Mechanisms of Prostate Cancer Prevention by Selenium: Implications for Cancer Survivorship

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American Institute for Cancer Research
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Cancer Death Rates* for Men
US, 1930-2003

*Age-adjusted to the 2000 US standard population.
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated Cancer Cases:</strong></td>
<td><strong>Estimated Cancer Deaths:</strong></td>
</tr>
<tr>
<td>186,320</td>
<td>679,000</td>
</tr>
<tr>
<td>28,660</td>
<td></td>
</tr>
</tbody>
</table>

Global Cancer Statistics, 2002
CA Cancer J. Clin., 2005
CA Cancer J. Clin., 2008
Cancer Survivors*

Definition: Cancer survivors are people who are living with a diagnosis of cancer including those who have recovered.

<table>
<thead>
<tr>
<th>Year</th>
<th>1970</th>
<th>2002**</th>
<th>2025</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>3x10^6 (1.5% of population)</td>
<td>&gt;10x10^6 (4% of population)</td>
<td>N.A.</td>
<td>&gt;6x10^6</td>
</tr>
<tr>
<td>Worldwide</td>
<td>N.A.</td>
<td>25x10^6</td>
<td>50x10^6</td>
<td>70x10^6</td>
</tr>
</tbody>
</table>

* World Cancer Research Fund Report, 2007

** Among cancer survivors, the values for breast, prostate and colorectal cancers are 22%, 18% and 10% (men and women)
Prostate Cancer Progression Model

Radical Prostatectomy
Radiation
Hormonal therapy
Neo-adjuvant chemotherapy

Normal | Prostatic Intraepithelial Neoplasia (PIN) | Localized Cancer | Metastasis | Hormone Refractory

### Risk Factors

<table>
<thead>
<tr>
<th>Factors That <em>Cannot</em> Be Modified</th>
<th>Factors That <em>Can</em> Be Modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Race/Ethnicity</td>
<td>• Smoking (?)</td>
</tr>
<tr>
<td>• Family History and Genetics (&lt;10%)</td>
<td>• Alcohol (?)</td>
</tr>
<tr>
<td>• Age</td>
<td>• Diet:</td>
</tr>
<tr>
<td></td>
<td>• Saturated fat, meat, dairy products, calcium (↑)</td>
</tr>
<tr>
<td></td>
<td>• Selenium, Vitamin E, Soy (genistein), Tomato (lycopene) (↓)</td>
</tr>
</tbody>
</table>

Strategies for Cancer Prevention

Lifestyle Changes
Chemoprevention

Rationale for Selenium*

Intervention

- Epidemiological studies
- Preclinical Investigations
- Clinical Chemoprevention Trials

*Selenium is a micronutrient found in whole wheat, fish, Brazilian nuts and is essential for normal body function.

The Bright Side of the Moon
Element (Clark Study)

- 200 μg Selenium-enriched yeast
- Subjects with a history of non-melanoma skin cancer
- The duration of supplementation was 4.5 years and they were followed up at 6.2 years (means)

Results
- Prostate, lung and colon cancer reduction related to baseline selenium levels
- No effect on non-melanoma skin cancer; increased risk of recurrence in follow-up
- Insufficient breast cancer cases to draw conclusions

Structures of Selected Selenium Compounds

1. Selenite
2. Selenate
3. Selenomethionine
4. Methylseleninic Acid
5. Methylselenocysteine
6. 1,4-phenylenebis(methylene)selenocyanate
Selenium and Cancer Prevention
“The world is my laboratory.”
Sir Francis Bacon
Does the Moon Element Have A Dark Side (SELECT)?

- Supplements did not prevent prostate cancer together or alone.
  - Vitamin E increased – but not significant – prostate cancer
  - Selenomethionine increased – but not significant -- the number of cases of adult onset diabetes.
Press Releases

“Prostate Cancer Not Warded Off by Supplements: Study”
Washington (Router), October 27, 2008

“No Prostate Benefit from Vitamin E, Selenium”
By Lauran Neergaard, AP Medical Writer, October 27, 2008

“Select Trial Used Selenomethionine Instead of High-Selenium Yeast, SelenoExcell (R), says Cypress Systems”, October 29, 2008 By Cindy Holden (editor with the Neotrope News Network)

Flawed SELECT Study Attacks Vitamin E
Byron J. Richards, CCN, October 30, 2008
## The Effects of Selenium Compounds on Prostate Cancer in Animal Models

<table>
<thead>
<tr>
<th>Se form</th>
<th>Doses and Administration</th>
<th>Model</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM, SeY</td>
<td>3 mg/kg and 6 mg/kg per day in the diet</td>
<td>Canine</td>
<td>SM and SeY decrease DNA damage, increase apoptosis (in prostate epithelial cells and peripheral blood lymphocytes). SeY at 6 mg/kg/day was more effective at inhibiting DNA damage than SM at the same dose.</td>
<td>Waters et al. JNCI 2003; 95:237</td>
</tr>
<tr>
<td>SM</td>
<td>mg/kg diet</td>
<td>MNU-induced Wistar-Unilever rat</td>
<td>SM is ineffective at protecting against prostate carcinogenesis</td>
<td>McCormick and Rao. Eur Urol 1999; 35:464</td>
</tr>
<tr>
<td>Combination: Sm, α-tocopherol succinate, and lycopene</td>
<td>Human equivalent of 200 µg, 800 IU, and 50 µg, respectively, per day in the diet</td>
<td>Lady transgenic mice</td>
<td>SM in combination with vitamin E and lycopene decreases prostate cancer incidence</td>
<td>Venkateswaran et al. Cancer Res 2004; 64:5891</td>
</tr>
<tr>
<td>Selenite, SM, MSC, SeY</td>
<td>0.3 and 3 ppm in drinking water</td>
<td>PC3 xenograft</td>
<td>Selenite (3 ppm) decreases primary tumor growth and lymph metastases</td>
<td>Corcoran et al. J Urol 2004 171:907</td>
</tr>
<tr>
<td>MSC</td>
<td>100 µg per day by IP injection for 14 days</td>
<td>LNCaP xenograft</td>
<td>MSC decreases tumor growth, AR expression, serum PSA</td>
<td>Lee at al. Prostate 2006; 66:1070</td>
</tr>
<tr>
<td>MSeA</td>
<td>1 mg/kg and 3 mg/kg daily oral administration</td>
<td>DU145 xenograft</td>
<td>MSeA decreases tumor growth (3 mg/kg), microvesicle density (1 and 3 mg/kg)</td>
<td>Wang et al. Int J Cancer 2008; 122:15</td>
</tr>
<tr>
<td>MSeA, MSC, Selenite, SM</td>
<td>1 mg/kg and 3 mg/kg daily oral administration</td>
<td>DU145, PC-3 xenograft</td>
<td>MSeA and MSC more effectively inhibit DU145 tumor growth than selenite or SM. MSC induces apoptosis in DU145 tumors; MSeA decreases microvesicle density. Only MSeA at 3 mg/kg decreased PC-3 tumor growth.</td>
<td>Li et al. Carcinogensis 2008; 29:1005</td>
</tr>
</tbody>
</table>
The Effects of Selenium Compounds on Cancer in Target Organs Other than the Prostate

<table>
<thead>
<tr>
<th>Se Forms</th>
<th>Animal Model</th>
<th>Target Organ</th>
<th>Results</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM, Selenite, SeY</td>
<td>B(a)P-induced C3H mice</td>
<td>Forestomach</td>
<td>SeY causes largest increase in serum GPx activity &gt; selenite &gt; SM. No form affected forestomach tumor incidence.</td>
<td>Bergman and Slaninia. Anticancer Res 1986; 6:785</td>
</tr>
<tr>
<td>SeGarlic (73% MSC), SeY (85% SM)</td>
<td>DMBA-, MNU-induced Sprague-Dawley rats</td>
<td>Mammary</td>
<td>SeY showed higher total tissue Se accumulation. SeG twice as effective in suppressing the development of premalignant lesions and adenocarcinomas.</td>
<td>Ip et al. J Agric Food Chem 2000; 48:2062</td>
</tr>
<tr>
<td>SeCasein, SeY</td>
<td>AOM-induced Sprague-Dawley rats</td>
<td>Colon</td>
<td>SeCasein reduced colon tumor incidence. SeY at similar and higher does had no effect.</td>
<td>McIntosh et al. Nutr Cancer 2006; 54:209</td>
</tr>
</tbody>
</table>
Multiple Stages for Intervention

- Normal
- Prostatic Intraepithelial Neoplasia (PIN)
- Localized Cancer (AR)
- Metastasis
- Hormone Refractory


Chemoprevention

Chemotherapy
Influence of Selenium-Enriched Yeast on Biomarkers of Prostate Cancer Risk in Healthy Males

A Clinical Pilot Study

Support: Cancer Treatment Research Foundation
Selenium Chemoprevention: Role of Glutathione and Oxidative Stress

Preclinical Studies:

- Organoselenium compounds (e.g., p-XSC) are effective at inhibiting tumorigenesis in numerous carcinogen-induced models.
- Reduced tumorigenesis is accompanied by reduced levels of oxidative damage (Rosa et al., Carcinogenesis 17:749, 1998).
- GSH levels and biosynthesis are induced by selenium-based chemopreventive agents (Richie, et al., Chem Biol Interact 161:93, 2006).
- Results suggest that reduced levels of oxidative stress through GSH induction may be involved in the mechanism of chemoprevention by selenium agents.
Working Hypotheses

- Selenium supplementation inhibits carcinogenesis by reducing oxidative stress; such inhibition is, in part, due to selenium interaction with redox-sensitive proteins that may be involved in cell proliferation and apoptosis.

- Selenium-induced changes in testosterone* metabolism may also be involved.

- Selenium supplementation inhibits PSA levels.

* Prostate cancer rarely occurs in eunuchs (castrated men) or in men with a deficiency in α-reductase.
### Comparison of Study Populations

<table>
<thead>
<tr>
<th></th>
<th>PLACEBO</th>
<th>SELENIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>Recruited 26</td>
<td>Recruited 26</td>
</tr>
<tr>
<td></td>
<td>Finished Study 19</td>
<td>Finished Study 17</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>31.1 ± 4.2</td>
<td>30.7 ± 4.4</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Black 6 (31.6%)</td>
<td>Black 5 (29.4%)</td>
</tr>
<tr>
<td></td>
<td>White 13 (68.4%)</td>
<td>White 12 (70.6%)</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>25.2 ± 4.13</td>
<td>24.2 ± 4.57</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>&gt; 95%</td>
<td>&gt; 95%</td>
</tr>
</tbody>
</table>

*All subjects were nonsmokers.*
Selenium Supplementation Increases Plasma Selenium Levels

Source of Se: Nutrition 21, San Diego, CA.
Effect of Selenium Supplementation on Glutathione (left) and Plasma Androgen (right) Levels

Baseline values
- Placebo: 0.826 ng/ml
- Selenium: 0.780 ng/ml

Baseline values
- Placebo: 5.05 ng/ml
- Selenium: 4.63 ng/ml

Baseline values
- Placebo: 0.156 ng/ml
- Selenium: 0.173 ng/ml

Baseline values
- Placebo: 0.634 ng/ml
- Selenium: 0.797 ng/ml

Baseline values
- Placebo: 0.198 ng/ml
- Selenium: 0.238 ng/ml

Baseline values
- Placebo: 6.32 ng/ml
- Selenium: 6.49 ng/ml

* p < 0.005 (paired comparison)
Racial Differences in Blood Selenium Levels During Selenium Yeast Supplementation

![Graph showing plasma selenium levels over time for Whites and Blacks after selenium yeast supplementation.]

- Whites (n=12)
- Blacks (n=5)

* *Significantly different from placebo, P<0.05
† *Significantly different by race, P<0.05

Richie et al. (in preparation)
Racial Differences in Blood GSH Levels During Selenium Yeast Supplementation

* Significantly different from placebo, P<0.05
† Significantly different by race, P<0.05

Richie et al. (in preparation)
Selenium Supplementation Decreases Plasma PSA Levels

Baseline PSA
Placebo: 0.53±0.38 ng/ml
Selenium: 0.72±0.70 ng/ml**

* $p < 0.001$ (paired comparison)
** NS
Is the PSA Test Reliable?

Despite the widespread clinical use of the PSA test, it is neither sufficiently sensitive nor specific for early detection of prostate cancer; it is not predictive of biological behaviors of tumors.

Working Hypotheses

- A panel of proteins could serve better than PSA as a “signature” for modulation of the molecular and cellular events occurring during carcinogenesis, chemoprevention, and therapeutic interventions.
- The inhibition of cell growth and/or induction of apoptosis is due, in part, to selenium interaction with redox-sensitive proteins.

A Proteomics Approach

- We compared plasma proteomic profiles of healthy individuals from the selenium-enriched yeast group and regular yeast (placebo).
- Five plasma samples from individuals in each arm were either cleared of:
  a. > 95% albumin (less drastic and inexpensive)
  b. The six most abundant proteins including albumin and IgG (more drastic and expensive)
- Appropriately paired samples were labeled with Cy5 or Cy3 (dye swapping was also performed); a pool of all samples was labeled with Cy2 and used as a universal internal standard.
- Samples were subjected to 2D-DIGE process.
- Images were captured and differences in levels of protein spots were determined.
Selection Criteria

Proteins were considered strong candidates if:

a) They showed a statistically significant difference ($p \leq 0.05$) in expression between selenium and placebo

b) There is $> 1.5$ fold difference in abundance between selenium and placebo

c) The candidate protein spot of interest appeared in at least 75% of the gels
Overlay Images of Cy3 and Cy5 Labeled Samples for a Single DIGE Gel Following Partial Albumin Removal

Placebo (Cy3 or Green)
Selenium (Cy5 or Red)
Proteins that were not altered (yellow)
Differentially Expressed Protein Spots Between Placebo and Selenium-Enriched Yeast Supplemented Groups

<table>
<thead>
<tr>
<th>Proteins Altered by SY Supplementation</th>
<th>Accession No.</th>
<th>Protein MW</th>
<th>pl</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-antitrypsin*</td>
<td>NP_000286</td>
<td>46694</td>
<td>4.25</td>
</tr>
<tr>
<td>Plectin</td>
<td>143506</td>
<td>64921</td>
<td>5.38</td>
</tr>
<tr>
<td>Fibrinogen gamma chain*</td>
<td>182439</td>
<td>49450</td>
<td>5.61</td>
</tr>
<tr>
<td>Alpha 1B-glycoprotein*</td>
<td>21071030</td>
<td>54220</td>
<td>6.00</td>
</tr>
<tr>
<td>Transferrin*</td>
<td>4557871</td>
<td>77001</td>
<td>6.00</td>
</tr>
<tr>
<td>Complement component 4B</td>
<td>4502501</td>
<td>192678</td>
<td>6.00</td>
</tr>
<tr>
<td>proprotein*</td>
<td>4502027</td>
<td>69322</td>
<td>6.00</td>
</tr>
<tr>
<td>Albumin precursor*</td>
<td>42716297</td>
<td>57797</td>
<td>6.00</td>
</tr>
<tr>
<td><strong>Clusterin isoform 1</strong></td>
<td>4507725</td>
<td>15878</td>
<td>6.00</td>
</tr>
<tr>
<td>Transthyretin*</td>
<td>337758</td>
<td>23244</td>
<td>6.12</td>
</tr>
<tr>
<td>Pre-serum amyloid P component*</td>
<td>17318569</td>
<td>66028</td>
<td>8.33</td>
</tr>
<tr>
<td>Keratin 1*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Redox-sensitive proteins are indicated by *
α-1 Antitrypsin (AAT)

• Elevated in serum levels in prostate cancer patients \(^1,2\)
• Like PSA, AAT levels are correlated with disease severity and decreased in patients with favorable response to treatment \(^2-6\)
• Levels of AAT are correlated with PSA levels\(^7\)
• African Americans have higher levels of ATT than Caucasian, and the former group tends to have higher PSA levels than men from other ethnic groups\(^7\)
• AAT levels increased with age especially in African Americans\(^7\)

\(^3\) Kaneti et. al., Urol. Res. 12:239-241, 1984
Effect of Selenium-Enriched Yeast Supplementation on AAT Levels in Healthy Men

AAT Baseline levels (g/L)

- Placebo (3.14±0.12)
- Se-Yeast (3.19±0.11)

A: (p<0.05) compared to baseline & 3 Months

AAT change from baseline (%)

0  3  9  12

Time (Months)
Effect of Selenium-Enriched Yeast Supplementation on AAT Levels in Black and White Men

AAT levels (g/L)

- **Blacks**
- **Whites**

- **a:** (p<0.05) compared to base line
- **b:** (p<0.05) compared to 3 Months
- **c:** (p<0.05) compared to 3 Months
- **d:** (p<0.05) compared to 9 months
- **e:** (p<0.05) compared to whites
Clusterin

- The gene is up-regulated during prostate gland involution\(^1\)
- Down-regulated in human prostate cancer specimens\(^2,3\)
- Antiproliferative\(^4\) and proapoptotic in both SV40-immortalized (PNTIA) and tumorigenic (PC-3) human prostate cells\(^5-8\)

\(^1\) Bettuzzi et. al., Biochem J. 257:293-296, 1989
\(^2\) Bettuzzi et. al., Cancer Res. 60:28-34, 2000
\(^3\) Scaltriti et. al., Int. J. Cancer 108:123-139, 2004
\(^4\) Bettuzzi et. al., Oncogene 21:4328-4334, 2002
\(^5\) Scaltriti, et. al., Br. J. Cancer 91:1842-1850, 2004
\(^6\) Caccamo, et. al., Biochem. J. 382:157-168, 2004
\(^7\) Scaltriti, et. al., Cancer Res. 64:6174-6182, 2004
\(^8\) Caccamo, et. al., Cell Death Diff. 12:101-104, 2005
Summary of Clinical Findings

- Supplementation with selenium-yeast:
  - ↑ plasma selenium
  - ↑ blood GSH
  - ↓ protein-bound GSH
  - ↓ plasma PSA
  - → T/DHT

- Selenium appears to alter the levels of certain redox-sensitive proteins (AAT, CLU)

- In a study of 336 healthy unsupplemented adults, blood selenium was positively correlated with GSH and negatively correlated with protein-bound GSH (Richie et al., CEBP, submitted 2008)

- Results support the role of enhanced GSH and reduced oxidative stress in the mechanism of chemoprevention by selenium
Rationale for Further Studies

If a positive chemopreventive efficacy of selenomethionine is shown in the SELECT trial, the impact on public health will be a tremendous victory.

But

If a negative outcome, the search for more effective forms of selenium (MSC, a component of SY) will be urgently needed.

And

Assessment of a panel of protein biomarkers will provide better understanding of the mechanisms of carcinogenesis and provide clues that may explain the outcome of the SELECT.
Influence of Selenium on Biomarkers of Prostate Cancer Risk, A New Trial
Working Hypothesis

Aim 1. Compliance and Bioavailability
- Plasma Selenium
- Urine Selenium

Aim 2. Biomarkers of Prostate Cancer Risk
- PSA, DHT/T

Aim 3. Oxidative Stress
- GSSP/GSH

Aim 4. Novel Redox-Sensitive Proteins
- 8-OHdG, F2-IP, 3-NT
- e.g., α-1 antitrypsin (ATT)

Selenium Supplementation
(young, mature, and old men)
- Selenium yeast (240, 350 µg/day)
- Selenomethionine (200 µg/day)

Basic Scientists:
- Sinha, Boyiri, Das (C3), Richie (CCPS), Somiari

Clinicians:
- Reese (ET), DiPaola (NJCI)

Prostate Cancer
The Search for More Effective Selenium Compounds in Prostate Cancer Prevention: A Proteomics Approach

Preclinical Investigations
**In vitro model of prostate cancer progression**

**LNCaP Cells**
- Androgen Responsive (AR)
- Derived from lymph node metastatic lesion of human prostatic adenocarcinoma

**LNCaP C4-2 Cells**
- Androgen Independent (AI)
- LNCaP subline established in castrated athymic mice

*Both cell types express comparable levels of androgen receptor.*
Dose Response of Organoselenium Compounds on Growth of (AR) LNCaP and (AI) LNCaP C4-2 Cells

p-XSC induces apoptosis in AR and AI cells, whereas SM does not.

Apoptosis
Proteomic Profiles of LNCaP Cells Treated with 5 mM \( p \)-XSC for 24 hours

- Nucleoside diphosphate kinase 6*: 17.3 kDa, pI 8.5
- Chaperonin 10: 10.6 kDa, pI 8.9
- Cofilin-2*: 18.7 kDa, pI 8.1
- Heterogenous nuclear ribonucleoprotein*: 36 kDa, pI 8.3
- Single stranded mitochondrial DNA binding protein: 17.2 kDa, pI 8.0
- Chain A Horf6 human peroxidase enzyme*: 25.1 kDa, pI 7.6
- Cofilin-2*: 18.7 kDa, pI 8.1
- Chaperonin 10: 10.6 kDa, pI 8.9

* Redox-sensitive protein

Inhibition of NF-κB DNA Binding by Organoselenocyanates Through Covalent Modification of the p50 Subunit
Summary of Preclinical Findings

• Synthetic organoselenium compounds (e.g., \( p \)-xsc) (inhibitors of cell growth and inducer of apoptosis) are more effective than naturally-occurring compounds (e.g., SM).

• SM and \( p \)-XSC may exert their apoptotic and anti-proliferative effects by differentially interfering with certain redox-sensitive proteins (e.g., Cofilin2).

• These effects differ depending on the dose and structure of the selenium compound and the androgen status of the cell line.

• Proteins identified following selenium treatment of prostate cancer cells may serve as biomarkers in clinical intervention trials using selenium.
The Selenium Circle

Potential Stages for Intervention

Healthy Subjects Including High-Risk

Prostatic Intraepithelial Neoplasia (PIN)
- Low-Grade ➔ High-Grade*

Localized Cancer Stages I - II
- Radical Prostatectomy
- Radiation (Watchful Waiting)

Metastasis to Local and Distant Sites Stages III - IV
- Hormonal therapy
- Other therapy

Potential Stages for Intervention with Selenium

*30% of men with HGPIN develop cancer within one year

**5 year survival rates for androgen responsive (AR) and androgen independent (AI) cancers are 99% and 30% respectively

Questions Remain To Be Answered

- Do men at different ages require different levels of selenium?
- What is the most effective form of (synthetic or naturally occurring) selenium?
- Do African Americans need more selenium than White Americans?
- Do we have sensitive biomarkers to monitor disease progression and the efficacy of selenium?
- Do different forms of selenium have different effects on biomarkers of risk (PSA, T/DHT, oxidative stress, etc.)?
Acknowledgements

“In If I have seen further, it is by standing upon the shoulders of giants.”

Sir Isaac Newton
(paraphrasing Bernard of Charters)

In over twenty-five years of research, I am grateful for interactions with a number of “giants,” at the American Health Foundation and elsewhere, in the field of cancer etiology and prevention research:

- E. L. Wynder, M.D. (Deceased)
- John Pinto, Raghu Sinha, Nicole FaCompre, John Baatz (Med. Univ. South Carolina): *In vitro* studies
- John Richie, Raghu Sinha, Indu Sinha, Telih Boyiri, Wayne Kleinman, Brian Pitman, Richard Somiari (ITSI-Biosciences), Steven Colosimo: Clinical pilot study
- Bogdan Prokopczyk, Neil Trushin: Analysis of Selenium in Se-Yeast
- Kum-Ming Chen (NF-KB), Shantu Amin, Dhimant Desai: Synthesis of Organoselenium compounds
- Benoit Chabot, Univ. Sherbrooke, Quebec, Canada: HnRNP A1/A2 antibody
- Christian Thirion, Ludwig-Maximilian Univ., Munich, Germany: Cofilin-2 antibody
- Warren Heston, Lerner Res. Inst., Cleveland Clinic Foundation, Cleveland, Ohio: LNCaP C 4-2 cells (AI)
- Nutrition 21, San Diego, CA and Cypress Systems, Fresno, CA: Sources of Se-Yeast

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