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.
Environmental Insults and Oxidative Lung Disease
Oxidative Lung Damage

Airborne Toxins

Asbestos fibers

Blood-borne Toxins

Radiation
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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema</td>
<td>Tissue injury by oxidants in cigarette smoke</td>
</tr>
<tr>
<td></td>
<td>Tissue injury by inflammatory cell oxidants- $\alpha_1$ proteinase inhibitor ($\alpha_1$PI) inactivation by cigarette smoke and inflammatory cells</td>
</tr>
<tr>
<td>Adult respiratory distress syndrome</td>
<td>Inflammatory cell release of oxidants- $\alpha_1$PI oxidative inactivation by inflammation cells</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>Hyperoxia-mediated oxygen radical synthesis in cells</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>Inflammatory cell oxidant release</td>
</tr>
<tr>
<td>Asthma</td>
<td>Glutathione deficiency</td>
</tr>
<tr>
<td></td>
<td>Inflammatory cell release of oxidants</td>
</tr>
<tr>
<td></td>
<td>Decrease in superoxide dismutase activity in bronchial epithelial cells</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Proposed therapy</th>
<th>Year(s)</th>
<th>Impact on patient outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Multiple</td>
<td>Mixed results&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1996</td>
<td>No effect</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>1998, 1999</td>
<td>No effect</td>
</tr>
<tr>
<td>Liposomal prostaglandin E1</td>
<td>1999</td>
<td>No effect</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>2000</td>
<td>No effect</td>
</tr>
<tr>
<td>Lisofylline</td>
<td>2002</td>
<td>No effect</td>
</tr>
<tr>
<td>Neutrophil elastase inhibitor</td>
<td>2004</td>
<td>No effect</td>
</tr>
<tr>
<td>Activated protein C</td>
<td>2008</td>
<td>No effect&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beta-adrenergic agonist</td>
<td>Unpublished</td>
<td>No effect</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Unpublished</td>
<td>No effect</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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; <sup>b</sup> in ARDS alone, independent of severe sepsis.

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.
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.
Pharmacotreatment 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 less use of nutrition 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 pharmacotreatment, attenuating any treatment effect if one exists. Therefore, investigations in pharmacotreatment call for pharmacotreatment to be dissociated from the baseline nutrition. Rice and colleagues' 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
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

Dietary Antioxidants (Vegetables and Fruits) → Purification Of Main Active Components → Evaluation in Cell Culture and Animal Models

Testing in Clinical Trials → Determining Bioavailability/Biospecificity → Elucidation of Mechanism of Action

DRUG DEVELOPMENT
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)
- Resveratrol
- Lycopene
- Delphinidin
- Sulforaphane

Dietary Agents

- Grapes
- Tomatoes
- Pomegranate
- Broccoli
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

Intestinal Bacteria

Plant Lignan Precursors
• Secoisolarisiresinol diglycoside (SDG)
• Matairesinol

Lignans
• Enterodiol (ED)
• Enterolactone (EL)

Biological Properties
*** Antioxidative
Antiproliferative
Antiangiogenic
Estrogenic/Antiestrogenic

Cancer Protection

Omega-3 Fatty Acids
α-Linolenic Acid
EPA (eicosapentanoic Acid)
DHA (Docosahexanoic Acid)

Anti-inflammatory

DHA (Docosahexanoic Acid)
α-Linolenic Acid
EPA (eicosapentanoic Acid)

FLAXSEED

Intestinal Bacteria

Plant Lignan Precursors
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Omega-3 Fatty Acids
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EPA (eicosapentanoic Acid)
DHA (Docosahexanoic Acid)

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

- Hypoxic 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

Control Diet 10% Flax Diet

Principle Component Analysis

Control (0% FS) Treated (10% FS)

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

Phase II Enzymes

Cell Survival genes

Nrf2

Keap-1

19S

20S

PKC

PERK

PI3K

MAPK

??

Increased Antioxidant Enzyme Expression in Lungs

Flaxseed Lignans

Degradation

Transcription (H0-1, NQO1, GST)

Nucleus

ARE

Phase II Enzymes

Cell Survival genes

Increased Antioxidant Enzyme Expression in Lungs

Flaxseed Lignans
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

**INDIRECT OXIDANT STRESS**
- Neutrophils
- Macrophages
- Endothelial Cells

**Flaxseed/FS Lignans**

**ROS**

**Apoptosis**

**DNA damage**

**Chemokine Release**

**Lung leakiness / Edema**

**Inflammatory Cells**

**Tissue oxidation**

**Cytokine release**

**OXIDATIVE LUNG INJURY**
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

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 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

Lee et al., 2009
Antifibrotic Role of Flaxseed

Flaxseed Decreased Radiation-Induced Collagen Deposition in Lungs

Fibrotic Index (Pathology)

OH-Proline Content

Trichrome Blue Staining for Collagen (Marker for Lung Fibrosis)

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

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

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 accidents 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. 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.
JAPAN REELS AS TOLL RISES AND NUCLEAR RISKS LOOM

ANOTHER EXPLOSION
Radioactive Steam May Be Released From Reactors for Weeks

NUCLEAR CRISIS IN JAPAN
STRUGGLE MAY TAKE WEEKS

NEC"ALL THE NEWS
THAT’S FIT TO PRINT"
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...
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)

**EXPERIMENTAL MODEL**

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

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

Melpo Christofidou-Solomidou¹, Sonia Tyagi¹, Kay-See Tan², Sarah Hagan³, Ralph Pietrofesa¹, Floyd Dukes¹, Evguenia Arguiri¹, Daniel F Heitjan², Charalambos C Solomides⁴ and Keith A Cengel³
Flaxseed Might Protect Against Death From Radiation

Published August 12, 2011 | MyHealthNewsDaily

Flaxseed may protect against the damaging effects of radiation from a terrorist’s dirty bomb or in cancer treatment, a new study suggests.

Mice that ate flaxseed died from up to six weeks after receiving a lethal radiation dose to the chest, but they were likely to survive and have normal livers when radiation was blocked by flaxseed.

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.

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...
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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 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

Sacrifice Mice Evaluate tumor burden

5 Mo

4 Months Recovery)

Months 1-5

9 Mo

Collecting and mixing chamber for rodent exposure studies

Microprocessor-controlled cigarette smoking machine
1. Benzo-alpha pyrene (B[\text{\alpha}]P)
2. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
3. Dimethylbenz(a)anthracene (DMBA)
4. Urethane

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

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

Sacrifice Mice
Evaluate tumor burden
Histological Detection of Lung Tumor Nodules in Mice Exposed to B[α]P
BENZO[a]PYRENE-CHEMICAL CARCINOGENESIS MODEL

Percent of Tumor Infiltrate

Total Tumor Infiltrate

Average Tumor Nodule Size

Tumor Morphometry / Image Analysis System
Tobacco smoke exposure

Generation of DNA reactive products

PAH, NNK, other carcinogens (example: Benzo[a]pyrene)

ROS, peroxynitrite, lipid peroxidation, 8-hydroxy-deoxyguanosine

DNA Adducts, Chromosomal Effects

Methyl Adducts, pyridyloxybutyl Adducts, SCE, Micronuclei, chromosome instability

Mutations

P53, K-Ras, others

LUNG CANCER

Adapted from Hecht, 1999
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.
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 Whippin 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.
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
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-κB and the inflammasome inducing the release of numerous cytokines and mutagenic ROS.
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 \textit{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.
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

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