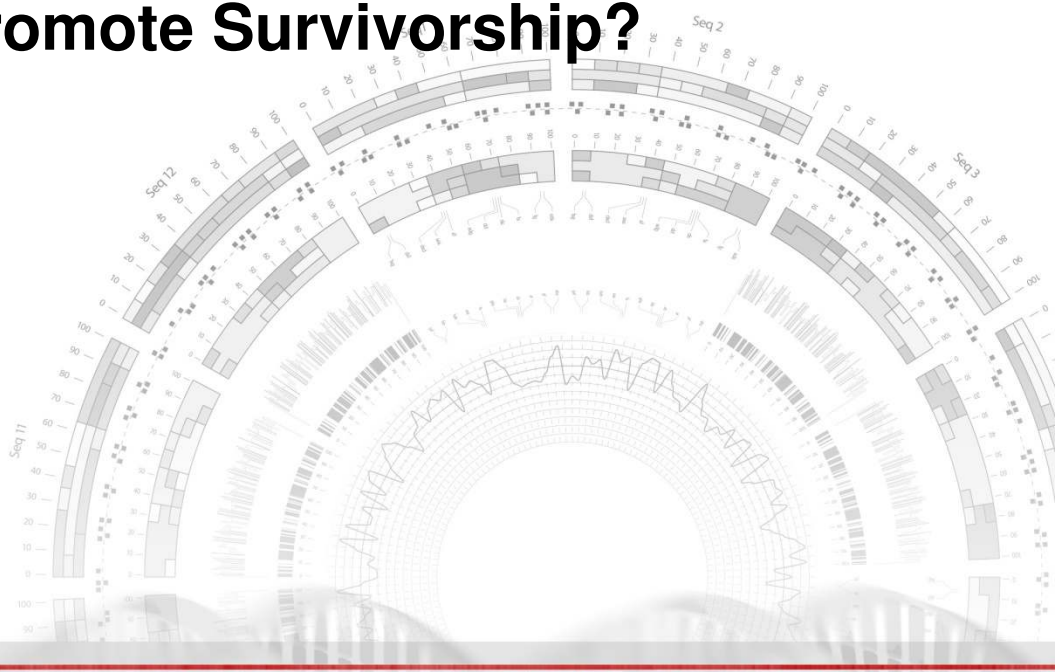
Can Dietary Interventions Impact Cancer risk, Enhance Efficacy of Therapy, and Promote Survivorship?

Steven K. Clinton, MD, Ph.D

January 22, 2017



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COMPREHENSIVE CANCER CENTER

Food-based Cancer Prevention Strategies

Steven K. Clinton, MD, Ph.D

January 22, 2017

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COMPREHENSIVE CANCER CENTER

Conflicts of Interest: None

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Comprehensive Cancer Center

Opinions: Many !

Research Funding:

NIH: NCI

AICR

ACS

OSU

- Pelotonia (The James)
- Growing the Cure (OSU)
- OSU-CCC
- Food Innovation Center

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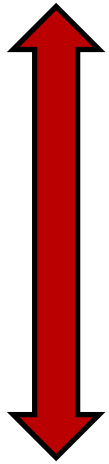
The Conceptual Framework: Diet and Nutrition-Based Cancer Prevention Strategies

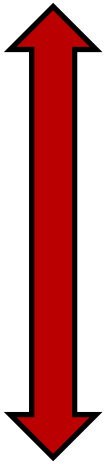


- Dietary Patterns
- Foods (*whole, processed, functional*)
- Nutraceuticals
- Chemoprevention (*chemically pure*)
  - Nutrients (*vitamins, minerals, FA, etc.*)
  - Natural compounds (*phytochemicals*)

The Conceptual Framework: Diet and Nutrition-Based Cancer Prevention Strategies

- Energy Balance
  - Intake
  - Metabolism
  - Exercise

Holism



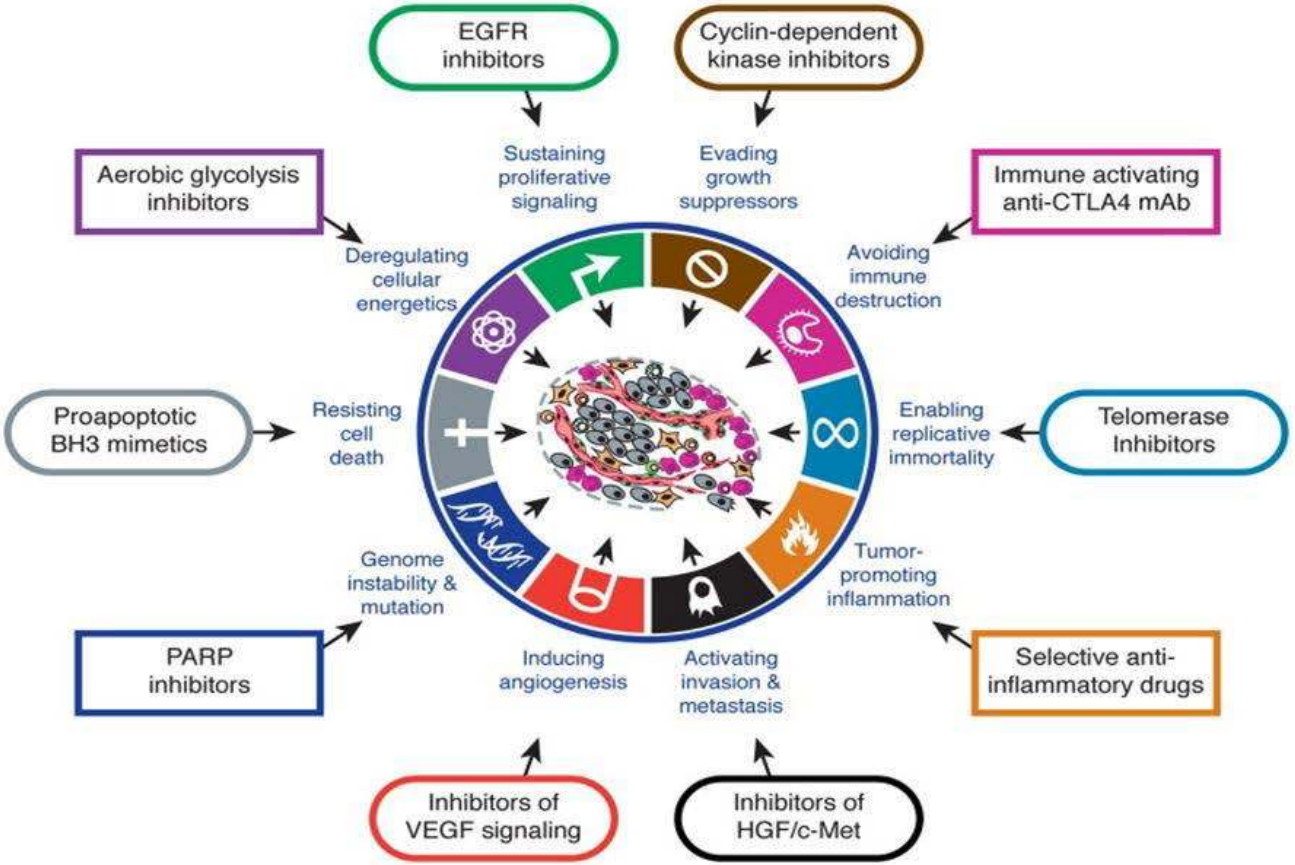
Reductionism

- Dietary Patterns
- Foods (*whole, processed, functional*)
- Nutraceuticals
- Chemoprevention (*chemically pure*)
  - Nutrients (*vitamins, minerals, FA, etc.*)
  - Natural compounds (*phytochemicals*)

Foods and Functional Foods:

Key Assumptions and Principles

- Get comfortable with the “black box” !
- Multiple bioactives with diverse mechanisms of action, multiple targets, will be “more” effective.
- Multiple bioactives at modest dose with non-overlapping toxicity provide a margin of safety.



Hannahan and Weinberg: Cell 144:646 2011

Foods and Functional Foods for Cancer Prevention: Strategic and Scientific Principles for Trials

- Agent / Product Development
  - Target a specific exposure (dose) based upon “science”
  - Design a vehicle (food) to assure compliance
  - Components / Ingredients
    - Cultivar (genetics, horticulture, senescence, processing/storage)
    - Extract or concentrate
  - Analytic chemistry
  - Taste / sensory testing
  - Packaging and stability

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Consistency

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Food Products for Cancer Prevention at OSU: Examples

- Tomato Products

- Soy Bread

- Black Raspberry

Food Products for Cancer Prevention : Clinical Trials

- Phase I *(short term)*
  - Healthy or target population
  - Dose (single or multiple)
  - Feasibility and compliance
    - Distribution and storage
    - Test intake assessment/monitoring tools/strategies
  - “Pharmacokinetics” (biomarkers of exposure)
    - Single dose and prolonged (days or weeks)
    - Begin to elucidate heterogeneity/variation
  - Safety
    - NCI Toxicity Criteria
    - Laboratory testing

Food Products for Cancer Prevention : Clinical Trials

- Phase II *(intermediate duration)*
  - Target or diseased population *(dozens)*
  - Dose *(single or few)*
  - Feasibility, compliance, safety
  - Biomarkers of exposure *(food)*
    - Blood, urine, tissue
    - Define heterogeneity of the population *(genetics, drugs, supplements, diet)*
  - Biomarkers of activity
    - Endocrine, immune, microbiome, metabolomics, etc.
  - Biomarkers of impact Target tissues and microenvironment
    - Carcinogenic cascade *(hyperplasia, dysplasia, PIN, cancer)*

Food Products for Cancer Prevention : Clinical Trials

- Phase III *(long term)*
  - Target population
    - Population-based ($$$$$)
    - High-risk ($)
      - Genetics / Inheritance
      - Carcinogen exposure
      - Premalignant lesions
  - Biosamples
    - Mechanistic studies
    - Define sensitive and resistant subgroups
  - Cancer outcome

Challenges for Food Based Cancer Prevention

- "Gold Standard"
  - Randomized double-blinded placebo controlled trial
- Placebo
  - Difficult to create a true "placebo"
  - Patient awareness
    - Crossover by controls
- Background "noise"
  - Population exposure to food of interest
- Sufficient duration of exposure
- Appropriate timing of exposure

Tomato-based Food Products for Cancer Prevention

Bohn et al. Phase I Trial Nutr Cancer. 65:919-29, 2013

Tomatoes and Prostate Cancer: Scientific Basis

- ***Enhanced Risk*** of Prostate Cancer
  - None.
- ***No Association*** with Prostate Cancer
  - Raisins, prunes, bananas, cantaloupe, watermelon, apples, pears, oranges, grapefruit, blueberries, peaches, apricots, plums, chili sauce, tofu, soybeans, string beans, broccoli, cabbage, Brussels sprouts, carrots, corn, peas, beans, lentils, squash, eggplant, zucchini, yams, sweet potatoes, spinach, kale, chard, lettuce, celery, alfalfa sprouts, garlic, tomato juice.
- ***Reduced Risk*** of Prostate Cancer
  - Tomatoes ($P < 0.03$), tomato sauce ($P < 0.001$), pizza ($P < 0.05$).

Giovannucci et al. JNCI 87: 1767, 1995

Tomatoes, Lycopene and Prostate Cancer: Scientific Basis

β,β-carotene-9',10'-dioxygenase (BCO2) impacts the anticancer activity of tomato and lycopene in the TRAMP model

- TRAMP model of prostate cancer
- Feed from weaning until 18 weeks of age (early cancer)

Diet	TRAMP+/:*Bco2*+/+	TRAMP+/-:*Bco2* -/-
AIN-93G Control	N=46	N=40
10% Tomato Powder	N=44	N=43
0.25% Lycopene Beadlets	N=45	N=39

10% tomato powder diet contained 0.384 +/- 0.040 g LYC per kg diet
0.25% lycopene beadlet diet contained 0.462 +/- 0.065 g LYC per kg diet

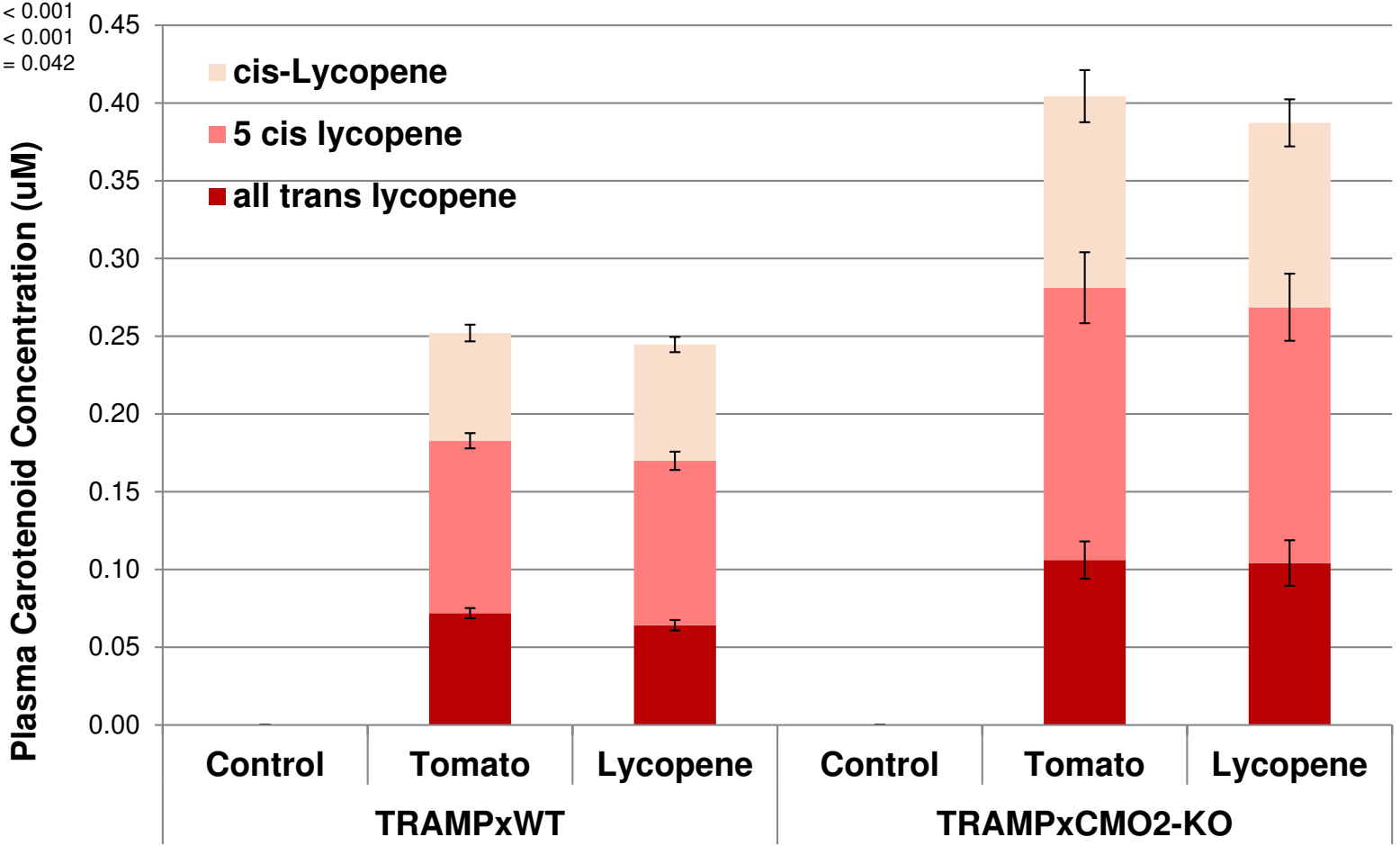
Serum Carotenoids: Lycopene

2 way ANOVA:

Diet: $P < 0.001$

Genotype: $P < 0.001$

Interaction: $P = 0.042$



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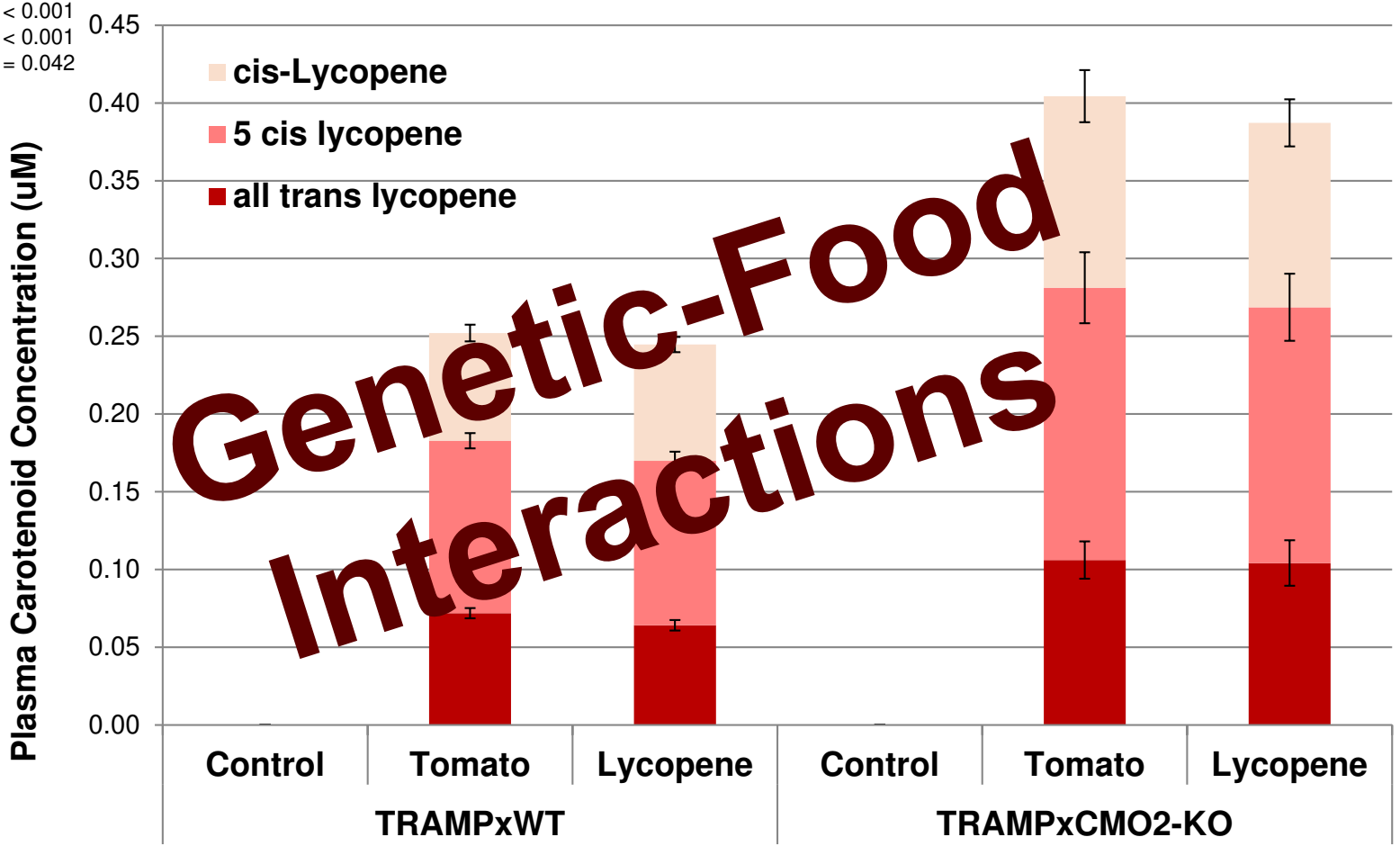
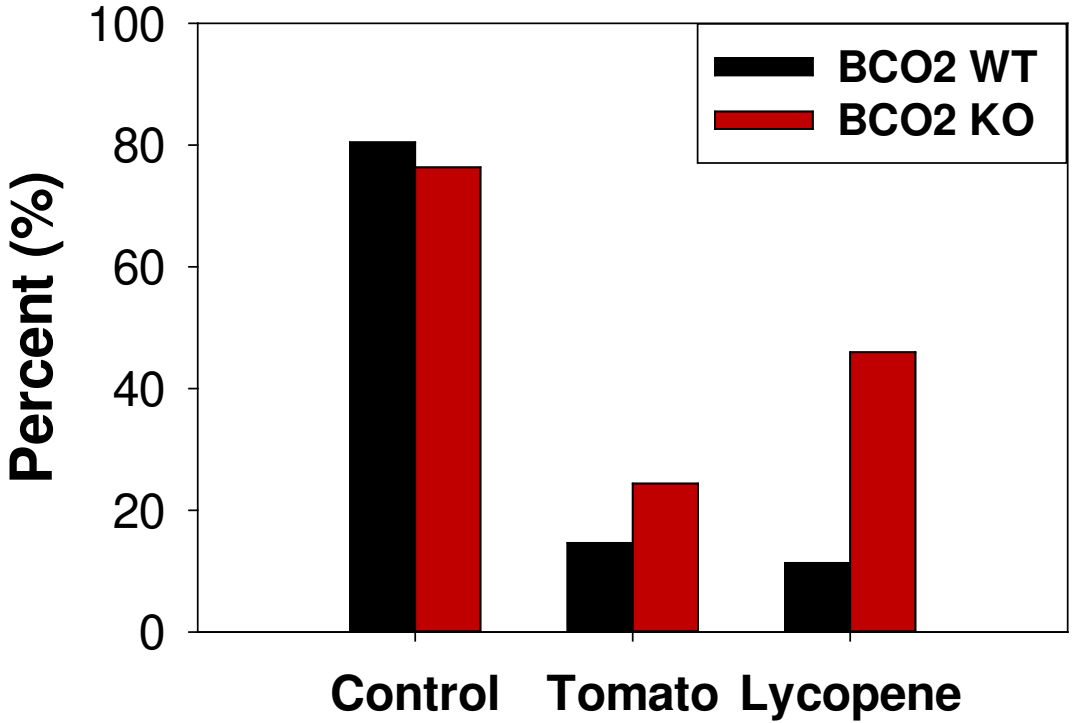


Genetic-Food Interactions

Prostate Carcinoma Incidence - TRAMP model.

Tan et al., Cancer Prev Res 2016 Nov 2. [Epub ahead of print]



Multiple Logistic Regression
Genotype P < 0.037
Diet P < 0.001

Grading Schema from Berman-Booty, L *et al.*
***Toxicologic Pathology,* 40: 5-17, 2012**

Supportive Studies

Grainger EM et al.
A comparison of plasma and prostate lycopene in response to typical servings of tomato soup, sauce or juice in men before prostatectomy.
Br J Nutr. 2015 Aug 28;114(4):596-607.

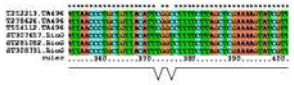
Wan L, et al.
Dietary tomato and lycopene impact androgen signaling- and carcinogenesis-related gene expression during early TRAMP prostate carcinogenesis.
Cancer Prev Res; 6(6); 548–57, 2014.

Ke Zu, et al.
Dietary Lycopene, Angiogenesis, and Prostate Cancer: A Prospective Study in the Prostate-Specific Antigen Era.
J Natl Cancer Inst. 106 (2): djt430, 2014.

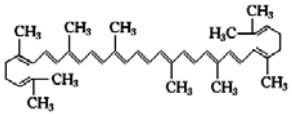
Zuniga KE et al.
The Interactions of Dietary Tomato Powder and Soy Germ on Prostate Carcinogenesis in the TRAMP Model
Cancer Prev Res; 6(6); 548–57, 2013

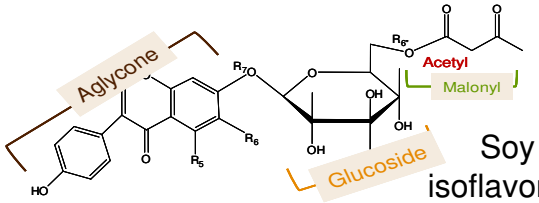
Tomato-soy food products for cancer prevention.

Plant (Tomato) Genetics



Lycopene





Soy isoflavones

OSU Farms Horticulture Crop Science

Steven Schwartz, PhD

Food Science and Technology

OSU Comprehensive Cancer Center

Clinical trials Office

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Tomato-Soy Juice: Phase I/II Study in Men with Prostate Cancer

- 0,1,2,3 cans per day (total n=60)
- Dose escalation design
- Pre-prostatectomy design
- Blood carotenoids
- Prostate carotenoids
- Urinary isoflavone metabolites
- Blood isoflavones
- Prostate isoflavones
- Genetics
- Metabolomics

1 can = 150 ml of juice (6 oz.)
22.5 mg lycopene
33 mg isoflavones

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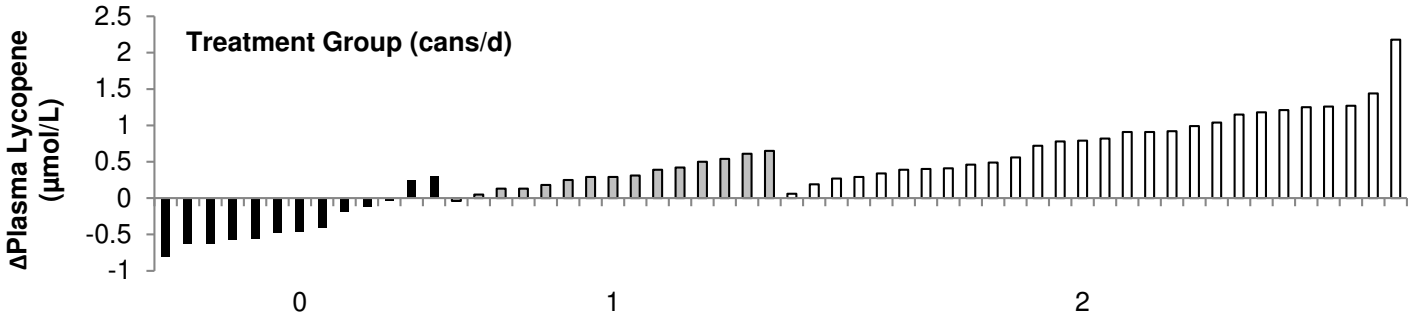
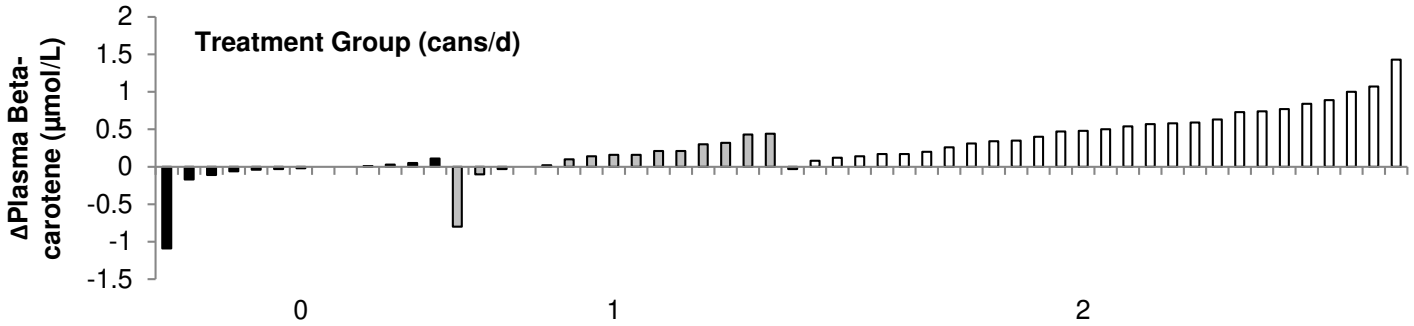
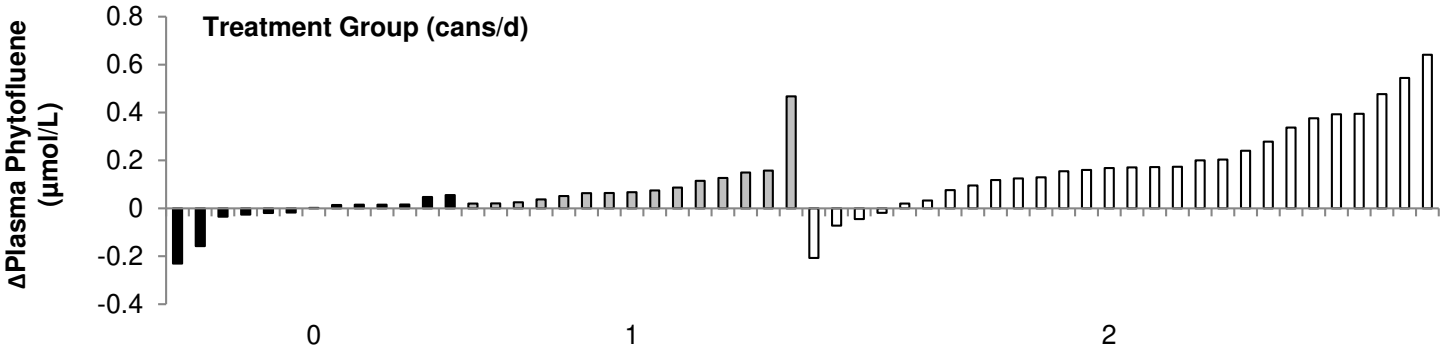
Biomarkers of Exposure

Change in Plasma Carotenoids with Tomato-Soy Juice

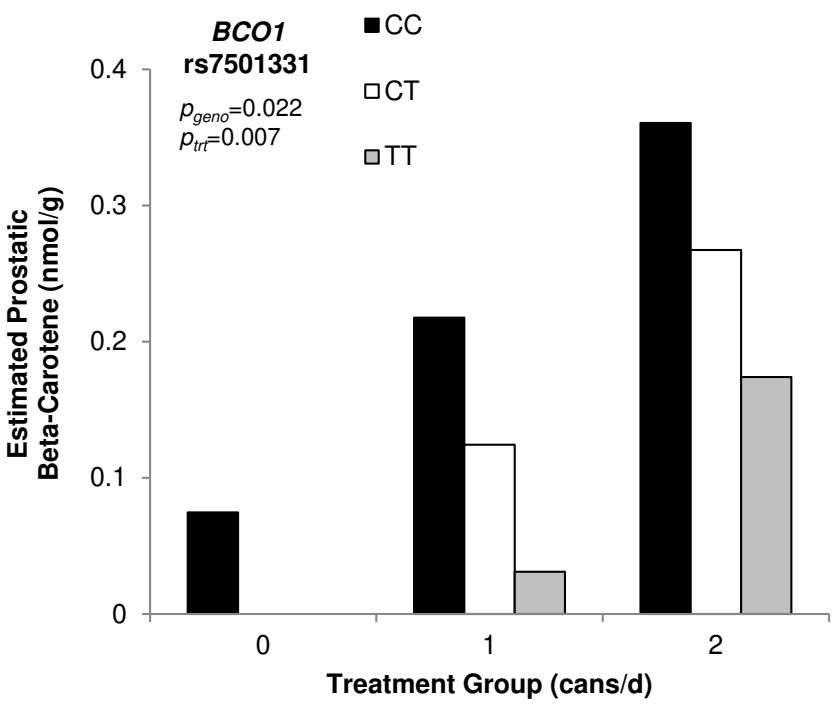
Biological Variation

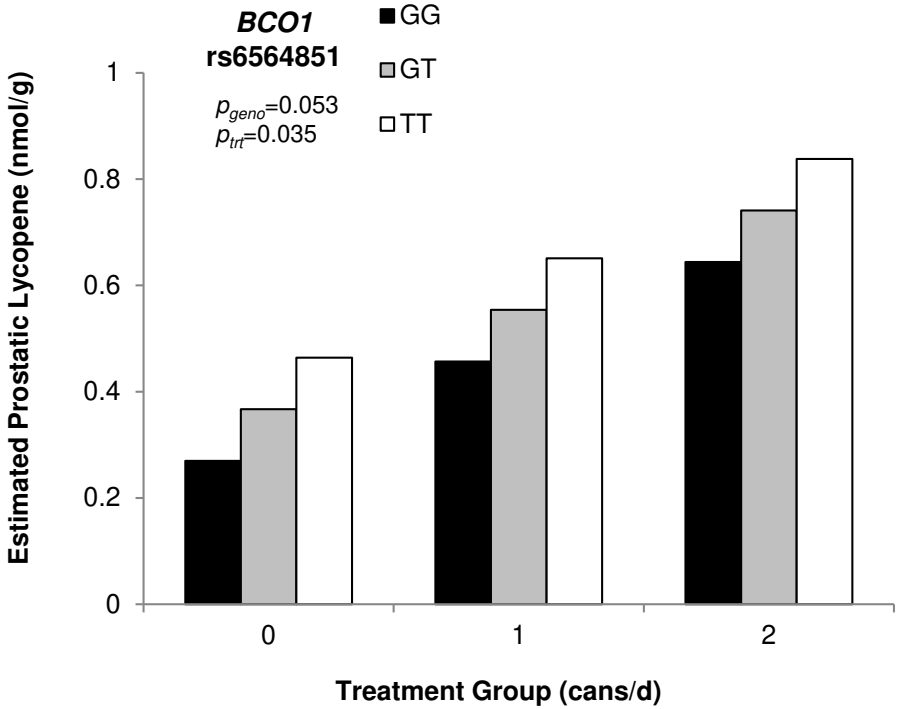






Genetics Impacts on Tomato Carotenoid Distribution and Metabolism





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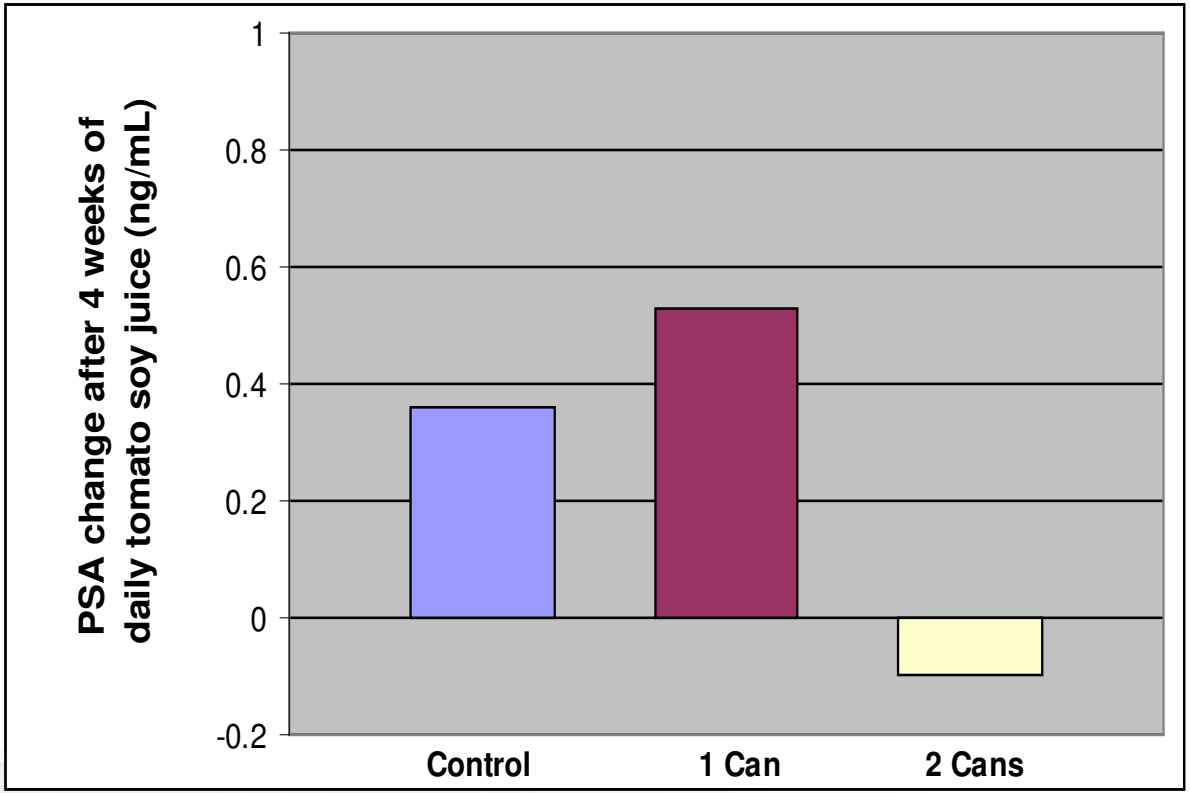
Biomarkers of Impact:
PSA changes (4 wks) in men consuming Tomato-Soy Juice



Where are we going?

- Enhanced phytochemical bioavailability
  - Tomato varieties (genetics)
    - Tangerine vs Red
- Metabolomics of tomato phytochemicals
- Human genetics impacting phytochemical metabolism
- Preclinical
  - Tomato varieties and TRAMP
  - miRNA, mRNA, proteomic signatures
  - Impact on androgen signaling
  - Prevention of castrate resistance in TRAMP
- Human bioactivity studies.

Soy Bread

Soy Bread: Product Development

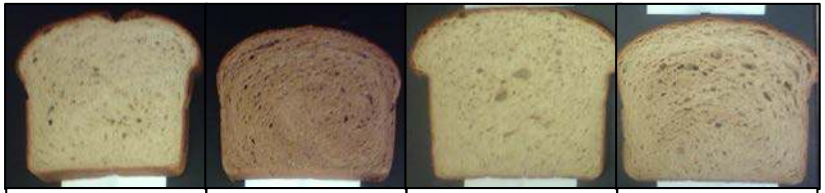
Dr. Yael Vodovotz

Research
- Sensory
- Shelf stability
- Analytics

The goal is to deliver 60 mg of soy isoflavone in 2 slices of bread.

40% Soy Bread | 30% Soy Bread | 20% Soy Bread

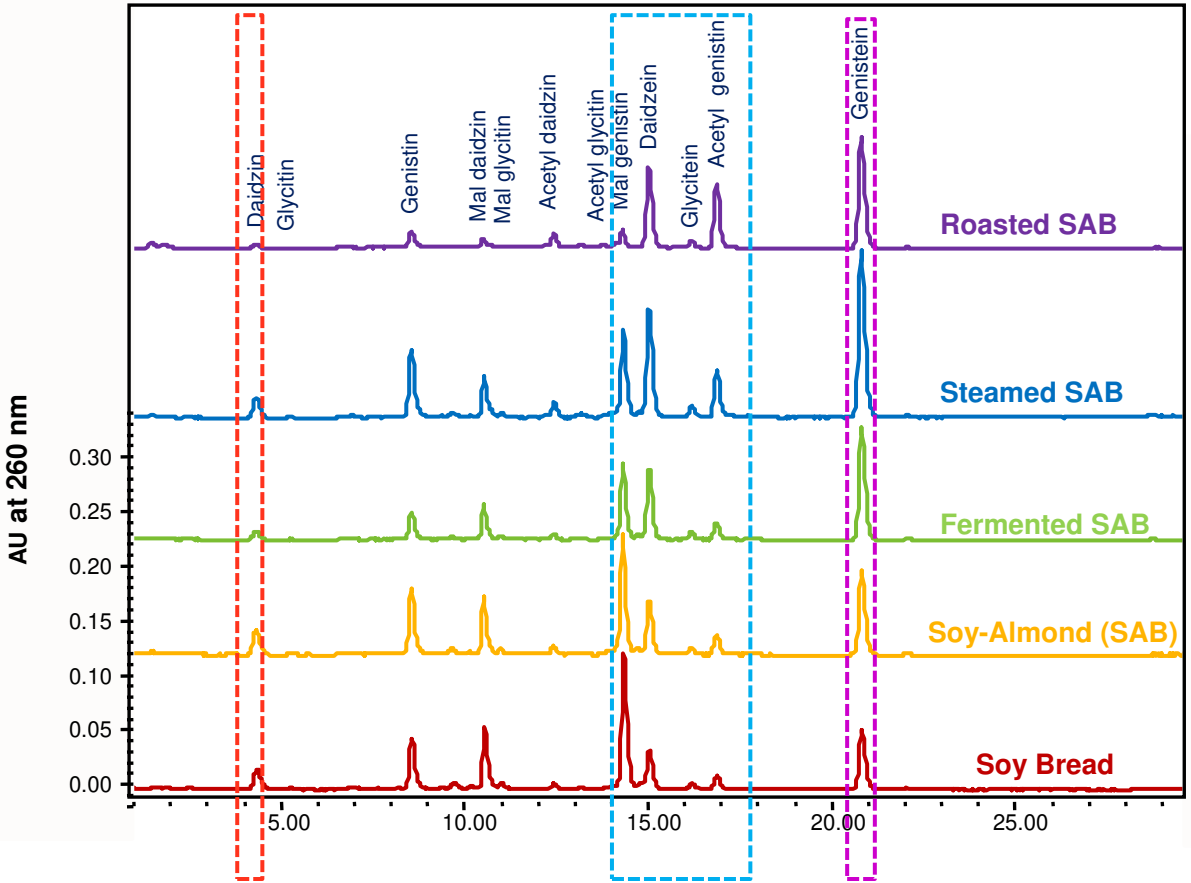
Almonds provide enzymes to cleave soy isoflavones



Soy-Almond (SAB) | Roast SAB | Ferment SAB | Steam SAB

Ahn-Jarvis, et al Journal of Agriculture and Food Chemistry, 61: 3111–3120, 2013. .

Soy vs Soy-Almond Bread HPLC / MS Analysis: Variation in Processing



“Upscaling" Soy Bread for Human Clinical Studies








National Institutes of Health-NCI R21 and R01 Grant

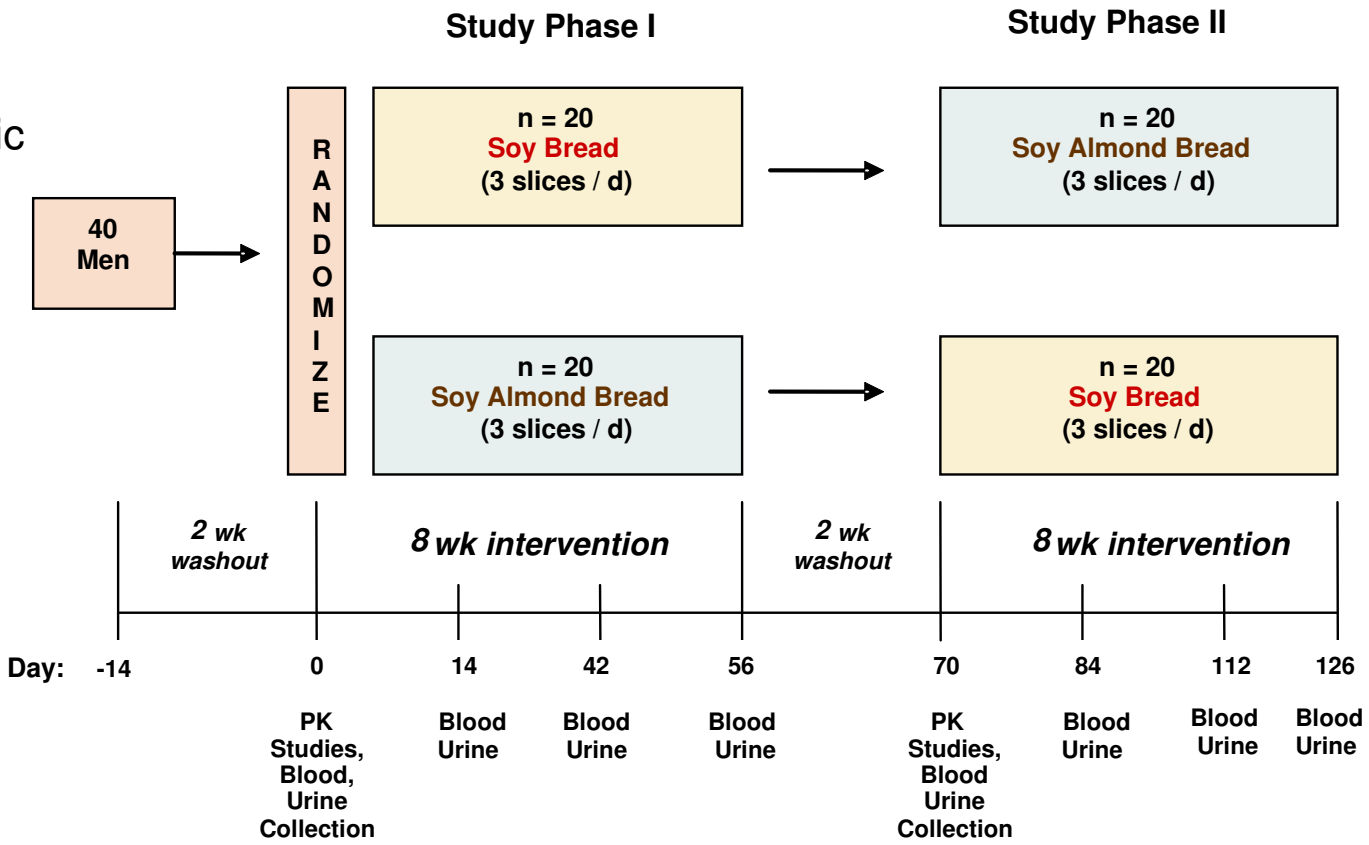
Soy Almond Bread and Prostate Cancer

Soy vs Soy-Almond Bread in Men with Prostate Cancer

Target Cohort

- Prostate Ca
- Micrometastatic
- Rising PSA

Randomized Crossover Design



Research Article

Cancer Prevention Research

Isoflavone Pharmacokinetics and Metabolism after Consumption of a Standardized Soy and Soy–Almond Bread in Men with Asymptomatic Prostate Cancer

Jennifer H. Ahn-Jarvis[1], Steven K. Clinton[2,3], Elizabeth M. Grainger[3], Kenneth M. Riedl[1,3], Steven J. Schwartz[1,3], Mei-Ling T. Lee[4], Raul Cruz-Cano[4], Gregory S. Young[5], Gregory B. Lesinski[2,3], and Yael Vodovotz[1,3]

Jen Ahn-Jarvis, Ph.D.

HPLC / MS
4 metabolic phenotypes

Almonds alter isoflavone metabolism

Soy alters PSA kinetics

Research Article

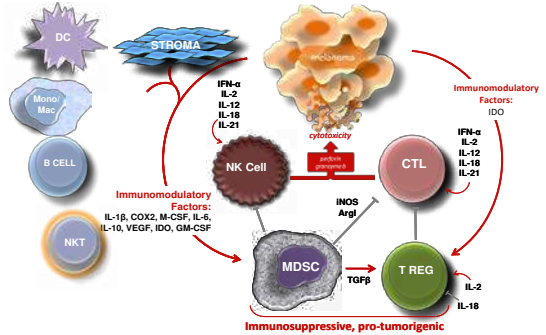
Cancer Prevention Research

Consumption of Soy Isoflavone Enriched Bread in Men with Prostate Cancer Is Associated with Reduced Proinflammatory Cytokines and Immunosuppressive Cells

Gregory B. Lesinski[1,2], Patrick K. Reville[1], Thomas A. Mace[1], Gregory S. Young[3], Jennifer Ahn-Jarvis[4], Jennifer Thomas-Ahner[1], Yael Vodovotz[2,4], Zeenath Ameen[1], Elizabeth Grainger[1], Kenneth Riedl[2,4], Steven Schwartz[2,4], and Steven K. Clinton[1,2]

Greg Lesinski, Ph.D.

Soy impacts anti-cancer immunity



Black Raspberry Food Products

Hard candy

Pectin gummy

Starch gummy

Nectar

Clinical Trials:
The Oral Carcinogenesis Study

NIH-NCI U01 2014-2019

Weghorst, Schwartz, Kumar, Clinton

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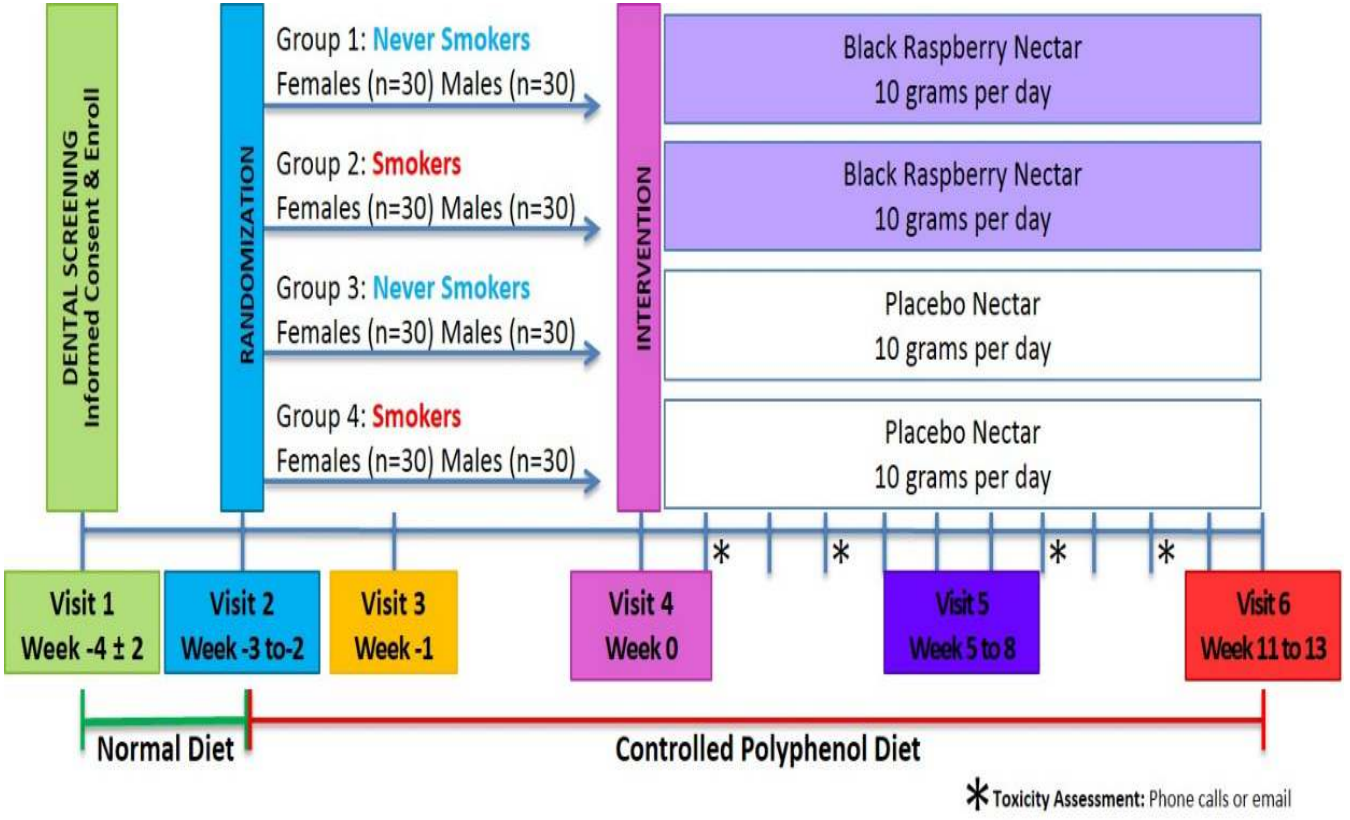
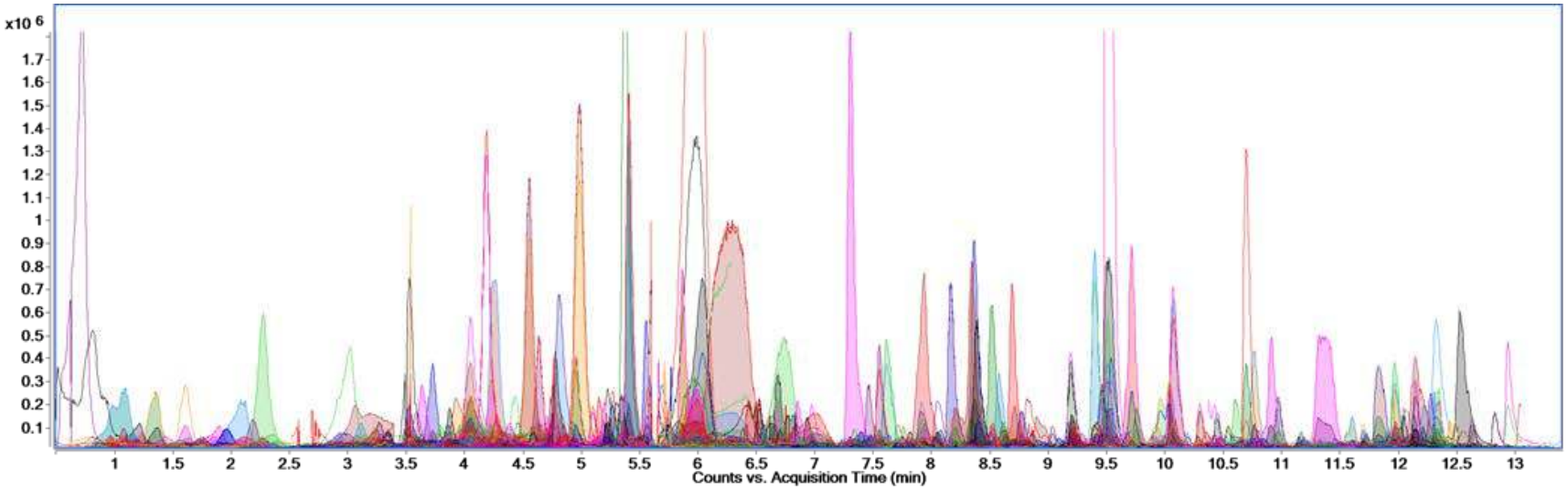
Interactions:

Gender, Smoking, BRB, on the oral microbiome and mucosal gene expression associated with early carcinogenesis.



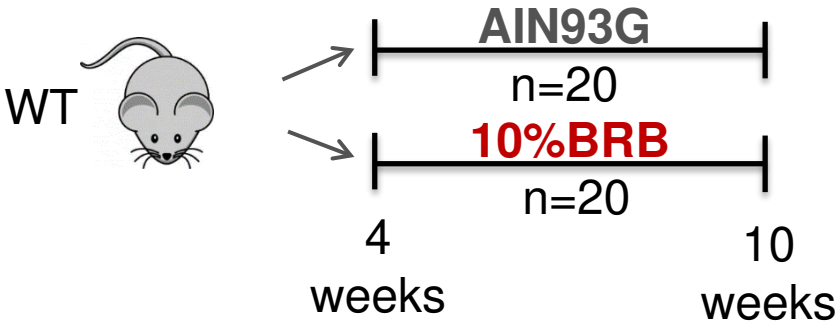
The black raspberry portfolio of phytochemicals

"Multiple interactive bioactives with diverse mechanisms of action"



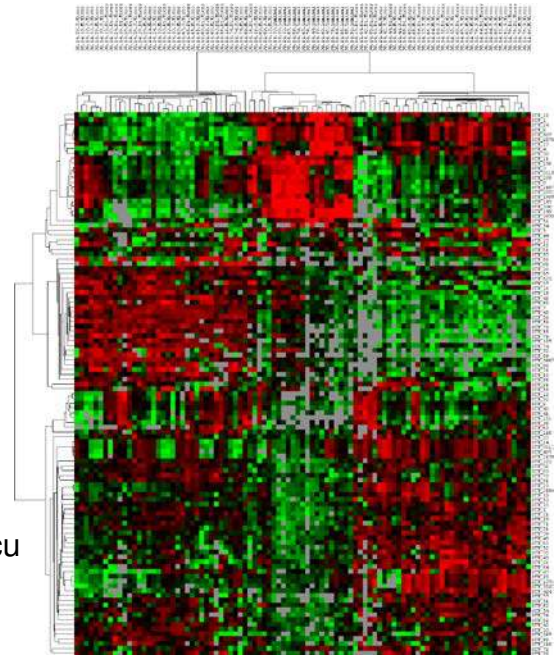
Analytical Chemistry: Overlaid extracted ion chromatograms of the over 4000 compounds detected in freeze-dried BRB powder and nectar using an untargeted metabolomics LC-MS approach (Matthew Teegarden / Steven Schwartz et al Abstract/Poster)

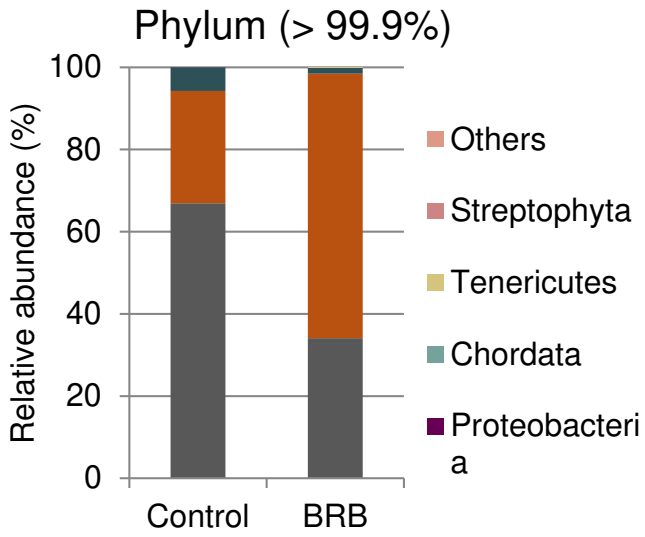
BRB Polyphenols and the Murine Gut Microbiome

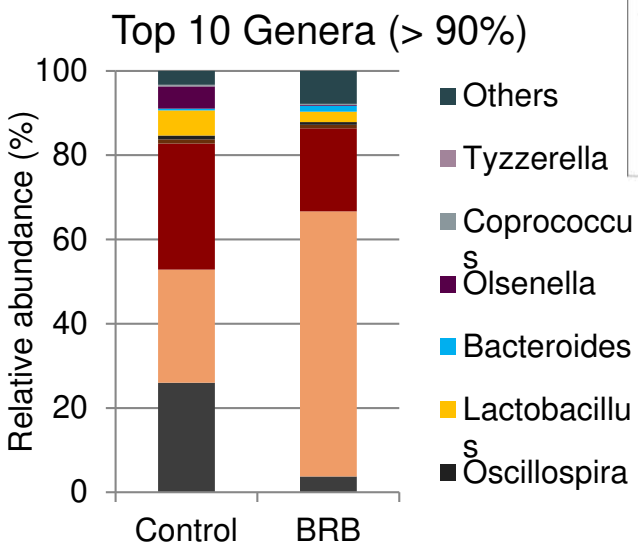


16s rRNA Sequencing

Taxonomic & Diversity Analysis







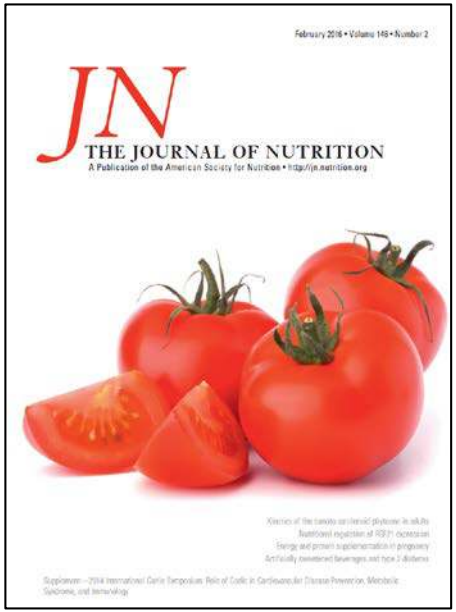
Publication in review

Cohorts: Food-based interventions.

- **Prevention**
- **Therapy**
  - Recovery from surgery
  - Enhance efficacy of therapeutics
    - Chemotherapy, radiation, biological, hormonal
  - Reduce toxicity of therapy
- **Survivors (remission)**
  - Reduce recurrence rates
  - Reduce second primary risk
  - Reduce long-term complications of therapy
    - Cancers, cardiovascular, renal, cognitive, metabolic, etc.

Collaborators on Food Projects

- Steven K. Clinton Laboratory
  - Nancy E. Moran
  - Jennifer Thomas-Ahner
  - Elizabeth Grainger
  - Shirley Hsueh-Li Tan
  - Jenny Lei Wan
- Biostatistics – OSU CCC
  - Dennis Pearl
  - Greg Young
- OSU College of Agriculture
  - Steven J. Schwartz
  - Yael Vodovotz
  - David Francis
  - Ken M. Riedl
  - Jessica Cooperstone
  - Matt Teegarden
- Michael Bailey (OSU Nationwide Children's)
- Janet A. Novotny (USDA Beltsville)
- John W. Erdman, Jr. (Univ. of Illinois)
- Ed Giovannucci (HSPH)



Thank You

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