"The synthetic lignan Secoisolaricirecinol Diglucoside (LGM2605) prevents asbestos-induced inflammasome activation and cytokine secretion in murine macrophages"

Melpo Christofidou-Solomidou, Ph.D.

Professor of Medicine

Aegean Conferences, Crete, 2017

University of Pennsylvania, Department of Medicine, Pulmonary, Allergy and Critical Care Division, Philadelphia, PA, USA

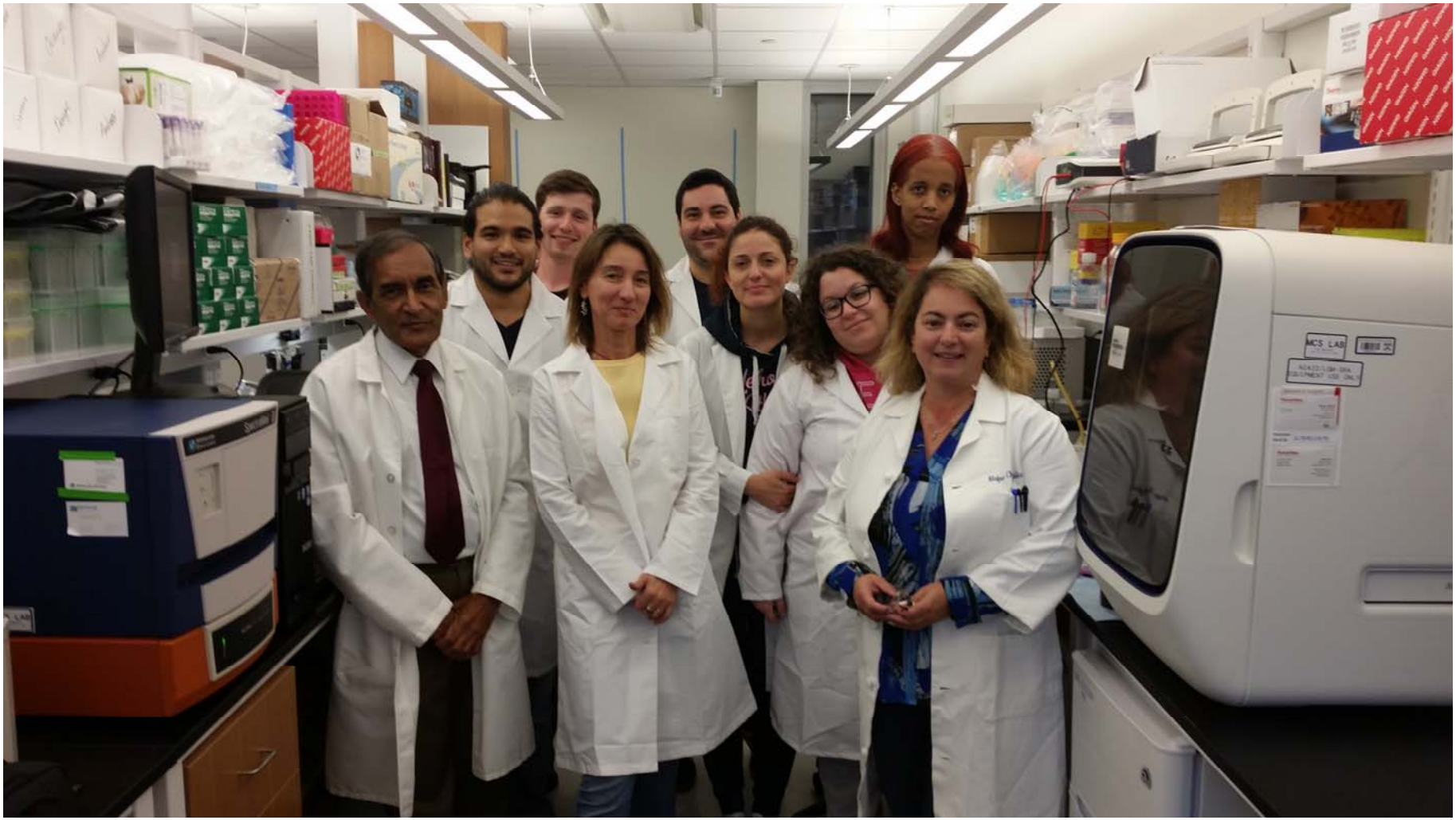
DISCLOSURES

- **Dr. Christofidou-Solomidou reports grants from:**
  - **National Cancer Institute (NCI),**
  - **National Institute of Environmental Health Sciences (NIEHS),**
  - **National Institute of Allergy and Infectious Diseases (NIAID)**
  - **National Institute for Mental Health (NIMH) and**
  - **National Center for Complementary and Integrative Health (NCCIH).**
  - **National Aeronautics and Space Administration (NASA)**

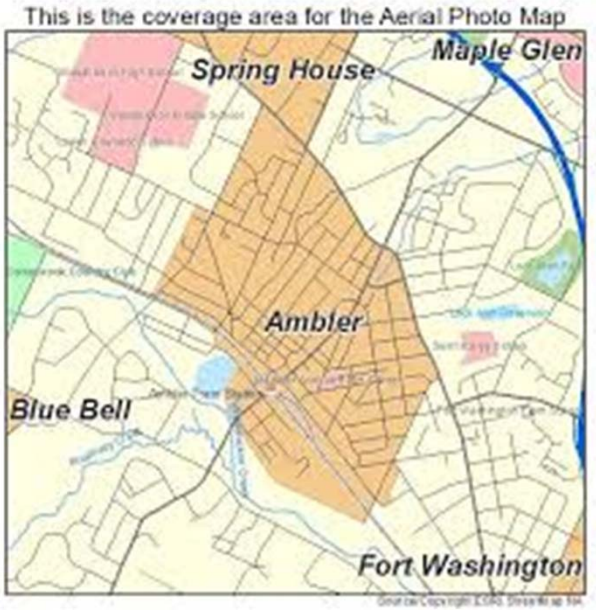
- **Dr. Christofidou-Solomidou has a patent No. PCT/US14/41636 pending, and patent No.PCT/US15/22501 pending.**

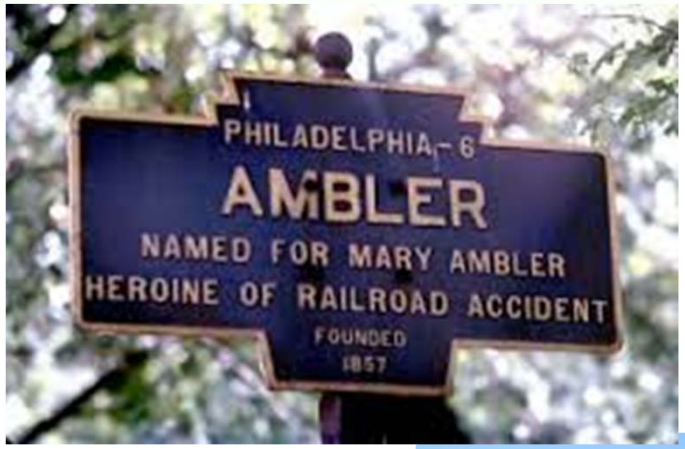
- **Dr. Christofidou-Solomidou is founder of LignaMed LLC, devoted to developing radioprotective agents.**

Our Research Team

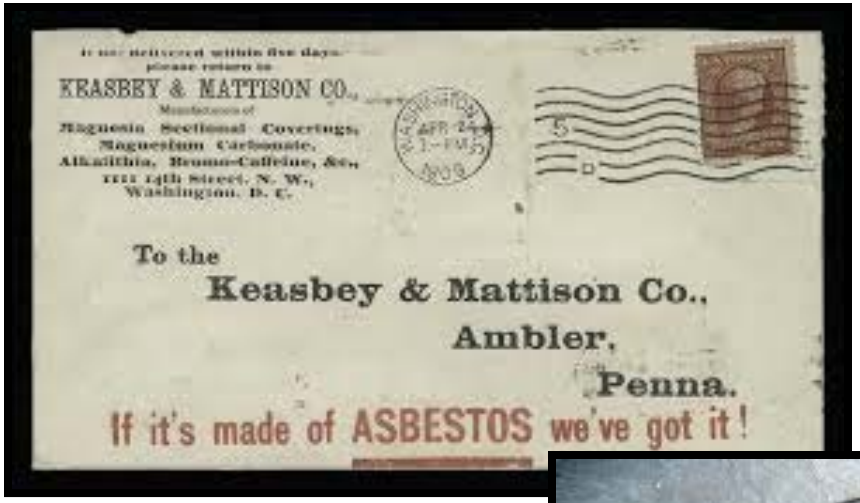



Ambler, PA


This is the coverage area for the Aerial Photo Map
Spring House
Maple Glen
Ambler
Blue Bell
Fort Washington


PHILADELPHIA - 6
AMBLER
NAMED FOR MARY AMBLER
HEROINE OF RAILROAD ACCIDENT
FOUNDED
1857


AMBLER



The BoRit Asbestos Site was used, from the early 1900s to the late 1960s, to dispose of asbestos-containing material (ACM) that came from a nearby asbestos products manufacturing plant.

The BoRit site was added to the EPA's National Priorities List of the most hazardous waste sites on April 9, 2009, making it eligible for cleanup using federal Superfund program funding.

The Ambler zip code had 28 cases of mesothelioma rather than the expected 9 for a population of its size - about 30,000.

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Monday, December 1, 2014 Last Update: 12/01/14 03:15 pm

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

July 11, 2014 9:52 AM

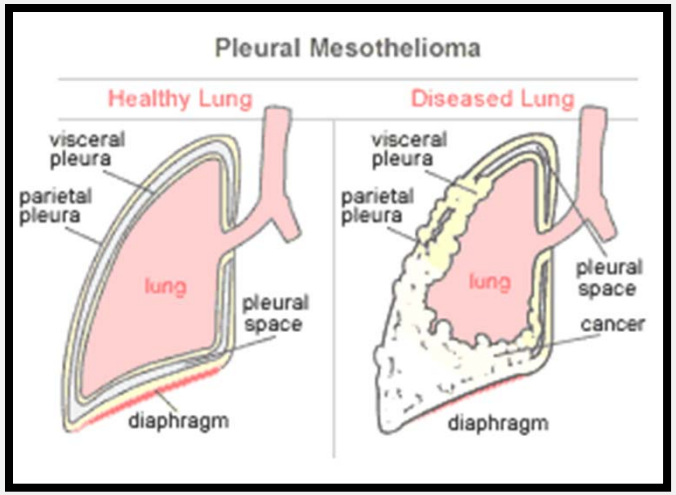
By HEATHER ISRINGHAUSEN GVILLO

PHILADELPHIA (Legal Newsline) – Researchers with the University of Pennsylvania received a $10 million grant to study asbestos and how the toxic fiber leads to asbestos-related disease in response to America's 10 Superfund sites.

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

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.

ROS/Inflammation in Mesothelioma:

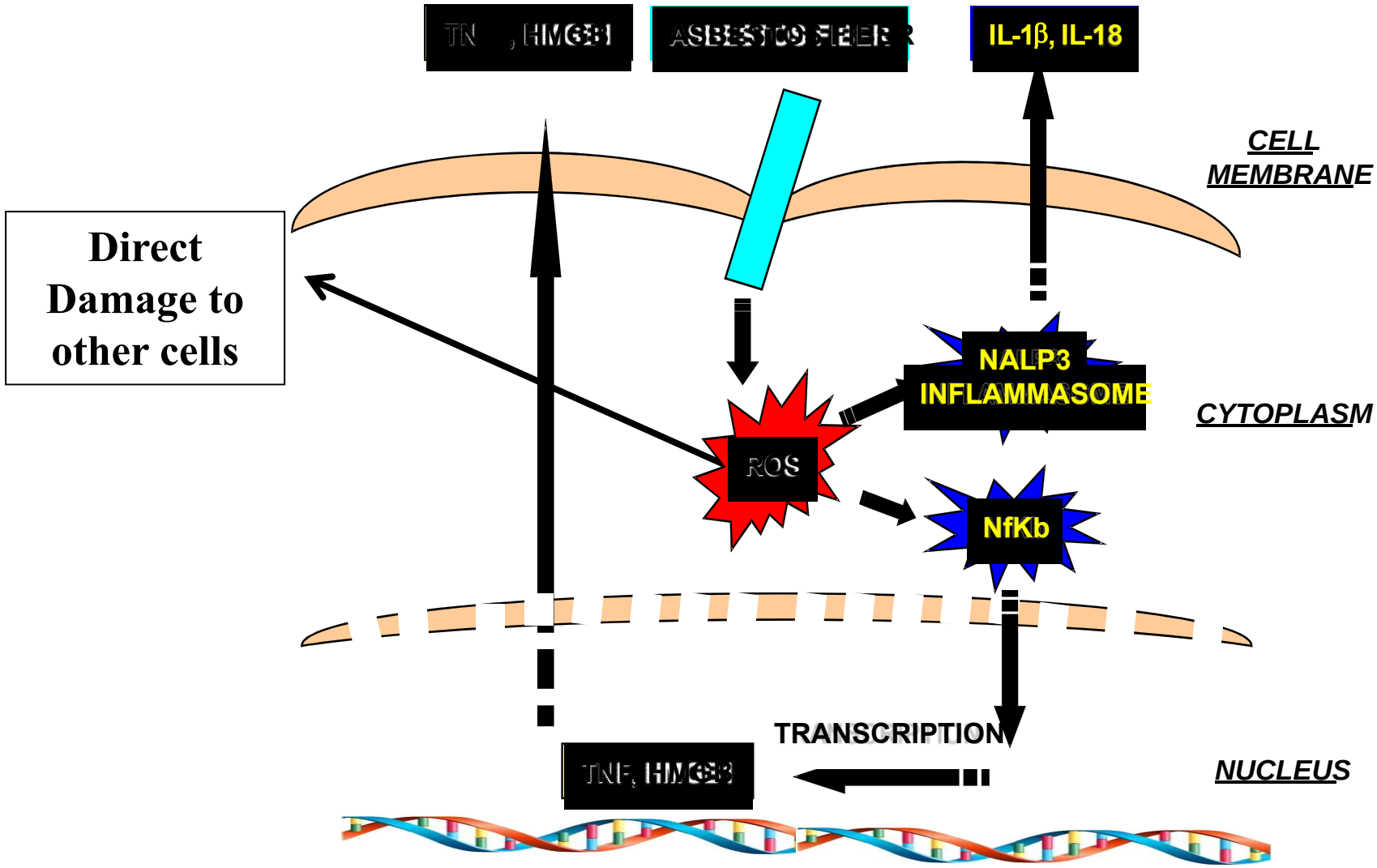
The working paradigm of mesothelioma carcinogenesis is that asbestos induces a state of chronic inflammation in the pleura that ultimately leads to mutagenesis and tumor formation (especially in those with a genetic predisposition).

Key roles of:

HMGB1, TNF-α, IL-1ß, IL-18, TGF-β1

AND

REACTIVE OXYGEN SPECIES



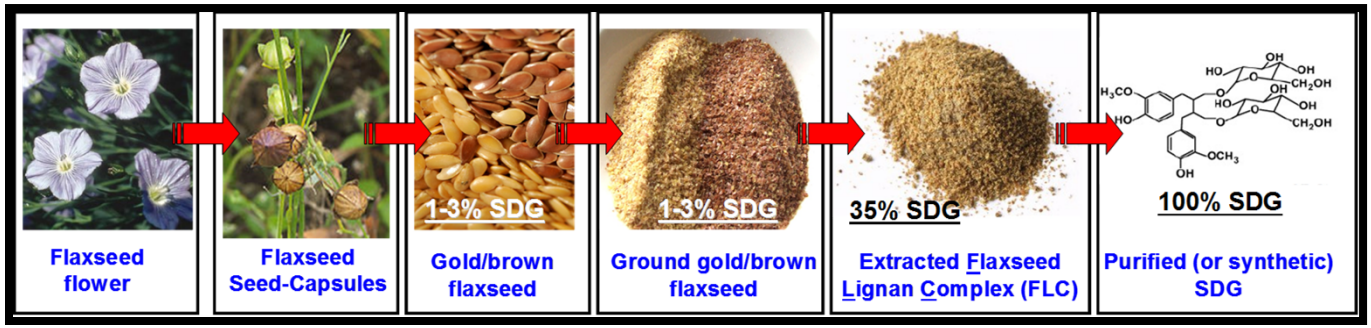
From the cellular perspective, asbestos induces chronic production of reactive oxygen species (ROS) which results in chronic pulmonary inflammation and cytokine (i.e. TNFα, HMGB1, IL-1ß) release through ROS-mediated activation of NFκB and through inflammasome activation.

Hypothesis

Inhibition of inflammation and/or ROS will delay or prevent the induction of asbestos-induced mesothelioma.

We want to test this using Flaxseed and the main lignan found in Flaxseed: the SDG

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



FLAXSEED (wholegrain) & SDG

- THORACIC RADIATION PNEUMONOPATHY
- HYPEROXIC LUNG DAMAGE
- ISCHEMIA-REPERFUSION LUNG DAMAGE
- ACID ASPIRATION-INDUCED LUNG DAMAGE
- TOBACCO CARCINOGEN-INDUCED LUNG CANCER
- ASBESTOS-DISEASES

CHEMICAL SYNTHESIS OF SDG

Bioorganic & Medicinal Chemistry Letters 23 (2013) 5325–5328

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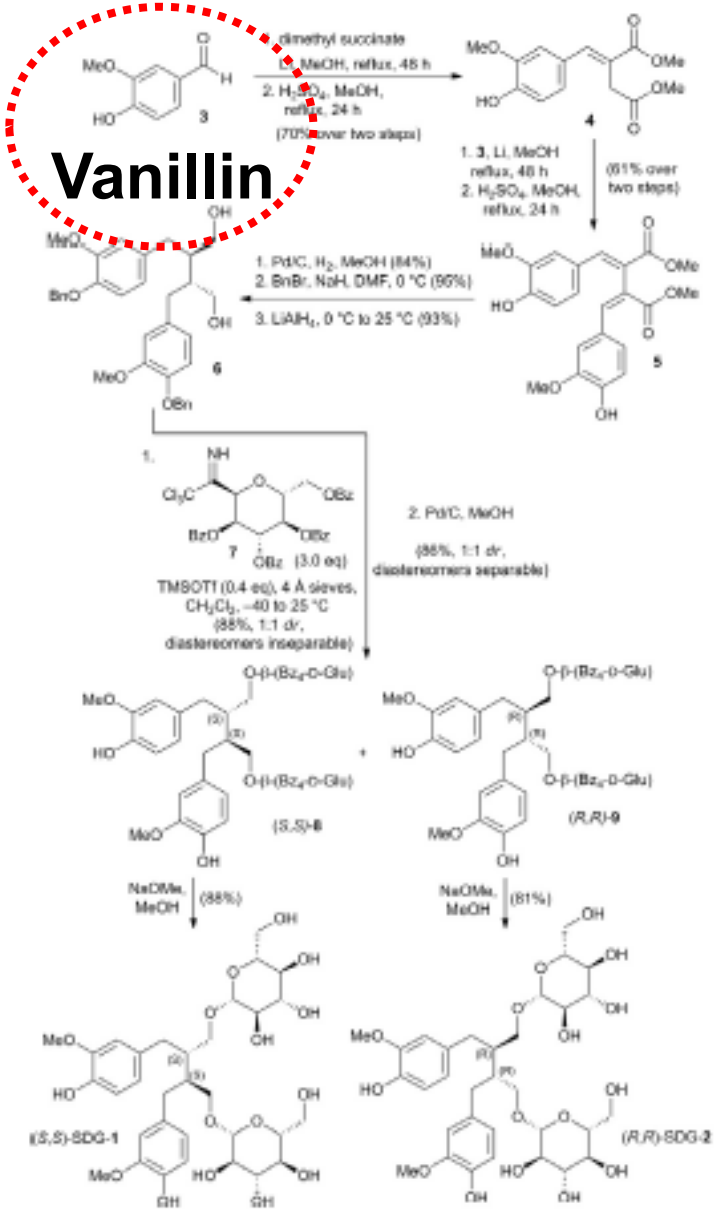
Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and antioxidant evaluation of (*S,S*)- and (*R,R*)-secoisolariciresinol diglucosides (SDGs)

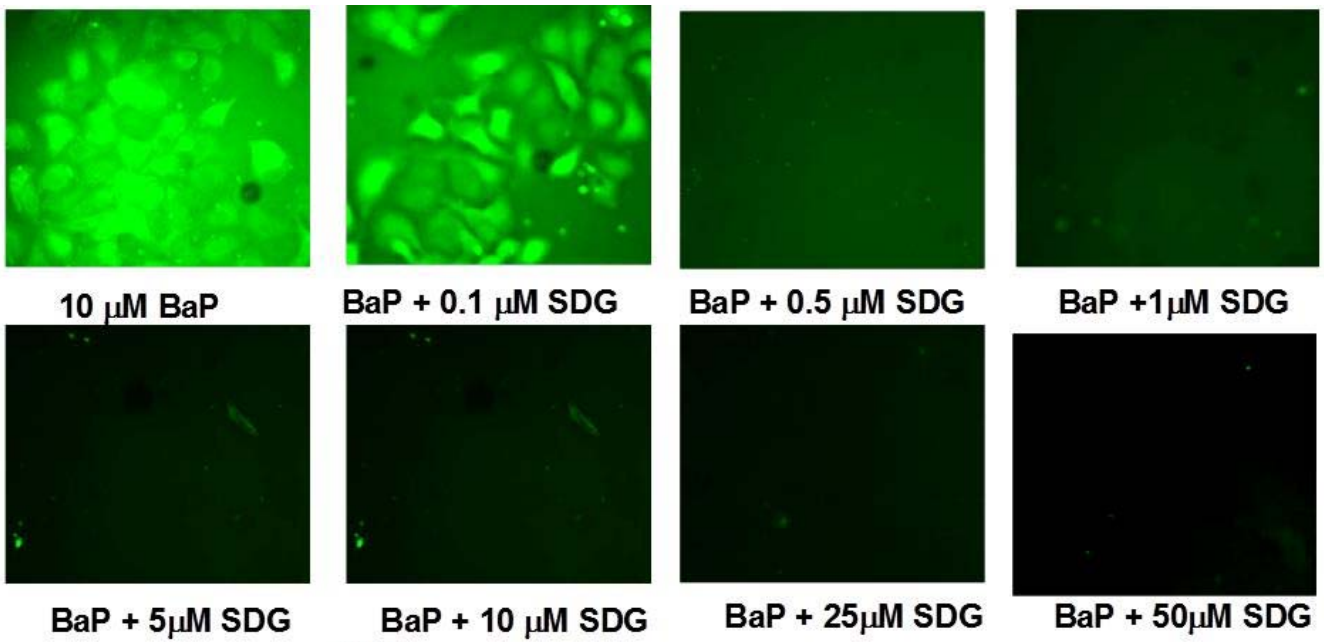
Om P. Mishra [a,†], Nicholas Simmons [b,†], Sonia Tyagi [a], Ralph Pietrofesa [a], Vladimir V. Shuvaev [c], Roman A. Valiulin [b], Philipp Heretsch [b,e], K. C. Nicolaou [b,d,e,*], Melpo Christofidou-Solomidou [a,*]

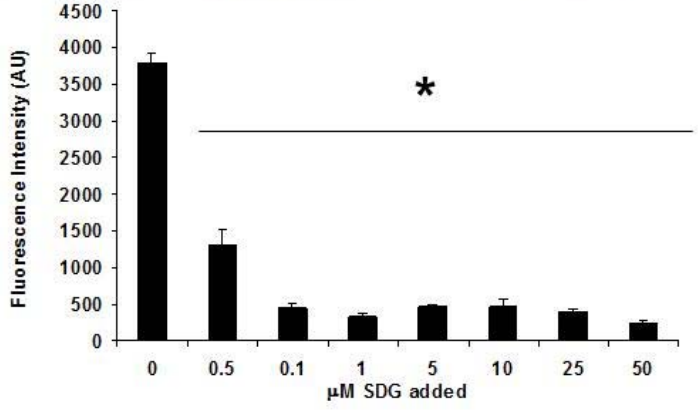
Manufactured in scalable amounts that now allow *in vivo* evaluation



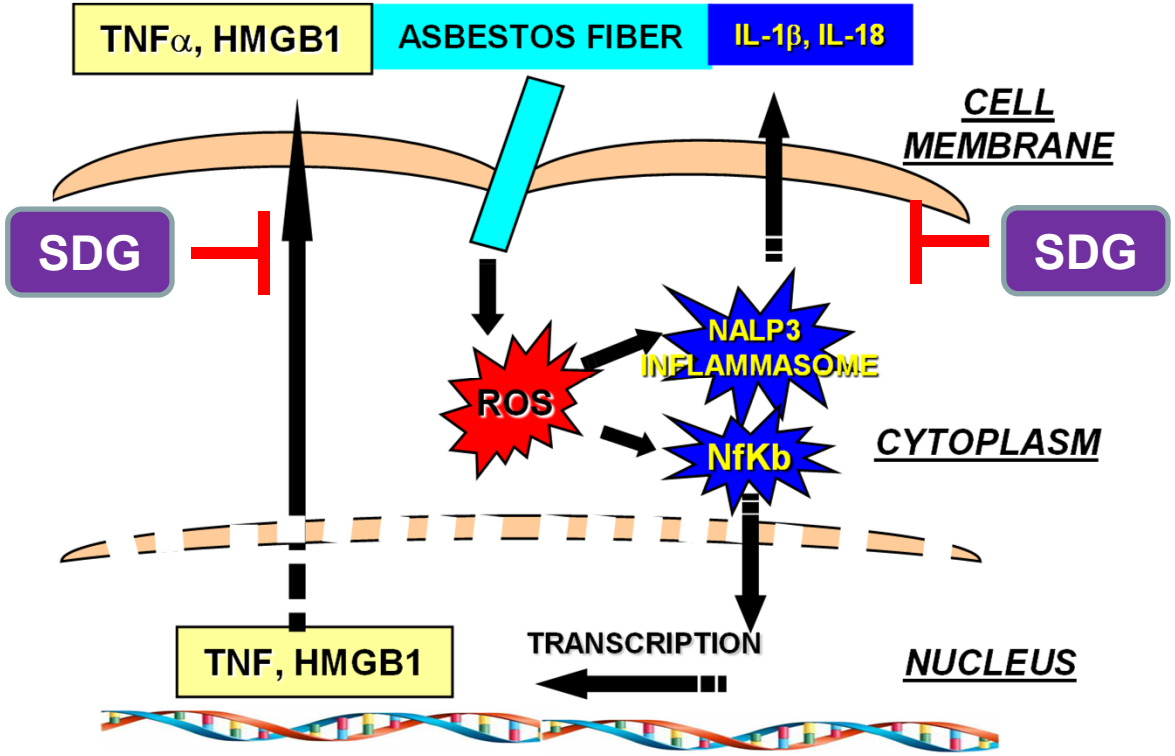
Flaxseed Lignan SDG blunts B[a]P-Induced ROS

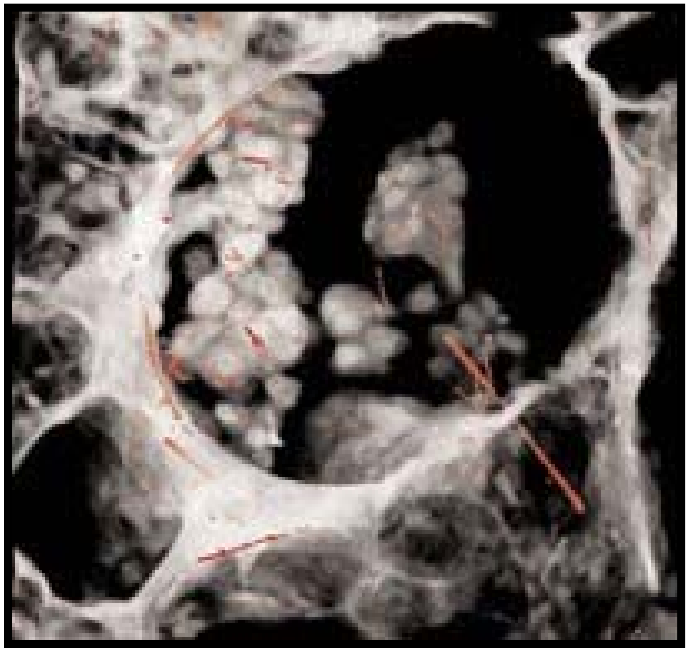
Testing SDG in ROS scavenging in lung epithelial cells exposed to the tobacco carcinogen benzo-alpha-pyrene (B[a]P)





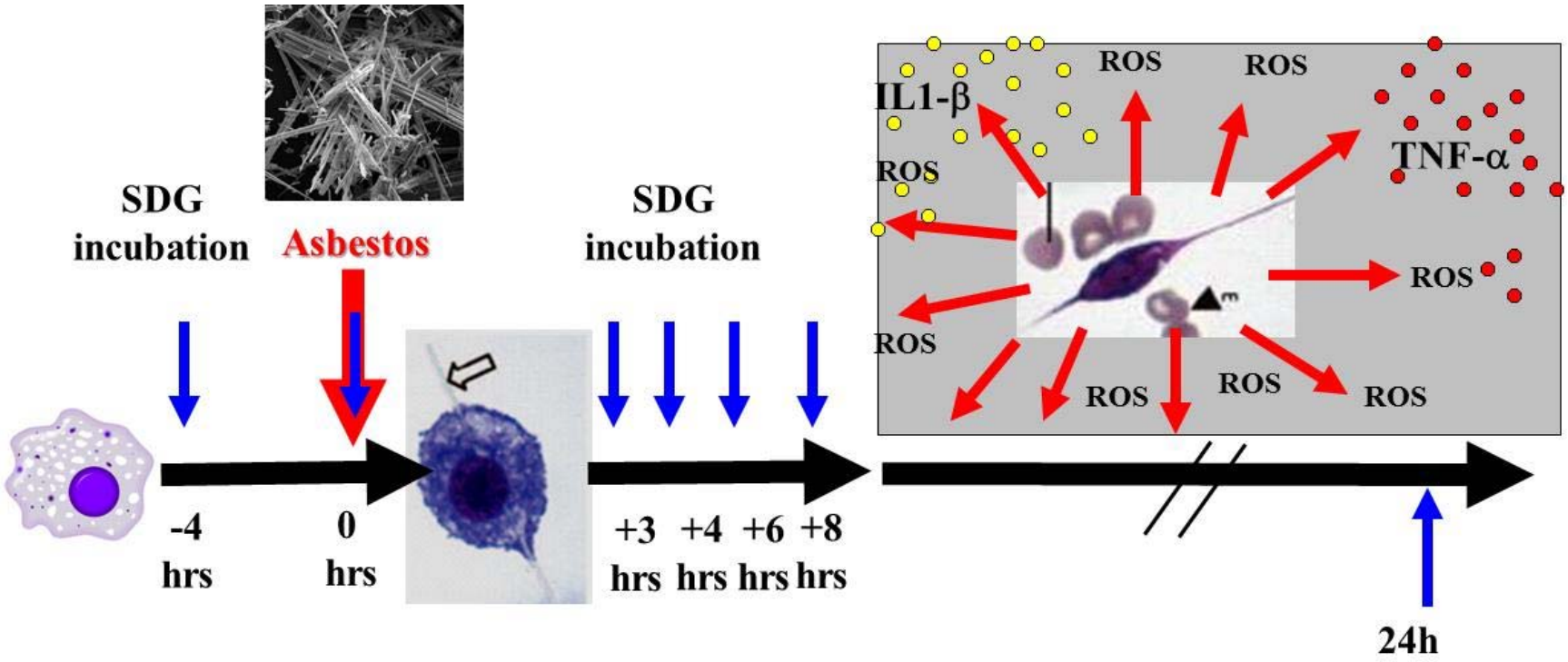
Role of Flaxseed and SDG in Preventing Asbestos-Induced Mesothelioma





We hypothesize that flaxseed or SDG-rich diets will decrease asbestos induced ROS/inflammation leading to: 1) ROS, 2) decreased cytokines, 3) decreased HMGB1, 4) less tumorigenic foci, and 5) less tumors

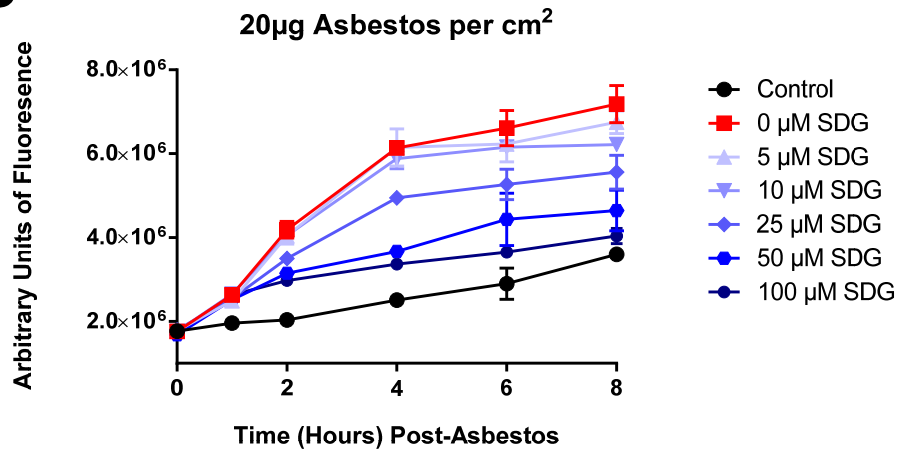
Experimental Plan



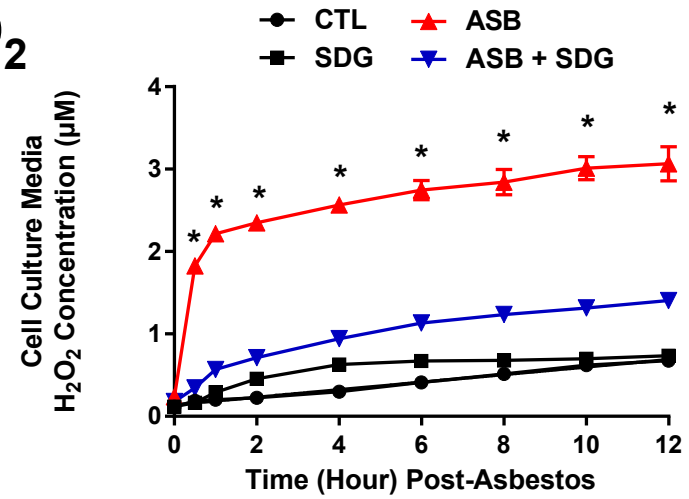
1. ROS levels using H_2DCFDA
2. Supernatant → Cytokine (TNF-α; IL-1β)
3. Cells → Inflammasome activation
4. MDA (Lipid Peroxidation)
5. Nitrite/Nitrate levels

SDG scavenges ROS and prevents asbestos-induced cytotoxicity & oxidative cell damage

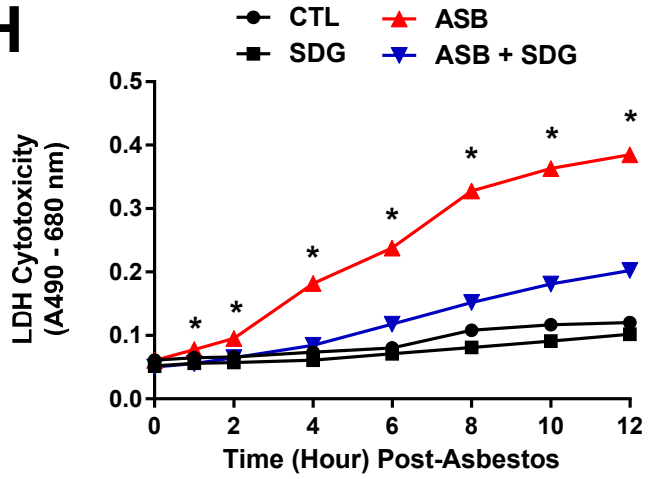
ROS



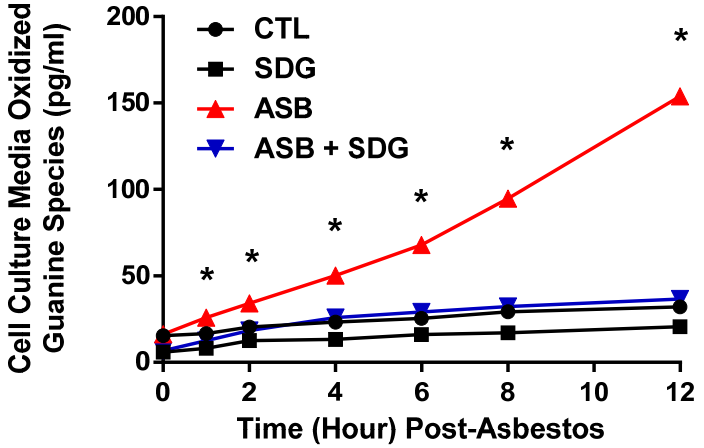
H_2O_2



LDH

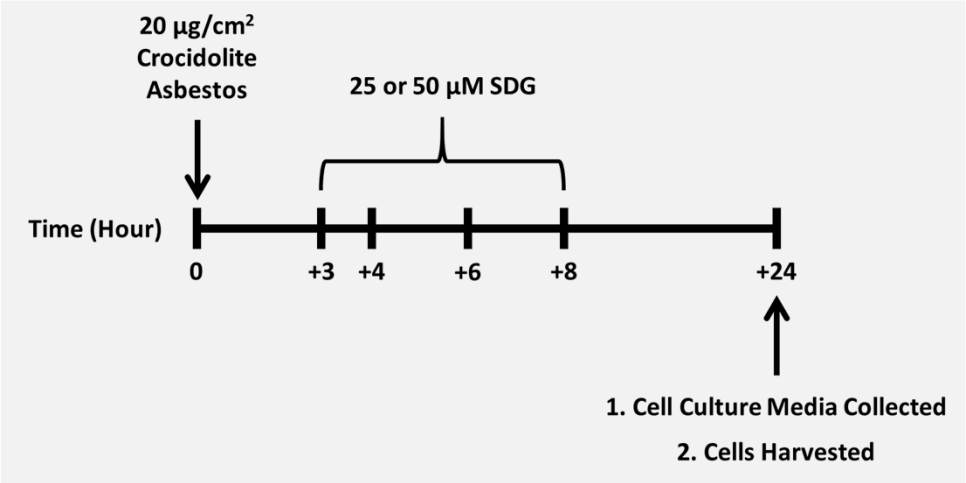


Oxo-G

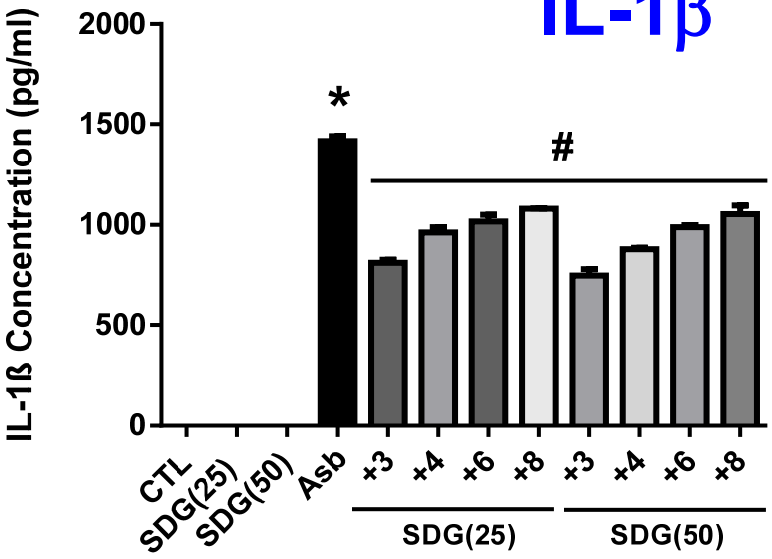


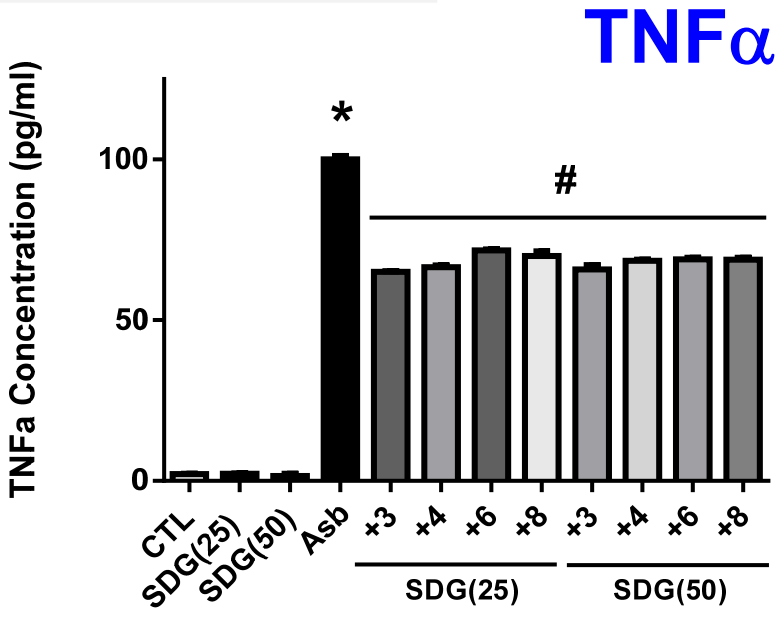
Pietrofesa et al, IJMS, 2016

SDG mitigates asbestos-induced inflammation and oxidative stress

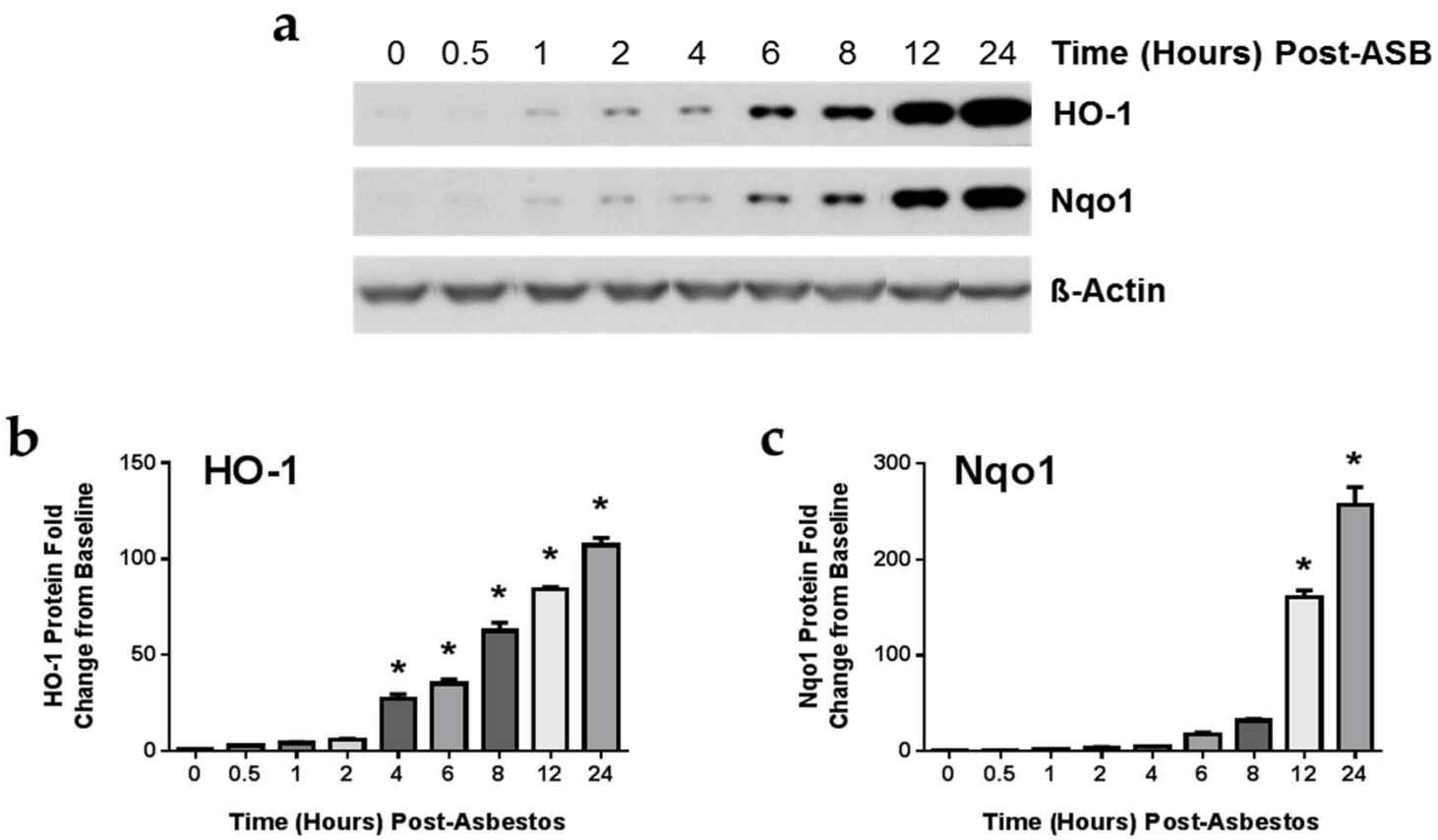


SDG given post-asbestos





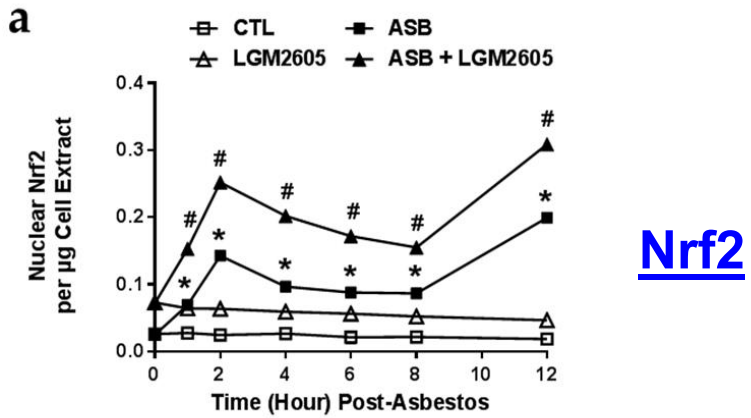
Asbestos Exposure Induces the Expression of Phase II Antioxidant Enzymes



Elicited murine peritoneal macrophages were harvested after 0, 0.5, 1, 2, 4, 5, 8, 12, and 24 hours of asbestos exposure and evaluated by western blotting for (**a and b**) HO-1 and (**a and c**) Nqo1.

Pietrofesa et al, IJMS, 2016

SDG (LGM2605) Boosts Asbestos-induced Expression of Nrf2-regulated Antioxidant Enzymes

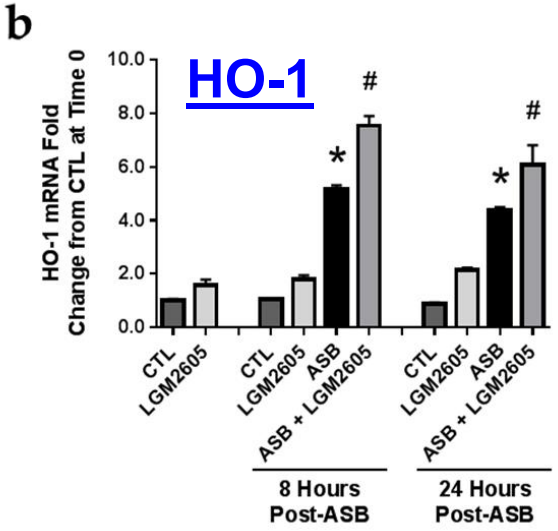


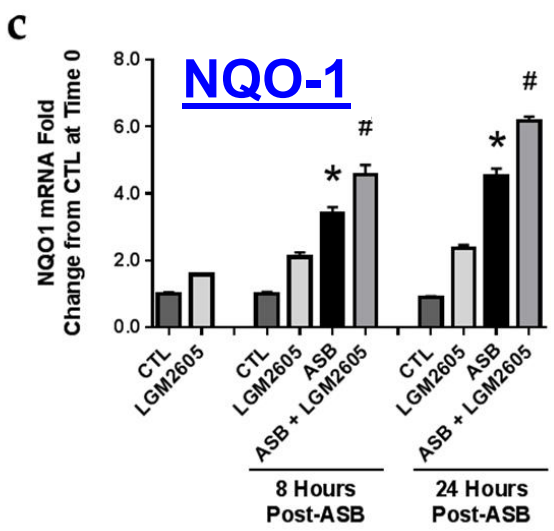
Nrf2

(a) Levels of active, nuclear Nrf2 were determined at 0, 1, 2, 4, 6, 8, and 12-hours post asbestos exposure.

(b) Macrophage mRNA expression of HO-1.

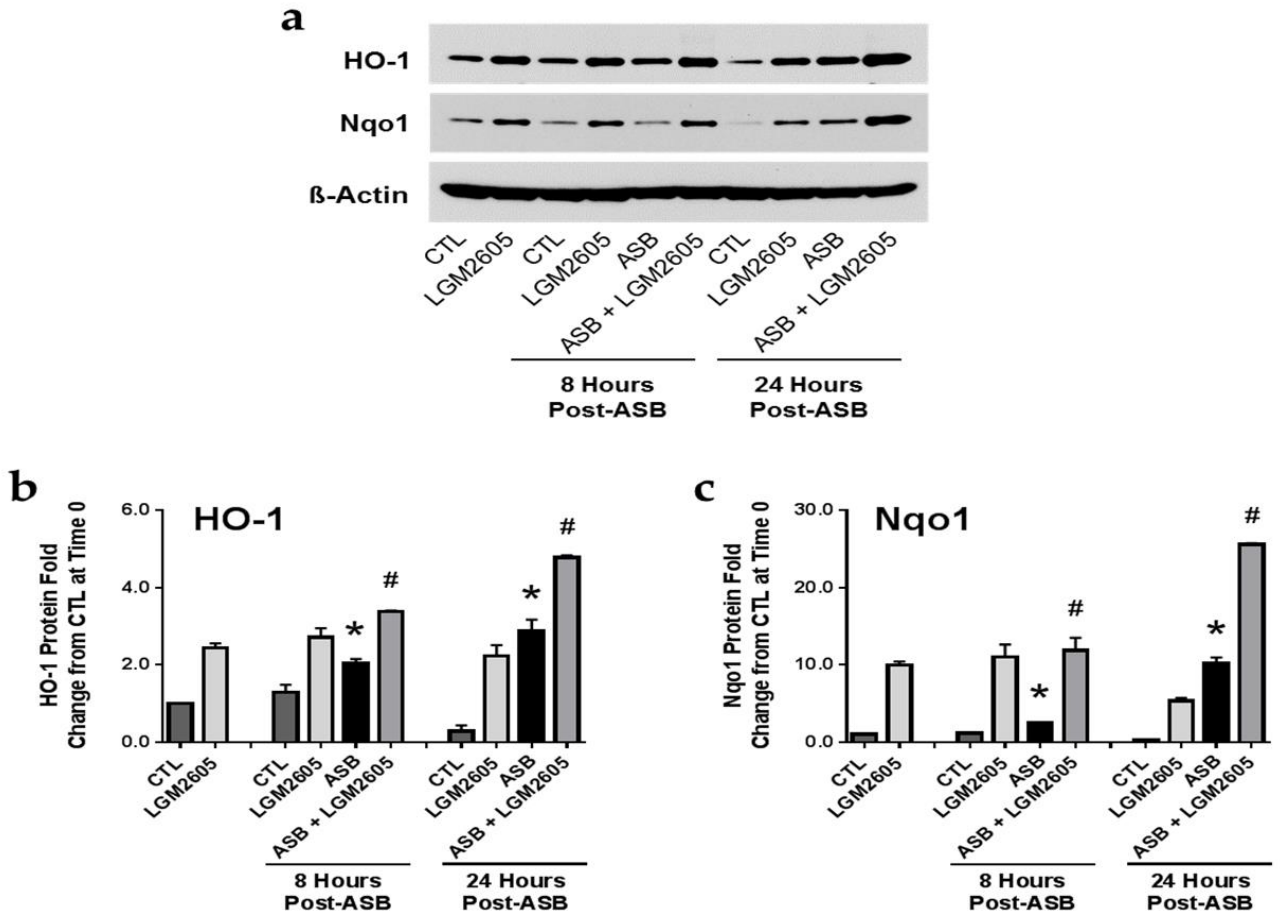
(c) mRNA expression levels of NQO1 determined at 0, 8, and 24 hours post asbestos exposure using qPCR.





Pietrofesa et al, Int. J. Mol. Sci. 2016

SDG (LGM2605) Boosts Asbestos-induced Levels of Nrf2-regulated Antioxidant Enzymes



Levels of antioxidant enzymes were determined by (**a**) western blotting for HO-1 and Nqo1. Densitometric analysis of band intensity for (**b**) HO-1 and (**c**) Nqo1 was normalized to β-actin and values are expressed as fold change from CTL at time 0.

Pietrofesa et al, IJMS, 2016

Publication of Findings

International Journal of *Molecular Sciences*

Int. J. Mol. Sci. **2016**, *17*, 322; doi:10.3390/ijms17030322

MDPI

Article

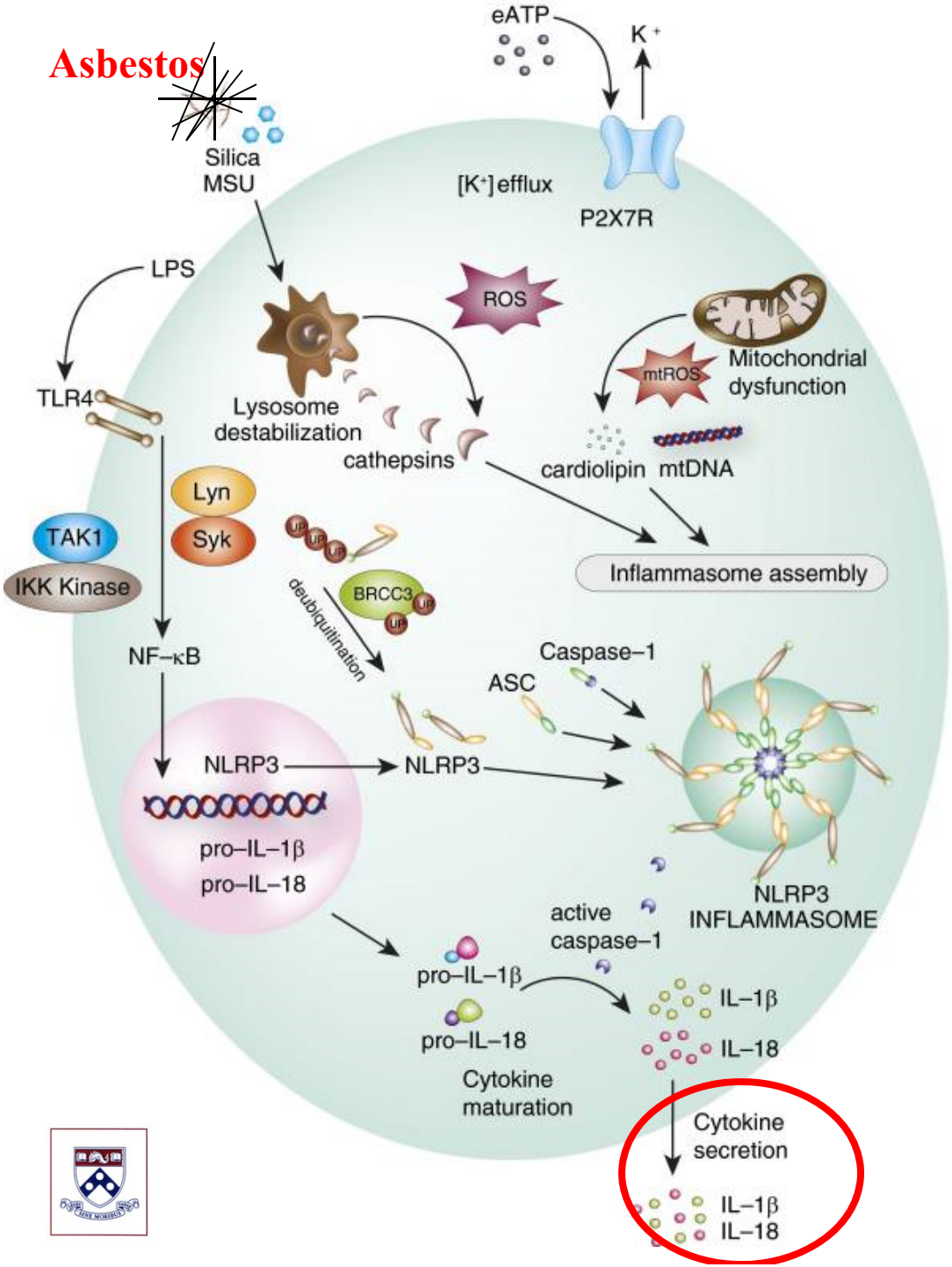
Asbestos Induces Oxidative Stress and Activation of Nrf2 Signaling in Murine Macrophages: Chemopreventive Role of the Synthetic Lignan Secoisolariciresinol Diglucoside (LGM2605)

Ralph A. Pietrofesa, Anastasia Velalopoulou, Steven M. Albelda and Melpo Christofidou-Solomidou *

Role of Inflammasomes in Asbestos Disease & Mesothelioma

Inflammasomes are specialized inflammatory signaling platforms that govern the maturation and secretion of proinflammatory cytokines, such as IL-1β and IL-18, through the regulation of caspase-1-dependent proteolytic processing.

Inhalation of fibers like asbestos can induce the formation of the NLRP3 inflammasome

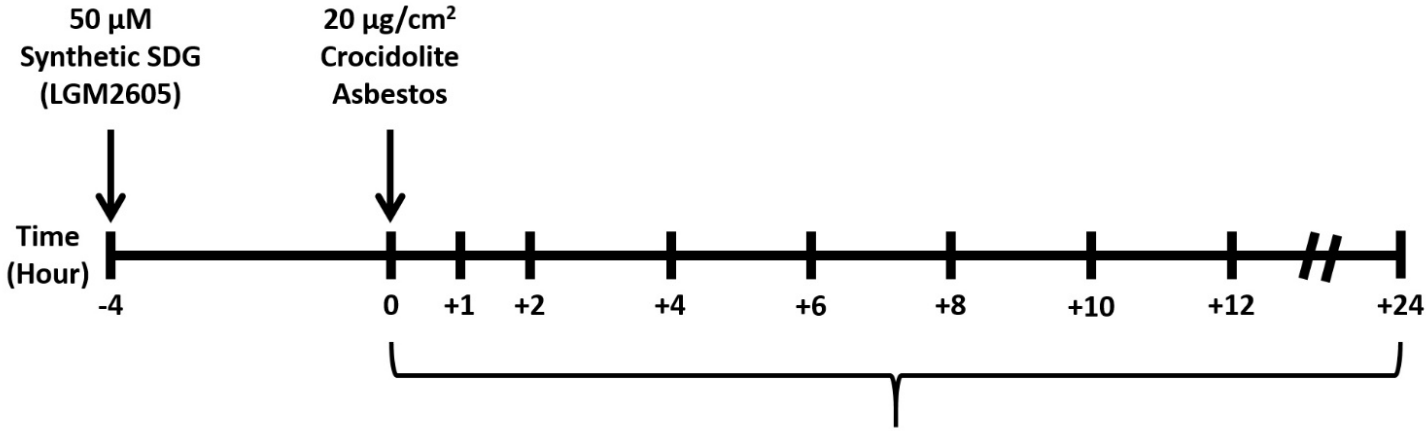


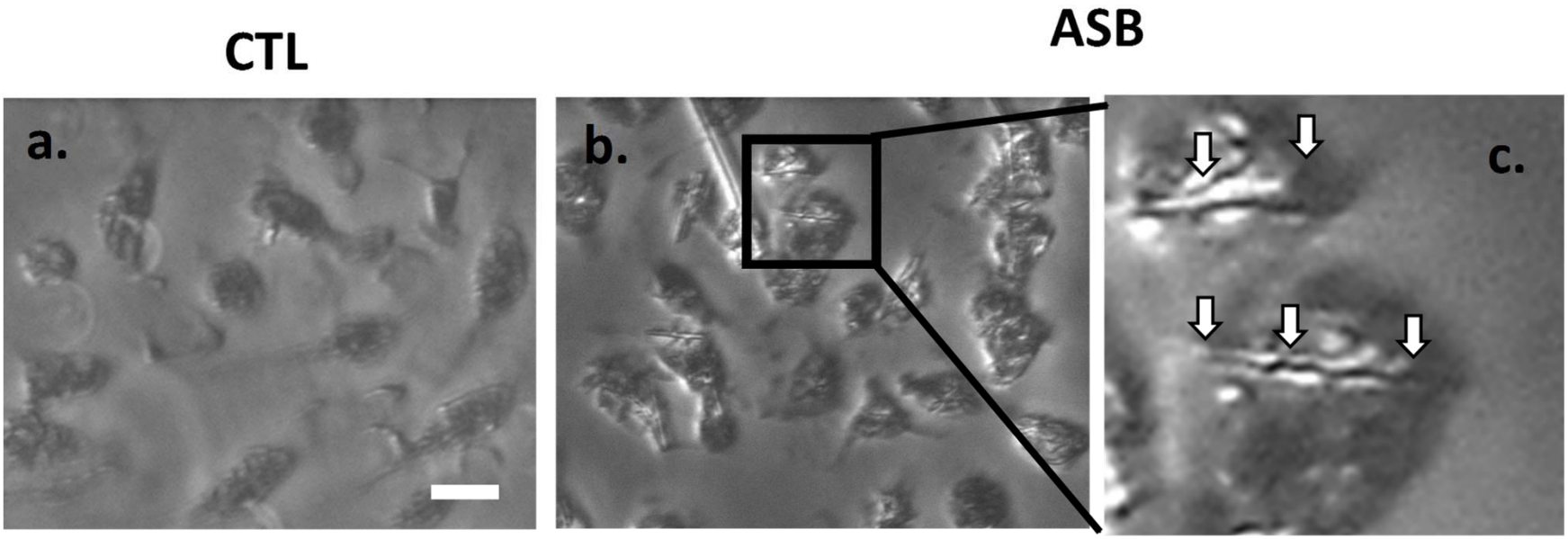
1. The NLRP3 inflammasome responds to activating signals through a two-step activation model. Initiation is typically triggered by ligand binding (e.g., LPS) to Toll-like receptors (TLR; e.g., TLR4) and related receptors. This results in **activation of NF-κB**, which translocates to the nucleus and activates the

2. **transcription of inflammasome components, including NLRP3**, and the pro forms of inflammasome-related cytokines (i.e., pro–IL-1β and pro–IL-18).

3. Activation of inflammasome-associated caspase-1 results in the **activation (cleavage) of proinflammatory cytokines** (e.g., IL-1β, IL-18) before their secretion.

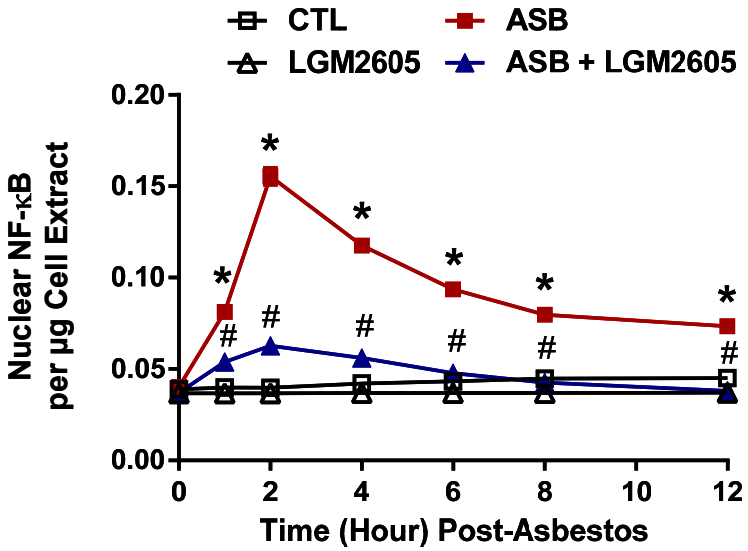
Am J Respir Cell Mol Biol. 2016 Feb;54(2):151-60

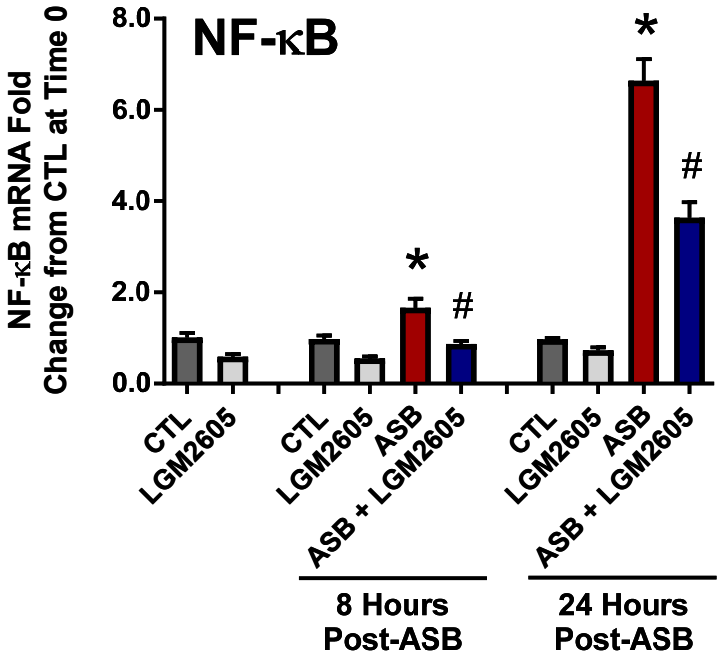




Pietrofesa et al, in review

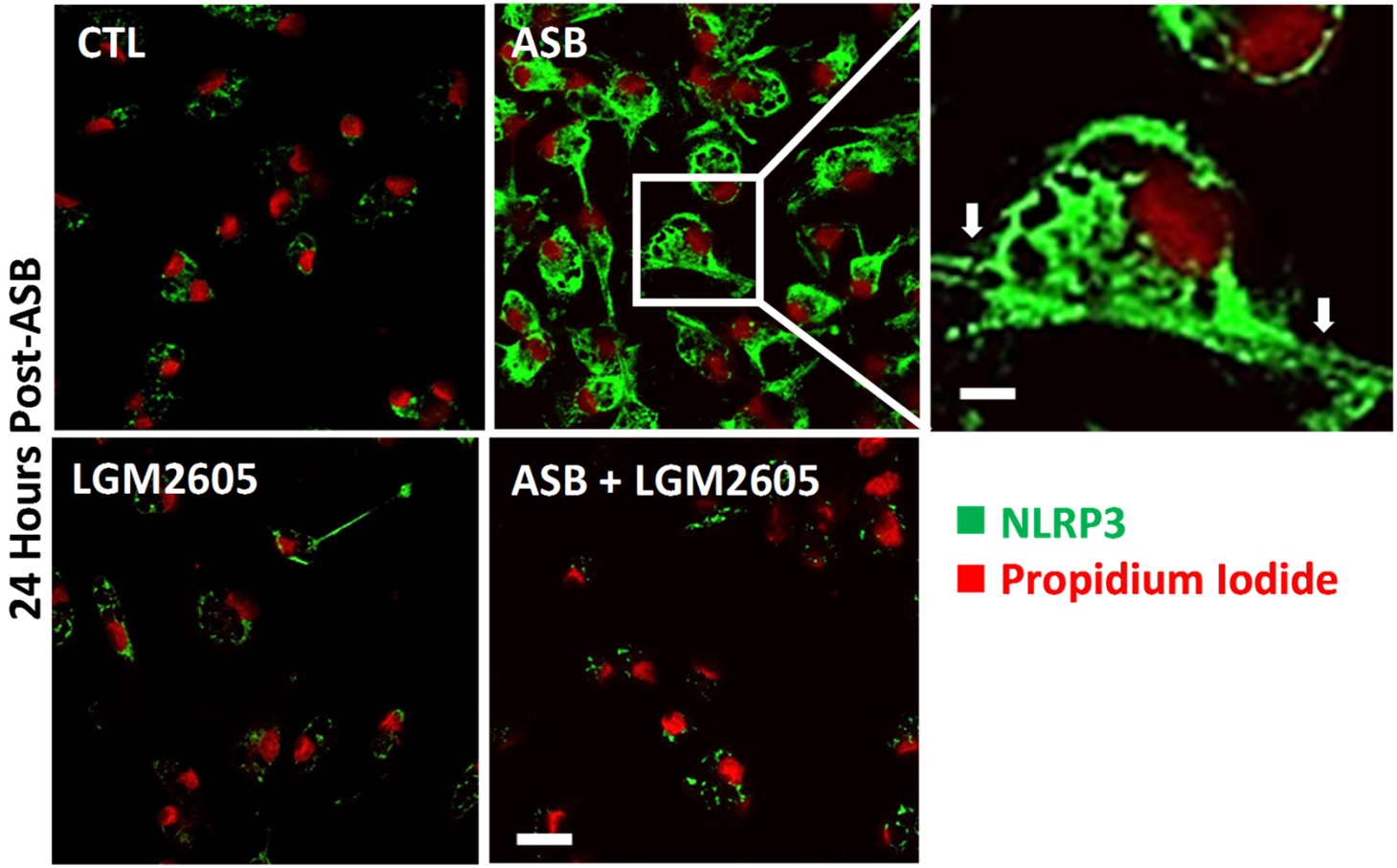
SDG (LGM2605) prevents NF-κB Activation in Peritoneal Macrophages- (1)





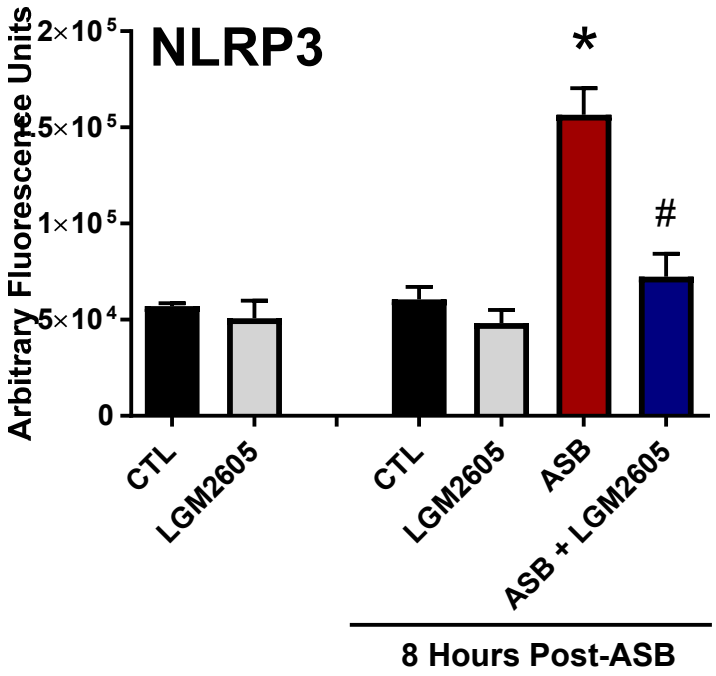
Pietrofesa et al, in review

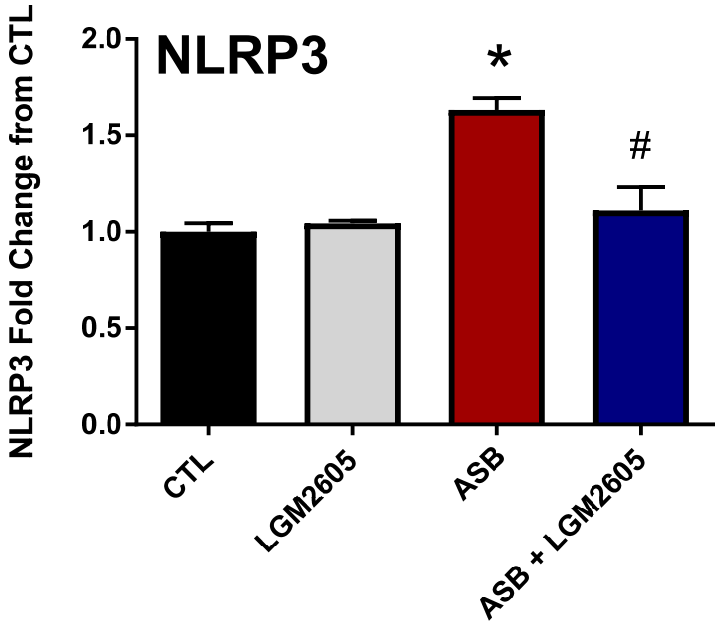
SDG (LGM2605) prevents Asbestos-Induced Inflammasome Activation in Macrophages-(2)

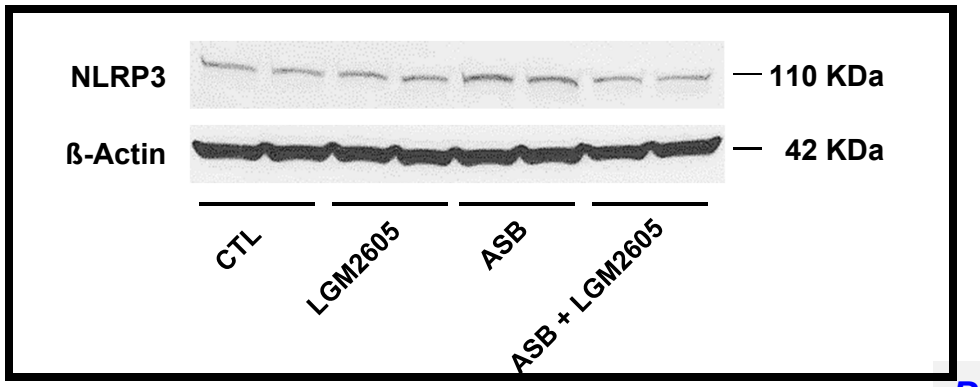


Pietrofesa et al, in review

SDG (LGM2605) prevents Asbestos-Induced Inflammasome Activation in Macrophages



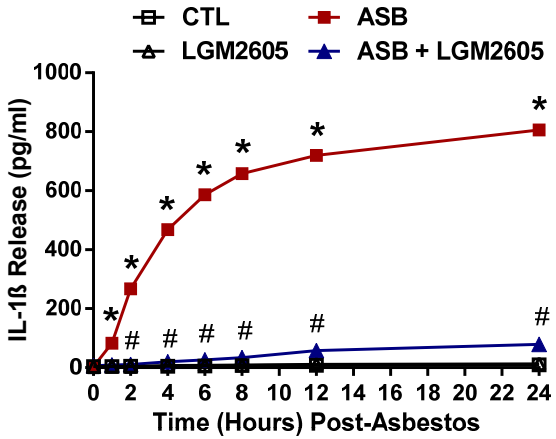


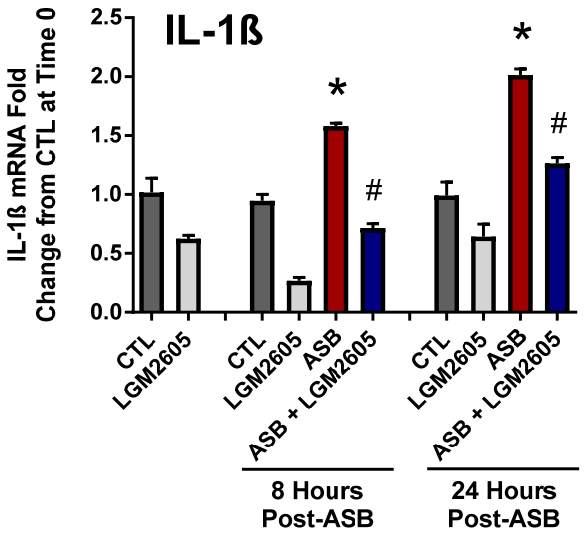


Pietrofesa et al, in review

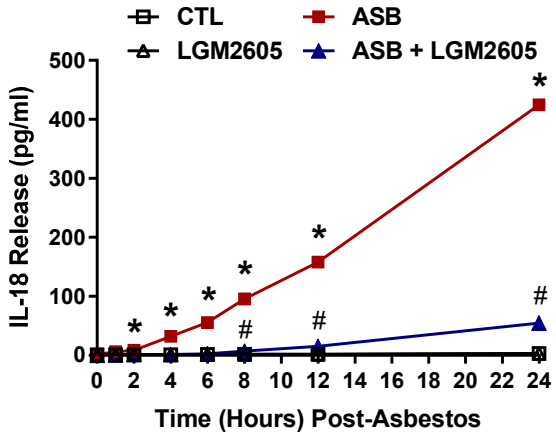
SDG (LGM2605) prevents Inflammasome-regulated Cytokine Secretion in Macrophages-(3)

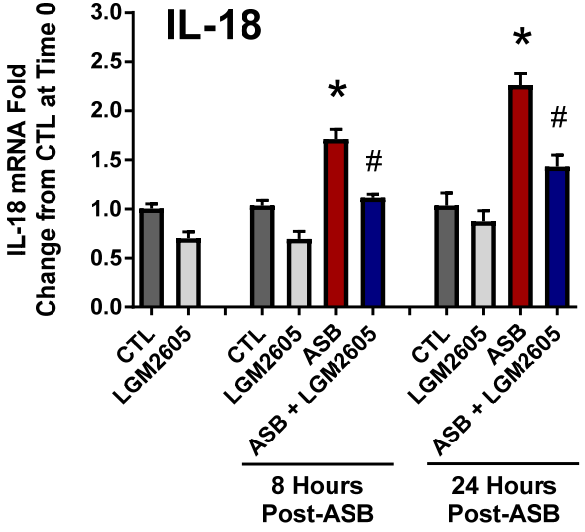
IL-1β





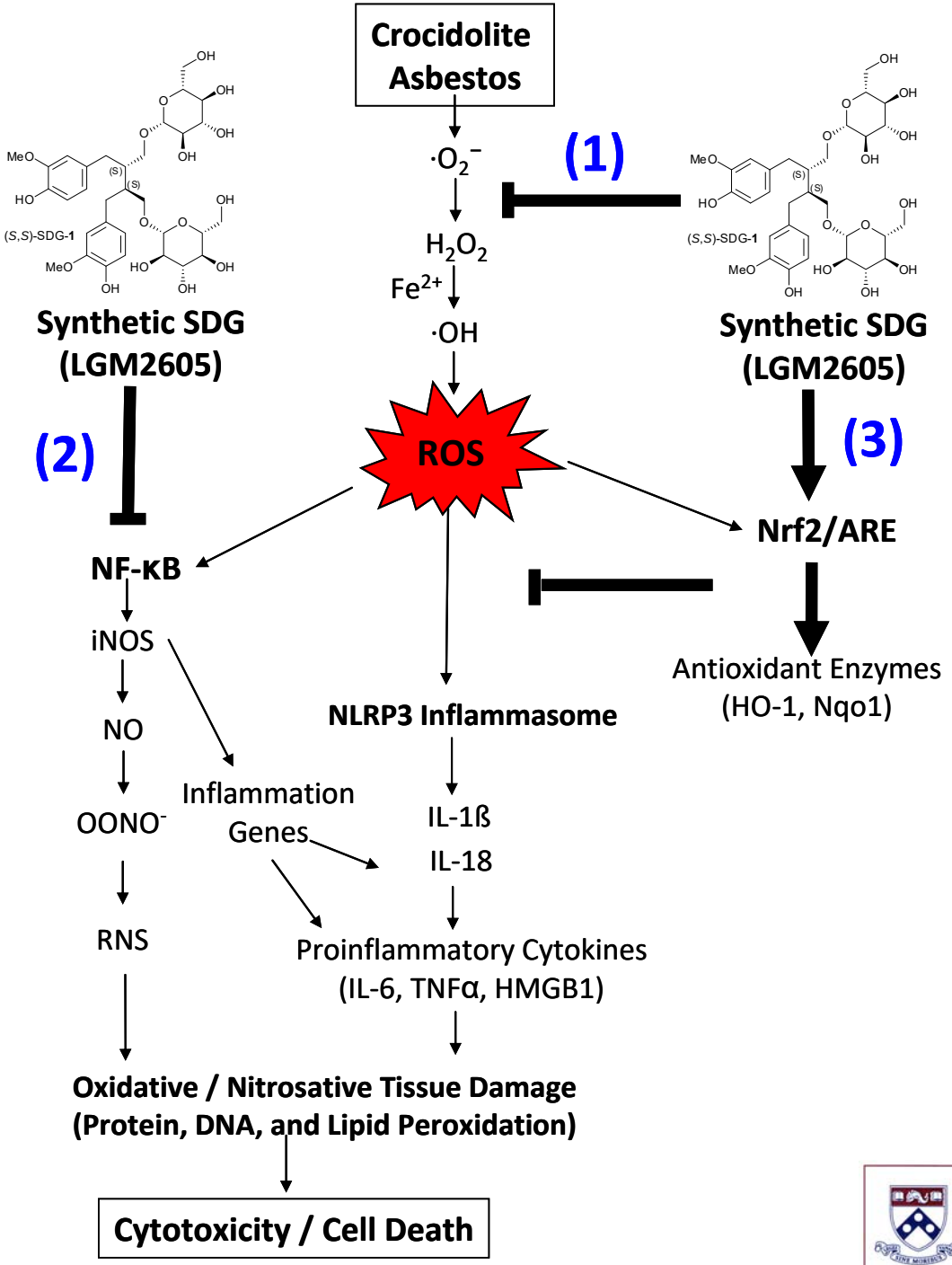
IL-18





Pietrofesa et al, in review

Proposed Mechanisms of SDG (LGM2605) Protection from Asbestos-Induced Cell Damage and Death



Pietrofesa et al, in review

Funding

National Institute of Allergy and Infectious Diseases (NIAID)
RC1AI081251

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

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