- Circulating mesothelial precursor cells -

A new opportunity to detect pleural damage and mesothelioma after asbestos exposure?

Marc de Perrot, MD, MSc
Director, Toronto Mesothelioma Research Program
Professor of Surgery and Immunology, University of Toronto
Division of Thoracic Surgery
University Health Network
Toronto, Canada
Conflict of interest

- Bayer (speaker fees)
- Astra-Zeneca (Ad board)
Acknowledgement

Bill Duong
(Shana Kelley’s lab)

Licun Wu

Work in progress
Mesothelioma characteristics

- Rapid progression
- Late diagnosis
- Invasion of local structures (heart, chest wall)
- Symptoms are
  - Chest pain
  - Shortness of breath
  - Weight loss
  - Fatigue
Outcome of mesothelioma after diagnosis

Median survival
• 6 - 12 months

Prognostic factors
• Performance status
• Histology
• Gender
• Inflammatory markers (CRP, WBC, platelets, fibrinogen)

Screening program is active since 2005 in Toronto

Low dose CT chest for patients with history of asbestos exposure or pleural plaques

Characterize plaques at risk of transformation to mesothelioma
Screening program

• 2005 - 2019

• Enrolled about 1,500 individuals

• Previous asbestos exposure or presence of pleural plaques

• Median age of participants is 61 yo (32-85 yo)

• Smoking history: 73% of participants

• Blood sample collected at each visit
Number of cancer detected

Number of participants 1156
Total number of thoracic malignancies 16
  Lung cancer 8
  Pleural mesothelioma 4
  Abdominal mesothelioma 4

Mesothelioma in situ (BAP1 lost with no invasion on histology)
Role of serum markers for early detection

**Mesothelin**

**Osteopontin**

Lancet 2003;362:1612-16

NEJM 2005;353:1564-73
Fibulin-3 in mesothelioma

How asbestos drives the tissue towards tumors: YAP activation, macrophage and mesothelial precursor recruitment, RNA editing, and somatic mutations

Hubert Rehrauer 1 • Licun Wu 2 • Walter Blum 3 • Laszlo Pecze 3 • Thomas Henzi 3 • Véronique Serre-Beinier 4 • Catherine Aquino 1 • Bart Vrugt 5 • Marc de Perrot 2 • Beat Schwaller 3 • Emanuela Felley-Bosco 6

6-8wks old C57/Bl6

21 wks
8 x 400 μg Crocidolite ip every 3 weeks OR sham

12 wks

33 wks after first exposure

Blood Peritoneal lavage

Immune cell population mesothelial precursor
Cytokines /chemokines
Pathology, IHC

Mesothelium/mesothelioma

Spleen/pancreas/fat/ liver
Mesothelium/mesothelioma

Variation of gene expression
Peritoneal lavage after asbestos exposure

Mesothelial progenitor cells

Oncogene 2018;37:2645-59
Tracking the dynamics of circulating tumour cell phenotypes using nanoparticle-mediated magnetic ranking

Mahla Poudineh¹, Peter M. Aldridge², Sharif Ahmed³, Brenda J. Green², Leyla Kermanshah², Vivian Nguyen³, Carmen Tu³, Reza M. Mohamadi³, Robert K. Nam⁴, Aaron Hansen⁵, Srikala S. Sridhar⁵, Antonio Finelli⁵, Neil E. Fleshner⁵, Anthony M. Joshua⁵, Edward H. Sargent¹* and Shana O. Kelley²,3,6*
Magnetic ranking cytometry

• New approach that leverage immunomagnetic separation for profiling circulating cells based on their cell surface markers

• Whole blood sample is incubated with antibody-functionalized magnetic nanoparticles

• Phenotypic profile at a single cell level

• Very high level of sensitivity with the ability to profile cells at very low level of 10 cell per ml of blood
zxViva Device Overview

Simple Sample Preparation

Cell + Ab-MNP →

Magnetic Capture

F_{drag} → F_{mag}

Zone 1
Linear increment in height

Zone 8

Inlet
Z1 Z2 Z3 Z4 Z5 Z6 Z7 Z8 Outlet

Flow velocity
High Low

Courtesy of Bill Duong and Shana Kelley
Magnetic ranking cytometry

Intraperitoneal mesothelioma model (x 6 weeks)

Flow cytometry of peritoneal lavage

**MSLN+CD34+CD90+ in lavage**

**CTC counts / 1000 cells loaded**

**CTC counts / 0.5 mL of blood**

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**Zones**

- Naive
- 2 weeks
- 4 weeks
- 6 weeks
Presence of mesothelial progenitor cells after asbestos exposure and mesothelioma

1. HD: healthy donors (n=7)
2. Asb: asbestos-exposed individuals (n=-31)
3. MPM: mesothelioma patients (n=38)
Conclusions

• Important role for screening in asbestos exposed individuals

• CT scan is not ideal for screening

• Blood based or breath condensate screening methods are more adequate

• Serum tumor markers are not (yet) used clinically for screening

• Circulating mesothelial progenitor cells may offer new opportunities for screening population at risk after asbestos exposure (study in preparation)
Thank you