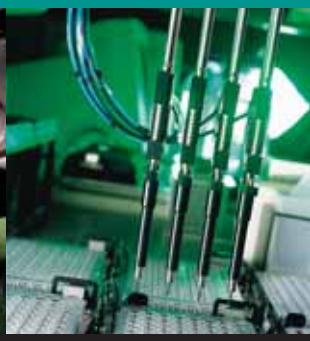
NMS Innovation News

Incorporating the former MET Newsletter

2007 | issue 01







ADVANCED MATERIALS | MEDICAL | COMMUNICATIONS | ENERGY | MANUFACTURING

New NMS Innovation R&D Programme

In April 2007, the NMS projects funded by the former DTI (now DIUS) were rearranged into a new set of programmes following the recommendation of the NMS Review in 2005-2006. With a simplified structure of fewer and larger programmes that group together projects with similar objectives, timescales and impacts, the programmes will be more efficient to operate and manage.

The NMS Innovation R&D programme within the NMS portfolio builds on the success of the Measurement for Emerging Technologies Programme, which comes to a close at the end of March 2008. It will have a new scope in line with the new NMS structure, focussing on developing new measurement capabilities in the government's Technology Strategy priority areas of advanced manufacturing, information and communication technologies, healthcare, security, transport, energy and the environment.

For further information on the NMS please contact the NPL Helpline on 020 8943 6880 or e-mail enquiry@npl.co.uk

Can Bigger Really Be Better?

Regenerative medicine can be defined as "the use of cell therapies and/or tissue engineered products to replace, repair and regenerate tissues in the body". The current focus in this area relates to the use of stem cells and their tremendous potential in many experimental and therapeutic applications. However, there are several fundamental issues that pose scientific challenges. One particular measurement challenge concerns the availability of sufficient quantities of cells. This can only be accomplished by increasing the scale of reproducible cell production in combination with culture condition optimisation. Traditionally, automation (such as robotic manipulation) or bioprocessing (larger scale manufacture/culture) have been considered. To date such approaches have proven difficult and challenging.

Existing bioreactor technologies point one way for larger-scale cell expansion. However, whilst many of these systems work well on the small scale, engineering, reliability or performance issues are encountered when capacity is increased to that of a production scale. In the case of bioreactor design for tissue growth, the field is even more exploratory.

Bioreactor design is dependent on the type of tissue to be grown, and must accommodate clinical and Good Manufacturing Practice (GMP) requirements. In both cases, the provision of nutrients to the cells and efficient withdrawal of toxic or inhibitory metabolic by-products are critical to maintain a stable environment conducive to cell growth. Physical stimuli may also be necessary for tissue constructs. Continuous monitoring and control of environmental parameters are needed to ensure production of a reproducible and uniform product.

Against this background, work led by LGC is helping to provide robust, controlled and intelligent technology, operable by generalists within a quality control process and therefore capable of aiding the commercialisation of regenerative medicine products. The overall focus is on being able ultimately to monitor the differentiation status of cells and cell selection using non-invasive strategies.

Key measurement issues associated with applicability, functionality and use of a range of platform technologies are being assessed, to help understand how variations in input factors, such as

nel technology for life

LGC Setting standards in analytical science

NPL National Physical Laboratory

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temperature and stimulus, affect output parameters such as cell status and development, and tissue formation.

We have successfully grown human embryonic carcinoma (EC) cells (University of Sheffield) on microparticles in an environmentally controlled, continuous-stirred tank bioreactor, maintaining viability and without eliciting trans-differentiation. This has been followed by selective differentiation of the cells down a neural lineage using retinoic acid. However, the yields of neuronal cells from this differentiation step have typically been low and result in a highly mixed cell population. One of the biggest challenges, therefore, lies with improving the yield and/or the separation of the required cells from a background of undifferentiated cells.

Current efforts are focused on the latter and use dielectrophoresis to manipulate cells allowing single cell selection and visualisation. This technique exerts a force on a particle though application of a non-uniform electric field and offers a powerful technique that has great potential for use as part of an automated high throughput system when combined with cell harvesting and online cell fractionation. All particles exhibit dielectrophoretic activity in the presence of electric fields and do not require the particles to be charged themselves. However, the strength of the force depends strongly on the medium, shape and size, and the frequency of the electric field.

The commercially available dielectrophoresis equipment here consists of flow chambers (50 µm diameter) within chips containing miniature elements that provide directional flow or entrapment (Cytocon 400, Perkin Elmer). This platform has been established successfully at LGC as a new National Metrology Institute capability. It is being used to test the feasibility of cell identification and separation involving associated cell labelling with specific biomarkers (NCAM, Nestin, SSEA4 and Oct4).

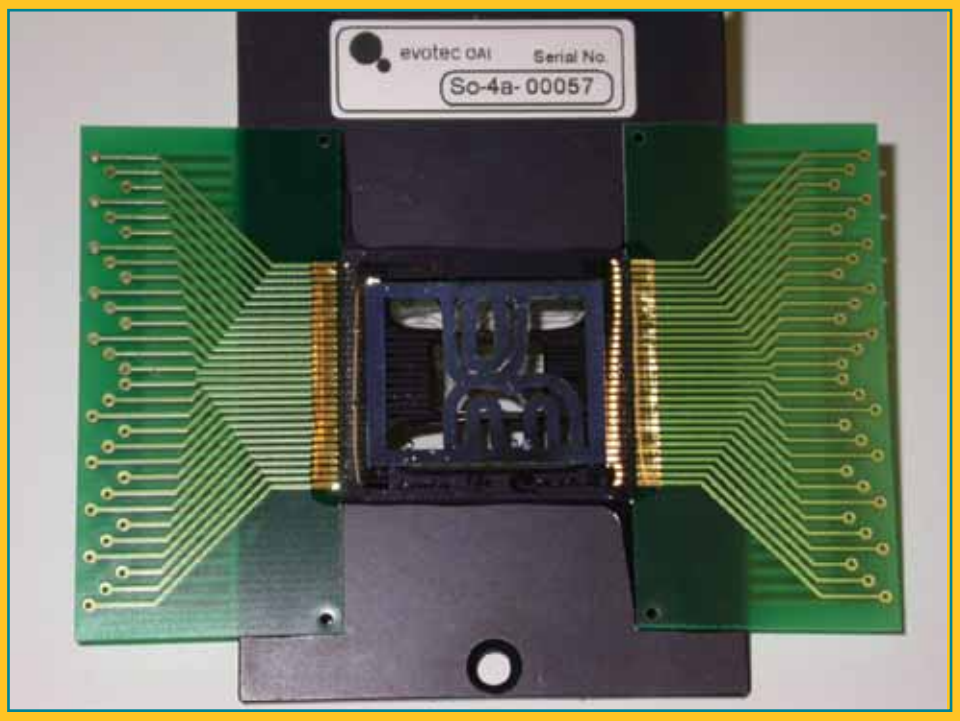

Figure 1: Dielectrophoresis chip for single cell analysis and separation

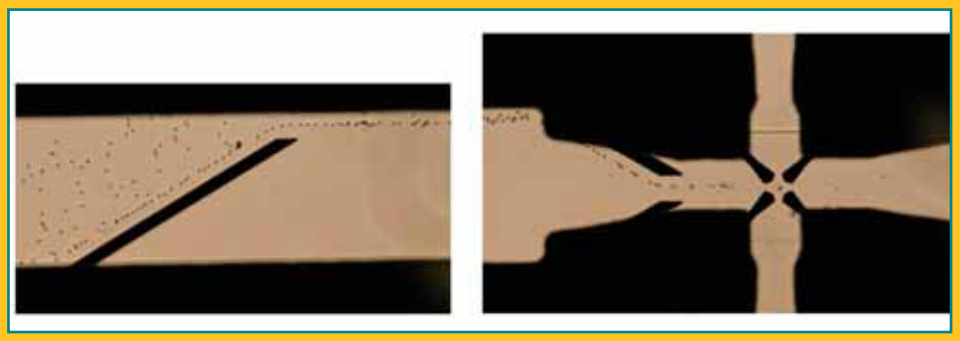

Figure 2: Deflector element (left) aligning cells for the funnel element. Funnel element with cell trapped in cage element (right). Cells can be manipulated within the cage (i.e. rotated x/y axis) and labelled with antibody staining via flow channels (top and bottom of cage)

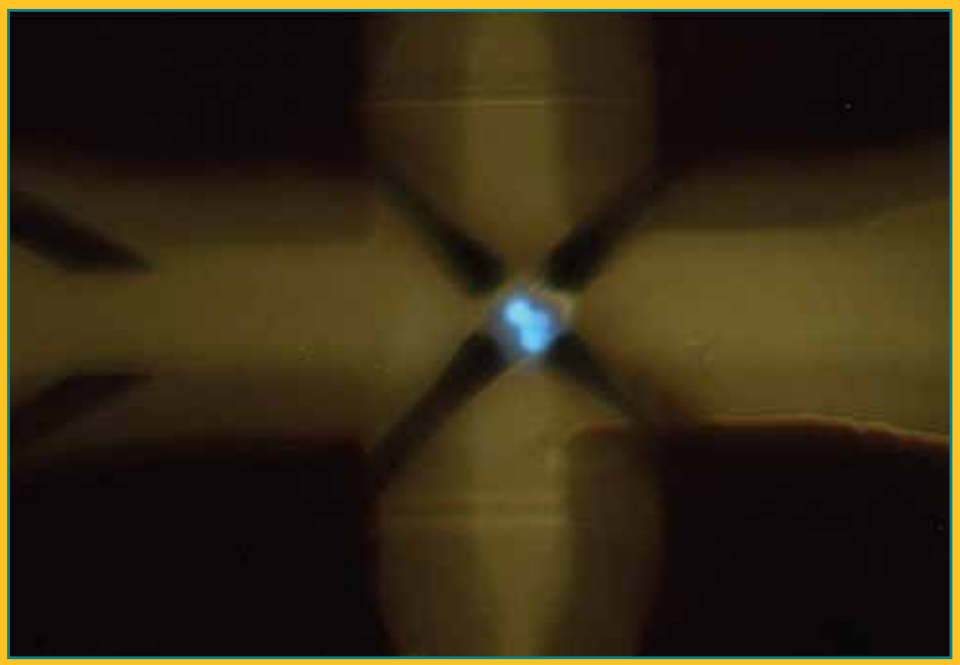

Figure 3: Three cells held in cage element and stained with Hoechst stain to visualise via fluorescent microscopy.

This approach will pave the way for further detailed analysis via our current collaboration with the University of Southampton, who will assess the impedance properties of both EC and neuronal cells with a view to achieving proof of principle for a 'label free' method of cell identification and separation. Such an approach would allow enrichment of target cells for further cell culture without compromising cell health as a result of attached antibodies and hence any automated manufacturing process.

In tandem, non-invasive optical measurement techniques are under development at NPL. One arm of this aims to measure cells on beads in a bioreactor or comparable model by constructing and utilising a full field Optical Coherence Tomography (OCT) system. In parallel, a backscattering spectroscopy method is also being investigated to distinguish, non-invasively, different kinds and states of cells (live/dead) on surfaces or on single particles.

It is essential that intelligent, robust and integrated cell culture systems appropriate to the clinical application under consideration, are available in the future to enable the efficient and cost-effective production of regenerative medicine therapies. This multi-centred, multi-technique approach specifically addresses critical metrology issues to enable proof of principle of techniques for improving the production of new therapeutic treatments in the volumes and of the quality required to help speed transfer into the clinic.

Current collaborators include:

Reneuron, Cerestem/KCL, ReInnervate, Abcellute, Nova Biomedical, NPL, CELS, University of Sheffield, University of Southampton. UCL and QMUL act as external advisors.

For further information on this project please contact neil.harris@lgc.co.uk or visit the MET website at http://www.metprog.org.uk

Multiferroic Materials - New Measurement System Developed at NPL

Multiferroic materials are very promising candidates for the development of advanced sensors and technologies because they uniquely exhibit simultaneously magnetic, electric and piezo properties. The electric and magnetic phases that coexist in a multiferroic material can couple to each other directly or via strain mediated effects leading to the occurrence of the magneto-electric (ME) coupling. The ME coupling can be induced either magnetically or electrically and this effect is described by the ME coupling coefficient. The measurement and modelling of the ME coupling of multiferroics is highly complex and requires the development of specialized equipment currently unavailable. As part of the MET 2.1 project, NPL has developed brand new metrology for the measurement of the magnetic induced ME coupling coefficient of multiferroics. Our first unique experimental system has been designed for room temperature measurement of multiferroics and is based on the quasi-static piezoelectric coefficient measurement under applied magnetic field.

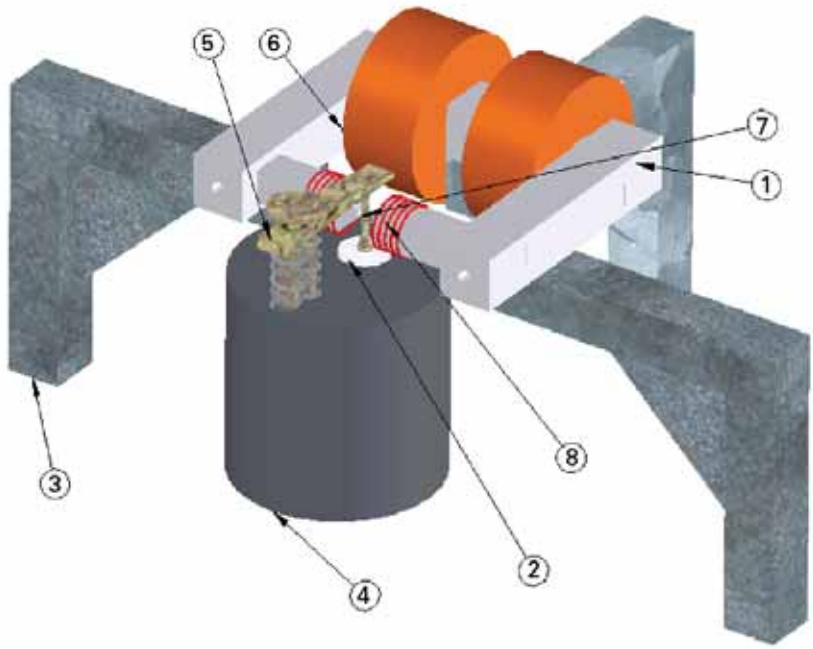

Figure 1.

1. Electromagnet's poles
2. Lower contact and AC load system
3. Electromagnet support
4. BerlinCourt d33 measurement system
5. Top sample contact
6. DC coils of the electromagnet
7. Sample
8. AC coils

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If you would like further information on any aspect of NMS Innovation R&D Programme, see www.metprog.org.uk
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This has been achieved by modifying a quasi-static 'Berlincourt' instrument in order to measure both piezoelectric and multiferroic properties. Our measurement system can, for the first time, provide simultaneously the d_{33} piezo-coefficient of a multiferroic and the ME coupling coefficient, which can be extracted from a set of d_{33} measurements. Figure 1 shows the experimental diagram, which requires the simultaneous application of DC and AC magnetic fields in addition to a weak constant applied AC stress. The samples successfully examined so far have been laminated tri-layer multiferroic structures CoFeV (160 µm) / PZT(320 µm) / CoFeV (160 µm) with a disk shape of 8 mm diameter. These samples are extremely sensitive to AC magnetic fields showing a linear response in d_{33} or the induced open circuit voltage, which makes them suitable for advanced actuators or multifunctional sensors. NPL's studies continue with the extension of our multiferroic metrologies to micro / nano scale spatial resolution through the realisation of a unique SPM based approach, which will provide NPL with the world's first fully traceable measurement system for multifunctional, multiferroic materials used for the next generation of smart sensors and actuators.

Figure 2. Multiferroic structures studied

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Forthcoming Events

EMAN / NPL @ GTMA "Make Measurement Matter" Roadshow
14 November 2007
RAF Cosford, Shropshire
Contact: leanne.gardener@npl.co.uk

EMAN: Thermal Effects on Machine Tools - an Update
21 November 2007,
University of Huddersfield, Huddersfield
Contact: leanne.gardener@npl.co.uk

Joint Time and Frequency Club Meeting
27 November 2007
NPL, Teddington
http://www.npl.co.uk/time/club/

UKAS Electrical Day @ NPL
28 November 2007
NPL, Teddington
http://www.npl.co.uk/electromagnetic/clubs/

EM Day 2007
29 November 2007
NPL, Teddington
http://www.npl.co.uk/electromagnetic/clubs/

Seminar for SMEs: A Smarter Way to Develop New Products & Processes
5 December 2007
NPL, Teddington
Contact: christine.reilly@npl.co.uk

CEM 2008 - Seventh International Conference on Computation in Electromagnetics
7 - 10 April 2008
Quality Hotel, Brighton
Note: Call for papers deadline for submission 12 November 2007
http://conferences.theiet.org/cem