

and biology of transplanted stem cells in the living subject. Recent advances in molecular biology and imaging have allowed the successful non-invasive monitoring of transplanted stem cells in the living subject. The ideal imaging method should provide the information of (1) Real-time visualization of stem cell delivery; and (2) Determination of location(s) and Quantification of cells over time. The chosen labeling modality should not interact with the normal functions of the stem cell and provides a good contrast between background and the target signal under study, achieving a large signal-to-noise ratio.

Reporter gene-bioluminescence imaging (BLI) is based on light emission and detection by specific cooled charge coupled device (CCD) cameras. Similar to other reporter gene strategies, the BLI signal is only emitted when cells are viable, and thus can be used for the longitudinal monitoring of stem cell survival and study of cell status. BLI has been successfully used for *in vivo* study of cell delivery and monitoring of stem cell viability, fate, interaction between stem cells and microenvironments in small living animals.

We have investigated the distribution of systemically delivered luciferase labeled MSCs in fracture animal model and tumor bearing animals. The whereabouts of the labelled stem cells are monitored using the *in vivo* imaging system (IVIS 200, Exogen, USA), and accessed the efficiency of using stem cells therapy for promoting fracture repair (Fig. 1) and anti-cancer gene therapy.

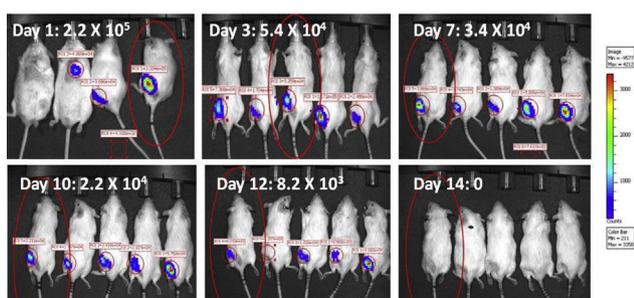


Fig. 1. Allogenic Luc-MSCs were injected into the fracture site in mice, and were monitored using *in vivo* imaging system. Allogenic MSCs became undetectable 14 days after injection. All animals did not show obvious adverse side effects.

#### Brief CV

**Research Area(s):** Stem cell biology and musculoskeletal tissue engineering

**Technical Expertise:** Circulating MSCs; stem cell gene therapy

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#### UPDATE ON OPTICAL IMAGING DEVELOPED FOR PRECLINICAL STUDIES OF BONE

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Optical imaging techniques are among the most powerful techniques in preclinical research, specifically for the imaging of rodents. It includes (i) methods suited for mesoscopic (spatial resolution of about 1 mm) whole body non-invasive imaging, specifically fluorescent and bioluminescent imaging, (ii) microscopic techniques, most notably multiphoton and confocal microscopy, and (iii) spectroscopic approaches such as Raman and Fourier Transform Infrared imaging and mass spectroscopy imaging.

A key reason for the attractiveness of optical imaging is the possibility to exploit the extremely powerful methods of genetic engineering. For example, transgenic mouse models can be generated that feature near infrared reporter signals associated with specific gene expression. By this mechanism of molecular imaging, morphologic imaging can be extended to *in vivo* functional imaging.

Optical imaging of bone is feasible but presents specific hurdles that to date have only partially been overcome. Light is strongly scattered and absorbed leading to strong attenuation and resulting limits in spatial resolution, decreasing rapidly with increasing depth. This also leads to bias in the quantitative evaluation of optical signals. On the positive side, due to the strong bone binding properties of bisphosphonates, bone labeling molecules have been developed. These bind to mineral on bone surface and permit *in vivo* insight into bone turnover. In this way, they work similar to serum markers of bone turnover, but they provide this information in a spatially resolved way, including 3-D depiction using fluorescent molecular tomography (FMT).

*Ex vivo* optical imaging provides powerful assessment tools specifically for the organic components of bone tissue. Second harmonic generation (SHG) is a contrast mechanism of multiphoton microscopy specific to collagen. Mineral to matrix ratios and subtype analysis of collagen is feasible with the aforementioned spectroscopic imaging approaches, promising to help elucidating bone fragility in secondary osteoporosis and other disorders, e.g. effects of diabetes on bone.

The goals for research in the coming years include the refinement of these methods, the linking of mesoscopic with microscopy techniques in order to obtain a comprehensive assessment of as many dimensions of bone quality as possible, the *in vivo* assessment of bone function down to the cellular level, in order to improve the assessment of bone metabolism and other skeletal disorders.

#### Brief CV

**Research Area(s):** Preclinical and clinical imaging of bone metabolism, bone fragility, and bone metastases

**Technical Expertise:** QCT, QUS, molecular imaging, statistics

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Dr. Claus-C. Glüer is a Professor of Medical Physics at the Department of Radiology and Neuroradiology, University Hospital Schleswig-Holstein in Kiel, Christian-Albrechts-Universität zu Kiel, Germany. His research is aimed at the development of innovative parametric imaging techniques and their quantitative evaluation. Since 1987 when he started his postdoc in the *Osteoporosis Research Group* of Prof. Harry K. Genant at the University of California, San Francisco, Dr Glüer has focused his research on osteoporosis and other bone disorders. He has contributed specifically to the development of bone densitometry, quantitative ultrasound and high resolution computed tomography approaches. He has coordinated several multicentre studies including *OPUS*, a European project on epidemiology and optimised diagnostic assessment of osteoporosis.

Dr. Glüer also has a strong research interest in multimodal methods for molecular imaging with applications in oncology, inflammation, and skeletal research. He co-founded the *Molecular Imaging North Competence Center (MOIN CC)* at the *Christian-Albrechts-Universität zu Kiel*, a preclinical imaging lab. At *MOIN CC*, multi modal imaging studies combining micro computed tomography, high-field magnetic resonance imaging, high resolution ultrasound, fluorescence and bioluminescence imaging can be carried out to study morphological, functional, cellular, and molecular processes in health and disease and to assess therapeutic effects.

Dr. Glüer is the current president of the *German Society for Osteology (DGO)*, past president of the *German Academy of Bone & Joint Sciences (DAdorW)* and *President of the European Calcified Tissue Society*. He has published more than 175 original papers, 20 books and book chapters, and holds 3 patents

#### MUSCULOSKELETAL IMAGING TECHNOLOGIES IN R&D OF 3D BONE COMPOSITE SCAFFOLD BIOMATERIALS

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Musculoskeletal imaging techniques, especially those non-destructive ones, such as clinical or laboratory CT, MRI, and ultrasound are able to provide not only 2-D and 3-D reconstructed images of the related organs or tissues, but also quantifications of the relevant parameters. The advance bioimaging technologies developed for the above applications are also extended by incorporating imaging contrast-enhancement materials. All the data-set enable us to design 3D tissue or organ structures of our musculoskeletal system using rapid 3D prototyping technologies. Above imaging technologies and application protocols also provide an excellent evaluation tools qualitatively and quantitatively for assessment of the implanted 3-D rapid-prototyped scaffolds preclinically and clinically. Multidisciplinary collaborations with biomedical engineers, biomaterial engineers, basic and clinical scientists are essential.

The author's group has been using a unique low temperature 3D rapid-prototyping technology to design and produce bioactive and degradable bone scaffold composite materials. Innovative bioactive materials are from nature herbs, biological factors, and cost-effective biometallic elements. Clinical indication-orientated animal models have been established for preclinical evaluations. Efforts are made for optimization of the implantable products to ensure maximal biocompatibility and osteoconductivity with sufficient mechanical properties.

Additional efforts are also be made towards translational medicine, here refer to product registration and multi-center clinical trials for innovative rapid-prototyped 3D skeletal scaffolds before becoming commercial available products for our routine clinical applications.

#### Brief CV

**Research Area(s):** Musculoskeletal imaging, R&D of orthopaedic drugs and biomaterials, preclinical and clinical studies of diagnosis, prevention and treatment of bone metabolic disorders and regeneration

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#### HIGH RESOLUTION IMAGING OF BONE MICROARCHITECTURE IN THE HUMAN APPENDICULAR SKELETON

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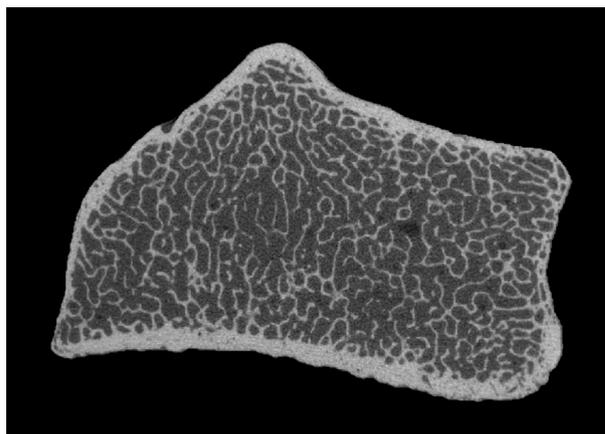
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Osteoporotic fractures are associated with considerable morbidity and mortality, and the use of 3D high resolution imaging has offered new opportunities to learn about bone quality that may help in the development of novel treatments and diagnostic techniques aimed at improving bone

health. The advent of high-resolution peripheral quantitative computed tomography scanners (HR-pQCT, XtremeCT, Scanco Medical) a decade ago opened new opportunities to investigate natural changes in bone quality with aging, the effects of treatments on the underlying bone micro-architecture, and the ability to apply techniques such as the finite element analysis to non-invasively assess bone strength. In the past year, a new version of HR-pQCT has become available (XtremeCTII) which further advances the potential to assess bone quality.

In this work we present our population-based cohort that has been a major focus of our laboratory over the past decade. We have previously established the age-related changes in bone microarchitecture based on a cross-sectional study design recently, and here we begin to explore the longitudinal analysis of that same population, and use that information to understand the true individual age-related changes in bone architecture. With the newfound ability to measure at a 61  $\mu\text{m}$  voxel size (Fig. 1), we explore the challenges of having a continuity of research studies that will span two generations of these systems. Specially, we will address the major issues that need to be resolved so that the wealth of longitudinal data collected by all users of HR-pQCT can be effectively continued. Also, we explore the ability to apply advanced analysis methods to the new technology, including both the finite element method and direct measures of bone microarchitecture. Finally, we will demonstrate the potential to being studying bone quality for other research applications, such as the periarticular bone quality at the knee and elbow, which is important for learning about diseases such as osteoarthritis and with implications for total joint replacement. In summary, the introduction of new HR-pQCT technology offers exciting new opportunities for the study of bone quality.



#### Brief CV

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Dr. Boyd is a Professor of Biomedical Engineering in the Faculty of Medicine performing research in the area of osteoporosis, with a particular focus on bone microarchitecture and non-invasive estimation of strength. He has published over sixty journal articles and had continuous funding from Canadian national agencies (e.g., CIHR, NSERC) since his appointment at the University of Calgary in 2002. His research ranges from in vivo  $\mu\text{CT}$  studies showing bone microarchitectural development in animal models of osteoporosis, to clinical research using recently developed HR-pQCT. He co-leads a Calgary-based population study using HR-pQCT to determine normative bone microarchitecture and strength across the lifespan in both sexes. He is appointed a Senior Scholar by Alberta Innovates – Health Solutions, the Bob and Nola Rintoul Chair in Bone and Joint Research, and is a member of the McCaig Institute for Bone and Joint Research with cross appointments in the Faculty of Kinesiology and Schulich School of Engineering.

#### POSITION TITLE

Professor, Faculty of Medicine, Schulich School of Engineering, Faculty of Kinesiology, University of Calgary, Canada

#### FUNDING

Canada Foundation for Innovation (CFI) Leading Edge Fund "An integrative approach for translating research to improve musculoskeletal health". Canadian Institutes of Health Research (CIHR) "A biomedical engineering

composite scaffolds for bone tissue engineering - IOS Press. engineering. Yueh-Lung Yang a. , Ching-Hsien Chang gDepartment of Life Science, Fu Jen Catholic University, New Taipei City, Taiwan. Abstract. Numerous ... image analysis and thresholding features to define the bone. Following mCT scanning, the scaffolds were demineralized using RDO (APEX Engineering Products Corp, Plainfield, IL). The scaffolds were then embedded in paraffin, sectioned at 7 mm, and stained with hematoxylin and eosin (H&E). 2.6. Mandibular condyle design and fabrication In order to provide a proof of concept, a minipig condyle scaffold was designed using image-based techniques [45]. A global anatomic design was first created directly from a CT scan of the minipig mandible.