

ASSESSMENT OF NIOSH RESEARCH ROADMAP AND FUTURE DIRECTIONS

- State of the Science (Literature Review)
- Future Research Directions*
- Focus on *In Vitro* Studies*

STATE OF THE SCIENCE: WHAT'S MISSING!*

- Frustrated phagocytosis → ROS → TNF α (p32, Blake 1998).
 - TNF α + LPS are primers in human alveolar macrophages for many other cytokines (IL-1 β , IL-6, etc.)
- Asbestos fibers induce antioxidant defense enzymes, increases in glutathione synthesis repair, DNA repair enzymes, and iron mobilization.
- Asbestos fibers interact with membrane receptors and integrins (add to 1.6.4.3.2 membrane interactions.)
- Asbestos stimulates the inflammasome, chemokine production and inflammation.
- Asbestos stimulates proto-oncogene expression *in vivo* and other gene expression after inhalation.
- Apoptosis, necrosis, and autophagy vs. “membranolytic” toxicity.

* Current Concepts (peer reviewed 2005 + papers)

FRAMEWORK FOR RESEARCH

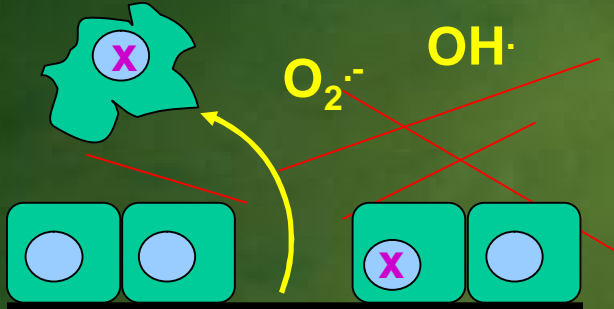
- Develop a broader understanding of the important determinants of toxicity for mineral fibers and other EMPs [2.2].
 - Conduct in vitro studies to ascertain what physical, chemical, and surface properties influence the toxicity of mineral fibers and other EMPs [2.2.1].*
 - Conduct animal studies to ascertain what physical and chemical properties influence the toxicity of minerals and other EMPs [2.2.2].

SUGGESTIONS

- Focus on molecular mechanisms of compensatory cell proliferation and transformation to malignancy rather than toxicity – dead cells don't give rise to cancers and fibrosis.
- Mechanisms of nonlethal DNA damage and repair.

STAGES OF CANCER

Initiation



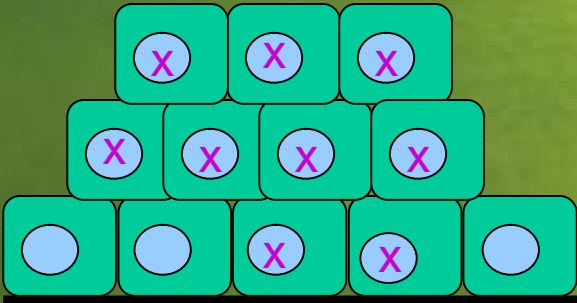
DNA damage/mutations

Epigenetic changes

↑ Oncogenes

↓ Tumor suppressor genes

Promotion

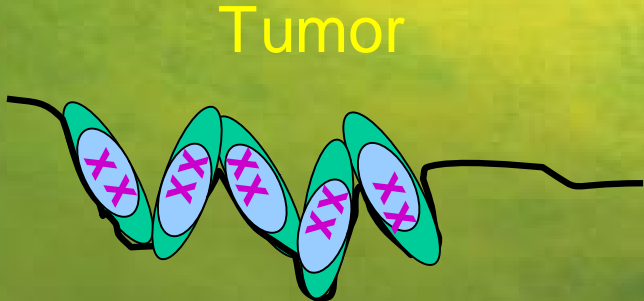


Expansion of initiated cells

Altered gene expression

**Chronic cell proliferation
and inflammation (fibrosis)**

Progression (Both)

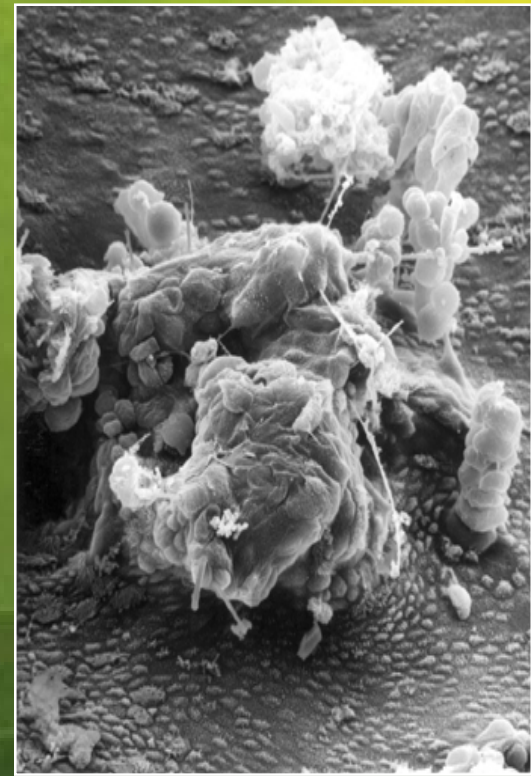
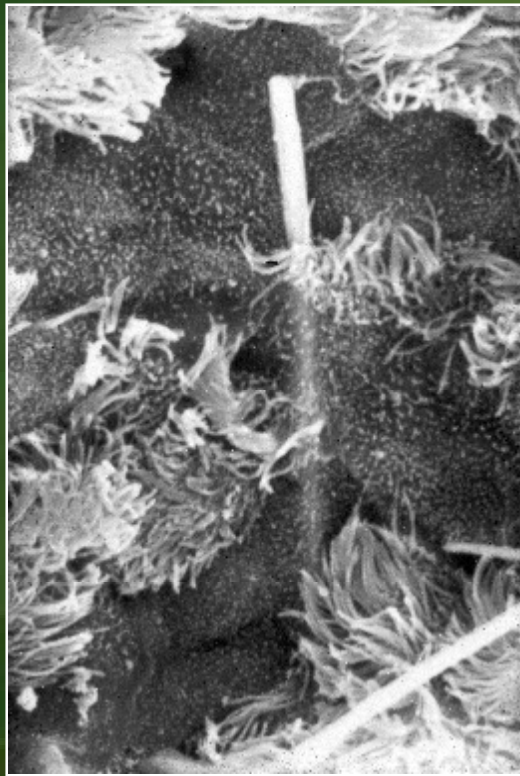


Additional genetic/
proliferative events

Invasion

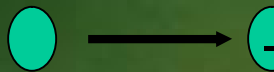
Metastasis

ASBESTOS FIBERS CAUSE CHRONIC CELL PROLIFERATION AND INFLAMMATION

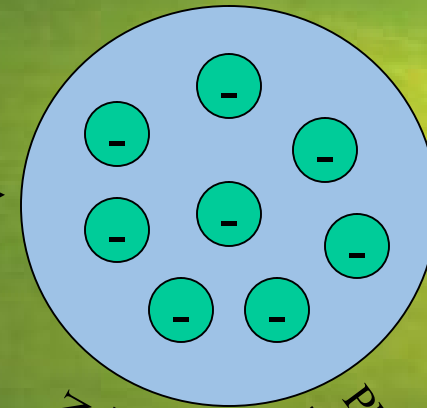


MULTIPLE MECHANISMS OF ASBESTOS-INDUCED CANCERS

INITIATION
(Genetic Damage)
Cell Replication



PROMOTION
(Fibrosis)
Cell Replication

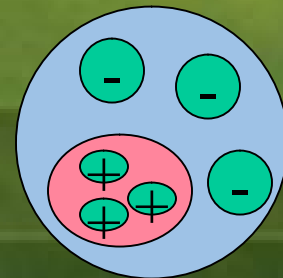
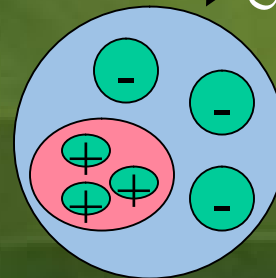


? SV40 (Mesothelioma)

? Smoking (Lung Cancer)

PROGRESSION
Cell Replication

PROGRESSION
Cell Replication



MESOTHELIOMA

LUNG CANCER

SUGGESTIONS

- Epigenetic changes
- Cell defense mechanisms
- Individual susceptibility factors/co-factors
(smoking, infection)
- Genomics, proteomics, and RNA interference
- Human telomerase immortalized cell lines
(hSAEC, and LP9-TERT) if primary cells are
unavailable

ADDITIONAL SUGGESTIONS 2.2.1

- 1) Less focus on genotoxicity, but more on inflammation and proliferation as prerequisites to fibroproliferative diseases and cancers – co-cultures, 3D, or *in vitro/in vivo* models.
- 2) Studies to verify whether fibers interact directly with genetic material *in vivo*.
- 3) Amounts of EMPs added to cells in culture cannot be extrapolated to inhalation exposures in man, but trends in responses should correlate with rodent and epidemiologic studies.
- 4) Dose response studies may produce different endpoints (ROS) and are necessary.
- 5) An interdisciplinary team of investigators including mineralogists to characterize reference samples prior to experiments is imperative!

Questions ?