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Alternative Approaches to Lung Insults

Melpo Christofidou-Solomidou, Ph.D.

Research Associate Professor of Medicine University of Pennsylvania Department of Medicine Pulmonary, Allergy, and Critical Care Division, melpo@mail.med.upenn.edu

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“Alternative Approaches to Lung Insults”

Melpo Christofidou-Solomidou, Ph.D.
Associate Professor of Medicine

*University of Pennsylvania, Perelman School of Medicine, Pulmonary,
Allergy and Critical Care Division, Philadelphia, PA, USA*



Presentation Outline:

1. Overview of environmental challenges and oxidative lung damage.
2. Introducing alternative remedies to oxidative lung disease.
3. Ameliorating side effects of: a) therapeutic and b) accidental radiation lung exposure in mouse model.
4. Chemoprevention of lung tumorigenesis in a rodent model of chemical carcinogen exposure (tobacco).
5. Chemoprevention of mesothelioma and lung cancer in a rodent model of environmental carcinogen exposure (asbestos).



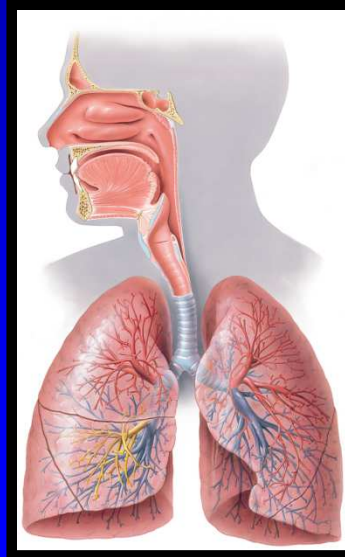
Environmental Insults and Oxidative Lung Disease



Oxidative Lung Damage



Airborne Toxins



Asbestos fibers



Blood-borne Toxins



Radiation



Oxidative Stress and Tissue Damage

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated throughout the human body.

Enzymatic and nonenzymatic antioxidants detoxify ROS and RNS and minimize damage to biomolecules.

Environmental insults Create an imbalance between the production of ROS/RNS and antioxidant capacity leads to "**oxidative stress**" that contributes to the pathogenesis of a number of human diseases by damaging lipids, protein, and DNA.

In general, environmental insults to the lung cause lung diseases associated with inflammatory processes that generate increased ROS and RNS.



Lung Diseases Associated with Oxygen Radicals

Disease

Mechanism

Emphysema

Tissue injury by oxidants in cigarette smoke

Tissue injury by inflammatory cell oxidants-
 α 1 proteinase inhibitor (α 1PI) inactivation by
cigarette smoke and inflammatory cells

Adult respiratory
distress syndrome

Inflammatory cell release of oxidants- α 1PI
oxidative inactivation by inflammation cells

Hyperoxia

Hyperoxia-mediated oxygen radical synthesis
in cells

Idiopathic
pulmonary fibrosis

Inflammatory cell oxidant release
Glutathione deficiency

Asthma

Inflammatory cell release of oxidants
Decrease in superoxide dismutase activity in
bronchial epithelial cells



Pharmacologic Therapy for Treatment of Acute Respiratory Distress Syndrome

Research on pathophysiology & genetics of ALI/ARDS continues to advance.

Critical molecular pathways in disease development and specific genetic factors that alter the expression of disease are identified.

Despite these advances, pharmacologic therapies have yet to be developed for the prevention or treatment of disease.



Pharmacologic Therapy for Treatment of Acute Respiratory Distress Syndrome

TABLE III.—Selected list of pharmacologic therapies attempted for treatment of acute lung injury and acute respiratory distress syndrome.

Proposed therapy	Year (s)	Impact on patient outcomes
Corticosteroids ⁴⁸⁻⁵³	Multiple investigations	Mixed results ^a
Surfactant ⁵⁴	1996	No effect
Inhaled nitric oxide ^{55, 56}	1998, 1999	No effect
Liposomal prostaglandin E1 ⁵⁷	1999	No effect
Ketoconazole ⁵⁸	2000	No effect
Lisofylline ⁵⁹	2002	No effect
Neutrophil elastase inhibitor ⁶⁰	2004	No effect
Activated protein C ⁶¹	2008	No effect ^b
Beta-adrenergic agonist ⁶²	Unpublished data	No effect
Omega-3 fatty acids ⁶³	Unpublished data	No effect

^a The use of corticosteroids in ARDS is debated among both clinicians and researchers. Two clinical trials have reported improvement in patient outcomes, but designs of these trials has been criticized. Additional studies have consistently shown no impact on mortality; ^b in ARDS alone, independent of severe sepsis.



The Need for New Safe and Effective Drugs to Treat Lung Disease



U.S. Department of Health and Human Services

NIH News

National Institutes of Health

National Heart, Lung, and Blood
Institute

<http://www.nhlbi.nih.gov>

For Immediate Release:

October 21, 2011

Contact:

NHLBI Communications Office

(301) 496-4236

nhlbi_news@nhlbi.nih.gov

Commonly used three-drug regimen for idiopathic pulmonary fibrosis found harmful

NIH stops one treatment arm of trial; other two treatments to continue

The National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, has stopped one arm of a three arm multi-center, clinical trial studying treatments for the lung-scarring disease idiopathic pulmonary fibrosis (IPF) for safety concerns. **The trial found that people with IPF receiving a currently used triple-drug therapy consisting of prednisone, azathioprine, and N-acetylcysteine (NAC) had worse outcomes than those who received placebos or inactive substances.**



Use of Botanicals And Dietary Supplements Derived From Natural Substances

An expanding body of preclinical evidence suggests that a number of botanicals have the potential to impact a variety of human diseases including oxidative lung disease.

Therefore, **non-toxic natural agents** could be useful either alone or in combination with conventional therapeutics for the prevention or therapy of oxidative lung disease.



Nutrition As Therapy And Not Simply “Supportive Care”

JAMA, October 12, 2011—Vol 306, No. 14 1599

EDITORIAL

Editorials represent the opinions of the authors and JAMA and not those of the American Medical Association.

ONLINE FIRST

Pharmac nutrition in Acute Lung Injury

Deborah J. Cook, MD, MSc(Epid)

Daren K. Heyland, MD, MSc(Epid)

DURING THE LAST DECADE, THERE HAS BEEN A MAJOR conceptual shift in thinking about artificial nutrition provided to critically ill patients. Because of its modulating effect on pathophysiology and emerging evidence about potential effects on clinical outcomes, nutrition is now considered “therapy” and not simply “supportive care.” For example, arginine-supplemented diets are associated with reduced infections and lengths of

tion solutions renders their delivery dependent on patient tolerance of the baseline nutrition solution. In the setting of enteral nutrition, feeding intolerance can preclude contemporary delivery of supplemental pharmac nutrients, attenuating any treatment effect if one exists. Therefore, investigations in pharmac nutrition call for pharmac nutrients to be dissociated from the baseline nutrition.⁵ Rice and colleagues⁴ devised an innovative approach to this issue, removing key nutrients from a commercially available solution, then using small-volume bolus administration twice daily to maximize adherence. A comparable

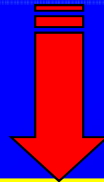
JAMA, Oct 2011



Usefulness of Dietary Supplements

Annual sale of Medicinal Herbs in the US is > **3 Billion \$\$\$**

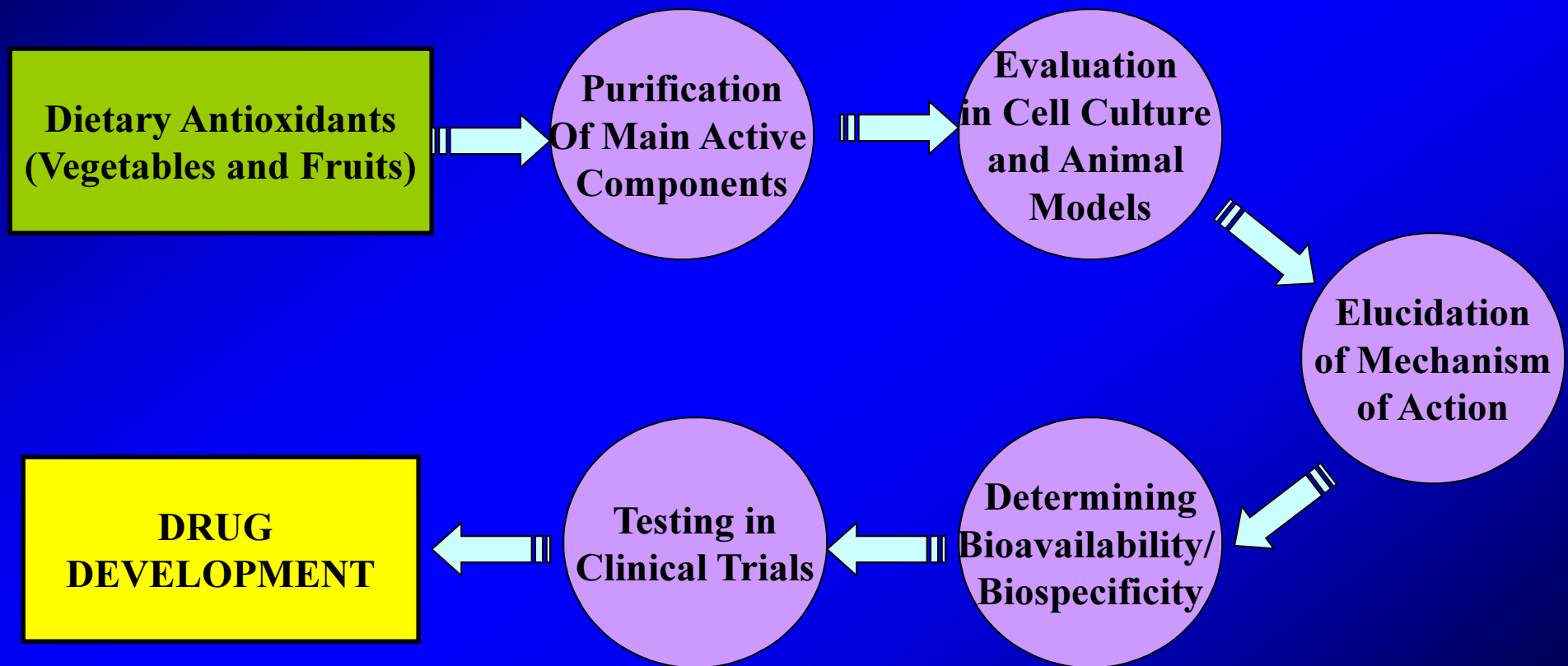
More than **60 million consumers** in the U.S. take herbal remedies. More physicians are recommending herbal medicines and some health insurance plans offer coverage for alternative health treatments such as **herbal remedies**.



In 1993 the NIH opened the National Center for Complementary and Alternative Medicine (NCCAM) which along with the Office of Dietary Supplements (ODS) aim to promote the safety, effectiveness, and biological action of botanical products.



Drug Development From Bioactive Dietary Agents





**Flaxseed:
“an ancient remedy
in a modern world”**



**Hippocrates,
the Greek physician
and philosopher,
by 650 B.C. wrote
about the use of flax.**



**The father of modern medicine,
Hippocrates, the Greek physician, by 650
B.C. wrote about the use of flax to relieve
inflammation of mucous membrane and for
the relief of abdominal pains and diarrhea.**

*By the 8th Century A.D.
Charlemagne one the greatest
medieval kings, considered flax
so important that for the health of
his subjects he passed laws and
regulation requiring its consumption.*



**By the 8th Century A.D. Charlemagne one
the greatest medieval kings, considered flax
so important that for the health of his
subjects he passed laws and regulation
requiring its consumption.**



**Why
Mahatma Gandhi
recommended
flaxseed for
everybody.**

**Mahatma Gandhi said that when flaxseed
was added to people's diet their health
improved.**

FLAXSEED

Plant Lignan Precursors

- Secoisolarisresinol diglycoside (SDG)
- matairesinol

Intestinal Bacteria

Lignans

- Enterodiol (ED)
- Enterolactone (EL)

Omega-3 Fatty Acids

α-Linolenic Acid

EPA

(eicosapentanoic Acid)

DHA

(Docosahexanoic Acid)

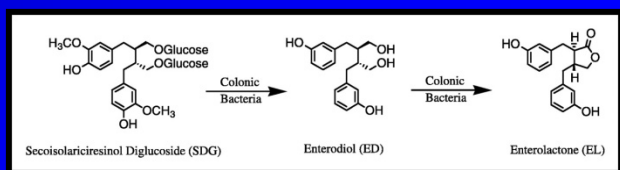
Biological Properties

- *** Antioxidative
- Antiproliferative
- Antiangiogenic

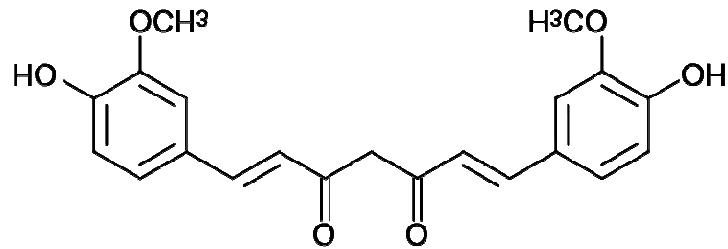
Estrogenic/Antiestrogenic

Cancer Protection

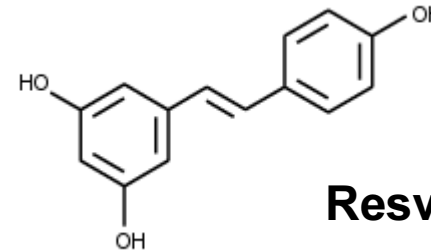
**Anti-inflammatory



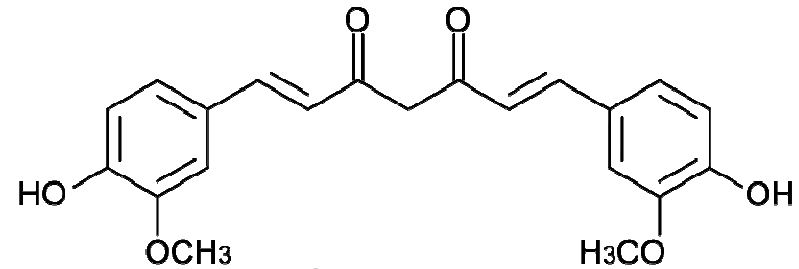
Flaxseed Lignan Structure



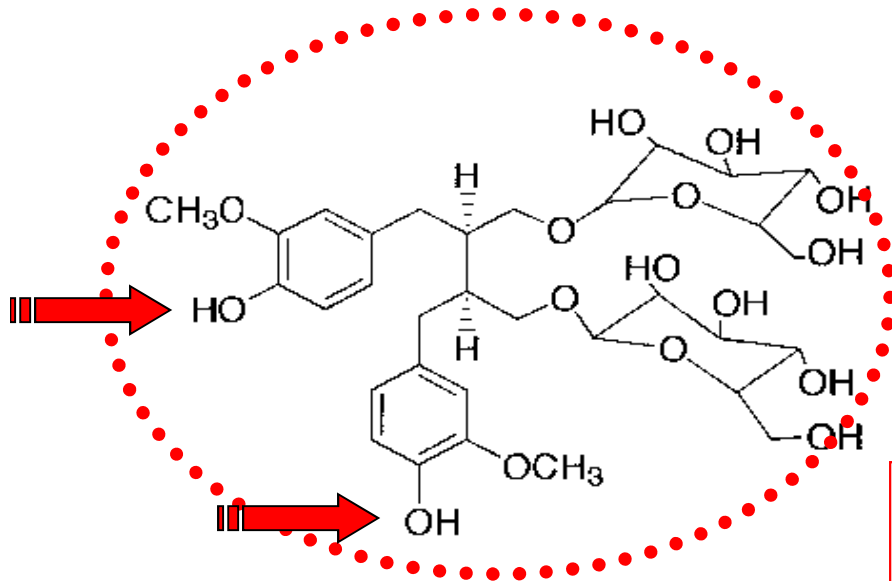
Curcumin



Resveratrol



Quercetin



**Secoisolariciresinol
diglucoside (SDG)**

**A bi-phenolic with potent
antioxidant properties**





We Identified Flaxseed and its main Lignan (SDG) As A Potent Inhibitors Of Oxidative Lung Injury In Diverse Animal Models



Protective Properties of Flaxseed in Preclinical Models of Cancer & Acute/Chronic Lung Damage

**Flaxseed
and SDG
Lignan**

HYPEROXIC LUNG INJURY

**ISCHEMIA-REPERFUSION
LUNG INJURY**

**ACID ASPIRATION-INDUCED
LUNG INJURY**

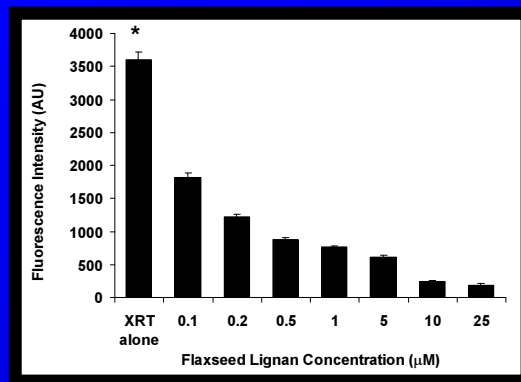
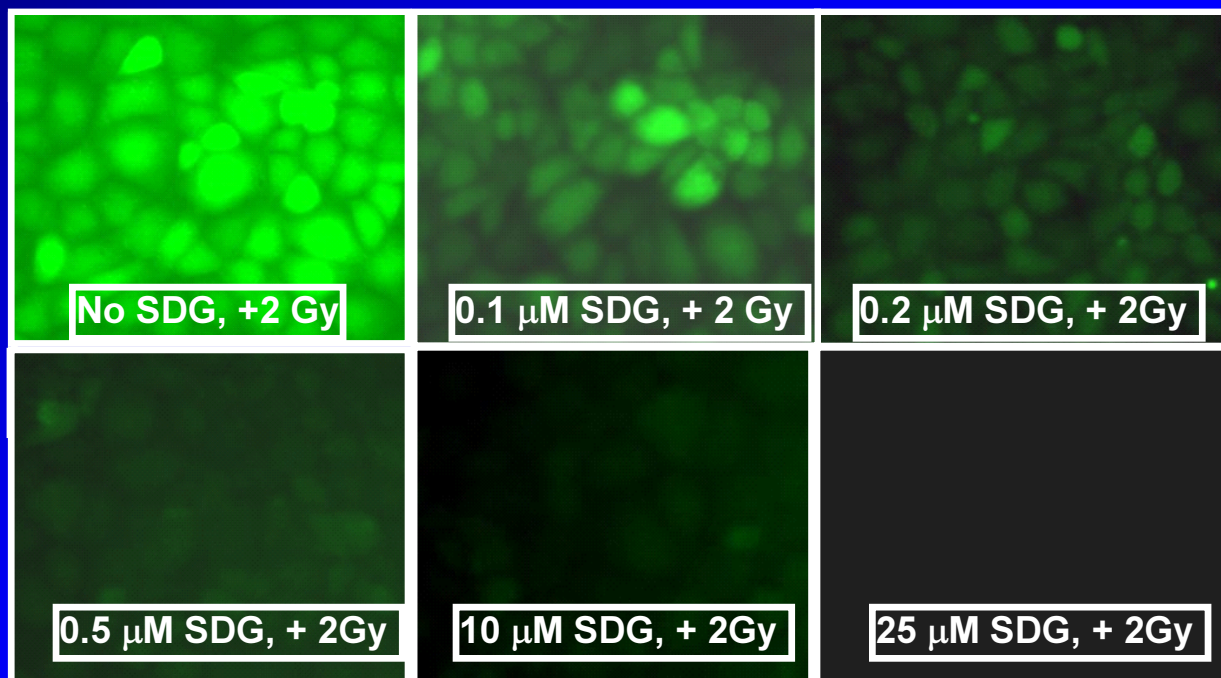
**RADIATION
PNEUMONOPATHY (acute/chronic)**

**ASBESTOS-INDUCED MALIGNANT
MESOTHELIOMA**

**TOBACCO CARCINOGEN-
INDUCED LUNG CANCER**



Free Radical Scavenging by Flaxseed Lignan SDG in γ -irradiated lung Endothelial cells

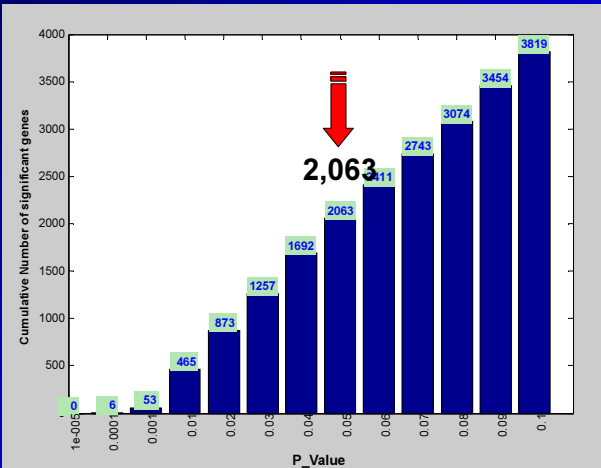


Lee et.al, 2009

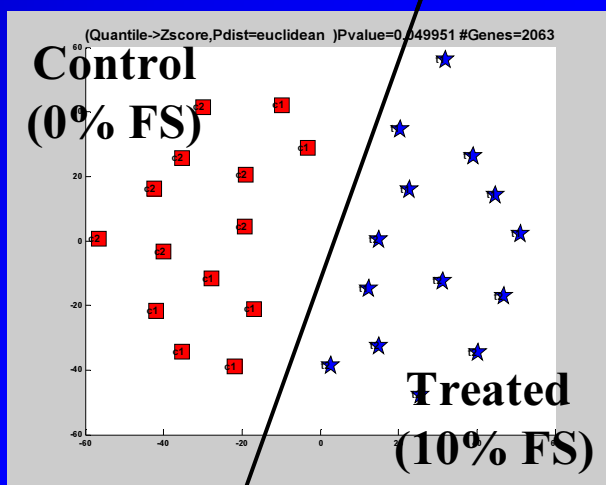


Genetic profiling of flaxseed in lung (30,000 gene array of entire mouse genome)

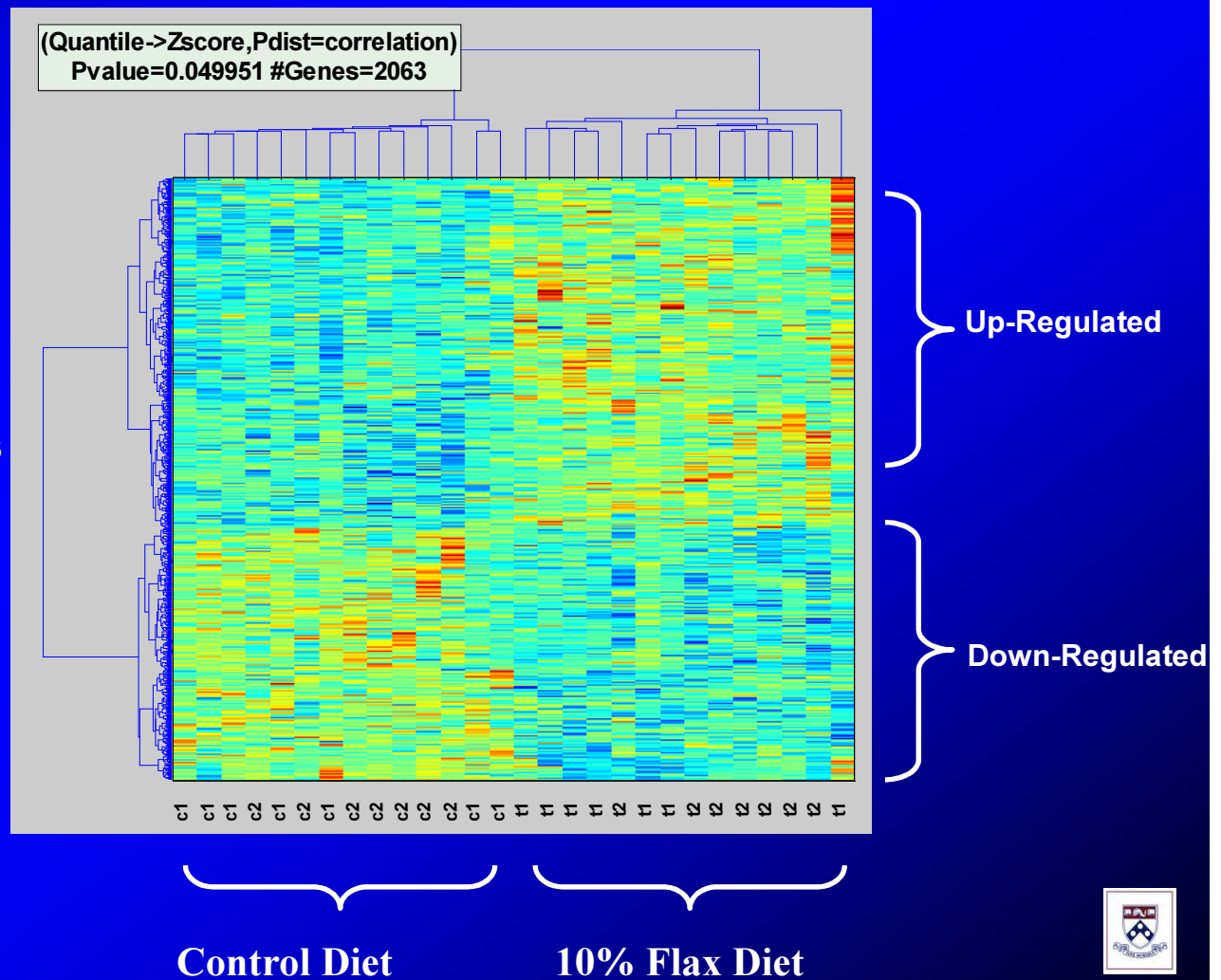
6.8% of all mouse genes in lung tissues are significantly modified by flaxseed



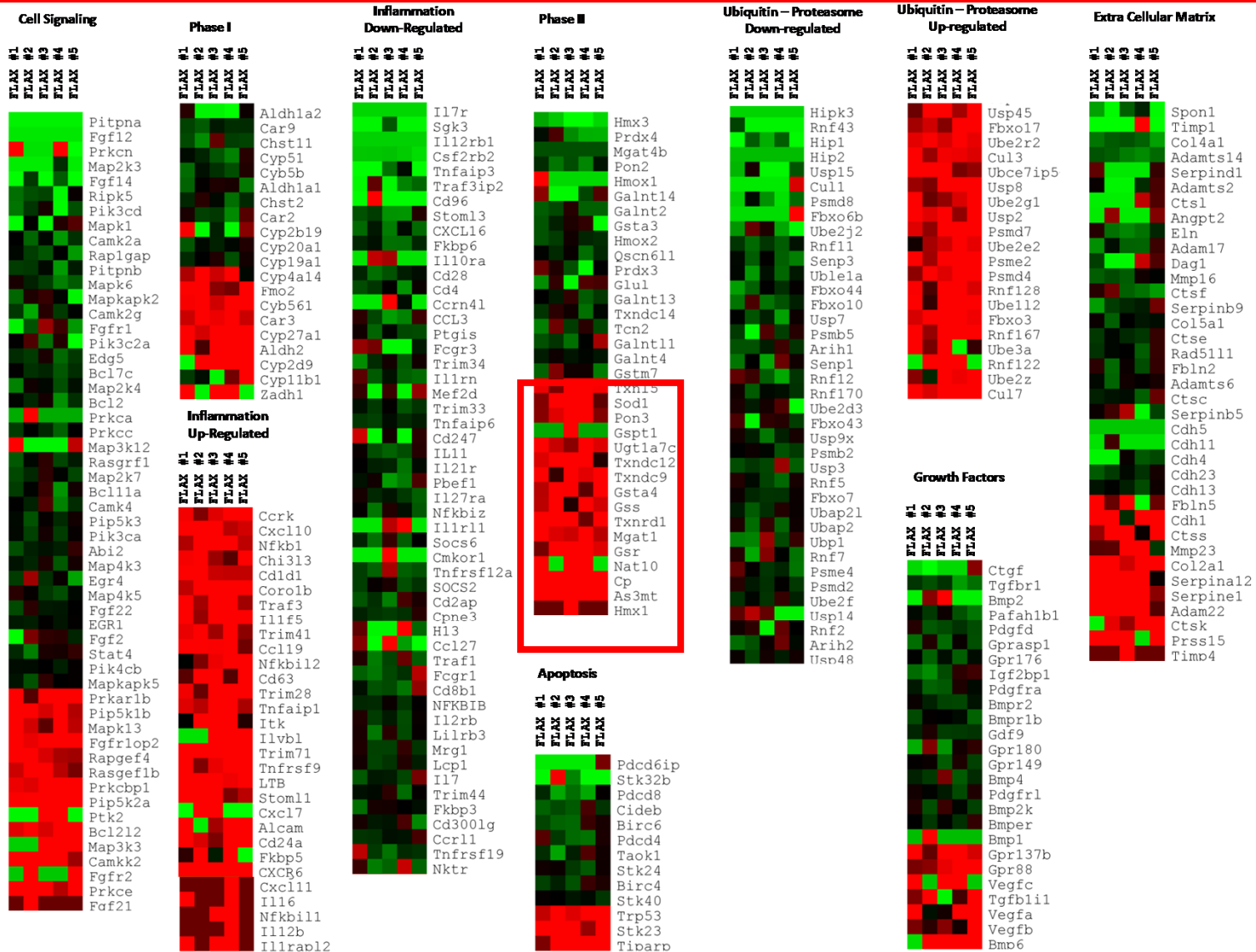
Principle Component Analysis



Dukes et.al, 2012



Lung Gene Expression Profiling of Genes With >1.5x fold Change in Individual Flax-fed Mice as Compared to Mean of Control



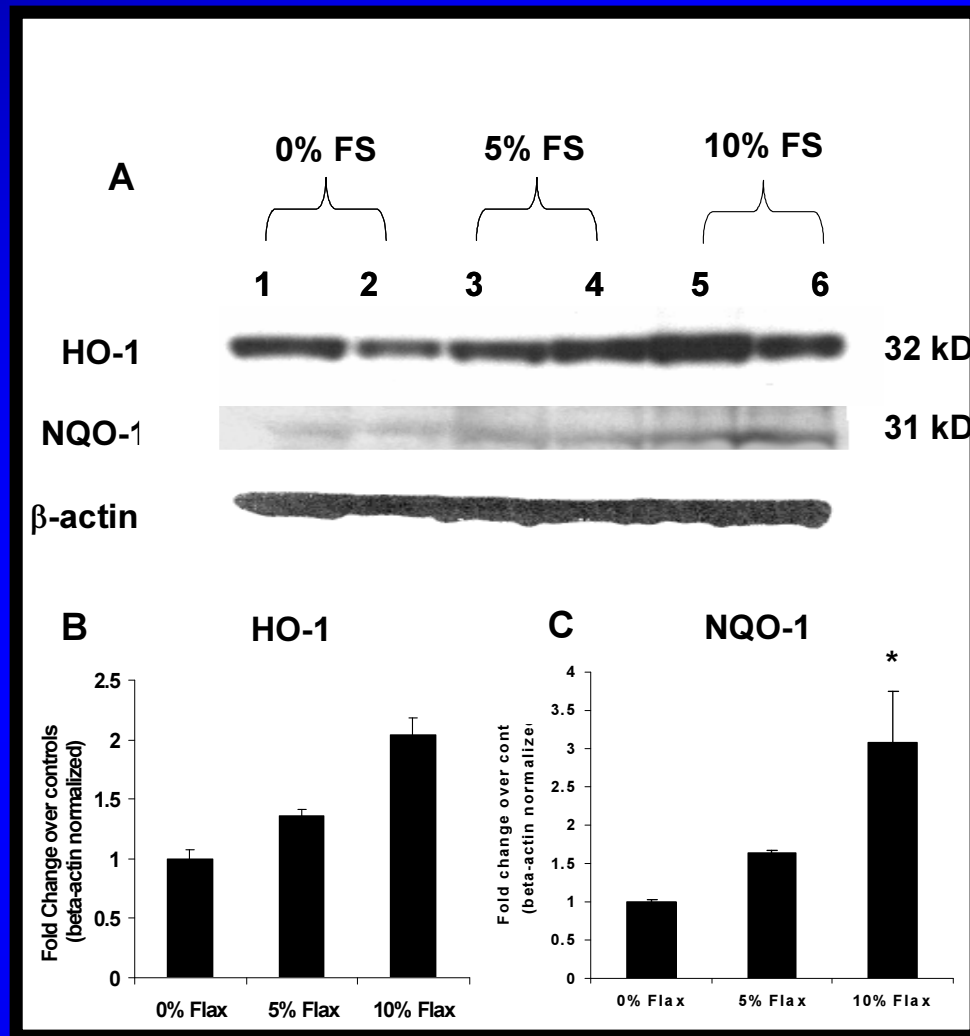
Red indicates up-regulation, green down-regulation

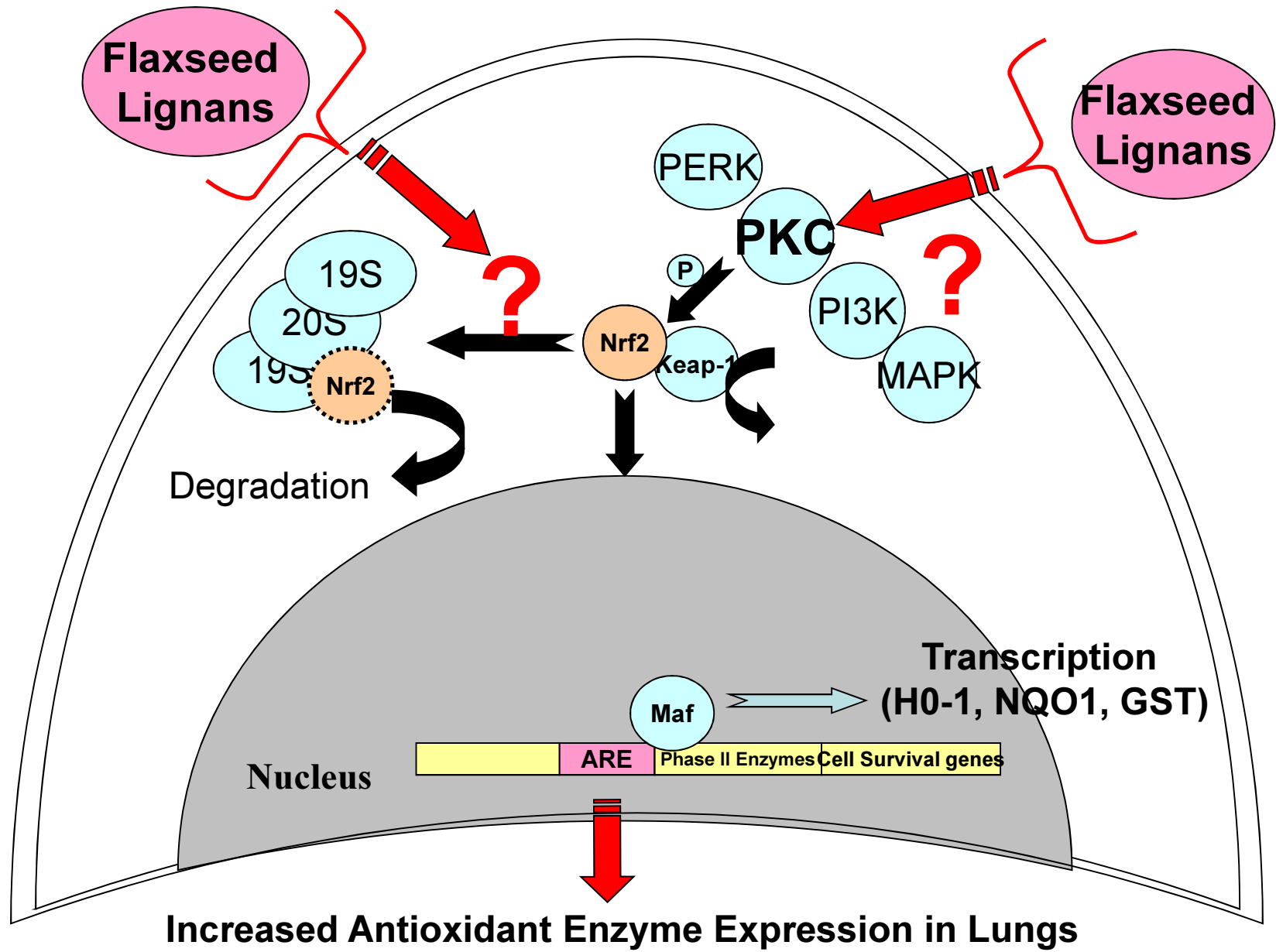
Dukes et.al, 2012

Flaxseed induces in lung dose-dependent expression of antioxidant enzymes

Heme oxygenase-1 (**HO-1**) confers protection against a variety of oxidant-induced cell and tissue injury.

Nicotinamide quinone oxidoreductase 1 (**NQO1**) protects against toxicity of electrophiles and reactive oxygen intermediates





HYPOTHESIS

Given the direct **free radical scavenging** properties of the flaxseed lignans and the robust **boost of antioxidant tissue** defenses,

We Hypothesized, That Dietary Flaxseed and Will Ameliorate Oxidative Acute and Chronic Lung Damage such as that resulting from **Radiation Exposure**, Modeled In Mice



DIRECT OXIDANT STRESS

- Radiation

**Flaxseed/
FS Lignans**

INDIRECT OXIDANT STRESS

- Neutrophils
- Macrophages
- Endothelial Cells

ROS

**Flaxseed/
FS Lignans**

**OXIDATIVE
LUNG INJURY**

Apoptosis

DNA damage

Chemokine Release

Lung leakiness / Edema

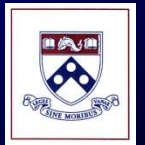
Inflammatory Cells

Tissue oxidation

Cytokine release



RADIATION PNEUMONOPATHY



Radiation Pneumonopathy Resulting from Radiotherapy

Radiation Therapy is commonly used to treat lung cancer and other thoracic malignancies (mesothelioma, breast cancer, esophageal cancer, lymphomas).

Up to **30% of patients** irradiated for lung cancer and **10-15%** of other thoracic oncology patients develop clinically significant radiation lung injury.

Radiation Damage to the Lung is characterized by:

- A) Pneumonia-like symptoms (Inflammation)
- B) Fibrotic lung damage (irreversible).



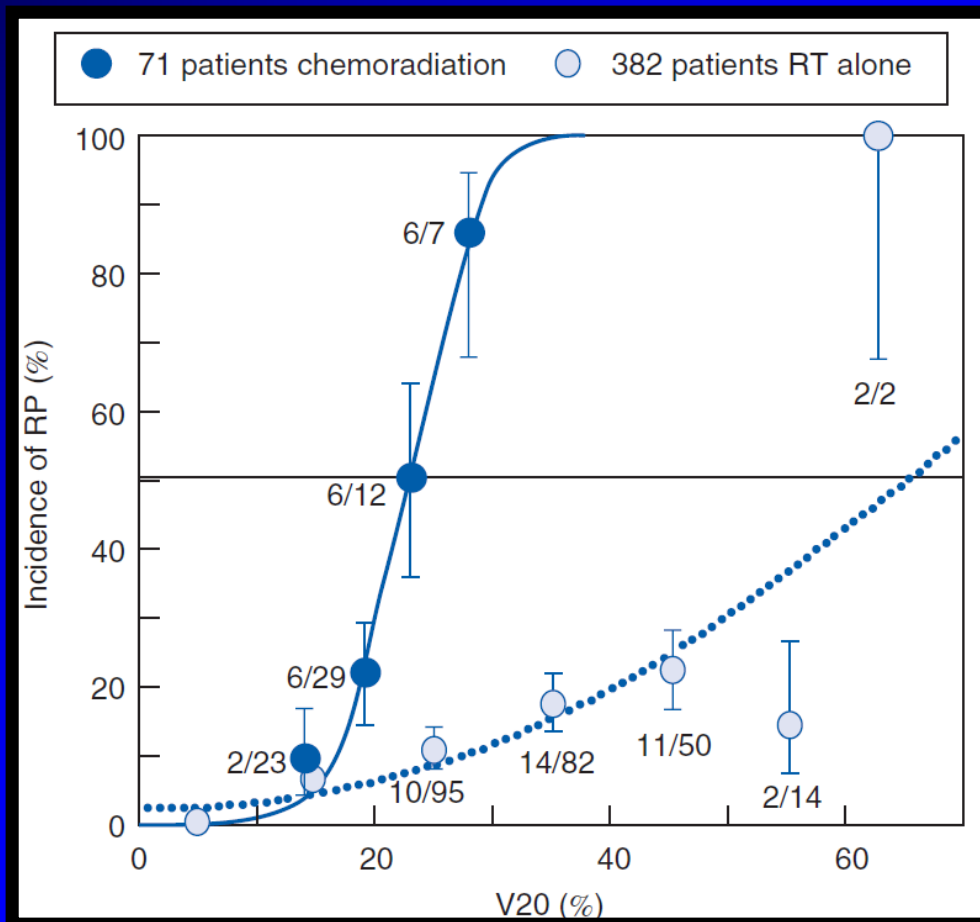
Radiation Toxicity to Normal Tissues

The usefulness of thoracic radiotherapy in the treatment of cancer is greatly limited by toxicity of ionizing radiation (radiation pneumonopathy).

Therefore, if we protect “normal” lung parenchyma from radiation injury, we will increase the ability to deliver tumoricidal radiotherapy doses.



Incidence of Radiation Pneumonitis is Exacerbated when Concurrent Chemoradiation is Administered



Incidence of Grade 2 radiation pneumonitis as a function of the relative lung volume irradiated to more than 20 Gy (V20) of patients treated with radiotherapy alone (open circles) or with chemo-radiotherapy (closed circles).

Patients receiving chemotherapy had a sharper increase in risk of radiation pneumonitis as the volume of normal lung exposed to 20 Gy increased.



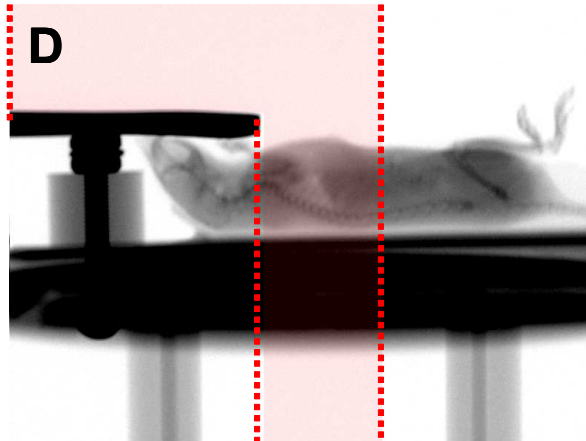
SARRP: Small Animal Radiation Research Platform



- A powerful research platform based on state-of-the-art Image Guided Micro-Irradiation techniques
- The SARRP research platform incorporates CT imaging with precise radiation delivery to enable pinpointing of an exact anatomical target to confidently deliver 0.5 mm beams to that point.
- The SARRP platform can then deliver single or multiple beams of radiation to the target with the utmost accuracy, matching the clinical techniques used in oncology departments around the world



Irradiation of Mouse Thorax Using the Small Animal Radiation Research Platform (SARRP)



Use of the SARRP, to deliver a single fraction 13.5 Gy X-ray irradiation to the thorax.

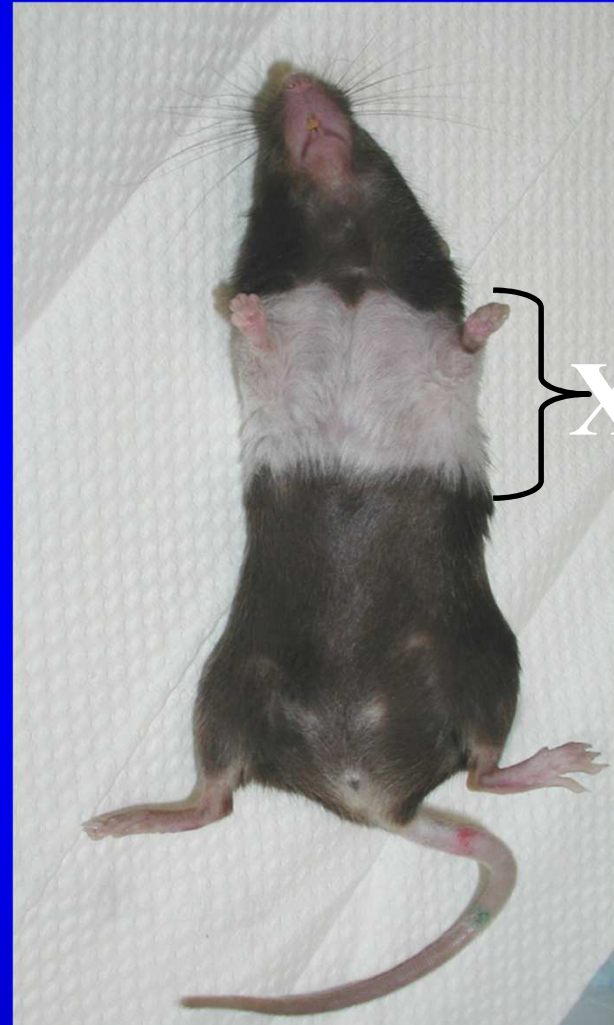
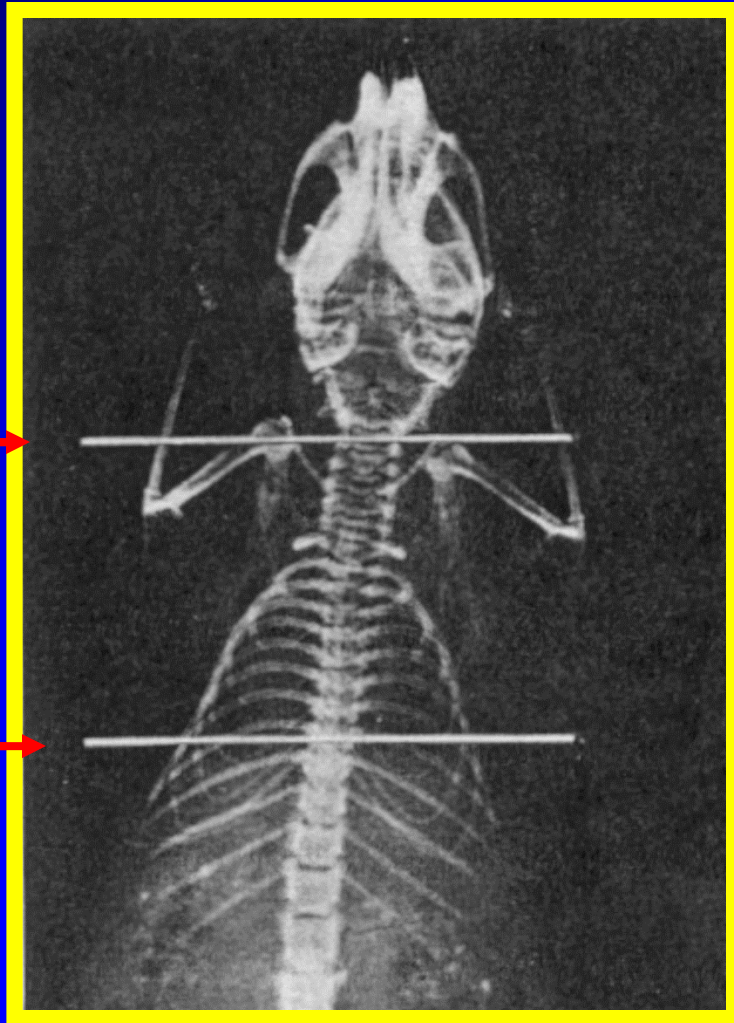
Shielding is provided for the head only as the highly collimated field edge already limits dose to the abdomen/pelvis.



Mouse Radiographs

Cephalic
margin

Caudal
margin

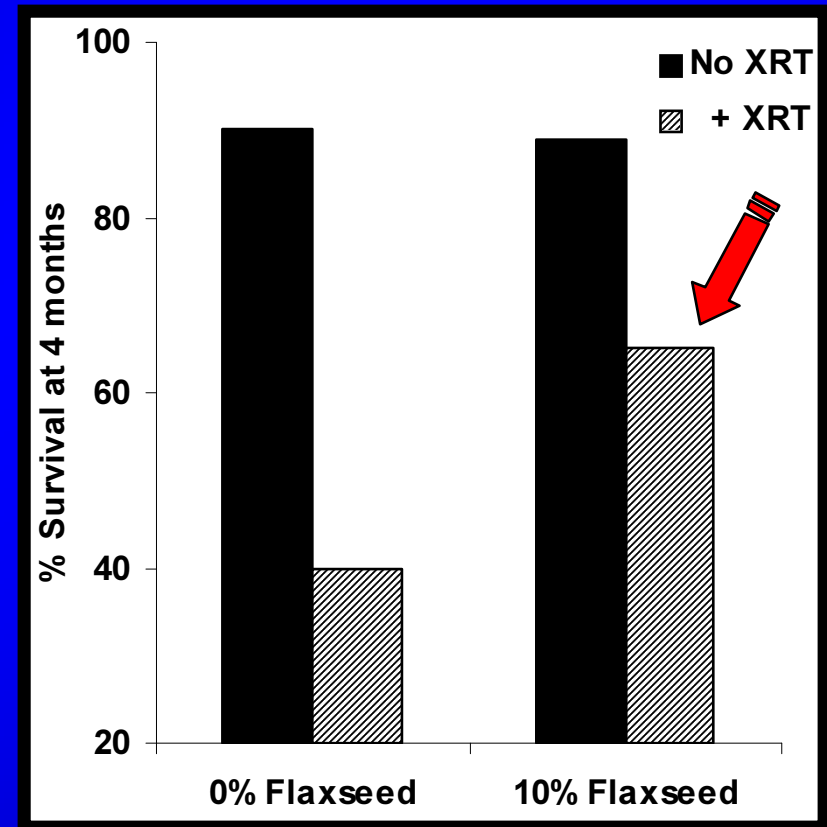
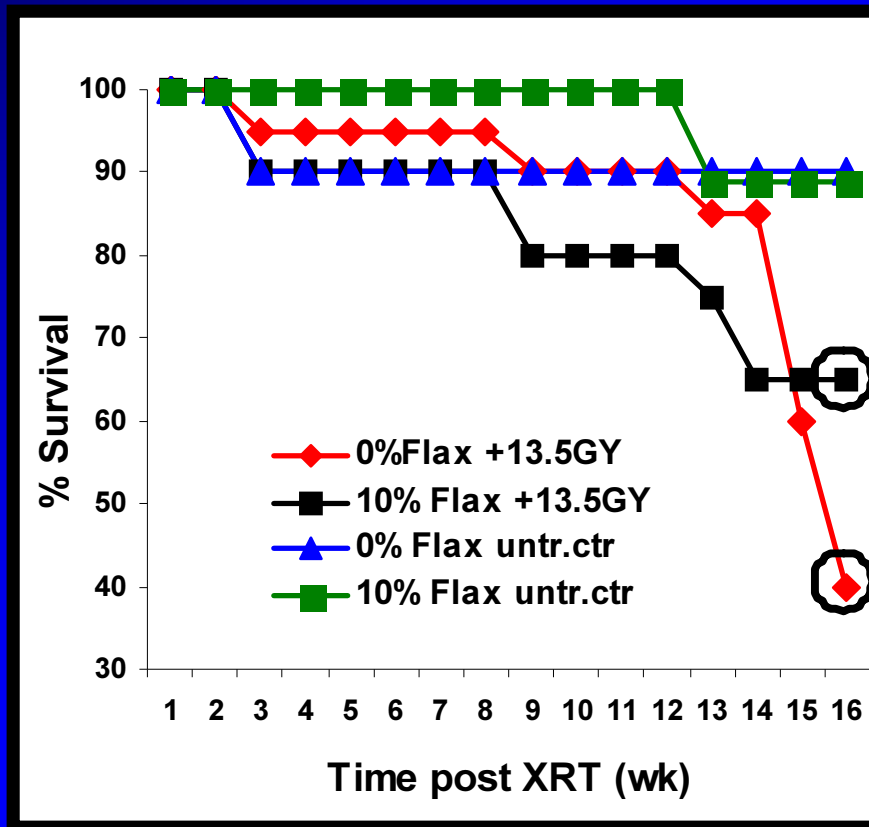


XRT

(XRT=X-Ray Treatment)



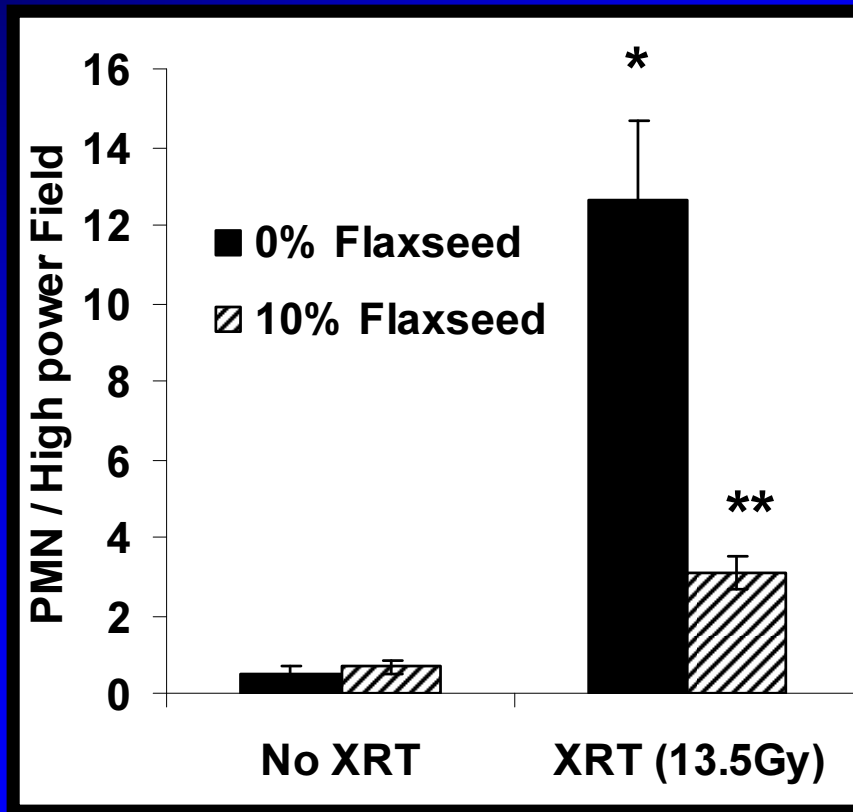
Flaxseed Improves Mouse Survival 4 Months Post Thoracic Irradiation



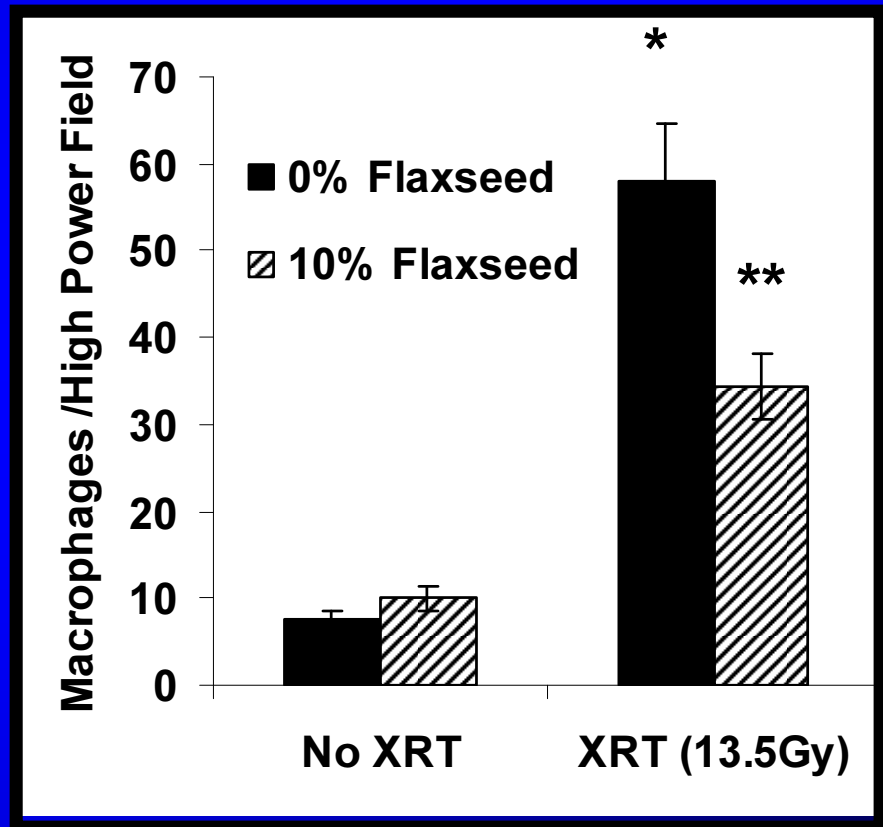
35% vs. 65% Survival for Control and Flaxseed-supplemented diets, respectively



Dietary Flaxseed Ameliorates Radiation-Induced Pneumonitis (Inflammation) in Mice



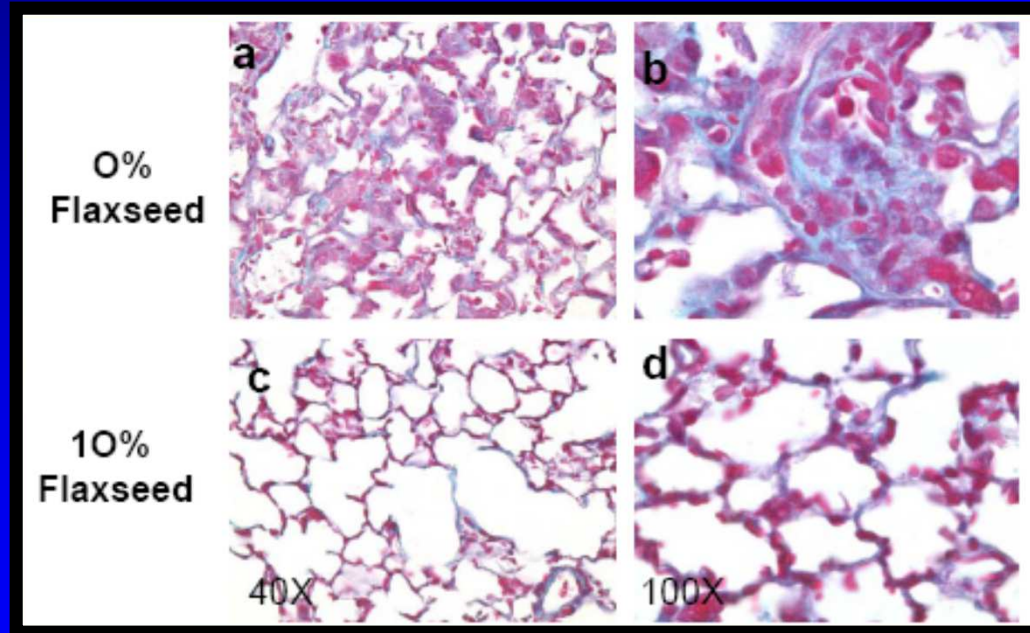
Alveolar Neutrophils



Alveolar Macrophages

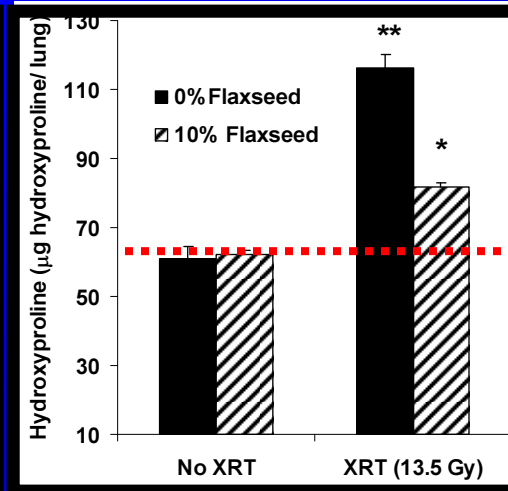
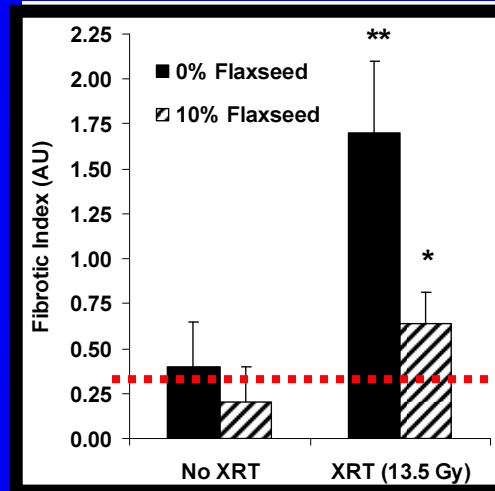
Antifibrotic Role of Flaxseed

Flaxseed
Decreased
Radiation-
Induced
Collagen
Deposition in
Lungs



Trichrome
Blue Staining
for Collagen
(Marker for
Lung
Fibrosis)

Fibrotic Index
(Pathology)



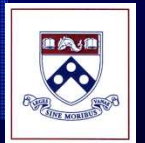
OH-Proline
Content



Summary

Dietary Flaxseed given Preventively:

- ❖ Improves Survival
- ❖ Prevents Radiation-induced
 - Oxidative Tissue Injury
 - Pneumonitis
 - Inflammation
 - Lung Fibrosis
 - Cytokine Secretion
 - Does NOT protect Tumor



Lung-Related Symptoms Linked to Incidents of Accidental Exposure to Radiation

Date	Accident	Lung-related symptoms	Estimated radiation dose	Ref
1945–1964	Los Alamos and Wood River, USA	Oedema, haemorrhage, aspiration pneumonia, focal atelectasis, focal emphysema, hydrothorax	5.1–> 100 Gy	2
1948–1958	Mayak, USSR	Dyspnoea, tachypnea	7–46 Gy	3
1987	Goiania	Severe haemorrhage, pneumonia, right ventricular hypertrophy, pleuritis, enlarged lungs	4.5–6 Gy including internal contamination	4
1990	Israel	Tachypnea, hypoxia, acidosis, infiltrate, severe RP and CMV infection	10–20 Gy	5
1990	Shanghai, China	Pneumonia, haemorrhage, ARDS, decreased oxygen saturation, CMV infection, tachypnea, hypertrophy and dilatation of the right heart, severe pulmonary fibrosis	11–12 Gy	6
1997	Selected report from Chernobyl, USSR	Hypoxemia, ARDS	>10 Gy	7
1999	Tokai-mura, Japan	Transient hypoxemia, interstitial oedema	>2 Gy	8
2000	Samut Prakam, Thailand	Tachypnea, septic shock, pneumonia, acidosis, pulmonary oedema	Not in report	9
2001	Bialystok, Poland	Pleural effusion	Not in report	10

A brief summary of some examples of direct and indirect injury to the lungs due to accidental exposure are listed in the table. These events include criticality and other incidents at nuclear plants and overexposure from medical sources during radiotherapy, sterilization and other accidental exposures. Most accidents involved male workers though a few involved females and one included a child.⁴ Lung injuries resulted from total body or localized exposures and were often a part of multi-organ failure and not the single cause of death. Patients were often treated, and the interventions may have affected the outcomes. The one case of lung fibrosis in the Shanghai accident may have resulted from treatment with oxygen.⁶

Respirology (2012) 17, 66–71



"All the News
That's Fit to Print"

The New York Times

Late Edition

Today, partly sunny, more season-
able, high 46. Tonight, clearing, sea-
sonably cold, low 34. Tomorrow,
sunny, milder in the afternoon, high
51. Weather map is on Page D12.

VOL. CLX . . No. 55,344

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NEW YORK, MONDAY, MARCH 14, 2011

\$2.00

JAPAN REELS AS TOLL RISES AND NUCLEAR RISKS LOOM



ANOTHER EXPLOSION

Radioactive Steam May Be
Released From Fukushima
for Weeks



LA NACION

lanacion.com
Buenos Aires, lunes 14 de marzo de 2011

EL HORROR

En la ciudad de Nihonmatsu, los servicios médicos trasladan a una persona...

CHICAGO SPORTS FINAL | FRIDAY, MARCH 11

NUCLEAR CRISIS GROWS

NUCLEAR CRISIS IN JAPAN STRUGGLE MAY TAKE WEEKS



Damage at the Fukushima nuclear complex on Thursday. | AP

...possibly weeks' to get nuke complex under control PAGE 14-15



The NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats outlines support for: a) basic and translational research on the mechanisms of radiation injury, repair, and restoration; b) bioassays and tools for



National Institute of Allergy and Infectious Diseases

Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

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Radiation and Nuclear Countermeasures Program

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This is a program of the U.S. Department of Health and Human Services, Office of Public Health Emergency Medical Countermeasures, and the National Institutes of Health. The program is coordinated by NIAID, with the involvement of the National Cancer Institute.

▣ Radiation Nuclear Countermeasures

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2012 NIH Strategic Plan

Summary of NIH's progress and future plans for radiation and nuclear countermeasures research (PDF).

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Medical Countermeasures Enterprise Review

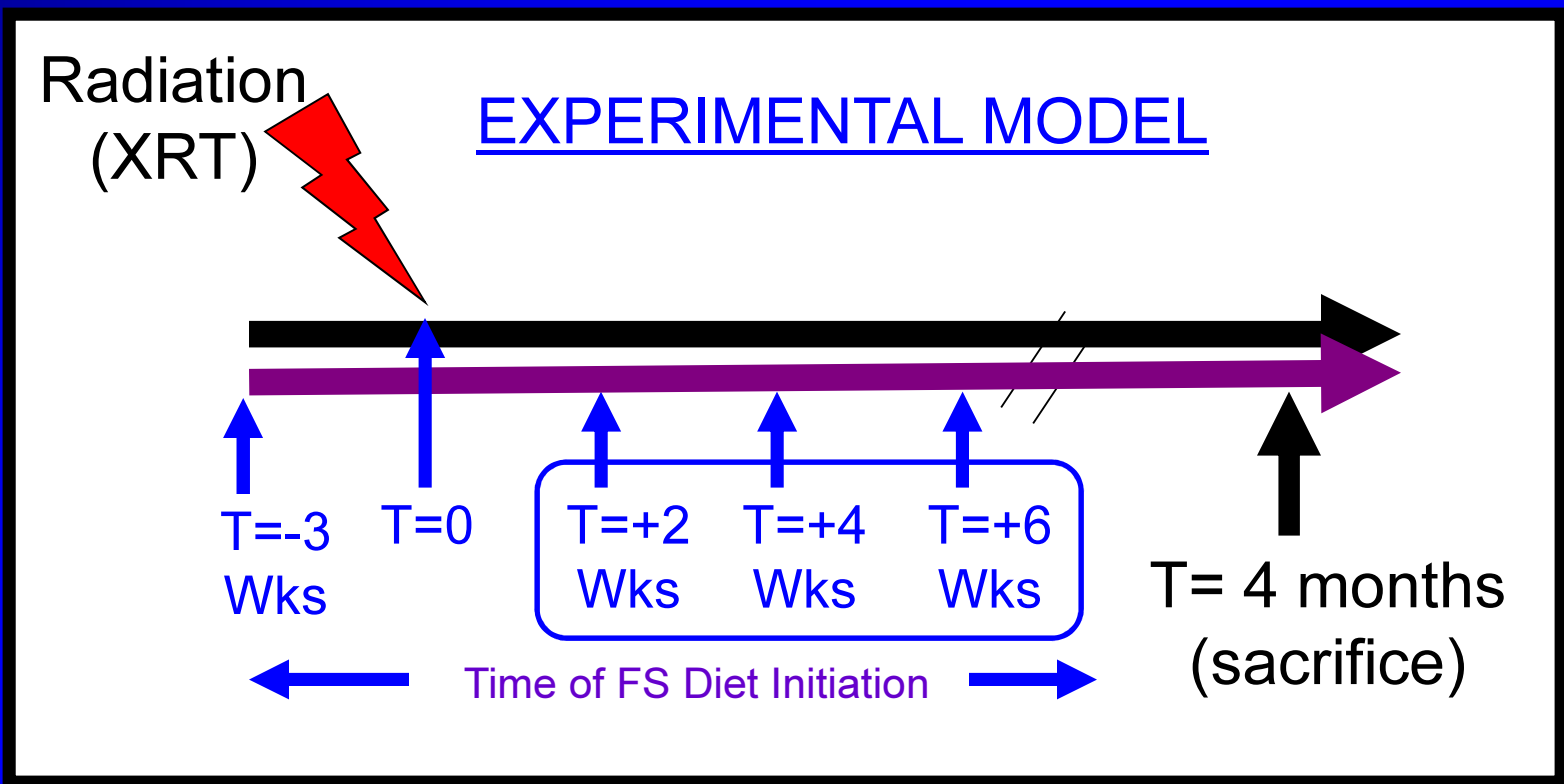
Related Links

- [Division of Allergy, Immunology, and Transplantation \(DAIT\)](#)
- [Biodefense and Related](#)



Mitigation of Radiation Pneumonopathy by Wholegrain Flaxseed

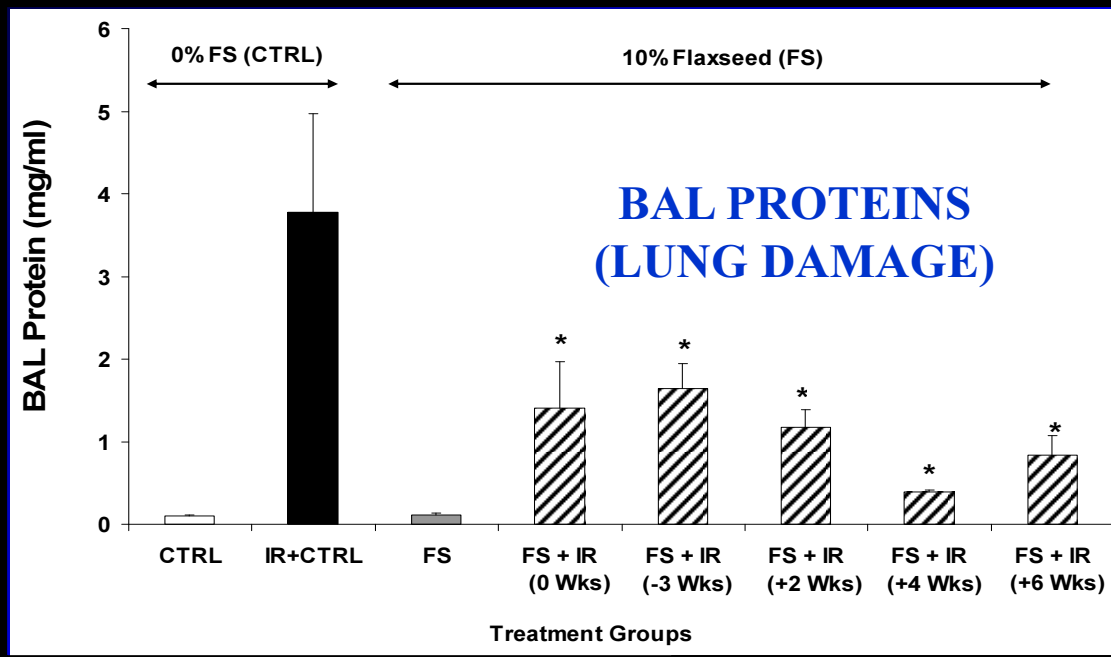
GOAL: Determine whether Flaxseed (FS) attenuates lung toxicity and lethality related to thoracic radiation (external exposure to ionizing radiation)



Separate mouse cohorts for each time-point



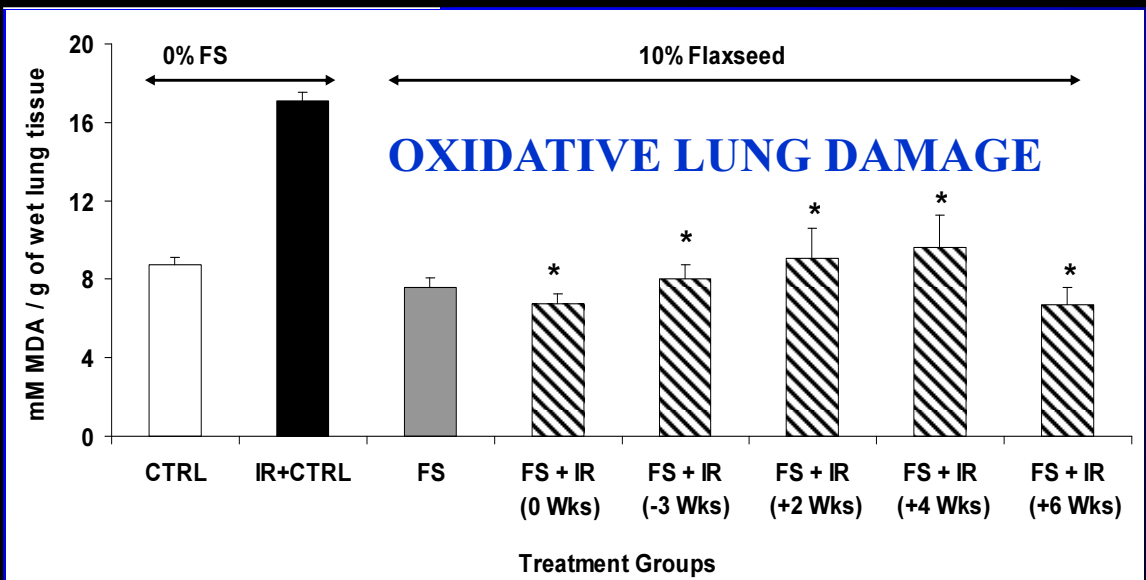
Mitigation of Radiation Damage by Flaxseed



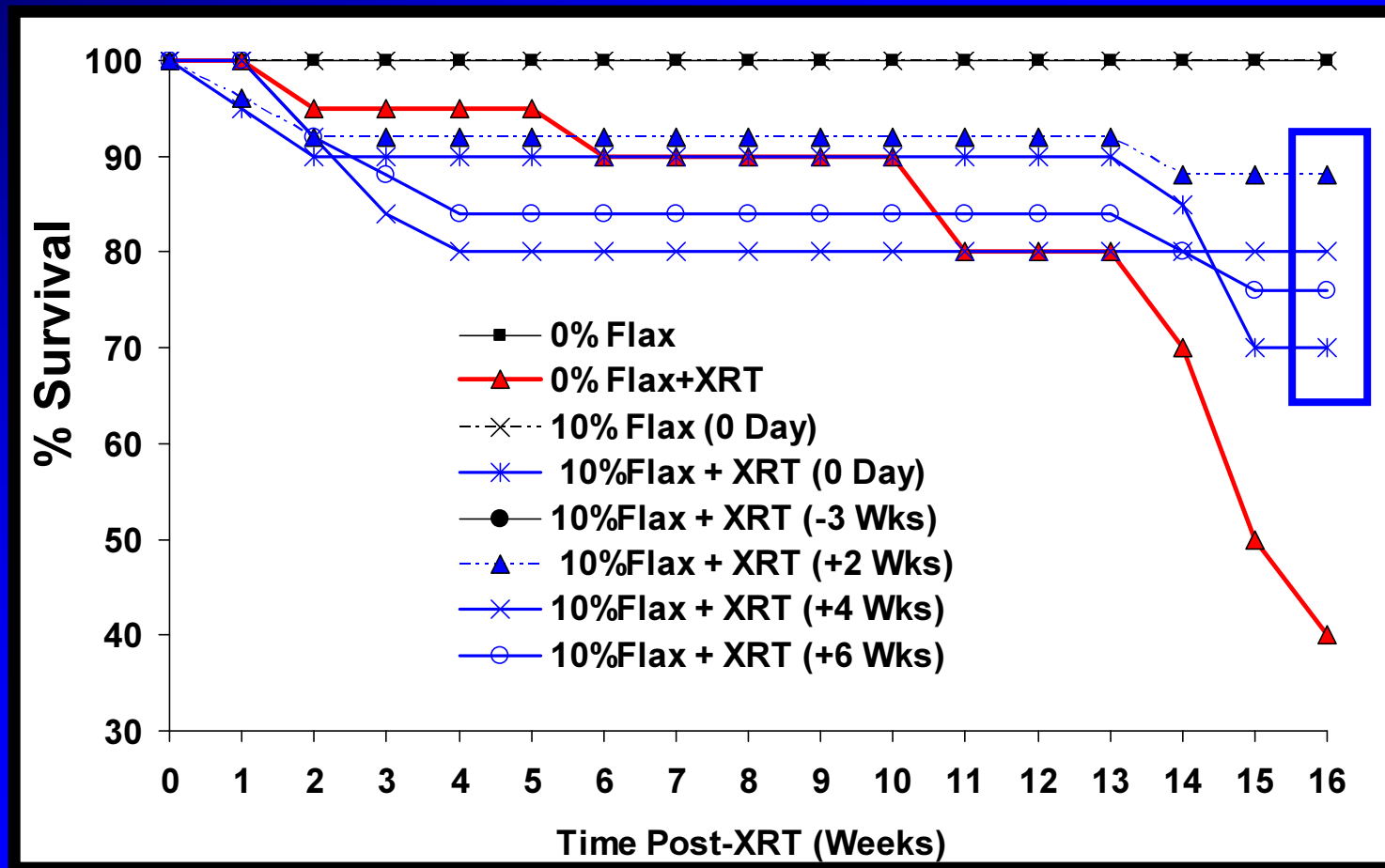
Administering flaxseed 2,4,6 weeks POST radiation exposure is still protective from radiation damage



Christofidou-Solomidou, BMC Cancer, 2011



Improvement of Animal Survival by Flaxseed Given Post Radiation Exposure



40% Survival with 0% Flaxseed vs. 78-88% survival with flaxseed given 2-6 weeks post-exposure



Mitigation of Radiation Damage by Dietary Flaxseed

Christofidou-Solomidou *et al.* *BMC Cancer* 2011, **11**:269
<http://www.biomedcentral.com/1471-2407/11/269>



RESEARCH ARTICLE

Open Access

Dietary flaxseed administered **post** thoracic radiation treatment improves survival and mitigates radiation-induced pneumonopathy in mice

Melpo Christofidou-Solomidou^{1*}, Sonia Tyagi¹, Kay-See Tan², Sarah Hagan³, Ralph Pietrofesa¹, Floyd Dukes¹, Evguenia Arguiri¹, Daniel F Heitjan², Charalambos C Solomides⁴ and Keith A Cengel³





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Flaxseed Might Protect Against Death From Radiation

Published August 12, 2011 | MyHealthNewsDaily

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Flaxseed may protect against the damaging effects of radiation from a terrorist's dirty bomb. In a new study, researchers suggest that mice that ate flaxseed up to six weeks after receiving a radiation dose to the chest were more likely to survive and had



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University of Pennsylvania Study Finds Flaxseed Protects Against Radiation

Date Posted: August 15, 2011

Philadelphia—Flax has been part of human history for well over 30,000 years, used for weaving cloth, feeding people and animals, and even making paint.

Now, researchers from the Perelman School of Medicine at the University of Pennsylvania have discovered that it might have a new use for the 21st century: protecting healthy tissues and organs from the harmful effects of radiation.

ScienceDaily

Web address:

<http://www.sciencedaily.com/releases/2011/08/110809111821.htm>

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Flaxseed May Be Effective in Protecting Against Harmful Effects of Radiation

ScienceDaily (Aug. 9, 2011) — Flax has been part of human history for well over 30,000 years, used for weaving cloth, feeding people and animals, and even making paint. Now, researchers from the Perelman School of Medicine



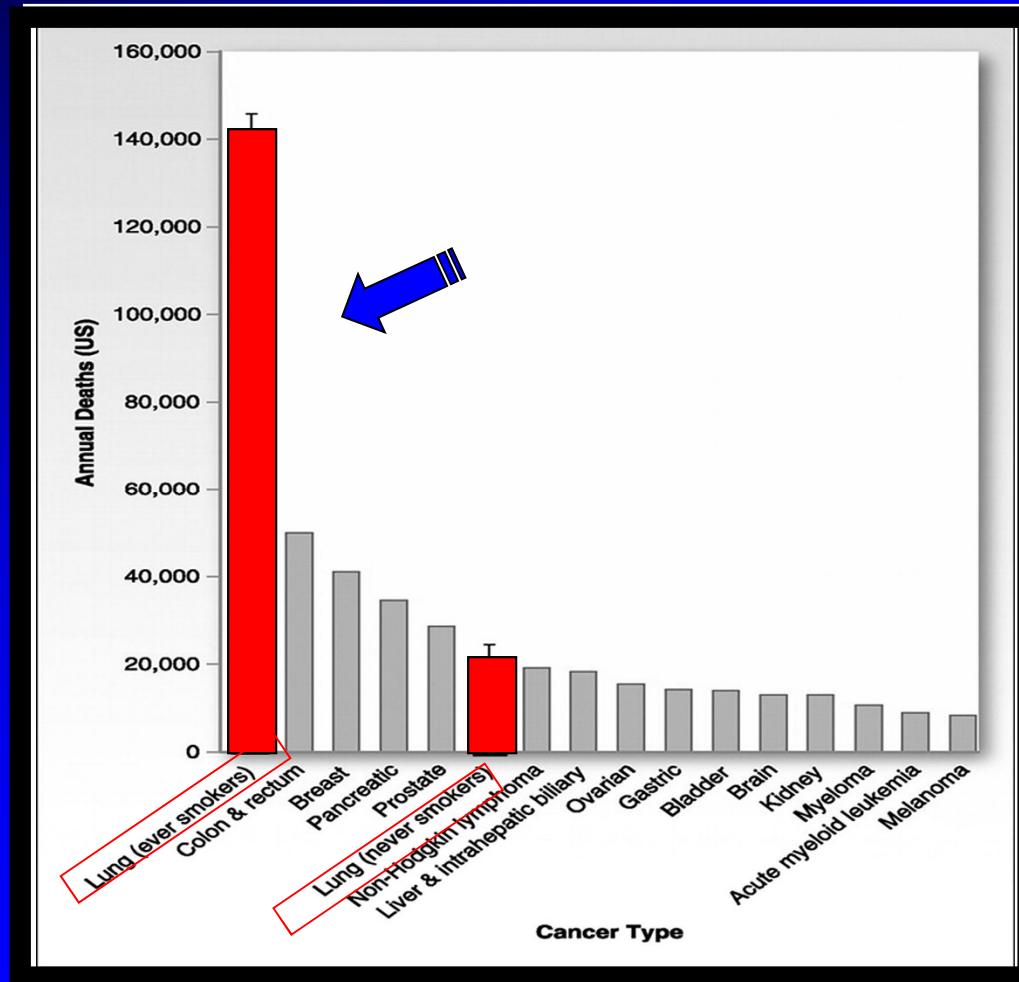
Presentation Outline:

1. Overview of environmental challenges and oxidative lung damage.
2. Introducing alternative remedies to oxidative lung disease.
3. Ameliorating side effects of: a) therapeutic and b) accidental radiation lung exposure in mouse model.
4. Chemoprevention of lung tumorigenesis in a rodent model of chemical carcinogen exposure (tobacco).
5. Chemoprevention of mesothelioma and lung cancer in a rodent model of environmental carcinogen exposure (asbestos).



TOBACCO CARCINOGENS

Lung Cancer



- Leading cause of cancer deaths in the US (>160,000 per year).

- Probably >90% due to tobacco smoke exposure.



Lung Cancer

- Surgery offers the sole prospect for cure-a small percentage of lung cancer patients are candidates.
- Focus on novel **PREVENTIVE** strategies whereby known industrial, environmental or tobacco-derived carcinogens can be prevented from causing tissue damage leading to cancer development.
- Dietary modulation and Chemoprevention may be considered for control of the lung cancer epidemic.



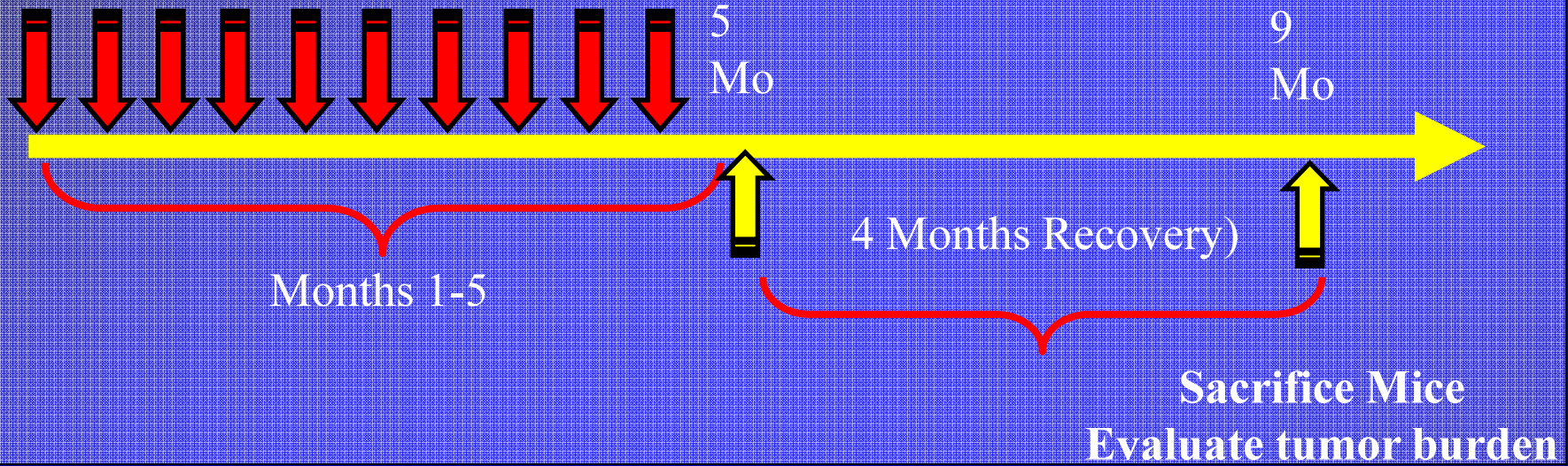
Rodent Models Of Chemical Carcinogenesis-lung Cancer

Rodent models of lung cancer that develop after exposure to **a chemical carcinogen** are valuable to study mechanisms of carcinogenesis and pathogenesis, for early detection, and to test **chemopreventive and therapeutic agents**.

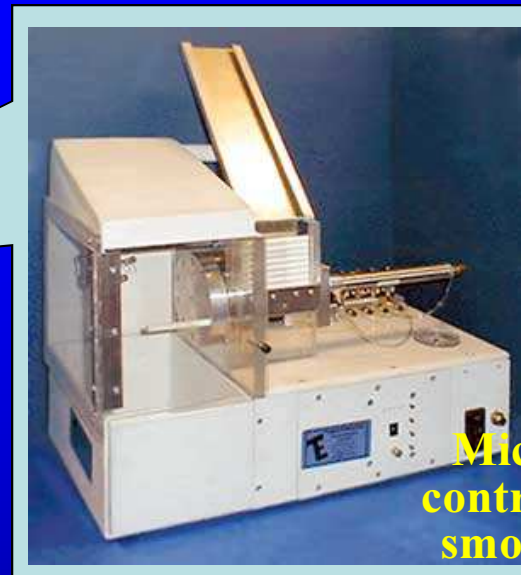


Tobacco Smoke Exposure (Rodents)

Daily Exposure to Tobacco Smoke for 6 hrs



Collecting and mixing chamber for rodent exposure studies



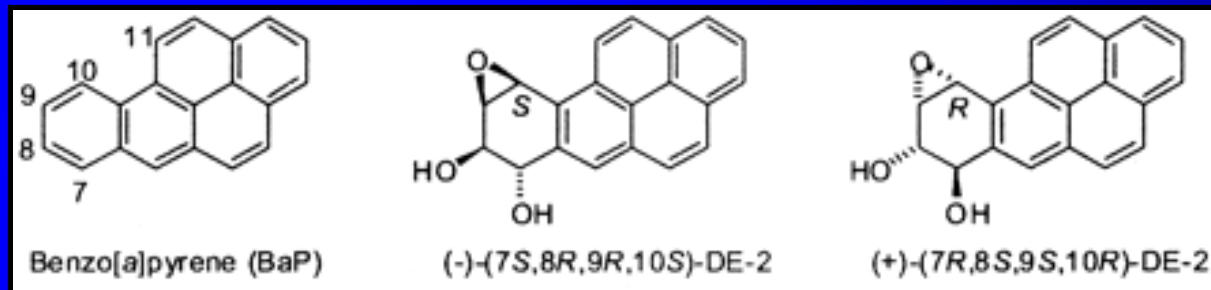
Microprocessor-controlled cigarette smoking machine



Alternative: Purified TobaccoCarcinogen(s)

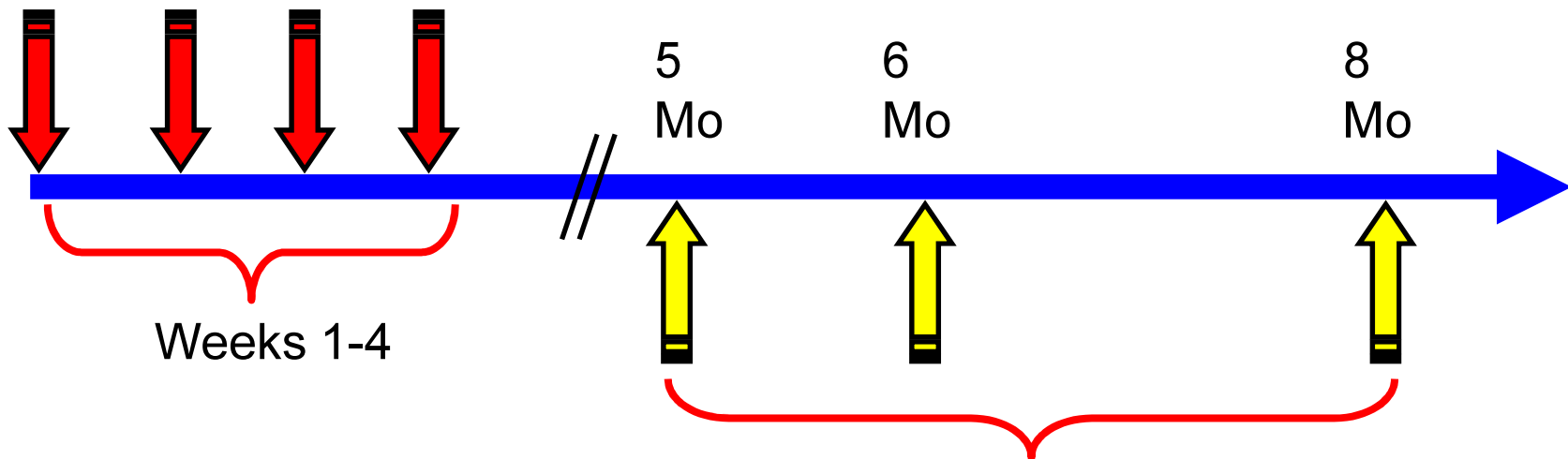
1. Benzo-alpha pyrene (B[α]P)
2. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
3. Dimethylbenz(a)anthracene (DMBA)
4. Urethane

•The polycyclic aromatic hydrocarbon (PAH) **Benzo[a]pyrene (B[a]P)** is one of the most prevalent environmental carcinogens-(Combustion of coal, oil, gas, wood, garbage, tobacco, and charbroiled meat).



Rodent Model of Benzo[*a*]Pyrene-Induced Chemical Carcinogenesis

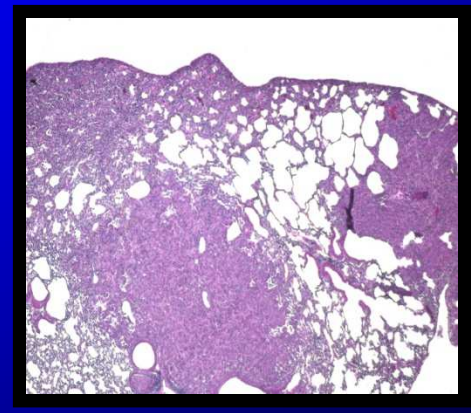
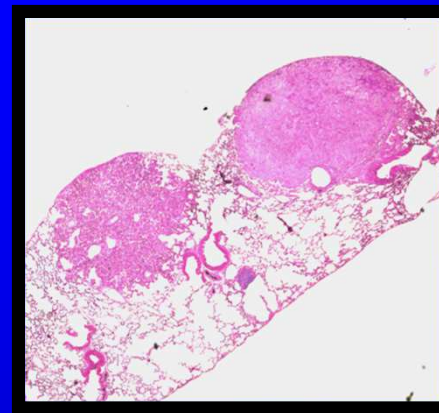
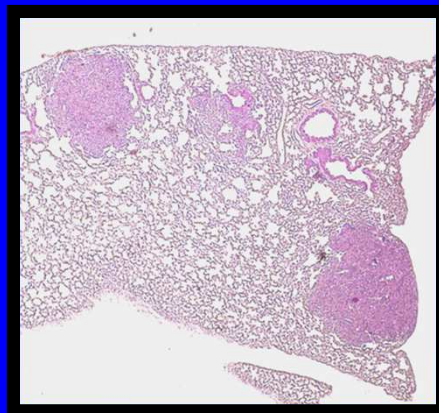
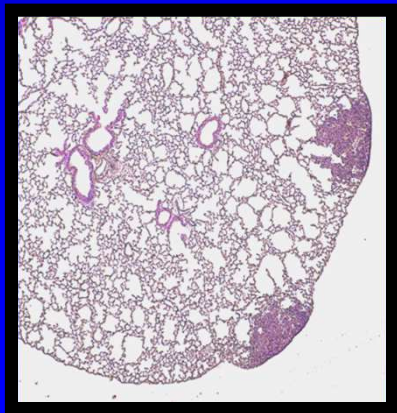
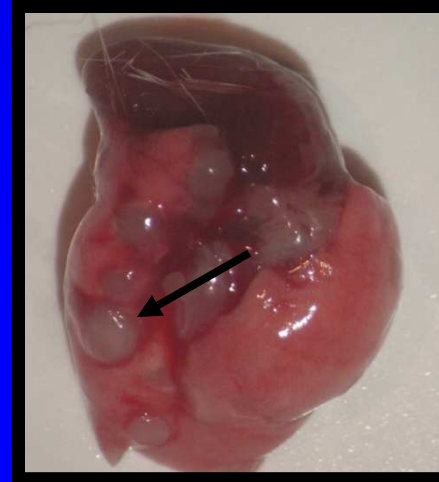
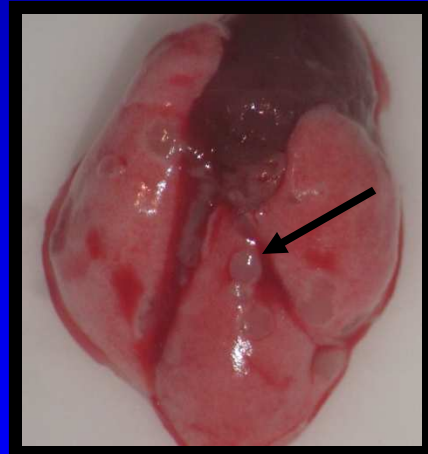
Weekly
i.p injections of
B[*a*]P (1 mg/mouse)



Use of an inbred mouse strain
(A/J) with increased sensitivity to
chemical carcinogen-induced
lung carcinogenesis



Histological Detection of Lung Tumor Nodules in Mice Exposed to B[α]P



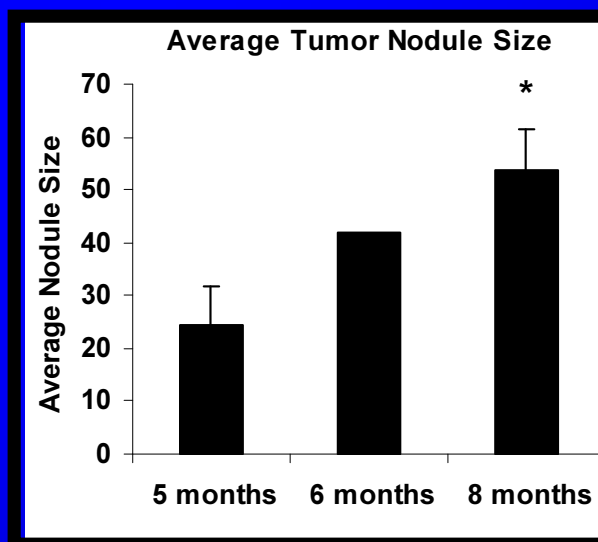
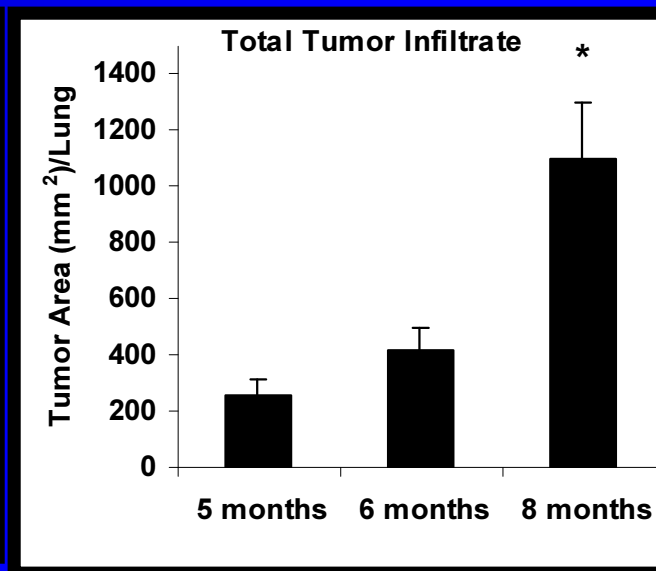
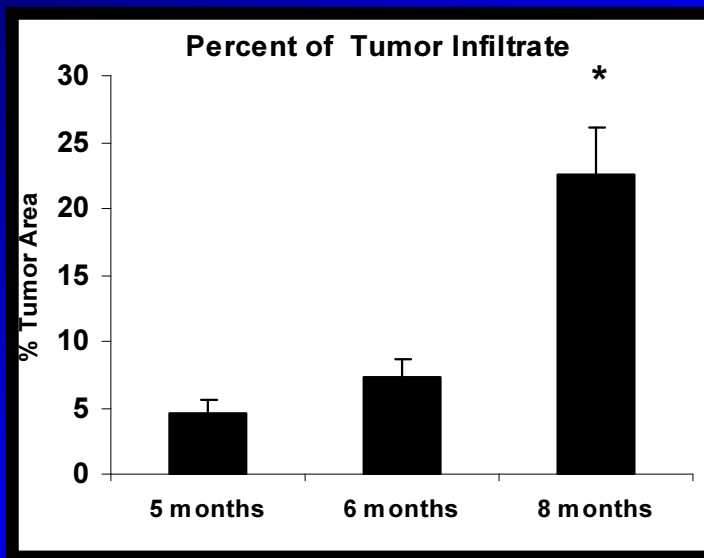
4 Months

5 Months

6 Months

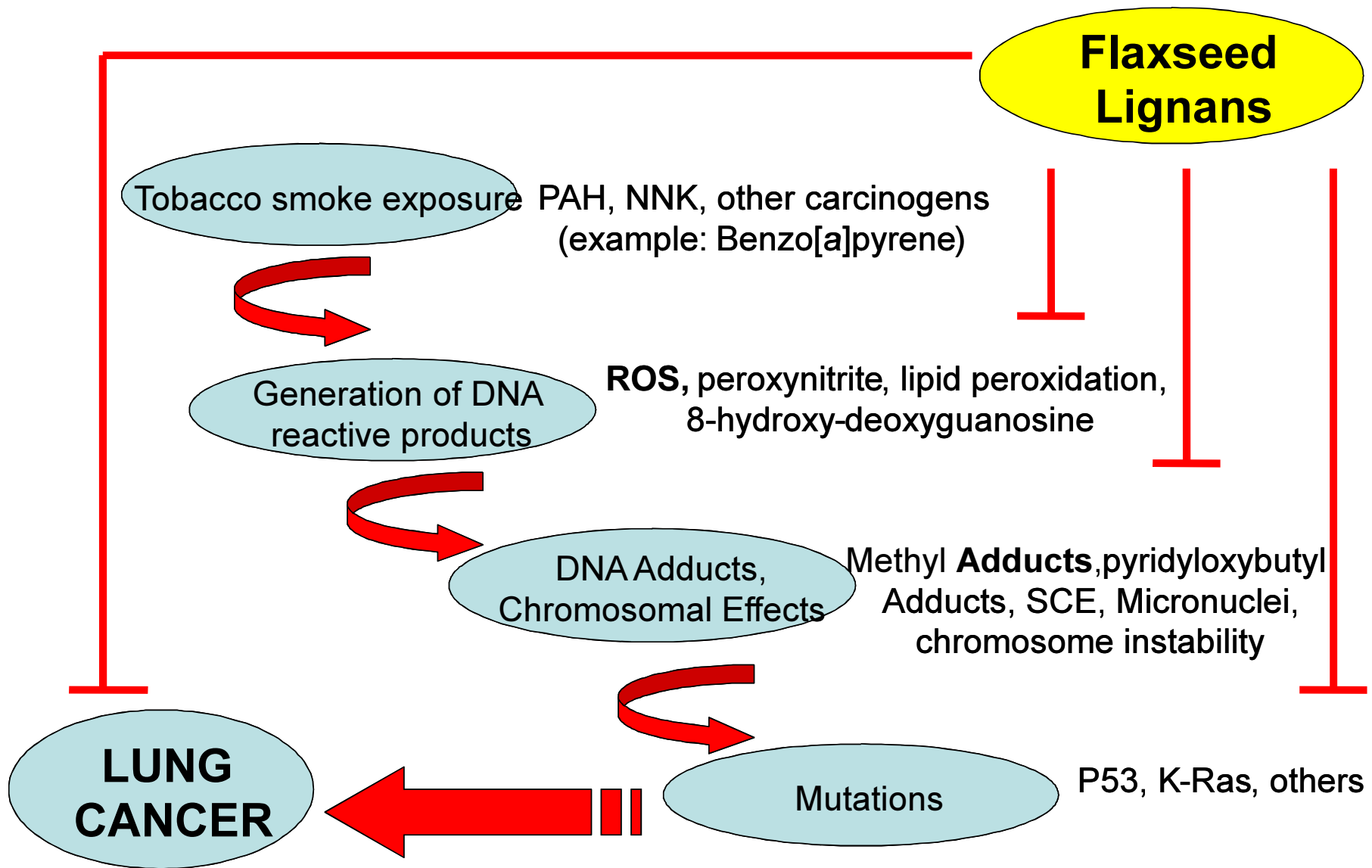
8 Months

BENZO[*a*]PYRENE-CHEMICAL CARCINOGENESIS MODEL



Tumor
Morphometry /
Image Analysis
System



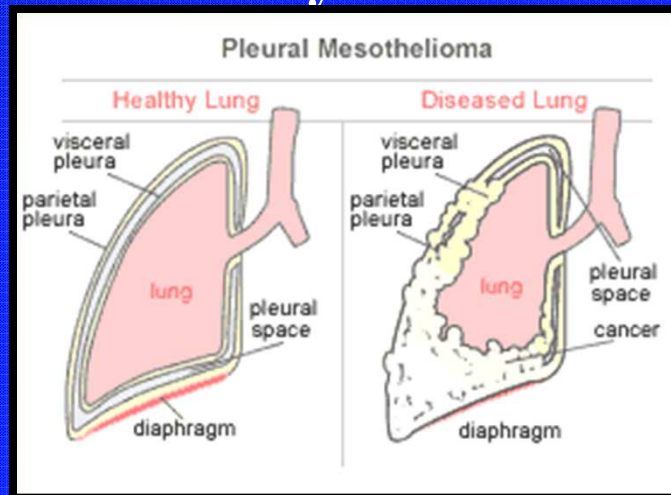


Adapted from Hecht, 1999

ASBESTOS EXPOSURE

Asbestos Exposure and Malignant Mesothelioma

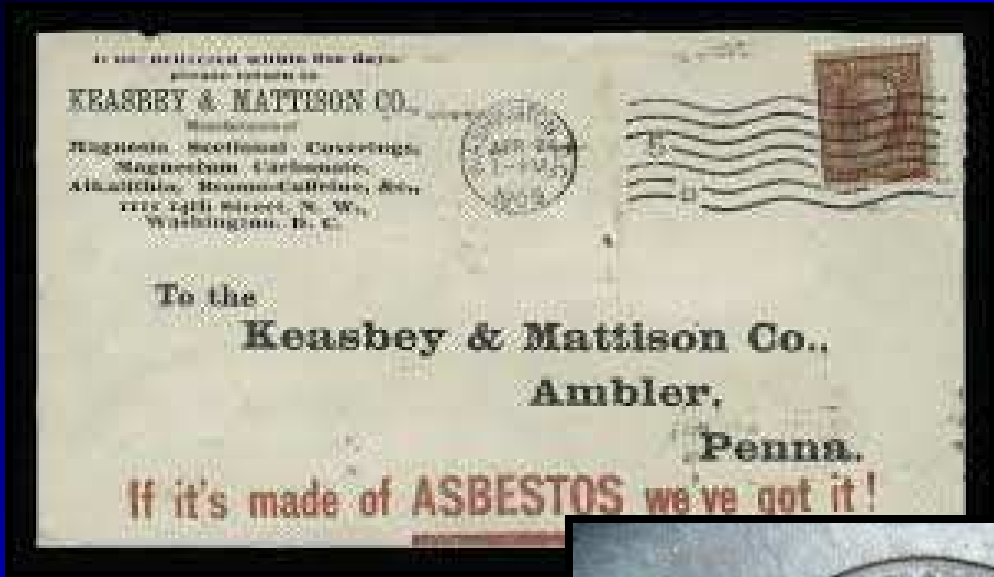
- Asbestos fiber inhalation can lead to malignant mesothelioma, lung cancer, as well as pulmonary fibrosis.
- MM is a highly aggressive cancer that arises from the mesothelial cells of the pleura and peritoneum with a median survival of about 1 year.



- Current therapies, other than surgery in very early disease, are not curative.

Presently, MM causes about 3,000 deaths per year in the US and an additional 5,000 deaths/year in Western Europe.





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University of Pennsylvania receives \$10M to study Superfund asbestos site

July 11, 2014 9:52 AM

By HEATHER ISRINGHAUSEN GVILLO

PHILADELPHIA (Legal Newsline) – Researchers with the University of Pennsylvania have received a \$10 million grant to study asbestos and how the toxic fiber leads to cancer at America's 10 Superfund sites.

The grant, which came from the National Institute of Environmental Health Sciences, will help researchers from the school's Center of Excellence in Environmental Health Sciences and the Perelman School of Medicine to study asbestos, mesothelioma and other asbestos-related diseases over the next four years.

University of Pennsylvania researchers receive \$10 million to study asbestos in Ambler

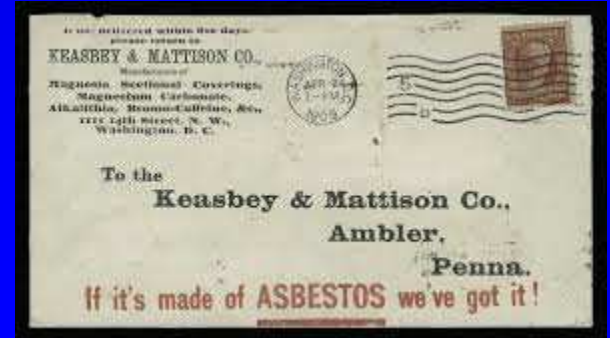
Published: Tuesday, June 24, 2014

By Eric Devlin
edevlin@montgomerynews.com

The University of Pennsylvania recently announced it has received a \$10 million grant from the National Institute of Environmental Health Sciences to study asbestos and its impact on the Ambler community.

The grant will allow researchers from Penn's Center of Excellence in Environmental Toxicology to, over the next four years, study asbestos, the rare asbestos-related cancer, mesothelioma, and other asbestos-related diseases, according to a press release. Researchers from the Abramson Cancer Center, the Penn School of Arts and Sciences and Fox Chase Cancer Center are also lead investigators on the grant.

The BoRit site where research will take place, located in Ambler Borough, Upper Dublin and Whitpain townships between Butler Avenue, North Maple Street and the Wissahickon Creek, was placed on the Environmental Protection Agency's Superfund National Priorities List in April 2009.



A 2010 aerial view of the BoRit asbestos site following two phases of removal action. Photo by: salbocutti.com

[View and purchase photos](#)



Asbestos fate, exposure, remediation, and adverse health effects”

1. Can we remediate asbestos without moving it from the original disposal site?
2. What do we know about the fate and transport of asbestos in the environment by water and air?
3. What do we know about the exposure pathways that were responsible for the mesothelioma cluster in Ambler? And why is the incidence higher in women?
4. Is susceptibility to mesothelioma genetic?
- 5. Can asbestos-related disease be prevented?**
6. Is there a blood test to determine whether a person will get asbestos-related disease?



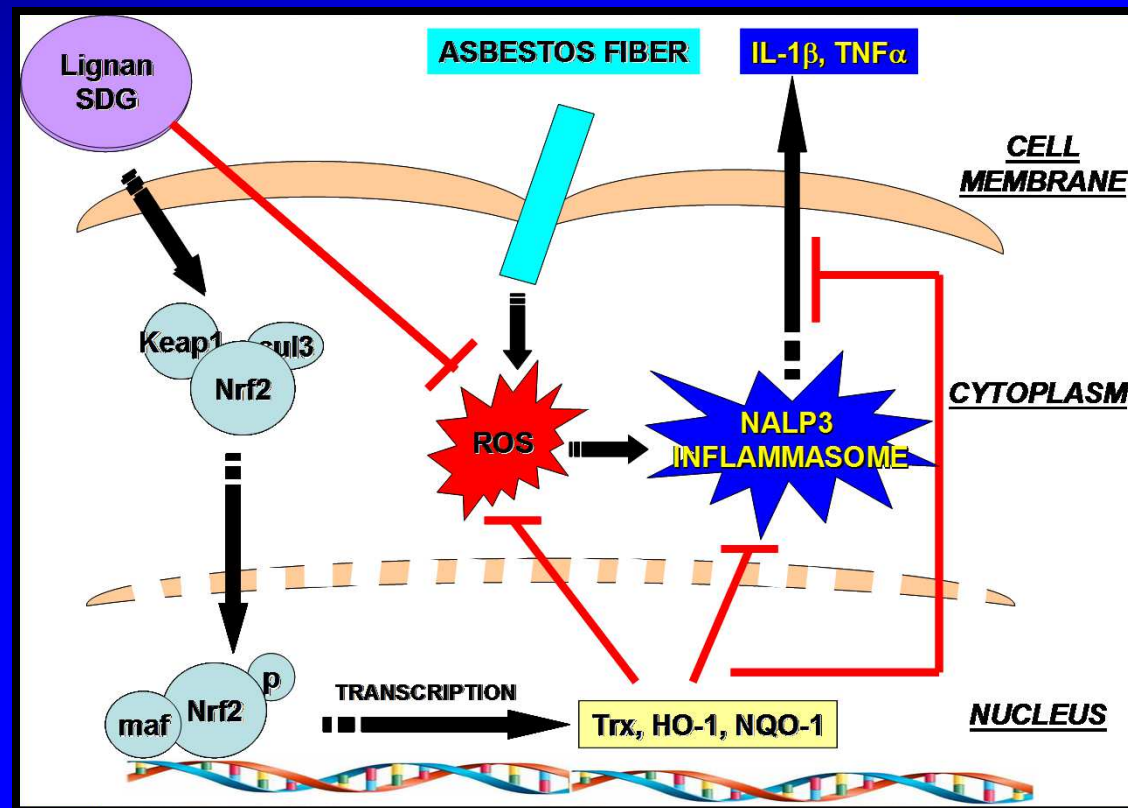
**Evaluation of Flaxseed and its
Lignan SDG in Asbestos-
Exposed Cells**

AND

**Rodent Models of Accelerated
Malignant Mesothelioma**

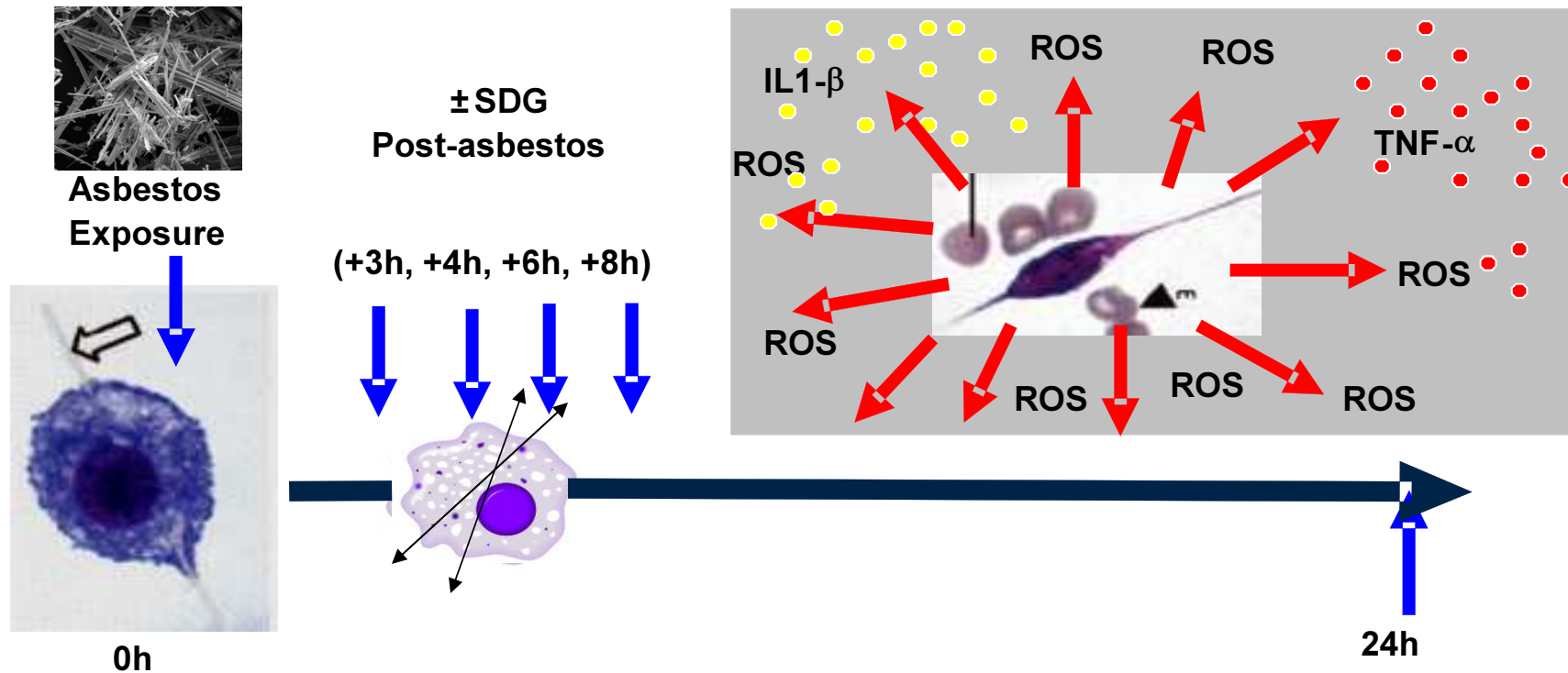


Modeling Asbestos Exposure to Study of Mechanism of Inflammatory Cell Activation



Inhaled asbestos fibers work their way into the lung and ultimately to the pleural surface. They are taken up by tissue phagocytes, primarily macrophages. This stimulates intracellular ROS and activates NF- κ B and the inflammasome inducing the release of numerous cytokines and mutagenic ROS

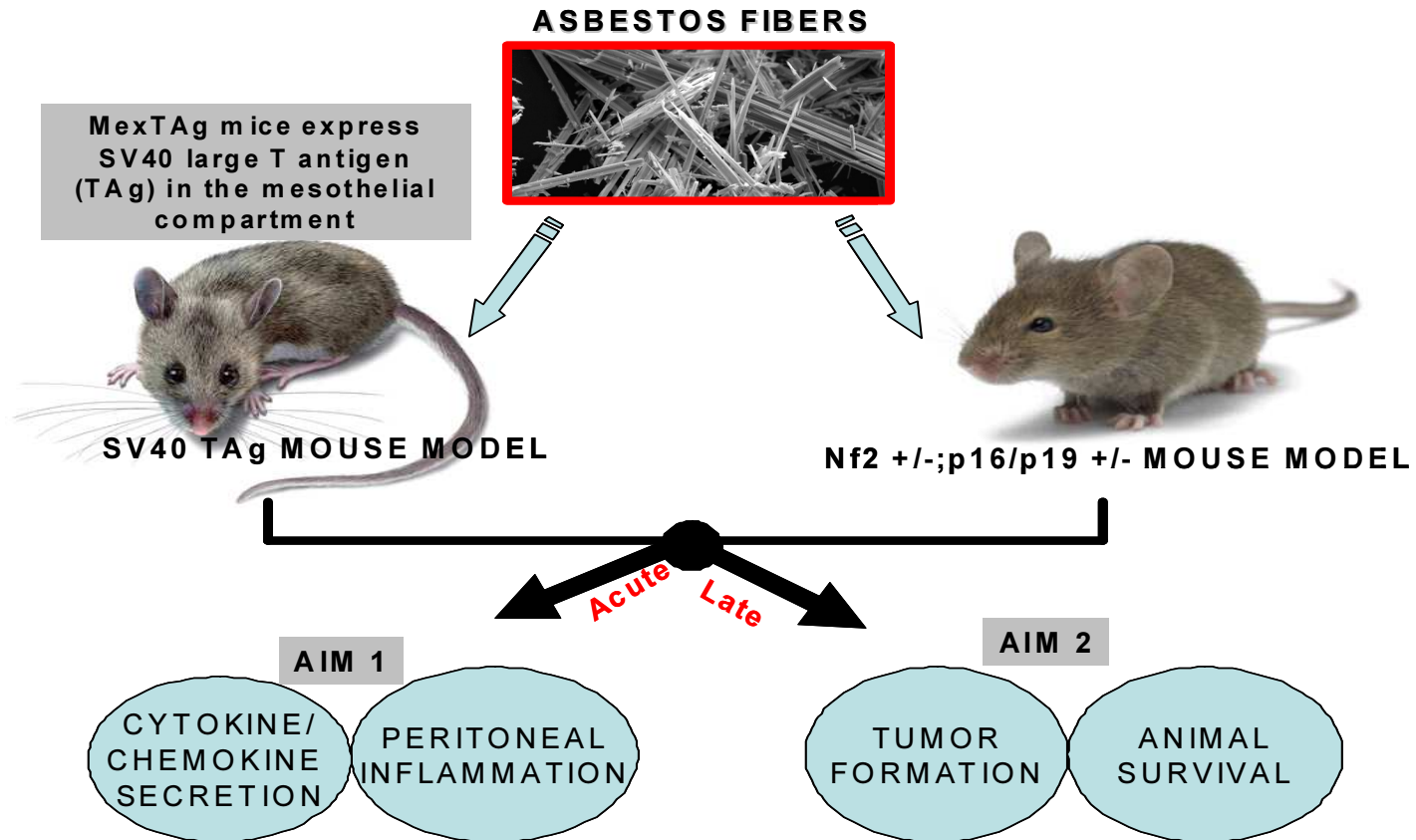
Evaluation of the Lignan SDG in Blocking Asbestos-Induced Macrophage Activation



Using human and mouse macrophages and mesothelial cells, we will evaluate the ability of the anti-oxidant Secoisolariciresinol diglucoside (SDG) to interfere with asbestos-induced ROS generation, cytokine secretion and inflammasome activation *in vitro*.



Testing SDG in Asbestos-Induced Mesothelioma



Using at least 2 models of mice genetically predisposed to develop mesothelioma after asbestos exposure, we will: Evaluate the **ACUTE** effects of Flaxseed and SDG on a single dose of asbestos in mice; test whether Flaxseed and SDG inhibits **CHRONIC** effects such as the development of tumors and lung fibrosis in genetic models of accelerated, asbestos induced MM.



Chemoprevention of Asbestos-Induced Malignant Mesothelioma Using Dietary Flaxseed

Data from this work will provide important evidence for the usefulness of this bioactive natural product in blunting cancer development from asbestos exposure and provide insight in the mechanisms involved.

If our studies show efficacy with safety, our long-term goal would be the evaluation of Flaxseed and SDG as chemopreventive agents for mesothelioma in exposed populations.



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RC1AI081251

National Cancer Institute (NCI/NIH)

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NIH-1R21CA-118111

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(NIEHS/NIH)

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