Christini Fund

MMDC UCSD

The Metabolic Features of Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS)

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Talk for the Centers for Disease Control SEC Program
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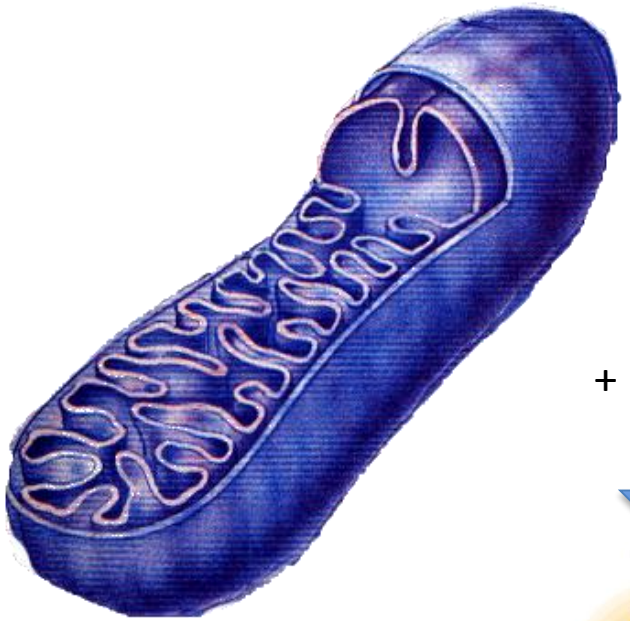
Outline

- What is the Cell Danger Response (CDR)?
- Metabolic reflexes and the healing cycle
- Purinergic Sensory processing receptors needed for cell danger and safety detection
- Metabolic lessons from the Antiviral response
- Metabolic features of ME/CFS
- Metabolic features of Dauer Exit—clues for treatment

Mitochondria are the Cell's
"Canaries in the Coal Mine"

Their Metabolism is so Fast,
They are the First to Sense
Danger or Toxicity

=



Regulators of cell <u>oxygen</u>

Regulators of Cell Defense
And Innate Immunity

Cellular Power Plants

Regulators of 500
Reactions in Metabolism

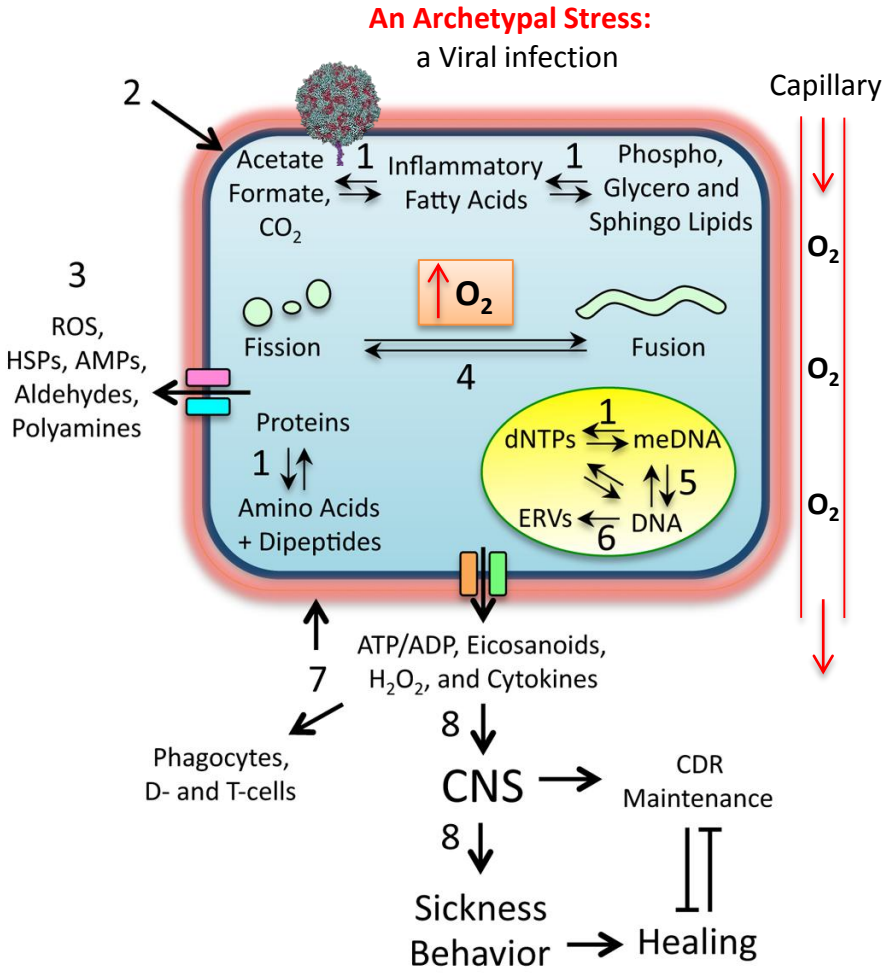
+ Danger

Universal
Alarm Signals
Trigger the **Cell**
Danger Response

Self-defense is Nature's oldest law.

John Dryden (1681)

What is the Cell Danger Response (CDR)?



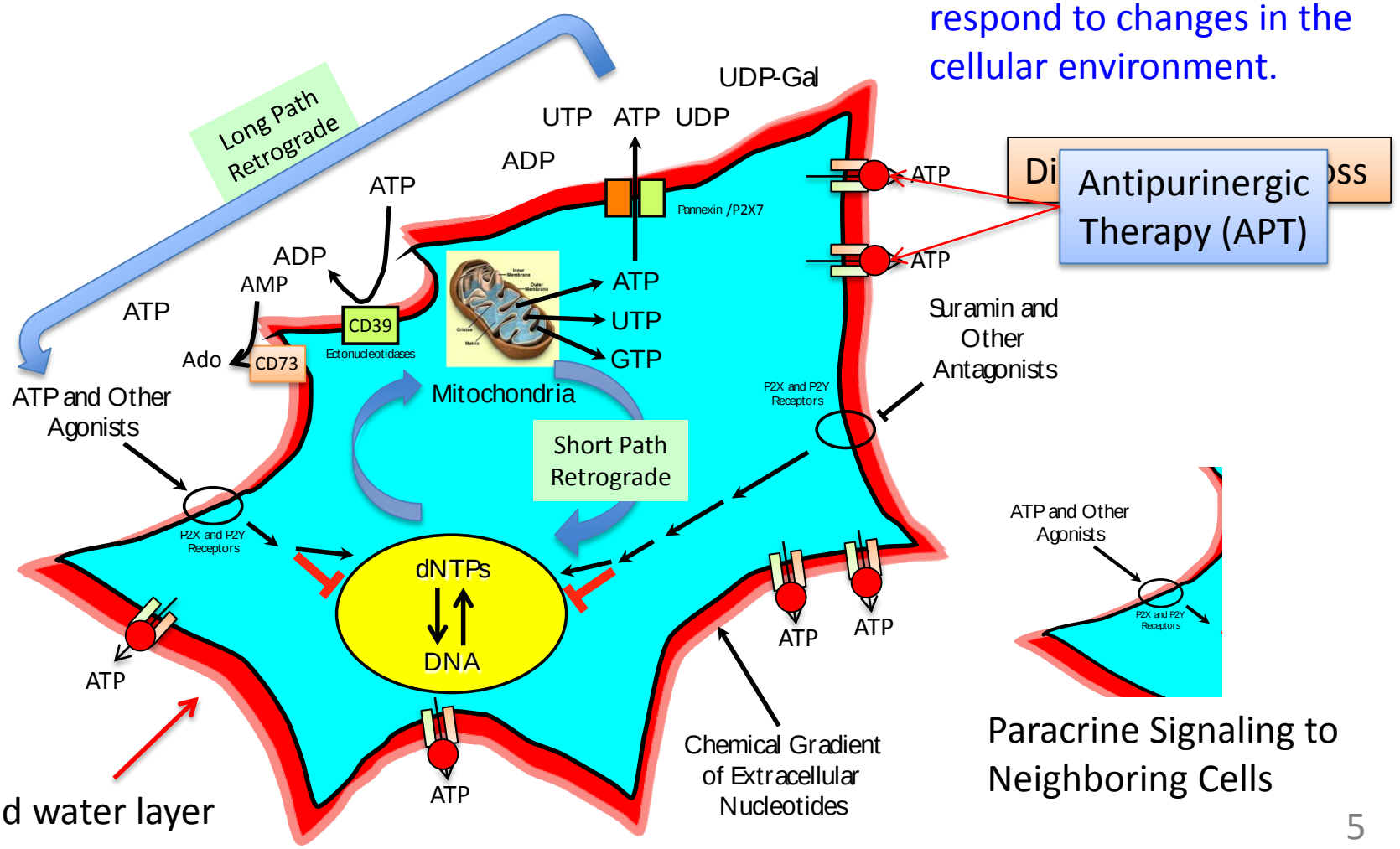
The CDR is a Coordinated, Multisystem, "Metabolic Reflex" Caused by an Electron Steal

0. Decrease oxygen consumption → increase dissolved O_2 concentration
1. Shift from polymer to monomer synthesis (ΔG; FA, AA, Dipeptides, NTs)
2. Stiffen cell membranes, lipid rafts
3. Release anti-viral and anti-microbial chemicals
4. Increase mitochondrial fission and autophagy & unfolded protein response
5. Change DNA and histone methylation—chromatin structure
6. Mobilize endogenous retroviruses, LINEs, and SVAs
7. Warn neighboring cells and call in effector cells—the "purinergic halo"
8. Alter host **behavior** to prevent spread of disease to kin

From Naviaux RK. Metabolic Features of the Cell Danger Response. *Mitochondrion*, 2014.

Starting the CDR is Universal with Every Stress or Threat

Mitochondria sense and respond to changes in the cellular environment.



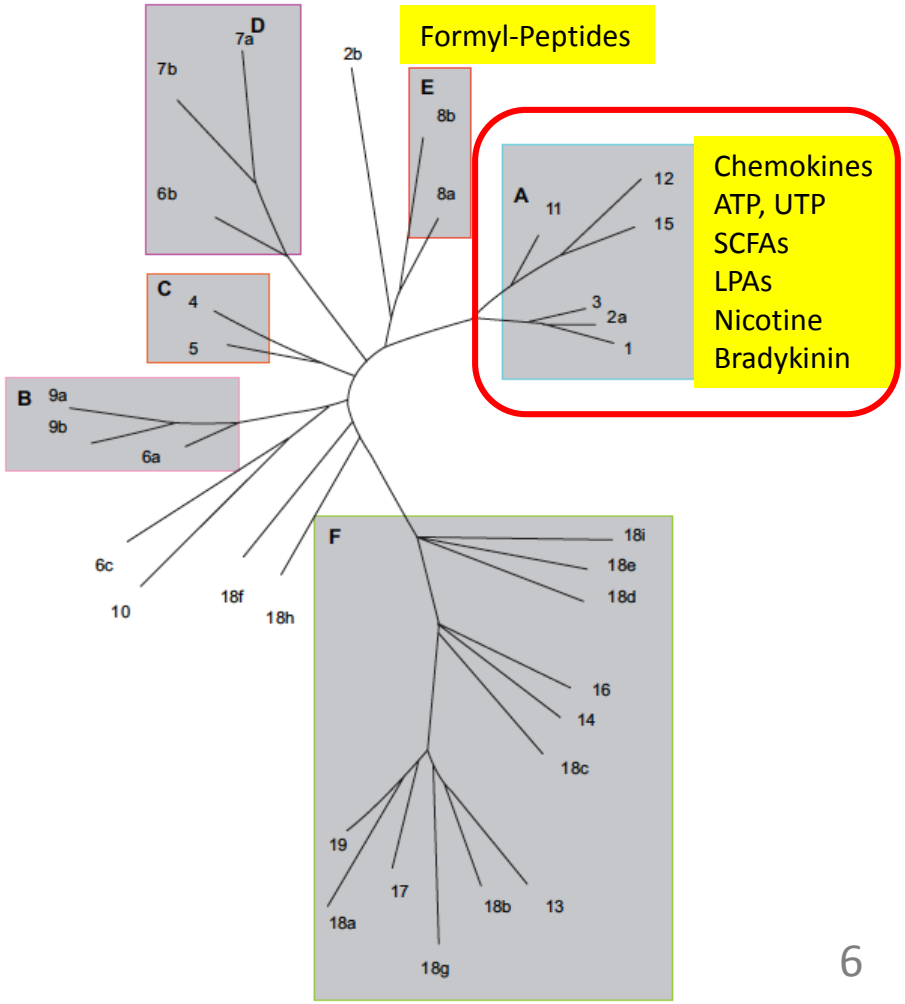
How do cells "smell" safety and danger in the world?

(Hint: It's all about metabolism.)

Vertebrate Chemosensory Receptor Evolution

7 Transmembrane GPCRs

	Sight	Smell	Pheremones		Taste	
					Bitter	Sweet Umami
	Opsin	OR	V1R	V2R	T2R	T1R
Mouse	3	1,037(354)	165(165)	61(148)	35(6)	3
Human	4	388(414)	2(115)	0	25(11)	3



Liman ER. *Adv Exp Med Biol*, 2012. PMID 22399404

Shi/Zhang. *Results Probl Cell Diff,* 2009. PMID 19145414

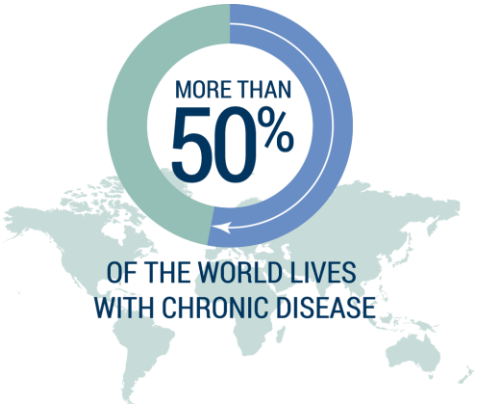
Q: What causes chronic disease?

H: Failure to to complete the healing cycle.

Health and Fitness

Mitochondria

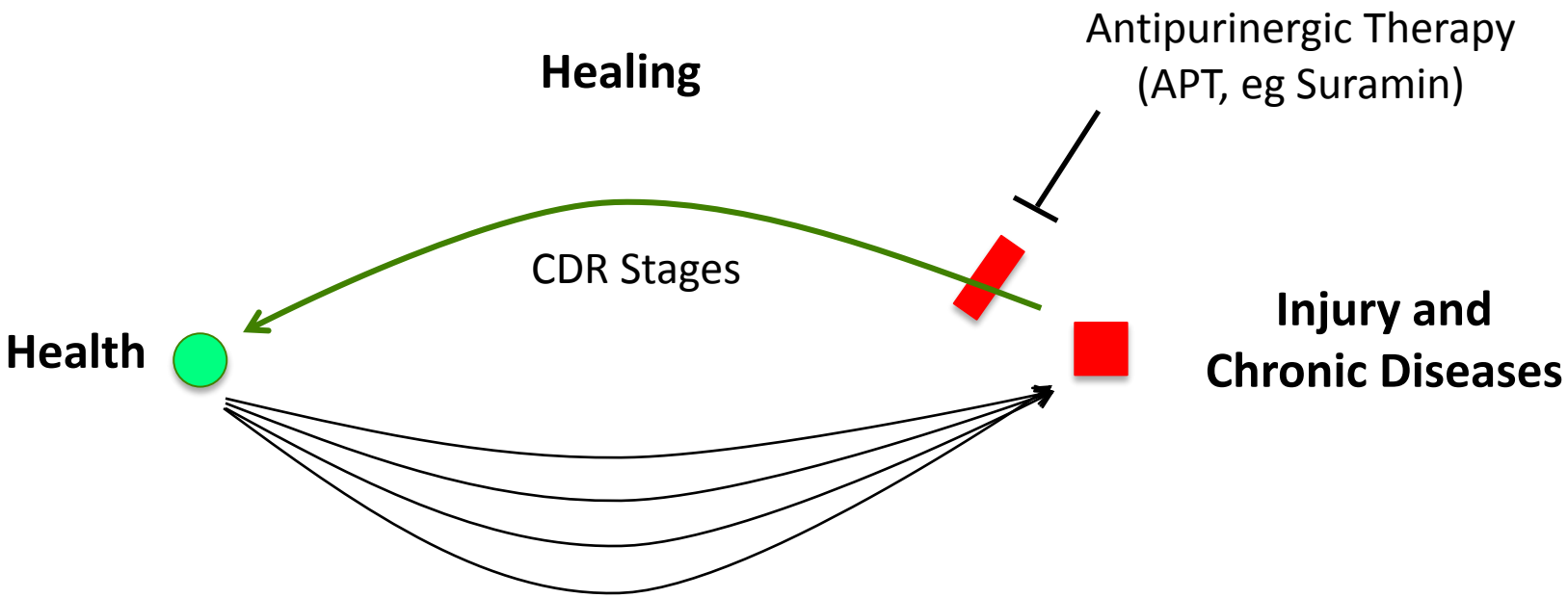
Healing



Chronic Disease

(30% of Children in US)

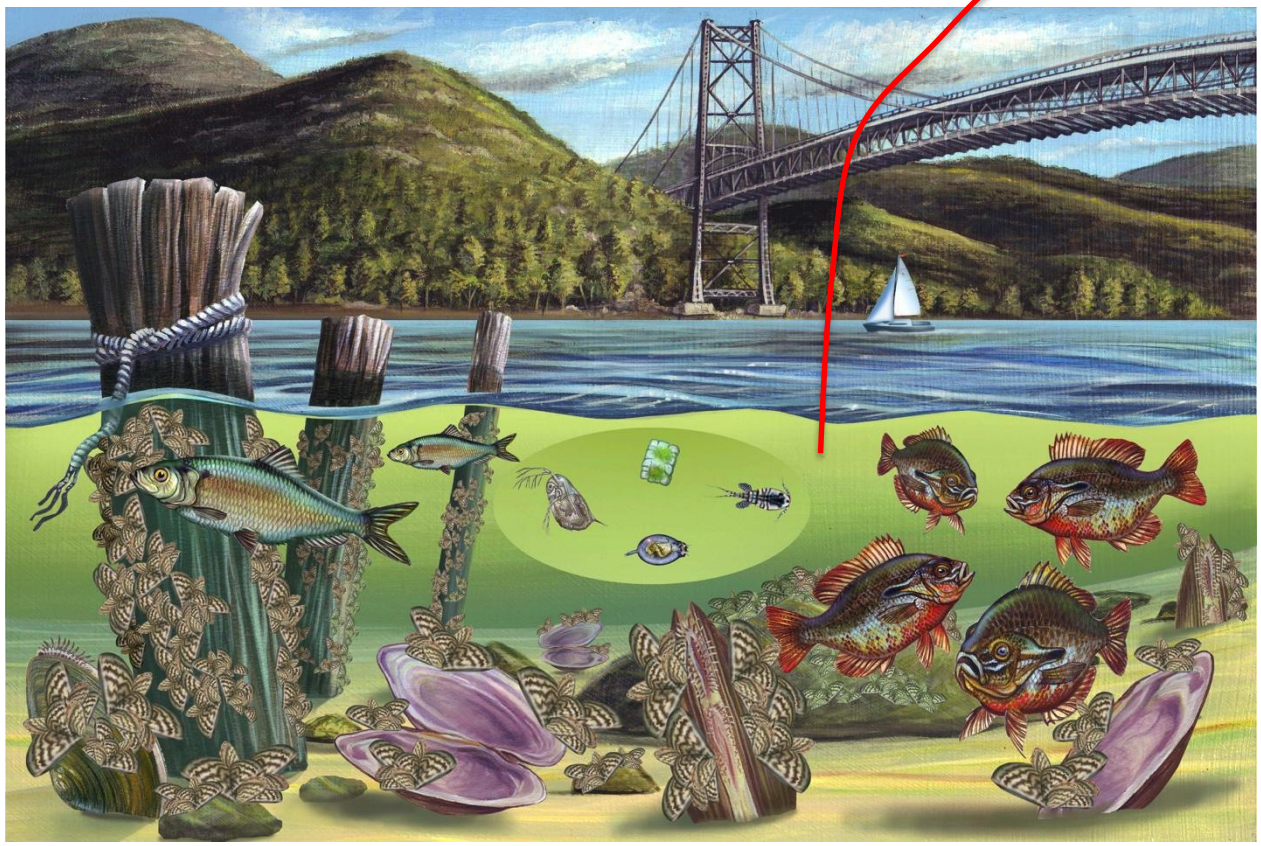
The Healing Cycle and its Regulation



Fatigue in ME/CFS

- Fatigue is the result of two main factors:
  - Dissipative losses of ATP through channels in the cell membrane, and
  - Reallocation of cellular resources *away from* mitochondrial energy production (oxphos)
    - This is the result of mitochondria following "new orders" from the nucleus, ie, "*regulated mitochondrial dysfunction*"
    - This is not from an intrinsic "defect" in mitochondria themselves or a specific genetic mutation, ie, recovery is possible
- "It takes more energy to relax than to react."
  - Anxiety, restlessness, irritability, fear of change, OCD behaviors, sensory & chemical hypersensitivities, meltdowns, and bouts of hyperactivity, and even seizures, are hallmarks of a low energy state

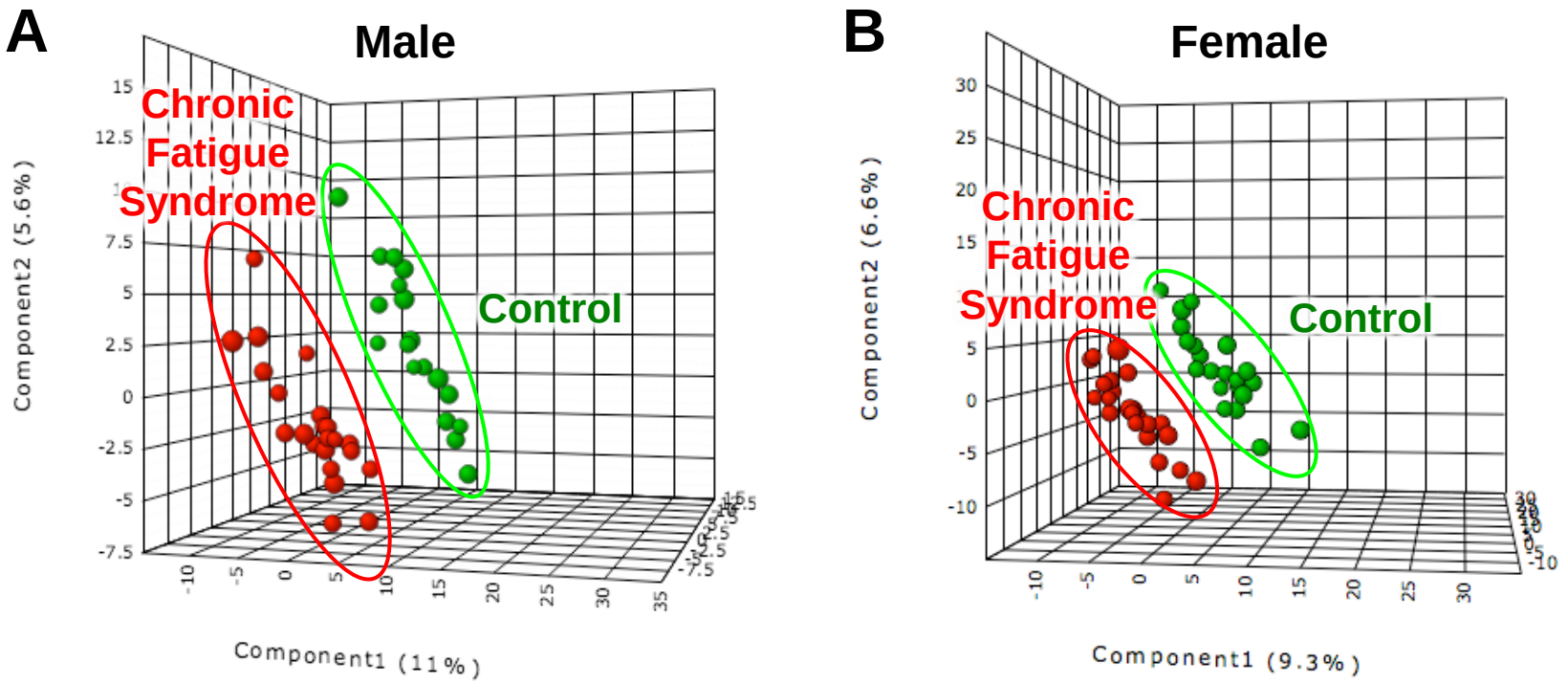
Metabolomics—A Drop of Blood is Like a Sample of Water from a River or Ocean Ecosystem



LC-MS/MS

Chemical Basis of Health and Disease

Metabolomics Permits Diagnosis of ME/CFS



Naviaux, et al. Metabolic features of chronic fatigue syndrome. *PNAS* 113: E5472, 2016.

Pathway Abnormalities—Defining the *Metabolic Reflex* of the CDR

The CDR

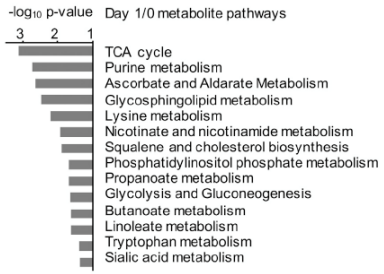
Chronic Fatigue Syndrome

- Sphingolipids
- Phospholipids
- Sterols/Cholesterol
- Purines
- Methionine/Cysteine
- Propionate
- Krebs cycle
- Folate/B12
- Ascorbate

Naviaux, et al. Metabolic features of chronic Fatigue syndrome. *PNAS* 113: E5472, 2016. Gender-selective responses noted.

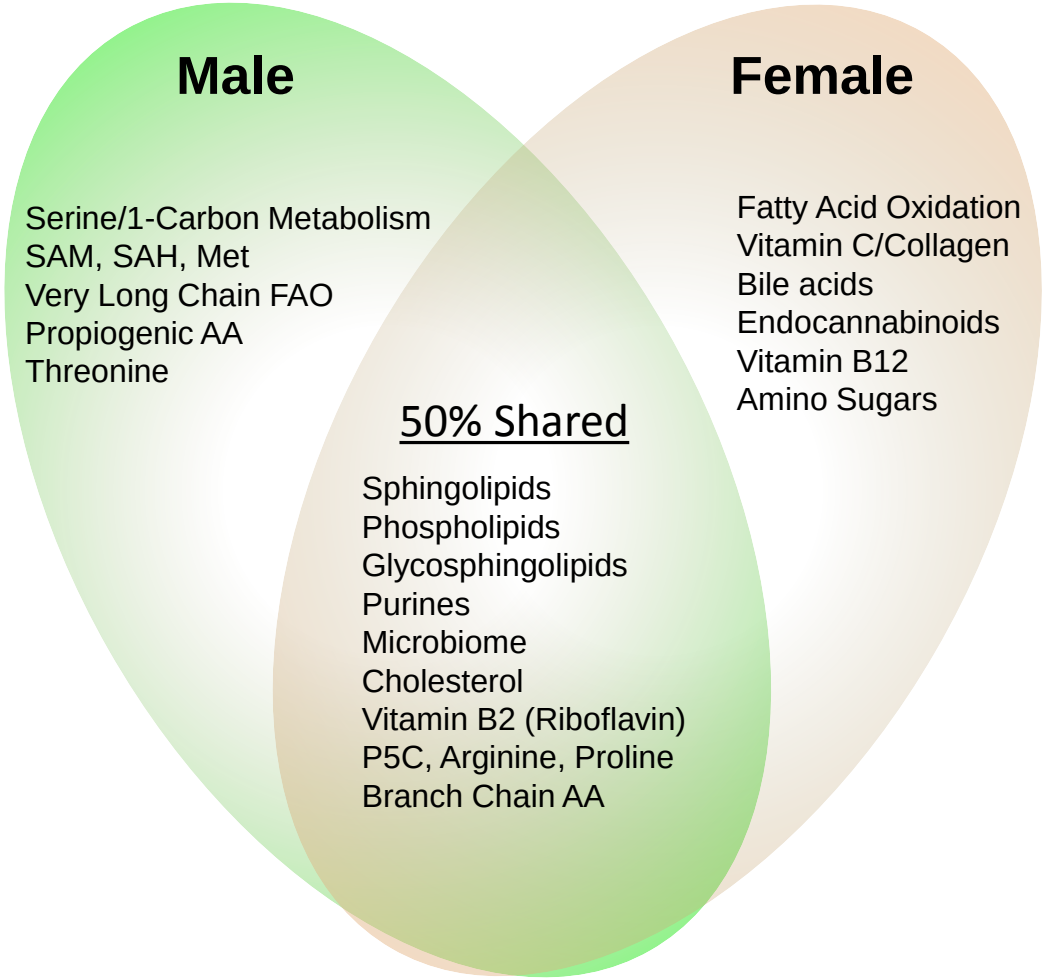
Post-Zostavax Vaccination[1]

- Krebs cycle
- Purines
- Sphingolipids
- Sterols/Cholesterol
- Methionine/Cysteine
- Propionate
- Inositol lipids
- Porphyrin/Heme/Glycine
- Amino/Sialic acid sugars

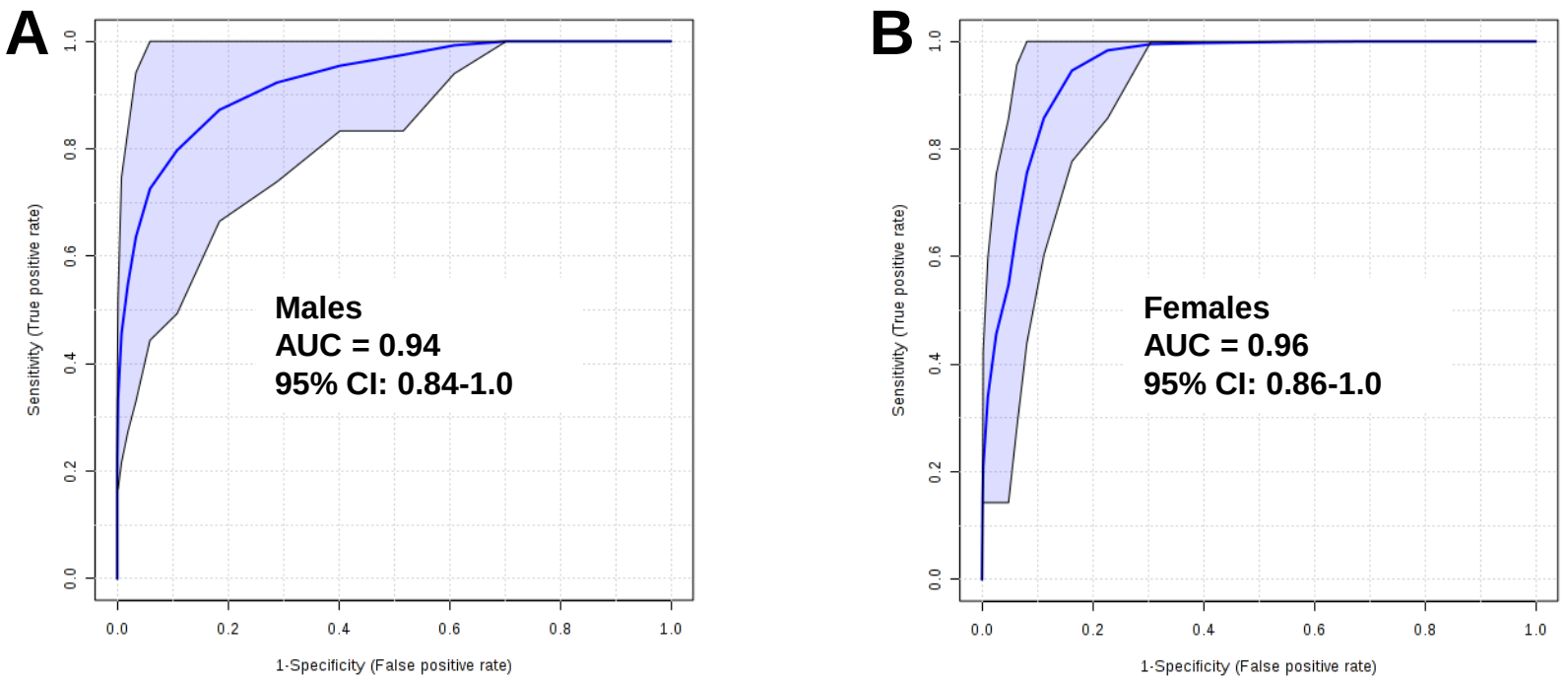


Li, et al. Metabolic phenotypes of response to Vaccination in humans. *Cell* 169:862, 2017.
[1]PBMC transcription and metabolism.
Mixed male and female responses.

Metabolic Pathway Abnormalities in Males and Females with ME/CFS

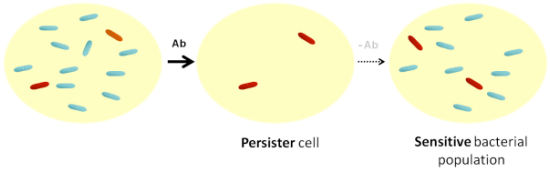


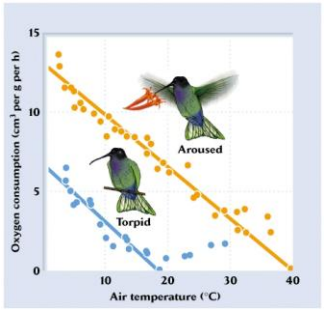
ROC Curve Accuracy Analysis—Metabolomic Diagnosis of ME/CFS

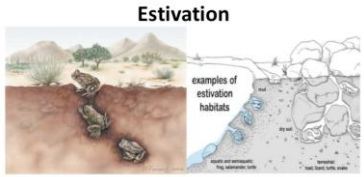


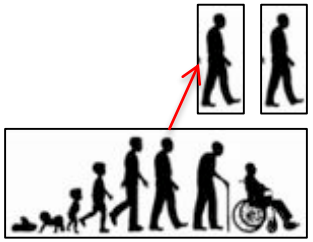
Hypometabolic Persistence and Survival States in Nature

- Persister Cells
  - Lyme
  - Tuberculosis
- Embryonic Diapause
- Hibernation
- Torpor
- Estivation
- Tun
- Dauer
- Caloric restriction/Longevity research



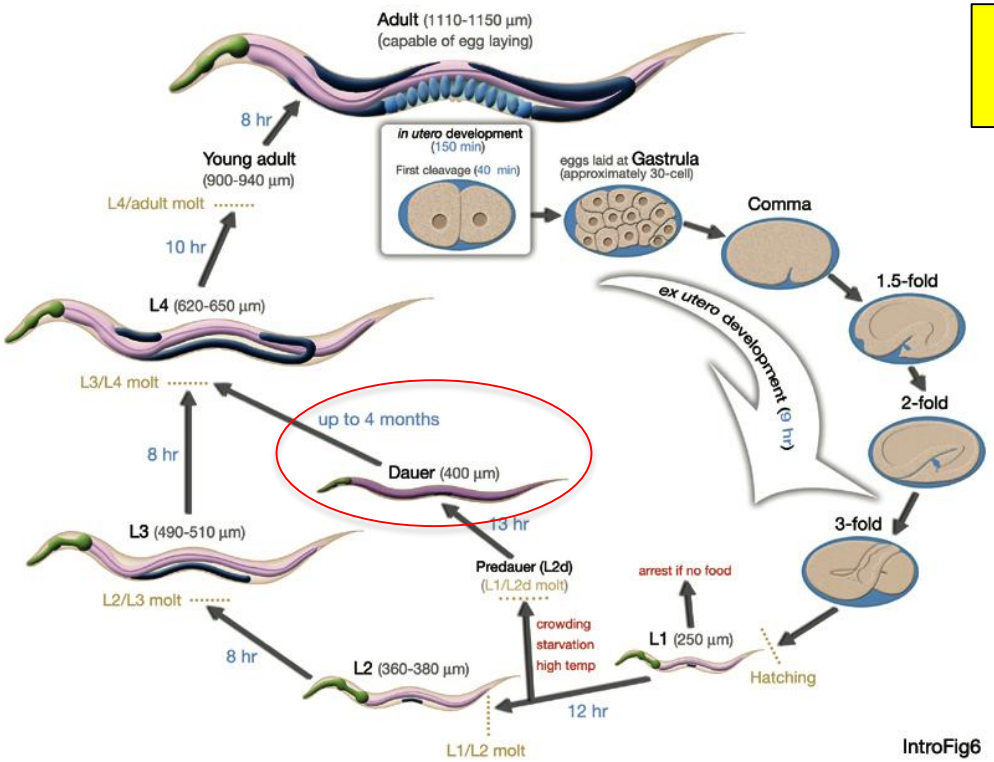






C. elegans

Reproductive Cycle
= 3 days
Menopause After
6 days
Normal life span
= 14 days

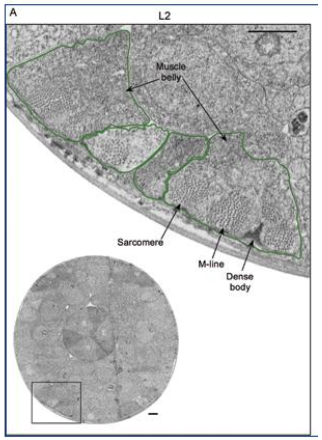


Normal

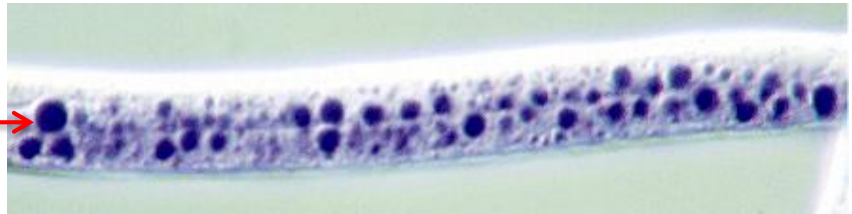
Dauer

Dauer Shifts

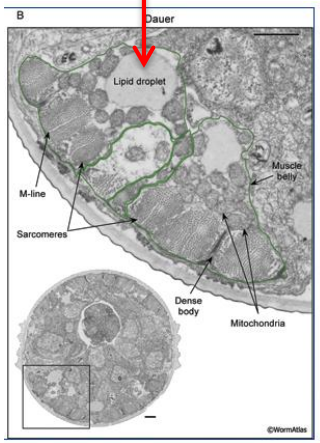
- Stop eating → caloric restriction
- Mitochondrial oxphos declines
- Oxygen consumption declines
- Lipid droplets accumulate
- Glycolysis increases
- Glyoxylate shunt increases to increase OAA and gluconeogenesis



Lipid Droplets



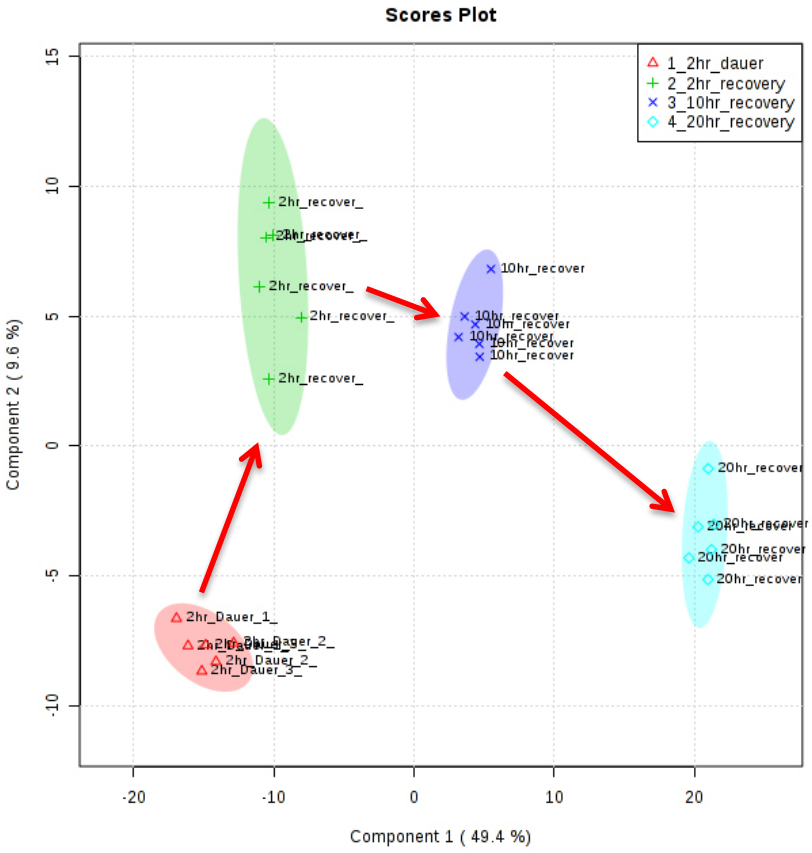
Lipid Droplets



www.wormatlas.org

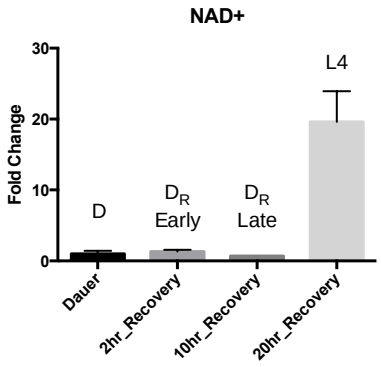
Metabolic Changes Associated with Recovery/Exit from Dauer

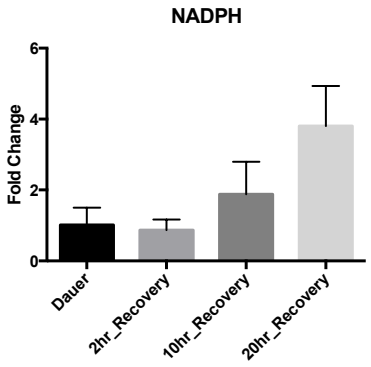
Choreographed Metabolic Features of Dauer Exit

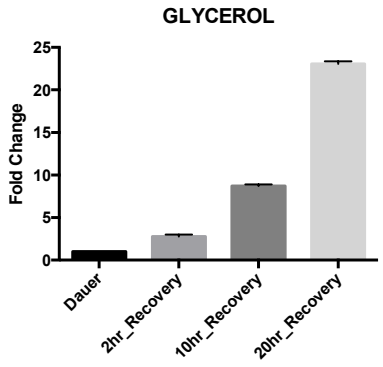


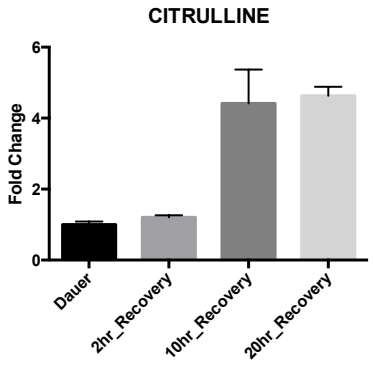
The sequence (timing) of changes is important

Dauer Exit—
Clues for CFS Treatment









Treatment Strategy for ME/CFS

- Remove the CDR trigger if it is still present
- Refill the metabolic tank—raw materials for exit from winter and return to“spring and summer metabolism”
  - Normalize calorie intake and nutrition
    - Restore depleted metabolic reserves as guided by metabolomics
- Use antipurinergic therapy (APT), e.g., low-dose suramin, to reprogram metabolism and to progress through the *healing cycle*
  - Pilot study of low-dose suramin in CFS is seeking funding to launch later this year.
  - See: http://naviauxlab.ucsd.edu/support/

Research Support

- Dan Wright Family Foundation
- The UCSD Christini Fund
- Autism Research Institute
- The Gupta Family and Satya Fund
- N of One: Autism Research Foundation
- The Rodakis Family
- Lennox Foundation
- The UCSD Mito Walk n' Roll 5K
- It Takes Guts Foundation
- Jane Botsford Johnson Foundation (the essential preclincal studies)
- Open Medicine Foundation (OMF)

Christine Shimizu
1996-1998

Thank You