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

Steven K. Clinton, MD, Ph.D

January 22, 2017
Food-based Cancer Prevention Strategies

Steven K. Clinton, MD, Ph.D

January 22, 2017
Conflicts of Interest: None
Opinions: Many!

Research Funding:
NIH: NCI
AICR
ACS
OSU
Pelotonia (The James)
Growing the Cure (OSU)
OSU-CCC
Food Innovation Center
The Conceptual Framework: Diet and Nutrition-Based Cancer Prevention Strategies

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

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

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

- **Reductionism**
  - Energy Balance
    - Intake
    - Metabolism
    - Exercise

---

The James
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
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
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
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

The James
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).
Tomatoes, Lycopene and Prostate Cancer: Scientific Basis

\[ \beta,\beta\text{-carotene-9',10'-dioxygenase (BCO2) impacts the anticancer activity of tomato and lycopene in the TRAMP model}\]

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

<table>
<thead>
<tr>
<th>Diet</th>
<th>TRAMP+/:Bco2+/+</th>
<th>TRAMP+/-:Bco2 -/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIN-93G Control</td>
<td>N=46</td>
<td>N=40</td>
</tr>
<tr>
<td>10% Tomato Powder</td>
<td>N=44</td>
<td>N=43</td>
</tr>
<tr>
<td>0.25% Lycopene Beadlets</td>
<td>N=45</td>
<td>N=39</td>
</tr>
</tbody>
</table>

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
2 way ANOVA:
Diet: $P < 0.001$
Genotype: $P < 0.001$
Interaction: $P = 0.042$

Serum Carotenoids: Lycopene

<table>
<thead>
<tr>
<th>Plasma Carotenoid Concentration (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-Lycopene</td>
</tr>
<tr>
<td>5 cis lycopene</td>
</tr>
<tr>
<td>all trans lycopene</td>
</tr>
</tbody>
</table>

Control Tomato Lycopene Control Tomato Lycopene TRAMPxWT TRAMPxCMO2-KO
Serum Carotenoids: Lycopene

2 way ANOVA:
Diet: $P < 0.001$
Genotype: $P < 0.001$
Interaction: $P = 0.042$

Plasma Carotenoid Concentration (μM)

<table>
<thead>
<tr>
<th></th>
<th>cis-Lycopene</th>
<th>5 cis lycopene</th>
<th>all trans lycopene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomato</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lycopeae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomato</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lycopeae</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. 

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. 

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

Soy isoflavones

OSU Farms Horticulture Crop Science

Food Science and Technology

Lycopene

Soy

Glucoside

Acetyl

Malonyl

Steven Schwartz, PhD

OSU Comprehensive Cancer Center

Clinical trials Office

The James
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

The James
Biomarkers of Exposure

Change in Plasma Carotenoids with Tomato-Soy Juice

Biological Variation
# Genetics Impacts on Tomato Carotenoid Distribution and Metabolism

## BCO1 rs7501331

- **Genotype (pgeno):** 0.022
- **Treatment (ptrt):** 0.007

## BCO1 rs6564851

- **Genotype (pgeno):** 0.053
- **Treatment (ptrt):** 0.035

<table>
<thead>
<tr>
<th>Treatment Group (cans/d)</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group (cans/d)</th>
<th>GG</th>
<th>GT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Biomarkers of Impact:
PSA changes (4 wks) in men consuming Tomato-Soy Juice

<table>
<thead>
<tr>
<th>PSA change after 4 weeks of daily tomato soy juice (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>0.4</td>
</tr>
</tbody>
</table>
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: Product Development

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

Almonds provide enzymes to cleave soy isoflavones

Dr. Yael Vodovotz

Research:
- Sensory
- Shelf stability
- Analytics

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

- Soy Bread
- Fermented SAB
- Steamed SAB
- Roasted SAB
- Soy-Almond (SAB)

AU at 260 nm

- Daidzin
- Glycitin
- Mal daidzin
- Mal glycitin
- Acetyl daidzin
- Acetyl glycitin
- Acetyl genistin
- Genistin
- Genistein
“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

Study Phase I
- n = 20 Soy Bread (3 slices / d)
- n = 20 Soy Almond Bread (3 slices / d)

Study Phase II
- n = 20 Soy Almond Bread (3 slices / d)
- n = 20 Soy Bread (3 slices / d)

Day: -14 0 14 42 56 70 84 112 126
2 wk washout 8 wk intervention 2 wk washout 8 wk intervention
PK Studies, Blood, Urine Collection Blood Urine Blood Urine Blood Urine
Blood Urine Blood Urine Blood Urine
Isoflavone Pharmacokinetics and Metabolism after Consumption of a Standardized Soy and Soy-Almond Bread in Men with Asymptomatic Prostate Cancer
Jennifer H. Ahn-Jarvis, Steven K. Clinton, Elizabeth M. Grainger, Kenneth M. Riedi, Steven J. Schwartz, Mei-Ling T. Lee, Raul Cruz-Cano, Gregory S. Young, Gregory B. Lesinski, and Yael Vodovotz

HPLC / MS
4 metabolic phenotypes

Almonds alter isoflavone metabolism

Soy alters PSA kinetics

Soy impacts anti-cancer immunity

Consumption of Soy Isoflavone Enriched Bread in Men with Prostate Cancer Is Associated with Reduced Proinflammatory Cytokines and Immunosuppressive Cells
Gregory B. Lesinski, Patrick K. Reville, Thomas A. Mace, Gregory S. Young, Jennifer Ahn-Jarvis, Jennifer Thomas-Ahner, Yael Vodovotz, Zeenath Ameen, Elizabeth Grainger, Kenneth Riedi, Steven Schwartz, and Steven K. Clinton
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
Interactions:
Gender, Smoking, BRB, on the oral microbiome and mucosal gene expression associated with early carcinogenesis.
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

WT

AIN93G
n=20

4 weeks

10%BRB
n=20

10 weeks

16s rRNA Sequencing
Taxonomic & Diversity Analysis

Publication in review

- Phylum (> 99.9%)
  - Control
  - BRB
  - Others
  - Streptophyta
  - Tenericutes
  - Chordata
  - Proteobacteria

- Top 10 Genera (> 90%)
  - Control
  - BRB
  - Others
  - Tyzzerella
  - Coprococcus
  - Olsenella
  - Bacteroides
  - Lactobacillus
  - Oscillospira
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