RESEARCH ANNOTATION

The 2009 British Orthopaedic Research Society/Orthopaedic Research Society Travelling Fellowship

This paper outlines the recent development of an exchange Travelling Fellowship scheme between the British and American Orthopaedic Research Societies.

In 2007 the British Orthopaedic Research Society (BORS), and its American counterpart the Orthopaedic Research Society (ORS), initiated a BORS/ORS Travelling Research Fellowship. In alternate years a group of six British Fellows comprising clinicians, engineers and biologists visit the United States, with a reciprocal visit the following year. Fellows travel for up to four weeks in the host country, where they visit four to eight orthopaedic research centres. At each centre the Fellows present their own research, listen to research lectures from faculty members of the host institution, and participate in discussion fora. They also visit research laboratories and engage in similar activities pertinent to musculoskeletal science. The purpose of this Fellowship is to promote transatlantic interaction, collaboration and enthusiasm for orthopaedic research among young surgeons, engineers and biologists. It is expected that as a result of their shared experience the Fellows will form strong, enduring professional and social ties with each other and with the other researchers they encounter. The concept of the Fellowship was laid down by Hamish Simpson (Edinburgh) and Christopher Evans (Boston). The 2009 BORS/ORS Travelling Fellowship was put together by the hard work of BORS President Brigitte Scammell (Nottingham), and the hosts at the American centres. The 2009 Fellows included three orthopaedic trainees, Wasim Khan (Royal National Orthopaedic Hospital, Stanmore), James Huntley (Edinburgh University) and Ines Reichert (Imperial College London); two mechanical engineers, Nicholas Dunne (Queen’s University Belfast) and Thomas Joyce (Newcastle University); and one cell biologist, Sarah Snelling (Oxford University). Their research interests represent the themes that are at the forefront of orthopaedic research today. Each fellow had a doctorate and prepared between six and ten lectures for the Fellowship.

Itinerary

The 2009 Fellowship began at the ORS and American Academy of Orthopaedic Surgeons (AAOS) Annual Meetings in Las Vegas between February 22nd and 27th. The Fellows then visited the Department of Orthopaedic Surgery Laboratories at the University of California, San Francisco, and the Orthopaedic Trauma Institute at San Francisco General Hospital, where they were hosted by Theodore Mclau and Ralph Marcucio between February 28th and March 4th. They also visited the Orthopaedic Research Laboratories at the Veterans’ Hospital in San Francisco. The Fellows then travelled to the Mayo Clinic in Rochester, Minnesota, where they were hosted by Peter Armadio and Kai-Nan An between March 5th and 7th. In Philadelphia the Fellows visited the Thomas Jefferson University, where they were hosted by Javad Parvizi and Maurizio Pacifici, and the University of Pennsylvania, where they were hosted by Lou Soslowsky between March 8th and 11th. At the Hospital for Special Surgery, New York, the Fellows were hosted by Adele Boskey, Mathias Bostrum and Steven and Mary Goldring between March 12th and 14th.

Each host institution put together an excellent, well-organised itinerary that included research laboratory visits, technical presentations and research discussion fora. These meetings presented many opportunities for the Fellows to discuss complementary research interests with the faculty members from each host institution, and to explore potential opportunities for collaborative projects.

Below is a personal account from the Fellows, detailing their research interests, highlights of the Fellowship, and how the interactions and collaborations have helped shape their own research strategies.
Wasim Khan
My main research interests include mesenchymal stem cells, cartilage repair and chondrogenesis. During the Fellowship I presented work on the cell surface characterisation of bone marrow and synovial fat pad-derived mesenchymal stem cells, and showed the presence of a perivascular marker on these cells suggesting pericytes as a possible candidate stem cell in these tissues. I have also shown that stem cells from both sources exhibit enhanced chondrogenesis using fibroblast growth factor-2 (FGF2) and hypoxic culture conditions, and this has potential implications for the use of these cells in cartilage repair.

During the visit to San Francisco, Chuanyong Lu from the host institution presented interesting work on the role of hypoxia in fracture repair, highlighting the importance and differential effects of oxygen tension on different tissue at different times. I have shown that the pericyte marker 3G5 is present in human stem cells. It was interesting to visit the Kurt Hankerson laboratories at the University of Philadelphia, which, using a different perivascular marker in a mouse model, has found similar results. At the Thomas Jefferson University, Vickram Srivinas gave a talk on the role of hypoxia in stem cells, and Markaran Rishbud spoke about the role of oxygen tension in cartilage metabolism. Dr Srivinas is a leader in hypoxia research and he allowed me to view his laboratory setup, including the hypoxic chambers, and discussed unpublished work on the little-known hypoxia-inducible factor-2 (HIF2) pathway in chondrogenesis.

Nicholas Dunne
On a personal level, this Fellowship was an excellent opportunity to meet and exchange research ideas with world-leading orthopaedic researchers and to visit their laboratories. Moreover, it provided the potential to foster collaborative opportunities with United States and United Kingdom researchers working in complementary areas. My field of expertise focuses on the development and understanding of cement-based materials for hard-tissue replacement, and the development of hierarchical constructs for tissue engineering.

I gave five research papers covering the development of bone substitutes and calcium phosphate cements for spinal repair, the augmentation of orthopaedic bone cement using additives such as multi-walled carbon nanotubes and chitosan, and the real-time monitoring of polymethylmethacrylate bone cement using novel spectroscopic techniques.

I found the exchange of ideas and views between the BORS/ORS Fellows highly stimulating, providing further evidence that to conduct good musculoskeletal research requires a strong interdisciplinary approach. I was impressed by the scientific quality of the research conducted by each host institution. These include the Biomechanics and Biomaterials Laboratory at Orthopaedic Trauma Institute (San Francisco), which encourages orthopaedic surgeons and engineers working together to overcome current challenges related to musculoskeletal diseases; the exceptional work being conducted at the Cartilage and Connective Tissue and the Tissue Engineering and Biomaterials Laboratories (Mayo Clinic), ranging from the development of novel electrically conductive biomaterials to the manufacturing of porous tissue-engineered bioresorbable scaffolds; the excellent research being conducted by Noreen Hickok and Javad Parvizi’s group (Thomas Jefferson University) developing novel drug delivery strategies to prevent bacterial adherence and biofilm formation around prosthetic implants following joint replacement surgery; and the excellent presentation by Timothy Wright (Hospital for Special Surgery) highlighting the pre-clinical experimental techniques used to assess the efficacy of novel hydrogel-based biomaterials for use in total joint replacements.

James Huntley
This Fellowship was inspiring and empowering for many reasons, both in general and specifically. My research interests are cartilage repair, articular physiology, growth plate function and musculoskeletal infection. These were all well represented at every stage of the Fellowship. I presented research showing chondrocyte death at the edge of articular wounds, and further that this response can be ameliorated by improvements in instrument design and modifications to the bathing solution. I also presented data concerning the salvage of implants in periprosthetic infection.

I benefited greatly from discussions with the engineering and cell biology representatives of our group, and was immensely impressed by the calibre of the teams at all the institutions we visited. A few of the many highlights were a presentation by Hubert Kim (San Francisco) on his laboratory’s work on the potential for disease-modifying drugs after articular injury, a presentation by Jim Fitzsimmon’s group (Mayo Clinic) on their experience in ‘neocartilage’ generation in vitro, and the clinical and scientific arms of Javad Parvizi’s group (Thomas Jefferson University). I also enjoyed several hours of discussion with Peter Torzilli (Hospital for Special Surgery) and a review of his laboratory. These discussions have been pivotal to guiding my future research plans and collaborative ventures.

Thomas Joyce
My orthopaedic research interests include explant analysis, in vitro testing of prostheses, and biotribology with special emphasis on resurfacing hip prostheses, metacarpophalangeal prostheses and the wear of orthopaedic biopolymers.

A combined symposium at the ORS/AAOS Meeting on ‘Current controversies in bearing surface science’ served to highlight not only the crucial relevance of bearing surfaces and wear in orthopaedic surgery today, but also the need for close collaborations between surgeons and engineers. At the Mayo Clinic I presented research showing that a biopolymer wear screening rig developed in my laboratory has been validated to the relevant international standard (ASTM F732) and, most importantly, provides in vitro wear rates that correlate well with clinical data. At the Hospital for Special...
Surgery I presented work on the analysis of *ex vivo* resurfacing hip prostheses and comparisons with clinical data showing that the longevity of these devices *in vivo* depends on a number of factors, including the angles of inclination and anteversion of the acetabular component as well as the diameter of the articulation. At the University of Pennsylvania I presented results from the *in vitro* wear testing of orthopaedic biopolymers when a visco-supplement was added to the lubricant. At the Hospital for Special Surgery both Nicholas and I had a chance to visit Timothy Wright’s laboratory and benefited from useful interactions. In addition, the discussions held at the Thomas Jefferson Institute with regard to *ex vivo* analysis of metal-on-metal hip prostheses were most fruitful, and opportunities for collaboration were discussed. Overall, the Fellowship was a remarkable and unique experience which I feel has massively informed and progressed my research interests.

**Ines Reichert**

The Fellowship offered me a tremendous chance to meet international basic science researchers and to discuss our respective results and concepts. I presented my data on blood flow changes and the role of the periosteum during fracture healing. My PhD established a significant increase in periosteal blood flow following intramedullary reaming, an effect which could also be observed systemically. My additional research interests encompass peripheral nerve repair and a novel ultra-short MRI sequence to evaluate changes in the vascularity of cortical bone.

Each of the host institutions welcomed us with their own, distinct style. This determined our experience as much as the different research foci we encountered in each centre. In San Francisco, at the impressive Orthopaedic Trauma Institute pioneered by Theodore Miclau, my talk was followed by a highly relevant presentation by Celine Colnot from the faculty on the medullary and periosteal origin of stem cells in fracture healing. At the Mayo Clinic I was conscious of the standards that had been set here for the measurement of bone blood flow by Patrick Kelly’s group. Indeed, the discussions, in particular with Kai-Nan An, were encouraging and fruitful. Philadelphia impressed with two centres, a generous social programme and lasting discussions on the significance of change in subchondral vascularity for the development of osteoarthritis. In New York, at the Hospital for Special Surgery, I learned about Fourier Transform Infrared (FTIR) Spectroscopic Imaging in Adele Boskey’s laboratory, of particular relevance to my interest in cortical blood flow and fluid space in bone. In the session on bone healing Marjolein van der Meulen and Philipp Mayer-Kuckuk presented up-to-date work on fracture healing and novel molecular imaging techniques of angiogenesis in bone. I took the opportunity to meet Dr Mayer-Kuckuk to discuss his ongoing work in more detail. As the Fellowship concluded, I felt that the stimuli experienced and contacts made will have a lasting effect on my research ambitions back in the United Kingdom.

**Sarah Snelling**

The BORS/ORS Travelling Fellowship was a rewarding and stimulating experience for me at an early stage in my career as a post-doctoral scientist. My interests are genetic and functional studies of osteoarthritis and my post-doctoral research is focused on the function and mechanism of action of signaling molecules that show altered expression in osteoarthritis. Through the Fellowship, I have been fortunate to secure mentorship and guidance from leading scientists in the field. A particular strength of the Fellowship is the diverse research interests and experience of the Fellows themselves. This exposed me to learning and expertise on aspects of engineering, biology and clinical science that would seldom be encountered in such intensity. This broadening of my knowledge of orthopaedic science from both Fellows and host institutions, combined with the potential collaborations, will certainly provide foundations for a career in clinically relevant research.

During the Fellowship I presented work on the differential allelic expression of the secreted frizzled-related protein 3 (FRZB) gene in osteoarthritis. Frank Secreto (Mayo Clinic) presented research showing that the over-expression of Lef1-short increases bone mass in mice, and Motomi Enomoto-Iwamoto (Thomas Jefferson University) presented interesting work on the β catenin and Wnt signalling pathway in osteoarthritis. This combination of talks provoked in-depth discussion on the importance of the precise regulation of the Wnt pathway for both cartilage development and homeostasis. I also presented on the functional characterisation of bone morphogenetic protein-5 (BMP5) in chondrocytes, research that complimented the fascinating work on disrupted BMP signalling in fibrodysplasia ossificans progressiva (FOP) by Eileen Shore (University of Pennsylvania) and of BMP-regulated genes, including GADD45b, in osteoarthritis by Mary Goldring. The role of various signalling pathways is greatly enhancing our understanding of the disease processes involved in osteoarthritis and other musculoskeletal disorders. The excellent research presentations from each host institution emphasised the importance of better understanding these signalling pathways in order to fully exploit their clinical benefits.

**Conclusion**

Other highlights of the Fellowship included a tutorial by Maurizio Pacifici on embryonic chondrogenesis, learning about the National Institutes of Health National Disease Register from Javad Parvizi, a presentation by Joanne Hanafin on ‘Being a Successful MD, PhD and Parent’, and dinner at the exclusive Union Club in New York hosted by Mathias Bostrom. Although the main emphasis was on research, there were also opportunities to attend some excellent clinical events. These included an elbow clinical conference at the Mayo Clinic facilitated by Bernard Morrey and Shawn O’Driscoll, William Hozack’s theatre lists at the Thomas Jefferson University with uncemented total hip replacements, and the Philadelphia Orthopaedic Society Lecture on ‘Total Ankle Replacement’ by Roger Mann.
In the coming year six ORS Fellows from the United States will visit orthopaedic research centres in the United Kingdom for the first time, representing an excellent prospect to highlight the state of the art research programmes being conducted in the United Kingdom. The orthopaedic research communities of both countries are very much aware that there is a need for inclusive and multidisciplinary collaborative research, allowing for the exchange of ideas and opinions to overcome the current challenges relating to musculoskeletal diseases. It is these mindsets that will strengthen the BORS/ORS Travelling Fellowship programme and facilitate the dissemination of contemporary research ideologies and principles to the wider community of orthopaedic surgeons, biologists and engineers. The survival of the Fellowship also depends on continuing industrial sponsorship. Judging from the impact and outcomes of the 2009 Fellowship, this is definitely a worthwhile cause to support.