

Impact case study (REF3b)

<p>Institution: University of Ulster</p>
<p>Unit of Assessment: 3B Allied Health Professions, Dentistry, Nursing and Pharmacy – Biomedical Sciences</p>
<p>Title of case study: Electron microscopy (EM) and nanobiology</p>
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>The microscopy facilities in the Biomedical Sciences Research Institute of the University of Ulster have been vastly improved through our collaboration with FEI, the largest European EM manufacturer, which has led them to manufacture a cryostage dual-beam instrument of our design with unique capabilities, and to set up their European reference laboratory here. This has generated two further sets of impacts: collaboration and consultancy with various firms wishing to use our advanced imaging facilities, and advice to national, EU and global bodies on the novel cytotoxic hazards of nanoparticles, a major but optically invisible by-product of modern industry, and consequent public health risks.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Dr George McKerr has for some years collaborated closely with FEI, the major European manufacturer of electron microscopes. Between 2002 and 2004 he visited their Nanoport Facility in Eindhoven and led the design of their groundbreaking Nova cryostage dual-beam instrument, and its application in emerging nanotechnologies. The Nova instrument generates a focused beam (FIB) of ions, from a liquid gallium source, that can remove material by sputtering, allowing precision milling of a specimen at the nanometre scale. We have shown this makes possible three-dimensional imaging of biological samples: each time the FIB removes a layer by high-current milling, it exposes a new face that can be imaged with a secondary scanning electron beam [1]. Dr McKerr’s modifications make possible the imaging of hydrated samples, including gels, foams and emulsions, which had previously been impossible to record at an ultrastructural level. With normal instruments, any residual water within the column significantly shortens the mean free path for accelerated ions, and thus degrades the imaging and machining capabilities. To deal with the hydration problem, a dual-beam instrument was reconfigured around a cryo-stage; rapidly frozen but fully hydrated samples can be entered into the column without any loss of vacuum [2]. The prototype built at Eindhoven has been developed into the production model, the Nova Nanolab 200 dual-beam microscope incorporating a Quorum cryostage: a very powerful tool for fundamental research and product development in the agri-food sector, pharmaceuticals, and biomedical technology.</p> <p>This collaboration has been a resounding success, establishing world firsts in bioimaging, and enabling us to generate previously inaccessible data. In consequence, FEI have established their European bioimaging reference laboratory in the BMSRI, with modern instruments for which we can develop further pioneering techniques, and to which scientists and industrialists wishing to make use of the most modern techniques are sent.</p> <p>This reference laboratory, created through a £1.457 M SRIF3 award to Prof Stephen Downes and Dr McKerr, contains three advanced instruments which have replaced the older equipment dating back to the early years of the University: a Tecnai 12 deep-field transmission EM for tomography, an environmental SEM that can image hydrated specimens, and a cryo-cooled Nova Nanolab 200 dual-beam instrument.</p> <p>With these electron microscopes we have also pursued research into the biological effects of nanoparticles, of sizes 1-100 nm, which of course cannot be visualised without electron microscopy. Both the potential benefits and the health hazards of these are receiving great attention, largely on account of the extreme reactivity of their surfaces, and their very high surface:mass ratio. Prof Vyvyan Howard has led research into a variety of toxic mechanisms that apply to nanoscale particles containing heavy metals [4-6], and has established our laboratory as a leading European nanotoxicology center, with nine papers on nanotoxicology over the last few years.</p>

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Key Researchers:

PhD student: Andreas Elsaesser (2007-2011);

HEI staff: George McKerr (Senior Lecturer and Director of Bioimaging, 1990 -); Vyvyan Howard (Professor of Bioimaging, 2005 -); Stephen Downes (Professor of Cancer Biology, 1995 -).

Research Staff: Barry O'Hagan (2006 -); Geza Staats de Yanés (2006 – 2012).

3. References to the research (indicative maximum of six references)**Publications**

1. Hazekamp J, Doherty S, Elsaesser A, Barnes CA, O'Hagan BM, McKerr G, Howard CV (2011) Focussed ion beam milling at grazing incidence angles. *J Microsc.* 242, 104-110.

2. Lamers E, Walboomers XF, Domanski M, McKerr G, O'Hagan BM, Barnes CA, Peto L, Lutge R, Winnubst LA, Gardeniers HJ, Jansen JA (2011) Cryo dualbeam focused ion beam–scanning electron microscopy to evaluate the interface between cells and nanopatterned scaffolds *Tissue Engineering Part C*, 17, DOI: 10.1089/ten.tec.2010.0251

3. Elsaesser A, Howard CV (2011) Toxicology of nanoparticles. *Adv Drug Deliv Rev.*, 64, 129-137.

4. Elsaesser A, Taylor A, de Yanés GS, McKerr G, Kim EM, O'Hare E, Howard CV (2010) Quantification of nanoparticle uptake by cells using microscopical and analytical techniques. *Nanomedicine* 5, 1447

5. Elsaesser A, Barnes CA, McKerr G, Salvati A, Lynch I, Dawson KA, Howard CV (2011) Quantification of nanoparticle uptake by cells using an unbiased sampling method and electron microscopy. *Nanomedicine* 6, 1189-1198.

6. Van Hoecke K, De Schamphelaere KA, Ali Z, Zhang F, Elsaesser A, Rivera-Gil P, Parak WJ, Smaghe G, Howard CV, Janssen CR (2013) Ecotoxicity and uptake of polymer coated gold nanoparticles. *Nanotoxicology* 7, 37-47.

Key research grants

Dr G McKerr, Prof CS Downes. "FEI Phillips Centre for Advanced Bioimaging", SRIF3, 2005-2008, £1,457,340.

Dr G McKerr, Prof CS Downes. "Center for advanced bioimaging"; FEI Phillips, 2006-2010, £438,585.

Prof CV Howard, Dr G McKerr. STREP project 'Nanointeract', EU Framework 6. 2006 – 2008, £330,000.

Prof CV Howard, Dr C Hoelscher, DR YM Kim. NMP project 'NeuroNano'. EU Framework 7, 2008-2011, £450,000.

Dr G McKerr. "Laboratory equipment for new tissue engineering facility". Research Council Infrastructure Fund, 2010, £650,000.

4. Details of the impact (indicative maximum 750 words)

The impact is best considered under two heads: industrial, and government policy.

The microscopy facilities in the University of Ulster have a long history of industrial collaboration, dating back to the analysis of cheese micro-structure, as part of an IDB-funded consultancy in 1998, that was a major factor in convincing Dairy Produce Packers Ireland (now Kerry Foods) to move their cheese production factory from Tipperary to Coleraine, near to the University of Ulster campus, bringing about 300 jobs with them. Our analysis of cheese continues [see item 1 in evidence below]

The ongoing collaboration with FEI, and our impact on their instrument design, have been described above. Our cooperation with them has led to the manufacture of a novel variant of dual-beam microscopes, uniquely suitable for detailed examination of biological cryosamples, currently retailing at over £1M each. As FEI's European Reference Laboratory for advanced EM techniques,

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we have had more than a dozen visits sponsored by FEI from laboratories in the UK and other parts of Europe [2] This is now being extended through our investment in a Leica tissue-imaging laboratory, with a STED instrument capable of resolving nanoparticles at below the normal limits of light resolution.

We led a gathering of scientists from Unilever's world-wide measuring and instrumentation laboratories (Coleraine, 2005), and the world's first Biological Dual-Beam EM Symposium (Coleraine, 2007). We are currently collaborating on dual-beam analysis of cryo-samples with Unilever, who have funded three CAST PhD awards (2 completed)

We are also providing EM imaging and analysis, on a consultancy basis, for a range of companies including:

Glanbia (Kilkenny): cheese analysis [1]

Kara Irish Pottery (Boston and Londonderry): natural stone imaging [3]

Nanoscope Services (Bristol) a relationship, which facilitates their customers in the oil exploration industry and investigation of new energy sources [4]

Nicobrand plc (Coleraine): powder rheology [5]

Patentnav Ireland Ltd (Belfast): cryo-EM images of milk-derived drinks [6]

Raptor Photonics (Larne): quantum dot and nanoparticle imaging development [7]

Tactility Factory (Belfast): nanocatalyst analysis [3]

Unilever, Port Sunlight, Wirral: cryo-EM images [8]

Warner-Chilcott (Larne plant of US-based company): EMs for pharmaceutical analysis [9]

The impact on government policy has been in terms of alerting national and EU bodies to the complex and not always fully appreciated hazards of nanoparticles. This first came to notice with Prof Howard's book 'Particulate Matter: Properties and Effects upon Health' (Maynard RL & Howard CV, BIOS Scientific Publishers, Oxford, 1999).

Since coming to the University of Ulster Prof Howard has made presentations to numerous fora, national, European and global, on the impacts of nanomaterials on health. These resulted in his contribution, pp 35-36 and 105-108, to the Health & Consumer Protection Directorate General of the European Commission's report "Nanotechnologies: a Preliminary Risk Analysis" [10]. This report was regarded by the Risk Assessment Unit of the Directorate as an important first step towards analyzing the potential risks of nanotechnologies and what they may imply. Subsequently, he was, at the invitation of the World Health Organisation Europe, the opening speaker at the Inaugural Meeting of the European Environment and Health Task Force, Bled, Slovenia, 2011, and was lead author of the subsequent draft report [11] on Nanomaterials and Health, Policy Implications, sponsored by the EU and WHO Europe under the EU PAVEL environmental footprinting project. This recommends that new risk assessments must be developed for the licensing of products containing nanomaterials. These recommendations have taken more concrete form in the recent report of the WHO expert meeting "Nanotechnology and human health: Scientific evidence and risk governance" (Bonn, 2012, of which Prof Howard is again a main author, advising a precautionary approach [12].

Prof Howard was also a contributor, interviewed at length on the subjects of low-dose nanotoxicology and the production of nanoparticles by incinerators, to the documentary film "Trashed", by Blenheim Films presented by Jeremy Irons, which addresses the way waste materials are generated and disposed of, and the consequences to human health and ecological problems of improper disposal. This was selected for the documentary section of the Cannes Film Festival, May 2012 9 [13].

5. Sources to corroborate the impact (indicative maximum of 10 references)**Microscope technology and applications:**

Letters of support have been provided from:

[1] Director of Technical Services, Glanbia Cheese Ltd., 35 Steps Road, Magheralin, Craigavon, Co. Armagh BT67 0QY

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- [2] FEI Company, Achtsweg Noord 5, 5600KA Eindhoven, The Netherlands
- [3] Innovation Ulster, Shore Road, Newtownabbey, Co. Antrim BT37 0QB (for Tactility Factory and Kara Irish Pottery)
- [4] Commercial Director, Nanoscope Services Ltd, 30 Station Road Workshops, Kingswood, Bristol BS15 4P
- [5] Director of Operations, Nicobrand Ltd, 189 Castleroe Road, Coleraine, Co. Londonderry BT51 3RP
- [6] Patentnav Ireland Ltd, 11 Fortwilliam Demesne, Belfast BT15 4FD
- [7] Raptor Photonics Ltd, Willowbank Business Park, Larne, Co. Antrim BT40 2SF
- [8] Open Innovation Director, Unilever R&D, Port Sunlight Laboratory, Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW
- [9] Warner Chilcott Ltd., Old Belfast Road, Millbrook, Larne, Co. Antrim BT40 2SH

Influence on governmental and NGO perception of hazards of nanoparticles:

Pdfs for the following policy documents:

- [10] EU Nanotechnology risk analysis, 2004
- [11] Draft report from WHO 2011 Slovenia meeting
- [12] Report from 2012 Bonn WHO meeting

are available at <http://biomed.science.ulster.ac.uk/nsb/-Reports-.html>

Also film quoted in text: [13] www.trashedfilm.com