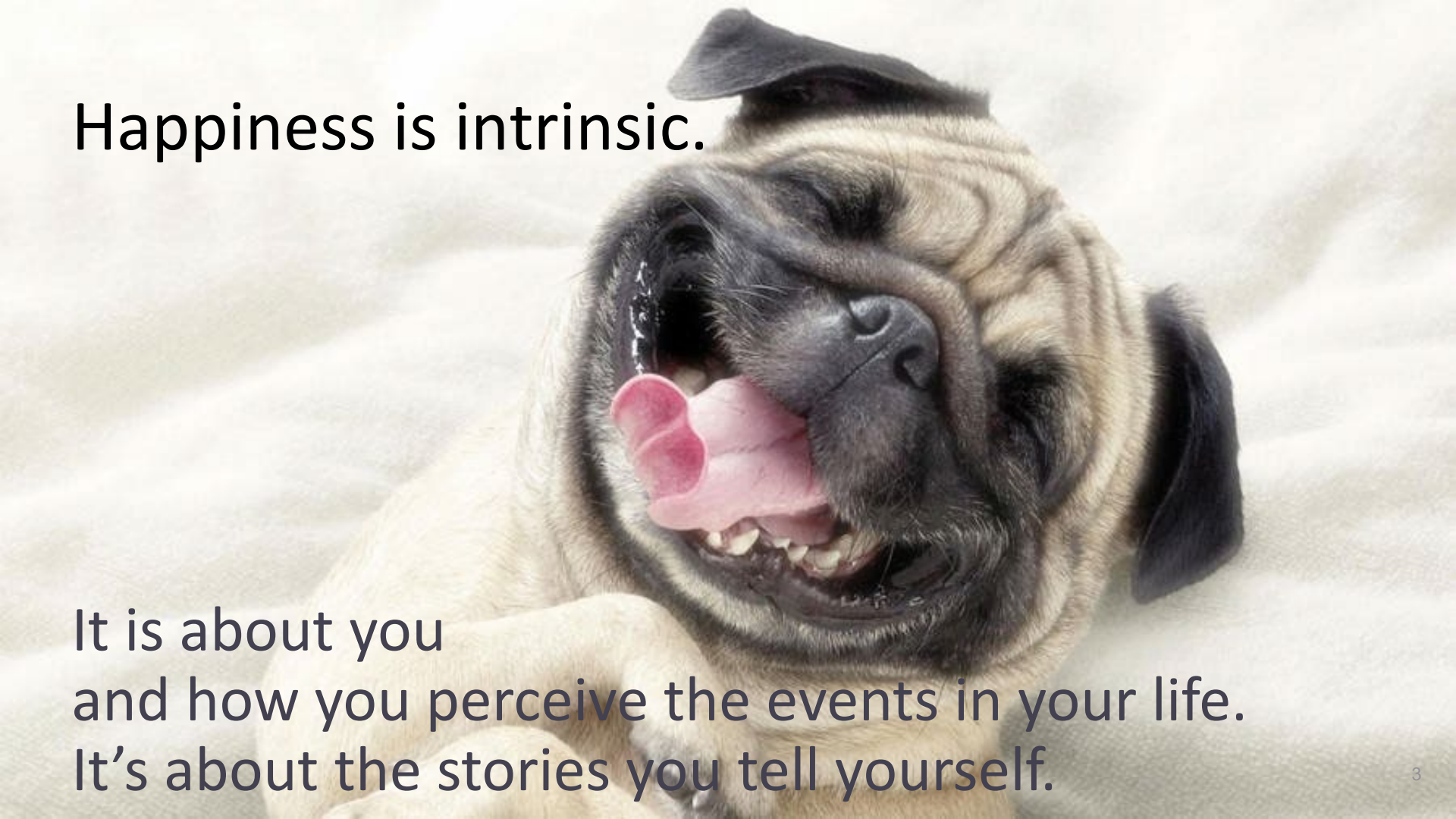
Spirit, Sleep & Immunity

Heather Zwickey, PhD

Disclosures

Role	Company
Director of Communication and Innovation	Thaena, Inc.
Professor/Faculty	National University of Natural Medicine University of Western States Academy of Integrative Health and Medicine
Scientific Advisory Board	Burt's Bees
Scientific Advisory Board	Clorox
Wellness Advisory Board	GSK
Speaker	Metagenics Institute
Researcher/Principal Investigator	National Center for Complementary and Integrative Health



Happiness is intrinsic.

It is about you
and how you perceive the events in your life.
It’s about the stories you tell yourself.

Objectives

Biology of Sleep;

Sleep & Immunity;

Pharmacology of Sleep;

Discuss how spiritual well being and life-purpose influences sleep and immunity

Part 1

Sleep

What is sleep?

Sleep: Behavioral. Sustained immobility or quiescence. Exceptions.

Dolphins

Seals

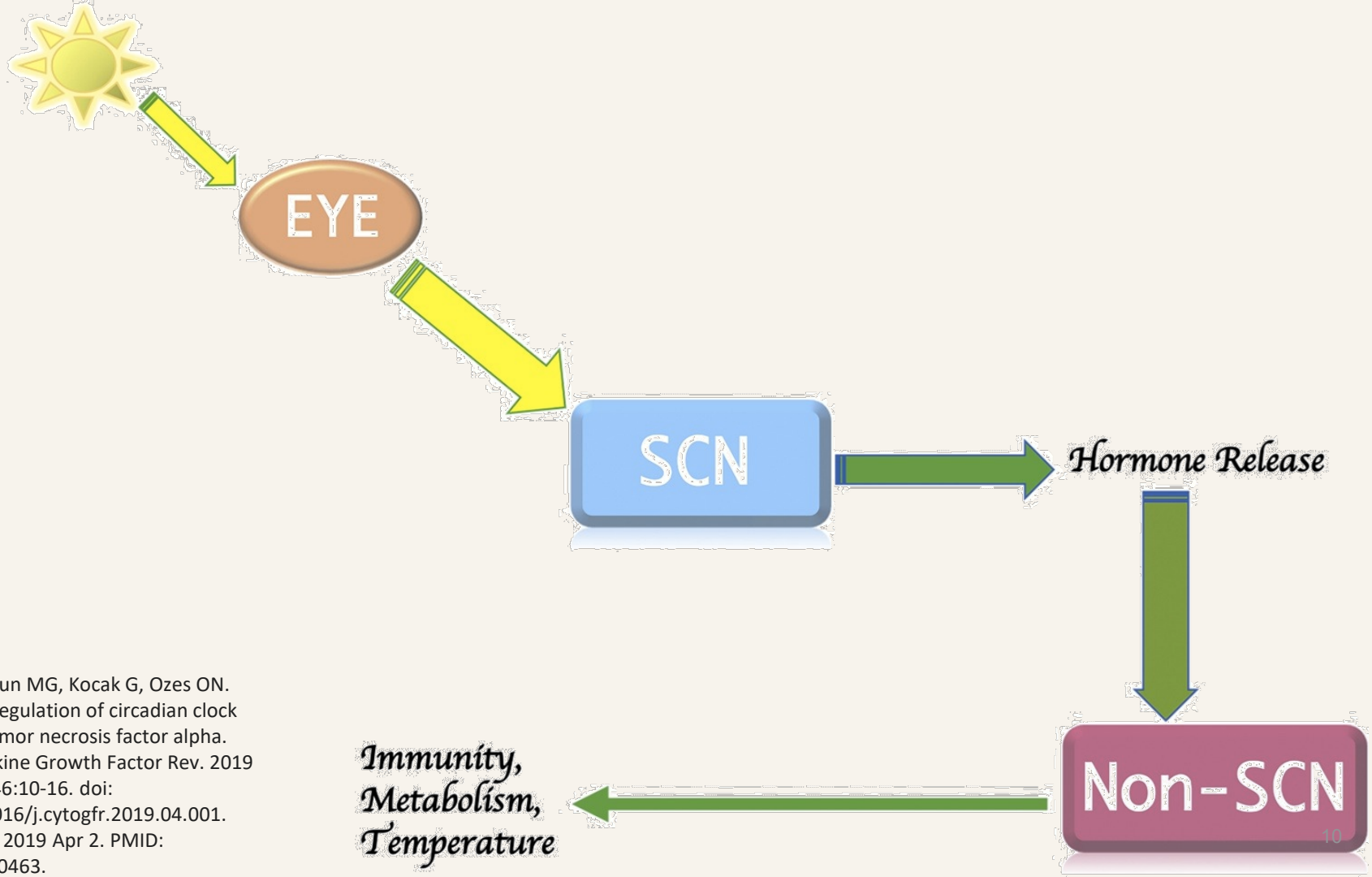
Whales

Sleep: Characteristic posture lying down. Exceptions.

Horses

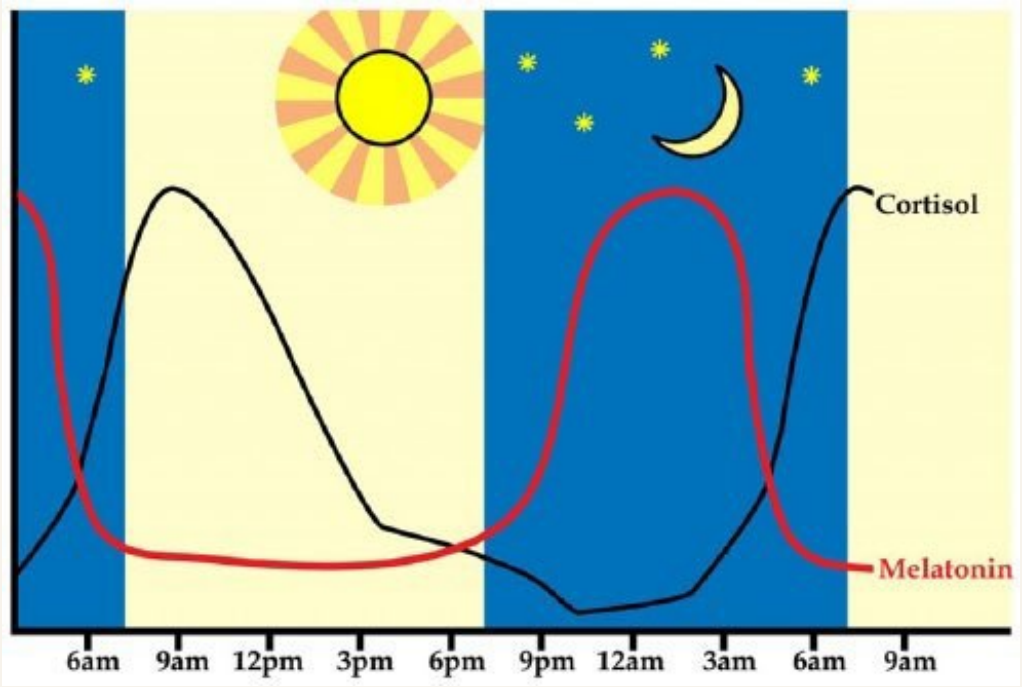
Elephants

Sleep: Reduced responsiveness to external stimuli

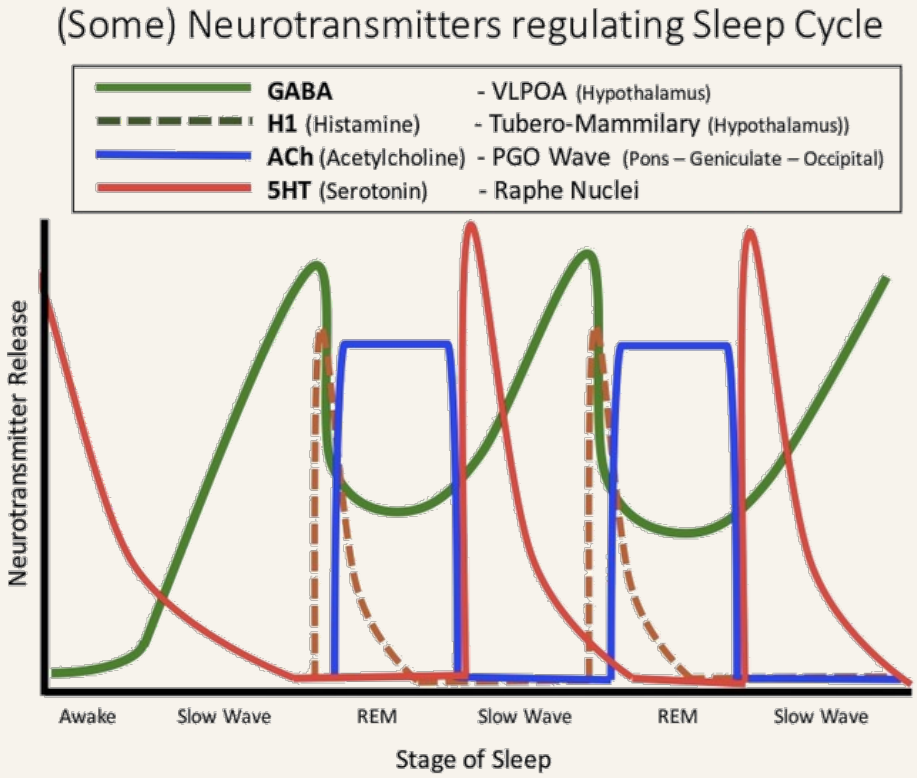


Ertosun MG, Kocak G, Ozes ON. The regulation of circadian clock by tumor necrosis factor alpha. Cytokine Growth Factor Rev. 2019 Apr;46:10-16. doi: 10.1016/j.cytogfr.2019.04.001. Epub 2019 Apr 2. PMID: 31000463.

Biology of Sleep: Cortisol and Melatonin



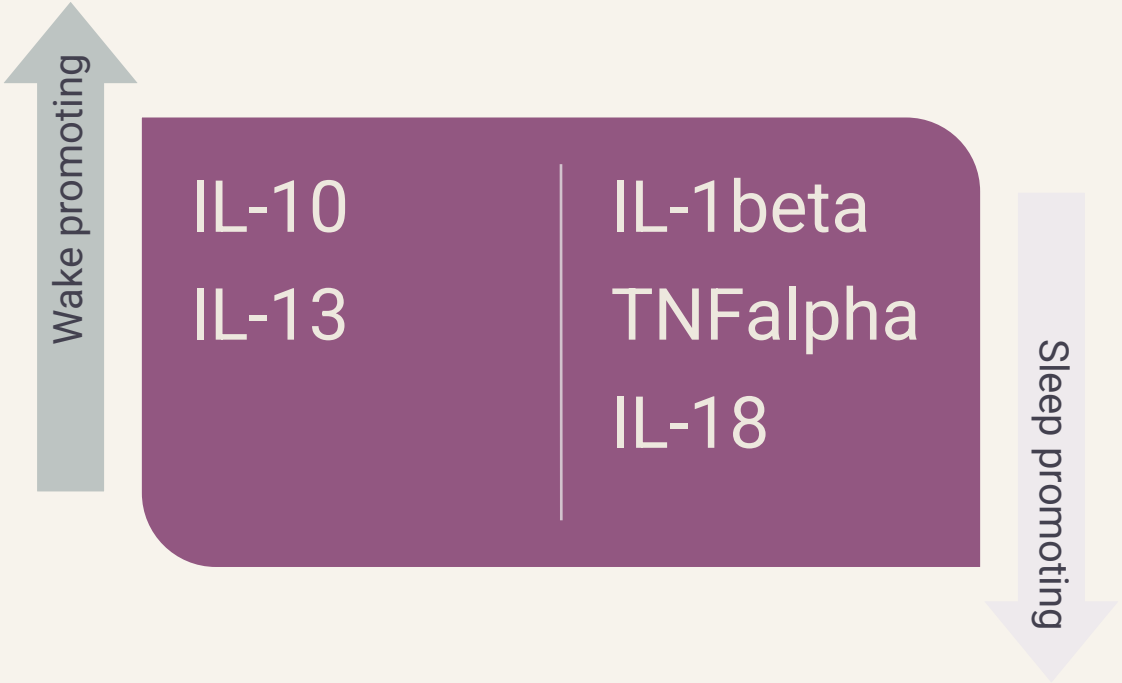
Biology of Sleep: Neurotransmitters



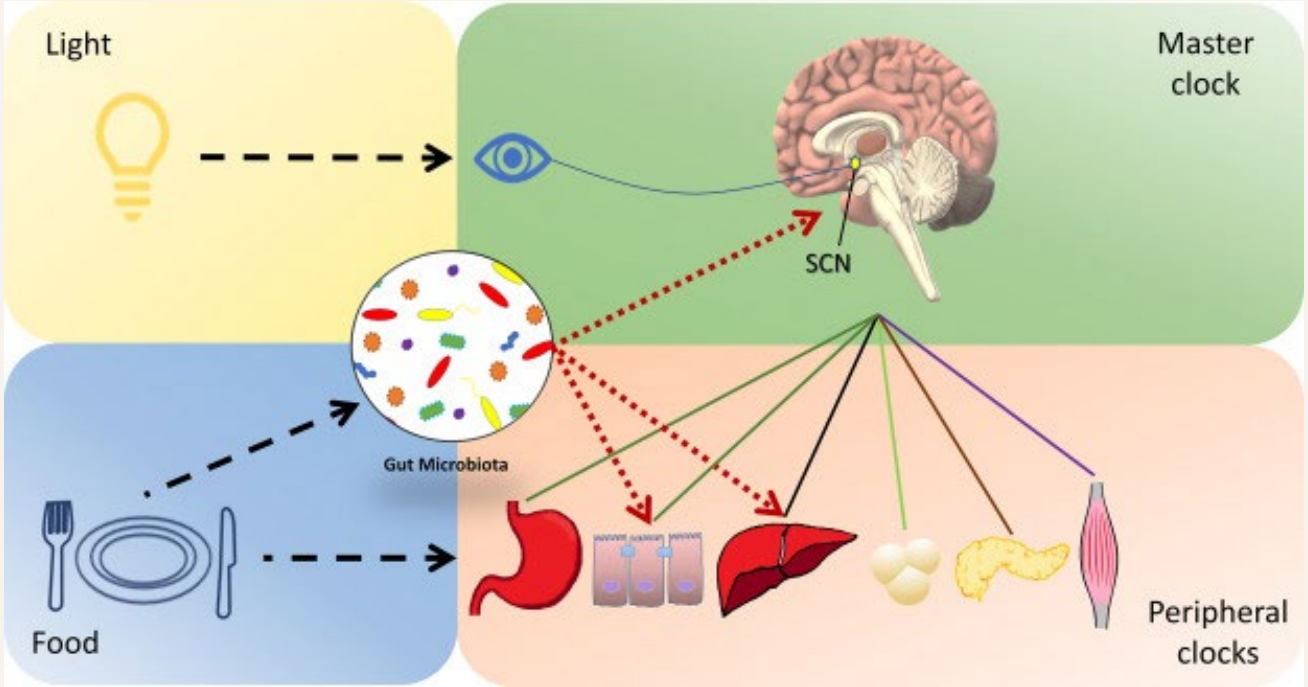
https://quizlet.com/276321380/sleep-and-arousal-diagram/

VW

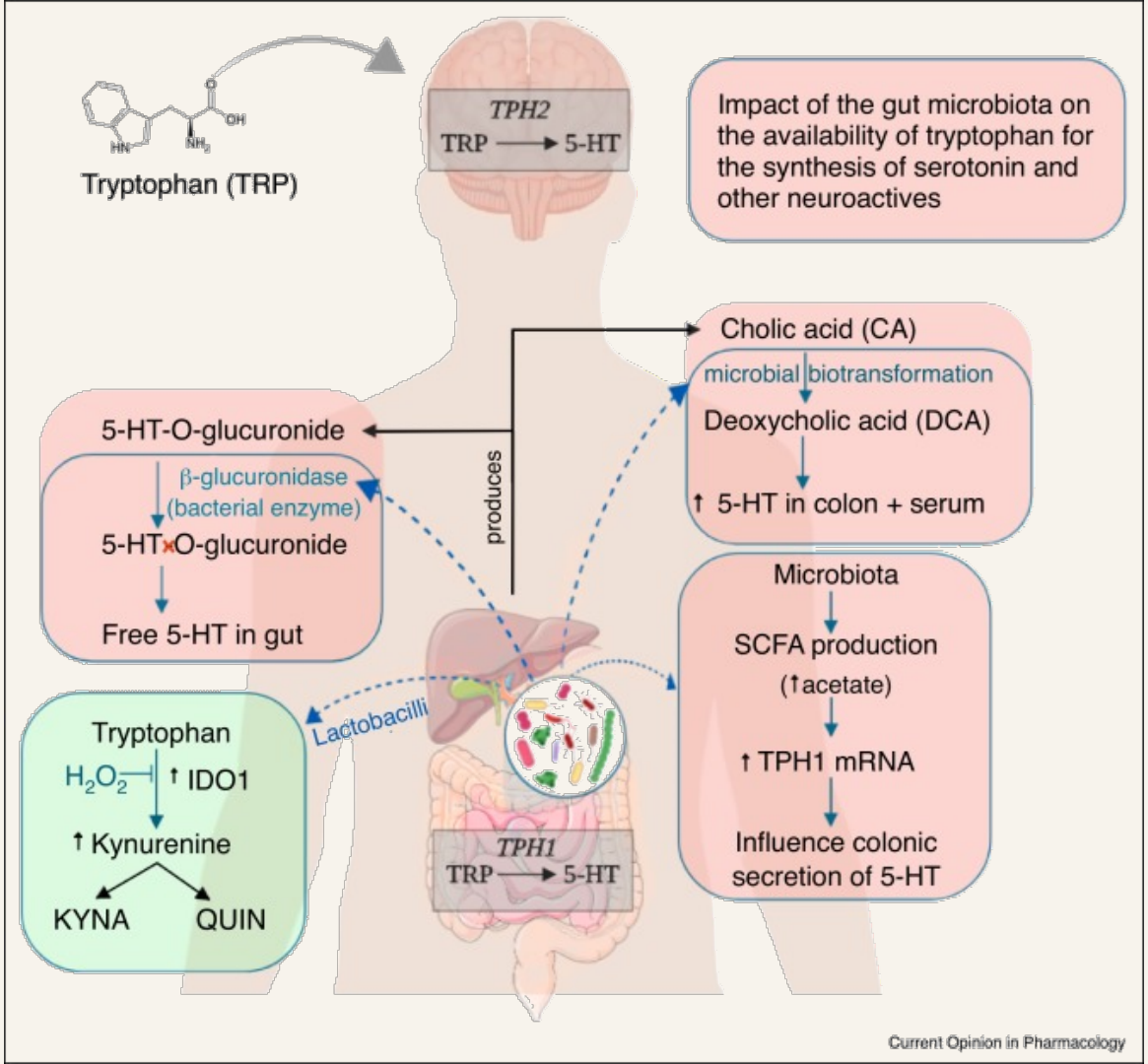
Biology of Sleep: Cytokines



Biology of Sleep: Microbiome

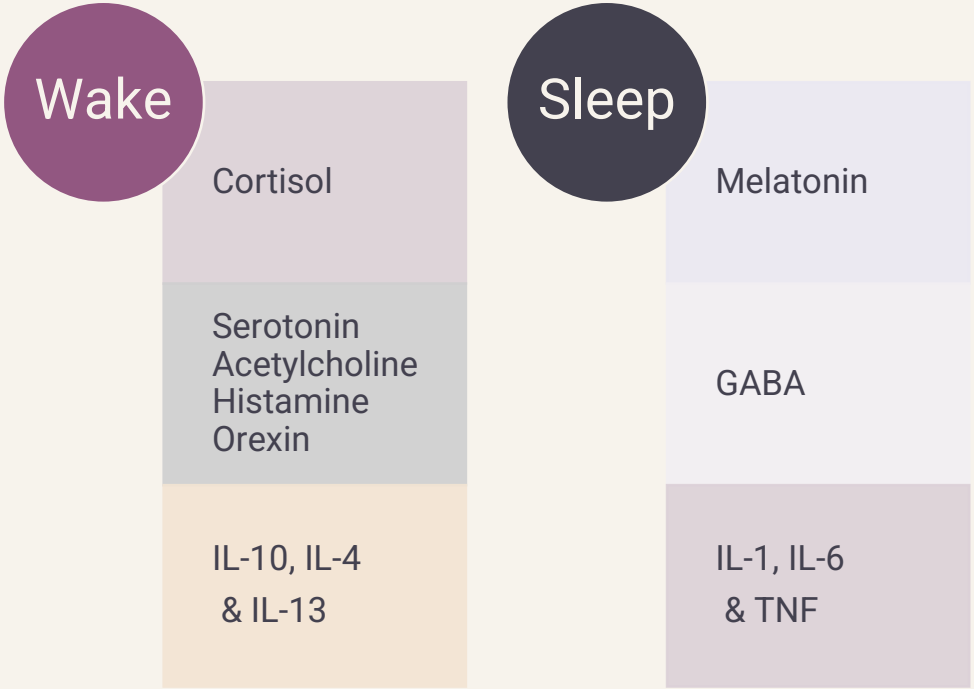


Matenchuk, B. A., Mandhane, P. J., & Kozyrskyj, A. L. (2020). Sleep, circadian rhythm, and gut microbiota. *Sleep medicine reviews*, *53*, 101340. https://doi-org.liboff.ohsu.edu/10.1016/j.smrv.2020.101340



Gheorghe, C. E., Martin, J. A., Manriquez, F. V., Dinan, T. G., Cryan, J. F., & Clarke, G. (2019). Focus on the essentials: tryptophan metabolism and the microbiome-gut-brain axis. *Current opinion in pharmacology*, *48*, 137–145. https://doi-org.liboff.ohsu.edu/10.1016/j.coph.2019.08.004

Putting it together



Melatonin, GABA, IL-1 & TNF-alpha

Part 2

Sleep and Immunity

Relationship between sleep and immunity

IL-1 beta
IL-6
TNF alpha
Promotes sleep

IL-4
IL-13

IL-10

Promotes wakefulness

Sleep deprivation

24/7 Society

Smart-phone addiction

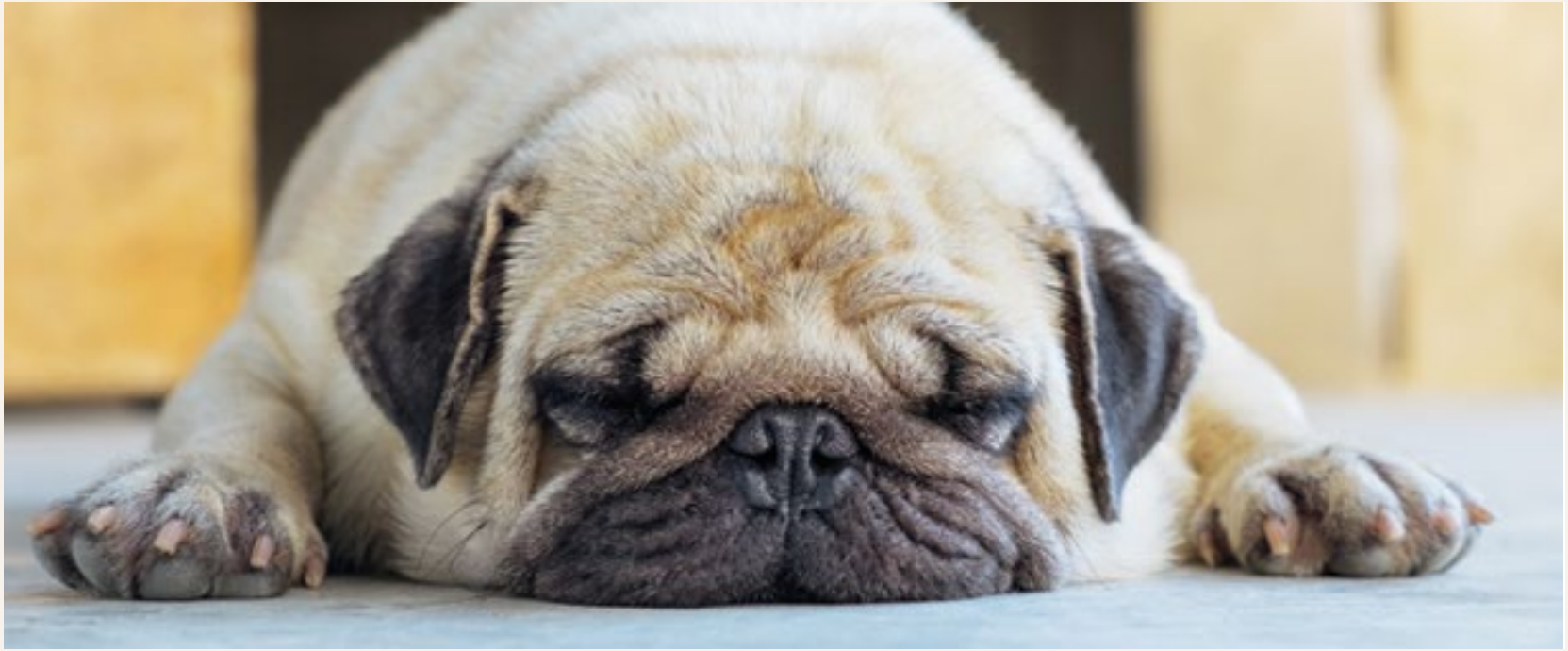
Blue light

Poor diet

Sleep apnea

Stress

Fatigue, excessive daytime sleepiness, and impaired cognitive performance



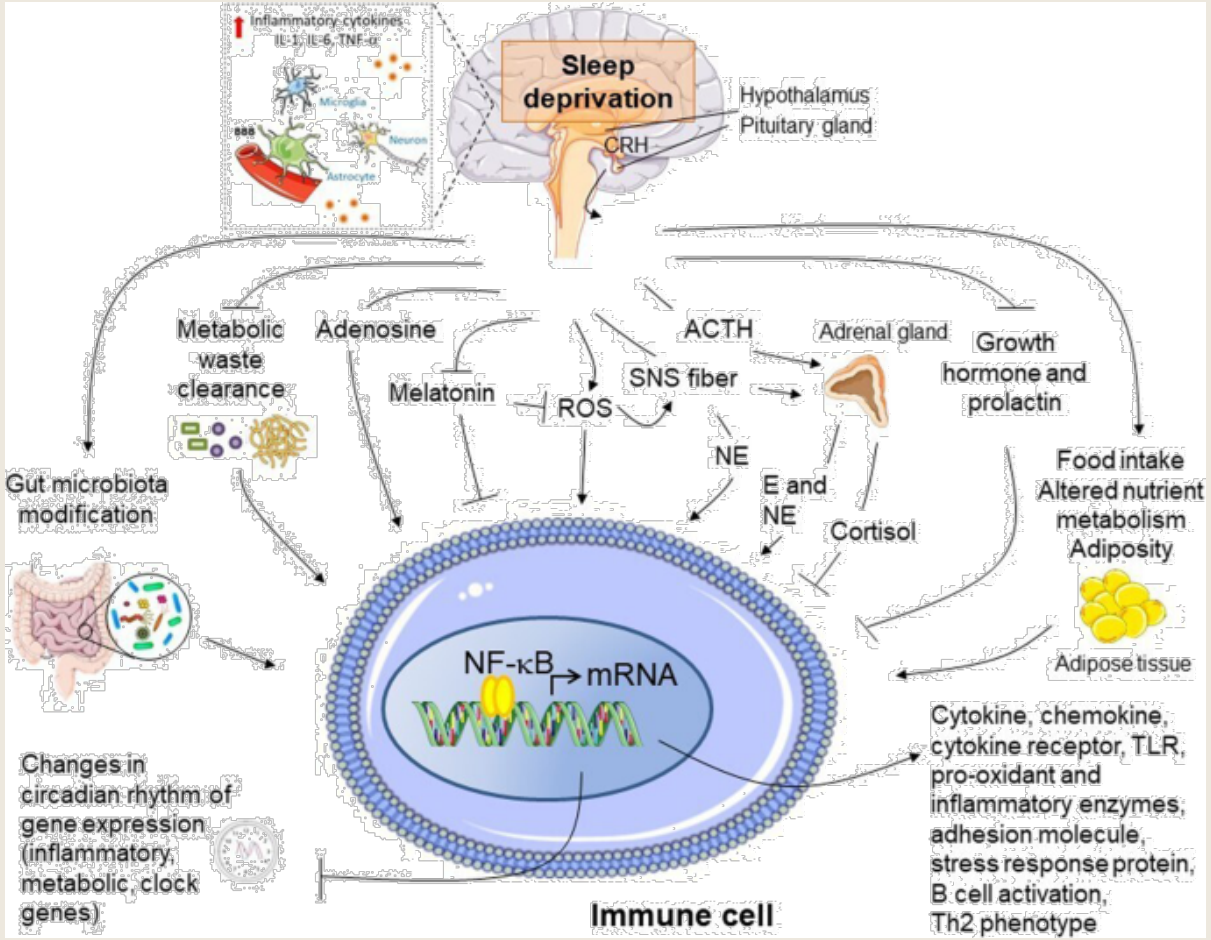
Relationship between sleep and immunity

Bacteria cell wall components (muramyl and LPS) induce sleep

Pro-inflammatory cytokines

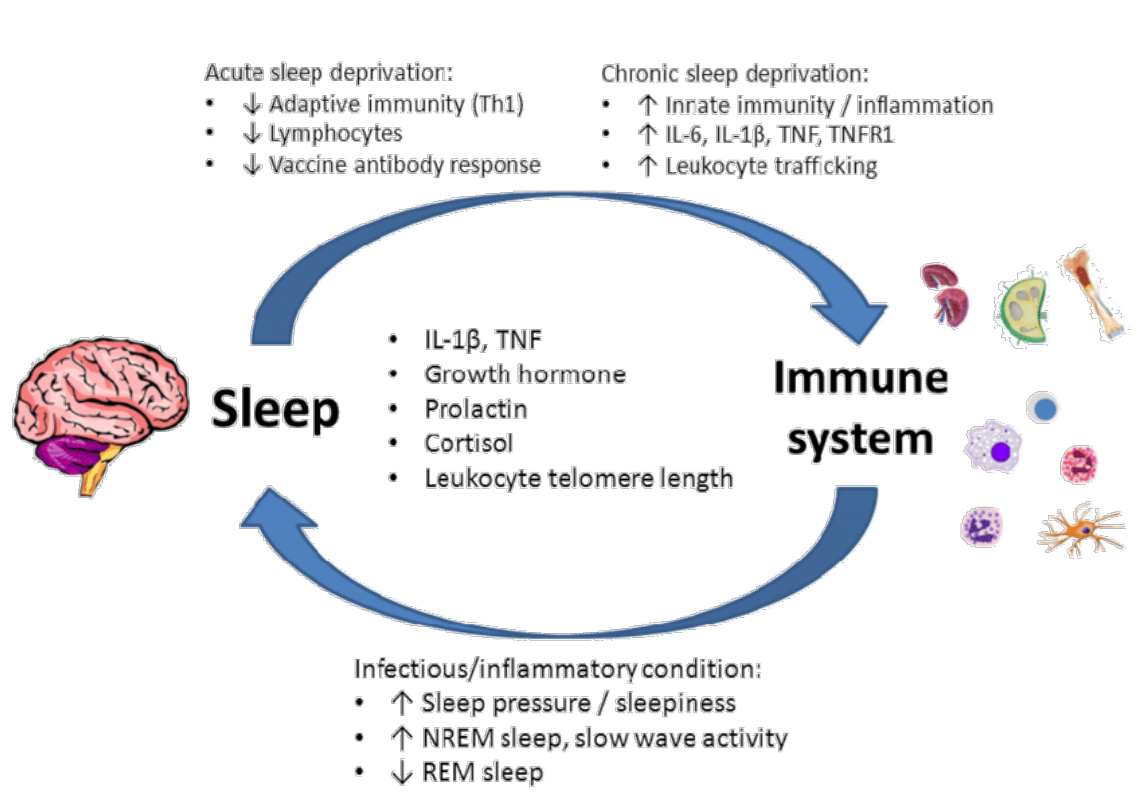
Cytokine receptors

Prostaglandins



Garbarino, S., Lanteri, P., Bragazzi, N.L. *et al.* Role of sleep deprivation in immune-related disease risk and outcomes. *Commun Biol* **4**, 1304 (2021). https://doi.org/10.1038/s42003-021-02825-4

Relationship between sleep and immunity



Garbarino, S., Lanteri, P., Sannita, W. G., Bragazzi, N. L., & Scoditti, E. (2020). Circadian Rhythms, Sleep, Immunity, and Fragility in the Elderly: The Model of the Susceptibility to Infections. *Frontiers in neurology*, *11*, 558417. https://doi-org.liboff.ohsu.edu/10.3389/fneur.2020.558417

Part 3

Pharmacology of Sleep

Sleep CBT (Cognitive Behavioral Therapy)

Sleep Consolidation

- Limit the amount of time spent in bed

Stimulus Control

- Only use bed for sleeping & sex (No reading, watching TV, etc.)

Cognitive Restructuring

- Change negative talk: Even if it takes a little while to fall asleep, I'll be fine tomorrow

Relaxation Techniques

- Mindfulness meditation, Yoga nidra, Breathing exercises

Sleep Hygiene

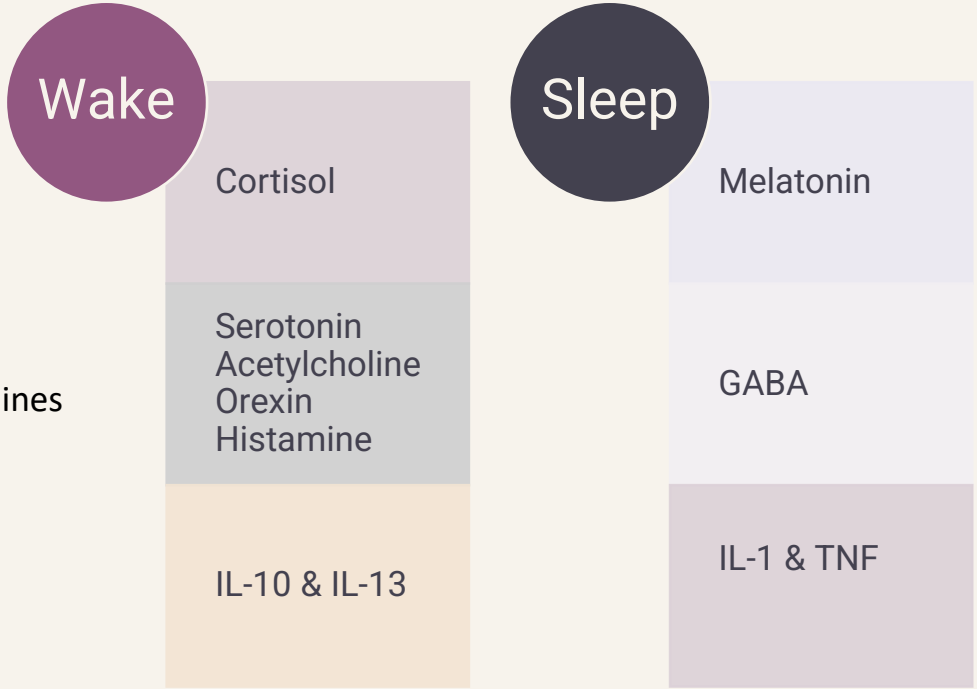
Rossman J. Cognitive-Behavioral Therapy for Insomnia: An Effective and Underutilized Treatment for Insomnia. Am J Lifestyle Med. 2019 Aug 12;13(6):544-547. doi: 10.1177/1559827619867677. PMID: 31662718; PMCID: PMC6796223.

Sleep Hygiene

- Go to bed at the same time each night and wake up at the same time each morning.
- Refrain from eating 2 to 3 hours before bedtime.
- Avoid alcohol 2 to 3 hours before bedtime.
- Avoid exposure to bright light 2 hours before bedtime.
- Avoid caffeine in the afternoon and evening.
- Engage in a relaxing evening routine.
- Expose yourself to bright outdoor light in the morning or early afternoon.
- Decrease exposure to computer screens and cell phones 1 to 2 hours before bedtime.

Rossman J. Cognitive-Behavioral Therapy for Insomnia: An Effective and Underutilized Treatment for Insomnia. Am J Lifestyle Med. 2019 Aug 12;13(6):544–547. doi: 10.1177/1559827619867677. PMID: 31662718; PMCID: PMC6796223.

Sleep Medications



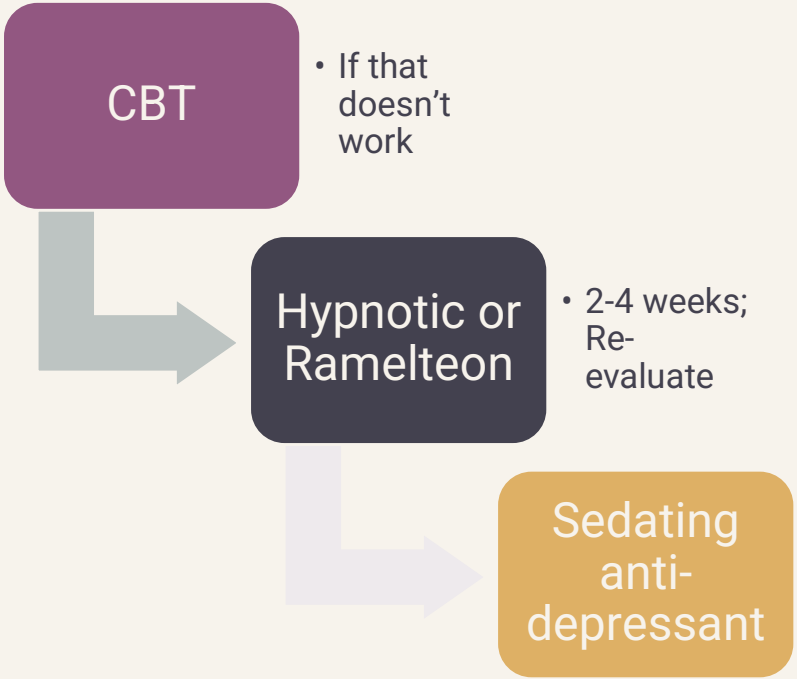
SSRI's
Anti-histamines

Ramelton

Benzodiazapines
Non-benzos

Anti-inflammatories
Biologics

Sleep Medications



Sleep Medications: Hypnotic

Bezodiazapines

Hypnotic Agent	Recommended Dose Range (mg)	Half-life (Hours)	Onset
Quazepam	7.5-15	39-200	fast
Flurazepam	15-30	4 days + metabolites	fast
Estazolam	0.5-2	10-24	Fast-moderate
Temazepam	7.5-30	8-20 hours	Fast-moderate
Triazolam	0.125-0.5	1.5-5.5	Fast

Sleep Medications: Benzos

- Commonly prescribed for treatment of anxiety and insomnia, despite many potential risks
- An estimated 1.8-8.2% of hip fractures in five Western European countries and the US may be attributable to benzo use (Khong, de Vries et al. 2012)
- Short-acting benzos appeared associated more with hip fractures than long-acting benzos
- Memory and cognitive impairment
- Increased risk of traffic accidents
- Risk of tolerance, dependence, abuse potential
- Avoid in: elderly, patients with TBI, OSA, dementia, substance use disorders, if receiving other CNS depressants

Sleep Medications: Hypnotic

Non-Bezodiazapines

Hypnotic Agent	Recommended Dose Range (mg)	Half-life (Hours)	Onset
Eszopiclone	1 - 3	6 - 9	fast
Zolpidem	5 – 10	2 - 5	fast
Zaleplon	5 - 20	1	fast

Abuse potential less than benzos
Insufficient evidence to say whether non-benzos are safer than benzos

Sleep Medications

Automatic sleep behaviors: may occur with zolpidem at high doses

Rebound insomnia

Impaired motor function

Falls

Impaired cognitive function, including amnesia

Daytime impairment

Dosing changes in 2013 (FDA)

Women:

- Recommended dose of zolpidem lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR)

Men:

- Consider prescribing the lower doses—5 mg for immediate-release products and 6.25 mg for extended- release products

Dosing changes in 2014 (FDA)

Eszopiclone

- 3 mg dose causes impairment to driving skills, memory, and coordination lasting more than 11 hours after evening dose
- Recommended starting dose of 1 mg for both men and women

Sleep Medications: Ramelton

- Melatonin agonist – binds to M1 and M2 receptors
- Half-life of 1.5 to 5 hours
- Metabolized by the liver; used with caution in hepatic insufficiency
- Weak evidence for reduction of sleep latency at recommended prescribed dosage (8 mg)
- No consistent evidence of improvement in other objective or subjective parameters
- Benign side effect profile

The Microbiome and Medications

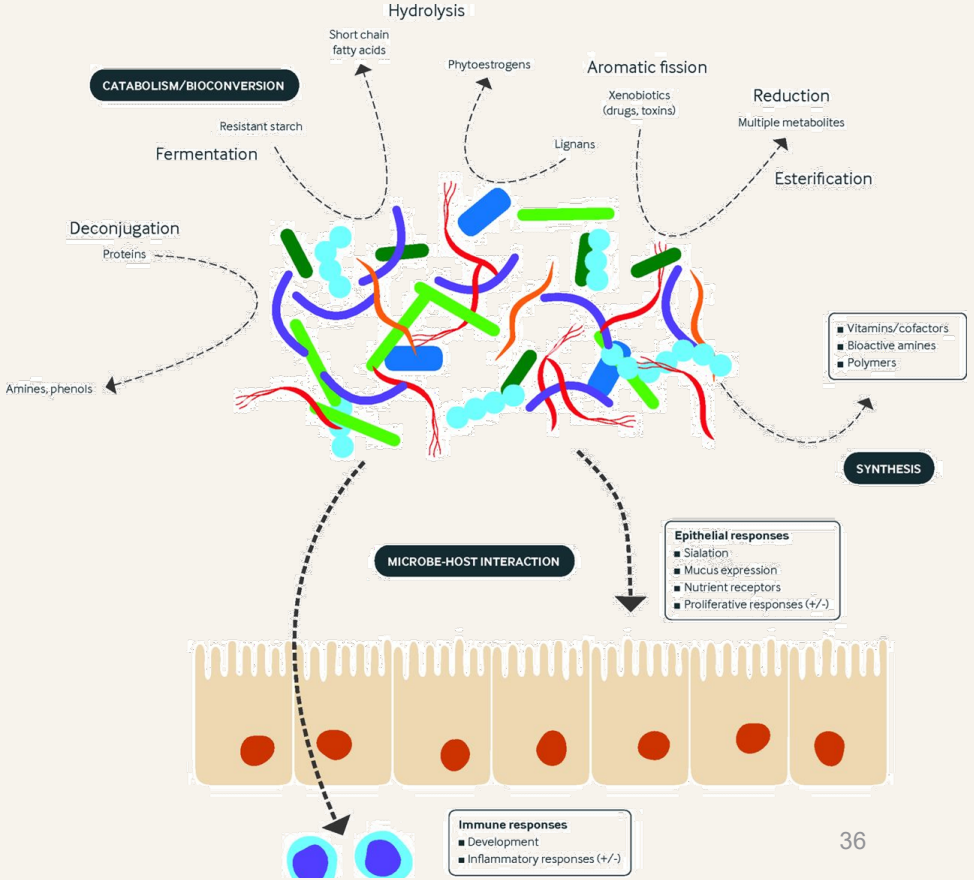
Direct vs Indirect Microbiome-Drug Interactions

Direct Interactions (Metabolism)

- Activation – 5-ASA, Prontosil
- Inactivation – Digoxin
- Enterohepatic recirculation – Diclofenac

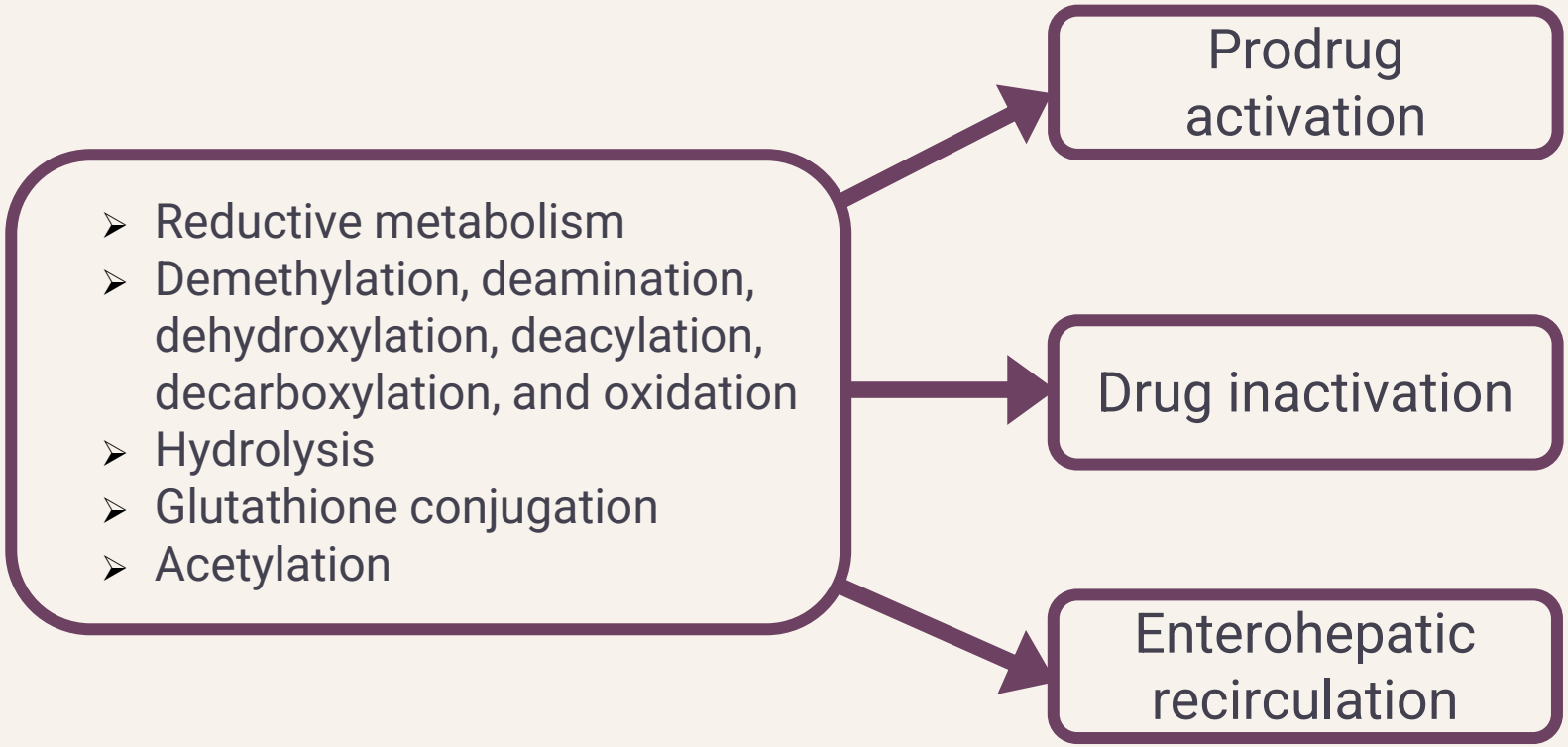
Indirect Interactions (Microbiome-host-drug)

- Competition for drug metabolizing enzymes or transporters by microbiome metabolites
- Modulation of drug metabolizing enzyme or transporter expression
- Changes in microbiome composition or expression



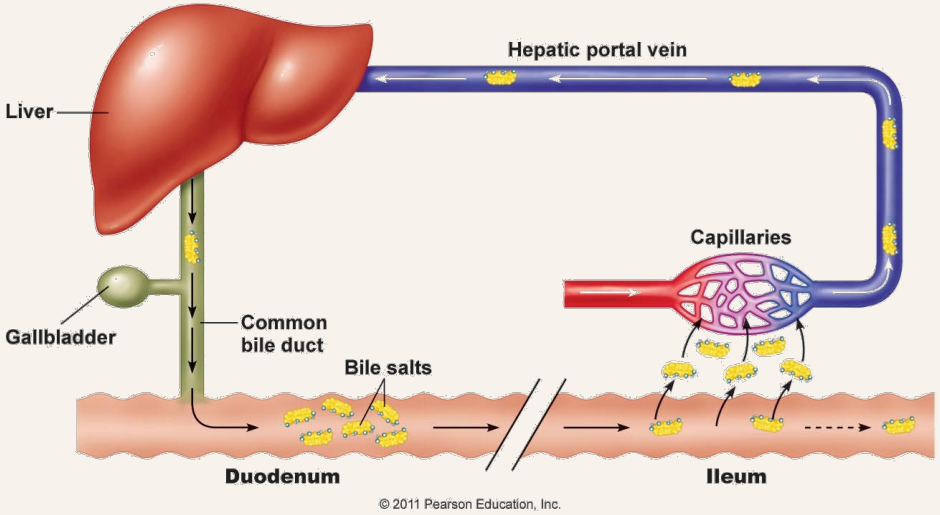
Young, 2017

Biotransformation by the Microbiome



Wilson and Nicholson, 2017

Enterohepatic Recirculation

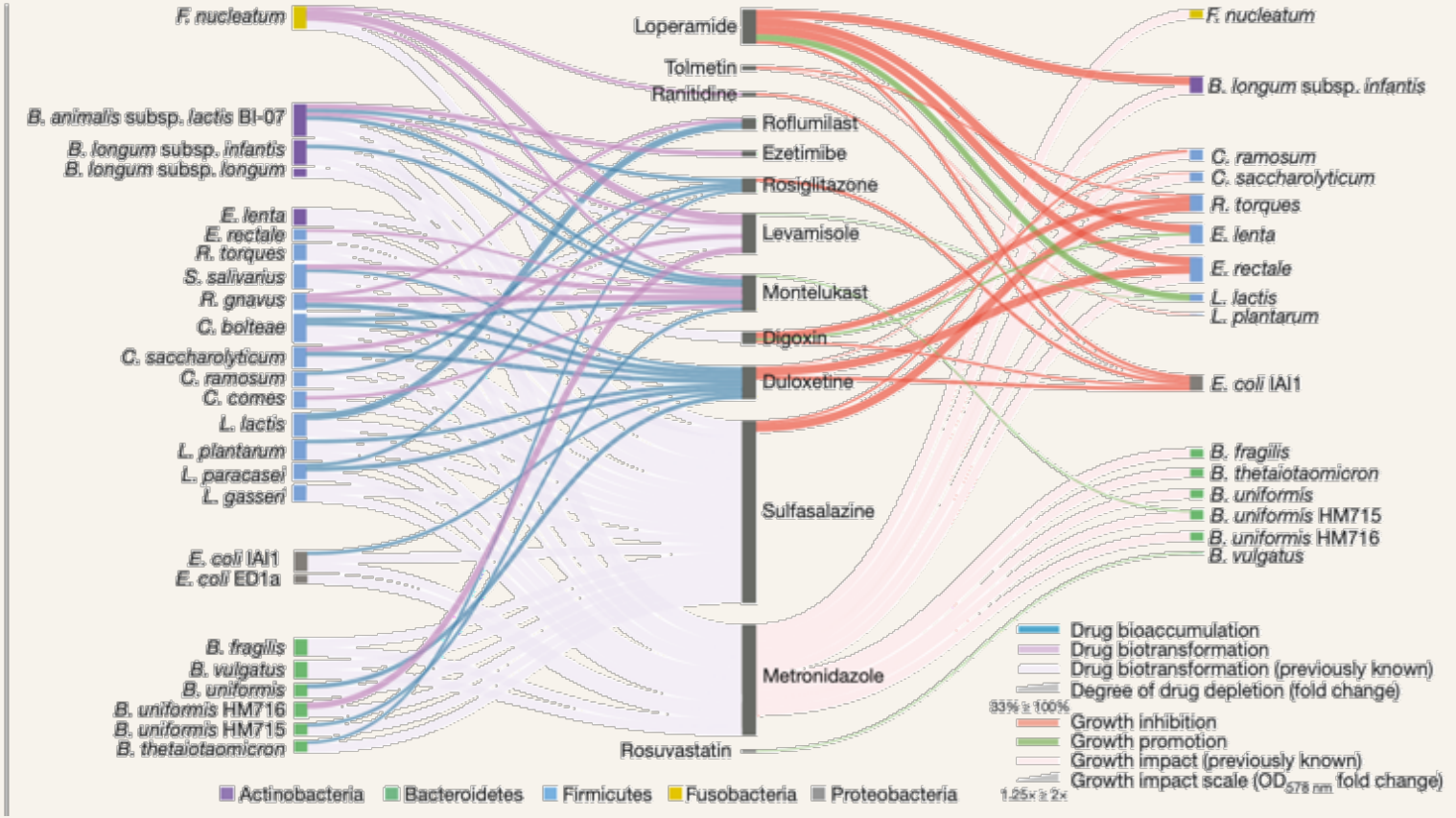


Phase II Enzymes	
UDP-glucuronosyl transferase (UGTs)	Thiopurine S-methyl transferase
Sulfotransferase (SULTs)	Catechol O-methyl transferase
Glutathione-S-transferase (GSTs)	N-/O-methyl transferase
N-acetyltransferase (NATs)	*Epoxide hydrolase (EO), heme oxygenase-1 (HO-1), etc.*

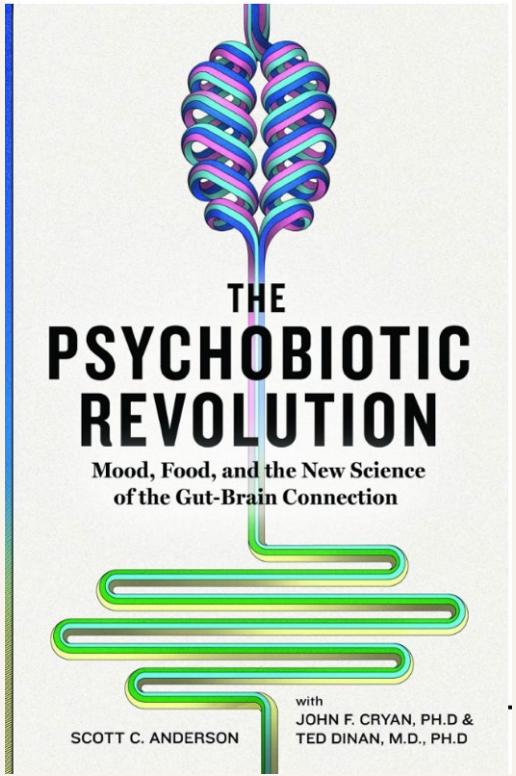
- Enterohepatic recycling occurs by biliary excretion and intestinal reabsorption of a drug.
- Drugs can undergo hepatic conjugation by Phase II metabolizing enzymes and intestinal deconjugation by gut microbiota.
- Cycling is often associated with multiple peaks and a longer apparent half-life in a plasma concentration-time profile.

Roberts et al., 2012

Bioaccumulation of Therapeutic Drugs By Gut Bacteria - Klünemann et al 2021

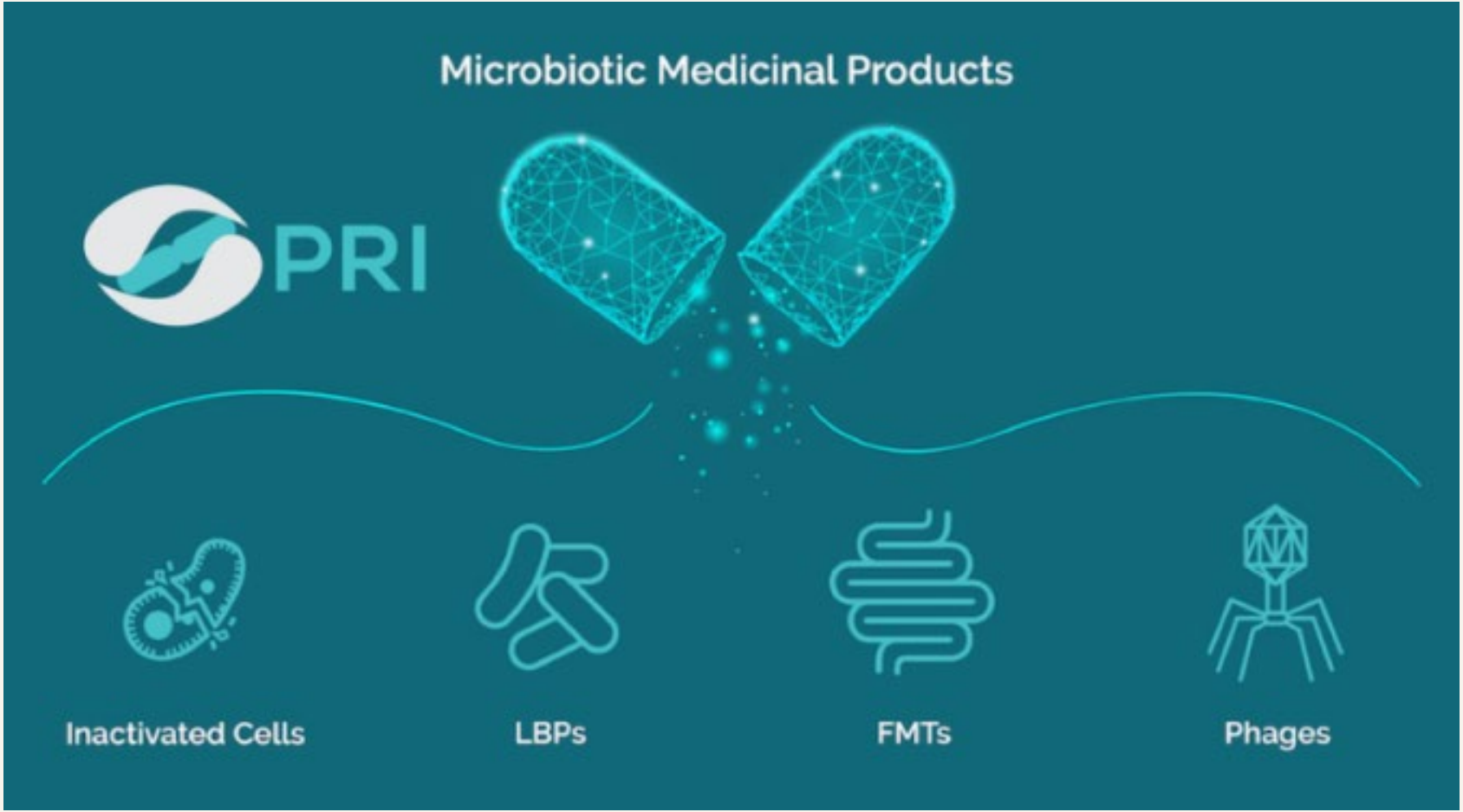


Psychobiotic - Probiotics that impact the brain



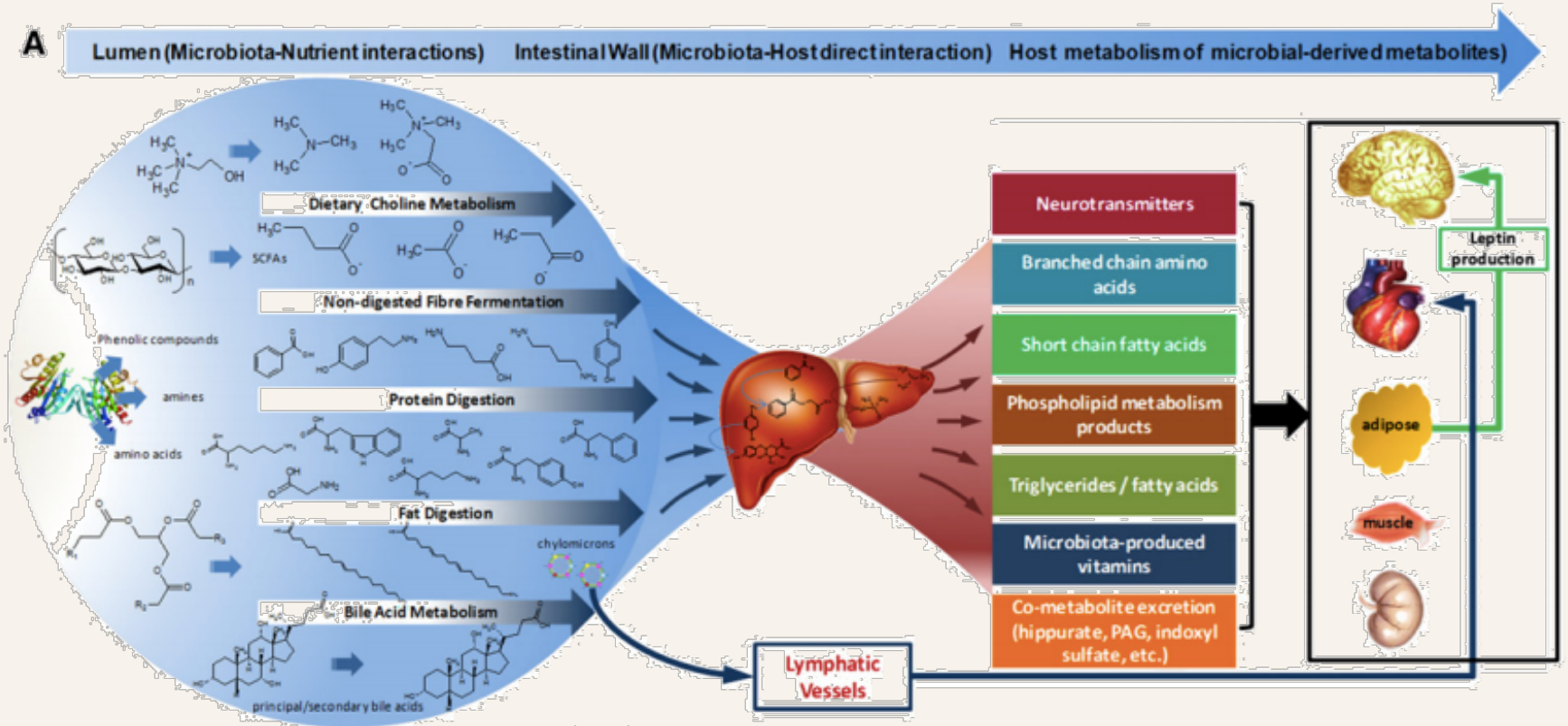
Chapter 7

- B. longum / infantis – Reduce cortisol, stress, and anxiety
- B. breve – anxiety
- B. animalis – IBS/IBD, mood
- B. Bifidum – MDD
- L. Acidophilus – anti-inflammatory
- L. Bulgaricus/helveticus – lowers blood pressure, anxiety, cognitive impairment
- L. rhamnosus – depression and anxiety, reduces cortisol
- L. reuteri – satiety, reduces inflammation and heart disease
- L. plantarum – IBS, reduces inflammation
- L. casei – Mood
- L. paracasei – Liver support and pain
- S. boulardii – immune support, diarrhea, IBS, IBD



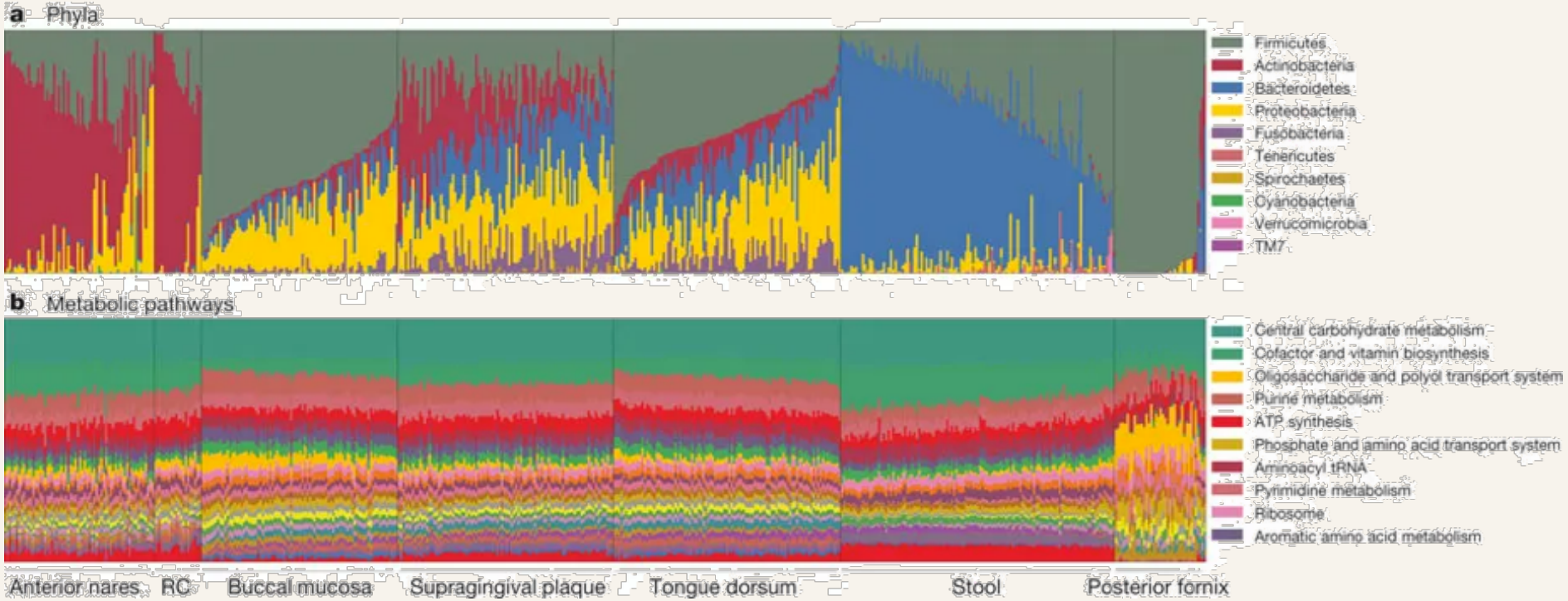
https://www.pharmabiotic.org/2019/11/06/addressing-the-unique-challenges-of-live-biotherapeutic-products-when-designing-clinical-trials/

Metabolites Are The Key To Communication



Holmes, E., Li, J. V., Marchesi, J. R., & Nicholson, J. K. (2012). Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. *Cell Metabolism*, *16*(5), 559–564.

Microbes Vary While Metabolic Pathways Remain Stable Within a Healthy Population



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Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486(7402):207-214.

Bacteria and Metabolite Genes

On average, two unrelated individuals shared 82% of metabolic pathways, but only 43% of the species

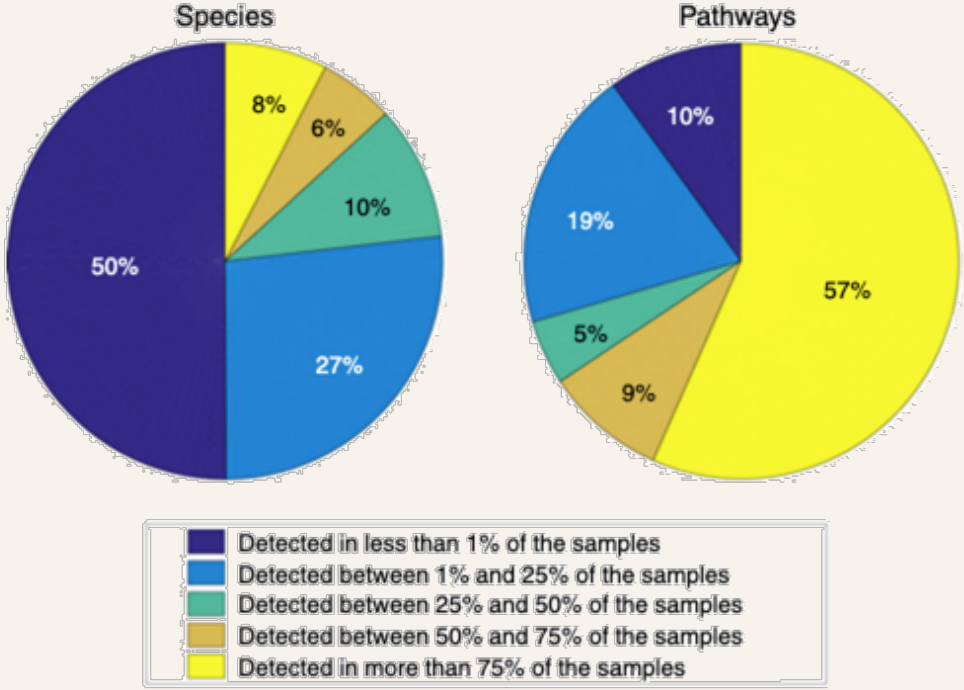


Fig. 1 Gut microbiome composition. The composition of the gut ecosystem is unique to an individual while its functionality is maintained across the population. Pie charts represent the percentage of species (on the left) and microbial metabolic pathways (on the right) present in <1% of the population (dark blue), between 1% and 25% (light blue), between 25% and 50% (turquoise), between 50% and 75% (brown), and more than 75% (yellow)

Visconti A, Le Roy CI, Rosa F, Rossi N, Martin TC, Mohney RP, Li W, de Rinaldis E, Bell JT, Venter JC, Nelson KE, Spector TD, Falchi M. Interplay between the human gut microbiome and host metabolism. Nat Commun. 2019 Oct 3;10(1):4505. doi: 10.1038/s41467-019-12476-z. PMID: 31582752; PMCID: PMC6776654.

YY

Sleep medications and microbiome

Baseline microbiome

Changes in metabolism of sleep medication

Differences in side-effects

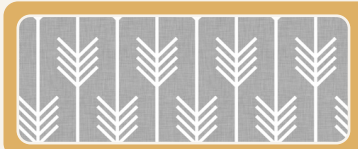
Part 4

Spirit

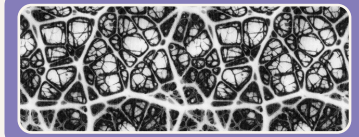
Why can’t we sleep?

2022 is "about as bad as it's been in two decades of Gallup measurement."

Just 20% of respondents reported being satisfied with the moral and ethical climate.



Only 30% were satisfied with the distribution of wealth and income.



Overall quality of life satisfaction in 2022 was 69%

Barbara Fredrickson – LOVE 2.0

Eudaimonic

Hedonic

Types of Happiness

Eudaimonic

- the type of happiness or contentment that is achieved through self-actualization and having meaningful purpose in one's life

Hedonic

- achieved through experiences of pleasure and enjoyment

FULFILLING LIFE versus HAPPY MOMENTS

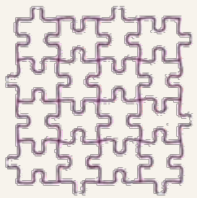
Eudaimonic

Life

that is satisfying

Holistic

Life as a whole

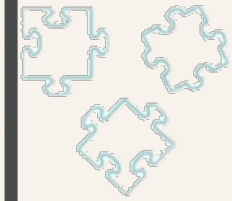


Feeling your life has meaning / purpose
Your experiences allow you to learn, grow & reach your full potential

Hedonic

Experiences

that are satisfying



Fragmented

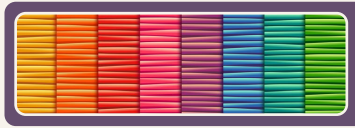
Elements of life

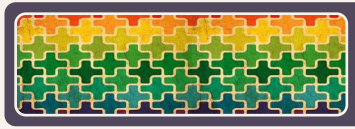
Pleasure or feeling good in the moment, reaching a goal feeling temporarily satisfied

Life satisfaction scale


how often in the past week they felt happy,


how often they felt satisfied,


that their life had a sense of direction,


that they had something to contribute to society, and


that they were challenged “to grow and become a better person.”

Fredrickson BL, Grewen KM, Coffey KA, Algoe SB, Firestine AM, Arevalo JM, Ma J, Cole SW. A functional genomic perspective on human well-being. Proc Natl Acad Sci U S A. 2013 Aug 13;110(33):13684-9. doi: 10.1073/pnas.1305419110. Epub 2013 Jul 29. PMID: 23898182; PMCID: PMC3746929.

stress-related conserved transcriptional response to adversity

Fredrickson BL, Grewen KM, Coffey KA, Algoe SB, Firestine AM, Arevalo JM, Ma J, Cole SW. A functional genomic perspective on human well-being. Proc Natl Acad Sci U S A. 2013 Aug 13;110(33):13684-9. doi: 10.1073/pnas.1305419110. Epub 2013 Jul 29. PMID: 23898182; PMCID: PMC3746929

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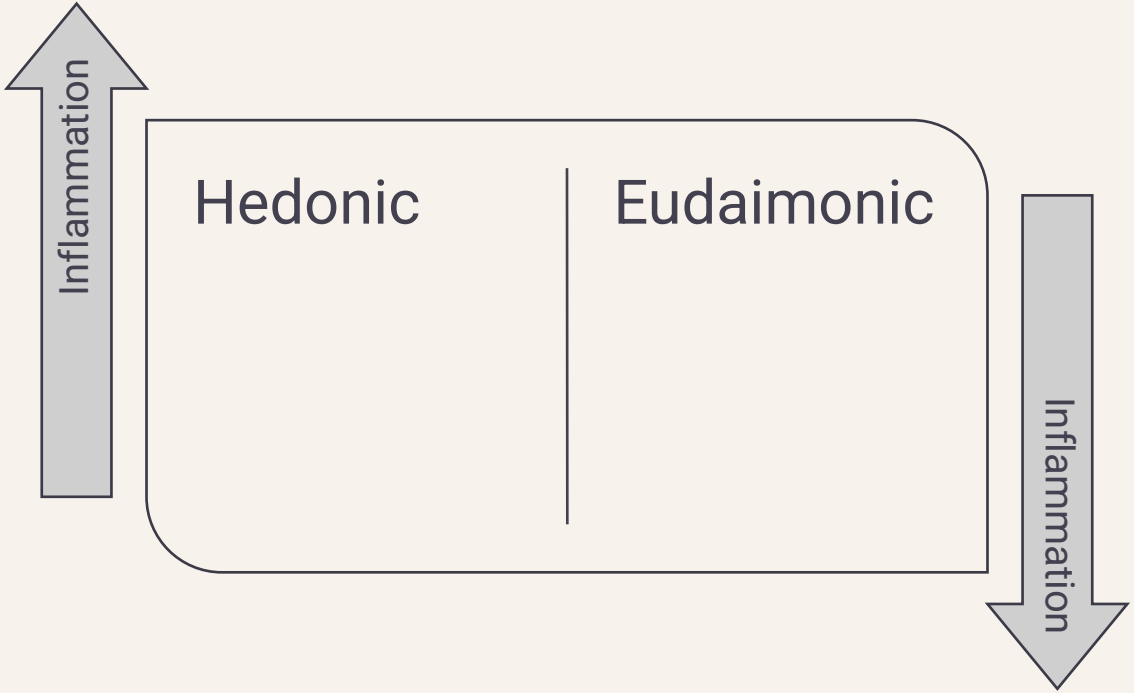
The punchline



Fredrickson BL, Grewen KM, Coffey KA, Algoe SB, Firestine AM, Arevalo JM, Ma J, Cole SW. A functional genomic perspective on human well-being. Proc Natl Acad Sci U S A. 2013 Aug 13;110(33):13684-9. doi: 10.1073/pnas.1305419110. Epub 2013 Jul 29. PMID: 23898182; PMCID: PMC3746929.

ZX


The Hedonic Treadmill
DESIRE
STRIVE
OBTAIN
ENJOY
ADAPT
DESIRE MORE

WHY PEOPLE BECOME UNHAPPY

by Anna Vital

set expectations unrealistically high

think they are special but can't explain why

measure happiness in the wrong units

get used to what they have and want more (hedonic adaptation)

confuse not being bad with being good

try to find meaning in being unhappy

hope that other people will make them happy

desire happiness less than fear disappointment

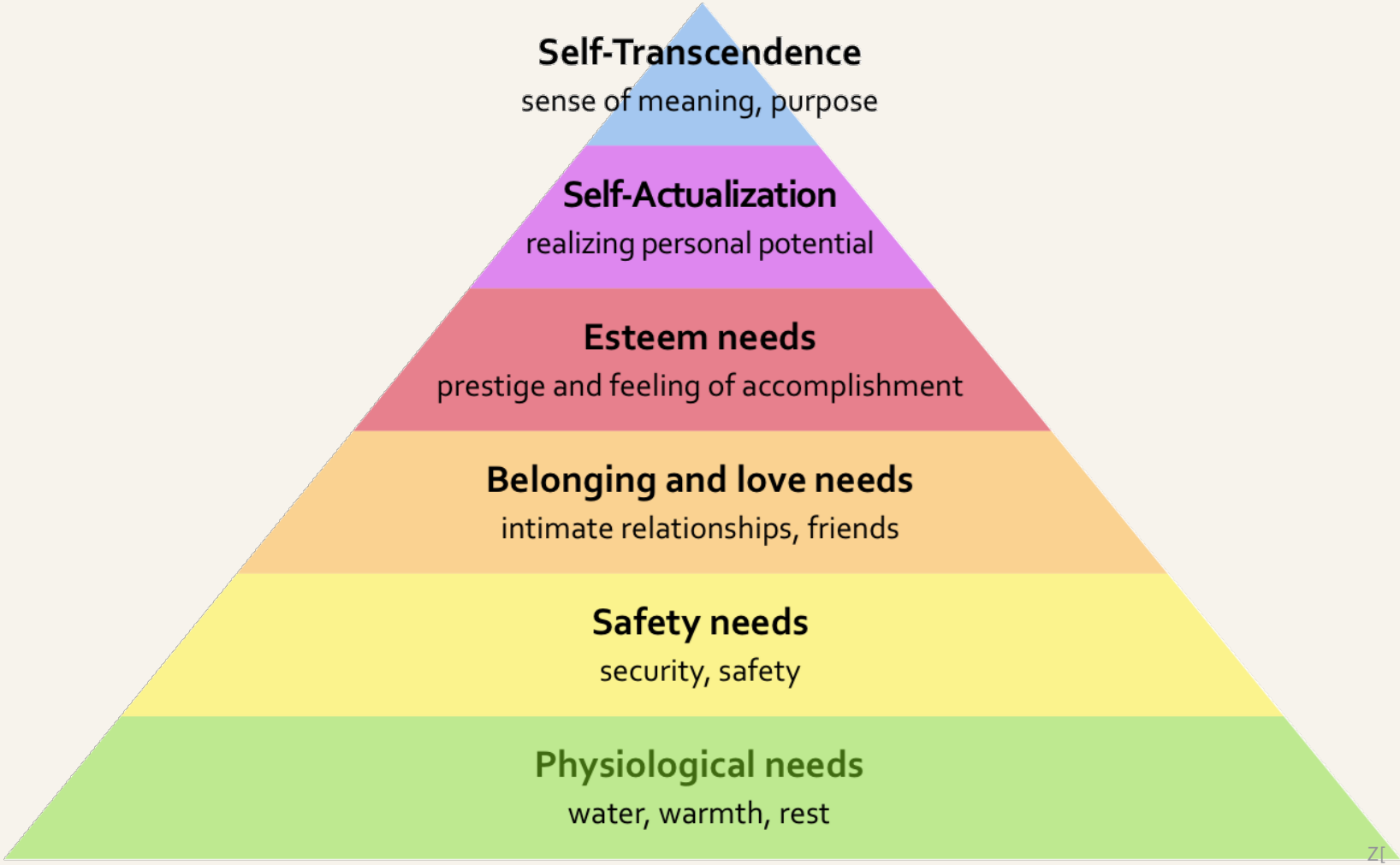
find commiserators

believe happiness is a selfish pursuit

think that misery follows happiness

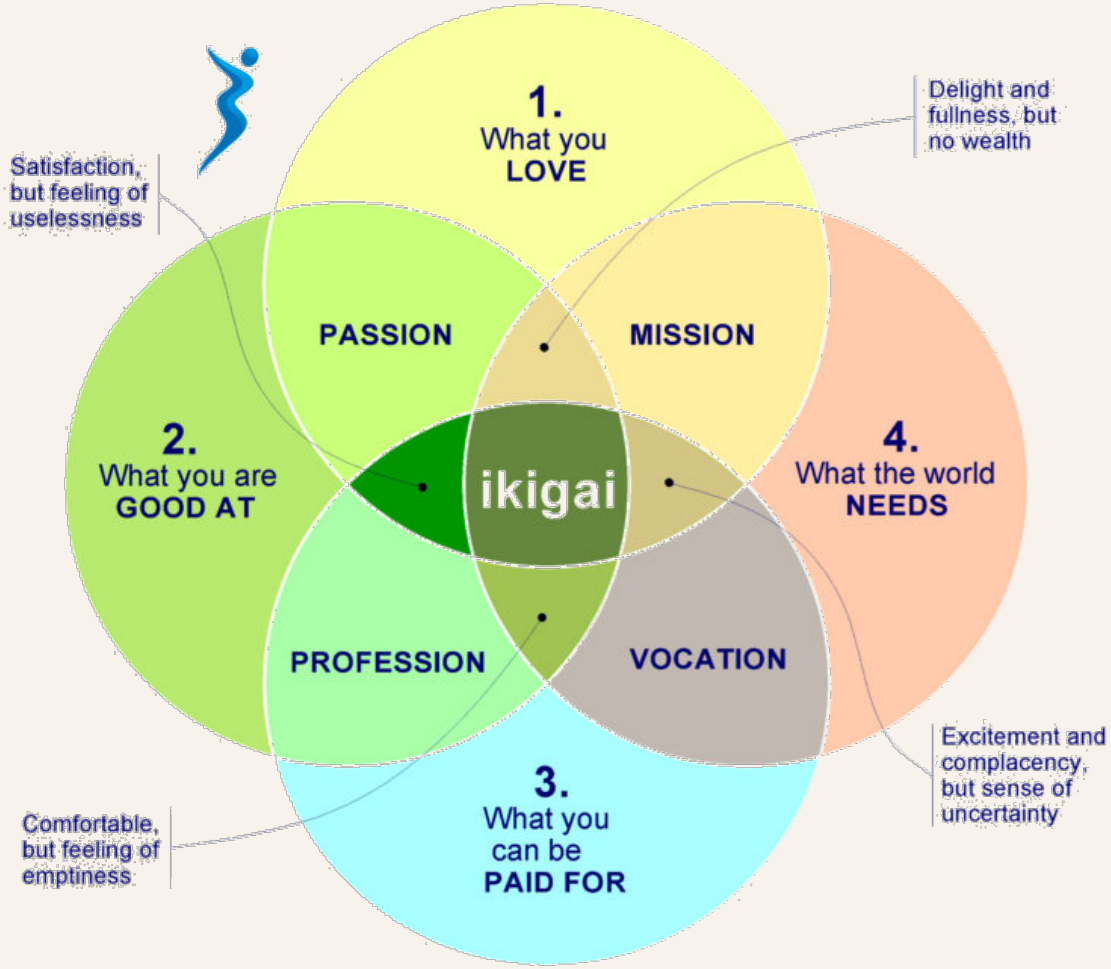
don't see the impact of their work

https://www.leadershipforces.com/hedonic-


Self-Transcendence
sense of meaning, purpose
Self-Actualization
realizing personal potential
Esteem needs
prestige and feeling of accomplishment
Belonging and love needs
intimate relationships, friends
Safety needs
security, safety
Physiological needs
water, warmth, rest

Building blocks of eudaimonic happiness

Self acceptance	Autonomy	Personal growth
Environmental mastery	Purpose in life	Positive relationships


1.
What you
LOVE
2.
What you are
GOOD AT
3.
What you
can be
PAID FOR
4.
What the world
NEEDS
PASSION
MISSION
PROFESSION
VOCATION
ikigai
Satisfaction,
but feeling of
uselessness
Delight and
fullness, but
no wealth
Comfortable,
but feeling of
emptiness
Excitement and
complacency,
but sense of
uncertainty

Summary

Sleep involves hormones, neurotransmitters, cytokines, and microbial metabolites

Inability to sleep may have as much to do with stress and life-purpose as blue light

How can we inspire ikigai in our patients and ourselves?

Thank you!

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