Bone graft or bone substitute?

Dr Alexander Hofmann and **Professor Pol Maria Rommens** describe their newly opened Department for Orthopaedics and Traumatology as well as their upcoming multicentre trial aimed at investigating the utility of synthetic filling materials in bone defects

Could you introduce the Department for Orthopaedics and Traumatology at the Johannes Gutenberg University of Mainz, Germany, and the work conducted there?

AH&PMR: The University Medical Center is part of the Johannes Gutenberg University of Mainz – the fifth largest university in Germany. With more than 50 clinical departments, institutes and divisions, there is an interdisciplinary network in the Center operating more than 1,600 inpatient beds. The Department for Orthopaedics and Traumatology, as one of the biggest facilities in the Center, including 120 inpatient beds, provides services for a wide range of musculoskeletal system injuries and diseases. It performs more than 4,500 surgical interventions per year. With our motto of 'Our Expertise for Your Health', we are always eager to help patients in the best possible way through application of our scientific knowledge and longstanding experience in medical healthcare within state-of-the-art facilities.

The Department for Orthopaedics and Traumatology was recently formed out of the merger of the Department for Traumatology and the Orthopaedic Clinic of the University Medical Center. How has this unification facilitated the development of orthopaedics and trauma surgery at the University?

AH&PMR: The decision to merge the departments was made to pool expertise and resources as well as to eliminate redundancies, which were visible in many fields like spine surgery and arthroplasty. With this broader view of musculoskeletal disorders' different pathologies, we hope to develop common sub-specialties and improve our quality of care. In the new Department, specialists with broad expertise in both orthopaedics and orthopaedic trauma surgery represent different sub-fields, such as hand surgery and reconstructive trauma surgery. This strengthens the visibility and transparency of their disciplines for colleagues, students and patients.

Could you introduce the 'CERament treatment of Tibial Fracture defects' (CERTiFy) study? What is the background and rationale behind the project?

AH&PMR: CERTiFy aims to investigate two different treatment methods for tibial plateau fracture – bone autografts and the synthetic bone filling material, Cerament Bone Void Filler – in a randomised, controlled clinical trial. The data from this project will provide reliable information about the treatment options and will help surgeons address ethical issues associated with the continued use of risky and invasive bone autografts, in spite of potentially equally effective synthetic alternatives in the market.

What are your respective roles within the trial? How did you become interested in this research?

AH: In a collaborative effort, Professor Pol Maria Rommens and I initiated and designed the study with our colleagues from the Interdisciplinary Center for Clinical Studies. I am mainly responsible for the local study management and Rommens is the Principal Clinical Investigator, but we work together to coordinate the project between the study centres.

Fracture healing and bone defect reconstruction has been one of the major topics and interests of our research for many years. Our department is a member of a research platform in the Mainz University Medical Center named BiomaTiCS – Biomaterials, Tissues and Cells in Science. In addition to many other projects in the field of biomaterials applications that are performed in our laboratory, we initiated the CERTiFy study as a sound addition to our basic research.

Clinical trials such as these produce vast amounts of information. Can you describe how you manage all these data?

AH&PMR: Data acquisition is performed using a web-based electronic case report form. The investigator enters the data directly into the trial database via remote data entry. The database has been developed and maintained by the Interdisciplinary Center for Clinical Trials Mainz. The system provides the option of making exact data copies in legible paper form for review and audits. Statistical analysis will be performed by independent statisticians.

BoneSupport, your commercial partner, funds this study. In what ways have you ensured its commercial interest has not affected the study's setup or the dissemination of its results?

PMR: This matter is handled by a legal contract between Bonesupport and the Department for Orthopaedics and Traumatology. The contract ensures that as the Principal Investigator, I have full responsibility for all aspects of the study and dissemination of the study results. In addition, all legal subcontracts are between the Center and others involved, such as the Interdisciplinary Center for Clinical Studies. This legal setup secures the study's full independence.

Better than gold?

Researchers at the **Johannes Gutenberg University of Mainz**, Germany, aim to demonstrate how synthetic filler materials can rival bone autografts, which are the current gold standard treatment for bone defects

IN THE FIELD of regenerative medicine, there has been significant progress towards repairing bone defects resulting from fractures, tumours and infections. Recent advances in treatments include injecting synthetic bone filling materials designed to support bone regeneration; however, the gold standard treatment for bone defects remains the autograft, a procedure that is highly invasive and carries risks of complications. Although autografts are often justified in the case of large and complicated bone defects, the use of synthetic materials in fractures and defects of cancellous bone, with its higher healing capacity, could potentially deliver similar healing efficacy but with fewer unwanted complications, facilitating the surgical process for surgeon and patient alike.

FILLING IN THE GAPS

In a collaborative project across 11 centres in Germany – with four more centres to join their ranks in the near future – research led by Professor Pol Maria Rommens and coordinated by Dr Alexander Hofmann at the Johannes Gutenberg University of Mainz are aiming to assess the clinical performance of synthetic fillers compared with bone autografts in cancellous bone fractures. This is an effort to provide more information for the efficacy of synthetic fillers. "There is a limited number of good clinical studies demonstrating the value of bone substitutes in comparison to autologous bone grafts. Thus, despite the availability of different synthetic bone substitutes, many surgeons keep on using invasive autologous bone grafts to achieve the best possible healing results". For this reason, the 'CERament treatment of Tibial Fracture defects' (CERTiFy) project, which is currently recruiting patients, looks to compare the clinical outcome of tibial fracture treatment using autografts and synthetic filler materials, with emphasis on the quality of life of patients six months post-surgery.

SYNTHETIC SOLUTIONS

Autologous iliac bone grafts (AIBGs) from the pelvis are the most commonly used bone graft, as they have the most favourable biological characteristics. These include biomechanical support for bone growth (osteoconduction), cells to grow into bone tissue (osteogenesis), proteins that induce bone tissue regeneration (osteoinduction) and a physiological rate of resorption, which is a vital component of bone remodelling and the repair process. Thus, the ideal synthetic substitute for AIBGs in the CERTiFy project is a material that provides similar structural and biological characteristics of autologous bone. At present, synthetic fillers in the market lack osteogenetic and osteoinductive characteristics. However, it is possible for synthetic materials to fulfil the osteoconductivity and resorption requirements, when following the correct recipe.

The material used in the CERTiFy project, Cerament Bone Void Filler (CVBF), is one of the most commonly used bone graft materials; it is produced by BoneSupport, a Swedish company that is funding the project. CVBF consists of 40 per cent hydroxyapatite crystals and 60 per cent calcium sulphate. Calcium sulphate and hydroxyapatite are both osteoconductive materials that, when injected into a bone defect, harden to fill it with porous implants. Since the body resorbs calcium sulphate much more easily than hydroxyapatite, this 60-40 split is an optimum mixture, as the calcium sulphate paste – which is injected into the bone intraoperatively – delivers the hydroxyapaptite particles to fill the fracture. The hydroxyapatite component can then stimulate the surrounding bone tissue to coat the implant with a layer of endogenous hydroxyapaptite, which slows the resorption process, allowing new bone tissue to regenerate and remodel over time. As an added benefit, the inclusion of a radiocontrast agent in CVBF allows the team to monitor the healing process closely. Recent preliminary cases from the group have shown encouraging results, as Hofmann enthuses: "We achieved not only good healing outcomes, but we have also found that this product became obviously resorbed within six to 12 months. Furthermore, for some distinct indications, the use of CBVF provided really safe healing results, thereby avoiding many possible complications that would play a role in case of AIBGs".

QUALITY OF LIFE

Throughout the CERTiFy trial, the researchers are assessing the patient's quality of life instead of the treatment's effect on joint function. This decision stems from the fact that the healing efficacy of the procedure mainly depends on the skill of the surgeon carrying out the intervention, regardless of the medium used to fill the fracture. Therefore, any differences in the procedures would chiefly affect the patient's pain levels and other aspects of daily life. "We decided to use well-established measures of the quality of life as the primary endpoint and pain as the co-primary endpoint," explains Hofmann. "We believe that these two measures will adequately reflect the overall recovery course, including factors like daily function, activity level and pain." Secondary endpoints of the project include surgical complications, hospital stay and costs; the researchers will also employ radiological techniques such as X-ray imaging to monitor the internal healing process.

STEPS TO REGENERATION

In the complete scope of regenerative medicine, the CERTiFy project demonstrates just one aspect of potential bone repair treatments: modifying implant materials with the goal of regulating local tissue formation. However, the team is not only working on this project. They have been busy following several ideas, including new ones based on the concept of tissue engineering for the reconstruction of bone defects. As such, they are in the process of tackling a common problem with the majority of synthetic bone repair materials: a lack of vascularisation in the implant. This is important because it leads to a shortage

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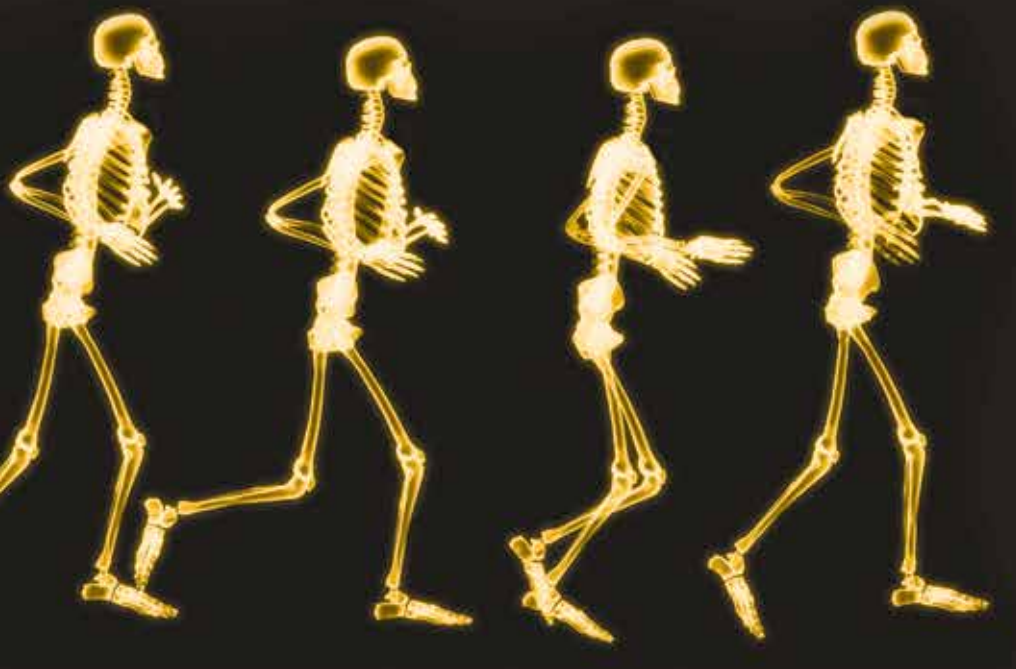
of nutrient delivery for bone regeneration. "We are addressing this issue in a couple of research projects using co-culture methods with mesenchymal stem cells and endothelial progenitor cells to engineer a pre-vascularised bone tissue construct with high regenerative capacity," Hofmann enthuses. Encouragingly, the technique is showing promising results in mouse models.

Although the repair of bone defects using stem cell regenerative medicine remains out of reach at present, it is clear from projects such as CERTiFy that current technological advances and shifts in clinical practice already show great promise for making considerable improvements to the quality of life for patients. "At this time it seems that a complex problem of bone defect reconstruction is difficult to solve using just one simple approach – we need to address many different issues and the solution becomes more complex than expected. Nevertheless, we also feel that our work helps us to move progressively closer towards solutions for this problem and this feeling is very inspiring," Hofmann states.



INTELLIGENCE

ORTHOPAEDICS & TRAUMATOLOGY

OBJECTIVES

To investigate the clinical outcome of treatment tibia plateau fracture-associated bone defects using either autologous bone grafting or bioresorbable hydroxyapatite/calcium sulphate cement (CERAMENT Bone Void Filler).

KEY COLLABORATORS

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POL MARIA ROMMENS has served as head of the Department for Orthopaedics and Traumatology at the Johannes Gutenberg University of Mainz, Germany, since 1996. He has developed new implants and techniques for the fixation of fractures near to joints.

ALEXANDER HOFMANN has worked as Senior Consultant Surgeon of the Department for Orthopaedics and Traumatology since 2010. He specialises in the treatment of severe injuries, and pelvic and acetabular fractures. He is also the head of the research laboratory of the Department.