

Musculoskeletal health

Professor Dr Lorenz C Hofbauer, MD leads the Division of Endocrinology, Diabetes and Bone Diseases at the Technische Universität Dresden Medical Center. Here, he outlines his interest in the field, describes his laboratory and explains how he sees research in this area progressing



What led to your interest in musculoskeletal health?

I have been interested in sports since I was a kid, trying out all sorts of games – football, basketball, swimming, running, mountain biking, skiing, etc. Thus, musculoskeletal health has always been high on my own personal agenda – and despite taking part in these risky sports I have thus far largely evaded injury. Scientifically, I became interested after my MD in 1996 when I joined the renowned bone researchers Drs Larry Riggs and Sundeep Khosla at the Mayo Clinic in Rochester, Minnesota for a three-year fellowship. They taught me the beauty of bone research.

Which issues are you hoping to address through your research into bone health?

We aim to increase bone health in different scenarios, including osteoporosis, rheumatoid arthritis, diabetes and cancer. Right now, we are conducting molecular and animal studies and participating in clinical trials on a new antibody-based therapy against osteoporosis focusing on sclerostin. This protein is secreted by a specific bone cell – the osteocyte – and inhibits bone formation. Taking this protein out of the game may boost bone strength.

Have you developed any novel therapies to improve the bone health of the ageing population?

We have participated in clinical phase III studies on the osteoporosis drug denosumab. Denosumab is a monoclonal antibody against the receptor activator of nuclear factor kappa B ligand (RANKL), a signal transduction molecule between osteoblasts and osteoclasts. This was approved in 2010 and is available for patients.

Could you describe the Bone Lab at the Technische Universität (TU) Dresden?

The Bone Lab is part of the Medical Faculty of TU Dresden and is located on the campus of the University Hospital. TU Dresden has its roots in the Royal Saxon Technical School, which was founded in 1828. It consists of a wide range of Schools: Engineering, Mathematics and Sciences, Humanities and Social Sciences, together with Medicine, offering a very broad set of courses. In 2012, TU Dresden became one of the top 10 German universities.

Does collaboration play an important role in your work?

I have the privilege of working with talented and highly cooperative colleagues from other areas such as haematology/immunology, diabetes, neuroscience, developmental biology and material sciences. These activities take place at the Center for Regenerative Therapies Dresden (CRTD) which has a strong focus on translating basic science into novel therapies. There is a vibrant pioneering spirit at the 'Dresden Biopolis' – the biomedical campus that was built some 15 years ago from scratch. Alongside the Medical Faculty, several renowned institutes such as the Max Planck Institute for Cell Biology and Genetics, B-Cube, the Max Bergmann Center and BIOTEC have since provided a fertile ground for research and have attracted internationally renowned scientists. In addition, our studies into osteooncology are embedded in the SKELMET consortium (www.skelmet.de), where several

partners from Munich, Kiel, Würzburg and Dresden have teamed up.

What have you discovered about the extracellular matrix (ECM) in bone?

We analysed major ECM components of the bone – glycosaminoglycans (GAGs) – for their regenerative potential, observing that when they are highly sulphated, bone resorption is reduced and bone formation increased. Also, mediators that control the activity of these bone cells were proven to interact with GAGs which results in changes in their bioactivity. GAGs are therefore a critical component of the ECM that should be utilised for further applications.

How can biomaterials help to meet the growing needs for bone replacement of our ageing population?

Biomaterials are versatile carriers that, when combined with biology, may serve as a scaffold or substitute until the organism has regenerated its tissue. In a large Transregio consortium (www.trr67.de) between researchers in Leipzig and Dresden, we aim to develop these biomaterials to enhance bone and skin regeneration. We have already found that sulphation of these biomaterials enhances some of the biological function and promotes tissue regeneration.

Could biomaterials enhance other areas of health?

Certainly, they work well with skin, which shares some similarities with bone. They may work in the bone marrow niche, haematopoiesis and immune function, as well as retinal or neural regeneration. However, the biological and cellular context is different for these applications, requiring rigorous and individual testing.

Bone field discoveries

Bone health is critical for our wellbeing. Strikingly, more than half of the elderly human population is affected by bone diseases. The Bone Lab at the **Technische Universität Dresden** leads the way in addressing the pressing medical need for improving bone health

Work at the Bone Lab provides state-of-the-art bone research that translates into better care for patients with bone disorders

MOBILITY IS CRITICAL for human life. It requires an intact skeleton, which in turn needs bone tissue to be constantly renewed. This relies on a balance between bone-forming osteoblasts and bone-resorbing osteoclasts. Yet small disturbances over time can lead to severe loss of bone substance. Currently, bone diseases affect over half of the elderly population in Germany, and have significant socioeconomic and medical consequences including immobility, pain and loss of autonomy. In light of our ageing society, there is a growing scientific and medical imperative to confront this challenge.

THE BONE LAB

Addressing this urgent need, Professor Lorenz C Hofbauer of the Technische Universität (TU) Dresden explores and develops strategies to improve bone health. Heading the Molecular and Translational Bone Laboratory at TU Dresden, Hofbauer follows a holistic approach combining bone research with other disciplines such as immunology, oncology or matrix engineering to identify and design novel treatments.

His work at the Bone Lab provides state-of-the-art bone research that translates into better care for patients with bone disorders and clinical studies to test drugs on the verge of entering clinical routine. The research is tried and tested on patients through the medical expertise of the University Clinics. What makes the team's work unique is the breadth of their collaborations and their 'bench to bedside to bench' approach. By exchanging basic

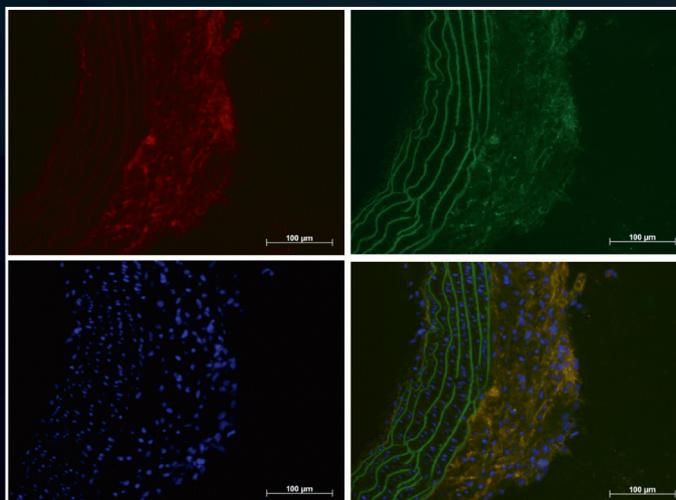
and preclinical expertise with biotechnology companies, clinical trials are initiated at the Osteoporosis Center. These trials improve bone health in patients and provoke novel hypotheses that need to be tested in a basic research setting, thus closing the translational circle and providing significant benefits.

A PLATFORM TO HEALTH

The central research focus of the Bone Lab is concerned with the communication between bone cells, and how molecular mechanisms and clinical sequelae change under different disease backgrounds. This involves studying bone in various disease conditions and pulling the new insights together in a central platform. Using classical cell and molecular biology methods, the research studies primary cells or cell lines. Yet the question for Hofbauer and his group is: "To what extent can we mimic a disease situation in the cell culture setting?". This is often impossible, so instead the German researchers use appropriate rodent models that mimic most features of a human disease. If they are successful with these models, their findings are validated using human samples. Using this translational approach, the team nurtures the knowledge platform containing the main research fields they are studying: matrix biology and bone remodelling, osteo-oncology, osteoimmunology and bone health of diabetics.

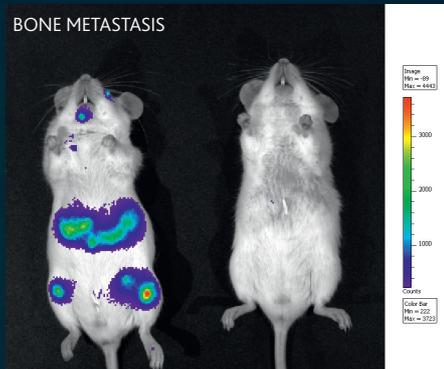
RESEARCH AREAS

Matrix biology and bone remodelling relies on glycosaminoglycans (GAGs) such as hyaluronan and chondroitin sulphate – the major organic extracellular matrix components in bone. The Bone Lab investigates how GAGs and their sulphation status control osteoclast functions and bone remodelling. Hoping to use these insights as part of their translation work, the team will develop and validate new adaptive biomaterials to effectively treat larger bone defects. Besides biomaterials, they also study



BONE PROTEINS IN VESSELS

BONE METASTASIS



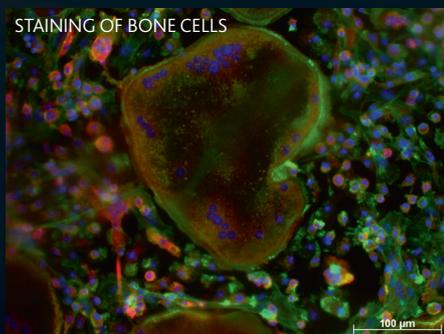
osteonecrosis, which enables them to examine the manner in which bone metastases arise from breast and prostate cancer. Through these investigations, the Bone Lab intends to improve the bone health of patients with cancer by identifying and validating potential targets.

PATHWAY TO TREATMENT

The team's work in osteoimmunology has also uncovered some key findings that could affect those suffering from cancer. They studied the interactions between the immune system and bone cells in conditions of excessive glucocorticoid exposure and arthritis. Central to this investigation was defining the role played in health and disease by the receptor activator of nuclear factor kappa B ligand (RANKL)/osteoprotegerin (OPG) system and the Wnt pathway, in particular Wnt5a. During a study assessing the Wnt profile of primary prostate cancer tissues and cell lines, the researchers found that prostate cancer cells express a distinct Wnt expression profile depending on where they home in on. Furthermore, the team discovered that zoledronic acid, a potent bisphosphonate used to treat bone loss, suppressed several Wnts including Wnt5a. The research has therefore identified the need for further investigation into the relevance of Wnt signalling in prostate cancer.

Alongside this, Hofbauer and his collaborator Dr Martina Rauner, junior group leader, also found that Wnt5a plays an important role as a bone marrow stromal cell (BMSC)-derived mediator of joint inflammation in arthritis. To come to this conclusion, they investigated the level of Wnt5a in arthritic joints compared with joints suffering from osteoarthritis, finding that patients with rheumatoid arthritis had much higher levels

STAINING OF BONE CELLS



of Wnt5a than patients with osteoarthritis. This was confirmed by the fact that arthritic mice models displayed high Wnt5a expression in inflamed joints, and the controls did not. Having undertaken further studies, results indicate that inflammatory stimuli upregulate Wnt5a, controlling cytokine and chemokine expression and the migration of immune cells. This all suggests that Wnt5a may be a critical regulator of inflammation and thus a potential target to counteract inflammatory bone loss. Hofbauer hopes to pursue this investigation further towards clinical application: "We are exploring the prospects of targeting Wnt5a to reverse disease processes".

DIABETIC BONES

The research into Wnt pathways has also enabled the Bone Lab to address the bone health of diabetics. Such work is crucial as diabetes mellitus is on the increase, and closely associated with osteoporosis and fragility fractures. The team studies the mechanisms of bone remodelling and bone repair using preclinical rodent models, alongside their hands-on work with patients. Their initial exploration found that rats with diabetes suffered from brittle bones and did not heal larger bone defects. The reason for this is that the rats' osteoblasts were not properly working and were incapable of producing sufficient new bone.

By combining these findings with what they had found about Wnt pathways, Hofbauer's group discovered that Wnt stimulation was a potential solution to boosting bone formation. This led to a fruitful collaboration with the biotechnology company Amgen, who provided the lab with the necessary sclerostin antibody to stimulate the Wnt pathway. Having been proven to be a very successful way of normalising bone health in diabetic rats, they now hope that these findings can eventually be applied to humans to substantially improve bone health for multi-morbid patients. However, moving the research from animal and laboratory-based experiments to human trials requires perseverance, as Hofbauer observes: "This whole translational process is like an ultra-marathon".

FUTURE PLANS

The researchers now intend to extend their current activities towards osteohaematology. Haematopoietic stem cells reside in the bone marrow compartment in close proximity to osteogenic cells. Several lines of experimental and clinical evidence demonstrate that both systems mutually affect one another. As such, the team will investigate the role of iron homeostasis on bone health with partners from Dresden, Austria and Italy. The study will rely on Hofbauer and his collaborators determining the role of the Wnt signalling pathway in osteohaematology, and investigating the role of erythropoietin in the osteohaematopoietic niche. Research is ongoing but the first results may be available by the end of 2013 or early 2014.

INTELLIGENCE

INFLUENCE OF EXTRACELLULAR MATRIX COMPONENTS ON OSTEOCLAST FUNCTION AND SIGNALLING PATHWAYS

OBJECTIVES

The main goal of the SFB-Tranregio67 is to develop functional artificial matrices to improve bone regeneration and wound healing. The role of the team in particular is to study the effects of functional matrices on bone cell biology and validate those findings in preclinical models of impaired fracture healing, for example, in diabetic animals.

The Bone Lab combines bone research with other disciplines such as immunology, oncology and matrix engineering to define novel targets and utilise the full expertise at the Technische Universität (TU) Dresden.

KEY COLLABORATORS

Dr Christine Hamann, Orthopedic Surgery;
Professor Stefan Rammelt, Trauma Surgery;
Dr Ricardo Bernhardt, Max Bergmann Center, TU Dresden, Germany

Professor Jan Simon, Dermatology, Universität Leipzig, Germany

Dr Graeme Campbell; **Professor Claus-C Glüer**, Universität Kiel, Germany

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PROFESSOR DR LORENZ C HOFBAUER

heads the Division of Endocrinology, Diabetes and Bone Diseases at TU Dresden Medical Center and the Comprehensive Osteoporosis Center that offers state-of-the-art care for patients with bone disorders, including clinical studies that involved denosumab and sclerostin antibodies. In addition, he heads the Molecular and Translational Bone Laboratory.

