12-3-2014

Alternative Approaches to Lung Insults

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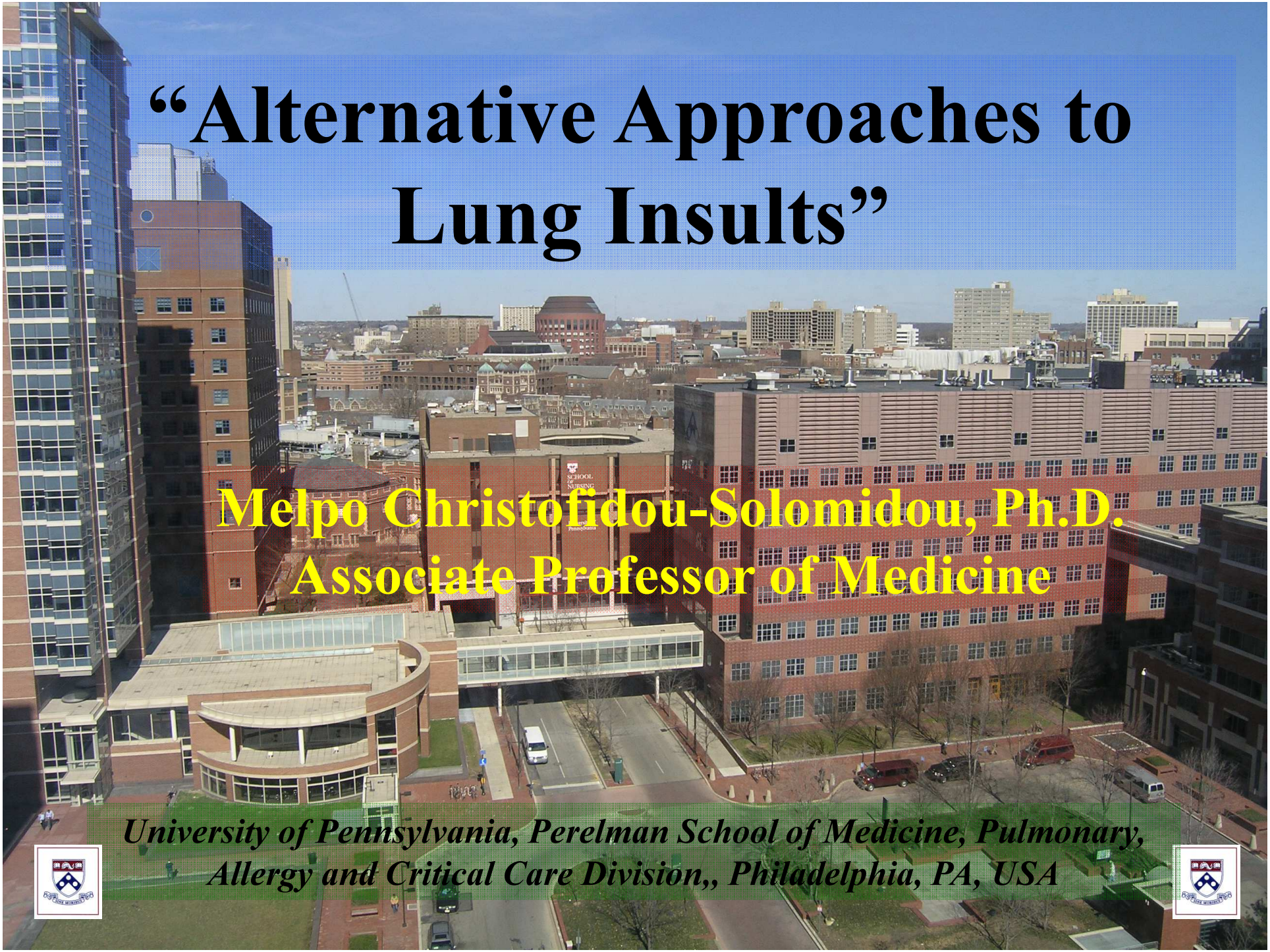
"Alternative Approaches to Lung Insults"



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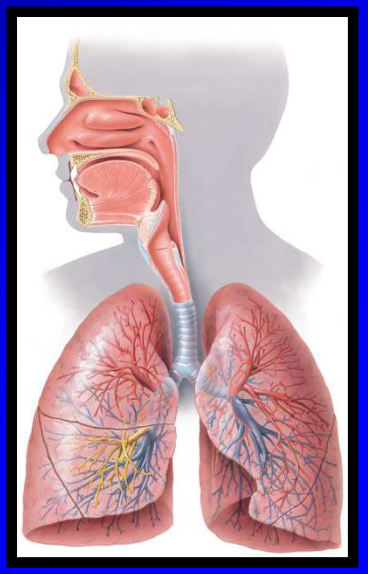
Presentation Outline:

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

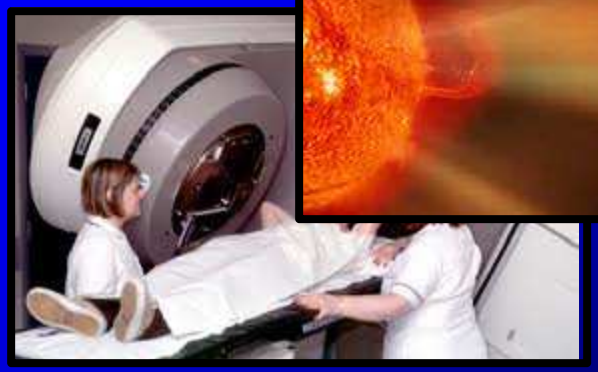
Oxidative Lung Damage

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- α1 proteinase inhibitor (α1PI) inactivation by cigarette smoke and inflammatory cells
Adult respiratory distress syndrome	Inflammatory cell release of oxidants- α1PI 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

Comhair SA, Erzurum SC, Am J Physiol Lung Cell Mol Physiol.

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.

Hooper M, Bernard G, June 2011.

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"

EDITORIAL

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

ONLINE FIRST

Pharmaconutrition 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 pharmaconutrients, attenuating any treatment effect if one exists. Therefore, investigations in pharmaconutrition call for pharmaconutrients to be dissociated from the baseline nutrition.[3] Rice and colleagues[4] 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

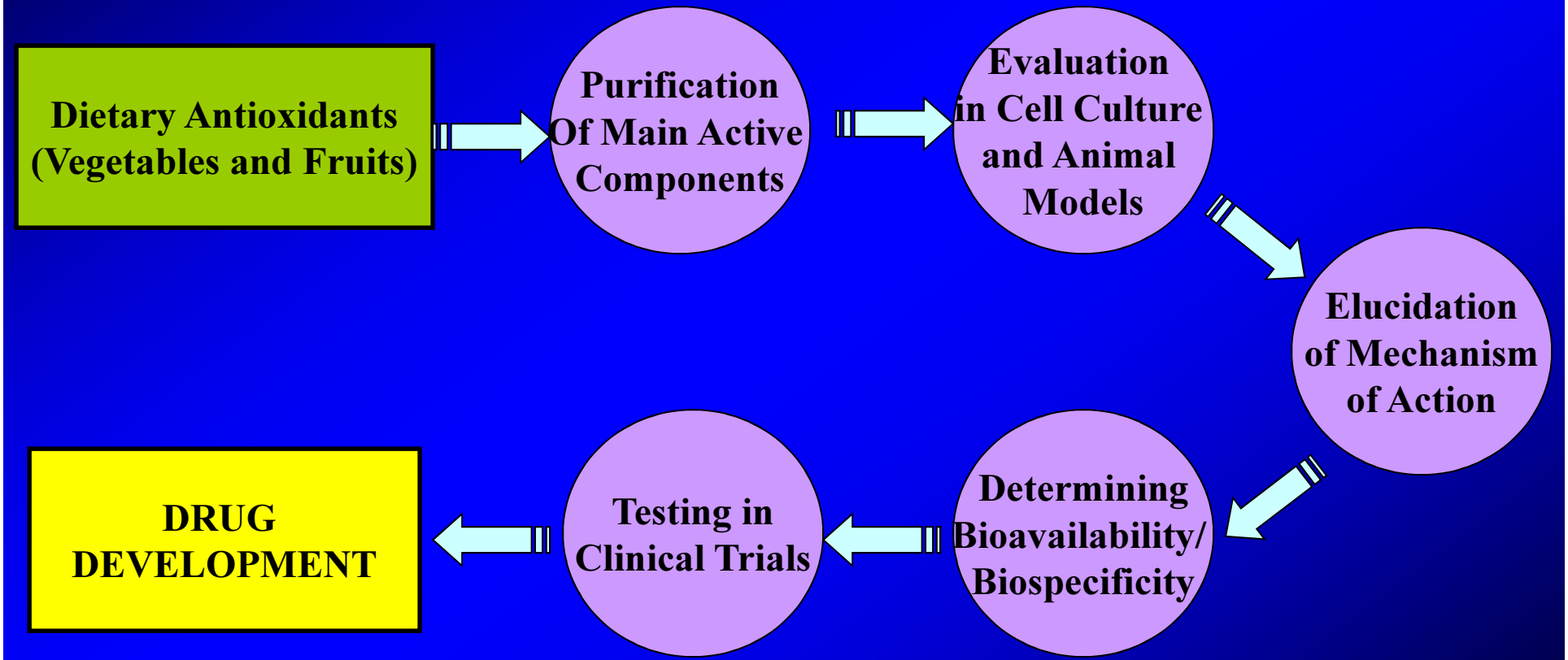
Usefulness of Dietary Supplements

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



Botanicals with antioxidant properties currently being evaluated in lung disease and cancer

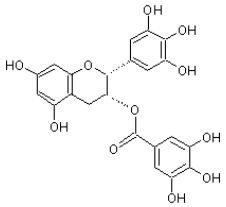
Dietary Agents

Green Tea

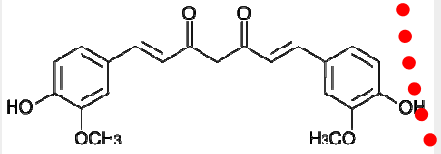
Turmeric

Flaxseed

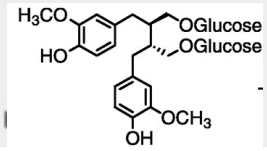
Chemical Structures



Epigallocatechin-3-gallate (EGCG)



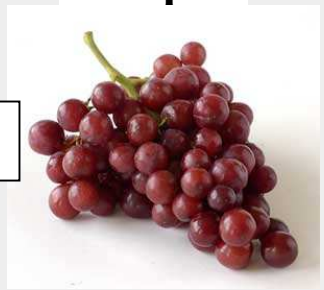
Curcumin



Secoisolariciresinol Diglucoside (SDG)

Dietary Agents

Grapes

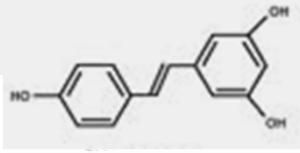


Tomatoes

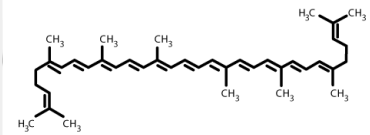
Pomegranate

Broccoli

Chemical Structures

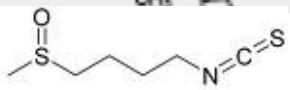


Resveratrol

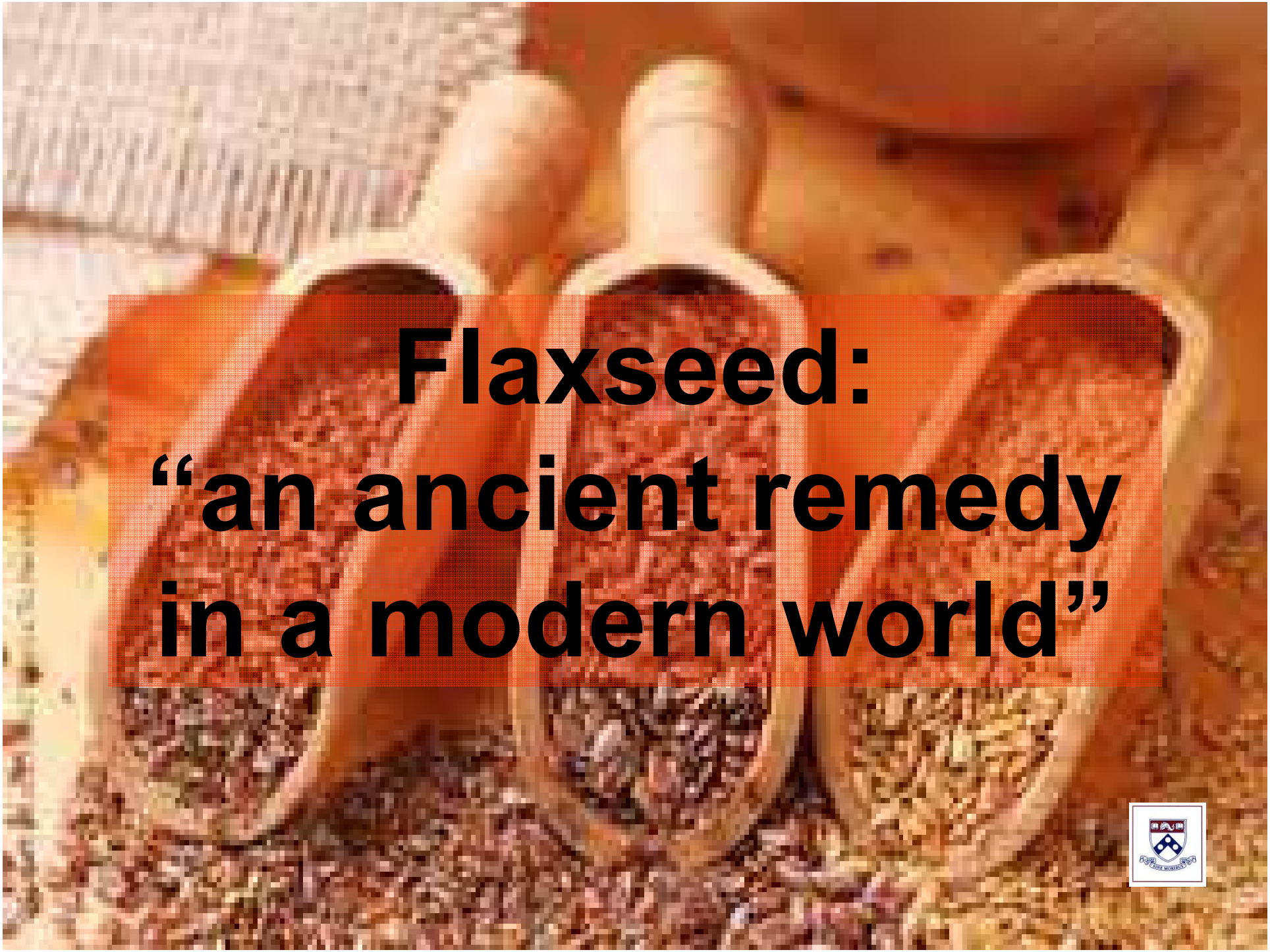


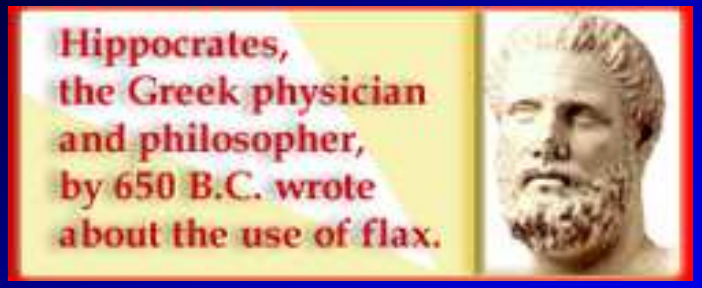
Lycopene

Delphinidin

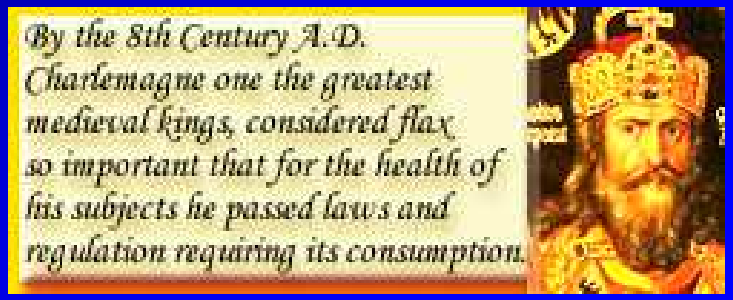


Sulforaphane


Flaxseed:
“an ancient remedy
in a modern world”



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.

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

FLAXSEED

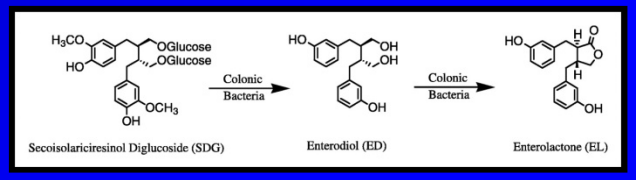
Plant Lignan Precursors

- Secoisolarisiresinol diglycoside (SDG)
- matairesinol

Intestinal Bacteria

Lignans

- Enterodiol (ED)
- Enterolactone (EL)



Biological Properties

***Antioxidative
Antiproliferative
Antiangiogenic
Estrogenic/Antiestrogenic

Omega-3 Fatty Acids

α-Linolenic Acid

EPA

(eicosapentanoic Acid)

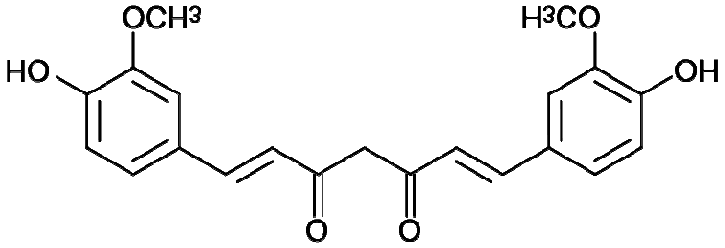
DHA

(Docosahexanoic Acid)

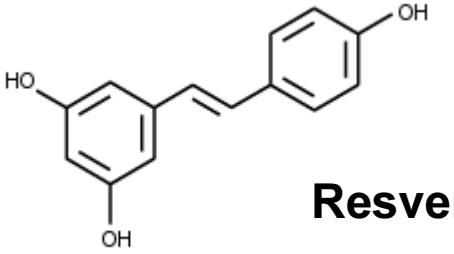
Cancer Protection

****Anti-inflammatory**

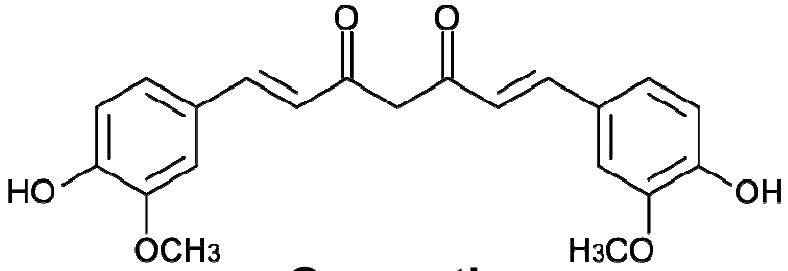
Flaxseed Lignan Structure



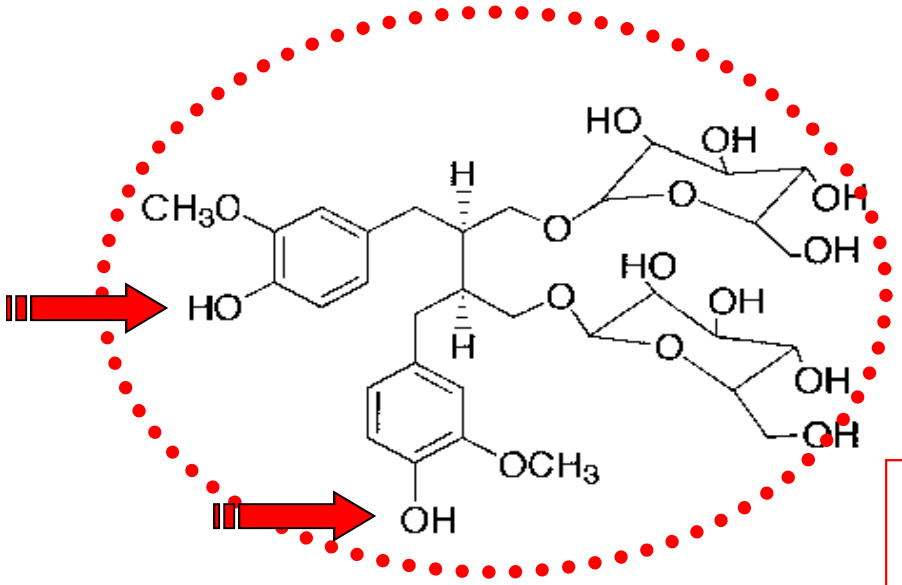
Curcumin



Resveratrol



Quercetin



Secoisolariciresinol diglucoside (SDG)

A bi-phenolic with potent antioxidant properties

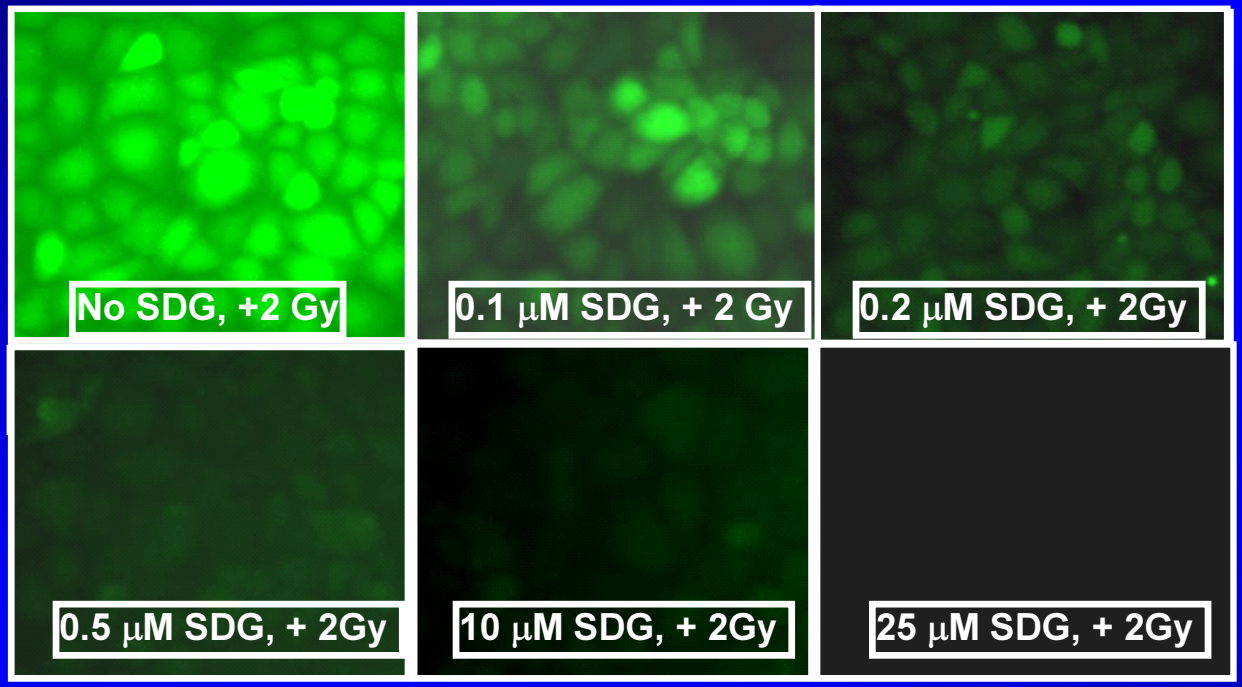
We Identified Flaxseed and its main Lignan (SDG) As A Potent Inhibitors Of Oxidative Lung Injury In Diverse Animal Models

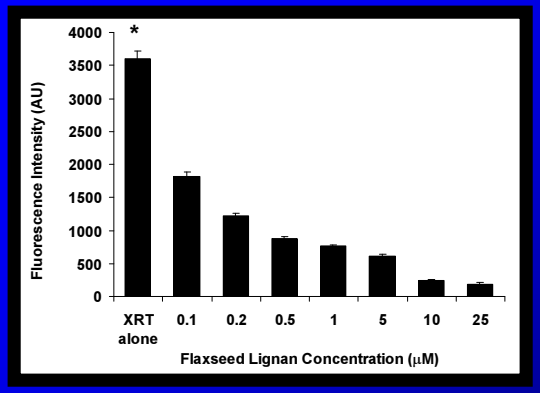
Protective Properties of Flaxseed in Preclinical Models of Cancer & Acute/Chronic Lung Damage

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

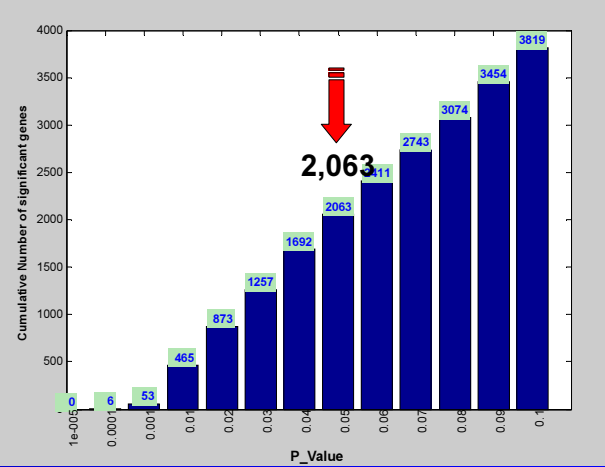




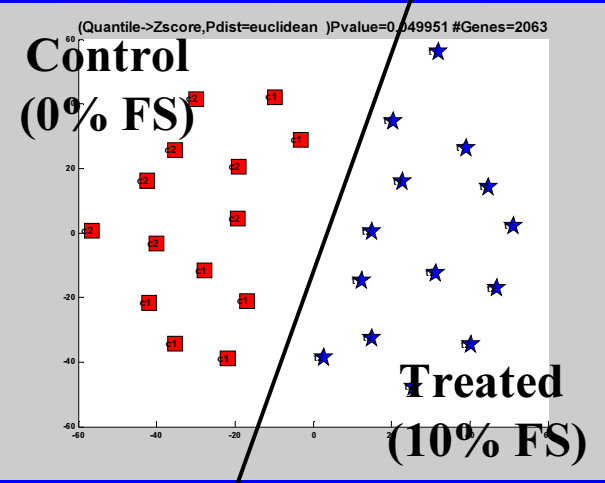
Lee et.al, 2009

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

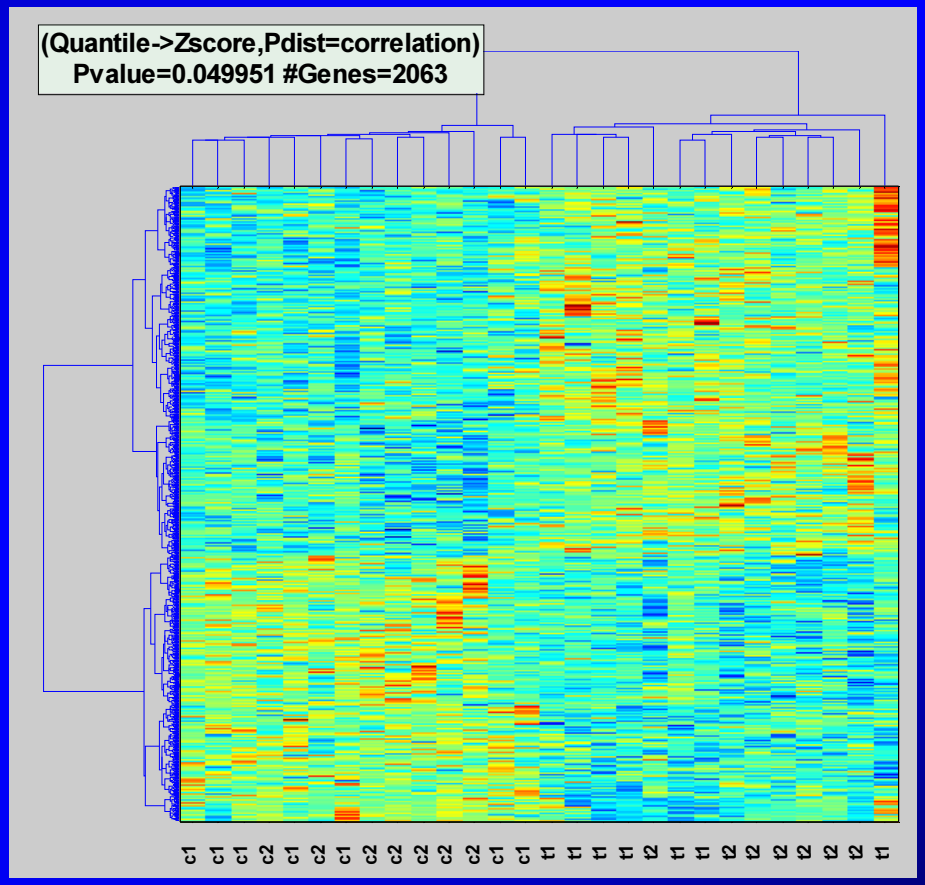
6.8% of all mouse genes in lung tissues are significantly modified by flaxseed



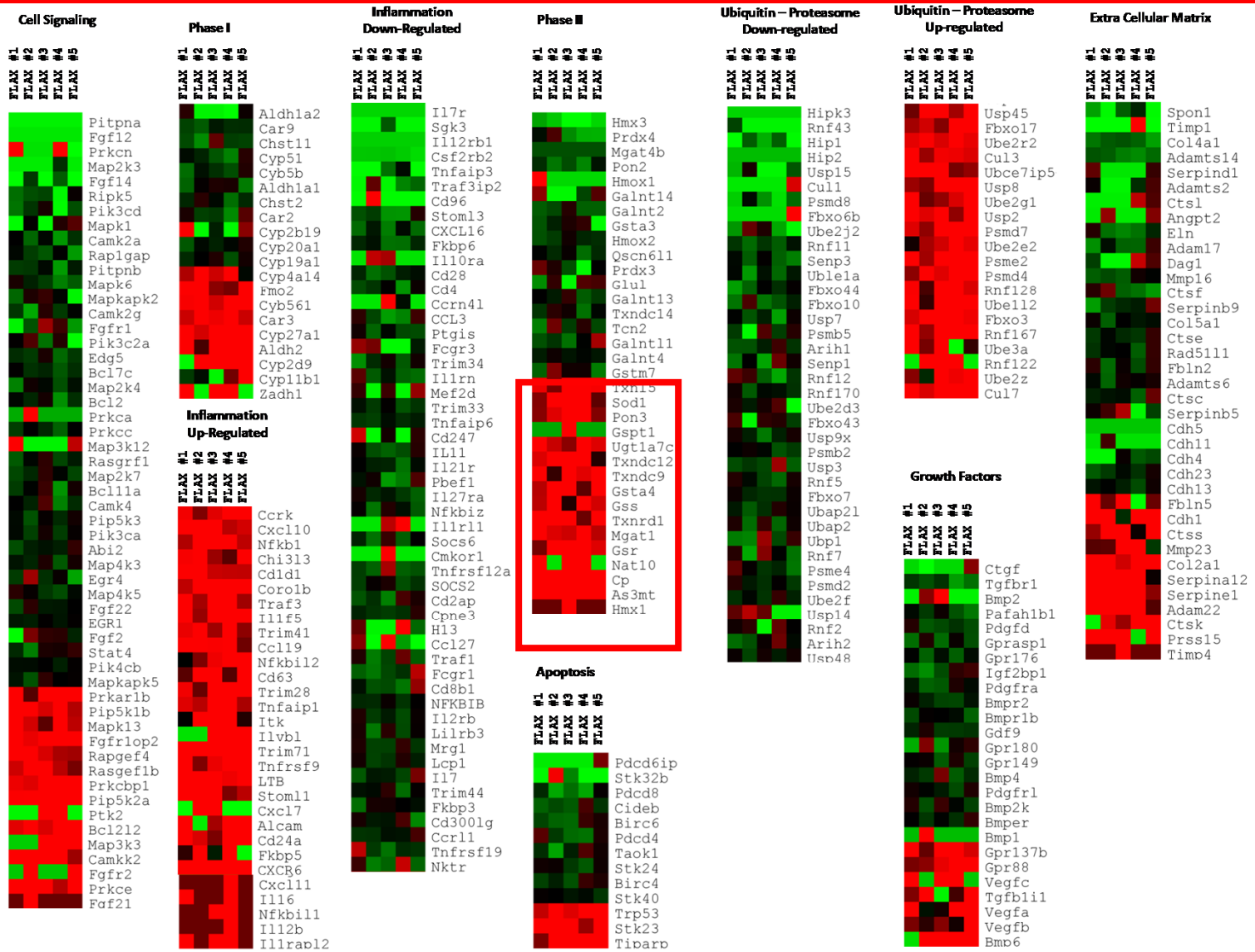
Principle Component Analysis



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



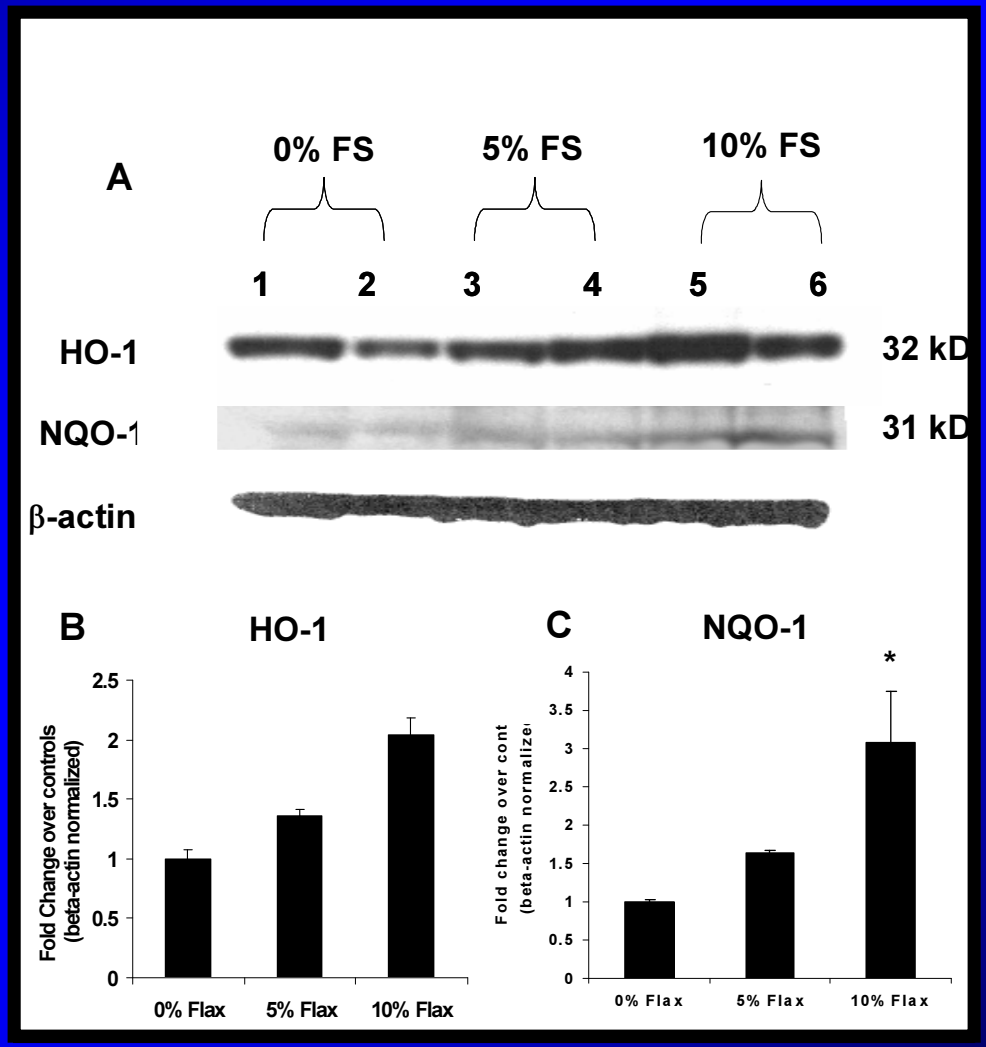
Red indicates up-regulation, green down-regulation

Dukes et.al, 2012

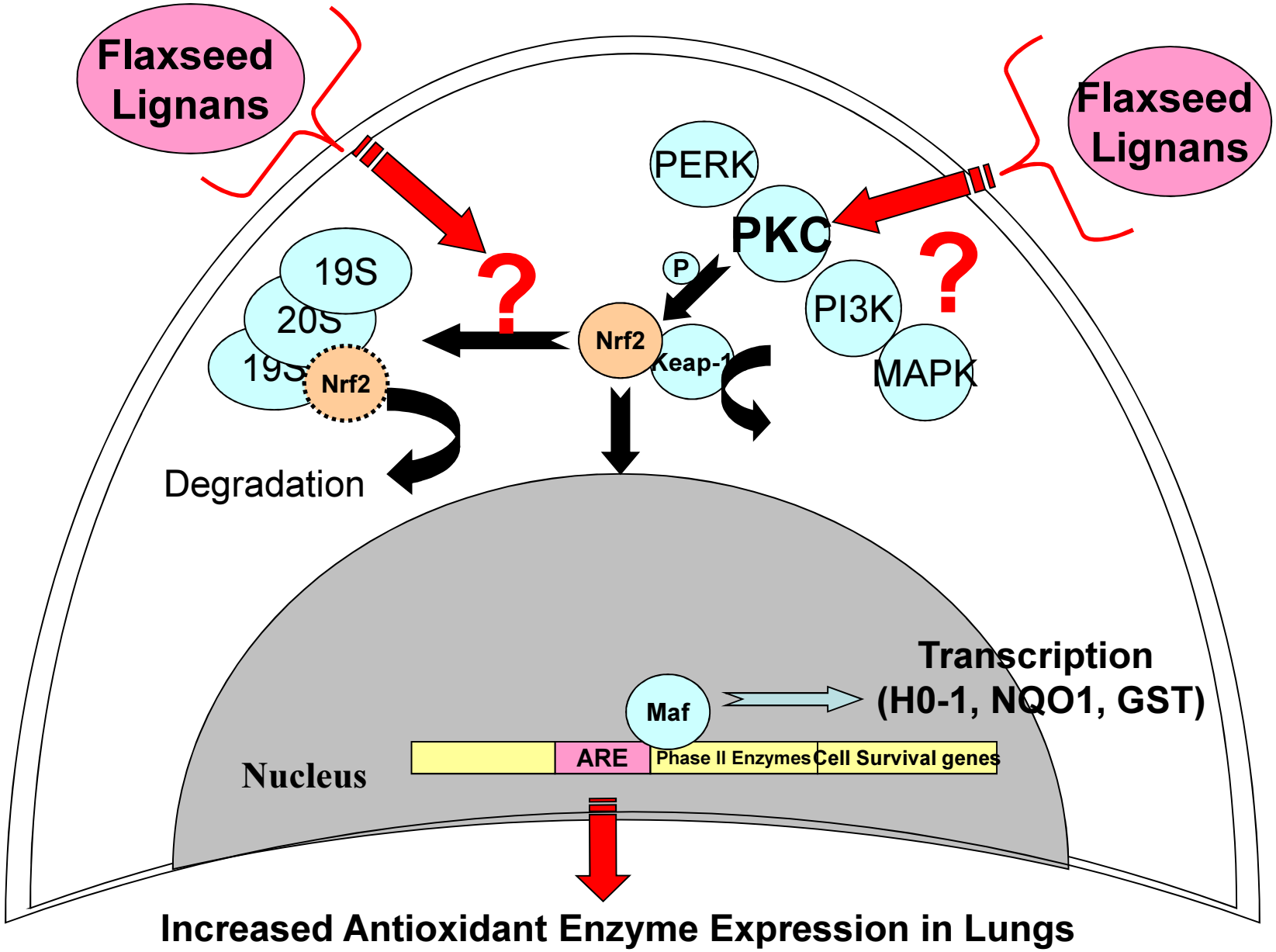
Flaxseed induces in lung dose-dependent expression of antioxidant enzymes

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



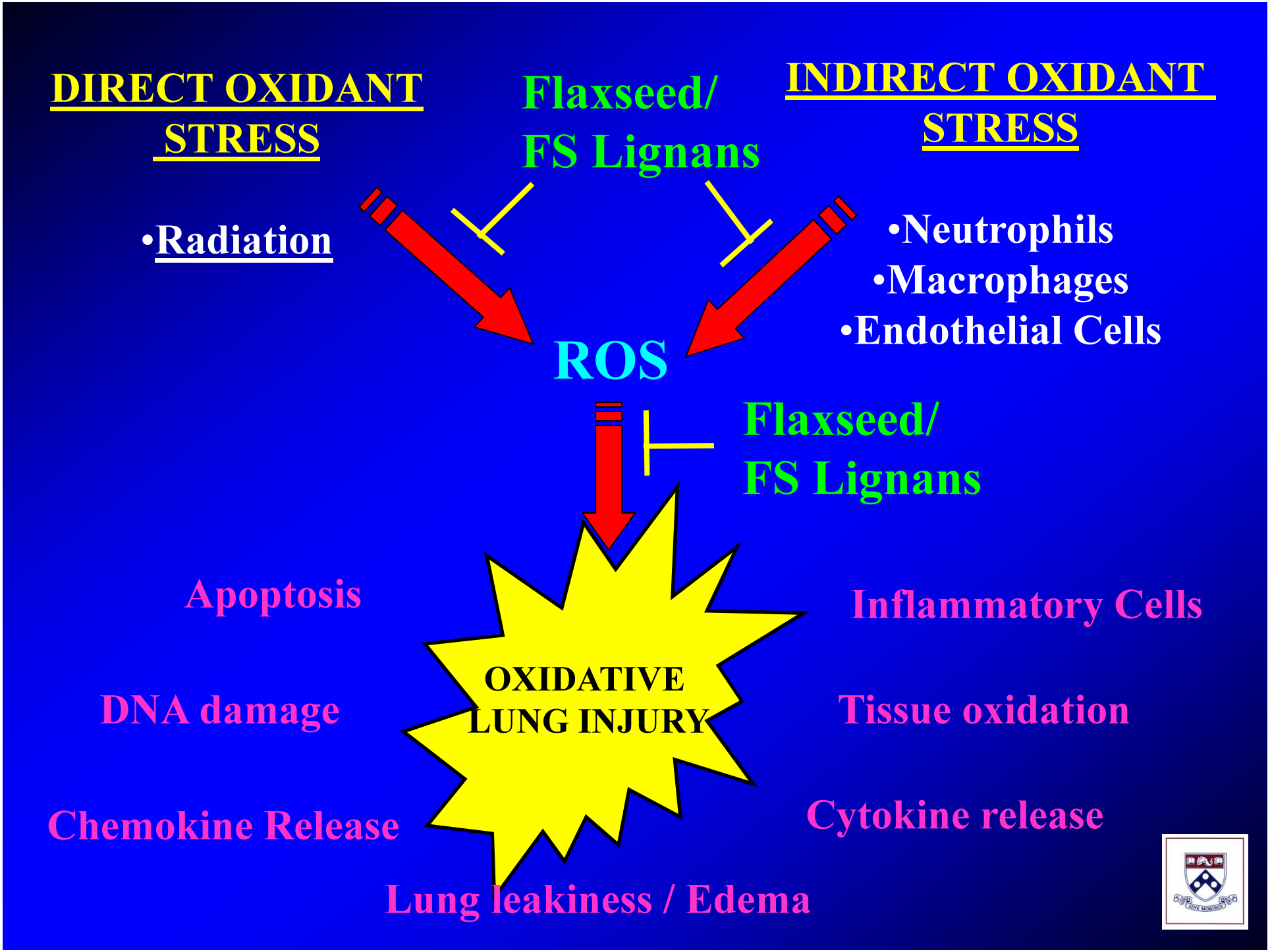
Lee et.al: Am J Physiol Lung Cell Mol Physiol. 2008;294(2):L255-65


Flaxseed Lignans
Flaxseed Lignans
PERK
PKC
P
19S
20S
19S
Nrf2
?
Nrf2
Keap-1
PI3K
MAPK
?
Degradation
Transcription
(H0-1, NQO1, GST)
Maf
Nucleus
ARE
Phase II Enzymes
Cell Survival genes
Increased Antioxidant Enzyme Expression in Lungs

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
Flaxseed/ FS Lignans
INDIRECT OXIDANT STRESS
•Radiation
•Neutrophils
•Macrophages
•Endothelial Cells
ROS
Flaxseed/ FS Lignans
Apoptosis
Inflammatory Cells
OXIDATIVE LUNG INJURY
DNA damage
Tissue oxidation
Chemokine Release
Cytokine release
Lung leakiness / Edema

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.

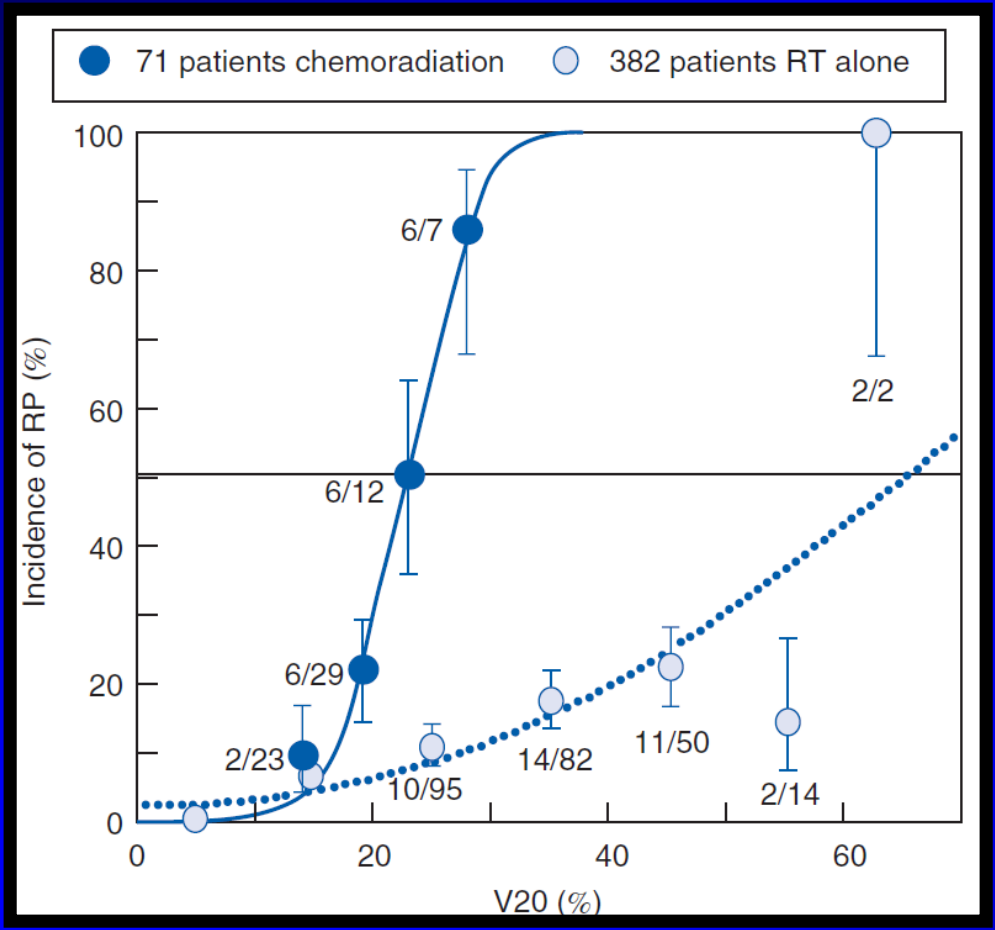
Radiation Damage to the Lung is characterized by:
A) Pneumonia-like symptoms (Inflammation)
B) Fibrotic lung damage (irreversible).

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) .

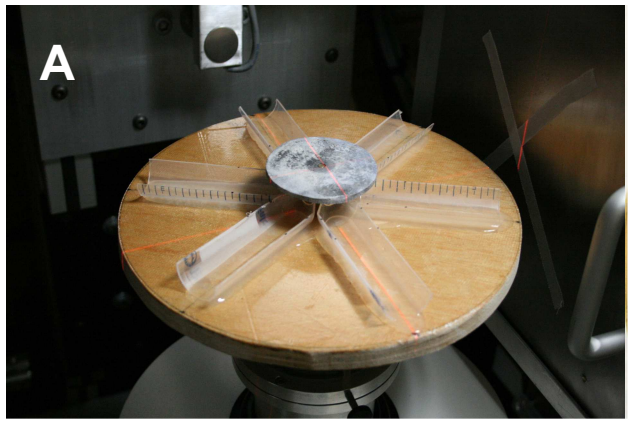
Patients receiving chemotherapy had a sharper increase in risk of radiation pneumonitis as the volume of normal lung exposed to 20 Gy increased.

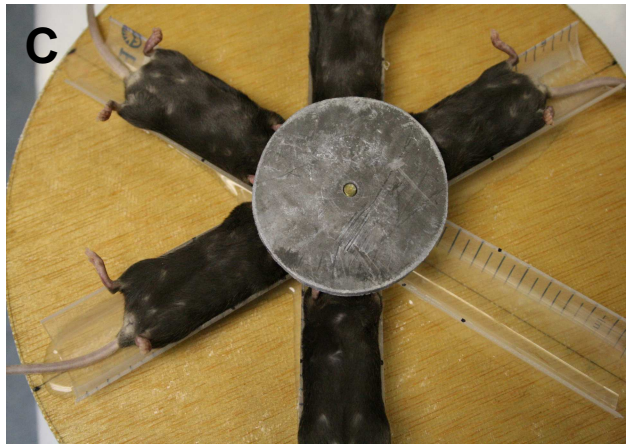
International Journal of Radiation Oncology, Biology, Physics 55(1): 110–115, 2005

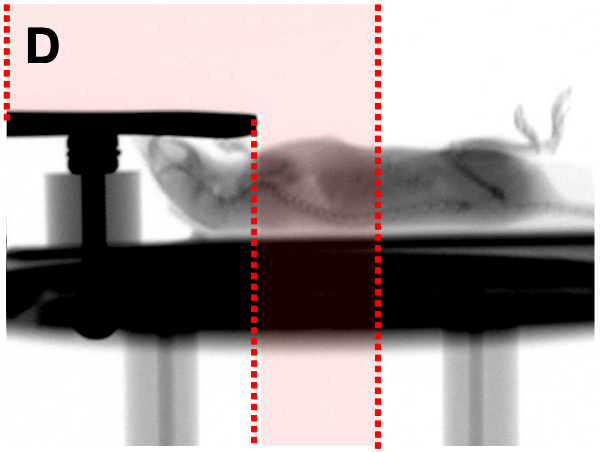
SARRP: Small Animal Radiation Research Platform

- 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 upmost accuracy, matching the clinical techniques used in oncology departments around the world

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







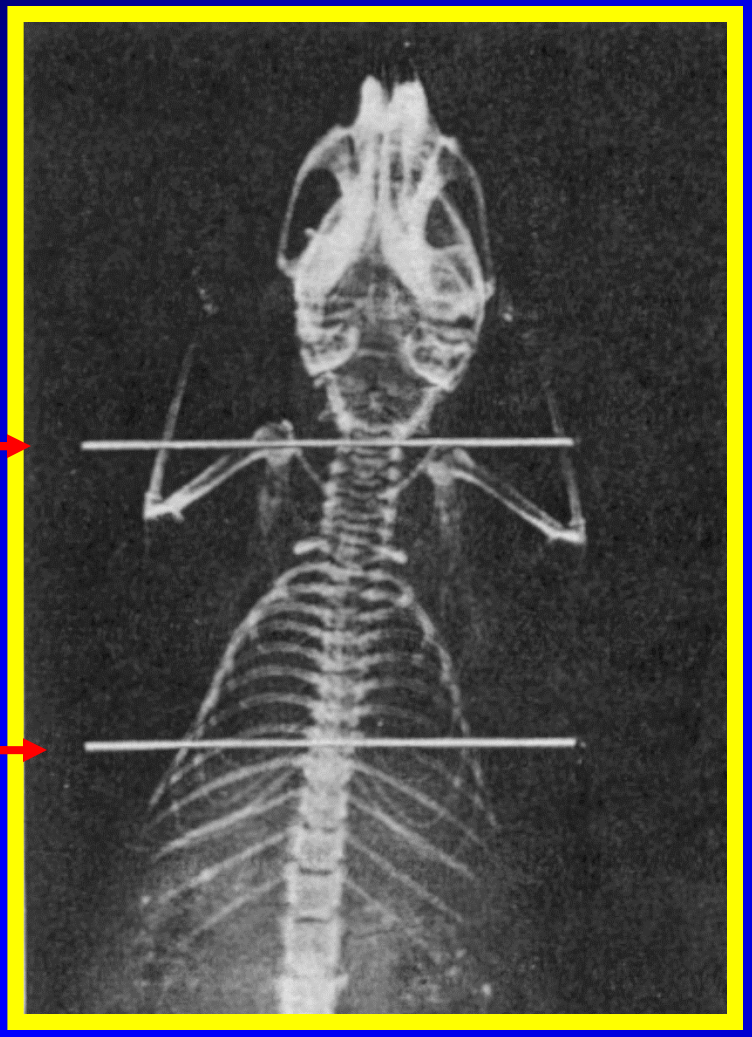
Use of the SARRP, to deliver a single fraction 13.5 Gy X-ray irradiation to the thorax.

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

Mouse Radiographs

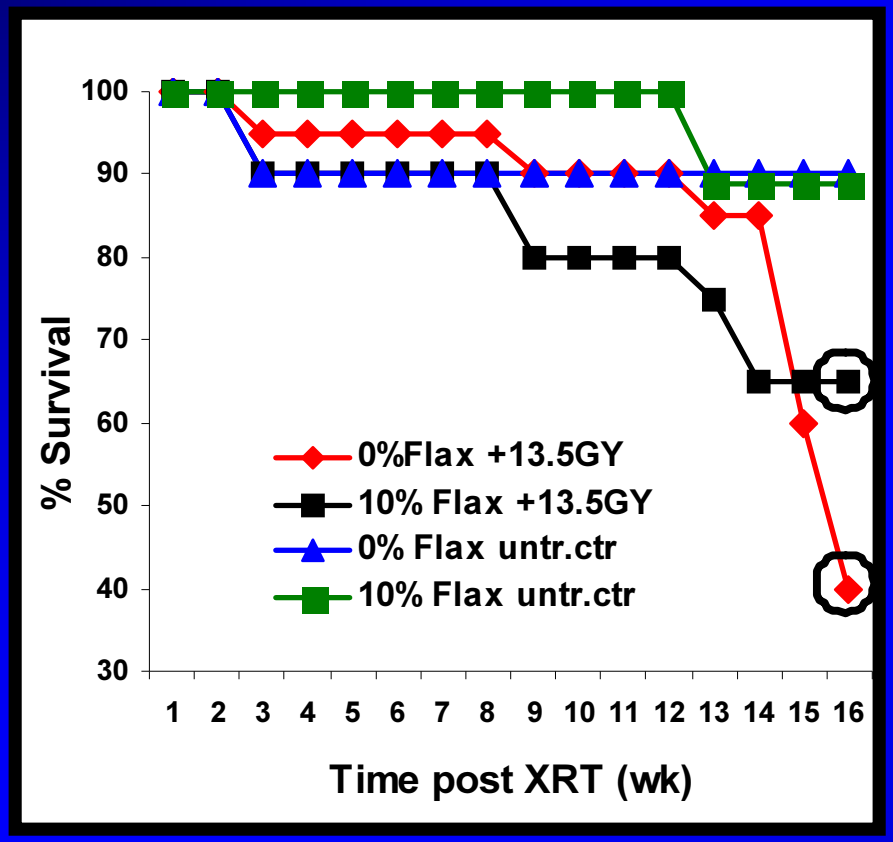
Cephalic margin

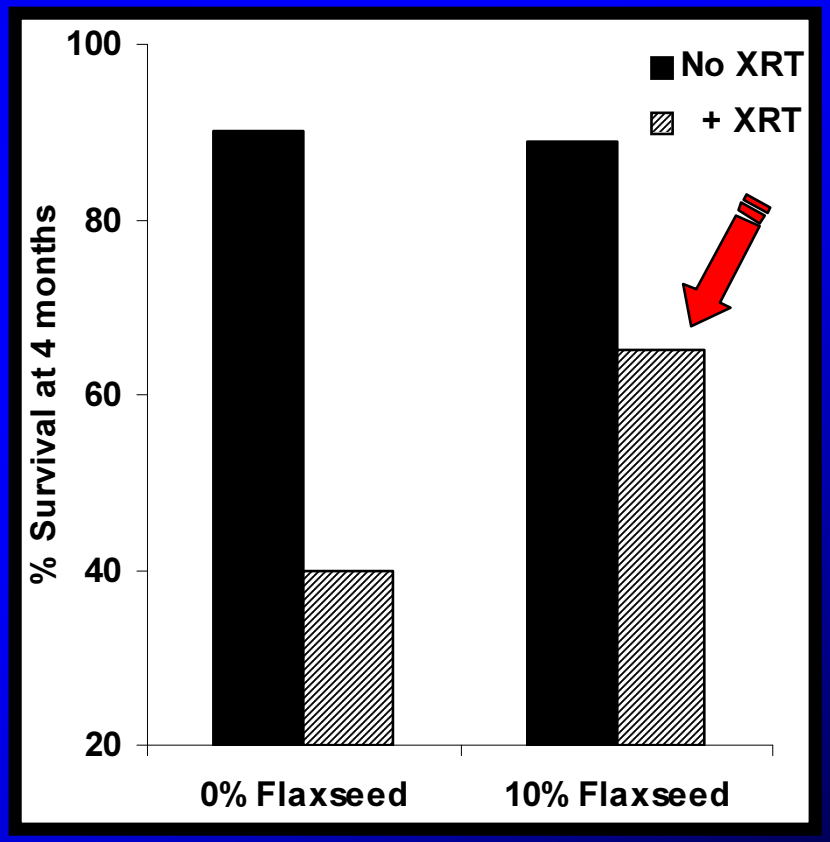
Caudal margin



(XRT=X-Ray Treatment)

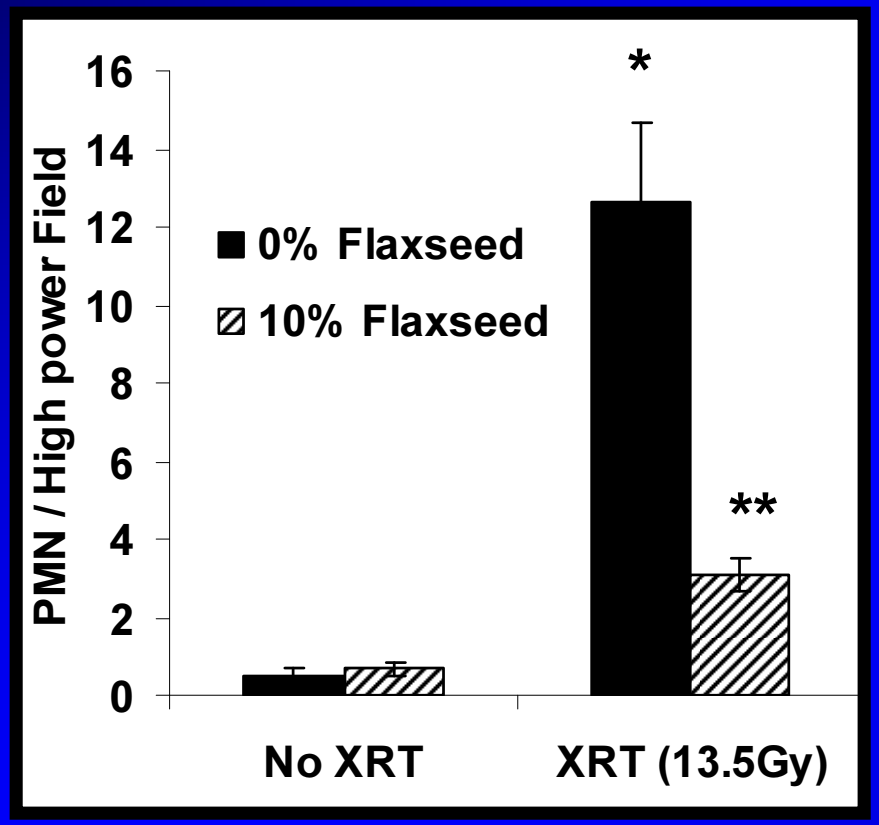
Flaxseed Improves Mouse Survival 4 Months Post Thoracic Irradiation



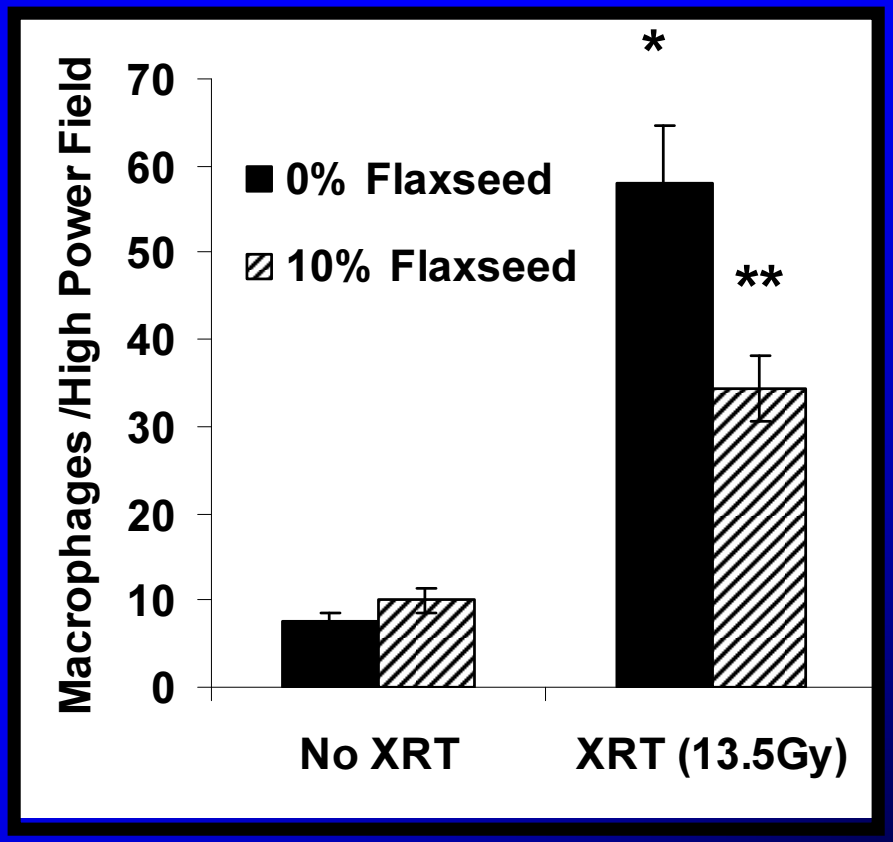


35% vs. 65% Survival for Control and Flaxseed-supplemented diets, respectively

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



Alveolar Neutrophils

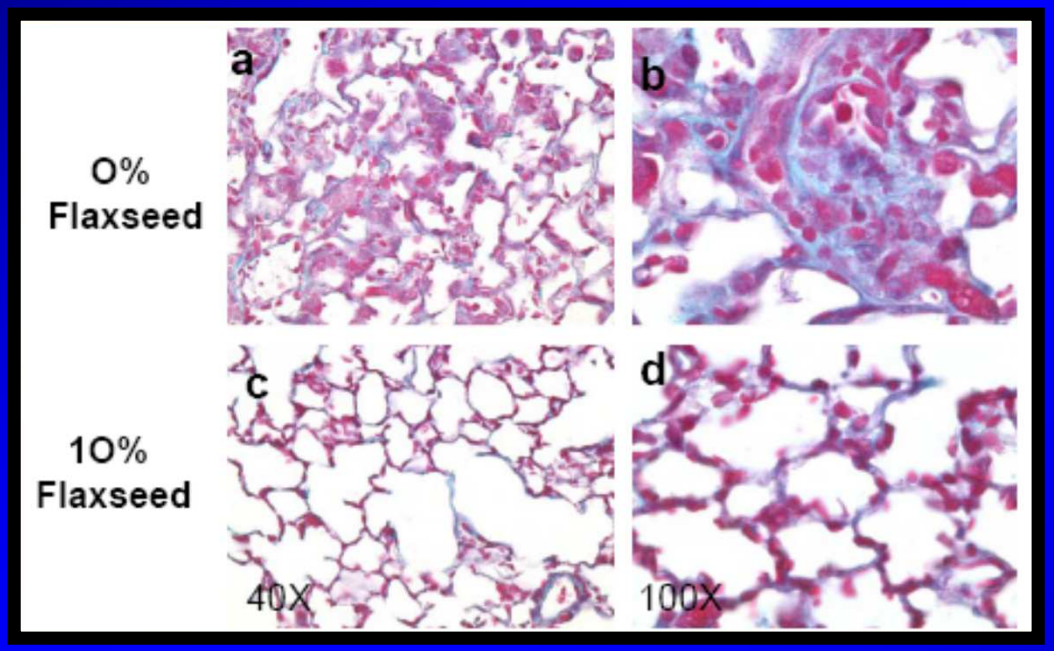


Alveolar Macrophages

Lee et.al, 2009

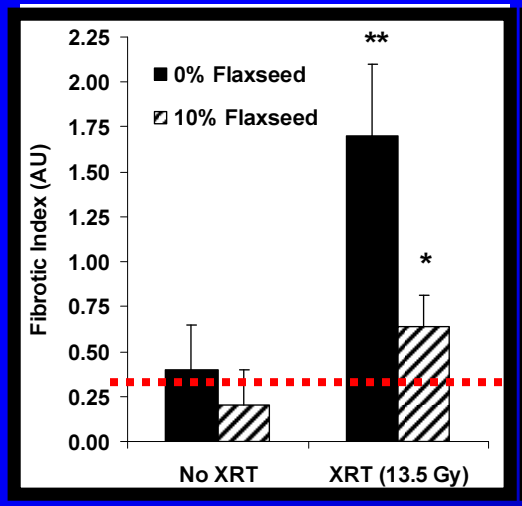
Antifibrotic Role of Flaxseed

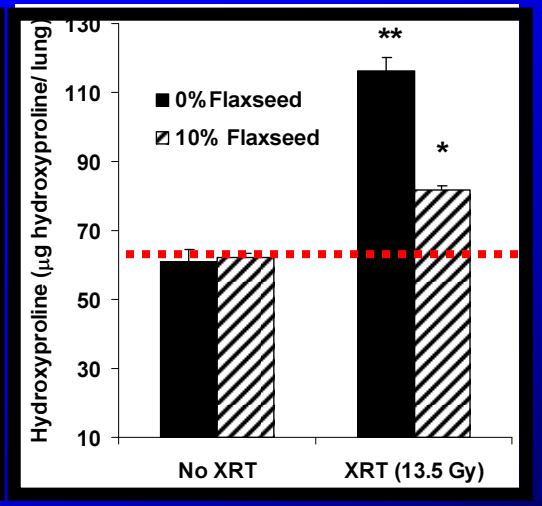
Flaxseed Decreased Radiation-Induced Collagen Deposition in Lungs



Trichrome Blue Staining for Collagen (Marker for Lung Fibrosis)

Fibrotic Index (Pathology)





OH-Proline Content

Cancer Biology and Therapy, 2009

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 atelactasis, 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 Prakarn, 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.[5]

Respirology (2012) 17, 66–71

"All the News That's Fit to Print"

The New York Times

Late Edition

Today, partly sunny, more seasonable, high 46. **Tonight**, clearing, seasonably cold, low 34. **Tomorrow**, sunny, milder in the afternoon, high 51. Weather map is on Page D12.

VOL. CLX . . No. 55,344 © 2011 The New York Times NEW YORK, MONDAY, MARCH 14, 2011 $2.00

JAPAN REELS AS TOLL RISES AND NUCLEAR RISKS LOOM

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

ANOTHER EXPLOSION

Radioactive Steam May

Released From

for Wee

CHICAGO SU

LATE SPORTS FINAL | FRIDAY, MARCH

NUCLEAR CRISIS IN JAPAN

STRUGGLE MAY TAKE WEEKS

Damage at the Fukushima nuclear complex on Thursday. | AP

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

NUCLEAR CRISIS GROWS

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

NIH 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

- Research Program
- Resources
- Funding
- Meetings and Publications

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

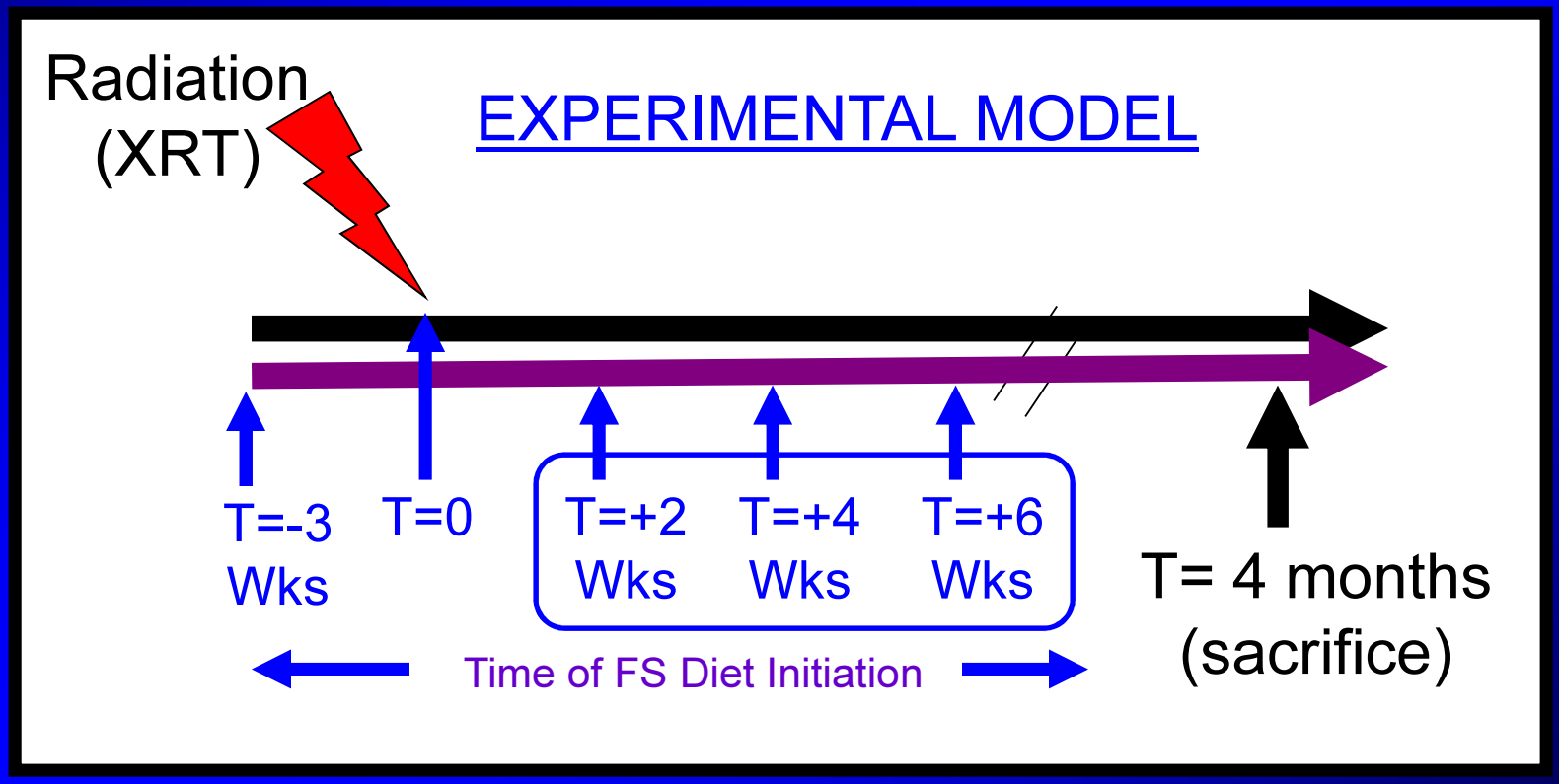
Related Links

Division of Allergy, Immunology, and Transplantation (DAIT)

Biodefense and Related

Mitigation of Radiation Pneumonopathy by Wholegrain Flaxseed

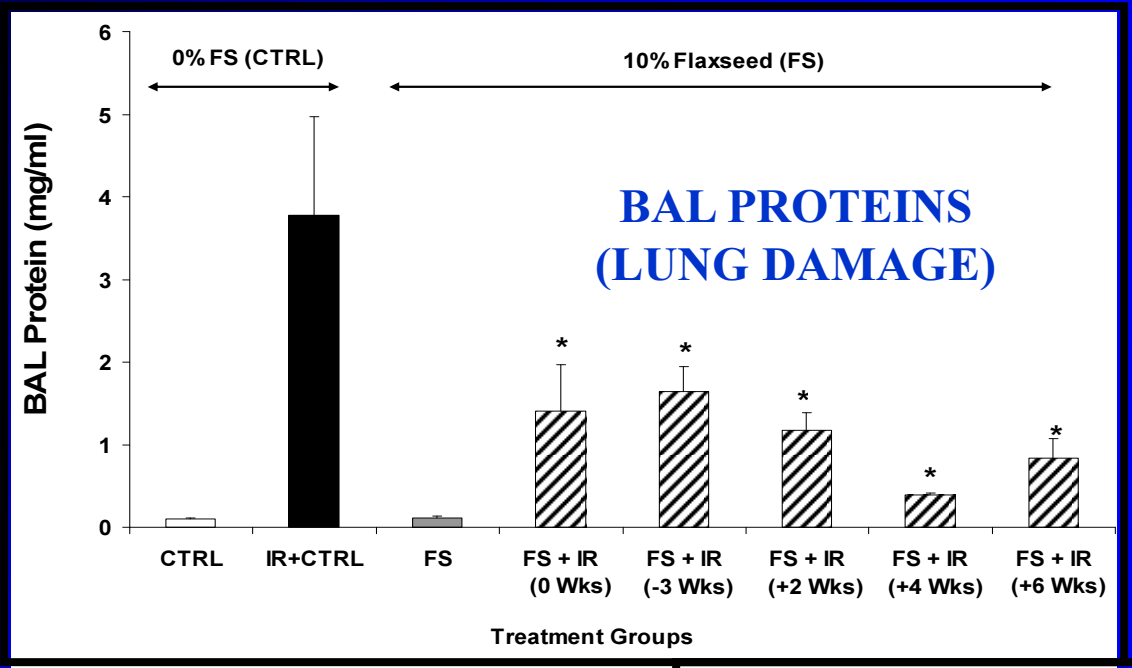
GOAL: Determine whether Flaxseed (FS) attenuates lung toxicity and lethality related to thoracic radiation (external exposure to ionizing radiation)



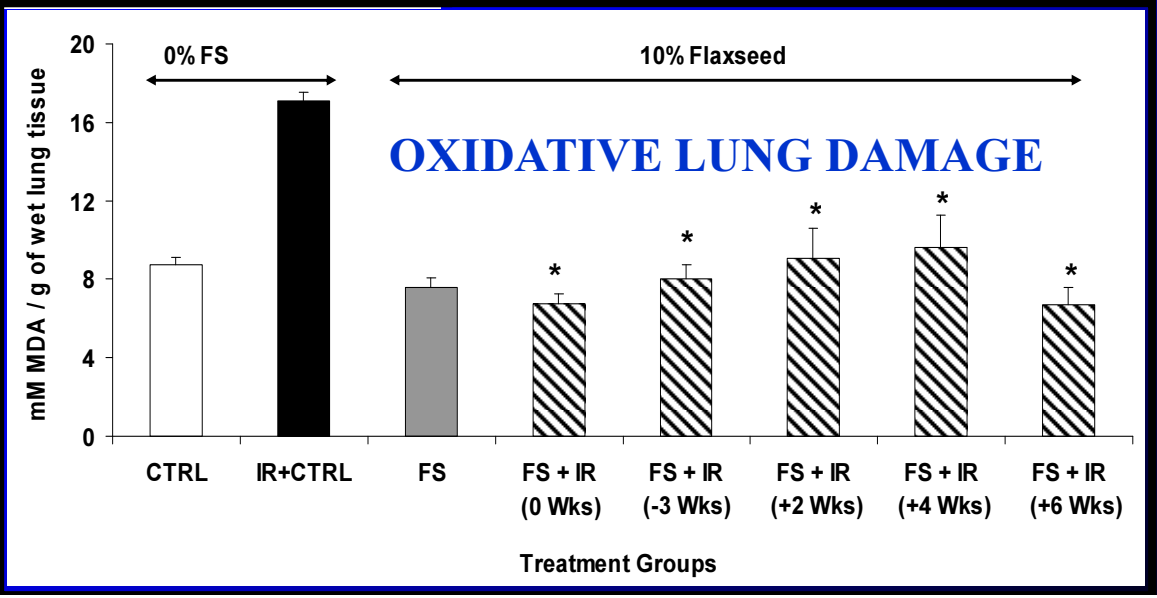
Separate mouse cohorts for each time-point

Christofidou-Solomidou, BMC Cancer, 2011

Mitigation of Radiation Damage by Flaxseed

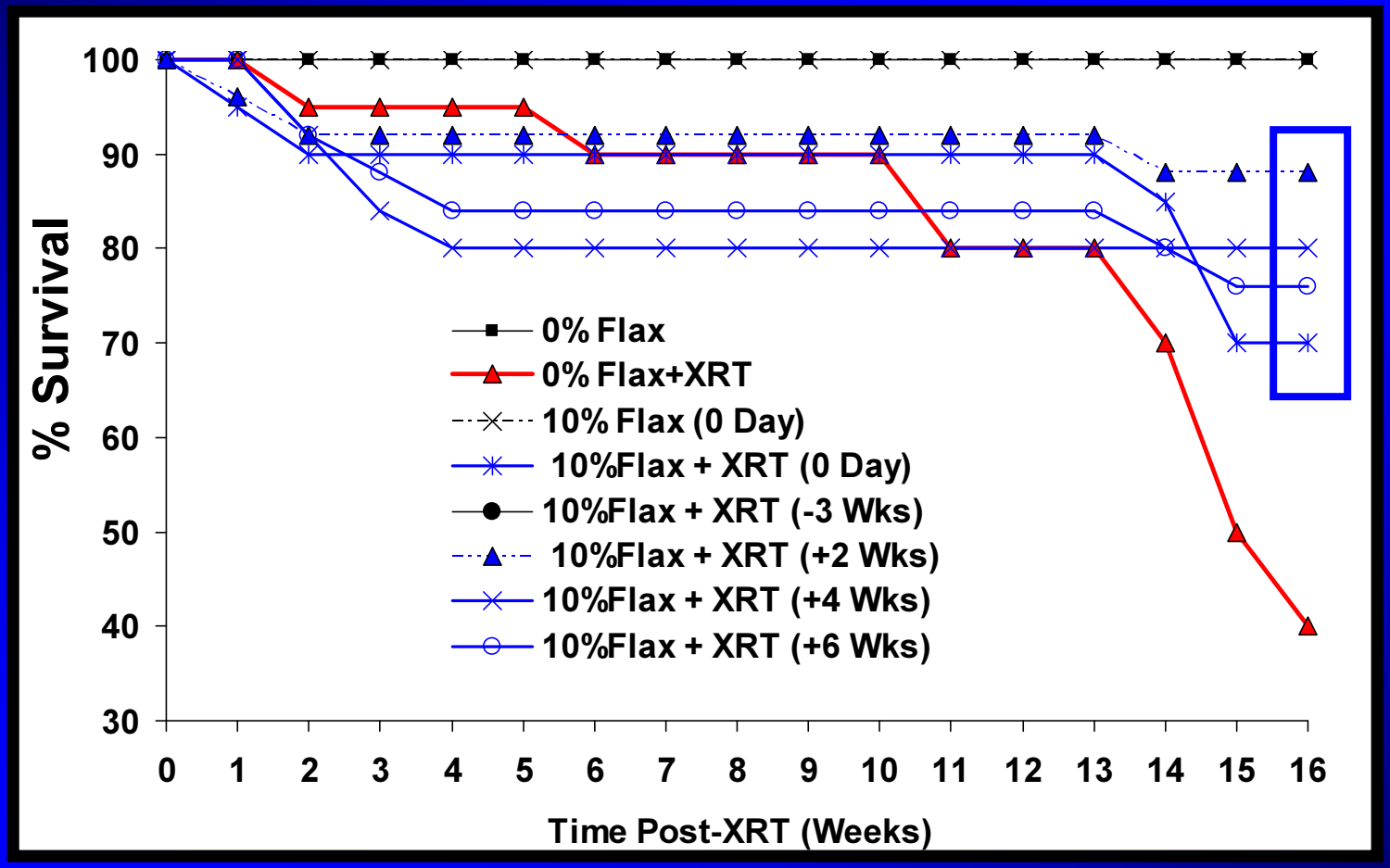


Administering flaxseed 2,4,6 weeks POST radiation exposure is still protective from radiation damage



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

Christofidou-Solomidou, BMC Cancer, 2011

Mitigation of Radiation Damage by Dietary Flaxseed

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

BMC Cancer

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 Tyagi[1], Kay-See Tan[2], Sarah Hagan[3], Ralph Pietrofesa[1], Floyd Dukes[1], Evguenia Arguiri[1], Daniel F Heitjan[2], Charalambos C Solomides[4] and Keith A Cengel[3]

Christofidou-Solomidou, BMC Cancer, 2011

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Flaxseed Might Protect Against Death From Radiation

Published August 12, 2011 | MyHealthNewsDaily

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Flaxseed may protect a
damaging effects of radi
from a terrorist's dirty bo
cancer treatment, a new
suggests.

Mice that ate flaxseed e
up to six weeks after rec
radiation dose to the ch
likely to survive and hac

GRAINNET

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TRANSPORTATION

University of Pennsylvania Study Finds Flaxseed Protects Against Radiation

Date Posted: August 15, 2011

Philidelphia—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
Your source for the latest research news

Web address:
http://www.sciencedaily.com/releases/2011/08/110809111821.htm

Print this page

Flaxseed May Be Effective in Protecting Against Harmful Effects of Radiation

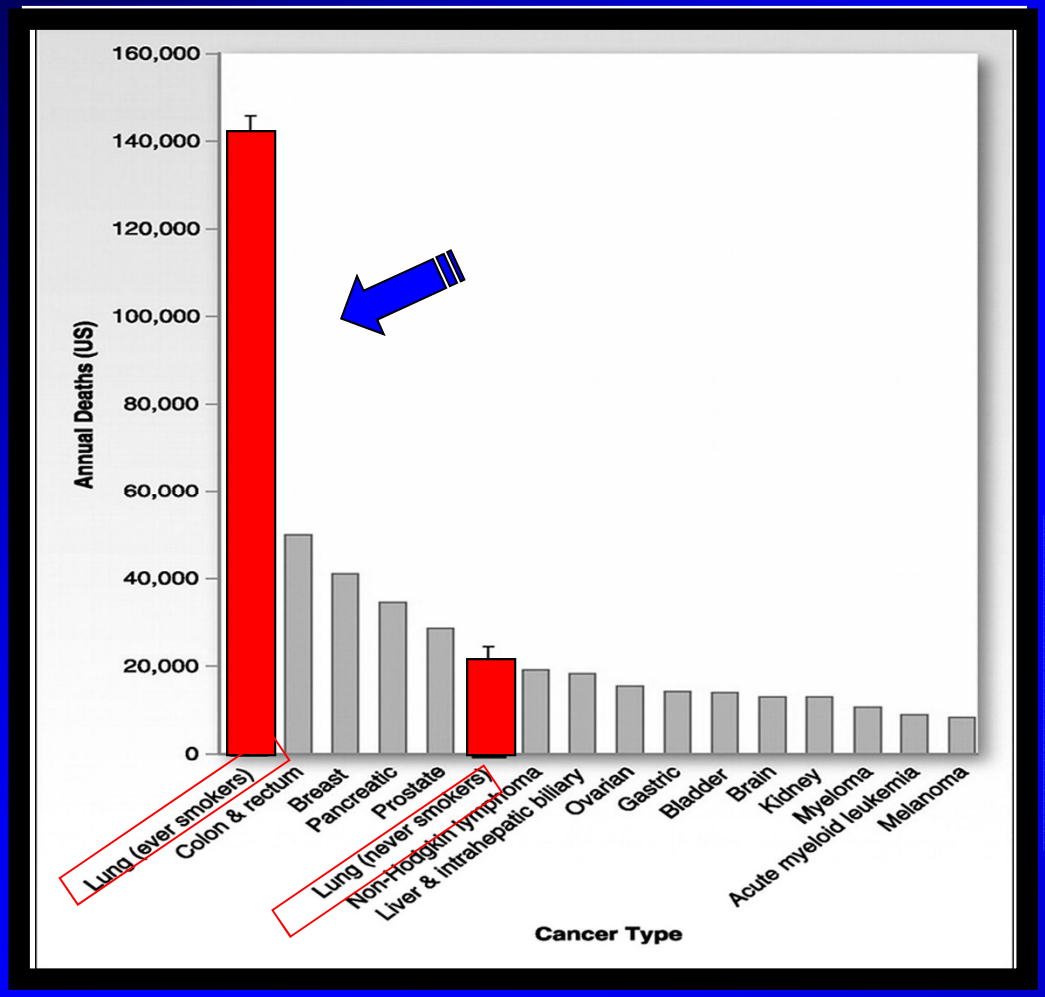
ScienceDaily (Aug. 9, 2011) — Flax has been part of human history for well over 30,000 years, used for weaving cloth, feeding people and animals, and even making paint. Now, researchers from the Perelman School of Medicine

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.**

Clinics In Chest Medicine 2011; 32:605-644
(DOI:10.1016/j.ccm.2011.09.001)-Copyright © 2011 Elsevier Inc.

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

5 Mo

9 Mo

Months 1-5

4 Months Recovery)

Sacrifice Mice
Evaluate tumor burden

Collecting and mixing chamber for rodent exposure studies

Microprocessor-controlled cigarette smoking machine

Alternative: Purified TobaccoCarcinogen(s)

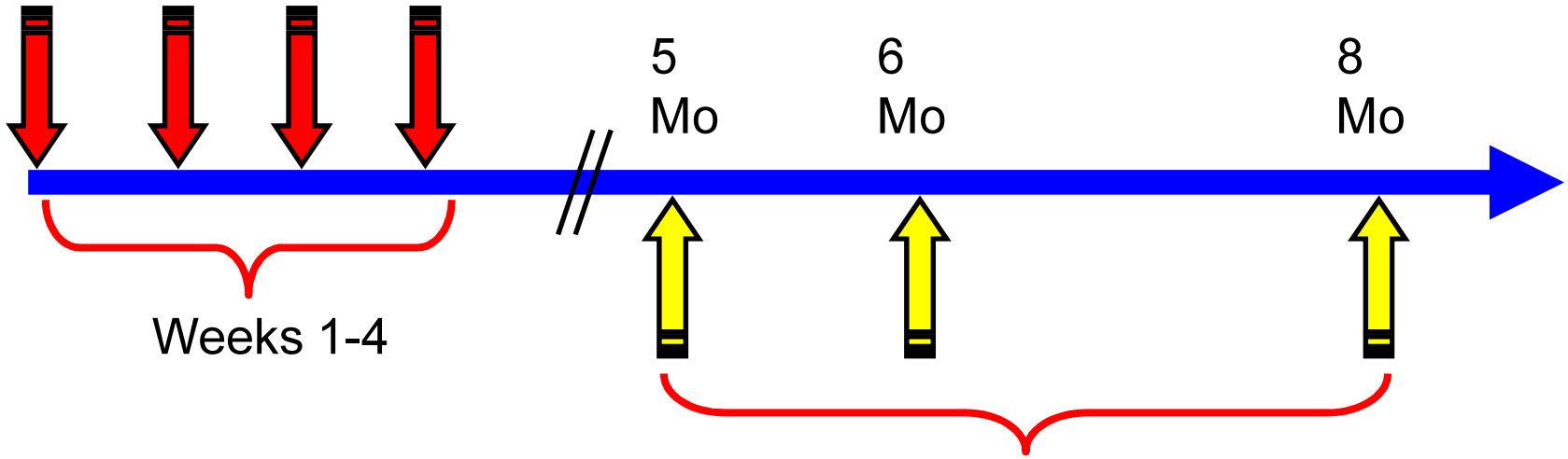
1. Benzo-alpha pyrene (B[α]P)
2. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
3. Dimethylbenz(a)anthracene (DMBA)
4. Urethane

•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).

Benzo[a]pyrene (BaP) (-)-(7*S*,8*R*,9*R*,10*S*)-DE-2 (+)-(7*R*,8*S*,9*S*,10*R*)-DE-2

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

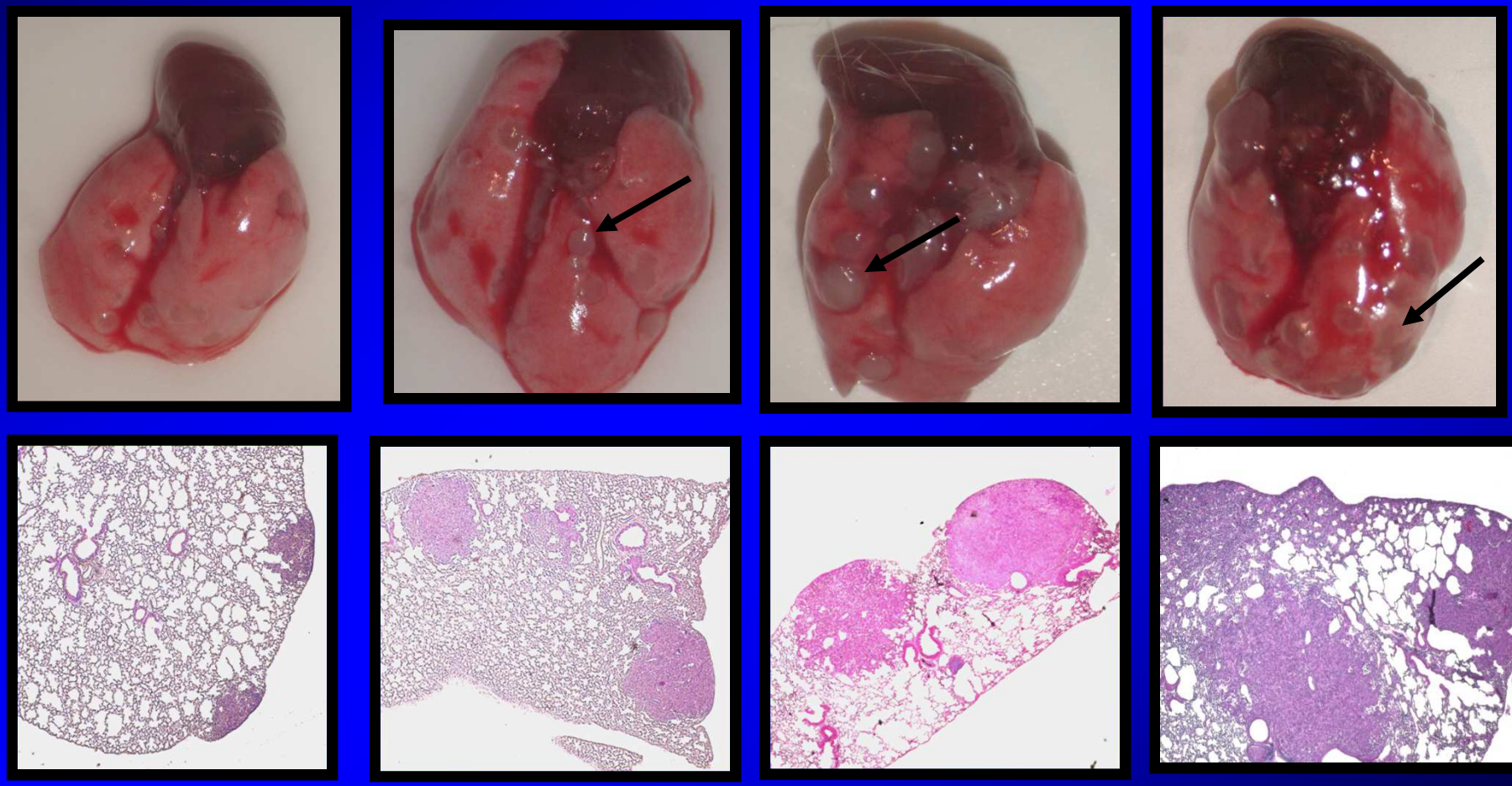
Weekly
i.p injections of
B[*a*]P (1 mg/mouse)



Sacrifice Mice
Evaluate tumor burden

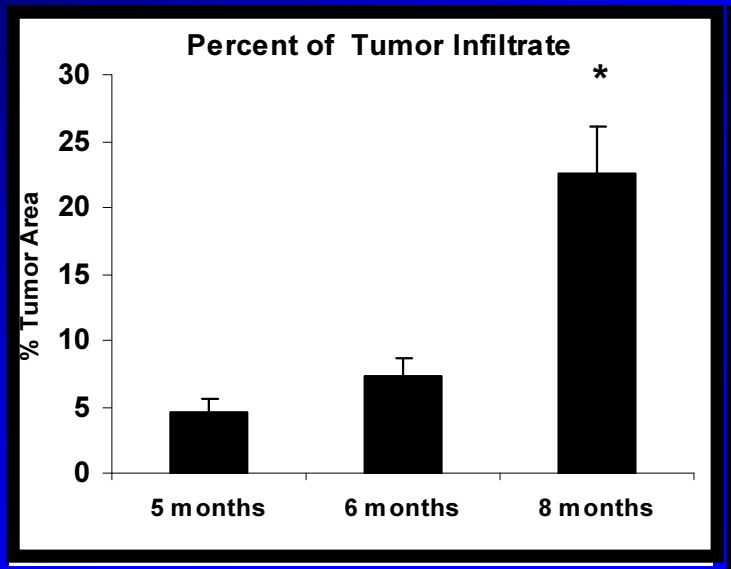
Use of an inbred mouse strain (A/J) with increased sensitivity to chemical carcinogen-induced lung carcinogenesis

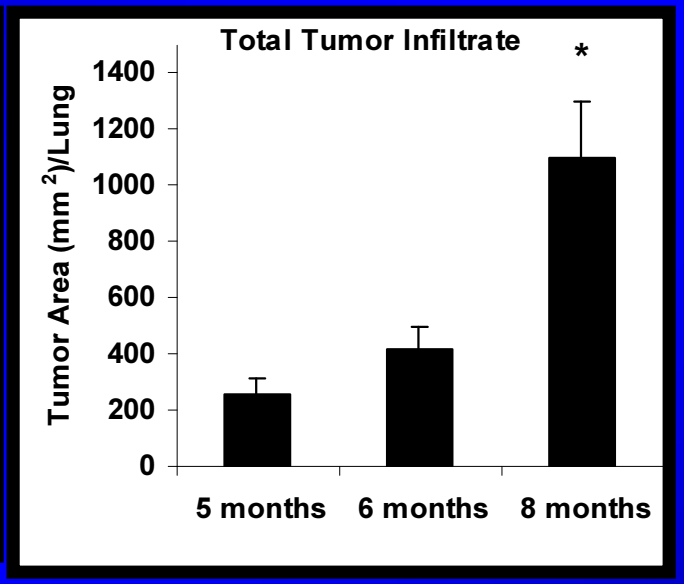
Histological Detection of Lung Tumor Nodules in Mice Exposed to B[α]P

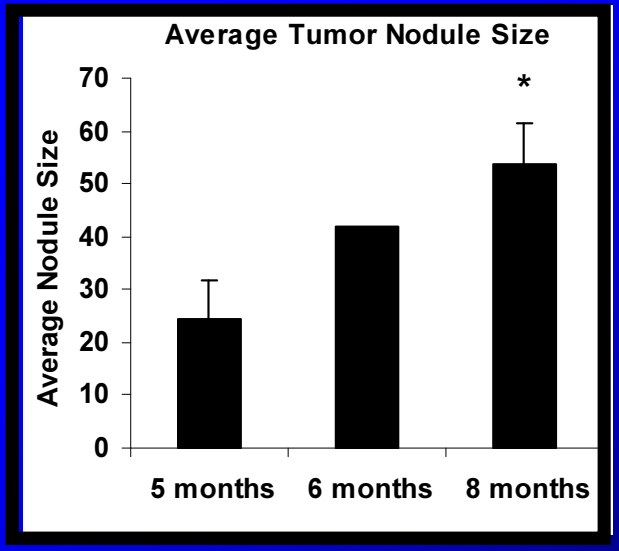


4 Months | 5 Months | 6 Months | 8 Months

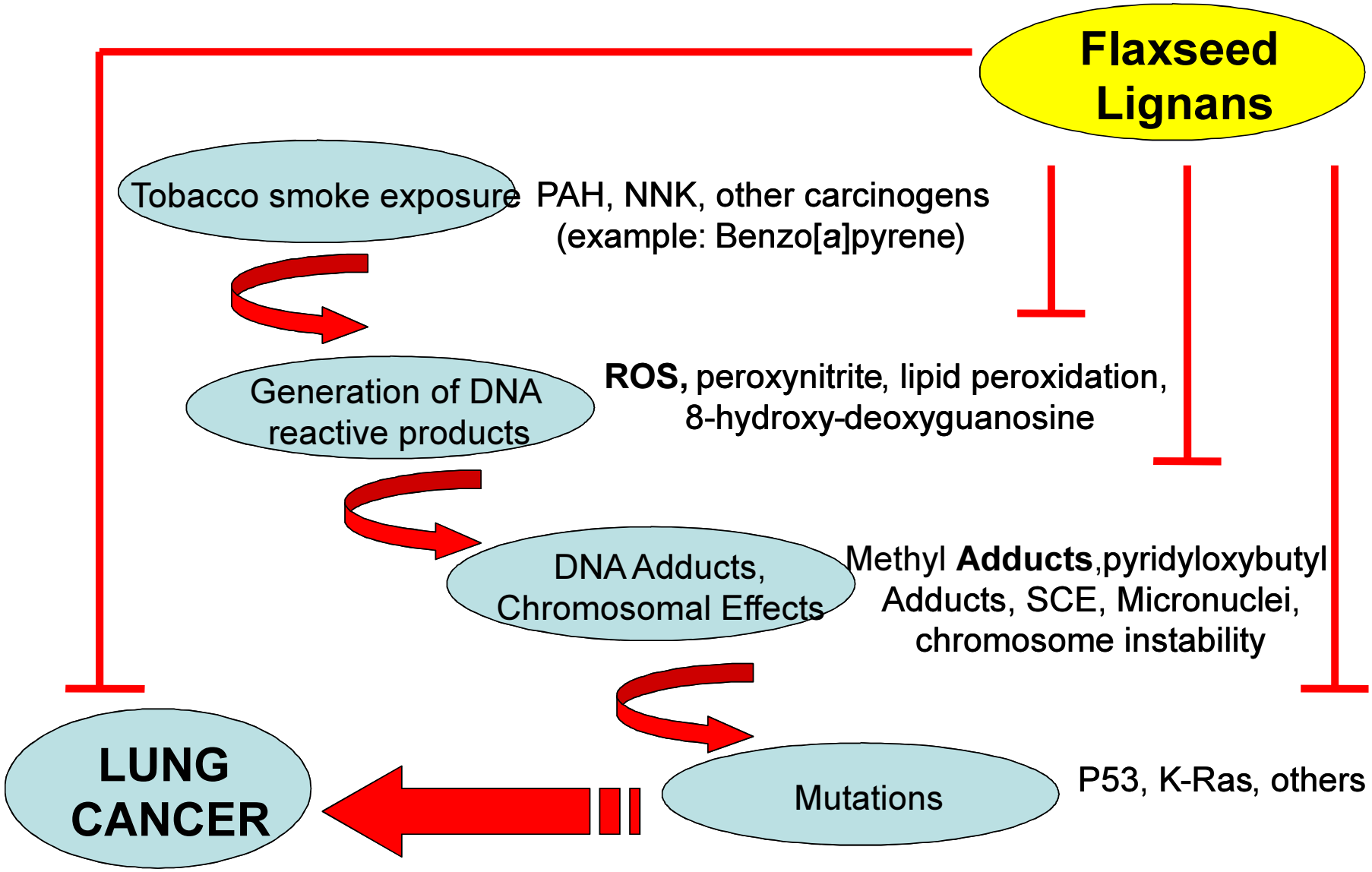
BENZO[*a*]PYRENE-CHEMICAL CARCINOGENESIS MODEL







Tumor Morphometry / Image Analysis System

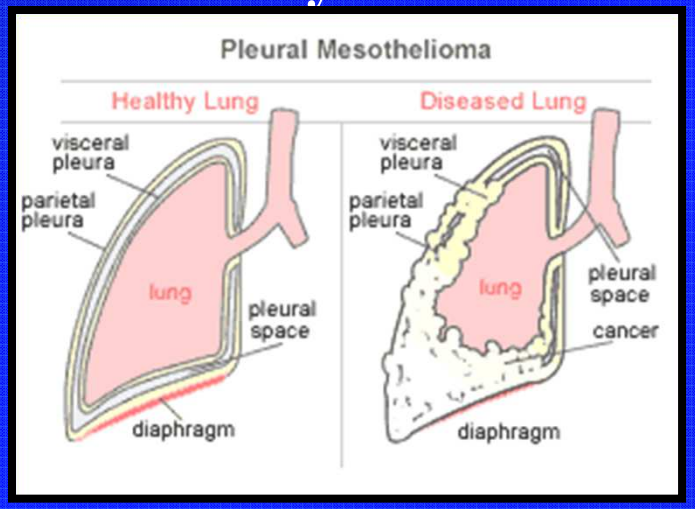


Adapted from Hecht, 1999

ASBESTOS EXPOSURE

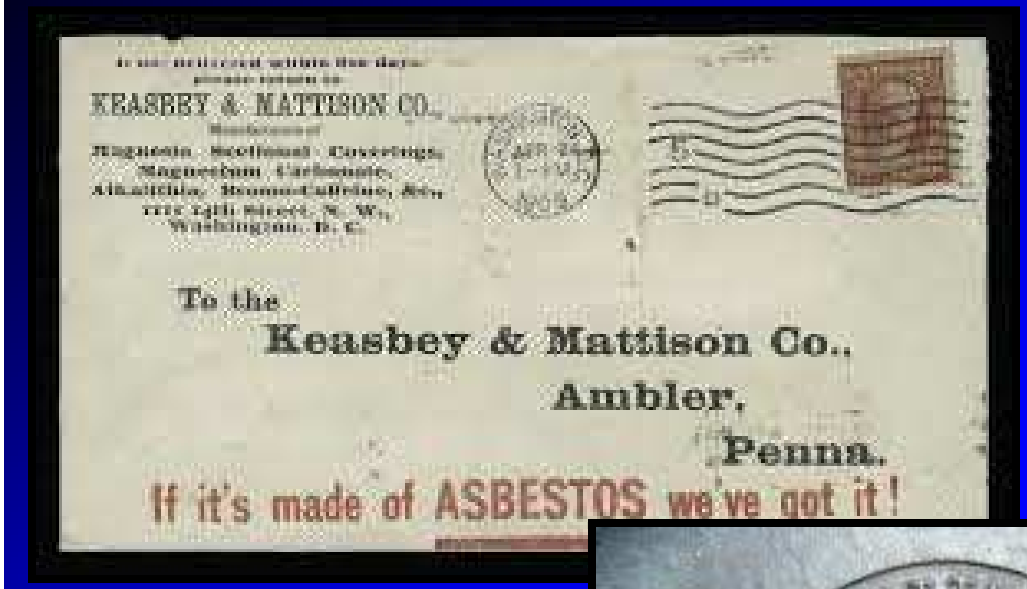
Asbestos Exposure and Malignant Mesothelioma

- 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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Keasbey & Mattison Co.,
Ambler,
Penna.
If it's made of ASBESTOS we've got it!


KEASBEY & MATTISON COMPANY
AMBLER
ASBESTOS


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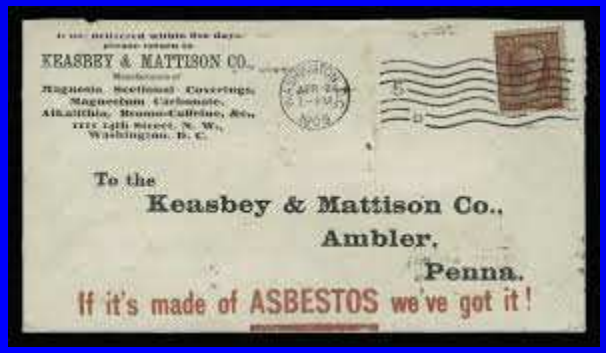
University of Pennsylvania receives $10M to study Superfund asbestos site

July 11, 2014 9:52 AM

By HEATHER ISRINGHAUSEN GVILLO

PHILADELPHIA (Legal Newsline) – Researchers with the U
million grant to study asbestos and how the toxic fiber leads
America's 10 Superfund sites.

The grant, which came from the National Institute of Environ
to help researchers from the school's Center of Excellence in
Perelman School of Medicine to study asbestos, mesotheliom
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.

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

View and purchase photos

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.

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

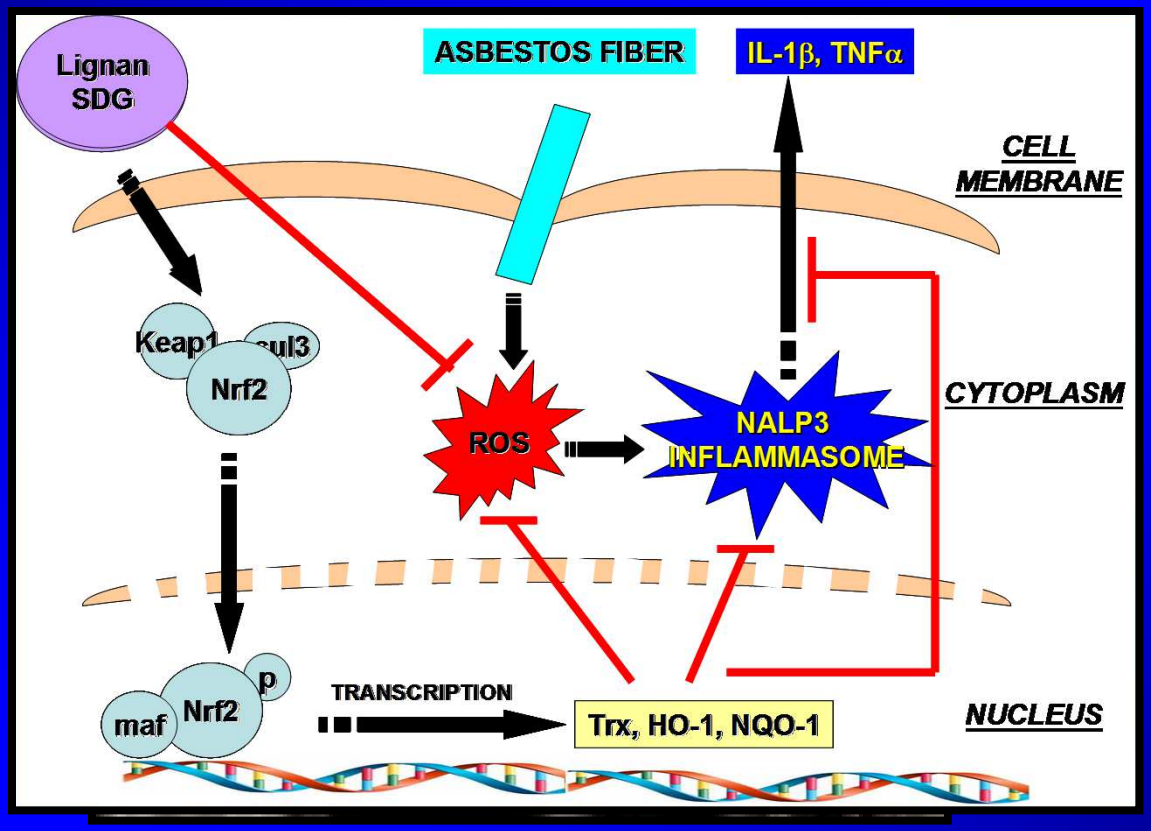
1. Can we remediate asbestos without moving it from the original disposal site?
2. What do we know about the fate and transport of asbestos in the environment by water and air?
3. What do we know about the exposure pathways that were responsible for the mesothelioma cluster in Ambler? And why is the 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

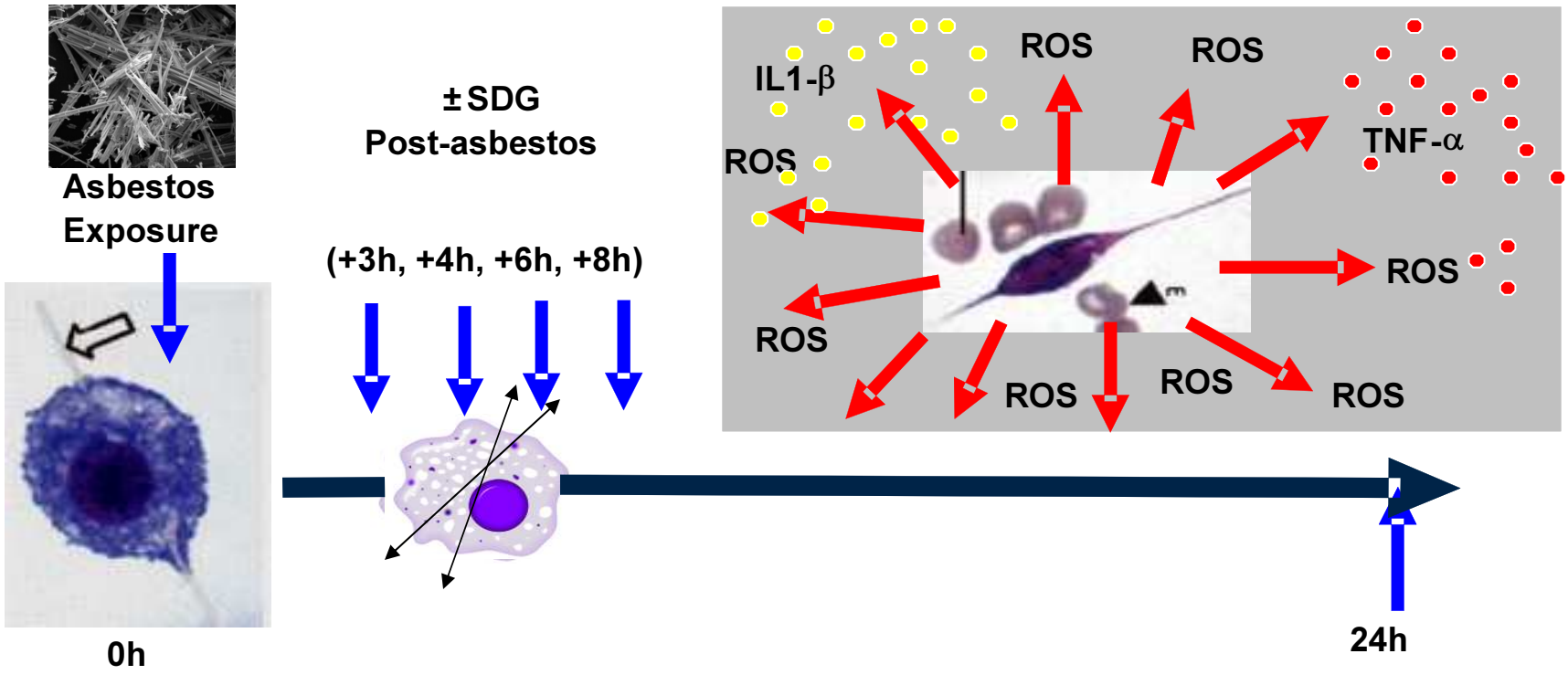
Rodent Models of Accelerated Malignant Mesothelioma

Modeling Asbestos Exposure to Study of Mechanism of Inflammatory Cell Activation



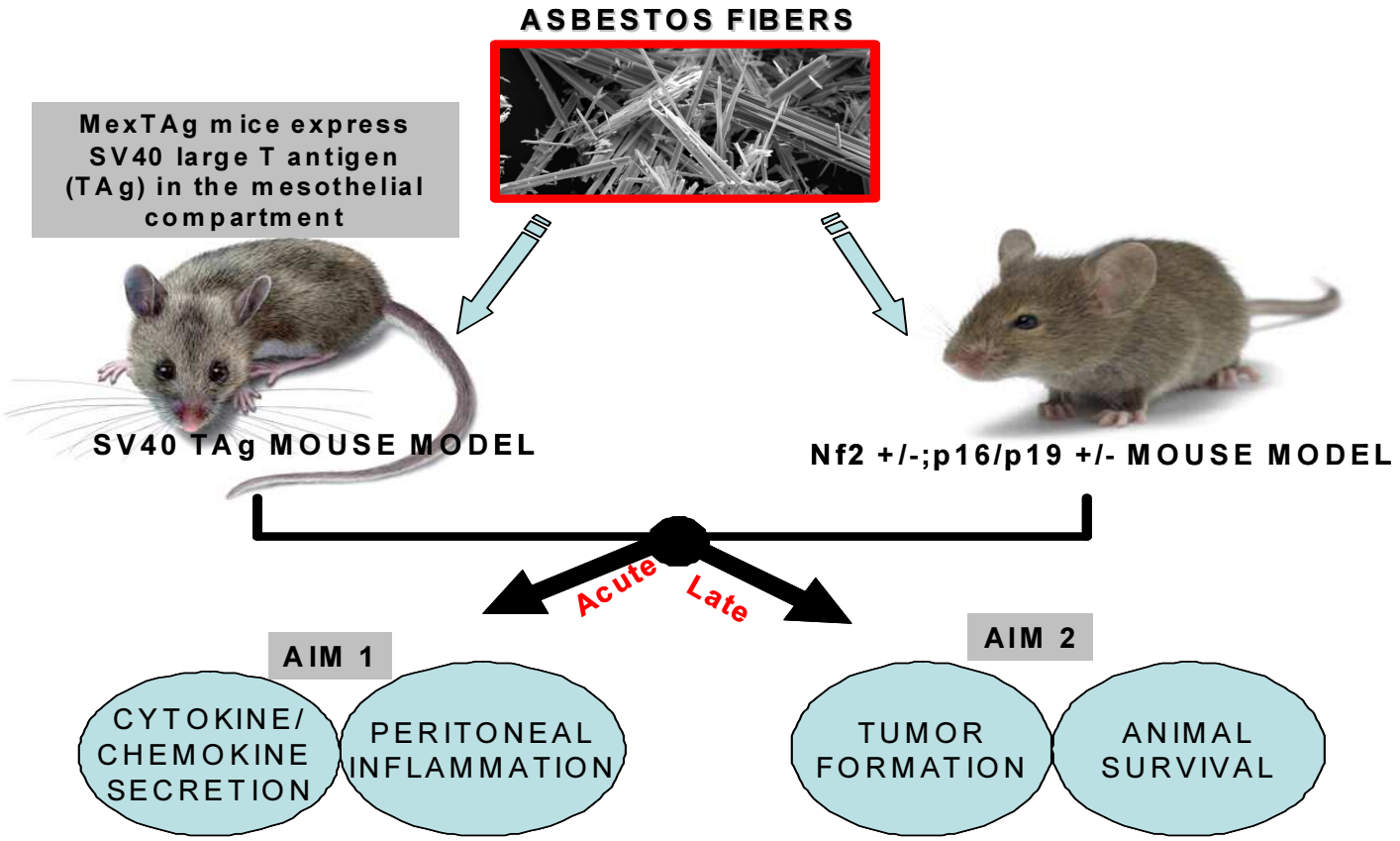
Inhaled asbestos fibers work their way into the lung and ultimately to the pleural surface. They are taken up by tissue phagocytes, primarily macrophages. This stimulates intracellular ROS and activates NF-kb and the inflammasome inducing the release of numerous cytokines and mutagenic ROS

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.

Funding Provided by:

National Institute of Allergy and Infectious Diseases (NIAID)
RC1AI081251

National Cancer Institute (NCI/NIH)
NIH-1R01CA-133470
NIH-1R21CA-118111

NASA Human Research Program through a NASA-NIH Interagency Agreement for supplemental award to NIH RO1
NNX12AK19G

National Institute of Environmental Health Sciences (NIEHS/NIH)
1P42ES023720-01 and
Pilot project support from 1P30 ES013508-02