Interview with Prof. Ken Donaldson
Professor of Respiratory Toxicology, ELEGI Colt Laboratory, Centre for Inflammation Research, Medical School, University of Edinburgh

ICON: What is the most important thing that readers should take away from your publication?

Ken Donaldson: The study places carbon nanotubes within the paradigm that controls the pathogenicity of fibers such as asbestos. According to the paradigm, long, thin, insoluble fibers are pathogenic. What we showed was that the long multi-walled carbon nanotubes (MWNT) did conform to the paradigm in that the long MWNTs were pathogenic. The short ones weren’t, which also complies with the paradigm. The results were unwelcome but unsurprising since several influential groups have identified that nanotubes might behave like asbestos, although no one had yet done a proper study.

ICON: Briefly describe your experiment and the findings.

KD: To test the rule of fiber length we took two samples of short nanotubes, and two samples of long nanotubes; the paradigm rules would suggest the short ones would be harmless and the long ones pathogenic. The test was based on the fact that the mesothelium is a tissue targeted by amphibole asbestos, the most harmful asbestos type, causing a range of pathologies, the most severe of which is the tumor mesothelioma. Because mesotheliomas take a long time to develop, short-term effects on the mesothelium were measured – inflammation and granuloma (scar) formation.

Back in the 1980s I had studied this model and showed that it was highly responsive to long fibers. The short nanotubes did nothing. The long caused inflammation and scarring.

We had important controls – short and long asbestos fibers. We put those alongside in the study with the same result: Short asbestos fibers are harmless and long asbestos caused inflammation and scar formation.

ICON: What was the source of your MWNTs, and how did you expose the mice?

KD: We purchased the two short ones from Nanolabs; one of the long ones was a gift from the Mitsui Corporation and the other long one was made at the University of Cambridge. In the case of asbestos, people get their exposure by inhalation. The fibers find their way to the mesothelium, which encompasses the outside surface of the lung between the lungs and chest wall. What we did was use the identical surface in the body cavity – the abdominal mesothelium; we injected the fibers into the abdominal cavity of the mouse. It was a rapid and easy way to expose the sensitive mesothelial tissue.

ICON: Was there anything special about the animals you used in the experiment?

KD: No, they were normal laboratory mice.
**ICON:** What controls did you run and what was their purpose?

**KD:** We had a number of controls. First, the vehicle control, which was the protein solution used to disperse the nanotubes. Also, we used the long and short amosite asbestos fibers, which we had used in previous studies. Finally, we used nanoparticulate carbon black; these nanoparticles are composed of sheets of graphene in a ball shape. The carbon black was chosen since graphene in tubular form is the essential structure of MWNT. The vehicle had no effect; the short amosite had no effect; and the carbon black and the short nanotubes had no effect - just the long nanotubes and long asbestos, so all particles conformed to the paradigm.

**ICON:** What experiments are you running now to expand upon this result?

**KD:** We're still doing dose response studies to see what the lowest dose is. The study is a long way from saying if you inhale long multi-walled carbon nanotubes you will get mesothelioma. This study shows it’s possible, but we have to go quite a distance to show that inhaled nanotubes can find their way to the mesothelium, as asbestos does. We’re looking at other kinds of nanofibers as well, such as nickel nanowires, to see if they conform to the paradigm. Also, we don’t know the cut-off length for pathogenicity of either nanotubes or asbestos. It’s somewhere between 10 and 20 micrometers, but we don’t know exactly.

An important next step is to go into work places and see what is in the air. We don’t have to worry if workers are not exposed to long nanotubes. But we need exposure measurements. Risk is composed of two parts – hazard and exposure; we showed that long nanotubes could be a considerable hazard to the mesothelium and we now need more exposure studies to be able to predict risk. It’s important to point out that the study exclusively addressed fiber effects of nanotubes; different studies are needed to address whether nanotubes can have adverse effects by virtue of being particles.

**ICON:** What is your opinion of the Japanese study?

**KD:** It claims to demonstrate that nanotubes have the potential to cause mesothelioma, but it is flawed. There are at least three things that were wrong with the paper:

1. **The delivery of the dose.** In toxicology the dose is everything. The dose drives the response. In our study, the effective dose is long nanotubes. Their dose was big clumps of nanotubes, 100 microns in diameter, far bigger than any cell. They would never have reached the part of the lung where macrophage phagocytosis, a key factor in determining fiber pathogenicity, would have occurred. Nor are such big lumps likely to reach the sensitive mesothelium.

2. **The use of genetically modified mice.** To provide a shortcut, they used p53 defective animals. These mice were far more likely to get cancer. That’s fine and an interesting model, but what we don’t know is if this model is anything like the norm. It’s so sensitive that anything could have been an irritant. There was no control. C60 was not a good control since it’s an anti-oxidant. In short, this is an unvalidated model for mesothelioma.

3. **The size of the dose.** Three milligrams, or 3,000 micrograms, is 30,000 times the dose that we find to be the lowest dose that has an effect. It’s one reason that the fibers clumped together, probably. They seemed to have used that dose in order to meet the fiber criteria of $10^9$, a dosage defined by the European Union that was in common usage for detecting the carcinogenicity of fibers in rats. But that’s a rat dose, and these are mice.

**Bio**

Professor Ken Donaldson (KD) is the Scientific Director of the ELEGI Colt Laboratory in the Medical School of the University of Edinburgh, where he is Professor of Respiratory Toxicology. Prior to this he was Professor of Pathobiology, Napier University and before that Head of the Toxicology Unit, Institute of
Occupational Medicine, Edinburgh. He has a PhD and a DSc from the University of Edinburgh and a BSc(Hons) (First Class) in Biology from the University of Stirling and is a Fellow of several distinguished societies, including the Royal College of Pathologists.

Professor Donaldson is recognized as an expert in the mechanisms of lung disease caused by inhaled agents especially particles and fibres and in this capacity has provided expert opinion and consultancy to the US Environmental Protection Agency (North Carolina), US Health Effects Institute (Massachusetts), World Health Organisation, International Agency for Research on Cancer (Lyon France), WHO Air Quality and Health (Bonn, Germany), UK Medical Research Council, UK Health and Safety Executive, etc. KD sits on three government committees pertaining to toxicology of air pollutants – Committee on the Medical Effects of Air Pollution (COMEAP) and Expert Panel on Air Quality Standards (EPAQS) and Advisory committee on Hazardous Substances. KD has given advice on the toxicology of fibres to the US EPA and UK HSE. In relation to inhaled nanoparticles (NP) and nanotubes, KD was one of the initial proponents of the NP theory of the toxicity of particulate air pollution and has acted as a consultant to various bodies on the risk from NPs such as EU (SCEHNIR, COST), European Science Foundation, Health and Safety Executive, ECETOC and the WHO. He has published over 280 scientific papers, a large number on mechanism of lung injury caused by inhaled agents and currently has a research programme into the adverse effects of nanoparticles on the lungs and cardiovascular system. He is Founding Editor of the journal ‘Particle and Fibre Toxicology’ and Co Editor of ‘Particle Toxicology’, 2007, CRC Press.