Conference Scene

Innovative medical devices and nanotechnology

Innovative medical devices and nanotechnology: 1-day interactive workshop Sheffield University North Campus, Sheffield, UK, 8 July 2009

The Institute of Nanotechnology, in collaboration with the University of Sheffield, organized this 1-day interactive workshop held at the Kroto Institute, Sheffield University North Campus, Sheffield, UK. The workshop provided a showcase of innovative and exciting new medical nanotechnologies. The topics addressed included diagnostics and imaging, tissue engineering, polymer therapeutics and drug delivery, and drug discovery and screening. The workshop was attended by clinicians, medical researchers, industry experts, healthcare managers, academics and students. The workshop was divided into four sessions: regenerative medicine and smart materials; innovations in medical diagnostics and sensing; new techniques for drug discovery and drug delivery; and novel therapeutics. A concluding talk was given by Richard Moore from the Institute of Nanotechnology on the importance of nanoscale hazard identification and risk management for medical nanotechnologies.

Ian Douglas from the School of Clinical Dentistry, University of Sheffield, UK, opened the first session and described a very interesting example of how tissue engineering can be used for testing and developing new diagnostic devices. Douglas presented work from a multi-disciplinary team comprising chemists, tissue engineers and microbiologists, aimed at the development of polymers that bind to bacteria and give an alarm signal above a threshold number of bacteria. The polymer is branched poly(isopropylacrylamide) (BPNIAM), to which the antibiotics vancomycin and modified polymyxin-B have been coupled. Vancomycin binds Gram-positive bacteria (such as *Staphylococcus aureus*) and polymyxin-B binds Gram-negative (such as *Pseudomonas aeruginosa*). Binding of the bacteria at 37°C causes the polymers to become hydrophobic and to collapse out of solution, with the bacteria attached. The novel aspect of this work is that the new technology was tested on recently developed 3D models of wounded human skin that had been infected with two species of bacteria. This allowed the study of the newly developed diagnostic device in a complex environment that resembles the clinical scenario closely. The work, still ongoing, shows that both BPNIAM-vancomycin and -polymyxin-B are sensitive to the presence of Gram-positive and Gram-negative bacteria, respectively. These polymers can effectively reduce the bacteria in infected tissue-engineered

human skin by simple application and removal of the polymers, either in soluble form or coated onto a biocompatible hydrogel membrane.

The second talk in the session on regenerative medicine, presented by Paul Hatton, also from the School of Clinical Dentistry, University of Sheffield, illustrated how materials and devices for regenerative medicine can benefit enormously from novel design opportunities enabled by nanotechnology. Hatton described how nanostructured composites exhibit significantly enhanced properties and that, as a consequence, they have the potential to significantly improve the clinical performance of biomaterials used in dentistry and medicine. He explained that the first generation of nanocomposites is already being used in restorative dentistry and provided examples of how nanostructured materials can overcome some of the challenges presented by the use of composites in orthopedics.

The final talk of the first session, from Chuh K Chong from the Department of Engineering Materials, University of Sheffield, discussed the importance of geometry in the design of vascular implants. An example based on coronary artery bypass grafting demonstrated the importance of geometry in controlling areas of flow separation, wall shear stress patterns and stagnation point. A change in geometry in the implant, for example involving a vein cuff, as used commonly in peripheral artery bypasses, results in a

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large coherent vortex, which alters the distribution of wall shear stress in the device and causes the stagnation point to move to and fro along the arterial flow during the cardiac cycle. The presentation ended with a discussion on the possible additional use of nanotechnology in the design of vascular grafts, with the suggestion of some possible interesting approaches.

The second session on medical diagnostics and sensing started with an industrial presentation by Paulo Ferreira do Santos from the Porto-based Tomorrow Options Microelectronics. Ferreira presented an approach based on microelectronics sensing devices. These can be engineered so as to provide quantitative data to assess patients' conditions (particularly in relation to diabetic complications, such as foot pressure sores resulting from peripheral neuropathies) that complements the physician's observation and analysis, helping them to prescribe optimal individual medical intervention in each case and assess the treatment results.

The session continued with a presentation by Steve Matcher from the Department of Engineering Materials at the University of Sheffield. Matcher described new advances in optical coherence tomography (OCT). OCT is an interferometric technique that uses near-infrared/infrared lasers that are able to penetrate relatively deeply into solid tissues. Matcher presented some new research from within his group on OCT advances, including the possibility of the generation of functional imaging and the detection of physiologically relevant parameters such as collagen orientation and blood flow. Finally, he showed some preliminary data on the design of nanoparticles that can be used as contrast agents in OCT.

The third speaker of the session was Ian L Pykett, from Phasefocus Ltd. Pykett presented a novel imaging technique known as coherent diffraction imaging. This is based on a ptychographical iterative engine that can generate high-definition images of an object without the need for lenses. This is achieved by transferring the task of image formation from physical components to the software algorithm. This approach is particularly suitable for the microscopy of specimens that have very low optical contrast (e.g., hydrogels, including contact

lenses) or that need to be maintained within a liquid microenvironment (e.g., live cell preparations).

The session on medical diagnostics and sensing was concluded by another industrial presentation by Sameer Kothari from Zilico Ltd. Kothari introduced the topic of electrical impedance spectroscopy and how this technique can measure the resistivity of cells and so detect changes as cells progress from a normal to precancerous state and then become cancerous. This technology is currently being evaluated and commercialized by Zilico for the diagnosis of cervical cancers. Kothari showed clinical data from trials with 500 women that demonstrated the superior performance of the new device based on this principle over existing diagnostic procedures (i.e., colposcopy) with almost 100% accuracy in detecting cervical cancer. These promising results suggest that assessing smear tests will no longer be a subjective process and the need for diagnostic biopsies will be greatly reduced. Kothari also pointed out that although this technology is currently focused on the detection of cervical cancer, the very promising clinical data so far augurs well for the translation into other types of cancer.

The afternoon part of the meeting started with the third session on new techniques for drug discovery and drug delivery. The first speaker was Giuseppe Battaglia from the University of Sheffield, previously in the Department of Engineering Materials and now in the Department of Biomedical Science. He presented a novel strategy for drug delivery engineered around one of the most important challenges of any therapeutics administration: the ability to deliver active compounds within living cells. Battaglia showed how natural vectors such as transporting vesicles or viruses could be mimicked using synthetic polymers. He presented the possibility of creating nanoscopic vesicles formed by the assembly of polymeric analogues of lipids. These nanostructures, known as polymerosomes, can be designed so as to encapsulate large quantities of hydrophilic and hydrophobic compounds and release them upon some external stimuli. Battaglia described, in particular, pH-sensitive polymerosomes that disassemble only when taken up by cells via endocytosis. As a consequence

of the natural endocytic mechanism, the internalized material experiences acidic environments. Under these conditions, the polymersomes dissolve and release their cargo, triggering a temporary osmotic destabilization of the endocytic organelle, thereby achieving the release of the compound within the cell cytosol. Battaglia showed that the size, surface chemistry and, more interestingly, surface topology of the polymersomes control cell internalization kinetics. He showed how this effective cytosolic delivery vector can be used for DNA, RNA, drug, protein and contrast agent delivery, with implications in both therapeutic and diagnostics applications.

The session continued with two contributions from industry by Malcolm Wilkinson from Kirkstall Ltd. and Jim Freeth from Retrogenix Ltd. The presentations showed two different approaches to enhancing cell cultures and their potential applications for drug discovery and biomaterial development.

Wilkinson showed an alternative to traditional 2D cell cultures that resembles more closely the complexity of the human physiological environment. Kirkstall Ltd. has recently developed the Quasi-Vivo™ systems, which incorporate modular multicompartmental bioreactor arrays for cell culture experiments. The new system offers mechanical stimuli in the form of flow and biochemical stimuli from cells placed in connected modules. Wilkinson described a number of macro-, micro- and nanoscale features of the cell culture chambers that give rise to dramatic improvements in cell viability and function compared with older technologies. Development is still in progress but the data available so far bode well for a future reduction in, or even eventual replacement of, animal studies by using sophisticated microbioreactor systems.

Along similar lines, Freeth from Retrogenix presented a different approach, again based on cell arrays, to improve drug screening. At Retrogenix, Freeth and colleagues are developing a cell microarray based on the controlled genetic manipulation of cells in a combinatorial fashion. This is based on culturing cells on microarrays previously embedded with lipid–DNA complexes that transfect the cell, triggering the expression of specific proteins. The

arrays are subsequently exposed to libraries of compounds and the drug–protein interactions are studied *in cellulo*. This technology will allow almost every known human protein to be produced in human cells on an array chip. This is expected to make a major contribution to shedding light on the ‘primary’ target of drugs or small molecules for which a desirable disease-relevant biological effect is known. Eventually, this could identify completely new disease treatment opportunities for existing (and safe) drugs as well as the determination of secondary targets that can help in understanding drug toxicity and side effects.

The final session of the workshop was centered on novel therapeutics. Richard Ross, from the Medical School at the University of Sheffield and Chief Scientific Officer of Asterion Ltd., described how therapeutic cytokine hormones (e.g., growth hormone [GH]) can be modified so as to improve their plasma circulation, limiting the number of administrations and improving their efficacy. Ross explained that cytokine formulations can be improved by binding the hormone with a genetically engineered ligand–receptor fusion (LR-fusion) of GH with its extracellular domain receptor. He explained that, in solution, the LR-fusion exists as both a dimer and monomer, forming a reciprocal, head-to-tail dimer that provides a reservoir of inactive hormone, as occurs naturally with GH and its binding protein. This leads to an LR-fusion of cytokine to its extracellular receptor, generating a potent long-acting agonist with exceptional pharmacokinetic properties, as illustrated by the results of animal studies presented.

The final presentation of the session, by Mimoun Azzouz from the Medical School at the University of Sheffield, described the possibility of engineering lentiviral vectors based on the equine infectious anemia virus for efficient and sustained transgene expression in cells of the nervous system. Azzouz explained how this effective gene-delivery vector can be used for treating human neurodegenerative diseases such as amyotrophic lateral sclerosis and spinal muscular atrophy. The data indicate tremendous potential at improving motor neuron survival in animal models of motor neuron diseases, either by inducing the

expression of neuroprotective factors in spinal motor neurons or by silencing malfunctioning gene expression using RNA interference approaches. The presented results, which are about to be expanded into clinical trials, indicate that gene therapy using engineered viruses could prove beneficial in the treatment of motor neurone diseases.

The final talk of the workshop was given by Richard Moore of the Institute of Nanotechnology. Moore pointed out that the application of nanotechnology in medicine brings new challenges in relation to the identification of hazards arising from the nanoscale aspects involved and the estimation of the risks arising from those hazards. He discussed how the challenge is furthermore compounded by the fact that some products may fall under more than one regulatory system, each of which has different traditions in terms of addressing risk issues. Moore explained some of the key concepts and aspects of hazards and risks that are pertinent to medicine at the nanoscale, as well as highlighting how important it is to obtain knowledge of these

at an early stage in relation to both product safety and communication to professionals and the public.

The workshop concluded with a 20 min open discussion on the technologies presented during the day and the challenges involved in their commercialization. The discussion, chaired by Battaglia and Moore, examined how difficult, but nevertheless important, it is to generate the right level of information flow between the different disciplines involved in nanomedicine, and how this should be synergistically coordinated in order to make an impact on everyday medical practice.

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