

Impact case study (REF3b)

Institution: University of Kent
Unit of Assessment: 8, Chemistry
Title of case study: Nanoparticles for Biomedical Applications
<p>1. Summary of the impact</p> <p>The nanobiotechnology research group at the University of Kent (Bruce <i>et al.</i>) has pioneered the ability to control, manipulate and commercially process magnetite nanoparticles. Two spinout companies, EryDel and Diatheva have been formed, with a €6 million venture capital grant, as a direct result of the Kent-led research. EryDel (in collaboration with Philips Healthcare) are exploiting the materials worldwide for drug delivery (Erydex), with US and European approval for Orphan drug designation given in 2013 for genetic diseases, and Diatheva are marketing the technology for forensic diagnostic kits. The predicted five-year revenue is €35 million with a potential market of €17 billion.</p>
<p>2. Underpinning research</p> <p>The underpinning research originated from an €11.5 million European Commission funded FP6 project called "NACBO" - <i>Novel and Improved Nanomaterials, Chemistries and Apparatus for Nano-Biotechnology</i>, which ran from 2004-2009. The integrated research project, part of the NMP (nanotechnology) thematic priority, was led by Prof Ian Bruce at the University of Kent and brought together six universities (Shanghai, Moscow, Urbino, Tel Aviv, Jerusalem and Kent), three Government agencies (Central Public Health Laboratory in the UK and Criminalpol and Istituto Zooprofilattico in Italy) and three companies (Phillips, Proligo and Savyon). The project designed, synthesized and characterized a broad range of biological and non-biological nanocomposite silica, magnetite and carbon materials and their hybrids. Robust scale-up methodologies were developed leading to commercially viable applications in drug delivery, molecular diagnostics and forensics.</p> <p>Kent Research Focus</p> <ol style="list-style-type: none"> 1. Understanding and controlling the variables involved in producing defined geometry, composite, silica-iron oxide (magnetite) nanoparticles of sizes between 10 to 100nm diameters (2, 4). 2. Understanding and controlling the variables involved in the surface modification of such materials with organosilanes and ligands that would render them useful and stable in biological and biomedical applications (1, 3, 5, 6). 3. Scale-up production of the resultant materials (once best variants had been selected and evaluated in desired applications) to a level and cost that would render them commercially viable. <p>Underpinning Research Outcomes</p> <ol style="list-style-type: none"> 1. A library of composite silica-magnetite particles were successfully synthesized and produced on large scale. 2. Detailed understanding of their compositions and surface geometries and chemistries was obtained and how they could be chemically activated to amino-functionality in a controlled and measurable manner by treatment with aminosilanes. 3. Detailed knowledge of and ability to modify the particles surfaces with bioligands in a controlled fashion was obtained. <p>All basic and applied research was conducted between 2004 and 2011 at Kent, by the following key researchers (dates refer to period of employment at Kent):</p> <ul style="list-style-type: none"> • Prof Ian Bruce, 2004–2011, Head of Nanobiotechnology Group, University of Kent. Currently Emeritus Professor of Nanobiotechnology. • Dr Tapas Sen, 2003–2008, Postdoctoral Research Assistant, Nanobiotechnology Group. • Dr Stephen Bagshaw, 2005-2006, Postdoctoral Research Assistant, Nanobiotechnology

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Group.

- [Dr Stefano Biagini](#), 1999 - present, Senior Lecturer in Organic Chemistry, Functional Materials Group.
- Dr Marion Van De Waterbeem, 2005-2009, , PhD student, Functional Materials Group and Nanobiotechnology Group, co-supervised by Prof Ian Bruce and Dr Stefano Biagini.
- Dr Antonio Sebastianelli, PhD student, Nanobiotechnology Group, supervised by Prof Ian Bruce.

The project has been used as an exemplar of European excellence in science meetings across the World by the European Commission. The project was recently nominated a success story for Europe (page 44):

http://ec.europa.eu/research/industrial_technologies/pdf/successful-eu-nanotech-research_en.pdf).

The 2011 report stated that “NACBO was a highly successful project that reached or exceeded all of its objectives... NACBO hit on a key that seemed to unlock a treasure box, namely that certain well- made and characterized materials, their surfaces and architectures possess the ability to be used almost universally in a very wide range of applications”.

Subsequent fundamental research has been funded by two further European Commission nanotechnology grants, detailed in section 3.

3. References to the research

References [1], [2] and [6] best indicate the quality of the underpinning research):

1. **Bruce IJ, Sen T** “Surface modification of magnetic nanoparticles with alkoxy silanes and their application in magnetic bioseparations”, *Langmuir*, 2005, **21(15)**, 7029-7035, DOI: <http://dx.doi.org/10.1021/la050553t>
2. **Sen T, Sebastianelli A, Bruce IJ** “Mesoporous silica-magnetite nanocomposite: Fabrication and applications in magnetic bioseparations”, *Journal of the American Chemical Society*, 2006, **128(22)**, 7130-7131 DOI: <http://dx.doi.org/10.1021/ja061393q>
3. Amagliani G, Omiccioli E, Del Campo A, **Bruce IJ**, Brandi G, Magnani M, “Development of a magnetic capture hybridization-PCR assay for *Listeria monocytogenes* direct detection in milk samples”, *Journal of Applied Microbiology*, 2006, **100(2)**, 375-383. DOI: <http://dx.doi.org/10.1111/j.1365-2672.2005.02761.x>
4. **Sen T, Bruce IJ**, “Mesoporous silica-magnetite nanocomposites: Fabrication, characterization and applications in biosciences”, *Microporous and Mesoporous Materials*, 2009, **120(3)**, 246-251, DOI: <http://dx.doi.org/10.1016/j.micromeso.2008.11.012>
5. **Van De Waterbeemd M, Sen T, Biagini S, Bruce IJ**, “Surface functionalisation of magnetic nanoparticles: Quantification of surface to bulk amine density”, *Micro and Nano Letters*, 2010, **5(5)**, 282-285. DOI: <http://dx.doi.org/10.1049/mnl.2010.0112>
6. Antonelli A, Sfara C, Manuali E, **Bruce IJ**, Magnani M “Encapsulation of superparamagnetic nanoparticles into red blood cells as new carriers of MRI contrast agents”, *Nanomedicine*, 2011, **6(2)**, 211-223. DOI: <http://dx.doi.org/10.2217/NNM.10.163>

Key competitive research grants

- EU FP6 *Integrated Project* “NACBO: Novel and improved nanomaterials, chemistries and apparatus for nanobiotechnology”. €11.5 million, 13 partner 6 country consortium 2004-2009. NMP4-CT-2004-500804 **Led by Prof Bruce, University of Kent**
- European Union FP6 *Network* “SELECTNANO: Development of multifunctional nanometallic particles using a new process – sonoelectrochemistry” 2005-2009 €3.3 million, 13 partner, 7 country consortium. **Project Partner, (2nd) Prof Bruce, University of Kent, €270K**

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- European Union FP6 *Integrated Project* “CHILL ON” 2006 – 2011 €15Million, 32 partner, 12 country consortium. **Project partner (7th), Prof Bruce, University of Kent, €307K**

4. Details of the impact

Exploiting nanomaterials for drug delivery

The Kent research into nanoparticulate magnetite (described in section 2) laid the foundation for EryDel's (<http://www.erydel.com/>) preliminary studies into stability, functionality and delivery of iron base contrast agents using Erythrocyte ghosts.

EryDel is an SME, founded in 2007 by the University of Urbino, Italy as a direct result of the Kent-led European Commission NACBO project. The Kent research was conducted in close collaboration with the Healthcare Division of Royal Philips Electronics at Hamburg, Germany using their experimental medical imaging platforms for small mammals. It led to the signature of a joint accord between Phillips and EryDel relating to the development and exploitation of the processes and materials involved. These processes and materials are unique, covered by international patents, and possess the potential to significantly impact a global market estimated to be worth in excess of €11 billion by 2015. Together, Royal Philips Electronics and EryDel are actively pursuing the commercial development and exploitation of the materials and processes involved. As a consequence of this work and optimisation of the erythrocyte encapsulation process, the company has developed the erythrocyte ghost system into a platform for drug delivery. It has successfully concluded the Phase II Proof of Concept Study “*Evaluation of Effects of Intra-Erythrocyte Dexamethasone Sodium Phosphate (EryDex) on Neurological Symptoms in Ataxia-Telangiectasia (A-T) Patients*”, EudraCT Number 2010-022315-19 and has just announced (June 2013) that the European Medicinal Agency has [approved Orphan Drug Designation for EryDex](#) for the treatment of Ataxia Telangiectasia. A-T is a rare, neurodegenerative, inherited disease causing severe disability. Orphan Drug status allows the company 10 years of marketing exclusivity from the time of approval.

EryDex also has the potential for use in the treatment for a variety of other conditions and clinical pilot studies have already been conducted in Europe in patients with chronic obstructive pulmonary disease, cystic fibrosis, ulcerative colitis and Crohn's disease.

The Kent research team and EryDel's founders (Prof Magnami) were co-collaborators on three European Commission nanotechnology grants (section 3), have published a number of joint publications since 2004 (including the key reference 6, section 3) and have jointly presented at numerous conferences.

Molecular diagnostics and forensics

The nanomaterials produced at Kent as part of the NACBO project have underwritten the development of, and have been incorporated into, a number of molecular diagnostic kits for the extraction of nucleic acids, e.g. Bacterial DNA isolation ([MBK0005](#)), *Listeria monocytogenes* DNA ([MBK0002](#)), and the detection of microorganisms e.g. *Legionella* ([MBK0051](#)) and microalga ([MBK0003](#)). The diagnostic kits are marketed worldwide by Diatheva (www.diatheva.com), an SME founded in 2002, for research and therapeutic applications in the field of cancer, microbial infection and pharmacogenics. Reference 3, section 3 is the key joint publication between Kent and Diatheva's founders, outlining the joint research and potential impact. In 2012 a 51% share of Diatheva was [acquired by the SOL Group](#). The [SOL Group](#) is an Italian based multinational group present in 20 European countries and India, employing over 2,350 people and has an annual revenue of €555 million.

In 2011, the European Commission summed up the impact from the Kent-led NACBO project as follows: “Materials and processes generated by the [NACBO] consortium, particularly surface activation strategies, materials for use as contrast agents and/or in drug delivery and diagnostic kits, are already being commercially exploited by partners or in later stages of clinical evaluation. Future revenues over the next 5 years are estimated at least around € 35 million and projected additional future revenue based on market penetration by project outputs could be in the region of between €100 million to €500 million over the next 5 to 10 years.”

“Outputs from the project are already positively contributing to the improvement of diagnostics

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(health and forensics), not only within the European Union but also worldwide. In the context of forensics, improved detection limit sensitivities and better robustness in genetic profiling using materials and procedures developed in the project are already helping to solve criminal cases and increase individuals' security and protection from crime. Finally, the surface activation approaches developed in the project are already making fine chemical manufacturing processes (involved in the production of ultra-high quality pharmaceutical grade materials) more robust and reproducible reducing associated cost, time and undesirable environmental consequences."

5. Sources to corroborate the impact

Despite assurances of REF confidentiality the company was only willing to offer statements already in the public domain.

- "Successful European nanotechnology research: Outstanding science and technology to match the needs of a future society", Directorate-General for Research and Innovation, 2011, ISBN 978-92-79-15623-6:
http://ec.europa.eu/research/industrial_technologies/pdf/successful-eu-nanotech-research_en.pdf
EU document highlighting successful EU projects in nanotechnology, the NACBO project and its impact are highlighted on pages 44-46, Spotlight on NACBO.
- NACBO Final Activity Report, 2010:
http://cordis.europa.eu/publication/rcn/12321_en.html
The final report summarising all final outcomes and outputs of the NACBO project. The spin-out company EryDel is highlighted on pages 5, 10, 16, 28 and 48.
- EryDel's press releases for Orphan Drug approval in Europe and the US, 2013:
<http://www.erydel.com/en/press-releases>
- U.S. Department of Health and Human Services Orphan Drug List:
www.hrsa.gov/opa/programrequirements/orphandrugexclusion/orphandruglist.pdf
EryDel product listed on page 24.
- European Commission list of official designated Orphan Drugs:
<http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>
EU designation EU/3/13/1158.
- SOL Group acquires majority of Diatheva as further step in the biotech sector, 2012:
<http://www.diatheva.com/newsDettaglio.aspx?id=120>
- Novel and Improved Nanomaterials, Chemistries and apparatus for Nanobiotechnology: the NACBO project – Special Report, *Nanomedicine*, 2011, 6(2), 187-193, ISSN 1743-5889