view how the blood circulation inside and outside of bones are interconnected to mediate functional or dysfunctional immunity.

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SP0107 THE 4-D+ NANOSCOPE: THE RESOLUTION FOR BIOLOGICAL SAMPLES

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Background: In ageing societies all over the globe, the number of people suffering from bone disease, e.g. osteoporosis (OP) in the first place, has increased dramatically. OP considerably impairs patients' life quality, and results in high societal costs. However, current understanding of OP is still insufficient due to the lack of appropriate high resolution tools that permit a thorough analysis of scale bridging bone architectures from macro to nano with statistical significance to support the development of better treatments by drugs or surgical intervention.

Objectives: To revolutionize our knowledge of bone diseases based on an increase in understanding of the underlying bone anatomy, cutting-edge correlative high-resolution microscopy and spectroscopy together with advanced data analysis including machine learning approaches permit reaching the next, so far unprecedented level of understanding.

Methods: Correlative workflows starting from X-ray microscopy (XRM) volume analysis, with voxel sizes of <1µm, over light-sheet fluorescence microscopy and large scale scanning electron microscopy data acquisition, to dual beam microscope analysis (focused electron- and ion beams) permit the scale bridging investigation of bone architectures and thus merging the "big picture" and the underlying ultrastructure with statistical significance. In combination with additional analytical add-ons to these microscopes, physical properties such as optical, mechanical, compositional, structural etc. deliver a highly detailed correlative dataset of bone (cf. Figure 2).

The present paper demonstrates novel findings related to various partly age related bone diseases using advanced correlative data acquisition (cf. Figure 2).

Results: Figure 1 shows the different bone fine structures, composed of trabecular and vascular networks as well as a three-dimensional arrangement of osteolacunae that host osteocytes, as obtained by volume analysis in a new generation of lab-based x-ray microscope (Zeiss XRM Versa 520). These fine structures can be assessed quantitatively with statistical significance and can be correlated with additional modalities as shown in Figure 2. Elucidating examples demonstrating the power of such an approach will be given [ref 1, ref 2, ref 3, ref 4].

Figure 2 shows the an example correlative workflow from sample collection over sample preparation and the acquisition of various image modalities utilizing correlated data from electron-, ion-beam imaging and analytics, probes and focused laser light to study scale bridging bone architectures. We will demonstrate how these correlative workflows will permit to advance the current understanding of bone architectures and function substantially and will show some first systematic correlative microscopy and spectroscopy studies on mouse tibia and human bone [ref1, ref2, ref3, ref 4].

Abstract SP0107 Figure 1. Bone anatomy with scale – bridging architecture: mass oriented assessment with conventional methods such as DEXA and µCT and function-oriented assessment using correlative microscopy including volume analysis of trans-cortical vessels, osteo-lacunae and canaliculi by XRM and FIB/SEM.

Abstract SP0107 Figure 2. Correlative microscopy/spectroscopy workflow in bone research including (i) the challenges of sample preparation, (ii) the interplay of various image and data modalities, (iii) data evaluation, resolution enhancement and data analysis based on deep learning strategies; finally, new insights in open questions related to bone remodelling and bone structure at various length scales in relation to vasculature will be extracted from statistical correlative microscopy data.

Conclusion: Based on our correlative analytics and the data availability, the advanced data interpretation using machine learning approaches will be discussed. Using this approach, all details of bone micro-/nano-architecture can be used to provide a novel clinical tool-set for future for early detection of bone diseases.

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SP0108 LSFM AND CATCHING UP IN JOINT IMAGING

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Background: Bone tissue differs from other organs by its hardness and high optical density. These physical characteristics are challenging in the context of fluorescence based imaging studies addressing bone anatomy and physiology. The development of novel imaging technologies, such as light-sheet fluorescence microscopy and X-ray microscopy, and tissue-specific preparation procedures like optical clearing allowed us to reveal a so far overseen network of blood vessels in the cortical bone. These trans-cortical vessels (TCVs) directly connect the bone marrow vascularization with the periosteum and make the major contribution to total blood flow in long bones. Furthermore, we could show that immune cells are recruited to the peripheral circulation via TCVs and that TCVs are highly remodeled under inflammatory conditions. In case of chronic arthritis we observed a massive increase in TCV numbers, especially at the metaphysis of long bones. This increase in bone vascularization confirms observations of previous studies describing increasing numbers of microcanals in the bare area of metacarpal heads in the hands of rheumatoid arthritis patients. These alterations in bone anatomy might hint to an alternative mechanism by which immune cells are recruited into inflamed joint tissue. While current concepts describe the recruitment of immune cells from the systemic circulation, immune cells can potentially infiltrate the arthritic joints directly from the underlying bone marrow.

Objectives: Clarifying the anatomical routes of cell recruitment as well as exploring the regulatory mechanism guiding immune cells from the bone marrow to the site of inflammation might bear novel therapeutic strategies to resolve inflammation and tissue injury in rheumatoid arthritis.

Methods: 3D optical imaging approaches like Light-sheet fluorescence microscopy and 2-Photon laser-scanning microscopy enable the visualization of entire bones and joints. In combination with tissue-specific preparation procedures and labeling strategies inflammatory mediated changes in vascularization and cell recruitment can be analyzed.

Results: The joint tissue architecture is massively affected by inflammatory arthritic processes leading to changes in vascularization, permeability and cellular tissue composition. These processes are directly connected to the onset as well as the resolution of inflammatory arthritis.

Conclusion: Newly available imaging techniques as light-sheet fluorescence microscopy facilitate new insights into bone and joint tissue architecture, function and inflammatory processes. These findings might guide the identification of novel