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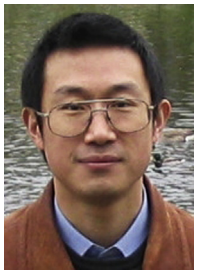
EDITORIAL

Biomedical imaging in translational orthopaedic research



Musculoskeletal disorder is a major burden on health care [1]. Musculoskeletal complaints are the second most common reason for consulting a doctor, and constitute, in most countries, up to 10—20% of primary care consultations [2]. At any one time, 30% of American adults are affected by joint pain, swelling, or limitation of movement [3]. According to the National Arthritis Data Workgroup, the best estimate of the national prevalence of arthritis—specifically, osteoarthritis (OA), rheumatoid arthritis, low back pain, gout, and certain autoimmune connective tissue diseases—was 15% in 1995 [4]. The total direct cost for use of health services that results from musculoskeletal conditions was 1.0% of the gross national product in Canada, and 1.2% in the USA [5,6]. The indirect costs of musculoskeletal conditions (loss of productivity and wages) were much greater than the direct costs. Radiographic evidence of knee OA is prevalent in $>$ 30% of persons aged 60 years or older [7]. It is expected that by 2020, this prevalence will increase to 20%, related in part to the advancing age of the population. Cartilage damage in OA is characterised as having an earlier dynamic phase, which is potentially reversible, followed by an irreversible pathological phase that ultimately leads to joint pain and immobility. The impetus to develop techniques to detect early lesions is to allow timely intervention to prevent the eventual evolution of radiographic joint space narrowing, osteophytosis, subchondral sclerosis, and cyst formation.

Animal models are an important part of orthopaedic research. They add to *in vitro* methods and provide the opportunity to study a specific biological mechanism *in vivo*. However, the read-out of such models is restricted because: (1) tissue sampling is time consuming and is subject to variability; (2) most read-outs have a time lag between tissue sampling and evaluation; and (3) readout often requires sacrificing the animal, and increases the costs. Biomedical imaging, being morphological, functional, or molecular, has been widely adopted in musculoskeletal research, and has bridged the gap between experimental research and clinical imaging. The detection of biological pathways *in vivo* is performed without tissue destruction nearly in real-time and biology can be studied under physiological conditions. An individual can be repeatedly analysed over time; a feature that simplifies data interpretation by minimizing consequences of variations between living individuals and increased statistical power. The ability to image a specific biological target *in vivo* can be translated into a part of orthopaedic diagnostic work-up [8—11].

Commonly used techniques include computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET). There is also an emerging imaging technology involving optical methods (fluorescence and bioluminescence) that are now used in preclinical animal models of disease. These particular tools are advancing the understanding and the related management of chronic musculoskeletal diseases, such as OA, rheumatoid arthritis, cancer, musculoskeletal pain, fracture healing, bone metabolism, chronic osteomyelitis, and osteoporosis. Through the use of multiple imaging modalities it is possible to study anatomy, physiology, and function in an *in vivo* model. Over the past several years, there has been significant development of dedicated instruments for small animal imaging applications in the modalities of MR, SPECT, PET, μCT, and *in vivo* optical imaging. MRI is a single imaging modality capable of high-resolution imaging, spectroscopy, and quantifying

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metabolic function. Perfusion MRI using dynamic contrast-enhanced MRI involves the rapid acquisition of serial MR images during and after administration of MR contrast agent. Based on the time following injection and the concentration of contrast in the tissues under investigation, a time intensity curve can be drawn allowing detection and quantification of *wash-in* and *wash-out* contrast kinetics. MR spectroscopy yields quantitative information on the chemicals that reside within the tissue. The commonly measured elements in the musculoskeletal system are hydrogen, phosphorus, and sodium. Muscle diffusion-tensor imaging has been used for *in vivo* structural analysis and it has the potential to detect segmentation of muscle fibers in disease states [12—14]. Blood oxygen level-dependent (BOLD) imaging was developed by Ogawa et al in 1990 for functional MRI imaging for evaluating brain activation. This technique has recently been applied to evaluate oxygenation level in normal and diseased muscle. It has been reported that BOLD signal-based muscle functional MRI could be beneficial in understanding microvascular-related disease such as muscular dystrophy, ischemia, and chronic/peripheral venous insufficiency [15].

SPECT and PET are functional imaging modalities that allow for molecular specific imaging in deep tissues of nano- and picomolar quantities, respectively. SPECT is a readily available technique for which there are a wide number of nuclear tracers available. PET is a quantitative modality with high sensitivity, imaging trace amounts (picomolar concentrations) of radiolabelled molecules. PET is most widely used to study metabolism through the labelling of glucose with fluorine-18. PET-based technologies have an advantage given their greater sensitivity, as well as the ability to use biological molecules that nearly simulate the structure and interactions of the native molecule being radiolabelled. Finally, advancements in deep tissue techniques for optical imaging have enabled the labelling and tracking of receptors, biochemical pathways, and cells in small animals. Osteoblasts have been labelled and imaged in an *in vivo* model of mouse bone disease. This technique is particularly useful in gaining further insight into the mechanisms of bone remodelling beyond simple measures of bone density [16]. In addition, biomedical imaging can be quantitatively and objectively assessed, which is superior to the traditional observer-based assessments that often have higher inter- and intraobserver variability [17,18].

Quantitative imaging methods that have been proven to correlate with clinical outcomes can play an important role in clinical decisions. Presently, a gap still exists between the physics-based development of new techniques and the applications used in the study of disease [19]. It is noticeable that nowadays there are more and more scientists with physical science or engineering background working on or starting to work on biomedical projects, but rarely vice versa. This reflects the multi-discipline nature of some projects, however, and at least partially can be explained by biomedical research being seen as more trendy and fundable [20]. It is also apparent from some publications and lectures that not all these physical scientists/engineers are well prepared to work on projects that do not align with their own expertise [21]. Manpower and financial resources are being wastefully spent [22]. In addition, ample examples exist where experienced physical scientists worked with inexperienced medical scientists and resulted in avoidable failures. Therefore close collaboration and frequent interaction of physical scientists/engineers, biologists, and clinicians are vital. Important research decisions have to be made after group debate rather than by a single senior scientist [22—24]. To this end, multidisciplinary translational orthopaedic imaging, and the *Journal of Orthopaedic Translation*, shall play a vital role.

Conflicts of interest

The authors have no conflicts of interest to declare.

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