High Aspect Ratio Nanoparticles (HARN)

Length-Dependent Pathogenic Behaviour mimics that of asbestos in a mesothelial response model

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Warnings About Carbon Nanotubes
Potential for Harm

‘...Given previous experience with asbestos, we believe that nanotubes deserve special toxicological attention...’ 2004

‘....Fibre-shaped nanomaterials possibly represent a unique inhalation hazard, and their pulmonary toxicity should be evaluated as a matter of urgency..... failure to pick up asbestos-like behaviour as early as possible would be potentially devastating to the health of exposed people and to the future of the nanotechnology industry....’ 2006
High aspect ratio (or being a fibre) as an ‘extra hazard’ factor in the toxicity of a particle.

Aspect ratio = \( \frac{\text{Length}}{\text{Diameter}} \)

or ‘fibre’
Diseases caused by particles and fibres

Caused by particles and fibres at high dose

- Bronchogenic carcinoma

Caused by fibres at low dose

- Pleural mesothelioma
- Pleural plaque

Mesothelioma is the hallmark tumour of asbestos (fibre) exposure
HARN: Carbon Nanotubes, nanowires and nanorods

- Hexagonal arrangement of carbon atoms built up to form a fibre
  - Diameter in nanometre range
  - Length nanometres to hundreds of microns

- Useful physicochemical characteristics
  - Exceptional strength, electrical and thermal conductance

- Global market for carbon nanotubes is predicted to grow to over $1 billion by 2014*

- Assumed that carbon nanotubes are no more harmful than graphite

- Nanowires
  - Metallic (Ni, Pt, Au),
  - Semiconducting (Si, InP, GaN, etc.),
  - Insulating (SiO$_2$, TiO$_2$).

- Nanorods
  - Gold
  - Diamond
  - Aluminium

The importance of fibre length in fibre toxicity: the 1986 Davis study

<table>
<thead>
<tr>
<th>Extent of Fibrosis (asbestosis)</th>
<th>Cancer</th>
<th>Mesotheblionoma (peritoneal instillation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Short amosite</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>Long amosite</td>
<td>11.0</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95</td>
</tr>
</tbody>
</table>

Testing the hypothesis that nanotubes had the same length–dependent pathogenicity as asbestos

Panel of Particles Used in The Study

Controls

- **Long fibre amosite (LFA)**
- **Short fibre amosite (SFA)**
- **Nano-Particulate carbon black (NPCB)**

Note scale bars

Panel of Particles Used in The Study

Short/ Tangled Nanotubes

Panel of Particles Used in The Study

Long Straight Nanotubes

Note scale bars

Determining whether MWCNT show length dependent pathogenic behaviour in a model of direct mesothelial exposure

- Inject 50 µg of particles into the peritoneal cavity and directly expose the mesothelium
- Measure inflammation in washings from the peritoneal cavity
- Measure early fibrosis on the diaphragm

In previous studies long asbestos caused inflammation and fibrosis and short asbestos did not
**Long and short nanotubes Assessing the Acute and Chronic Inflammatory Response**

**Acute Inflammatory Response**
(24-hr post instillation)

**Chronic Inflammatory Response**
(7-days post instillation)

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**Foreign body giant cell**

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*P*<0.05, **P**<0.01, ***P***<0.001 vs. vehicle control

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Long and short nanotubes
Assessing the ability to cause granulomas (scar/fibrosis)

***P<0.001 vs. vehicle control

Hypothesized Mechanism

**Complete phagocytosis by macrophages**

- Short amosite
- Short Tangled
  - NT\textsubscript{tang}1
- Long Tangled
  - NT\textsubscript{tang}2

**Incomplete or frustrated phagocytosis**

- Long straight
  - Long amosite, NT\textsubscript{long}1, NT\textsubscript{long}2

- Incomplete or frustrated phagocytosis

**Cleared**

**PRO-INFLAMMATORY**

- E
Does a completely different HARN show length–dependent pathogenic behaviour: preliminary results for Long and short Nickel-nanowires

Ni nanowires (50µg per mouse)

~5 µm

~30 µm

***

***P<0.001 vs. NiNW extract

Ni nanowires made by Dr Adriele Prina Mello, Trinity College, Dublin
HARN, probably of any biopersistent (insoluble) material can probably behave like long asbestos if long enough (>about 20 µm)

- i.e. they show rapid inflammatory and fibrogenic effects in a model of direct mesothelial exposure
- In a previous study i.p. long but not short amosite caused mesothelioma in rodents
- the longer, straighter and more fibre-like a HARN sample, the more pathogenic it is likely to be
- HARN look like they conform to the general fibre paradigm that determines carcinogenicity of asbestos, glass fibre etc

Caveats of this work

To be a true risk for mesothelioma any HARN would need to:-

- Get airborne in the workplace as long fibres in sufficient quantity
- Be biopersistent
- Be able to migrate from the lung airspaces to the pleura
- Produce mesothelioma at the pleura after they reach it
- More studies are urgently needed especially assessment of exposure to long fibres in workplaces that handle HARN
- All the above applies only to CNT as fibres, they may well have adverse effects as particles
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We have reduced our prices on all carbon nanotubes: high purity; single-, double- or multi-walled; various diameter and length options; surface functionalizations possible. Click to find out more.
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