5th Better Food for Better Health
Microbiota & Health: The Challenges of a Promising Approach
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Gut Microbial Metabolism of Plant-Food Bioactives:

Impact on Dietary Exposure and Cancer Risk

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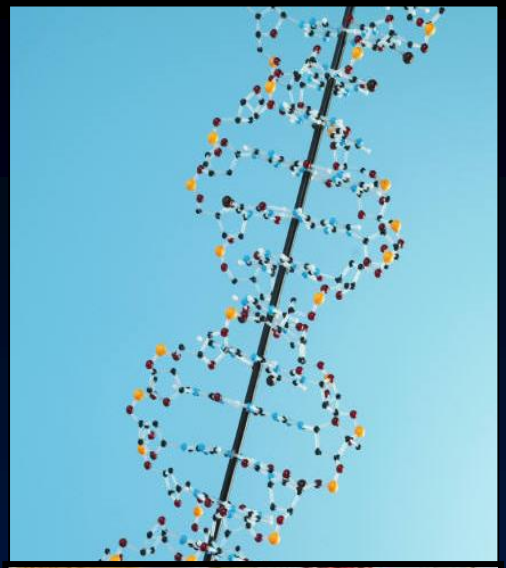
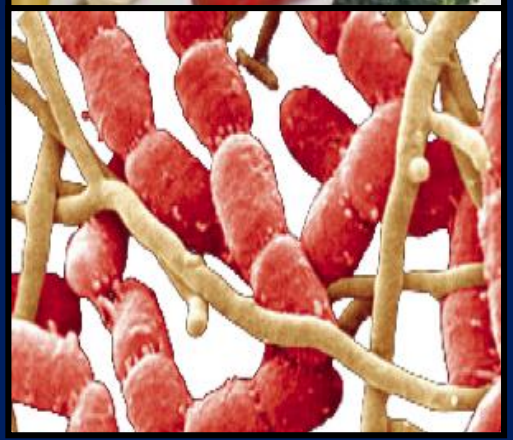
Microbes and Cancer

- **Microbes as infectious agents**
  - Account for ~20% of cancers worldwide
  - Cervical, hepatic, oropharyngeal, and gastric cancers
  - Direct effects
- **Microbes as modifiers of exposures**
  - Metabolizing carcinogens, chemopreventive agents
  - Affecting energetics
  - Indirect metabolic effects





Experimental Human Nutrition

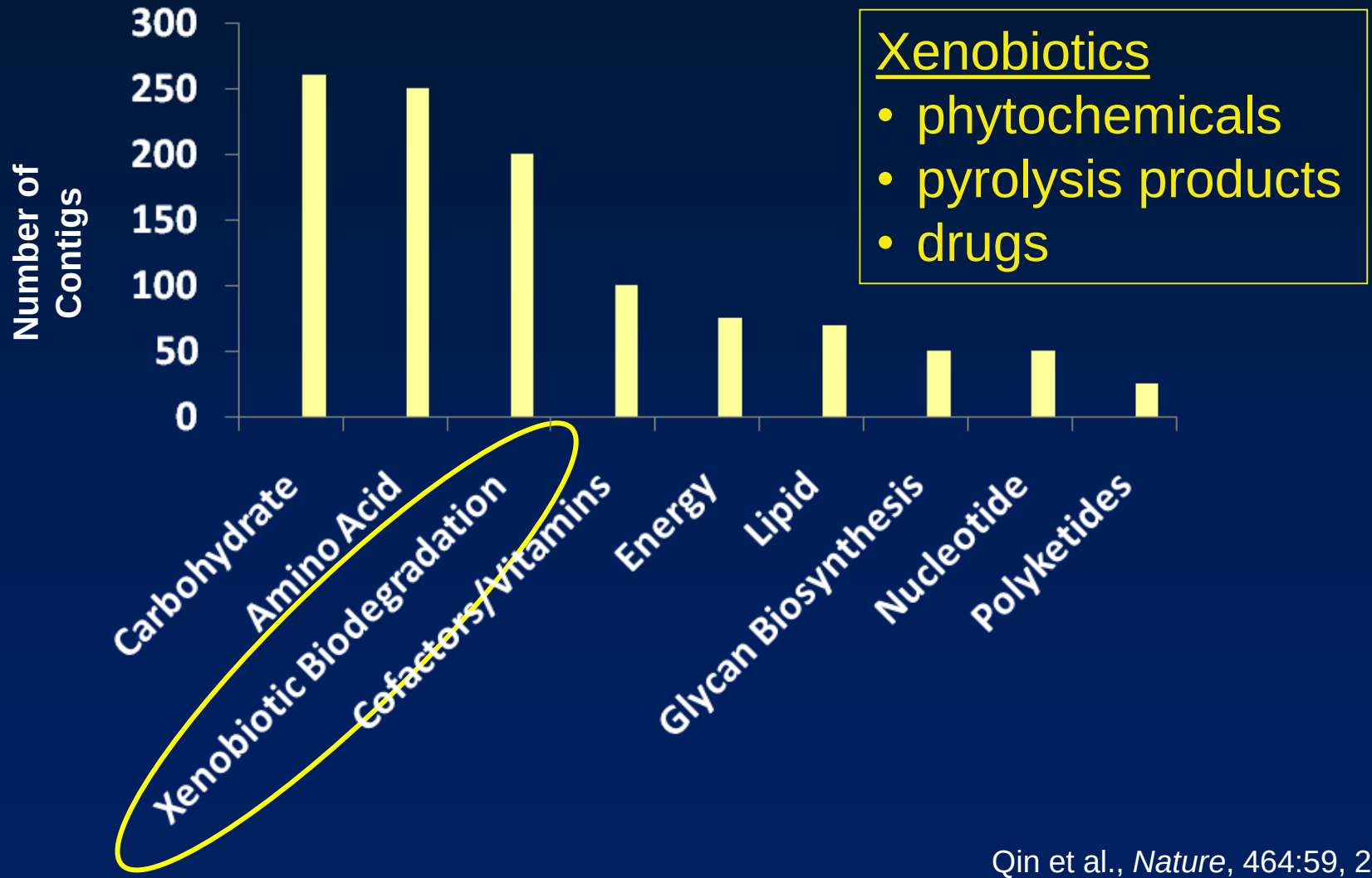
Research Questions

- How are biomarkers of cancer susceptibility in humans modulated by constituents of diet?
- What differences among individuals influence response to diet?

GENOTYPE-DIET INTERACTIONS

HOST MICROBIOME-DIET INTERACTIONS

Substantial Component of Microbial Genome Dedicated to Xenobiotic Metabolism



Qin et al., *Nature*, 464:59, 2010.

Dietary Bioactive Phytochemicals

- **Phenolics**
  - Phenolic acids
  - Stilbenes
  - Curcuminoids
  - Chalcones
  - Lignans
  - Flavonoids
  - Isoflavones
- **Terpenoids**
  - Phenolic terpenes
  - Carotenoids
  - Saponins
  - Phytosterols
- **Organosulfurs**
  - Thiosulfinates
- **N-containing compounds**
  - Glucosinolates
  - Indoles

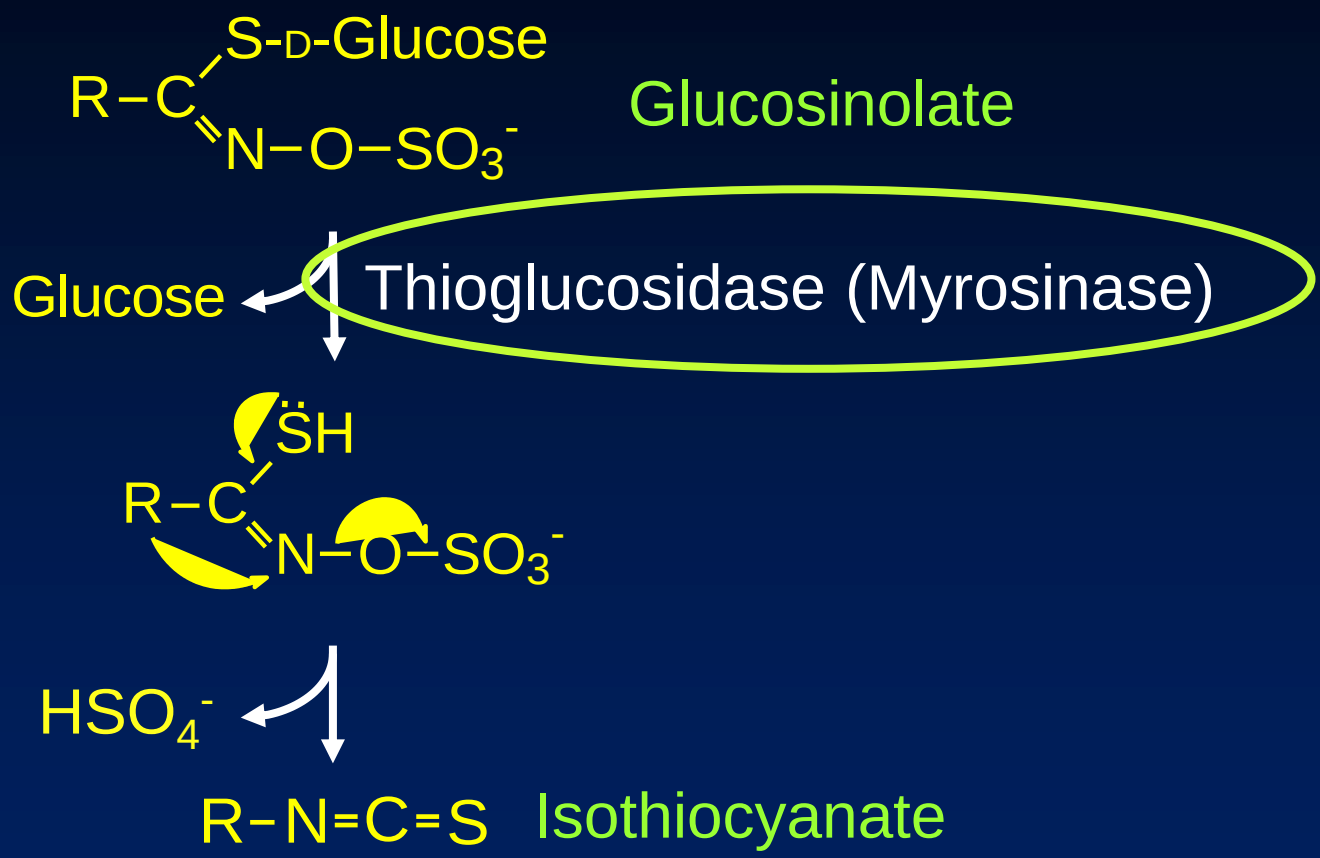
Adapted from Scalbert et al, J. Agric. Food Chem. 2011, 59, 4331–48

Cruciferous Vegetables and Cancer

- Cruciferous vegetable intake shows most consistent association with lower risk of certain cancers:
  - lung, colorectal, breast, prostate, pancreatic cancer
- Isothiocyanates and indoles:
  - Are chemopreventive in animal models
  - Decrease inflammation and oxidative stress
  - Induce cell differentiation and apoptosis
  - Improve carcinogen metabolizing capacity

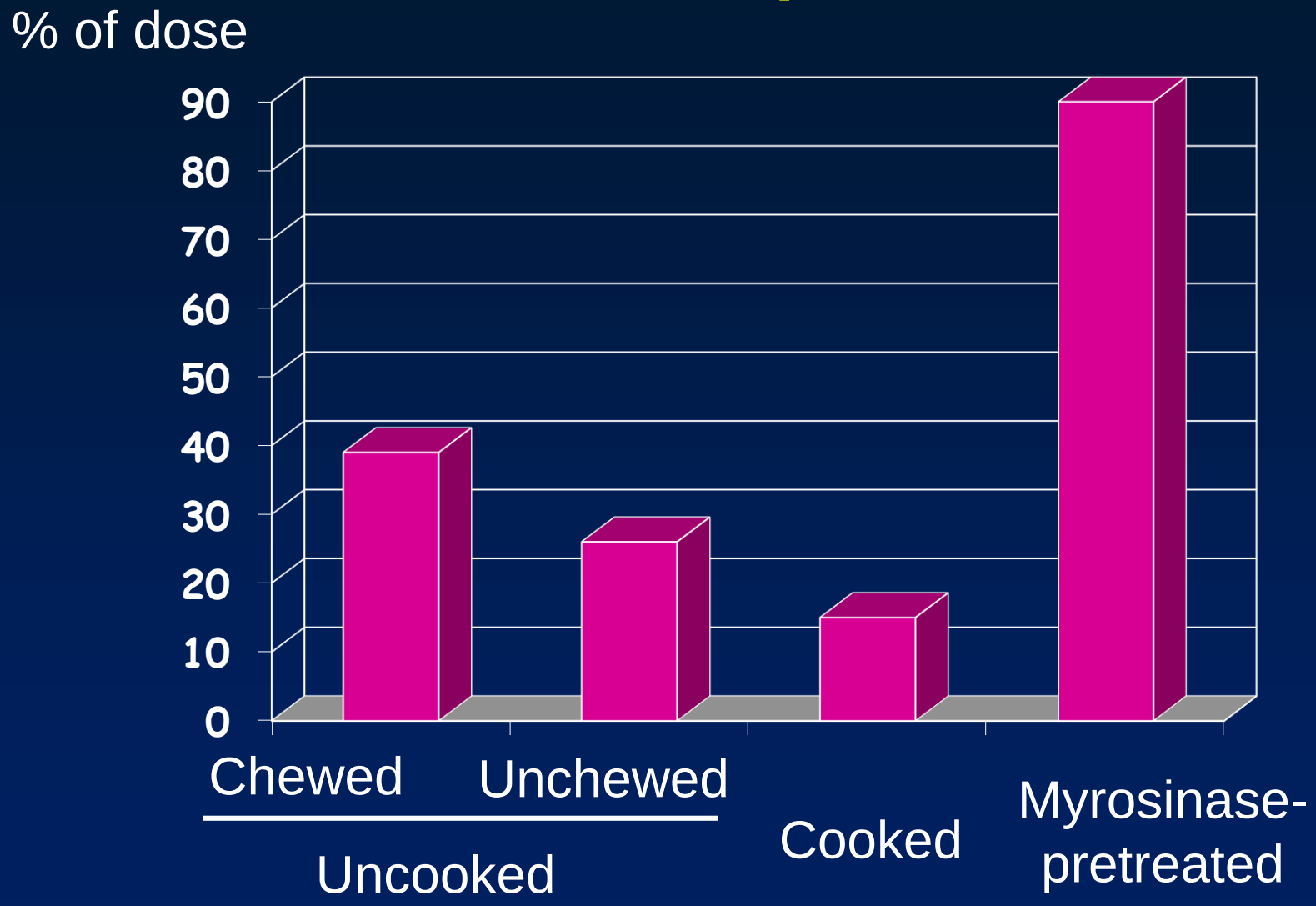
SL Navarro et al, *Food Funct*, 2:579-87, 2011

Isothiocyanates from Glucosinolates in Cruciferous Vegetables



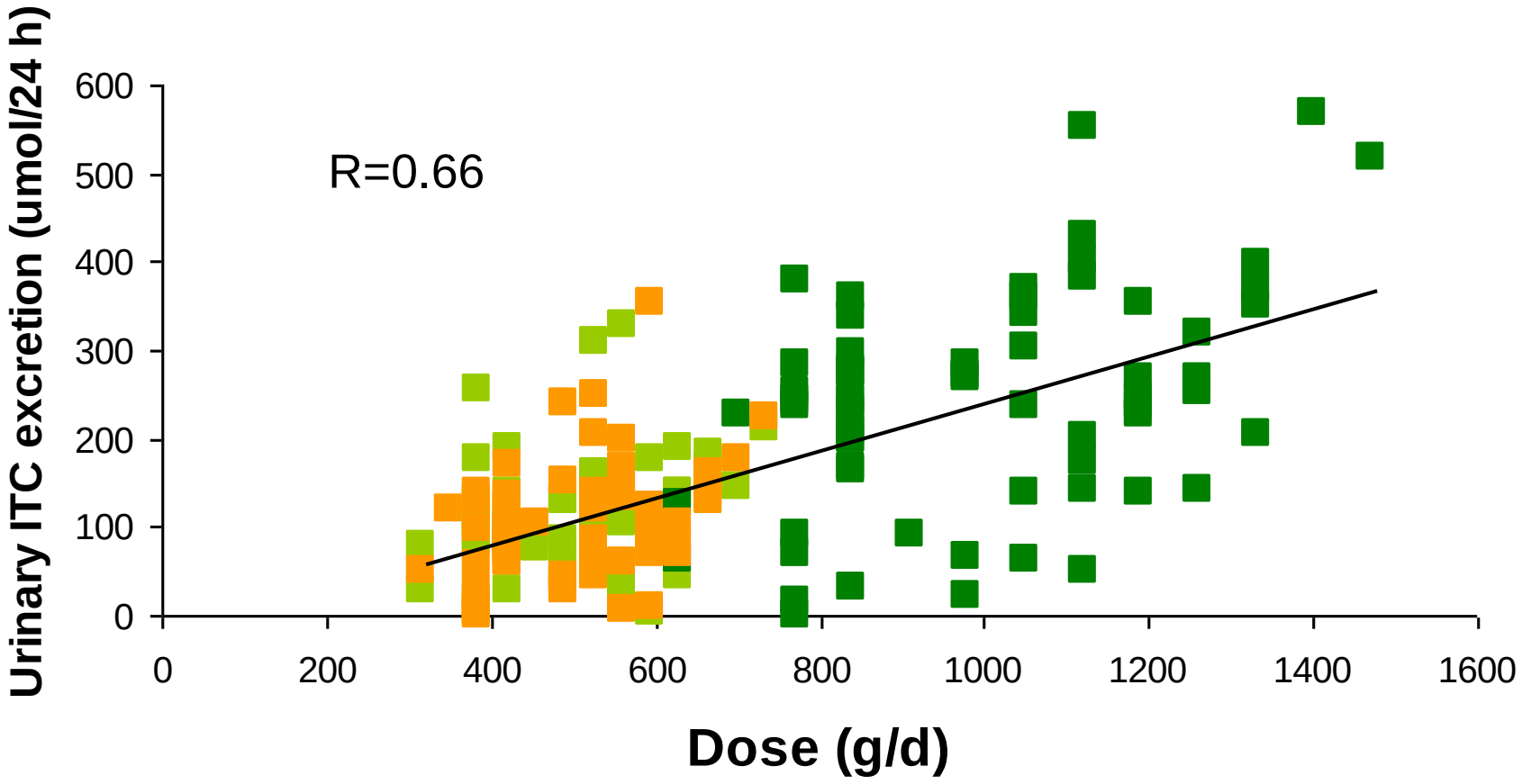
Yuesheng Zhang, Roswell Park Cancer Institute, Buffalo, NY

Availability of Isothiocyanates from Broccoli Sprouts



Shapiro et al, *Cancer Epidemiol Biomarkers Prev*, 2001

Urinary ITC Excretion Highly Variable Across Cruciferous Vegetable Doses



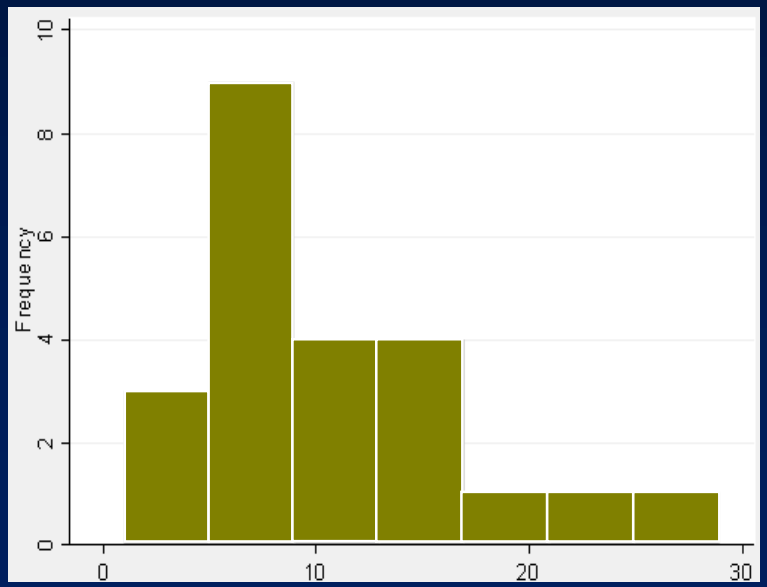
7 g crucifer/kg BW
14 g crucifer/kg BW
7 g crucifer + 4 g apiaceous /kg BW

SL Navarro et al, *J Nutr.* 2014;144:1850-7.

Fecal Bacterial Degradation of Glucosinolates In Vitro Differs by ITC-Excreter Status

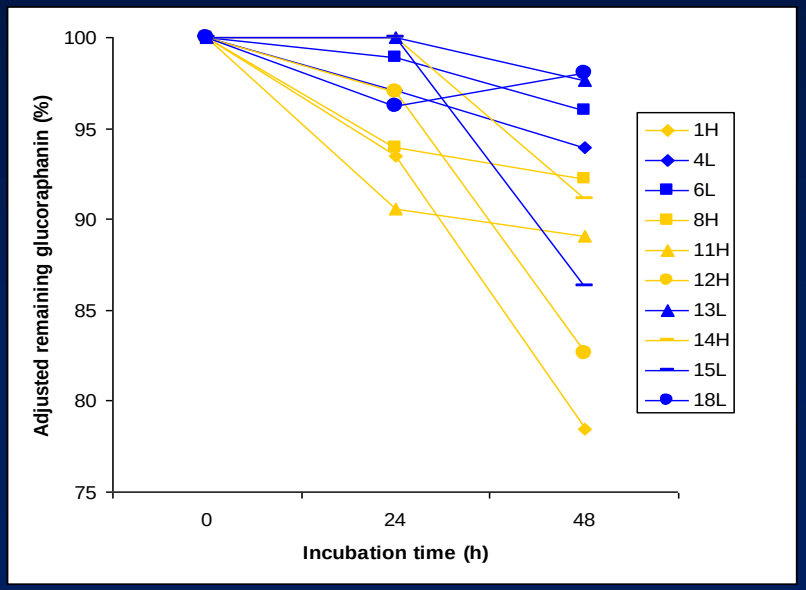
- Low- and high-ITC excreters identified with broccoli dose
- Fecal bacteria incubated with glucoraphanin for 48 h

Urine ITC recovery ranged from 1-28%



% ITC in urine after 200 g broccoli

Glucoraphanin degradation higher in high-ITC excreters



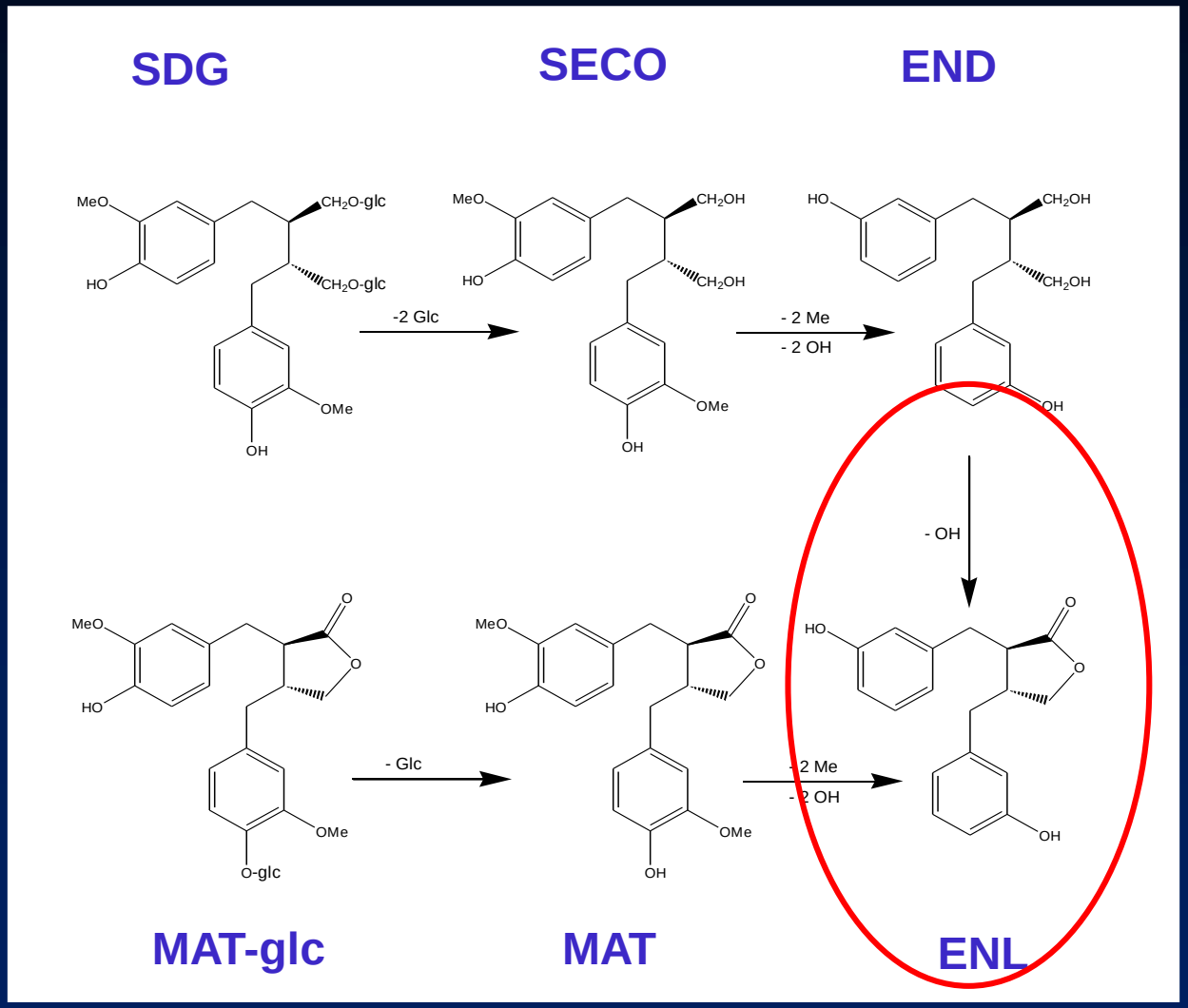
Li *et al.*, *Br J Nutr,* 106:408-16, 2011.

Plant Lignans and Microbially-Derived Enterolignans and Cancer Risk

- Prospective case-control studies
  - Support for reduced risk of colon and breast cancer
  - Less clear for prostate cancer
- Experimental human studies
  - Changes in estrogen metabolite profiles in women
  - Decrease in inflammation biomarkers
- Experimental animal studies
  - Flax lignans reduce colon, lung and mammary tumorigenesis
- Mechanisms of action
  - Anti-inflammatory
  - Anti-proliferative
  - Pro-apoptotic

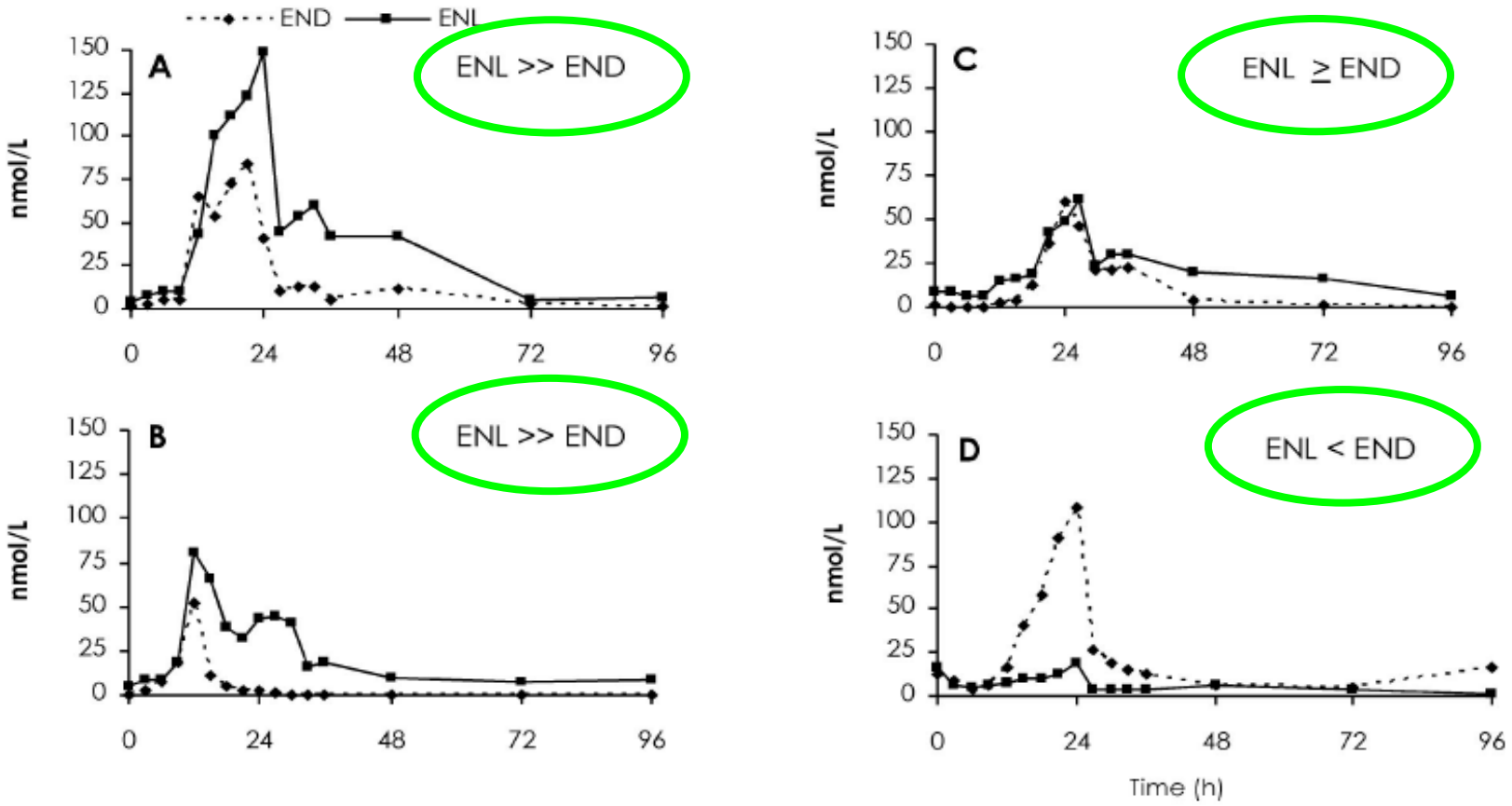
Reviewed by Yoder, Lampe et al,
in *Diet-Microbe Interactions in the Gut*, 2015

Gut Bacterial Metabolism of Plant Lignans to Enterolignans, Enterodiol and Enterolactone



- *Hydrolysis of glucosides*
- *Demethylation*
- *Dehydroxylation*

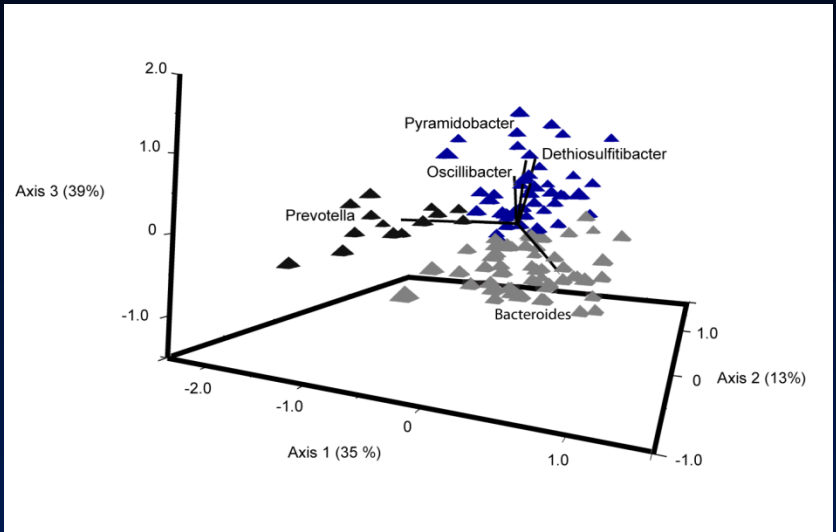
Large interindividual differences in enterodiol and enterlactone pharmacokinetics with dose of secoisolariciresinol diglycoside

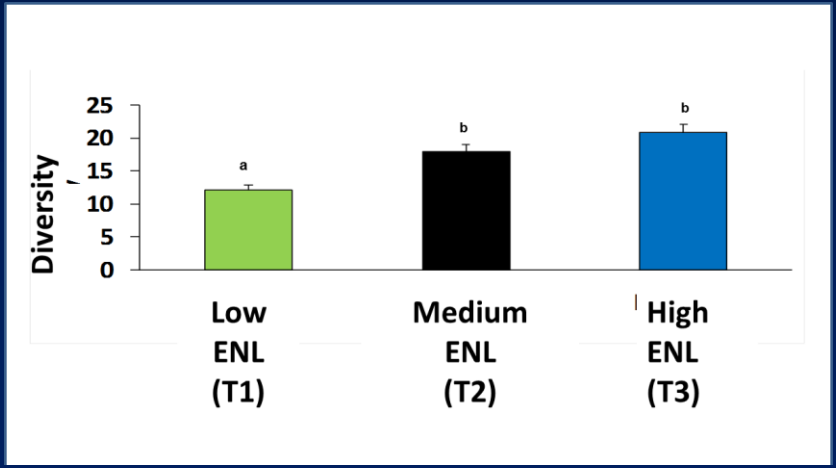


Kuijsten et al, *J Nutr,* 2005

Is There a Unique Gut Microbial Community Structure Associated with Lignan Metabolism?

Gut Microbial Community and Lignan Excretion in Premenopausal Women

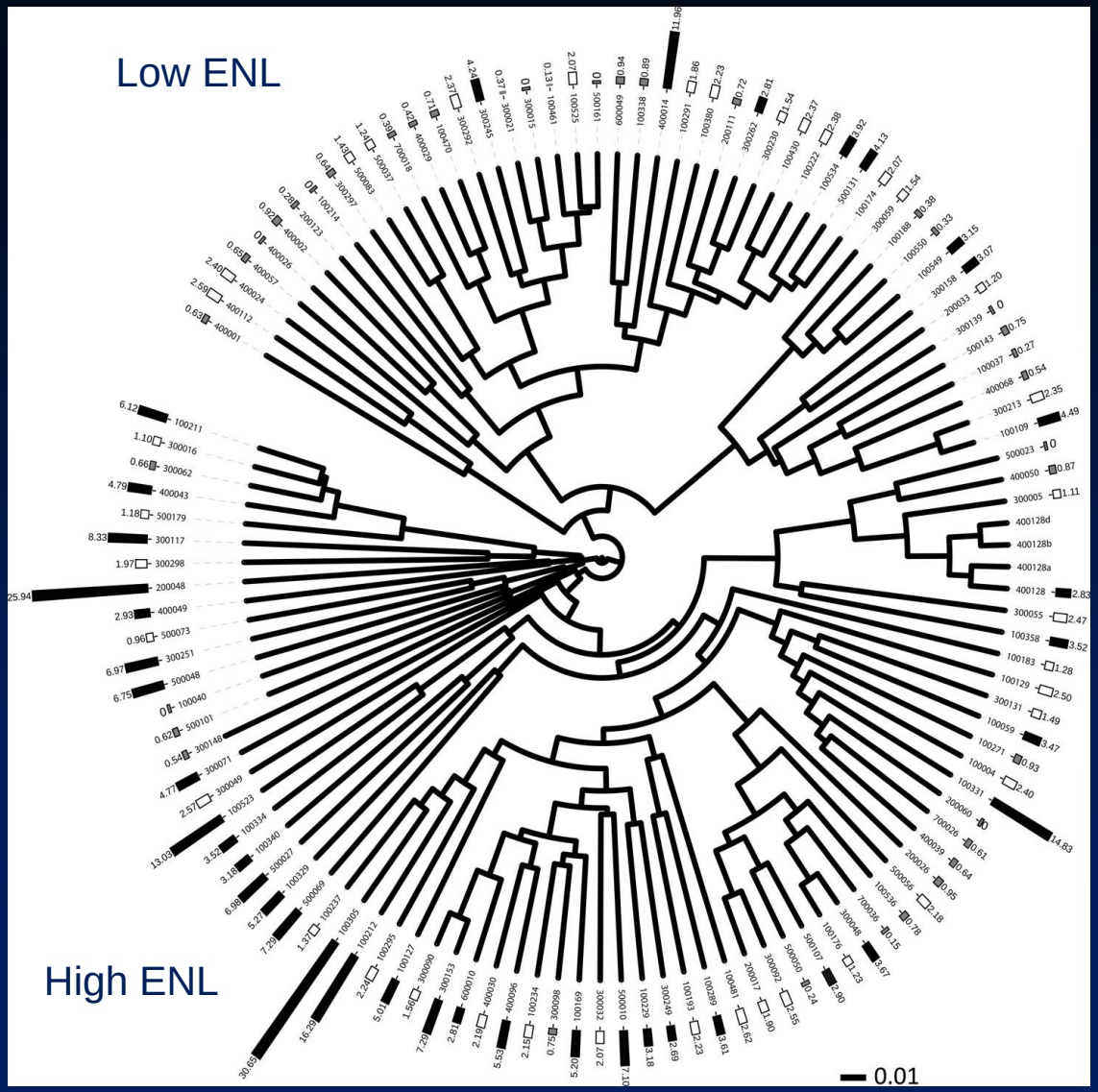




- 107 women, 40-45 y
- Participants clustered by dominant bacterial genera (enterotypes).
- No relationship between enterotypes and lignan metabolite phenotypes.
- Gut microbial diversity higher with higher ENL excretion.

Hullar et al, *Cancer Epidemiol Biomarkers Prev*, 24: 546-54, 2015

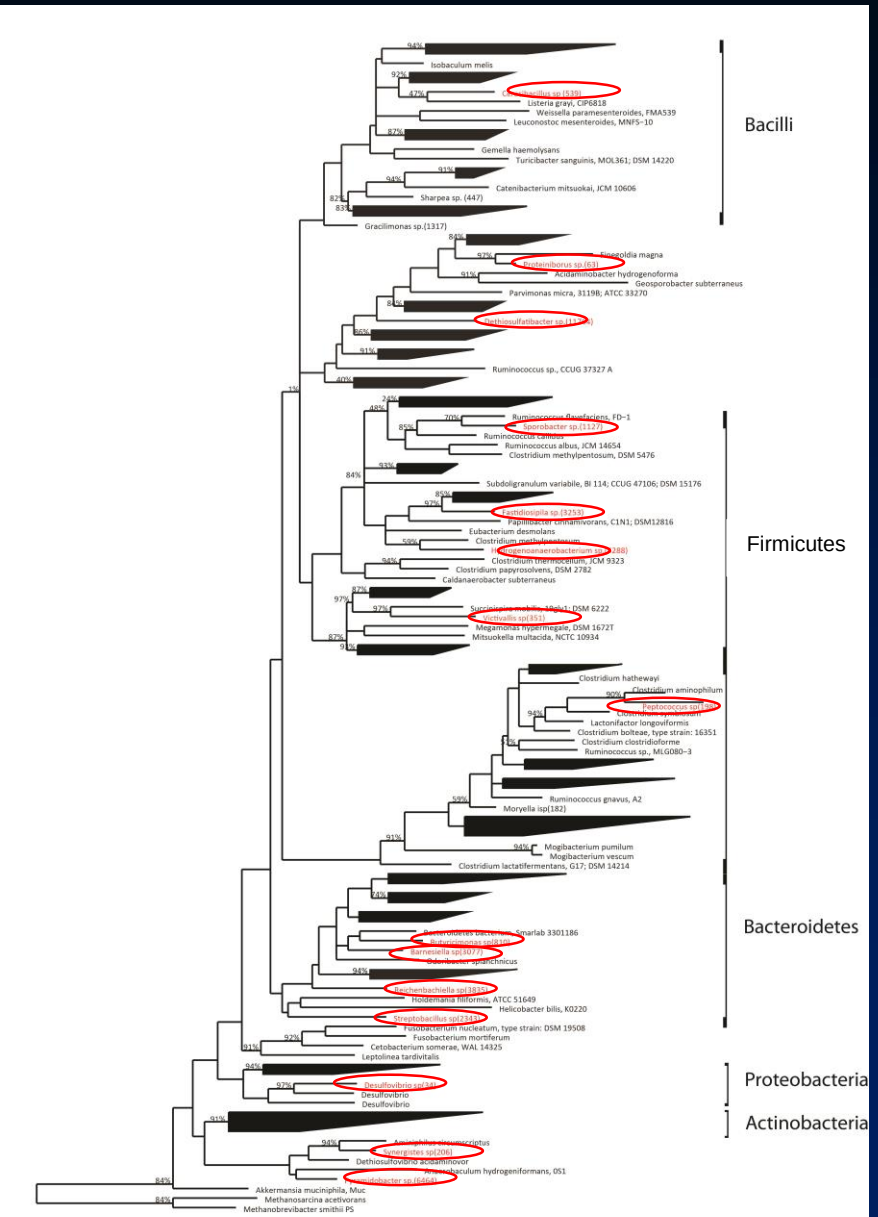
Gut Microbiome Associated with Urinary Enterolactone (ENL) Excretion



- GMC composition is significantly different between high and low ENL excreters (MRPP, p<0.0005).
- Association remains significant with adjustment for fiber intake and adiposity.
- Low ENL clusters together

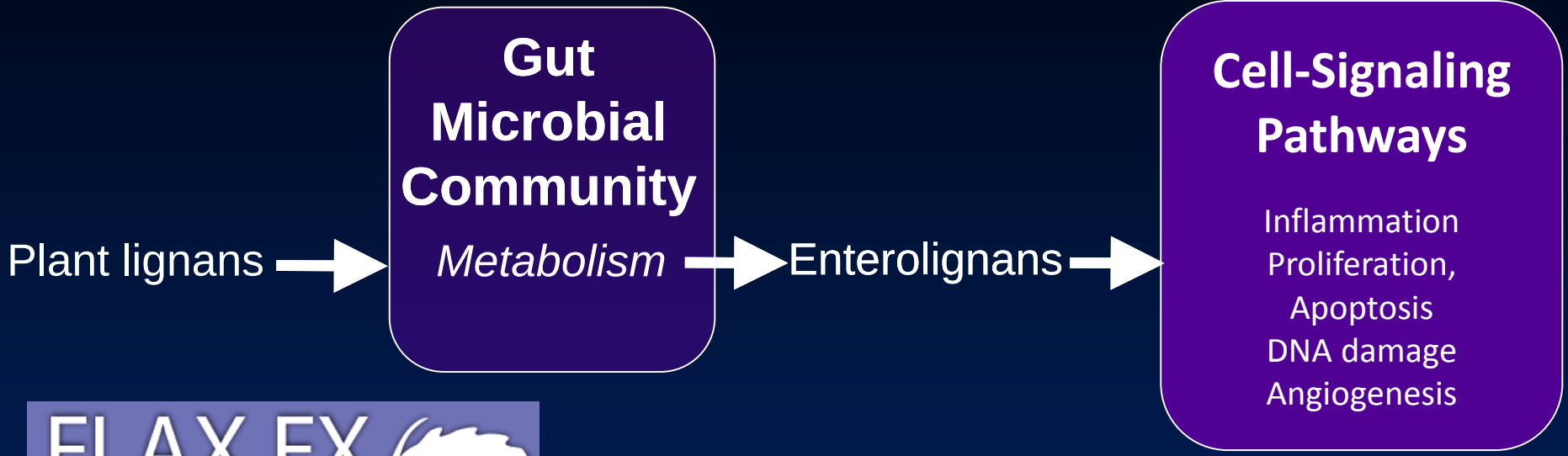
Hullar et al, *Cancer Epidemiol Biomarkers Prev,* 24: 546-54, 2015

Phylogenetic Distribution of Microbiome in High-ENL Excreters



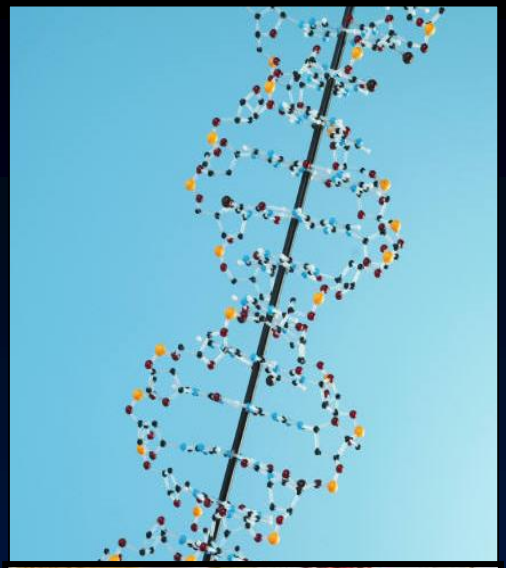
- Unique genera high ENL excreters
- Distributed across Phyla

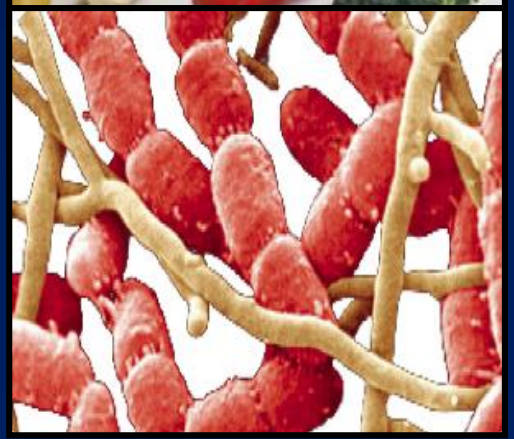
Lignans, Gut Microbiome and Colonocyte Cell-Signaling Pathways In Vivo



FLAX FX

- Randomized, controlled, crossover trial in healthy subjects:
  - Lignan capsules (50 mg secoisolariciresinol diglucoside)
  - Placebo capsules
- Measuring effects of lignan supplementation on:
  - colonic mucosal mRNA expression (stroma and epithelium)
  - gut microbiome structure





Summary

- Gut microbes modify a variety of dietary constituents to bioactive compounds not found in diet.
- Phytochemicals as consumed are not necessarily as experienced by the host.
- Usual approaches of characterizing diet in epidemiologic studies are unlikely to capture exposure accurately.
- Application of metabolite biomarkers and gut microbial characterization may better explain dietary exposures in relation to risk of cancer and other chronic diseases.

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