Kento Imajo, Koji Fujita, Masato Yoneda, Koshi Kataoka, Masataka Taguri, Takeharu

Treatment with glutathione significantly improved ALT levels. In addition, CAP values were significantly reduced in ALT responders. Our pilot study suggests that oral administration of glutathione supports hepatic metabolism and improves NAFLD. To elucidate the mechanism behind the beneficial effects of glutathione, further studies that examine the incorporation of orally administrated glutathione into the liver and the effects on the host redox system using stable isotope-labeled glutathione and animal models are required. Large-scale clinical trials are necessary to confirm the therapeutic effects of glutathione.



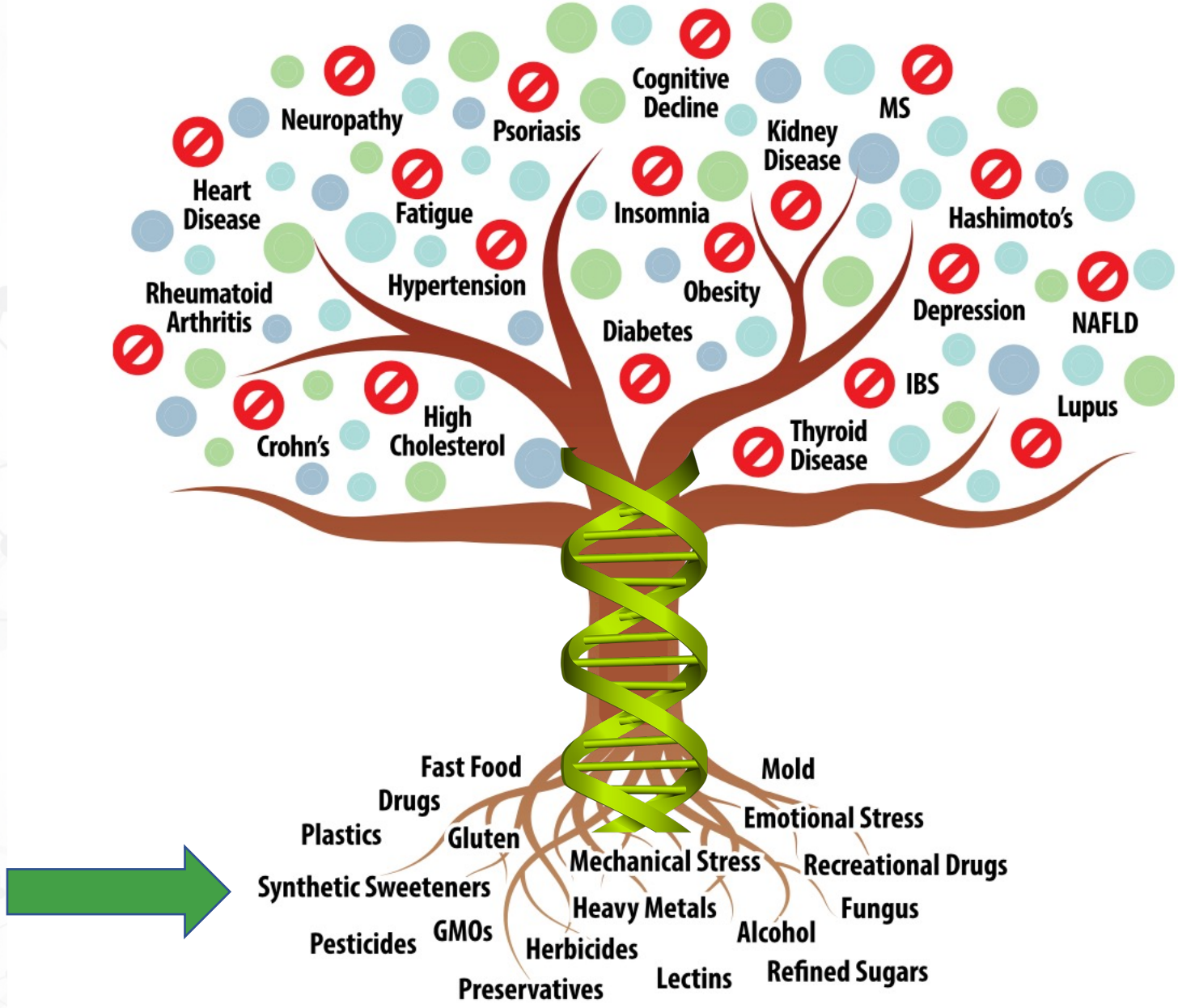
https://www.researchgate.net/publication/347694255/figure/fig1/AS:974032077852679@1609238752686/Pathogenesis-of-NAFLD-The-pathogenesis-of-NAFLD-is-suggested-to-be-driven-by-two-hit-1st.png

Adiponectin is a hormone and an adipokine protein that affects several metabolic processes and is mainly known for its insulin-sensitizing and anti-inflammatory effects. Your adipose tissue (body fat) is mainly responsible for producing adiponectin, though other tissues in your body produce it as well. Cleveland Clinic



O2, Glucose

Source: Weindrich_SciAm_1996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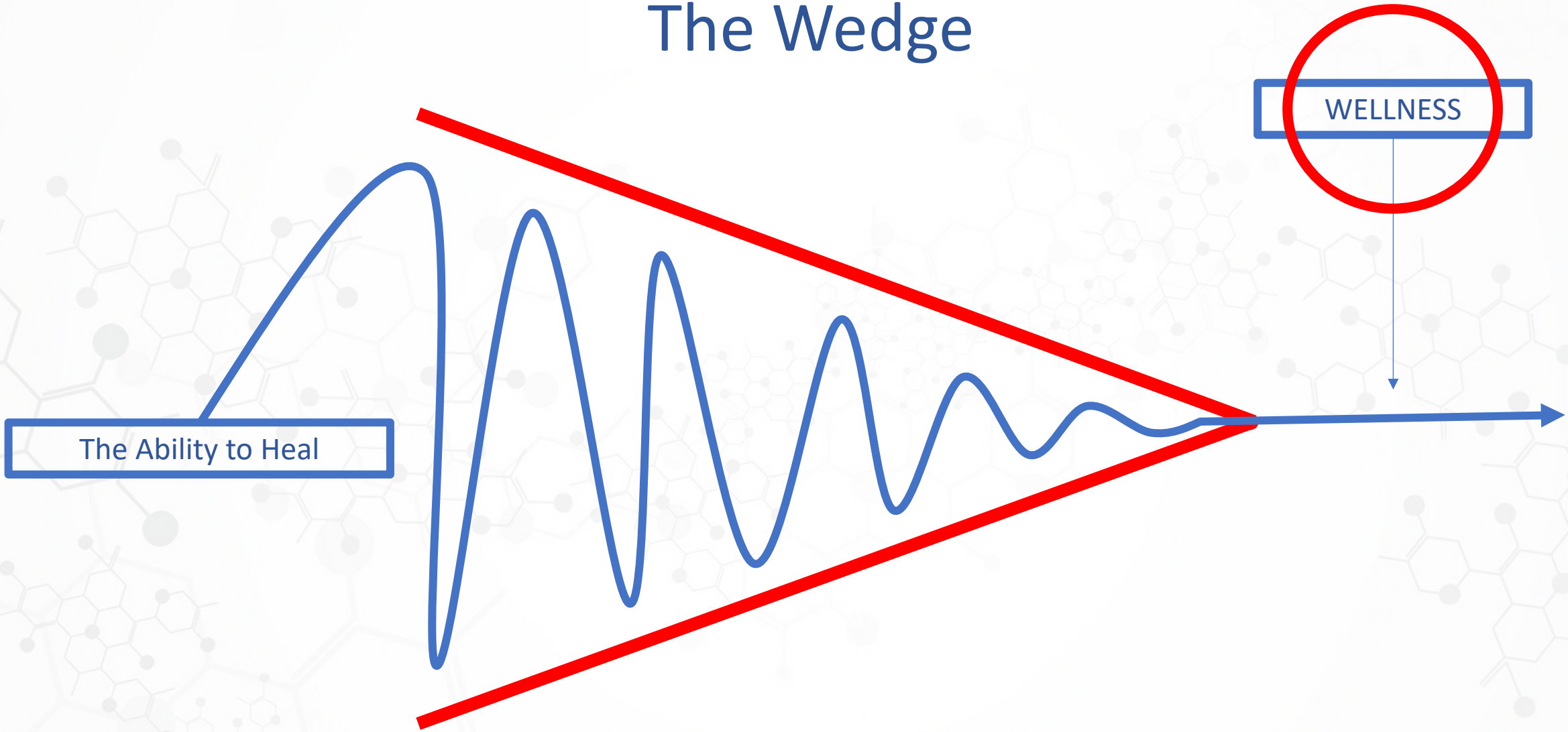
The Wedge



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