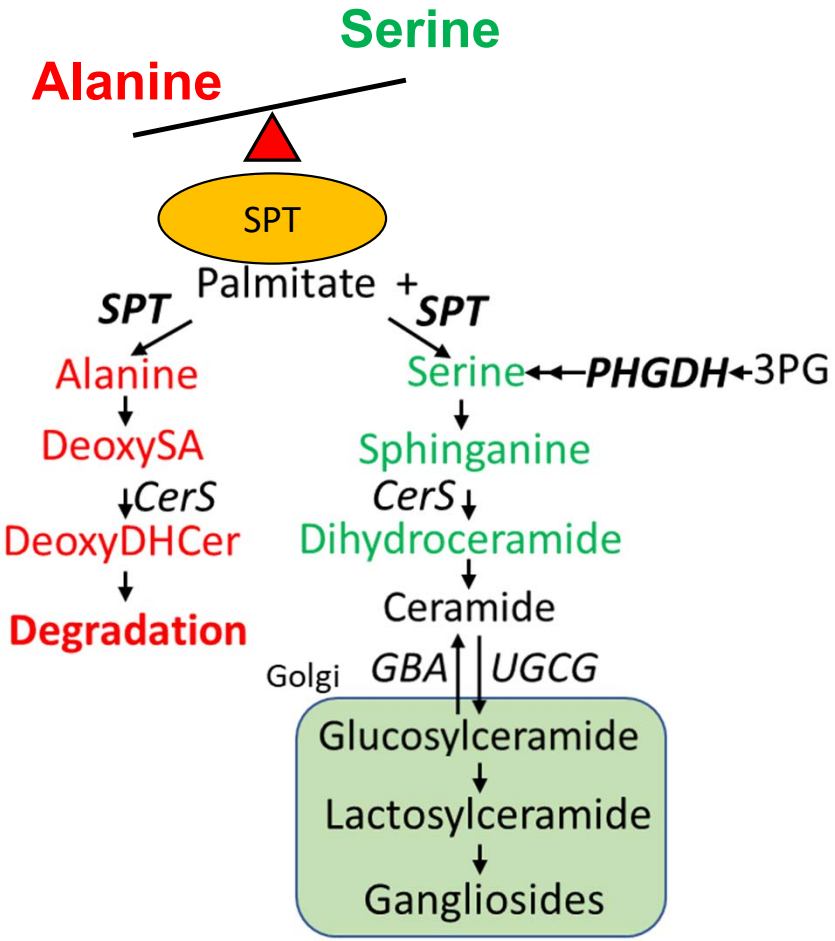
Opportunities and obstacles in precision nutrition → metabolic mechanisms

1. Applying metabolomics to understand nutrition and disease physiology

2. Altered amino acid metabolism influences sphingolipid diversity to drive peripheral neuropathy and macular disease

3. Is serine metabolism predictive of diabetic peripheral neuropathy?



Christian Metallo
Food Forum Workshop
Challenges and Opportunities for Precision and Personalized Nutrition
Aug 10 2021

Molecular & Cellular Biology Lab
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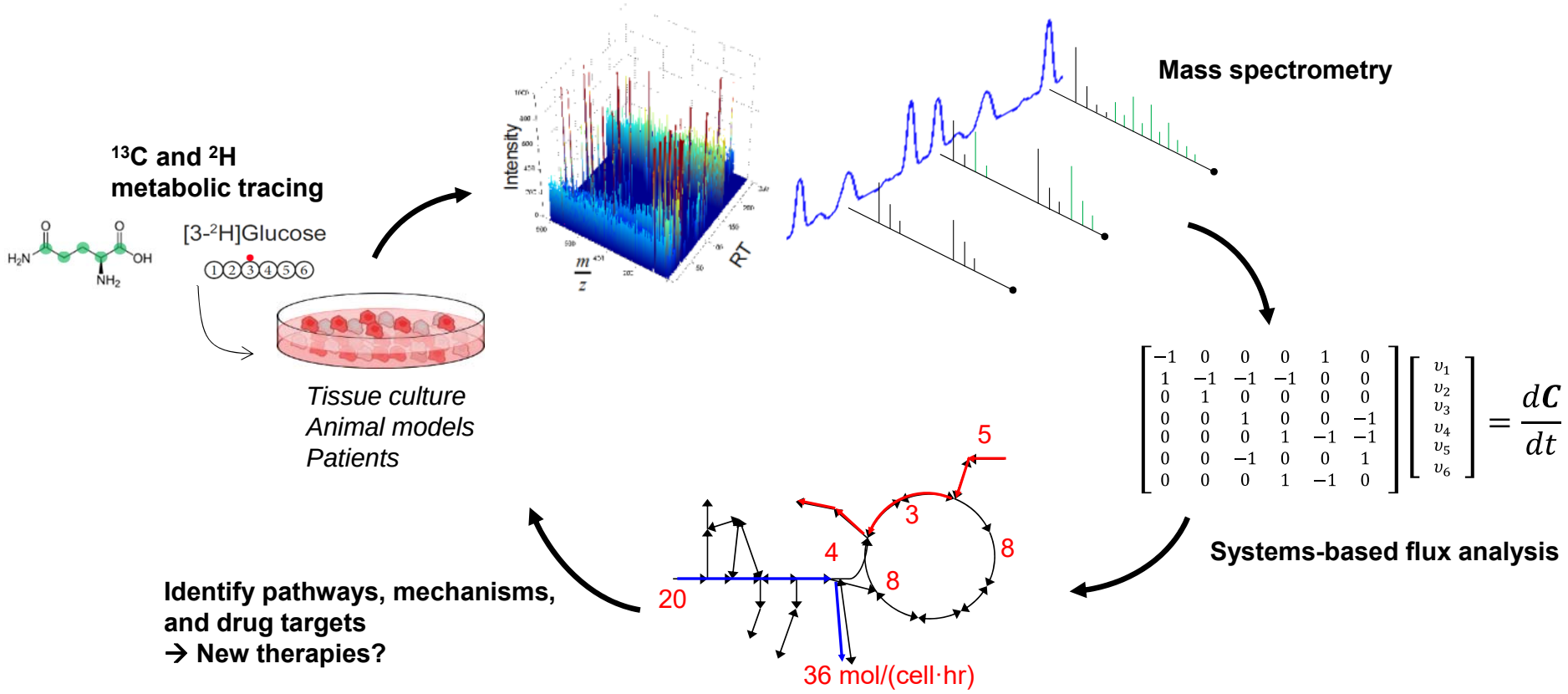
Tracing molecules through space and time to understand disease

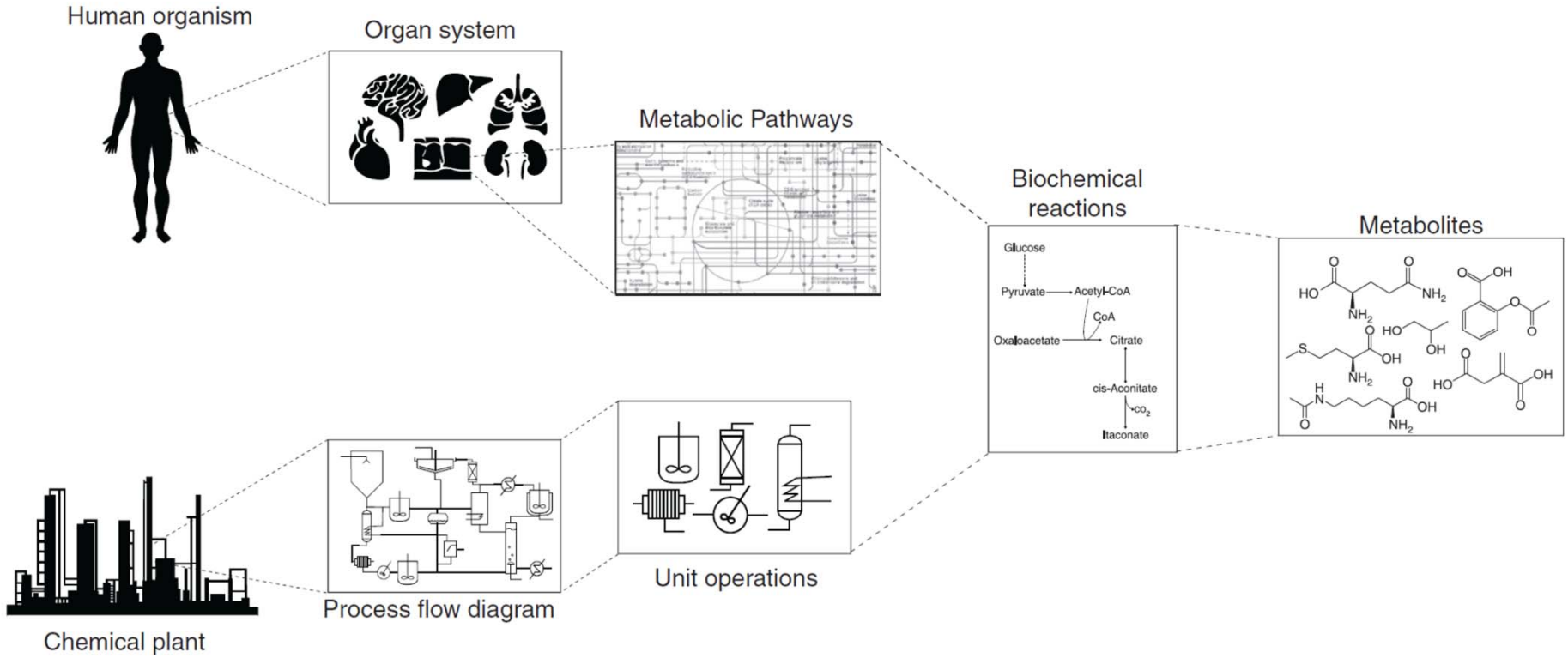


$$\begin{bmatrix} -1 & 0 & 0 & 0 & 1 & 0 \\ 1 & -1 & -1 & -1 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 0 & 1 & -1 & -1 \\ 0 & 0 & -1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & -1 & 0 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{bmatrix} = \frac{d\boldsymbol{C}}{dt}$$

Key areas of interest:

- Cancer metabolism: Parker et al. *Canc Res* 2014; Badur et al. *Cell Rep* 2018; Muthusamy et al. *Nature* 2020
- T2D, BCAA metabolism, and lipid diversity: Green et al. Nat Chem Bio 2016; Wallace et al. *Nat Chem Bio* 2018
- **Serine, neuropathy, and Macular Telangiectasia (MacTel)**: Gantner et al. *NEJM* 2019; Eade et al. *Nat Metab* 2021

Our bodies, tissues, and cells are more analogous to chemical plants than test tubes



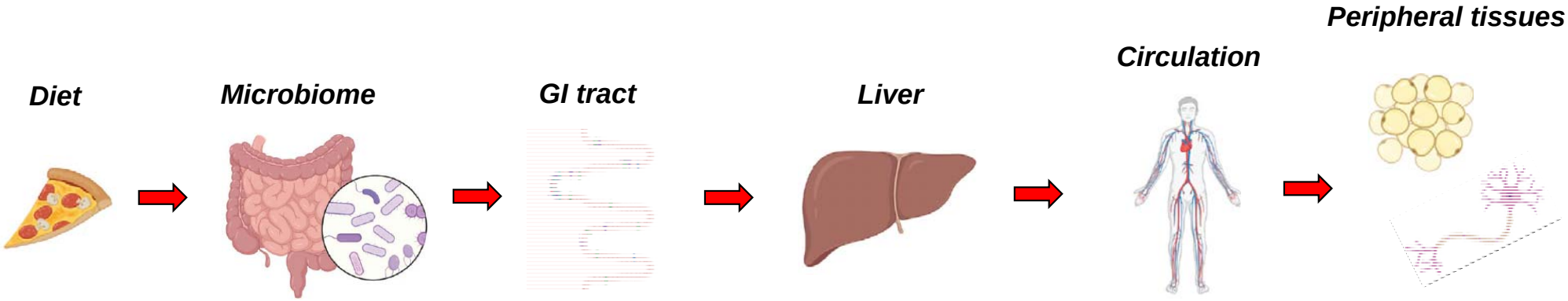
We need to understand these robust (genetically-evolved), biochemical engineering control mechanisms (metabolism) to exploit them therapeutically

Can precision nutrition be used to modulate health?

Absolutely… with the right patients and the right dietary approach to treat the right disease

Precision nutrition & precision medicine are both needed

Nutrition is inherently imprecise: the microbiome, digestive system, and systemic metabolism function to minimize or filter disturbances/fluctuations in organisms



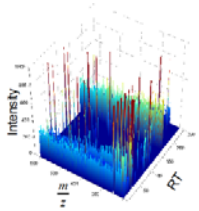
Dietary manipulations (good or bad) will be mitigated by this system

Defects in any step can impact systemic metabolism and drive disease

Nutritional science requires diverse expertise

Static metabolite measurements in one compartment can only tell you so much

→ Location and dynamics are critical!



Case study: serine, Macular Telangiactasia (MacTel), and peripheral neuropathy

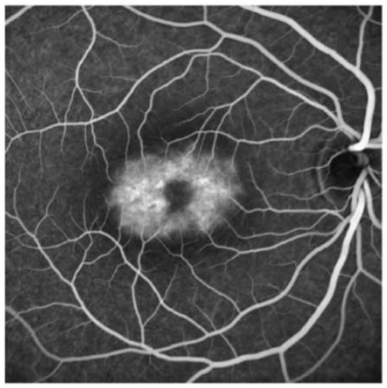
Macula
Responsible for high visual resolution
Accounts for ~50% of neural activity in retina

MacTel:
Idiopathic juxtafoveal retinal telangiectasis type 2
Familial disease of the retina (<0.1% of pop.)
Central vision loss → onset at ~40 years
Difficulty reading, driving, etc.

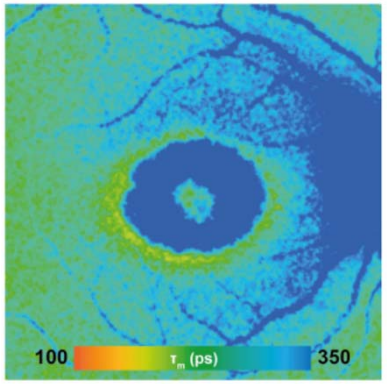
The MacTel project:
Started in 2005 to understand this disease
International group of clinicians and basic scientists
Recent genomic focus → 800 patients now sequenced
GWAS hits → *PHGDH*, *PSAT1*, *PSPH*

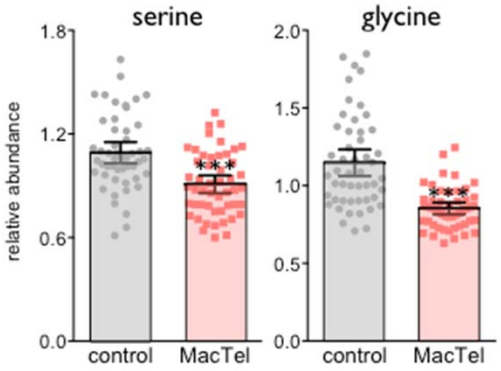
Serine biosynthesis enzymes!

Fluorescein angiogram



Fluorescence lifetime imaging ophthalmoscopy (FLIO)

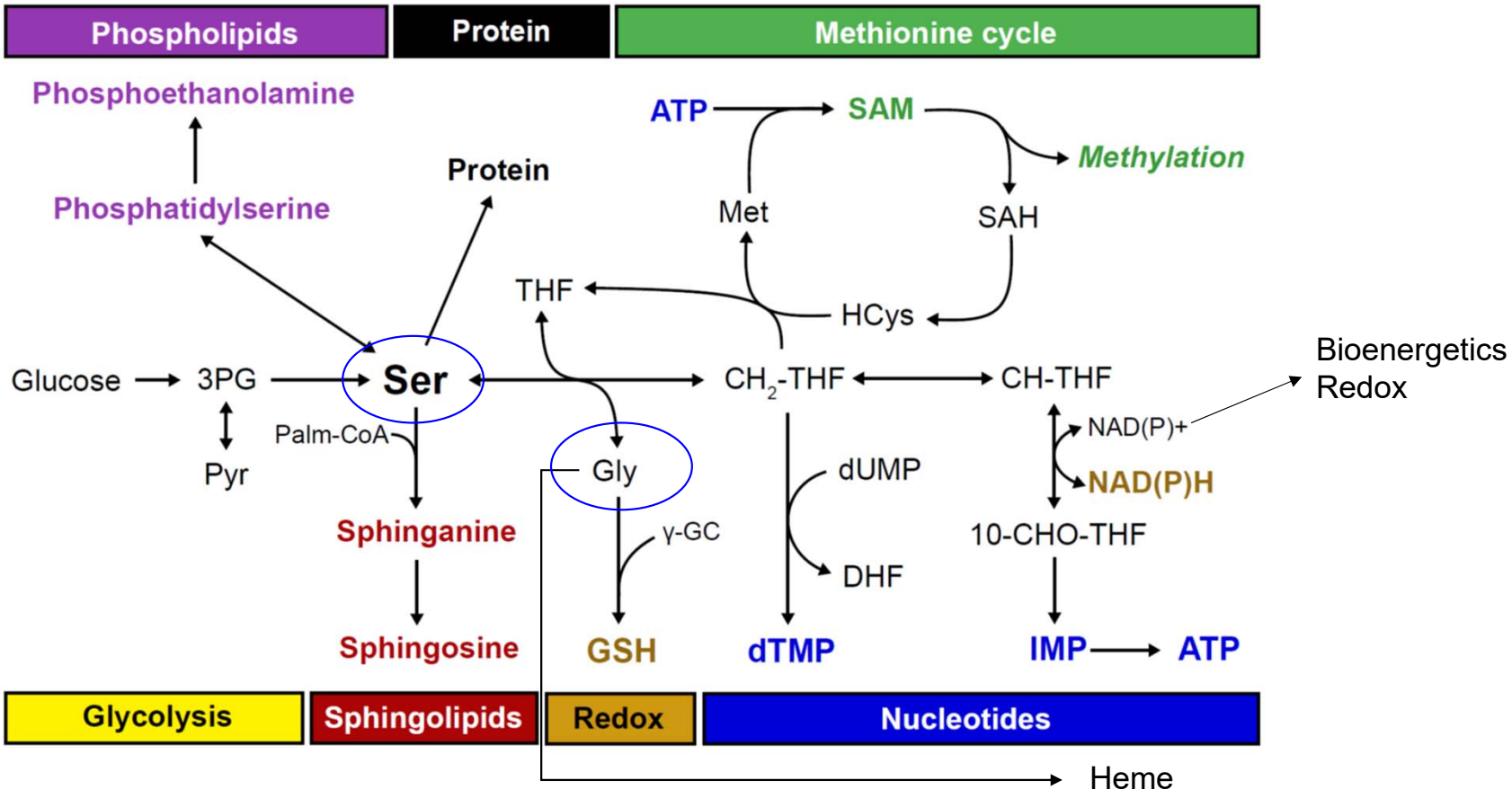




Serine and glycine levels down ~20% in MacTel patients plasma

Scerri et al. *Nat Genetics* 2017

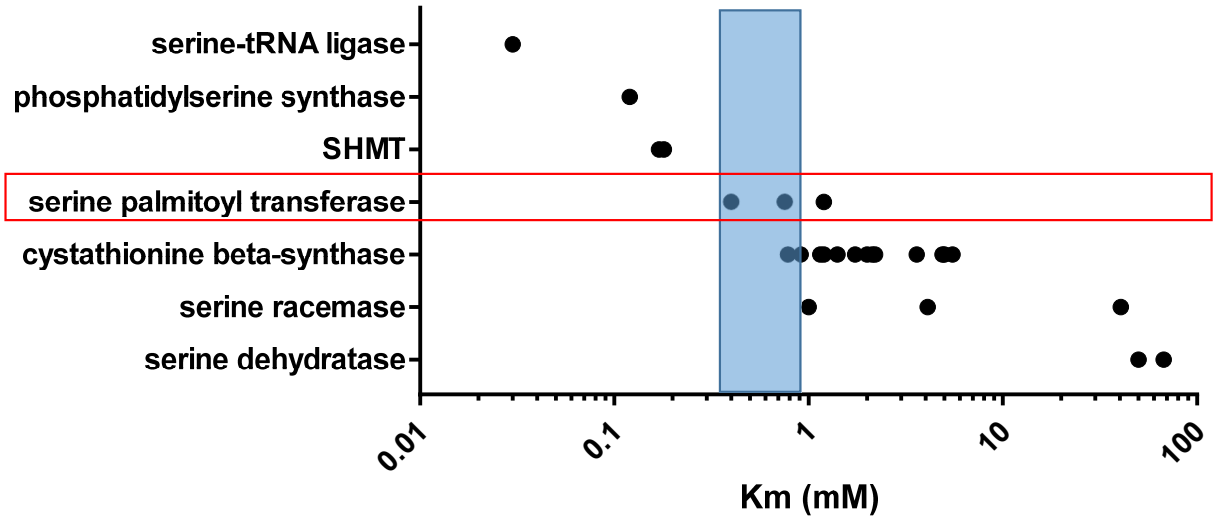
Why are serine and glycine metabolically important?



How do cells/organisms control substrate flux to divergent pathways?

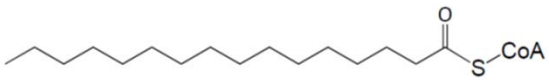
- Numerous enzymes will compete for serine in cells
- Consider Km values → enzyme substrate affinities for several (from the BRENDA database)
  - Tissue "[serine]" remains at 50-250 μM in mice fed a serine/glycine-free diet

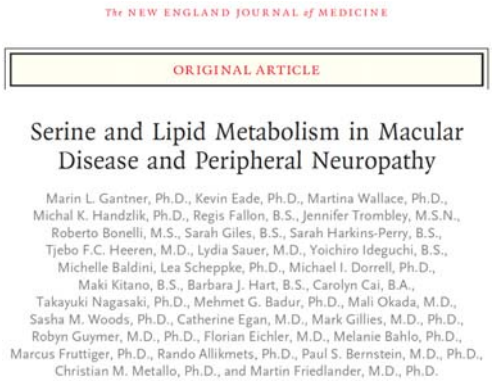
$$v = \frac{V_{max}[S]}{K_M + [S]}$$



- Evolution has "tuned" enzyme Km's to ensure that the "most important" enzymes find their substrate when concentrations are low
- Could moderately low serine (observed in vivo) drive alterations in sphingolipid metabolism?

Serine palmitoyltransferase generates bioactive sphingolipids
→ but acts promiscuously with different amino acids

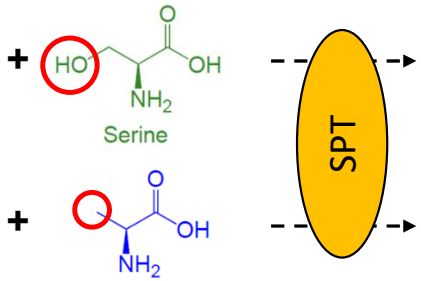


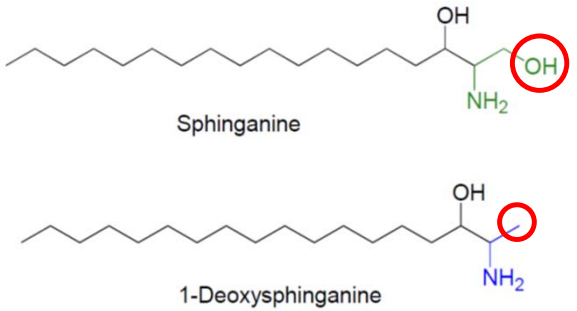

The NEW ENGLAND JOURNAL of MEDICINE

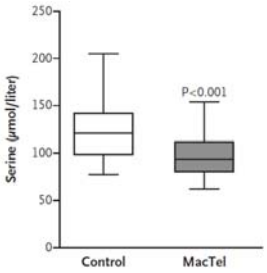
ORIGINAL ARTICLE

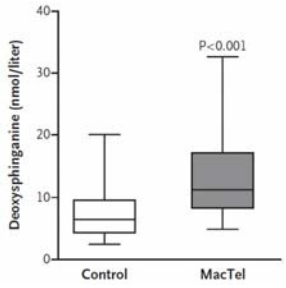
Serine and Lipid Metabolism in Macular Disease and Peripheral Neuropathy

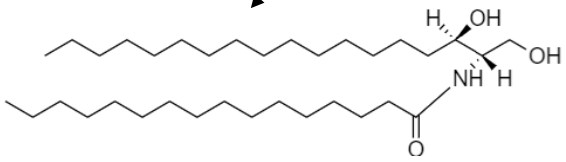
Marin L. Gantner, Ph.D., Kevin Eade, Ph.D., Martina Wallace, Ph.D., Michal K. Handzlik, Ph.D., Regis Fallon, B.S., Jennifer Trombley, M.S.N., Roberto Bonelli, M.S., Sarah Giles, B.S., Sarah Harkins-Perry, B.S., Tjebo F.C. Heeren, M.D., Lydia Sauer, M.D., Yoichiro Ideguchi, B.S., Michelle Baldini, Lea Scheppke, Ph.D., Michael I. Dorrell, Ph.D., Maki Kitano, B.S., Barbara J. Hart, B.S., Carolyn Cai, B.A., Takayuki Nagasaki, Ph.D., Mehmet G. Badur, Ph.D., Mali Okada, M.D., Sasha M. Woods, Ph.D., Catherine Egan, M.D., Mark Gillies, M.D., Ph.D., Robyn Guymer, M.D., Ph.D., Florian Eichler, M.D., Melanie Bahlo, Ph.D., Marcus Fruttiger, Ph.D., Rando Allikmets, Ph.D., Paul S. Bernstein, M.D., Ph.D., Christian M. Metallo, Ph.D., and Martin Friedlander, M.D., Ph.D.











Sphingolipids link amino acids to membrane biology

1-deoxysphingolipids are formed when SPT uses alanine instead of serine

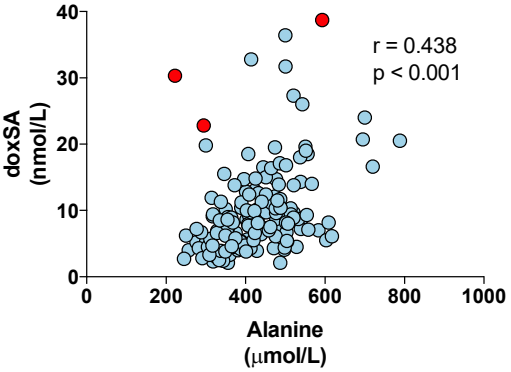
→ First identified as endogenous in Hereditary Sensory and Autonomic Neuropathy (HSAN1) patients (Eichler, Hornemann et al. *J. Neurosci.* 2009)

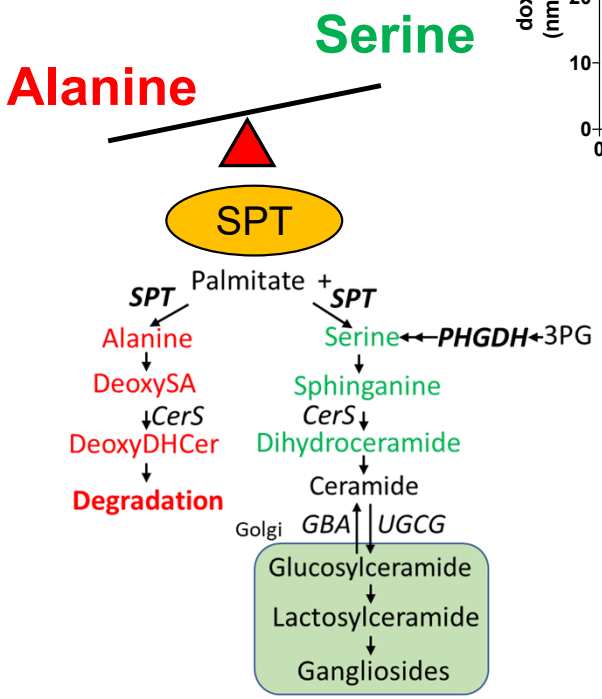
→ HSAN1 patients express coding variants in *SPTLC1* or *SPTLC2* → *peripheral neuropathy*

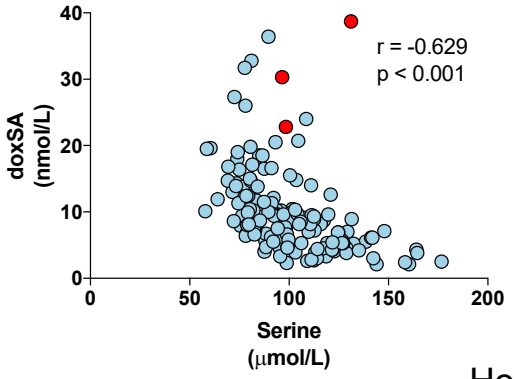
→ MacTel patients have elevated doxSL in serum

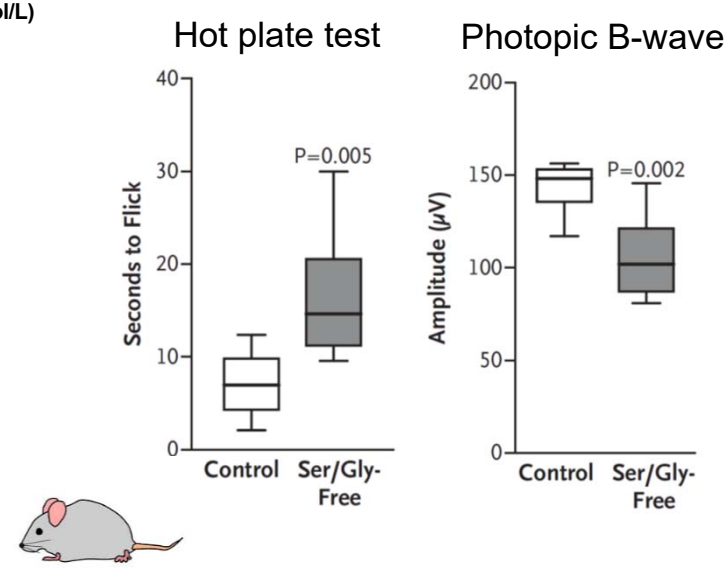
→ Some (but not all) HSAN1 patients have MacTel

Nature/nurture: serine/glycine-free diets induce retinal defects and peripheral neuropathy in mice









10 months on –SG diet

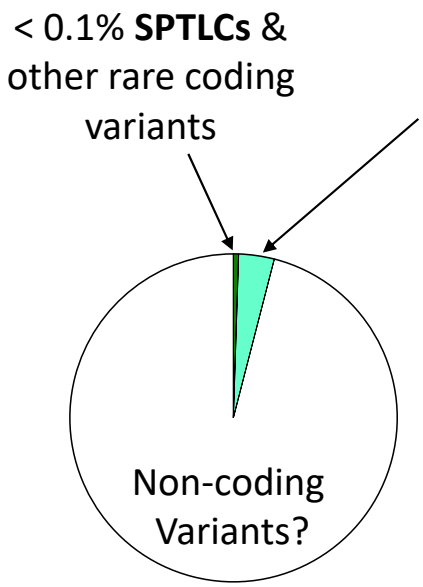
Environment (-SG diet) can cause similar phenotypes as patient genetics (MacTel/HSAN1) → penetrance
Gantner et al. *NEJM* 2019

MacTel is a disease of dysregulated amino acid metabolism

- *PHGDH* haploinsufficiency is significantly enriched in MacTel cohort (Eade et al. *Nat Met* 2021)
- PHGDH is rate-limiting for serine synthesis in the nervous system
- Familial disease, several lines of genetic evidence (GWAS, coding variants) linked to serine
- Systemic serine/glycine, alanine, and SLs altered

Key nutrition questions:
What factors (dietary or otherwise) influence these phenotypes?

Are there links to more common diseases and co-morbidities (e.g. type 2 diabetes)?



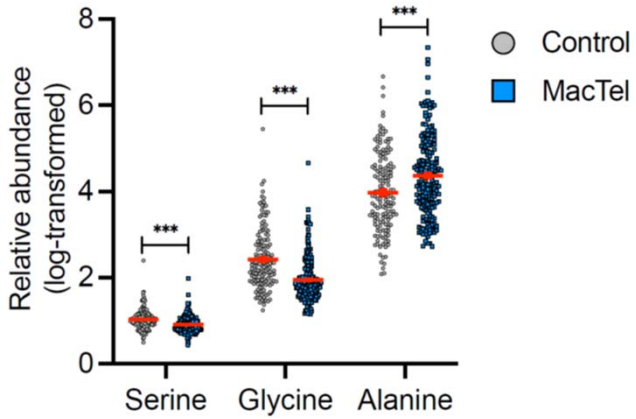


TABLE 4. Comparison of Macular Telangiectasia (MacTel) Natural History Observation Study with Population-based Cohorts: Results from Multivariate Logistic Regression.

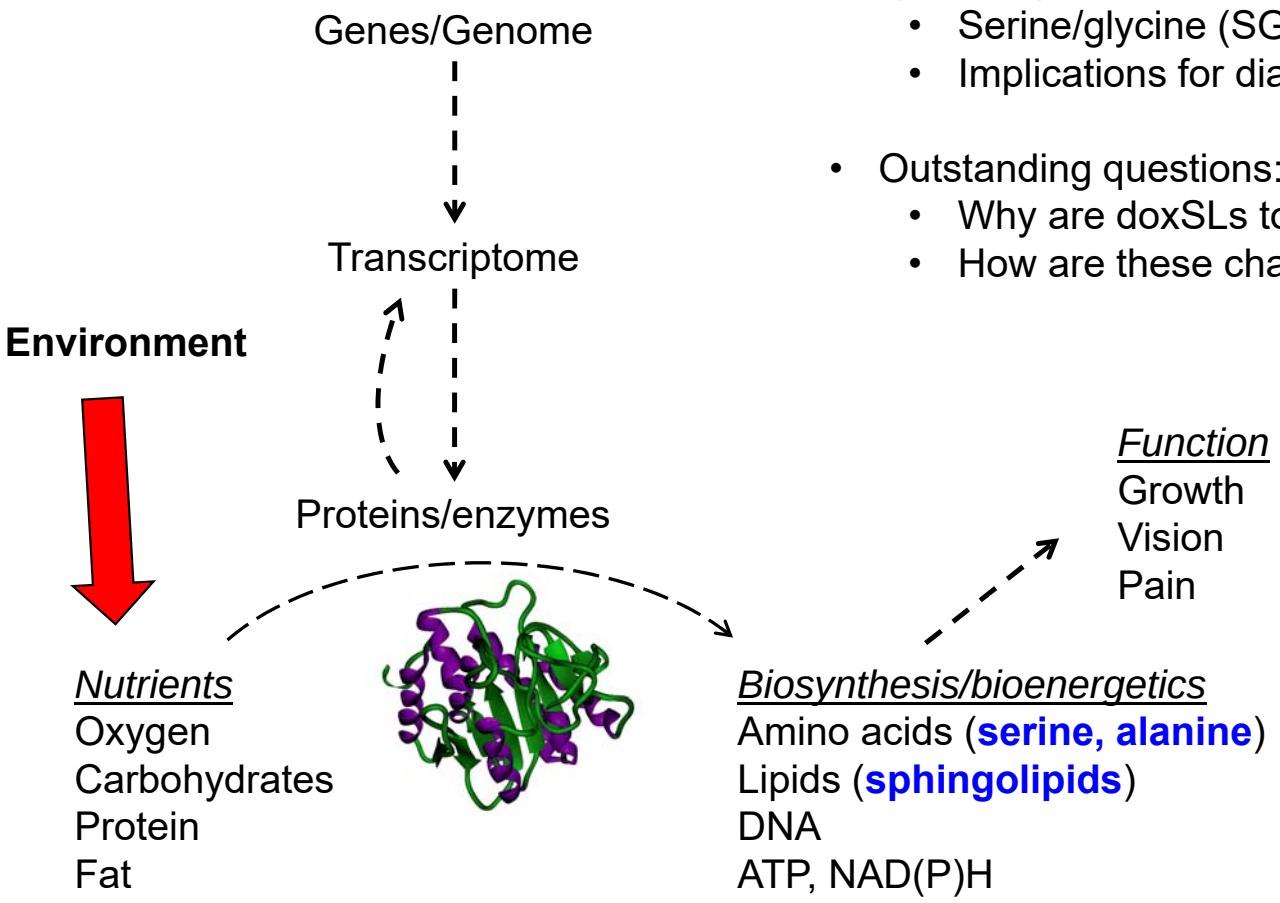
Characteristic*	Odds	Limits	*p* Value
US MacTel Cohort versus NHANES			
Diabetes mellitus	3.58	2.39–5.36	<0.0001
Overweight	2.45	1.47–4.07	0.0006
Australian MacTel Cohort versus BMES			
Cancer	2.81	1.54–5.10	0.0007
Diabetes mellitus	5.58	3.28–9.52	<0.0001
Overweight	3.50	1.86–6.57	<0.0001
European MacTel Cohort versus RS-I			
Hypertension	2.60	1.83–3.69	<0.0001
Diabetes mellitus	4.78	3.00–7.63	<0.0001
Thyroid Disease	2.13	1.30–3.50	0.0028
Overweight	1.97	1.31–2.95	0.0010

*All models include age and sex
NHANES, National Health and Nutrition Examination Study; BMES, Blue Mountains Eye Study; RS-I, Rotterdam Study-I

Collaborations with Friedlander (TSRI), Bernstein (Utah), Allikmets (Columbia), Bahlo (WEHI)

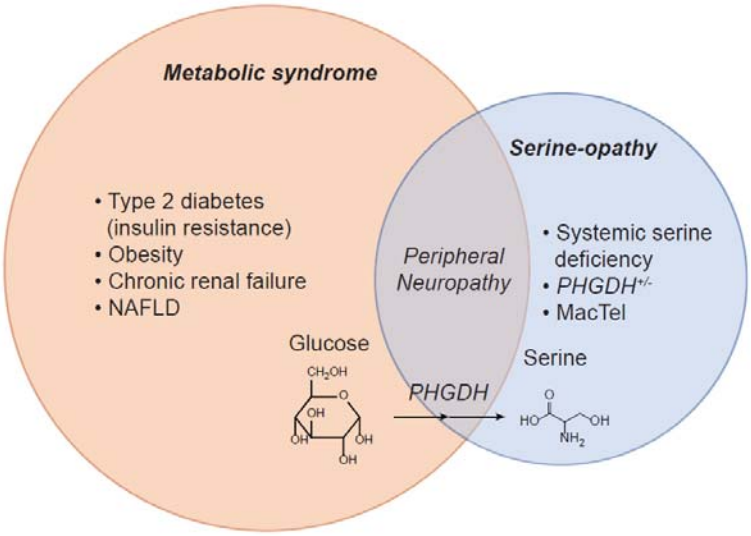
Clemons et al, *Opth Epidem* 2013

Environment (diet) can influence the same biochemical pathways as genetics



- Alterations in amino acid metabolism can impact membrane lipid composition and drive disease:
  - Serine/glycine (SG) and alanine impact SL/doxSLs
  - Implications for diabetic neuropathy, MacTel, and cancer

- Outstanding questions:
  - Why are doxSLs toxic?
  - How are these changes linked to 1C metabolism?



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